Epidemiological, quality of life and mental health aspects in patients with type 2 diabetes mellitus in Saudi Arabia

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(M.B.B.S., M.P.H.)

A thesis submitted in fulfilment of the requirement for the degree of *Doctor of Philosophy*

Sydney Medical School

Faculty of Medicine and Health

The University of Sydney

September 2024

Statement of originality

This is to certify that to the best of my knowledge, the included content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

All research in this thesis was approved by the local Ethics Committee, Unit of Biomedical Ethics, at the Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia (Reference No 324-22) (Appendix A). Informed consent was obtained from all participants.

Owiss Hasan A Alzahrani Date: 23/09/2024

Authorship attribution statement

Chapter 2 of this thesis is published as **Alzahrani, O.**, J.P. Fletcher, and K. Hitos, *Quality of life and mental health measurements among patients with type 2 diabetes mellitus: a systematic review.* Health Qual Life Outcomes, 2023. 21(1): p. 27. I participated in all sections of this manuscript (conceptualisation, methodology, data analysis, writing the drafts and original article) and prepared the tables and flow diagram. Associate Professor Kerry Hitos and Emeritus Professor John P. Fletcher reviewed, edited, and approved the manuscript.

Chapter 3 of this thesis is submitted for publication. I participated in all sections of this manuscript (conceptualisation, methodology, data analysis, data retrieving, writing the drafts and original article) and prepared the descriptive and analytical tables. Associate Professor Kerry Hitos and Emeritus Professor John P. Fletcher reviewed, edited, and approved the manuscript.

Chapter 4 of this thesis is submitted for publication. I participated in all sections of this manuscript (conceptualisation, methodology, data analysis, data collection, writing the drafts and original article) and prepared the descriptive and analytical tables. Associate Professor Kerry Hitos and Emeritus Professor John P. Fletcher reviewed, edited, and approved the manuscript.

Chapter 5 of this thesis is submitted for publication. I participated in all sections of this manuscript (conceptualisation, methodology, data analysis, data collection, writing the drafts and original article) and prepared the descriptive and analytical tables. Associate Professor Kerry Hitos and Emeritus Professor John P. Fletcher reviewed, edited, and approved the manuscript.

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Owiss Hasan A Alzahrani Date: 23/09/2024

As a supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Associate Professor Kerry Hitos Date: 23/09/2024

Acknowledgment

I am truly grateful for the strength, determination and patience that God has given me throughout my doctoral study journey.

I would like to express my heartfelt appreciation to my supervisors, **Associate Professor Kerry Hitos and Emeritus Professor John P. Fletcher**, for their unwavering support and willingness to share their scientific experience and knowledge with me. They have been like a second family to me, especially during those hard times when I felt far from my loved ones. Their encouragement has been my driving force during times of exhaustion. I am immensely thankful to them for everything they have provided. Also, I would like to thank my local supervisor, **Dr Rajaa Alraddadi**, for her support and kind guidance during my scholarship.

Furthermore, I would like to extend my heartfelt gratitude to my father (**Professor Hasan Alzahrani**) and mother (**Dr Balkees Bakhotmah**), who have been my rock and my guiding light. I am deeply grateful for their limitless support and constant presence in both the best and most challenging times.

Lastly, a huge thank you to my brothers (**Dr Ahmad and Dr Anas**), sister (**Afnan**), nephews (**Hasan and Malek**), and friends (**Abdullah, Ibrahim, Tariq, Mosab, Amro, Motaz, Yosef**, and so many others) for their sincere, uplifting words, which have been a constant source of motivation and strength along this journey. I want to thank the **Saudi Arabian Cultural Mission** (**SACM**) in Australia for awarding me their scholarship. Also, I would like to thank anyone who stood with me during the difficult times of the **COVID-19** period and its ups and downs that affected this thesis's studies settings and timeline.

Abstract

Worldwide Type 2 Diabetes Mellitus (T2DM) and its complications have a profound impact on Health-Related Quality of Life (HRQoL) and mental health. The magnitude of this health problem has not been fully explored in the Middle East and the North African region (MENA), including Saudi Arabia and its adjacent Gulf Cooperation Council (GCC) countries.

This thesis provides comprehensive investigations and offers valuable insights to explore this issue from various perspectives. The overall objectives of this thesis are as follows: i) to identify an appropriate measurement tool to evaluate the HRQoL and mental health in individuals with T2DM, ii) to evaluate the overall burden of T2DM risk factors and complications, iii) to investigate the cumulative impact of T2DM risk factors, HRQoL, and mental health on increasing the risk of developing complications associated with T2DM, and iv) to assess physicians' perspectives regarding their awareness and the importance of HRQoL and mental health in their patients with T2DM in Jeddah, Saudi Arabia.

To achieve the first objective, a systematic review of the relevant medical databases was performed. For the second objective, a retrospective study was conducted utilising the 10th revision of the International Classification of Diseases (ICD-10) codes between January 2010 to July 2022 from the Information Technology Department at King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia. To fulfil the third aim, a cross-sectional study involving 182 participants was conducted in Jeddah, Saudi Arabia, from September to December 2022, using a validated and reliable measurement tool. Lastly, a survey was distributed to 54 physicians in Jeddah, Saudi Arabia, between October and December 2022, to address the final objective using a modified questionnaire.

The systematic review in this thesis identified the Medical Outcomes Short Form 12-item Version 2 (SF-12v2) to be the most appropriate for evaluating HRQoL and mental health aspects in people with T2DM. The retrospective study conducted on 3,972 patients with T2DM at a tertiary care hospital in Jeddah, showed that 74.7% had T2DM-related complications. Findings highlighted that males, age > 45 years, poorly controlled high glycosylated haemoglobin test (HbA1c), elevated cholesterol levels and high Body Mass Index (BMI) significantly increase the risk of developing T2DM-related complications. The cross-sectional survey among people with T2DM in Jeddah, using the SF-12v2 as a measurement tool, demonstrated that below-average Mental Component Summary (MCS) score, Physical Component Summary (PCS) score, females, poorly controlled HbA1c, high cholesterol, long T2DM duration and low socioeconomic status or monthly income increased the risk of having T2DM-related complications. The last survey evaluated physician perspectives on HRQoL and mental health when treating patients with T2DM. Results indicated the need for raising awareness among physicians about HRQoL and mental health problems in patients with T2DM.

Collectively, these research studies shed light on the magnitude of the T2DM problem in the Saudi population. They underscore the need for more practical and effective partnerships between healthcare policymakers/decision-makers and physicians. Health promotion, community-based and preventive strategies to improve HRQoL and mental health aspects in people with T2DM and specifically those with T2DM-related complications are required.

List of publications and presentations

Publications arising from this thesis, published in peer-review journal

2023 **Alzahrani, O.**, J.P. Fletcher, and K. Hitos, *Quality of life and mental health measurements among patients with type 2 diabetes mellitus: a systematic review.* Health Qual Life Outcomes, 2023. 21(1): p. 27. (**Chapter 2**)

https://hqlo.biomedcentral.com/articles/10.1186/s12955-023-02111-3

2024 **Alzahrani O**, Fletcher JP, Hitos K. *Physicians' Perspectives on Health-Related Quality of Life and Mental Health Aspects of People with Type 2 Diabetes Mellitus: A Cross-Sectional Study in Jeddah, Saudi Arabia.* Diabetes Metab Syndr Obes. 2024;17:4287-97. (**Chapter 5**)

https://pubmed.ncbi.nlm.nih.gov/39564448

Publications arising from this thesis, submitted to peer-review journals

2024 **Alzahrani, O.**, J.P. Fletcher, and K. Hitos, *Contributing risk factors and complications in patients with type 2 diabetes mellitus: a retrospective cohort study.* (**Chapter 3)**

2024 **Alzahrani, O.**, J.P. Fletcher, and K. Hitos, *Health-related quality of life and mental health aspects among people with type 2 diabetes mellitus; with and without diabetes-related complications: a cross-sectional study in Jeddah, Saudi Arabia.* (**Chapter 4**)

Poster presentations and published abstracts

2023 **Alzahrani, O.**, J.P. Fletcher, and K. Hitos, *Quality of life and mental health measurements among patients with type 2 diabetes mellitus: a systematic review.* Metabolism - Clinical and Experimental Vol. 142, World Congress Insulin Resistance Diabetes & Cardiovascular Disease. (**Chapter 2**) https://doi.org/10.1016/j.metabol.2023.155420

https://www.metabolismjournal.com/article/S0026-0495(23)00023-9/abstract

2024 **Alzahrani, O.**, J.P. Fletcher, and K. Hitos, *Contributing risk factors and complications in patients with type 2 diabetes mellitus: a retrospective cohort study,* Diabetes Research and Clinical Practice, International Diabetes Federation (IDF). (**Chapter 3**)

https://dx.doi.org/10.1016/j.diabres.2024.111464

https://www.diabetesresearchclinicalpractice.com/article/S0168-8227(24)00469-8/fulltext

2024 **Alzahrani, O.**, J.P. Fletcher, and K. Hitos, *Comparison of physician perspective with quality of life and mental health aspects in type 2 diabetes mellitus patients,* Diabetes Research and Clinical Practice, International Diabetes Federation (IDF). (**Chapter 4 and 5**)

https://dx.doi.org/10.1016/j.diabres.2024.111465

https://www.diabetesresearchclinicalpractice.com/article/S0168-8227(24)00470-4/fulltext

Oral presentations

2022 Quality of life and mental health in patients with type 2 diabetes mellitus, Faculty of Medicine and Health, The University of Sydney.

2024 Epidemiological, quality of life and mental health aspects in patients with type 2 diabetes mellitus in Saudi Arabia, Vascular Biology Research Centre, Western Sydney Local Health District, Westmead Hospital, The University of Sydney.

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List of abbreviations

ADA:	American Diabetes Association
BMI:	Body Mass Index
BP:	Bodily Pain
BPGs:	Best Practice Guidelines
COVID-19:	Coronavirus Disease 2019
CPGs:	Clinical Practice Guides
CVD:	Cardiovascular Disease
DALYs:	Disability-Adjusted Life-Years
DD:	Diabetes Distress
DKA:	Diabetic Ketoacidosis
DM:	Diabetes Mellitus
GCC:	Gulf Cooperation Council
GFR:	Glomerular Filtration Rate
GH:	General Health
GI:	Glycaemic Index
GLP-1:	Glucagon-Like Peptide 1
HbA1c:	High glycosylated haemoglobin test

HHS:	Hyperosmolar Hyperglycaemic State
HRQoL:	Health-Related Quality of Life
ICD-10:	10th Revision of the International Classification of Diseases
IDF:	International Diabetes Federation
MCS:	Mental Component Summary
MENA:	Middle East and North Africa
MH:	Mental Health
NDSS:	National Diabetes Services Scheme
PCS:	Physical Component Summary
PF:	Physical Functioning
PROMs:	Patient-Reported Outcome Measures
QoL:	Quality of Life
RACGP:	Royal Australian College of General Practitioners
RE:	Role Emotional
RP:	Role Physical
SDCPG:	Saudi Diabetes Clinical Practice Guidelines
SF-12v2:	The 12-item Short Form Health Survey Version 2

SF-36:	Medical Outcomes Short Form 36
SF:	Social Functioning
SMI:	Severe Mental Illness
T2DM:	Type 2 Diabetes Mellitus
VT:	Vitality
WHO:	World Health Organisation

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Chapter 1. Type 2 diabetes mellitus (T2DM), health-related quality of life (HRQoL) and mental health: a review

1.1 What is T2DM?

Diabetes mellitus (DM) is a long-term disease that affects human health by how the body converts food into sugar and then releases it into the bloodstream. When blood sugar (glucose) levels rise, the pancreas produces insulin. However, this disease occurs when the body does not produce enough insulin or insulin resistance affects blood glucose regulation, leading to high blood glucose in the bloodstream. Over time, this disease causes severe health conditions such as cardiovascular illnesses, eye problems, kidney dysfunction, and nerve impairment (1).

1.2 Definition of T2DM

There are various types of diabetes due to other causes that are less common in populations. This includes monogenic diabetes syndrome, diseases of the exocrine pancreas and drug or chemical-induced diabetes (Figure 1.1). The most common types of diabetes include:

- Type 1 DM (T1DM), which is mainly caused by autoimmune β-cell destruction, resulting in absolute insulin deficiency shown usually in early life mainly; due to several factors, including genetic and familial factors, as demonstrated in Figure 1.1 below (2).
- Type 2 DM (T2DM), also known as T2DM, which is mostly caused by a severe and gradual loss of adequate β-cell insulin secretion. This frequently occurs in the context of insulin resistance following a long duration (2).
- Gestational DM, which mostly appears in the second or third trimester of pregnancy without any prior symptoms or signs of any type of diabetes (2).

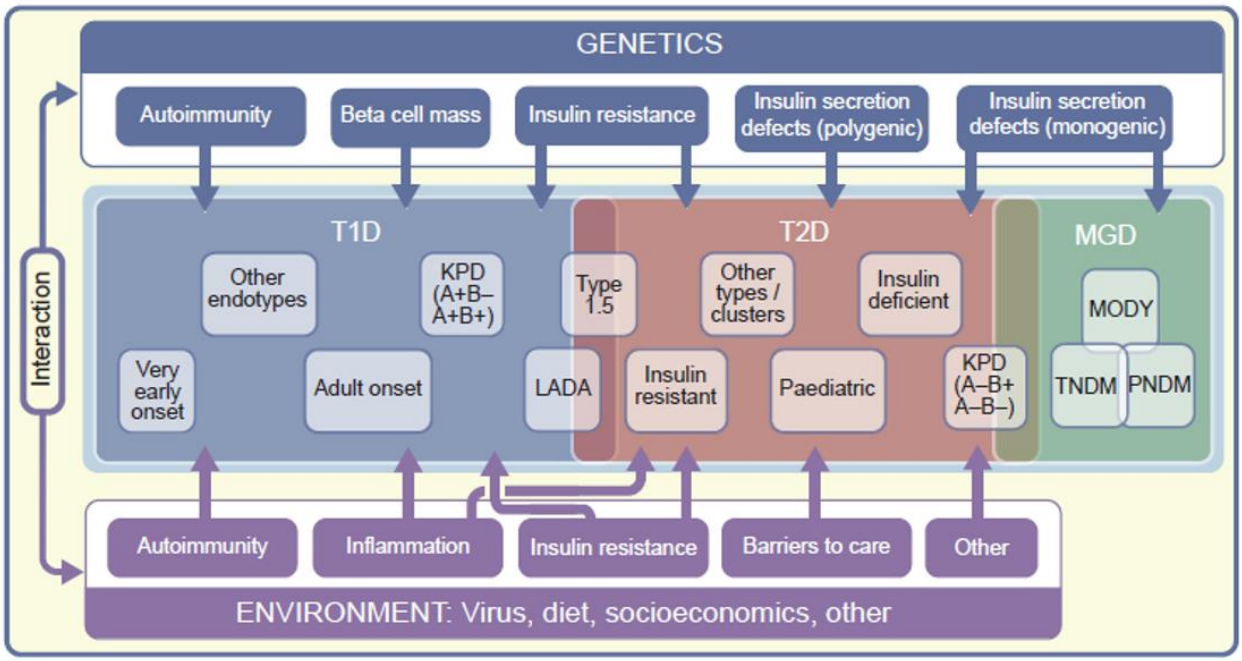


Figure 1.1 Heterogeneity within and between diabetes types (Adapted from: Redondo, M.J., et al., *The clinical consequences of heterogeneity within and between different diabetes types.* Diabetologia, 2020. 63(10): p. 2040-2048.)(2).

T2DM, is the most common type of diabetes. It accounts for approximately 90% of all diabetes cases overall and is influenced by environmental factors such as diet, physical activity, virus, socioeconomics and genetic factors (Figure 1.1). It is also linked to obesity, which might cause insulin resistance; however, the reason for this remains unknown. A person with T2DM is often an adult over 30 years of age with a Body Mass Index (BMI) of greater than 25 kg/m2. The presence of first-degree relatives diagnosed with T2DM is a strong additional risk factor (3).

1.3 Symptoms and signs of T2DM

A patient with T2DM might be asymptomatic at the beginning of the disease until symptoms appear later (4). This is why it is necessary to detect T2DM early by performing all the required tests for this disease on a regular and continuous basis (3).

After a long period of increasing blood glucose levels, some symptoms of hyperglycaemia may become apparent. This includes increasing thirst (polydipsia), general tiredness, frequent urination (polyuria), the feeling of hunger (polyphagia), recurrent infections, slow-healing wounds, numbness and blurred vision. In some cases, skin manifestations develop like acanthosis nigricans, eruptive xanthomas on the surface of the limps and hyperpigmented and hyperkeratotic in the axilla, groin and back of the neck (Table 1.1). A thorough medical history along with height, weight, BMI and assessment of vital signs including all pulses, must be noted when undertaking a physical examination of a patient with diabetes (4).

	T1DM	T2DM
Polyuria and Thirst	⊕⊕	⊕
Weakness or Fatigue	⊕⊕	⊕
Polyphagia with Weight Loss	⊕⊕	⊖
Recurrent Blurred Vision	⊕	⊕⊕
Vulvovaginitis or Pruritus	⊕	⊕⊕
Peripheral Neuropathy	⊕	⊕⊕

Nocturnal Enuresis	⊕⊕	⊖
Often Asymptomatic	⊖	⊕⊕

Table 1.1. A summary of the clinical differentiation between T1DM and T2DM through symptoms and signs (4).

1.4 The burden of T2DM globally

DM is one of the most important causes of death worldwide. This disease places these individuals (approximately 90% have T2DM) at a two to three times greater risk of death from all-cause mortality compared to healthy people (5). The global burden of DM is generally measured by prevalence, incidence, death and disability-adjusted life-years (DALYs). This equates to lost time of human life due to premature death. The time and life remaining for these patients is usually less than ideal when compared to healthy individuals. This is also reflected in the loss of total daily productivity, where one DALY is equivalent to the loss of one year of living a full and healthy life (6). Therefore, it is necessary to measure and further highlight the burden of DM globally, especially since DM has the second most significant negative impact on decreasing life expectancy worldwide. This major issue is expected to gradually increase during the upcoming decades (6).

1.5 Prevalence and epidemiology of T2DM

The prevalence of DM has been increasing globally from 211.2 million in 1990 to 476.0 million in 2017. Similarly, the incidence of DM has increased from 11.3 million in 1990 to 22.9 million in 2017. An increase in DALYs by 116.7% and 125.5% in deaths due to DM is predicted. This

highlights that these trends of T2DM burden will continue to increase over time. Without appropriate preventative strategies, the projected increase will be until at least 2025 (Figure 1.2) (6).

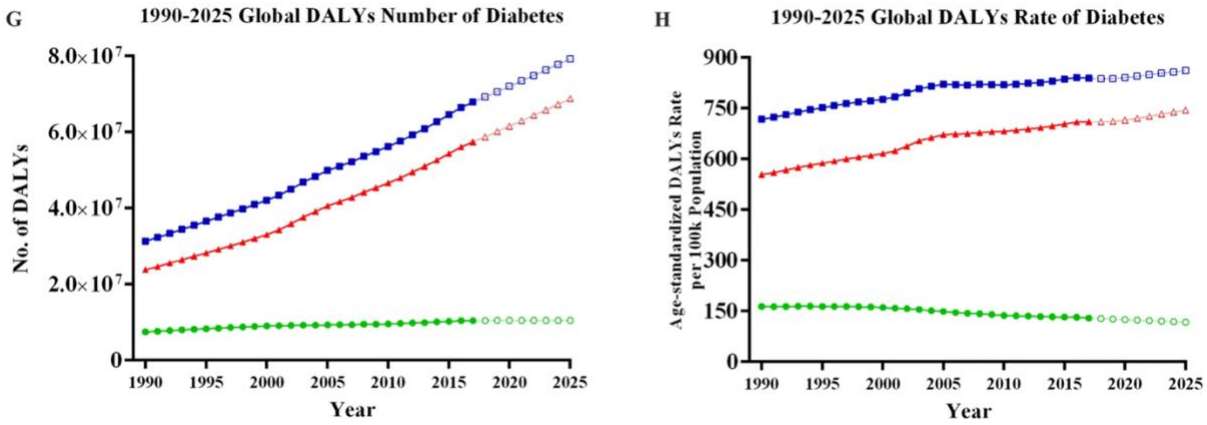


Figure 1.2. Global burden of DALYs related to DM from 1990 to 2025. (H) Age-standardised DALYs rates (Adapted from: Lin, X., et al., *Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025.* Scientific Reports, 2020. 10(1): p. 14790.) (6).

1.5.1 Worldwide

Generally, the comparative prevalence of DM in the world is about 9.8% (536.6 million) in 2021, and this percentage will increase to 11.2% (783.2 million) by 2045. From these cases, 8.4%, will come from high-income and 10.5% from middle-income countries. Most of these individuals will be between 75 to 79 years of age which reflects the highest estimated prevalence of DM (24%) among the various age groups. In 2021, the reported prevalence of DM in people living in urban areas was approximately 12.1% (360.0 million) when compared to individuals living in rural areas with a prevalence rate of 8.3% (176.6 million) (7).

According to the International Diabetes Federation (IDF) atlas, the Middle East and North Africa (MENA) region have the highest comparative prevalence of DM of 18.1% (72.7 million) in individuals aged between 20 to 79 years old in 2021. North America and the Caribbean (NAC) region is ranked as the second highest comparative prevalence of DM with 11.9% (50.5 million). These numbers are predicted to reach 20.4% (135.7 million) and 14.2% (62.8 million) by 2045 (7). Africa reported the least number (23.6 million) of people suffering from DM in the world in 2021. This is possibly a reflection of the low prevalence rates of people living with overweight or obesity. These numbers, however, are predicted to increase by 55 million by 2045 (7). In China, approximately 140.9 million people live with DM (i.e., 10% of the total population). In 2021, the IDF categorised China as the top country with the greatest number of patients with T2DM, followed by India, with 74.2 million people (i.e., 7% of the total population). These numbers are projected to rise to 174.4 and 124.9 million, respectively, during the next 25 years (Figure 1.3) (7).

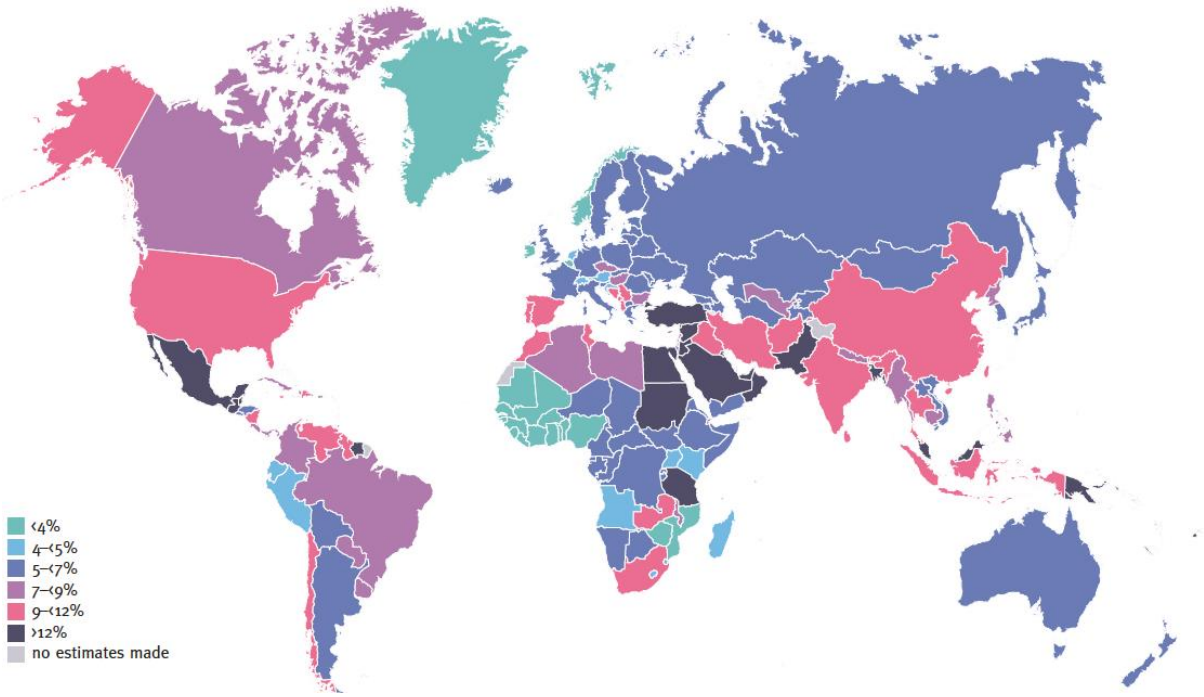


Figure 1.3. Estimated age-adjusted comparative prevalence of diabetes in adults (20–79 years) in 2021 (Adapted from: International Diabetes Federation*. IDF Diabetes Atlas, 10th edition*. 2021) (7).

1.5.2 Australia

Approximations for DM have been made for 38 countries at the level of the IDF Western Pacific (WP) region. This estimation showed that 38% of patients have diabetes in this region. Compared to the rest of the world, this is the third highest prevalence, 11.9% (205.6 million), in 2021 of DM among people aged between 20 and 79 years. This percentage is expected to increase to 14.4% (260.2 million) by 2045 (7). Australia has the lowest DM prevalence rate with almost one in twenty (1.3 million) Australians having DM, with an age-standardised prevalence rate of 4.3% in 2020. This is according to data collected between 2000 and 2020 from the National Diabetes Services Scheme (NDSS) and Australasian Paediatric Endocrine Group (APEG). State-based registries such as the Australian Bureau of Statistics have a similar prevalence rate of 5.3% (4.5% with T2DM), while the IDF age-adjusted comparative DM prevalence in 2021 was 6.4% (7-9). For 24 years, the average number of newly diagnosed patients with T2DM in Australia was estimated to be approximately 60,000 per year. These numbers were more notable in men than women, with a greater prevalence in major cities and inner regional areas than in outer and remote regions, especially for people aged 65 years and over (9).

1.5.3 Saudi Arabia

Saudi Arabia is one of the Middle East and North Africa (MENA) region countries that reports very high age-adjusted comparative prevalence rates of DM along with Pakistan and Egypt (18.7% around 4.3 million versus 30.8% and 20.9% respectively) in 2021. When Saudi Arabia

is compared to a country like Australia, the age-adjusted comparative prevalence of DM rate is almost triple than that reported by the IDF in Australia (Figure 1.4). These numbers are expected to increase to 20.4% by 2030 in Saudi Arabia compared to 7.4% in Australia and 21.4% in Saudi Arabia compared to 8.0% in Australia by 2045 among people aged between 20 to 79 years old (7). Unfortunately, the true DM prevalence rates for Saudi Arabia possibly remain underestimated due to undiagnosed individuals and the lack of up-to-date nationwide cross-sectional studies of DM or T2DM.

Figure 1.4. Age-adjusted comparative prevalence (%) of diabetes (20–79 years) in IDF WP Region compared to MENA Region in 2021 (Adapted from: International Diabetes Federation. *IDF Diabetes Atlas, 10th edition*. 2021) (7).

1.6 Pathophysiology of T2DM

Several pathways and molecular mechanisms inside the body lead to T2DM pathogenesis. This includes malfunctioning between insulin circulation and insulin secretion which affects

glucose levels in the bloodstream and glucose homeostasis, mainly because of genetic predisposition and environmental factors or lifestyle habits (10).

1.6.1 The role of the pancreas

The pancreas is an organ that monitors the processing of converting food intake into energy and regulates the glucose levels and metabolism in the body through endocrine (islet cells) glands that produce hormones and exocrine glands that produce enzymes like trypsin, chymotrypsin, amylase, and lipase to digest proteins, carbohydrates, and fats (11). Approximately 75% of the islet cells (an endocrine component of the pancreas) are beta cells, which are responsible for producing insulin (lower blood sugar) and a peptide named amylin. The rest of the islet cells are delta cells, pancreatic polypeptide cells and alpha cells, which produce glucagon (increase blood sugar) (11).

1.6.2 Fat, carbohydrate, and protein metabolism

Metabolism is the processing of converting foods like fats, carbohydrates and proteins into a source of energy through anabolic and catabolic pathways in two different situations: the fed and fasted states and whether stored or used depends on the body's needs (11).

Once the food enters the stomach and is absorbed, it will be divided into three primary macronutrients. This includes free fatty acids, glucose and amino acids in a glucose pool by glycogenesis. The body will store these as triglycerides by lipogenesis, if not used in most tissues and for brain metabolism. This can then be used again as energy if plasma glucose is low through glycogenolysis (Figure 1.5) (11).

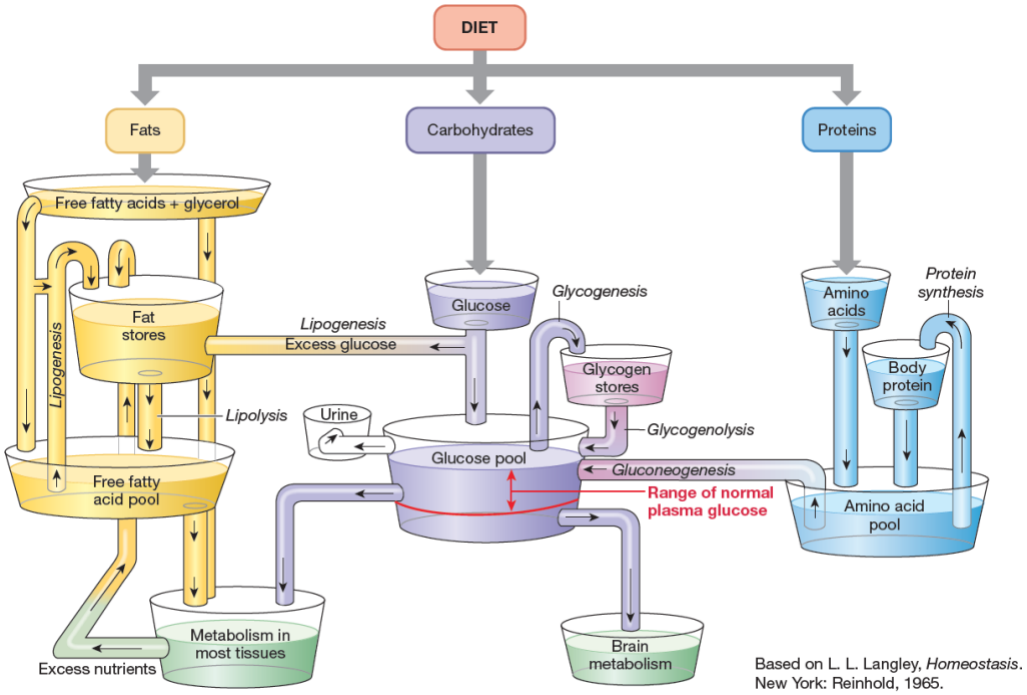


Figure 1.5. A descriptive schematic diagram shows the processing of the biomolecules to transform the diet into the three main nutrient pools inside the body (Adapted from: Silverthorn, D.U., *Human Physiology: An Integrated Approach, Global Edition*. 2015, Harlow, United Kingdom, UNITED KINGDOM: Pearson Education Limited.) (11).

After increasing plasma amino acids and glucose, the endocrine cells of the small intestine send signals to the glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) to stimulate the beta cells of the pancreas to secrete insulin into the liver. This will increase glycolysis, glycogenesis, lipogenesis and protein synthesis, which will then reach the final stage of this process, leading to a decrease in plasma glucose (11, 12).

1.6.3 Insulin and glucagon metabolism

The insulin aetiology and treatment for diabetes was discovered 100 years ago as an exocrine peptide hormone secreted from pancreatic beta cells. The insulin mRNA is precursor

preproinsulin with a single-chain polypeptide at the N-terminus which then breaks into A-chain, B-chain and C-peptide to generate proinsulin (11-13).

The proinsulin is delivered to the lumen of the endoplasmic reticulum; during this transition, the body creates three stabilising disulphide bonds (catalysed by chemical chaperoning) to attach the B-chain and A-chain after cutting the C-peptide in the secretory granules. This finally generates the mature insulin which will be stored in the Golgi apparatus along with free C-peptide to be secreted from beta cells in response to any metabolic signals (11, 12). However, the insulin and GLUT4 transporters will facilitate the glucose transportation and storage into the insulin-sensitive cells to decrease the plasma glucose (11, 12).

On the opposing side and during the fasted state, the alpha cells of the pancreas secreted the precursor proglucagon which is processed from proglucagon to glucagon in the pancreas by Prohormone Convertase 2 (PC2) together with another two peptides and in the intestine and the brain, proglucagon is transformed into GLP-1 and GLP-2 with another three peptides by prohormone convertase 1/3 (PC1/3) (11, 12). Glucagon and the ratio between glucagon and insulin play an essential role in preventing hypoglycaemia by stimulating glycogenolysis and gluconeogenesis to increase the glucose in the blood when the plasma glucose concentration is low (10, 12).

1.6.4 Beta-cell function

In the case of T2DM, the beta cells do not produce the appropriate amount of insulin to regulate the high plasma glucose concentration in hyperglycaemia and hyperlipidaemia due to several factors. This inlcudes genetics factors and deficiencies in various molecular pathways. This may lead to inflammation, oxidative stress, endoplasmic reticulum stress, glucotoxicity, glucolipotoxicity and lipotoxicity, leading to beta-cell dysfunction (11, 14).

1.6.5 Insulin resistance

One of the most critical hypotheses to explain the pathophysiology of T2DM is insulin resistance. This takes action towards the insulin sensitivity in the muscle for glucose to enter into their cells from the bloodstream, leading to hyperinsulinemia. This is commonly associated with T2DM and appears as acanthosis nigricans. When the free fatty acids increase in the blood, insulin sensitivity decreases, leading to excessive stored free fatty acids. Moreover, adipocyte dysfunction could inhibit the insulin receptors and transporters inside the cells, which leads to insulin resistance (11, 15, 16).

1.6.6 Glycaemic index and load

The Glycaemic Index (GI) is a term that refers to knowing and analysing the rank of carbohydrate foods based on how much plasma blood glucose increases on a numeric scale from 0 to 100 (high = 70 to 100, medium = 56 to 96 and low = 0 to 55) during food digestion. Blood sugar rises slower with a lower GI value. The glycaemic load (high = over 20, medium = 11 to 19 and low = 0 to 10) focuses on the amount of the carbohydrate in grams as well as the entire portion of the food. It considers both the glycaemic index and the amount of carbohydrate in grams (17, 18).

Maintaining a high GI continuously over the years may lead to an increase in blood glucose levels, insulin demand, oxidative stress, obesity and inflammation and eventually beta cell exhaustion and dysfunction. This results in an increase in free fatty acids, hyperinsulinemia, insulin resistance and finally T2DM (17, 18).

1.7 Risk factors

Identifying risk factors for T2DM, such as lifestyle, environmental and genetic traits has been challenging. This is mainly due to genetic and lifestyle factors being closely connected and associated with insulin resistance and metabolic disorders. Moreover, it is crucial to identify risk factors for T2DM that will lead to early disease detection and the use of preventative measures. Risk factors have a cumulative effect where the probability of suffering from severe diabetic-related complications increases as the number of significant risk factors in an individual has increased (19). Identifying these risk factors and commencing treatment early may help avoid diabetic complications in the long term. (19)

Results from a three-year follow-up study conducted in Australia among 59,210 individuals (7.1% with T2DM at baseline and 1.6% with newly diagnosed T2DM at the end of this study) showed that a family history of T2DM, cardiovascular diseases, high blood pressure and high cholesterol could contribute to developing the disease. Other factors such as lack of physical activity, obesity, prolonged sitting and severe psychological stress at follow-up also contributed to this disease (20).

1.7.1 Family history

Individuals with a family history of diabetes have been reported to have a two-to-six-fold increased risk of developing T2DM compared to those without a family history of the disease. This is due to several genetic mutations involved in producing and regulating insulin and blood glucose levels (21).

The National Health and Nutrition Examination Survey (NHANES) collected data between 1999-2002 from U.S. households (10,283 adult respondents) through in-home interviews and

physical examinations to evaluate the diabetes risk factors related to family history. Results showed that individuals with a sibling with diabetes had approximately a four times greater prevalence of having diabetes compared to those individuals without a sibling with diabetes. Individuals with a mother with diabetes (16.5%) had a higher diabetes prevalence than those with a father with diabetes (12.4%) (22). A large prospective case-cohort (EPIC-InterAct) study conducted in six countries (n= 13,869) evaluated the risk of developing T2DM in different family members with a history of diabetes. Findings showed that T2DM is associated with a similar hazard ratio of T2DM among other family members (23). However, having a biparental family history correlated with a more significant hazard (HR: 5.14 (3.74, 7.07)). If there was one family member living with diabetes, the T2DM risk increased by two-fold (HR: 2.56 (2.41, 2.72). While having two (HR: 3.99 (3.58, 4.43)) or three (HR: 5.73 (4.28, 7.67)) family members was associated with an even greater risk for developing T2DM (23).

1.7.2 Gender

Physiological differences between males and females are well addressed and caused by differences in sex chromosomes, gender-gene expression of autosomes, sex hormones, sociocultural factors, and differences in lifestyle and their effects on body functions. Additionally, females have been known to experience more significant changes in their hormones across their life span (24).

The gender differences regarding T2DM prevalence and incidence are similar with a slight increase in males than females, however, gender as a risk factor might be much more accurate if it is observed in relation to age, ethnicity and BMI (25).

Moreover, men and women differ in their experience of diabetes. Most studies on diabetes have focused almost exclusively on men. However, the prevalence of T2DM is increasing in

both sexes, however men are usually diagnosed at a younger age and have lower body fat mass than women. Worldwide, it is estimated that that there will be 17.7 million more men than women that will develop diabetes mellitus (26).

Women appear to bear a greater risk factor burden at the time of their T2DM diagnosis, in particular obesity. Moreover, psychosocial stress might play a significant role in diabetes risk in women. Pregnancies can unmask pre-existing metabolic abnormalities, resulting in the diagnosis of gestational diabetes, which appears to be the most prominent risk factor for progression to T2DM in women. Additionally, menopause increases women's cardiometabolic risk profile. Women with T2DM show a greater relative risk of cardiovascular mortality than men. In addition, young women with T2DM are currently less likely than men to receive the treatment and CVD risk reduction recommended by guidelines—prevention strategies and management (27).

1.7.3 Age

Results from a representative population-driven project (data collection between 1988-1994) from the National Health and Nutrition Examination Survey (NHANES III) showed the mean age at diagnosis of T2DM to be 52 years (i.e., whites 53.2 years, blacks 48.5 years and Hispanics 50.3 years). However, in the more recent NHANES project (data collection between 1999-2000), the mean age at diagnosis of T2DM was reduced to 46 years without any statistically significant changes regarding participant race or ethnicity (28).

Further work in Norway in the Trøndelag Health Study (HUNT) involving 52,856 participants highlighted the median age of patients with diabetes to be 68 years (53% men and 47% women) (29). Results from the United Kingdom (UK) on a total of 176,562 T2DM patients found that 26% were aged between 55 and 64 years, followed by 25% between 65 and 74

years. Over the years, the incidence of T2DM in younger patients was shown to increase in these studies (29, 30).

Further studies by Wang and colleagues involving 2,104,159 individuals in Beijing, China, revealed the mean age at T2DM diagnosis to be 62 years. This, however, significantly dropped to 56 years, with an increase in the prevalence among participants younger than 40 years (P<0.001). This study highlighted that middle-aged individuals were at greatest risk of developing T2DM (31).

In Saudi Arabia, a cross-sectional study conducted on patients attending a primary care clinic aimed to determine the prevalence of diabetes among 6024 Saudi nationals. Results showed that the mean (standard deviation SD) age of the patients was 55.3 (13.2) years. The prevalence of diabetes was higher in males compared to females (34.1% in males and 27.6% in females (P<0.0001); The mean (SD) age for onset of diabetes in males and females was 57.5 (13.1) and 53.4 (13.1) years, respectively (P<0.0001). Furthermore, females <50 years old had a higher prevalence than males in the corresponding age range by 34.1% and 25.1%, respectively (P<0.0001) (32).

1.7.4 Obesity

A systematic review and meta-analysis evaluated the association between obesity and overweight by various comorbidities such as T2DM. In total, 89 studies across different countries (i.e., 55% in the U.S. and 40% in European countries) were included and the overall average duration of follow-up was approximately 12.5 years and a total of 9 studies met the inclusion criteria for T2DM. Pooled findings from research showed the Incidence Rate Ratios (IRRs) of BMI and overweight to be 2.40 (95% CI: 2.12-2.72) and 6.74 (95% CI: 5.55-8.19) respectively, in males, while in females, it was 3.92 (95% CI: 3.10-4.97) and 12.41 (95% CI:

9.03-17.06). These findings revealed that both overweight and obesity are significantly associated with the occurrence of T2DM (33).

In 2015, a prospective cohort study conducted among 15,680 Chinese participants (overall mean age was 47.9 years and 46.4% were males) showed that 1099 individuals developed T2DM at eight years follow-up (34, 35). From this cohort, approximately 28.3% (95% CI: 20.1-36.2) of males were living with overweight (BMI=25.0-29.9 kg/m^2) compared to 31.3% (95% CI: 25.5-36.9) of females. These findings differ in comparison to that of an Australian study undertaken by Thakur and colleagues that showed that 42% of the participants had a BMI more than 35 kg/m^2 (34, 35). Further research performed in Jeddah, Saudi Arabia, on 6024 patients who visited the Department of Primary Health Care identified 1792 patients with diabetes. Findings showed that out of these patients, almost three-quarters (72.5%) had a BMI of more than 25 kg/$m^{2,}$ with a slight increase in females when compared to males (32). The variability in results between studies and countries may be due to inconsistent definitions, differences in sample size and study design, difficulties in assessing publication bias and the inability to control for confounding variables.

1.7.5 Sedentary lifestyle

Physical inactivity plays a significant role in developing T2DM worldwide. A prospective cohort study conducted in 2017 with a mean follow-up of 9.4 years showed that 120 incidents of T2DM had a positive association with a lack of physical activity. The hazard ratios for being at risk of having T2DM was 1.00, 0.85 and 0.43 when related to light, moderate and high physical activity, respectively (36). Poor physical activity or a sedentary lifestyle has been shown to be significantly associated with an increased incidence of T2DM. This was clearly explained in the Multi-Ethnic Study of Atherosclerosis (MESA) study involving 5829 males and females among

four different racial and ethnic groups. Results from this study showed that 655 patients who had a severe sedentary lifestyle developed T2DM during a median follow-up of 11.1 years. These findings were independent of any gene and environment interactions (37).

1.7.6 Pre-diabetes

A prospective population-based study by van Herpt and colleagues showed that out of 8844 individuals who had no diabetes, 3492 (i.e., prevalence 40%, 95% CI: 38 to 41%) had pre-diabetes diagnosed with different diagnostic approaches identified by the American Diabetes Association (ADA). When using the WHO definition in this study, the prevalence was slightly lower (prevalence 16%, 95% CI: 15 to 16%). Further investigation using the ADA diagnostic criteria revealed that the 10-year risk of developing diabetes in females and males that were pre-diabetic and 45 years of age was 14.2% and 9.2%, respectively. In comparison, when using the WHO criteria, this risk was 23.2% and 24.6% (38). Despite the importance of using an accurate pre-diabetes definition there has been a strong relationship between pre-diabetes and developing T2DM over the years. There have been numerous, high-quality studies with good methodology that support this fact (39).

1.7.7 Race and ethnicity disparities

There have been multiple studies evaluating diabetes disparities among racial and ethnic groups. One of the representative studies included 2866 non-Hispanic white, 1636 non-Hispanic black, 1952 Hispanic, 909 non-Hispanic Asian and 212 other non-Hispanic participants. Results from this work found that the prevalence of T2DM after adjusting for age and sex was 12.1% among non-Hispanic whites, 22.1% among Hispanics, 20.4% among non-Hispanic blacks and 19.1% among non-Hispanic Asian groups (40). However, the differences in the incidence and prevalence of T2DM regarding race or ethnicity might be affected by

other factors such as genetic variations, socioeconomic status, education, dietary habits and an unhealthy environment. Overall, T2DM was observed much more in Hispanics and black non-Hispanics compared to non-Hispanic whites and Asians (41).

Race and ethnicity were not addressed in the published studies of the Saudi and adjacent Arab Gulf Cooperation Council countries. A recent review article by M.Z Aljulifi evaluating the magnitude of the problem of T2DM in GCC and Saudi Arabia had the same issue. This review had similar population characteristics (for example, religion, language, lifestyle, diet, and income) but did not include ethnicity and race as a factor. Many factors impact the prevalence in this region, including obesity, unhealthy lifestyle, increased life expectancy, increased healthcare expenditures, increased incidence of T2DM among children and young persons, and genetic susceptibility (42).

However, ethnicity was indirectly studied in ethnic minorities in Europe and were compared to their host European populations. A meta-analysis of published data on T2DM in various ethnic minority populations resident in Europe who were compared to their host European populations classified the ethnic minority groups into five population groups by geographical origin. This included South Asian (SA), Sub-Saharan African (SSA), Middle Eastern and North African (MENA), South and Central American (SCA), and Western Pacific (WP). Results from this review found that compared with the host populations, SA-origin populations had the highest odds for T2DM (3.7, 95 % CI 2.7-5.1), followed by MENA (2.7, 95 % CI 1.8-3.9), SSA (2.6, 95 % CI 2.0-3.5), WP (2.3, 95 % CI 1.2-4.1), and lastly SCA (1.3, 95 % CI 1.1-1.6). Among SA subgroups, compared with Europeans, Bangladeshi had the highest odds ratio of 6.2 (95 % CI 3.9-9.8), followed by Pakistani (5.4, 95 % CI 3.2-9.3) and Indians (4.1, 95 % CI 3.0-5.7). So, overall, the risk of T2DM among ethnic minority groups living in Europe compared to

Europeans varies by the geographical origin of the group. It was shown to be three to five times higher among SA, 2 to 4 times higher among MENA, and 2 to 3 times higher among SSA origin (43).

1.7.8 Others

There are several other risk factors that have been identified to increase the risk of developing T2DM. These have been mentioned in systematic reviews and meta-analyses among 86 studies, which have revealed 142 associations that are positively or sometimes strongly related to T2DM. This includes factors such as high blood pressure, high level of cholesterol, high level of alanine aminotransferase (ALT), high level of adiponectin, low level of vitamin D, depressive or mental health disorder, weight gain in early adulthood, high level of serum C-reactive protein, smoking, age at menarche, gestational diabetes, low whole grain diet, high carbohydrates intake, sugar-sweetened beverages, increased processed meat intake and other unhealthy dietary patterns (44).

1.8 Diagnostic tests

Diagnostic tests for T2DM must be performed in a proper clinical setting based on the individual clinical presentation. This is after a physician detects the significant risk factors for T2DM, such as ≥ 40 years of age, BMI ≥ 25 kg/m^2, positive family history of T2DM, belonging to a specific ethnic group and having signs of insulin resistance (45). It should, however, be noted that most diabetes tests are different in terms of their definition, biomarkers and relevant cut-off values that define the correct diagnosis. In addition, some criteria may be

different based on the individual population evaluated and the environmental factors present (46).

1.8.1 Fasting plasma glucose tests

Fasting plasma glucose tests are a quick and simple way to diagnose diabetes. This is done by measuring blood glucose levels at a single point at a specified time. The concentration of glucagon hormone released and produced by the pancreas in the bloodstream after fasting for more than 8 hours without eating any meals (mostly overnight) is measured (47, 48). A normal range of fasting plasma glucose concentration ranges between 3.9 mmol/L (70 mg/dL) to 5.6 mmol/L (100 mg/dL), while levels of > 5.6 to 6.9 mmol/L (> 100 to 125 mg/dL) are considered as prediabetes and ≥ 7 mmol/L (≥ 126 mg/dL) is interpreted as likely diagnosis of diabetes (47-49). In contrast, the World Health Organisation (WHO) recommendations for diagnosis of diabetes include diabetes symptoms plus: a random venous plasma glucose concentration ≥ 11.1 mmol/l, or a fasting plasma glucose concentration ≥ 7.0 mmol/l (whole blood ≥ 6.1 mmol/l), or two-hour plasma glucose concentration ≥ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT) (50, 51).'

1.8.2 Random plasma glucose tests

Regardless of when the last meal was and whether the individual is fasting or not, a random plasma glucose test is usually performed randomly in emergency cases and in patients with T1DM or for a short period of evaluation of the glucose levels in the blood. This test reflects the efficacy of the insulin production or response (52). A normal result for this test is < 11.1 mmol/L (< 200 mg/dL) and for diagnoses of diabetes ≥ 11.1 mmol/L (≥ 200 mg/dL), this is similar to the 2-hour post-prandial test (49, 52).

1.8.3 High glycosylated haemoglobin test (HbA1c)

Unlike the previous tests, glycated haemoglobin (HbA1c) is a form of haemoglobin linked to glucose in the blood. This test captures the glucose levels in the red blood cells over a long period of time (53). Generally, people are diagnosed with T2DM if their HbA1c is ≥ 6.5%, whereas individuals with a level of < 6.5% are interpreted as pre-diabetic, while < 5.7% is considered a normal non-diabetic level (49, 53).

1.8.4 Oral glucose tolerance test and capillary glucose monitoring

This test is mainly based on measuring the baseline blood sugar level after fasting overnight. For this test, a person must fast the evening before the test. A fasting blood specimen is then taken at baseline followed by a drink of 75 grams dose of glucose. A blood specimen is again taken at two hours. These results examine the glucose levels and are interpreted as < 140 mg/dL normal, 140-199 mg/dL impaired glucose tolerance or pre-diabetes, ≥ 200 mg/dL diabetes. Both insulin resistance, and impaired beta function are pathogenic states that reflect the body's response and ability to regulate glucose metabolism. These both may lead to an increase in insulin demand (45, 48). Capillary glucose monitoring is known to be one of the most cost-effective and less invasive approaches used for screening for diabetes as well as self-monitoring for blood glucose levels (49).

1.8.5 Urine glucose test

Despite all the above forms of testing, urinalysis, depends on the albumin levels in the urine. This is called microalbuminuria, which is reflected as the first sign of kidney problems caused by T2DM. Moreover, the self-administered urine strip test might be used to monitor blood glucose levels or to screen for diabetes (54).

1.9 Complications

Uncontrolled or high blood sugar levels, also known as hyperglycaemia, may seriously damage various body systems and/or organs which may lead to severe disease affecting the heart, arteries, eyes, kidneys, nerves, feet, skin, gums and teeth. In addition to this, it can increase the risk of developing hypertension. Acute complications may happen at any time and include hyper- or hypo-glycaemic attacks, Hyperosmolar Hyperglycaemic State (HHS) and Diabetic Ketoacidosis (DKA) whereas chronic or long-term complications build up over time (55, 56). Conversely, chronic complications are subdivided into micro- and macrovascular complications that may lead to blindness, kidney failure, lower limb amputation and Cardiovascular Disease (CVD) (55-57). Hyperglycaemia is the leading cause and a critical initiating factor of chronic microvascular complications of T2DM. It is known to be a significant contributor to macrovascular complications (55-57). Additionally, life-long uncontrolled T2DM can profoundly impact an individual's HRQoL, mental health, relationships, work, income and overall health and well-being (55).

1.9.1 Microvascular complications

1.9.1.1 Diabetic retinopathy

One of the leading microvascular complications of prolonged hyperglycaemia is diabetic retinopathy, which may lead to blindness. It can be preventable and controllable if patients with T2DM monitor their blood glucose levels, blood pressure and blood lipids regularly (58). This complication occurs when diabetes damages the tiny vessels in the retina by causing microaneurysms or neovascularisation in the eyes and can be clinically divided into two main stages, which are non-proliferative and proliferative diabetic retinopathy (59).

1.9.1.2 Diabetic nephropathy

Diabetic nephropathy is known to be one of the leading causes of end-stage renal failure in people with T2DM. This occurs when there is a decrease in the Glomerular Filtration Rate (GFR) associated with glycosuria, polyuria, microalbuminuria (or albuminuria excretion rate of >300 mg/d or 200 μg/min) and hypertension (60).

1.9.1.3 Diabetic neuropathy

Progressive increases in glucose levels and dyslipidaemia can lead to an increase in nerve sorbitol that may cause nerve ischaemia as well as a decrease in the axon transport. This may lead to axon atrophy and a decline in the nerve conduction velocity through various pathways such as polyol and hexosamine. Symptoms such as numbness, loss of sensation, burning or tingling feet, painful cramps, imbalance and temperature changes are usually noticed in patients with T2DM (61).

1.9.2 Macrovascular complications

The free fatty acids, hyperglycaemia and insulin resistance provoke molecular mechanisms such as increased oxidative stress and activations of the portent kinase C, as well as the receptor for advanced glycation end products (RAGE) (62). Accordingly, the bioavailability of nitric oxide will be reduced. This may lead to vasoconstriction, inflammation and thrombosis which causes CVD, myocardial infarction or stroke, acute coronary syndrome, and other macrovascular complications in patients with T2DM (62, 63). This metabolic syndrome can be found in patients with T2DM that are considered to have high glucose levels (fasting plasma glucose ≥ 6.1 mmol/L), hypertension (blood pressure ≥ 140/90 mm Hg), increased triglyceride (≥ 1.7 mmol/L) or low HDL cholesterol, central obesity (BMI > 30 kg/m^2) and microalbuminuria

(albumin excretion > 20 μg/min) (64). In addition, diabetic foot problems stem from complex interactions between macrovascular and microvascular changes, neuropathy, inflammation, immune responses, hyperglycaemia, oxidative stress, and infection susceptibility. Macrovascular factors like atherosclerosis lead to tissue ischaemia, while microvascular dysfunction worsens perfusion deficits (65-68). This can lead to infections, foot ulcerations, gangrene and amputations, affecting quality of life and healthcare costs (69).

1.10 Prevention and management

Prevention of diabetes, early detection and tight management are the cornerstones in preventing or delaying all acute and chronic complications from T2DM.

1.10.1 Nutrition and exercise

Lifestyle modifications such as diet and physical activity are a crucial approach to T2DM prevention. Diet for patients with T2DM should consist of high-fibre carbohydrates that have a low GI, low in trans fatty acids, high in polyunsaturated fatty acids and high in whole grain vegetables. There should be an appropriate amount of protein foods, no added sugars, and low amounts of salt. It is also essential for patients to learn how to count carbohydrates and measure their meals (70). Aerobic exercises or moderate physical activity around 150 minutes per week have been shown to improve insulin sensitivity and overall health in patients with T2DM (71).

1.10.2 Oral medication and insulin

The life expectancy of people living with T2DM is increasing gradually due to the use of various types of antidiabetic drugs. These drugs reduce blood glucose levels by several mechanisms. For example, metformin, a commonly used hypoglycaemic drug, decreases glucose

production in the liver, reduces hepatic glucose output and improves insulin sensitivity (72). Sulfonylureas trigger insulin secretion from pancreatic βcells by declining binding affinity for the ATP-sensitive potassium channel. At the same time, thiazolidinediones (TZDs) improve adipogenesis, lipogenesis and skeletal muscles, which will decrease the plasma-free Fatty Acids (FFA) and leading to inhibition of hyperglycaemia (72).

Injectable insulin therapy, whether it is short or long-acting “basal”, can be initiated if the oral medications are not appropriate and HbA1c ≥ 11%. This helps maintain blood glucose levels and improve β-cell function in days or weeks (73).

Glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1 RAs) with exenatide b.i.d. first approved to treat T2DM in 2005 have been further developed to yield effective compounds/preparations that have overcome the original problem of rapid elimination (short half-life), initially necessitating short intervals between injections (74). Within 15 years of their initial introduction, GLP-1 RAs have become a well-established class of glucose-lowering agents that has the potential for further development and growing impact for treating T2DM (75). GLP-1 RAs was followed by other medications, including Dipeptidyl peptidase-4 (DPP-4), which is an important target for the treatment of T2DM because it can degrade GLP-1. DPP-4 inhibitors can enhance the blood glucose-lowering effect of GLP-1 by inhibiting DPP-4 (76). Sodium-glucose transport Protein 2 (SGLT2) Inhibitors have been used lately to act on the SGLT-2 proteins expressed in the renal proximal convoluted tubules to reduce the reabsorption of filtered glucose, decrease the renal threshold for glucose (RTG) and promote urinary glucose excretion (77).

1.11 HRQoL and mental health disorders in patients with T2DM

1.11.1 The link between HRQoL, mental health disorders and T2DM

Over the years, growing evidence has accumulated on the importance of HRQoL and mental health aspects when managing patients with diabetes (78). Recent studies have noted a bi-directional relationship between HRQoL and diabetes, with results showing that people with diabetes have worse HRQoL compared to individuals without diabetes (79-81). In addition, people living with both diabetes and depression have been shown to have reduced levels of HRQoL and poor glycaemic control which increases the risk of developing complications. This may consequently lead to a higher mortality rate in these patients (79). Interestingly, the increased risk of developing depressive symptoms among individuals with diabetes negatively impacts their HRQoL (79). This two-way link was evaluated in other studies related to mental health disorders identifying various complex mechanisms underlying this link. Findings from these studies suggested that both T2DM and mental disorders may be related to immune and inflammatory system dysfunction, oxidative stress, endothelial dysfunction, metabolic disturbances and more recently to impaired brain insulin signalling (80, 81). All of these factors may ultimately lead to cognitive dysfunction among patients with diabetes, which may range from mild diabetes-associated cognitive decline to pre-dementia and dementia (80, 81). The scientific literature is, however, mainly focused on addressing the correlation between T2DM at one end and the HRQoL and mental health disorders at the other end. This is mainly from a community epidemiological perspective with limited and heterogeneous evidence despite work from multiple previous studies that lifestyle changes can help in the prevention of complications and long-term management of T2DM (79, 82).

1.11.2 Poor HRQoL and T2DM

A poor HRQoL is a known risk factor for developing T2DM, with evidence showing that it shares a similar risk to obesity, low education and socioeconomic status (81, 83). Lack of good HRQoL is also related to poor control of T2DM, which may ultimately lead to diabetes-related complications. Factors such as low education level, lack of medication compliance and/or inaccessibility to optimum care due to lack of good healthcare systems and insufficient income have contributed to this (84).

Over the years, the prevalence of T2DM has been increasing with growing socioeconomic disadvantage. Furthermore, age-standardised rates are almost twice as high among individuals living in the lowest when compared to the highest economic areas. This discrepancy represents a 2.1-fold greater increase in females and 1.7 times in males (85). Evidence from another systematic review and meta-analysis showed that when sub-divided into high-, middle- and low-income countries, the overall risk of developing T2DM increases among those of a lower socioeconomic status, including lower levels of education (Relative Risk (RR): 1.41), occupation (RR: 1.31) and income (RR: 1.40) (86). In another systematic review and meta-analysis by Xing and colleagues showed that physical exercise, regular glucose checks, complications, hypertension, duration of diabetes, diet with more red meat and depression were associated with HRQoL in patients with T2DM (78).

Poor HRQoL influenced mental health adversely in people living with T2DM by increasing the suffering of individuals with diabetes from stress disorders, anxiety and depression, as mentioned in the subsequent sections (78).

1.11.3 HRQoL and T2DM in Gulf Cooperation Council countries and Saudi Arabia

Saudi Arabia is the largest and most populated country among the GCC countries. Therefore, one should not be surprised that Saudi Arabia is ahead in comparison all GCC countries and perhaps other Arab countries in publishing scientific studies relating to HRQoL and mental health issues among people with T2DM (87-91).

Recent work performed by Al-Abadla and colleagues examined the association between HRQoL in 240 randomly selected Emirati people living with diabetes treated at the Dubai Diabetes Center, United Arab Emirates. Results revealed that HRQoL satisfaction scores for physical and mental health domains to be extremely high for most patients. When compared to female gender, males ranked significantly higher in their median scores in all HRQoL domains (92). However, in these patients, HRQoL was associated with a significant increase in the number of diabetes-related complications, poor glycaemic control measured as HbAc1% and patient age (92). Findings from this research concur with that from an earlier study conducted by Bani-Issa in 2011 on 200 people with diabetes, which highlighted that diabetic-related complications had the strongest association (93).

An Omani cross-sectional study measuring HRQoL of T2DM patients (n=200) demonstrated comparable findings to that from the Emirati research conducted in Sultan Qaboos University Hospital. Findings from this research reported moderate HRQoL, which appeared to be related to factors such as medical history, demographic characteristics and the type of strategies used for treatment (93, 94). Patients with an HbA1c of less than 8% (and a diabetic duration of less than five years) showed significantly higher glycaemic control satisfaction scores, whereas patients that were less than 40 years of age had significantly better HRQoL compared to others (94).

Alowayesh and colleagues investigated factors that negatively impacted HRQoL among 1,182 people living with diabetes that were Kuwaiti nationals aged between 18 to 80 years. Findings showed that severe problems were more likely to be reported in older adults with mobility problems. Compared to males, females were more likely to report serious issues with anxiety and depression. Furthermore, patients with comorbidities and/or complications perceived their health to be worse. Other factors identified to have a negative influence on the Visual Analogue Scale (VAS) scores included female gender, obesity, insulin usage and lower levels of education (95). In 2022, a similar Kuwaiti cross-sectional study conducted by Al-Matrouk et al. on 604 Kuwaiti patients with T2DM, aged ≥45 years was performed. In this study, investigators used a validated demographic and WHOQOL-BREF questionnaire to identify factors associated with poor HRQoL. Kuwaiti patients in this study reported an overall good level of HRQoL with higher scores; however, health region, type of treatment, educational level, marital status, and BMI level were all statistically significant predictors of poor HRQoL (96).

A more recent cross-sectional study explored Diabetes Self-Management (DSM) practices and their relationship to the HRQoL using the DSM questionnaire (DSMQ) and the SF-12 among 105 patients with T2DM in primary health care centres (PHCCs) in Qatar. Findings showed that approximately 48.6% of patients with diabetes reported poor overall DSM practices and 50.5% reported poor HRQoL and mental health (97). Furthermore, females showed a significantly higher odds of reporting poor DSM than males. Based on these results, the authors underlined the importance of intensifying efforts to deliver culturally appropriate DSM education to patients and to empower them to take charge of their health (97).

Over the years several studies have been published from different regions of Saudi Arabia on HRQoL among patients with T2DM (88-91). Of these studies (n=10) that have been recently

published and reviewed, half were conducted in Riyadh, the capital of Saudi Arabia (88, 89, 98-100). The remaining five reviewed studies have been conducted across the whole country: two in the Eastern region and one in each of the Western, Southern and Northern regions of Saudi Arabia (90, 91, 101-103).

In summary, all studies aimed to assess HRQoL among patients with T2DM and to identify the possible risk factors associated with lower HRQoL using different instruments to measure the HRQoL among patients with T2DM in different settings (e.g., primary care clinics and/or hospitals). Out of these ten studies, eight were cross-sectional in design, one used a mixed method design, and one was a systematic review article. The number of enrolled participants varied between 131 to 420 participants with T2DM. Almost half of all studies were conducted in a primary care setting and two were hospital-based with all expressing concerns on the negative impacts of T2DM in relation to a patients' HRQoL and mental health aspects. In addition, the need for further actions to be taken to improve the low or moderate score on various aspects among patients with T2DM were highlighted. There was almost a consensus among the various studies that a worse HRQoL among patients with T2DM studies is associated with multiple factors starting from personal patient characteristics, including female gender, marital status, particularly in widowed patients or those in difficult relationships (100, 103).

A low socioeconomic status, like low education, unemployment, or low income, has been shown to be associated with poor HRQoL. In addition, a poor HRQoL among patients with T2DM was shown to be associated with greater age, a longer duration of diabetes, uncontrolled diabetes, the presence of associated comorbidities (e.g., obesity, hypertension, dyslipidaemia, depression), and/or having associated diabetes-related complications such as

retinopathy, neuropathy, and diabetic foot disorders. Interestingly, among all of the chronic complications reported, the latter complication attracted the greatest attention from researchers in Saudi Arabia and the GCC countries. Recently published studies demonstrated that diabetic foot disorders are strongly associated with poor HRQoL of patients with T2DM (104-108).

Overall, the available recent research data carried out in Saudi Arabia is cross-sectional in design with relatively small sample sizes. Furthermore, most of the research is limited to some of the larger cities in the country, indicating a greater need for more multidimensional and multisectoral research to strengthen the evidence base and accumulate greater knowledge about the negative influences of T2DM on HRQoL. Around the globe, there is an urgent need to confront the T2DM epidemic, particularly in countries reporting the highest prevalence rates of this disease, including its associated complications, particularly in Saudi Arabia and its adjacent GCC countries (88). However, there is a gap in the Saudi Arabian scientific literature, particularly in the city of Jeddah, which will be addressed in this thesis in the forthcoming chapters that will correlate HQoL and mental health problems in patients with T2DM, as well as to other previously reported variables, including complications.

*1.11.4 **Mental health disorders and T2DM***

It is well known that emotional and psychological elements such as thoughts, feelings, beliefs and attitudes influence ones' health, regardless as to whether they are living with diabetes or living without diabetes. This influence is more likely to be reflected in individuals with untreated mental health disorders which can lead to worse diabetes, whereas poorly controlled diabetes can make mental health issues worse (109).

A mental disorder is characterised by a clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour. It is usually associated with distress or impairment in important areas of functioning. There are many different types of mental disorders/mental health conditions. Mental health conditions, is a broader term covering mental disorders, psychosocial disabilities and (other) mental states associated with significant distress, impairment in functioning, or risk of self-harm (110)

A detailed discussion of the prevalence and/or incidence of mental health conditions in Saudi Arabia, in general, is beyond the scope of this thesis since the main focus is on people diagnosed with T2DM. However, a recent study indicated overall gaps in research on mental disorders as previous epidemiological research on mental disorders in Saudi Arabia has been limited. Therefore, the Ministry of Health (MoH) in Saudi Arabia has recently begun conducting research studies that aim at developing a new healthcare system based on a patient-centred model of care. This model integrates care of mental health disorders with care of physical disorders (111).

In this regard, early results of a research survey project on Saudi youth and adolescents indicated that the prevalence of a mental disorder among Saudi youth was 40.10%, where anxiety disorders affected 26.84% of the sample, followed by disruptive behaviour disorders (15.44%), mood disorders (9.67%), substance use disorders (4%) and eating disorders (7.06%); however, only 14.47% of Saudi youth with any mental disorder received treatment for a lifetime disorder (112).

The Saudi National Mental Health Survey (SNMHS) is currently underway and aims to explore the magnitude of mental health problems in Saudi Arabia in general. This SNMHS will provide valuable information on current gaps in epidemiology. It will also be important for policy

planning purposes to focus on the burden of untreated mental disorders in Saudi Arabia as well as the barriers to treatment. This will not only relate to the general population but also to people diagnosed with T2DM (113)

Studies have explored the link between mental health disorders in relation to both T2DM and HRQoL. Out of the 18 studies investigated in a systematic review and meta-analysis by Jing et al., only three showed depression as a possible cause in worsening HRQoL among T2DM patients. Another three studies demonstrated anxiety and worry in relation to T2DM to be a possible cause of worsening HRQoL among T2DM patients (78). In 2000, a cross-sectional survey performed in the United Kingdom on a total of 249 people living with diabetes demonstrated that these individuals were more likely to suffer from common mental disorders (OR: 1.5), particularly mixed anxiety and depression (OR: 1.7) after controlling for age, gender, ethnicity, and socioeconomic status (114). The study also indicated that the increased risk was uniform across diabetes subtypes and that common mental disorders were significantly associated with impaired HRQoL, more days off work, non-adherence and difficulties with diabetes self-care (114).

These findings highlight the importance of continuous assessment and care for patients with various mental health disorders, whether they have diabetes or not. The aim of delaying the onset of T2DM in individuals at the prediabetes stage and improving diabetes care in diagnosed patients with T2DM is important to consider (78).

1.11.5 Stress and T2DM

Stress has been considered a potential risk factor in the aetiology of diabetes (109, 115). Studies have shown that it has a significant impact on metabolic activity and energy mobilisation primarily due to the fight or flight response. This stimulates the release of numerous hormones and in people living with diabetes, where there is a stress-induced rise in blood glucose levels (i.e., hyperglycaemia). This eventually leads to difficulties for glucose to be metabolised correctly (115). Furthermore, growing evidence indicates that stressful psycho-social experiences in life may impact diabetes and play an important role in the onset of diabetes (116).

The risk of T2DM increases with chronic stressors. This includes low socioeconomic status, severe mental health problems, aggressive behaviour, demanding working conditions, exposure to traumatic situations, the presence of depression and different personality traits, including mental health problems that lead to conflict with type A personalities. Others to consider include particular racial or ethnic minority groups not associated with socioeconomic status (117).

The bidirectional link between stress and diabetes is a condition referred to as “diabetes distress” which is the psychological and emotional effect which burdens a person into worrying and feeling overwhelmed. It is the negative emotional feeling of being anxious, guilty, angry or frustrated about diabetes. It impacts a persons’ daily life, relationships, and work, including concern about self-management of diabetes (118-120). In a recent narrative review related to aspects of Diabetes Distress (DD) over the last 25 years indicated that DD is common among people with diabetes. It demonstrated an association with lower levels of self-care, general emotional well-being and possibly metabolic outcomes of diabetes care (119). DD may be influenced by the way healthcare professionals communicate with people

with diabetes. This may exacerbate DD or could contribute to its development. It is, therefore, important to ensure that the way healthcare professionals communicate with their patients does not add to the distress that they may already have. Therefore, DD assessment and management should be embedded in routine care services offered to people with diabetes (121).

1.11.6 Anxiety and T2DM

According to Diabetes UK, an anxiety disorder is a psychological condition characterised by frequent, intense and excessive worry that occurs for at least six months. Usually, it influences daily function, causing substantial distress (122). Symptoms include feeling nervous, anxious, or on the edge when individuals are unable to stop or control these feelings that usually interfere with their everyday life (82, 122).

A recent cross-sectional study from Hunan Province of China investigated the prevalence of anxiety and its associated factors among a total of 496 inpatients with T2DM using the Hospital Anxiety and Depression Scale-anxiety subscales. Findings from this research showed that almost one in five inpatients with T2DM suffered from anxiety in China. Factors such as age, educational level, regular physical activity, diabetes-specific complications and social support were independently associated with anxiety (123). Another controversial Australian longitudinal study investigated the association between transitions in anxiety symptoms and the risk of diabetes in women. Results demonstrated that women with persistent symptoms had a 1.85-fold greater risk of diabetes; therefore, anxiety can serve as a prognostic marker of future risk of DM (124).

In 2019, an international study by Chaturvedi, et al. evaluated both the prevalence and correlation of anxiety disorders in a total of 3170 people with T2DM. Researchers used the

Mini-International Neuropsychiatric Interview across 15 countries. Findings revealed a high prevalence of anxiety disorders, especially in women and in patients with diabetic complications, when the duration of diabetes was long and when blood glucose levels were poorly controlled. The study concluded that patients with diabetes were more anxious than depressed (82).

A population-based German study was performed in 2020 involving pre-diabetic individuals. Results from this study demonstrated that in comparison to low anxiety, high anxiety was associated with a three-fold increased risk of progression to T2DM. These findings remained the same even after controlling for socio-demographic and lifestyle variables such as smoking, drinking, poor diet, inactivity and metabolic risk factors. In addition, a considerable proportion of participants with T2DM had anxiety in addition to prediabetes (attributable risk proportion: 0.52; 95% CI:0.004 to 1.04, P=0.05). This research concluded that anxiety symptoms independently increased the risk of progression of prediabetes to T2DM and that additional methods should be developed to identify which patients may have an adverse risk profile for T2DM progression (125).

These findings were comparable and supported the Canadian community-based cohort follow-up study by Deschênes et al., where investigators assessed the potential synergistic associations between prediabetes, depressive and anxiety symptoms and the risk of T2DM development. Investigators showed that participants with prediabetes and elevated depressive symptoms had an increased risk of developing diabetes compared to people with no diabetes or low depressive symptoms (OR: 10.65, 95% CI:4.60-24.66, P=0.001). This was demonstrated after controlling for socioeconomic, lifestyle and metabolic risk factors (126).

Interestingly, findings from another large follow-up multi-disciplinary prospective population-based cohort study known as the “Lifelines Cohort Study” showed that depression with comorbid anxiety may be a subgroup of depression strongly associated with the risk of T2DM and not anxiety disorders alone (127). Collectively, the former more recent studies contradict the results of earlier research conducted more than a decade ago in the United States in the research performed by Edward and colleagues titled, “Baltimore Epidemiologic Catchment Area Study”. Work from this research did not find a significant association between anxiety disorders and increased risk of T2DM or risk of diabetes complications among those individuals with diabetes (128). This discrepancy of results in the literature may be explained by the wide variations in the methodologies and the type of instruments used.

Finally, in a letter to the editor by Mukhtar and colleagues published in 2020 discussed Coronavirus Disease 2019 (COVID-19) and its impacts related to psychological issues in individuals with diabetes. The authors discussed the psychosocial and mental health factors that impact individuals and their families. In addition, patients living with diabetes had increased anxiety, depressive symptoms, panic attacks and impaired functioning, especially when other stressors were included. Therefore, sound mental health, psychosocial functioning and emotional well-being are usually necessary for individuals with diabetes during the challenging times of the COVID-19 pandemic outbreaks (129).

1.11.7 Depression and T2DM

Depression can be long-lasting or recurrent and may dramatically affect a person’s ability to function and live a rewarding life (130). Recently, growing evidence has shown the complex uni or bidirectional link between depression and diabetes (79, 127, 131-133). In the United States, approximately 25% of individuals with T2DM are expected to be diagnosed with

significant depression. In comparison, the prevalence rate for depression has been reported to be much higher in other countries in this group (134). Moreover, in Iran, the prevalence rate of depression in people with T2DM was reported to be as high as 56.2% in women compared to 41% in men (135). Whereas the prevalence rate is 38.8% among people with T2DM patients in an Indian study and 32.2% in Vietnamese people with T2DM (136, 137). In addition, when depression is associated with T2DM, it increases the subsequent risk for hyperglycaemia, insulin resistance, cardiovascular disease and micro- and macrovascular complications (134, 138).

A more recent systematic review conducted by Bergmans and colleagues comprehensively synthesised findings from a diverse range of genetically informative studies on comorbid depression and T2DM that supported the uni or bidirectional phenotypic model of depression and T2DM. Results from this study demonstrated modest evidence indicating that T2DM was causally related to the risk of developing depression, however, there was much more limited evidence that depression is causally related to the risk of diabetes (132). Findings from a narrative review of 25 years of research on these complex links between depression and diabetes by Pouwer and colleagues showed that depression occurs more frequently in individuals with T2DM compared to individuals without diabetes (133).

The causal relationships and shared genetics between depression and T2DM were recently revisited by Diabetes UK. In this study, a two-sample, bidirectional Mendelian Randomisation (MR) to determine causality between T2DM and depression was applied. Findings from this work demonstrated a significant causal effect of depression on type T2DM but not in the reverse direction. These authors, therefore, highlighted that depression may play a direct role in the development of T2DM and they underscored the importance of maintaining a healthy

weight (139). Similarly, results from a large longitudinal MR study that used 34 T2DM risk genetic variants involving 11,506 East Asian participants found evidence suggesting a potential causal relationship between T2DM and depression (140). These research findings indicate that depression should be included among risk factors for T2DM and that the need early screening may be necessary (141).

In addition to this, an interesting Australian case-control study by Bruce and colleagues evaluated whether a personal history of depression assists in risk prediction for depression in T2DM. Findings from this study indicated that obtaining a lifetime history of major depression using the Brief Lifetime Depression Scale (BLDS) assists in depression risk prediction in T2DM, regardless of whether depression preceded diabetes onset or not (142).

In comparison, researchers from Saudi Arabia performed a cross-sectional study using a self-administered questionnaire in a total of 385 patients with T2DM in the Jazan area. The aim was to determine the prevalence of depression and related risk factors among people with T2DM using the Patient Health Questionnaire (PHQ-9). Findings from this study found that the overall prevalence of depression in these patients was 37.6%. They also demonstrated that significant predictors of depression included the presence of diabetic foot, cardiovascular diseases, eye complications and erectile dysfunction. These researchers recommended early screening for depression to improve the HRQoL and mental health of people with T2DM (143).

In conclusion, despite these studies reflecting the high prevalence rates of depression among people living with T2DM, there is still limited good-quality research that specifically addresses depression management in these patients (134).

1.11.8 Other mental health disorders and T2DM

In 2022, a nationwide Danish register-based dynamic cohort study was performed to investigate the association between several psychiatric disorders and T2DM. From this cohort, findings showed that the age-specific incidence rates of T2DM were higher (i.e., by 47% in men and 65% in women) in people with a psychiatric disorder compared to those without. Furthermore, it was exceptionally high in younger people of less than 50 years of age (144). A similar Korean large-scale prospective cohort study of more than 6.4 million younger adults was performed in South Korea in 2023. This study showed five psychiatric disorders (namely, schizophrenia, bipolar disorder, depressive disorder, anxiety disorder and sleep disorder) to be significantly associated with an increased risk of developing T2DM. Findings demonstrated that for individuals with and without psychiatric disorders, the incidence rates were reported to be 2.9 and 2.6 per 1000 person-years, respectively, for T2DM. In addition, younger adults with schizophrenia and bipolar disorder were at a substantially higher risk of developing T2DM (145). An umbrella review of systematic reviews with and without meta-analyses identified a total of 8612 abstracts, 180 full-text articles and 25 systematic reviews for comparison. Results from this study showed that all psychiatric disorders were associated with an increased risk of T2DM with depression. In particular, the use of antidepressant or antipsychotic medications, insomnia, and anxiety disorders were identified to be associated with an increased risk. Regardless of these findings, the authors indicated that these results should be interpreted with caution since the quality of the evidence was diverse and only 16% of the systematic reviews were of high methodological quality (146).

1.11.9 Assessment tools of HRQoL and mental health disorders in patients with T2DM

Over the last few decades, patients with T2DM have been known to have a worse HRQoL when compared to individuals without T2DM. An increased risk for mental disorders, particularly depression, may have consequently an additional negative influence on HRQoL (147). In 2008, an extensive systematic literature search was performed covering a period of 17 years (1990-2007) identified 20 studies that compared HRQoL in individuals with T2DM and which was then related to depressive symptoms. Findings from this study reported a negative association between depressive symptoms and at least one aspect of HRQoL. Results showed that higher levels of depressive symptoms seen in individuals with diabetes were associated with an impaired HRQoL (147). Since then, growing evidence has accumulated in relation to the uni and bidirectional links between diabetes, HRQoL and mental disorders, as well as what influence each of these has on each other (as previously mentioned) (139, 140, 148, 149). Understanding the magnitude of the problem and these influences will hopefully reflect positively on reaching better outcomes in the management of individuals with T2DM and any mental health disorders. This will also improve their HRQoL in different countries worldwide, particularly in Saudi Arabia and adjacent GCC countries, where high prevalence rates of T2DM have been reported (150).

Numerous scientific publications have addressed the importance of covering four components when discussing HRQoL. This includes the physical, mental and cognitive components (including beliefs, perceptions, and judgments) and the psychological as well as the social components. Consequently, the necessity for designing and developing special measuring psychometric tools like instruments/questionaries/ to measure HRQoL has risen rapidly over the years. Therefore, over the last few years, numerous tools have been introduced to help

determine the impact of chronic illnesses. This includes diabetes, along with diabetic-related complications affecting a person's quality of life (148). However, unfortunately, the search for a gold standard tool for the assessment of overall health related to and specifically focused on diabetes is still ongoing. Much needed work is still needed towards the development of valid, reliable and user-friendly assessment tools (87, 148, 151). In the meantime, researchers on HRQoL related to T2DM should do their best to select the best available tool that is appropriately suited for use in their research design and their local community.

Over the years, several reports have highlighted the difficulties, challenges, and research gaps in terms of the importance of having the appropriate research study design and methodologies, including the selection of the most suitable HRQoL measuring tool to assess the impact of diabetes on HRQoL. When measuring, one should consider the use of a standardised tool, balancing comprehensiveness, subjectivity and brevity. Over time, researchers have expressed concerns about the complexity of the rigorous assessment of diabetes-specific HRQoL (both conceptually and methodologically). This includes systematic assessment in HRQoL research on people with diabetes (152). A recent Dutch narrative review described their applications in both diabetes research and clinical practice. The authors debated their validity in the field of diabetes and suggested that relevant Patient-Reported Outcome Measures (PROMs) used in people with diabetes are related to disease-specific symptoms (like worries about hypoglycaemia and diabetes distress), general symptoms (e.g., fatigue and depression), functional status, general health perceptions and overall quality of life. The authors also indicated that generic PROMs such as the 36-Item Short Form Health Survey (SF-36), WHO Disability Assessment Schedule (WHODAS 2.0) or Patient-Reported Outcomes Measurement Information System (PROMIS) measures could be considered to assess commonly relevant PROMs supplemented with disease-specific PROMs where needed.

This study identified gaps and recommended that further validation studies of diabetes-specific PROMs that have sufficient content validity for measuring disease-specific symptoms are needed. The authors mentioned that generic item banks should be developed based on item response theory for measuring commonly relevant PROMs (153). Another systematic review that assessed developed or validated PROMs that measure aspects of HRQoL in people with T2DM indicated that there is a need for consensus on which aspects of HRQoL should be measured in people with T2DM and which PROMs to use in research and daily practice (154). Further research was performed in a qualitative study in Israel, which included three focus groups totalling 19 people with T2DM. The objective of this study was to identify which aspects may be valuable for people with T2DM that can be relevant for PROMs in diabetes care. Findings showed that the use of PROMs was essential in addressing issues that were largely and not usually addressed in routine diabetes care. In addition, only a limited number of domains were mentioned by people diagnosed with T2DM that were identified by healthcare clinicians in this study. This work reinforced the need for further research in this area to address the content gaps between the perspectives of people living with T2DM and their healthcare providers (155).

1.12 Interventions and economics in patients with T2DM related to HRQoL and mental health

1.12.1 Government measurement, guidelines, and health promotion initiatives

Studies stressed the importance of encouraging policymakers to develop more government measures, innovative programs and health promotion interventions/initiatives at all levels of care. Across the world, this will collectively aim to bridge the current gaps in care provided to people living with T2DM. This is particularly important in countries that already report high

prevalence rates of diabetes and are projected to do so over the coming decades, including low and middle-income countries. Such measures should be comprehensive in targeting both T2DM care, HRQoL and mental health aspects collectively. They should be implemented at all levels to be effective. In addition, measures and interventions should be based on primary, well-designed, multidimensional, multisectoral and multidisciplinary research studies in different countries that explore the perspectives of people with diabetes and healthcare providers, including physicians.

Clinical Practice Guides (CPGs) and/or Best Practice Guidelines (BPGs) are essential and important tools that serve as a framework for both clinical decision-making and for supporting best practices in the management of people with diabetes. Numerous CPGs and BPGs are available across the world that provide updated evidence-based recommendations. This includes those recent approaches related to HRQoL and mental health aspects that help guide comprehensive care to individuals with diabetes, clinicians and their caregivers, diabetes-care teams, other healthcare professionals and stakeholders (156-161).

Numerous researchers across the Middle East and North African (MENA) region, including Saudi Arabia, have over the years, raised concerns in relation to the gaps in knowledge and have highlighted the need to revise current policies. There is a requirement to initiate more healthcare policies to fight the negative impacts of the current T2DM problem and its related complications on both the physical and mental health components (162-165).

1.12.2 Economic burden of T2DM on HRQoL and mental health aspects

The economic burden and costs are influenced by the socioeconomic status of affected individuals with T2DM. This is influenced by government spending on nations' health on one side and on the other side by the impact of T2DM on HRQoL and mental health aspects. The

expenditure, therefore, will be higher if one takes the direct and indirect costs of T2DM on HRQoL aspects of people with T2DM. The cost has been noted to be particularly high when mental health issues coexist in older patients with multiple complications and comorbidities (166-170). Elderly patients with T2DM are considered a vulnerable group, given that these people may have varying degrees of physical and mental comorbidities that can increase their risk of hypoglycaemia, falls and depression (166).

In 2020, a population-based cohort study conducted in Maastricht, Netherlands, found that people living with T2DM have a substantially higher societal cost and lower HRQoL than people with normal glucose tolerance. In general, people diagnosed with T2DM have, on average 2.2 times greater societal costs and experience a lower HRQoL than people without T2DM. In addition, a subgroup analyses demonstrated that older age, being female and having two or more diabetes-related complications resulted in higher costs and lower utilities (167). Another cross-sectional study in Southern India showed that the cost of diabetes care was high and that increased spending was observed, particularly among the socioeconomically disadvantaged group, resulting in worse HRQoL (168). Further research demonstrated a transparent gradient between HRQoL and cost. It showed that increasing physical and mental HRQoL is associated with lower expenditures and out-of-pocket expenses. Furthermore, over a 10-year period, those individuals with the highest physical HRQoL had significantly lower health expenditures than those with the lowest physical HRQoL (169). In England, 60,000 people have coexisting T2DM and SMI, which adversely influences their overall health outcomes. These results reflect the need for more complex care pathways compared with those individuals with T2DM alone. This will ultimately increase healthcare resource expenditure and costs for people with both conditions. It has been shown to result in a higher

than average annual costs for people with T2DM and SMI (£1930 higher) than people with T2DM alone (170).

1.13 Summary of gaps in knowledge

The above-discussed published studies on the influence of T2DM on HRQoL and mental health aspects among people with T2DM, forms the theoretical framework of this thesis. It identified several gaps, especially regarding the limited knowledge and data-driven from the city of Jeddah, Saudi Arabia. The included research clearly demonstrates that despite the availability of a large volume of studies in the literature relating to the numerous influences of T2DM on HRQoL and mental health, there are still many concerns and research gaps to be addressed. This includes the different designs, settings and sampling methods used like primary care or hospital-based studies or both. The various methodologies used to include the different measuring tools for HRQoL and mental health are relevant to consider. Other factors include whether these tools were comprehensive or not and if they were translated into their local languages. Additional aspects include if they were validated and wisely selected to answer the research questions of the study in the sub-populations of that country like being urban or rural. The characteristics of the studied populations with regards to their ethnic, cultural, socioeconomic and educational backgrounds and the quality of healthcare provided to people with T2DM in various countries should also be considered. Furthermore, there was obvious heterogenicity in the studied variables with regards to the demographic and clinical characteristics of the included patients with T2DM. For example, age group, gender, duration of T2DM and any associated comorbidities, particularly mental health illnesses and associated T2DM-related complications.

Aims of this thesis

The primary objective of this thesis is to evaluate the epidemiology, HRQoL and mental health aspects among people with T2DM in Saudi Arabia. This includes the bidirectional link between HRQoL and mental health in relation to T2DM and T2DM associated complications. This thesis will also evaluate factors which may increase the risk of developing T2DM complications. Gaps in perspectives and/or knowledge among healthcare providers related to HRQoL and mental health characteristics among patients with T2DM will be examined in view of the paucity of published research on these aspects in Saudi Arabia and adjacent GCC countries, particularly in Jeddah city.

The specific aims of this thesis are:

i. To identify the most appropriate measurement tool to evaluate the HRQoL and mental health in people with T2DM that can be used for the intended studies in this thesis.

ii. To assess the prevalence of T2DM-related complications and associated risks for developing complications. This includes demographic characteristics, duration of diabetes, HbA1C, comorbidities and management modalities among a defined population of patients with T2DM in Jeddah, Saudi Arabia.

iii. To evaluate the impact of T2DM on HRQoL and mental health aspects in patients with T2DM-related complications compared to those without complications; and to identify the variables that correlate with increasing this risk in a group of patients with T2DM in Jeddah, Saudi Arabia.

iv. To explore physicians' knowledge, awareness and perspectives on the importance of HRQoL and mental health aspects in the routine care of their patients with T2DM and how to improve the current care.

Outlines of the chapters included in this thesis

Chapter 2 presents a systematic review examining the most common quality of life and mental health measures used for patients with T2DM.

Chapter 3 compares patients with T2DM-related complications to those without complications using a single-site retrospective, hospital-based cohort of patients over a 12-year timeframe.

Chapter 4 is a cross-sectional study that evaluates HRQoL and mental health aspects of patients with and without T2DM-related complications. This study involved patients attending either a tertiary hospital diabetes clinic or surrounding primary care centres.

Chapter 5 examines interviews with physicians managing patients with T2DM, using a newly developed questionnaire aimed at assessing their perspectives on HRQoL and mental health.

Chapter 6 concludes with the overall thesis outcomes by providing a comprehensive discussion that explores the implications of the findings from this thesis and provides suggestions for future research directions.

Chapter 2. Quality of life and mental health measurements among patients with type 2 diabetes mellitus: a systematic review

2.1 Abstract

Aims: To identify, review, summarise and evaluate the methodological quality for the most validated commonly used Health-Related Quality of Life (HRQoL) and mental health assessment measurements in patients with Type 2 Diabetes Mellitus (T2DM).

Methods: All original articles published on PubMed, MedLine, OVID, The Cochrane Register, Web of Science Conference Proceedings and Scopus databases were systematically reviewed between 2011 and 2022. A search strategy was developed for each database using all possible combinations of the following keywords: “type 2 diabetes mellitus”, “quality of life”, mental health” and “questionnaires”. Studies conducted on patients with T2DM of ≥18 years with or without other clinical illnesses were included. Articles designed as a literature or systematic review conducted on either children or adolescents, healthy adults and/or with a small sample size were excluded.

Results: A total of 489 articles were identified in all of the electronic medical databases. Of these articles, 40 were shown to meet the eligibility criteria to be included in this systematic review. Approximately, 60% of these studies were cross-sectional, 22.5% were clinical trials and 17.5% of cohort studies. The top commonly used QoL measurements are the SF-12 identified in 19 studies, the SF-36, included in 16 studies and the EuroQoL EQ-5D, found in 8 studies. Fifteen (37.5%) studies used only one questionnaire, while the remaining reviewed (62.5%) used more than one questionnaire. Finally, the majority (90%) of studies reported using self-administered questionnaires and only 4 used interviewer mode of administration.

Conclusions: This evidence highlights that the commonly used questionnaire to evaluate the QoL and mental health is the SF-12 followed by SF-36. Both of these questionnaires are validated, reliable and supported in different languages. Moreover, using single or combined questionnaires as well as the mode of administration depends on the clinical research question and aim of the study.

2.2 Introduction

Over the last few decades, the increasing recognition of the impact of Type 2 Diabetes Mellitus (T2DM) on HRQoL and/or Quality of Life (QoL), mental health and overall physical and psychological health along with their useful measurement instruments has been well addressed in scientific literature (171). The benefits of evaluating QoL and mental health in patients with T2DM have been appreciated. This includes the evaluation of the burden of the disease and its complications, which may contribute to the development of the most appropriate management and treatment plans in these vulnerable patient groups (172).

Moreover, physicians caring for patients with comorbid chronic illnesses that affect their QoL and mental health, such as T2DM, need to prioritise their diabetes management to ensure better care with the aim to focus on how healthcare systems influence these decisions (173). This includes the stability of these decisions over time, with continuous surveillance based on proper and validated measurements (173-176).

Overall, the nature of QoL and/or HRQoL is complex and multidimensional with a variation in tools used between studies. The Australian Centre for Quality of Life's directory of instruments reflects this further, where there are more than 1000 variables included and although these intend to measure QoL, each contains a variety of dependent variables (177). Findings from other studies have linked the wrong measure to the concept of interest and there are numerous occasions where incorrect or different tools have been used or where their data is misinterpreted as QoL (178, 179). Moreover, this will emphasise the importance of selecting an ideal, reliable and valid measure that is useful to use throughout different cultures. Also, it should include a broad range of potentially independent domains covering all critical aspects of QoL (180).

Furthermore, the assessment of mental health in patients with diabetes requires multiple transitions geographically and socially. In addition, there is a need to identify patients lacking medical follow-up and are, therefore, at increasing risk of poor mental health status, including psychosocial problems such as depression, diabetes-emotional distress, anxiety, eating disorders and cognitive impairment (181). Hence, it is essential for clinicians to use a standardised tool that is of dynamic construct that incorporates comprehensiveness, sensitivity, and balance relative to subjectivity and brevity to help identify gaps and monitor psychological well-being and care among adult patients with T2DM. However, to date, measuring QoL and mental health outcomes in these patients remains a challenge, and there are limited studies evaluating the quality of these tools.

Therefore, the aim of this systematic review is to identify, summarise and evaluate the methodological quality for the most commonly used and validated HRQoL and mental health assessment measurements in patients with T2DM.

2.3 Methodology

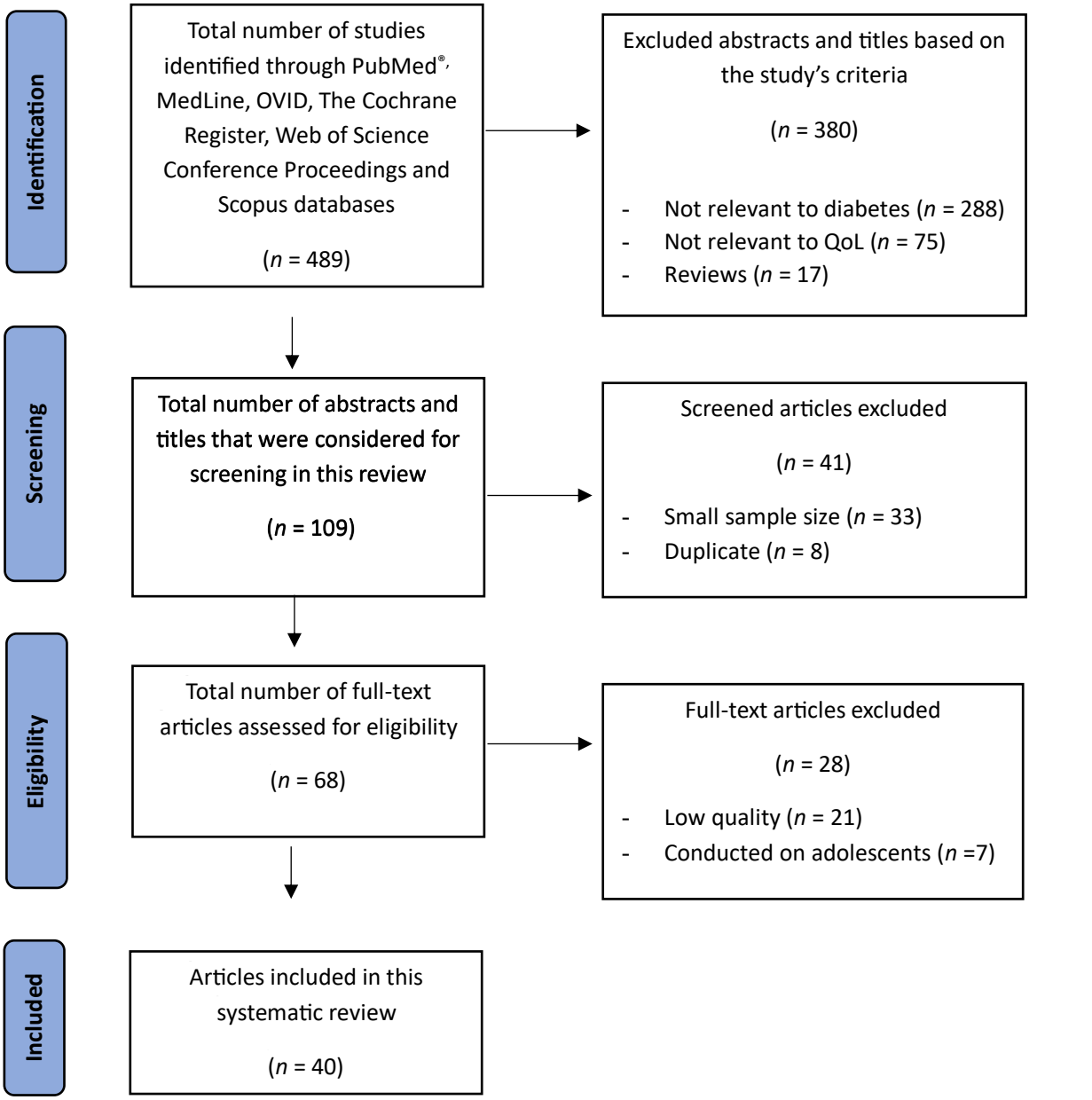
The Systematic review was conducted on QoL, and mental health surveys published in PubMed, MedLine, OVID, The Cochrane Register, Web of Science Conference Proceedings and Scopus databases between the 1st of January 2011 and the 31st of July 2022. In addition, reference lists of the included studies and previous reviews on the topic were hand-searched for potentially relevant studies. Search terms for each database included 'type 2 diabetes mellitus', 'quality of life', 'mental health', and 'questionnaires'. No language restrictions were applied. A systematic search in accordance with the *Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA) statement 2020* was performed (182). The formulated research question was based on Participants, Concept, and Context (PCC) on

'What is the most recent validated and commonly used measurement or questionnaire to assess the quality of life and mental health among adult patients with T2DM in different languages?'

2.3.1 Inclusion and exclusion criteria

All studies conducted during the last decade or more (1st of January 2011 to 31st of July 2022) were considered to be eligible if they met the following inclusion criteria: 1) Population-based studies; 2) Among adults sharing common characteristics and health conditions including T2DM; 3) Studies focusing on health-related QoL and mental health assessment questionnaires or surveys; 4) Any studies conducted on 50 patients or more; 5) Surveys mentioned in conference abstracts were only considered if sufficient information were available for data extraction (Figure 1). All publications were reviewed in full text to determine whether they met the inclusion criteria or not by two authors independently (Figure 2.1).

Figure 2.1. Flow diagram of identification, screening, eligibility and included studies via four databases



2.3.2 Synthesis and data extraction

According to the eligibility criteria, the main author (O.A.) carefully scanned the titles and abstracts to address any duplicated or irrelevant studies from the initial databases, PubMed and Scopus. This was followed by reviewing all chosen articles in their full manuscript and filling in a pre-structured table that summarises and assesses the quality of the selected studies and any general information. The table was designed into two sections one to cover the study characteristics and the other for study quality including the following items/ categories: 1) The primary author's name; 2) Year of publication; 3) Study location; 3) Study design; 4) Target population (included the number of participants, age, and gender); 5) Main objectives and questionnaires; 6) Mode of questionnaire administration; 7) Validity; 8) Reproducibility; 9) Responsiveness of the participants; 10) Type of bias; 11) Languages support (Table 2.1).

A 10% random sample was checked by a second reviewer (K.H.) to check for the search and reviewing of the articles, references and any additional relevant publications that may have been missed by the initial electronic databases was finally carried out independently by two senior examiners. Any inconsistencies were discussed by a third reviewer (J.F.) for a final decision.

2.3.3 Quality appraisal

The methodological quality of each included study in terms of validity, reliability, and consistency was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklists (https://jbi.global/critical-appraisal-tools) for cohort, Randomized Controlled Trials (RCTs), and cross-sectional studies which was the most appropriate and applicable tool for this review (183). The JBI checklist for cohort studies consists of 11 items, while 13 items for RCTs, and 8

items for cross-sectional studies. Each item was answered with either a Yes, No, Unclear, or Not Applicable response.

The categories of the studies were divided into: High quality (if 80% or more of the items were answered with a yes), Moderate (if more than 60% of the items were answered with a yes) and Low (if less than 60% of the items were answered with yes). Any study categorised as high or moderate quality was eligible to be included in this review. Any disagreement between the reviewers was solved by a discussion with the third reviewer (J.F.).

2.4 Results

2.4.1 Search and eligible studies

A total of 489 articles were identified in six electronic medical databases, 343 of which were selected (58.6% from Scopus) during the first screening. Following the first screening, 109 articles were identified and subjected to the next level of screening after reading the titles and abstracts. Of these, 68 articles were considered potentially eligible after reviewing the full text (Figure 2.1). Subsequently, 28 articles were excluded based on the defined inclusion and exclusion criteria and there were 21 articles (184-204) among them considered as low quality and excluded based on the JBI quality appraisal checklists used in this review (Figure 2.1) (Table 2.2). Finally, 40 articles were shown to meet the eligibility criteria and were, therefore, included in this systematic review (Figure 2.1) (Table 2.1) (Figure B.2.1, Appendix B).

Table 2.1. Overall studies characteristics

Article characteristics							Measurement characteristics					
S.N	Authors	Year	Study location	Study design	Target population	Questionnaires and main objectives	Mode of questionnaire administration	Validity	Reproducibility	Responsiveness of the participants	Type of bias	Languages support
1	Wadden et al.	2014	United States	Randomised clinical trial	5,145 overweight or obese adults with Type 2 Diabetes Mellitus (T2DM)	Questionnaires: The Medical Outcomes Study Short Form 36 (SF-36) and the Beck Depression Inventory (BDI). Main objectives: To assess the effects of long-term intensive lifestyle intervention on depression symptoms and Quality of Life (QoL) in patients with T2DM.	Self-administered	Yes	Yes	40% for QoL at the last year of the study	Self-report and non-response bias	Yes
2	Hajos, T.R.S. et al.	2013	Netherlands	Randomised clinical trial	2,055 adult patients with Type 1 Diabetes Mellitus (T1DM) or T2DM	Questionnaires: The Problem Areas in Diabetes scale (PAID), Medical Outcomes Short Form 12 (SF-12), the World Health Organisation - Five Well-Being Index (WHO-5) and the 9-item Patient Health Questionnaire (PHQ-9).	Self-administered	Yes	Yes	47% returned the first questionnaire and 38% of the initial population returned the second	Self-report and non-response bias	Yes, except the PAID questionnaire

						Main objectives: To evaluate the psychometric properties of the WHO-5 index in a large sample of Dutch outpatients with T1DM or T2DM.							
3	Green, A.J. et al.	2012	United States	Cross-sectional	2,718 US adult households with T2DM	Questionnaires: The SF-12 and the PHQ-9. Main objectives: To examine the association of hypoglycemia with QoL and depression among adults with T2DM.	Self-administered	Yes	Yes	71% from the 2008 annual follow-up Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD) survey	Self-report and non-response bias	Yes
4	Schunk, M. et al.	2012	German	Cross-sectional	846 adults between 45 and 74 years old with T2DM	Questionnaires: The SF-36 and SF-12. Main objectives: To compare the population values of QoL among patients with and without T2DM, across several large population-based survey studies from different regions in Germany and a nationwide survey.	Self-administered	Yes	Yes	Overall response rates ranged between 61% and 69% from national and four regional population-based surveys (KORA, CARLA, SHIP and	Self-report and non-response bias	Yes

											DHS) and the primary data which is the Diabetes Collaborative Research of Epidemiologic Studies (DIAB-CORE)		
5	Mazhar, K. et al.	2011	United States	Cohort	1,064 above 40 years old adults with T2DM	Questionnaires: The SF-12 and the National Eye Institute Vision- Specific Questionnaire (NEI-VFQ-25). Main objectives: To evaluate the relationship between diabetic retinopathy and its severity on QoL in a population-based sample of Latinos with T2DM.	Interviewer-administered	Yes	Yes	84% among the diabetic participants from the Los Angeles Latino Eye Study (LALES)	None	Yes
6	Siersma V. et al.	2013	Denmark	Cross-sectional	1,232 adult patients with T2DM	Questionnaires: The EuroQoL EQ-5D. Main objectives: To investigate factors determining clinical outcome, healthcare consumption and QoL in patients with new foot ulcers.	Self-administered	Yes	Yes	88.30%	Self-report	Yes

7	Nicolucci, A. et al.	2012	Italy	Randomised clinical trial	606 sedentary adult patients with T2DM. From the Italian Diabetes and Exercise Study (IDES)	Questionnaires: The SF-36. Main objectives: To assess the relationship between changes in QoL and volume of physical activity/exercise, in T2DM patients.	Self-administered	Yes	Yes	87.6% from the 691 assessed for eligibility in this study	Self-report and non-response bias	Yes
8	Williams, E.D. et al.	2012	Australia	Randomised clinical trial	120 adult participants with T2DM	Questionnaires: The SF-36. Main objectives: To evaluate the Telephone-Linked Care (TLC) Australian program designed to improve the T2DM management and QoL among the participants compared with a large Australian population study.	Self-administered	Yes	Yes	92.5% of the total sample completed the six-month assessment	Self-report and selection bias	Yes

9	Pintaudi, B. et al.	2015	Italy	Cross-sectional	2,374 adults with T2DM from the benchmarking network for clinical and humanistic outcomes in diabetes (BENCH-D) study	Questionnaires: The SF12, the WHO-5, Diabetes Empowerment Scale-Short Form (DES-SF), Patient Assessment of Chronic Illness Care-Short Form (PACIC-SF), Health Care Climate-Short Form (HCC-SF), Global Satisfaction with Diabetes Treatment (GSDT), Summary of Diabetes Self-Care Activities measure (SDSCA-6), Barriers to Medications (BM) and Perceived Social Support (PSS). Main objectives: To evaluate correlates of diabetes related distress in the context of the large sample of people with T2DM participating in the BENCH-D study.	Self-administered	Yes	Yes	Not mentioned	Self-report bias	Yes, all the instruments, with the only exceptions of the WHO-5 and SF-12, already available in Italian language.
10	Löndahl, M. et al.	2011	Sweden	Randomised clinical trial	75 adults with T2DM	Questionnaires: The SF-36. Main objectives: To evaluate whether hyperbaric oxygen therapy improves QoL in these patients or not.	Self-administered	Yes	Yes	98% the article mentioned that there were only two patients did not fill out the SF-36 at 12-month follow-up	Self-report bias	Yes

										due to their deteriorated medical condition		
11	Adriaanse, M.C. et al.	2016	Netherlands	Cross-sectional	1,676 with T2DM adult patients, aged between 31 and 96 years old	Questionnaires: The SF-12. Main objectives: To study the prevalence, impact and the dose–response relationship of comorbid chronic conditions on QoL in T2DM patients.	Self-administered	Yes	Yes	44% from the original data derived from two data sources	Self-report bias	Yes
12	Myers, V.H. et al.	2013	United States	Randomised clinical trial	212 sedentary adults with T2DM aged between 30 and 75 years old	Questionnaires: The SF-36. Main objectives: To compare the effects of aerobic, resistance, or a combination of both on QoL in sedentary individuals with T2DM.	Self-administered	Yes	Yes	70% who met a minimum criteria of attendance to their exercise prescription for at least 6 months and had SF-36 data at baseline and follow-up	Self-report and non-response bias	Yes
13	Chew, B.-H. et al.	2015	Malaysia	Cross-sectional	752 adults with T2DM	Questionnaires: The World Health Organization Quality of Life-Brief (WHOQOL-BREF), the 17-items Diabetes	Self-administered	Yes	Yes	93.10%	Self-report bias	Yes

					above 30 years old	Distress Scale (DDS-17), and the PHQ-9. Main objectives: To examine the effects of diabetes-related distress on QoL among patients with T2DM who received regular primary medical care in three public health clinics.						
14	Shi, L. et al.	2014	United States	Cross-sectional	3,999 adult patients with T2DM	Questionnaires: The EuroQoL EQ-5D and the SF-12. Main objectives: To test whether fear of hypoglycemia is independently associated with poorer QoL among patients with T2DM or not.	Self-administered	Yes	Yes	20.30%	Self-report and non-response bias	Yes
15	Kuznetsov, L. et al.	2014	United Kingdom	Cross-sectional	1,876 adults with T2DM aged between 40 and 69 years old	Questionnaires: The SF-36 and the Audit of Diabetes Dependent Quality of Life (ADDQoL19). Main objectives: To examine the association between health status, diabetes-specific	Self-administered	Yes	Yes	66% of the 2859 patients still alive at 5 years from the ADDITION-Europe trial cohort	Self-report, recall and social desirability bias	Yes

						QoL and glycemic control among individuals with T2DM.							
16	Bourdel-Marchasson, I. et al.	2013	France	Cross-sectional	2,832 patients with T2DM adults (18 years and older)	Questionnaires: The SF-12. Main objectives: To assess QoL in people with T2DM and to estimate the relative contributions of socio-demographic factors, diabetes characteristics, complications and treatment, social support and functional impairment in daily living, in mental and physical components of QoL.	Self-administered	Yes	Yes	59%	Self-report and non-response bias	Yes
17	Freemantle, N. et al.	2013	United Kingdom	Randomized clinical trial	1,922 adults with T2DM from three randomized clinical trials	Questionnaires: The SF-36. Main objectives: To compare the effect of insulin degludec and insulin glargine on QoL in patients with T2DM starting on basal insulin, in combination with oral antidiabetic drugs.	Self-administered	Yes	Yes	Not mentioned	Self-report bias	Yes
18	Kempf, K. et al.	2012	Germany	Cohort	327 adults with T2DM not older	Questionnaires: The SF-36 and the Center for Epidemiologic Studies Depression Scale questionnaires (CES-D).	Self-administered	Yes	Yes	70% from the participants who are completed the study	Self-report and non-response bias	Yes

					than 75 years old	Main objectives: To evaluate the impact of lifestyle intervention program on glucometabolic and QoL, with weight and HbA1c reduction as main outcome variables.						
19	Wermeling, P.R. et al.	2012	Netherlands	Cross-sectional	2,086 adults with T2DM aged between 40 and 80 years old	Questionnaires: The SF-36 and EuroQoL EQ-5D. Main objectives: To assess the association between the number and type of comorbidities and health status in a large sample of well-controlled T2DM in general practice.	Self-administered	Yes	Yes	95% from the invited participants	Self-report and selection bias	Yes
20	Reach, G. et al.	2013	France	Cross-sectional	1,933 adults above 18 with T2DM	Questionnaires: The SF-12. Main objectives: To evaluate the impact of insulin therapy on mental and physical quality QoL and patient adherence.	Self-administered (Internet-based or online)	Yes	Yes	Not mentioned	Self-report bias	Yes

21	Donald, M. et al.	2013	Australia	Cross-sectional	3,609 patients with T2DM aged between 18 years or older	Questionnaires: The Audit of Diabetes-Dependent Quality of Life (ADDQoL). Main objectives: To assess the diabetes-specific QoL of a large sample of patients with T2DM.	Self-administered	Yes	Yes	27.3% from the invited sample of 14,439 registrants to participate	Self-report and non-response bias	Yes
22	Zurita-Cruz, J.N. et al.	2018	Mexico	Cross-sectional	1,394 patients over 18 years of age with T2DM	Questionnaires: The SF-36 and the BDI. Main objectives: To understand the relationship between glycemic control and patient-centered care to better determine its legitimacy as a means of improving care for patients with T2DM.	Self-administered	Yes	Yes	Questionnaires that lacked an answer were returned to the patients to complete them	Self-report bias	Yes
23	Williams, J.S. et al.	2016	United States	Cross-sectional	615 adults with T2DM above 18 years old	Questionnaires: The SF-12. Main objectives: To evaluate the relationship between patient-centered care, diabetes self-care, glycemic control, and QoL in a sample of adults with T2DM.	Self-administered	Yes	Yes	Not mentioned	Self-report bias	Yes

24	Al Sayah, F. et al.	2015	Canada	Controlled clinical trial	157 adults with T2DM above 18 years old	Questionnaires: The SF-12, the PHQ-9 and the EuroQoL EQ-5D. Main objectives: To examine the longitudinal associations of inadequate health literacy with depression related and other health outcomes in patients with T2DM who had recently screened positive for depression in a clinical trial.	Self-administered	Yes	Yes	71%	Self-report and non-response bias	Yes
25	Jayasinghe, U.W. et al.	2013	Australian	Cross-sectional	2,181 adults with T2DM and/or hypertension /ischaemic heart disease patients aged 18 years or more	Questionnaires: The SF-12 and the Chronic Illness Care (PACIC). Main objectives: To investigate the relationship between patient or general practitioners' characteristics and QoL in a large sample of chronically-ill Australian adults from two states and the Australian Capital Territory.	Self-administered	Yes	Yes	70%	Self-report and non-response bias	Yes

26	Hunger, M. et al.	2014	German	Cohort	1,046 participants with T2DM aged between 55 and 74 years old	Questionnaires: The SF-12. Main objectives: To examine how changes between NGT, prediabetes and diabetes over a 7-year period are associated with change in QoL.	Face-to-face interview at baseline and self-administered at follow-up	Yes	Yes	67% from the population-based German KORA (Cooperative Health Research in the region of Augsburg) study	Self-report and non-response bias	Yes
27	Sayah, F.A. et al.	2016	Canada	Cohort	1,948 adults above 18 years old with T2DM	Questionnaires: The SF-12, the EuroQoL EQ-5D, and the PHQ8. Main objectives: To examine the association of health literacy (HL) with changes in QoL among patients with T2DM.	Self-administered	Yes	Yes	Not mentioned	Self-report bias	Yes
28	Pawaskar, M. et al.	2018	United States	Cross-sectional	3,630 participants above 18 years old with T2DM	Questionnaires: The SF-36. Main objectives: To explore the association between hypoglycaemia severity and QoL.	Self-administered (Internet-based or online)	Yes	Yes	Not mentioned	Self-report bias	Yes
29	Wan, E.Y.F. et al.	2016	Hong Kong	Cross-sectional	1,826 adults with T2DM	Questionnaires: The SF-12.	Interviewer-administered (By phone)	Yes	Yes	Between 75.5% and 59.7%	Non-response bias	Yes

					above 18 years old	Main objectives: To identify the predictors for poorer QoL in Chinese patients with T2DM over time and provide a 2-year estimate of preference-based measure for cost-effectiveness analysis of primary care interventions for patients with diabetes.						
30	Saffari, M. et al.	2019	Iran	Cross-sectional	793 adults 65 years or older with T2DM	Questionnaires: The World health organization quality of life scale brief version (WHOQOL-BREF) and Diabetes-specific quality of life questionnaire module (DMQoL).	Self-administered	Yes	Yes	Not mentioned	Self-report bias	Yes
						Main objectives: To investigate how religiosity may affect disease-specific QoL.						
31	Alenzi, E.O. et al.	2016	United States	Cross-sectional	1,033 adults aged over 21 years or older with DM	Questionnaires: The SF-12. Main objectives: To examine the association between depression treatment and QoL measures of adults with DM and	Interviewer-administered	Yes	Yes	Not mentioned	Self-report and recall bias.	Yes

					and depression	depression, comparing them to those who did not report any depression treatment.							
32	Abbatecola, A.M. et al.	2015	Italy	Cross-sectional	558 older people with T2DM	Questionnaires: The SF-12 and ADDQoL. Main objectives: To investigate the validity and reliability of the ADDQoL in older outpatients with T2DM and to investigate the association between the overall impact of diabetes assessed using the average weighted impact score from the ADDQoL, on improvement in glycemic control over time.	Self-administered	Yes	Yes	Not mentioned	Self-report and selection bias.	Yes
33	Thiel, D.M. et al.	2017	Canada	Cohort	1,948 adults above 18 years old with T2DM	Questionnaires: The SF-12 and the EuroQoL EQ-5D. Main objectives: To investigate the longitudinal relationship between physical activity and QoL in adults with T2DM.	Self-administered	Yes	Yes	Not mentioned	Self-report bias	Yes

34	Janssen, L.M.M. et al.	2020	United States	Cross-sectional	2,915 individuals aged between 40 and 75 years old with T2DM	Questionnaires: The SF-36 and the EuroQoL EQ-5D. Main objectives: To investigate the associations of diabetes related complications and other social determinants with the costs related to T2DM and with the QoL of people with the disease.	Self-administered	Yes	Yes	85% from the first participants in the Maastricht Study	Self-report and recall bias	Yes
35	Cai, J. et al.	2018	United States	Randomised clinical trial	2,536 adults with T2DM	Questionnaires: The SF-36, the Impact of Weight on Quality of Life-Lite (IWQoLLite) and Current Health Satisfaction Questionnaire (CHES-Q). Main objectives: To evaluate the effect of treatment with canagliflozin, a sodium glucose cotransporter 2 inhibitor, compared with placebo or sitagliptin on QoL outcomes in participants with T2DM from the clinical development program.	Self-administered	Yes	Yes	Ranged between 81% and 93%	Self-report bias	Yes

36	Zhao, H. et al.	2020	Canada	Cohort	969 adults above 18 years old with T2DM	Questionnaires: The SF-12 and the EuroQoL EQ-5D. Main objectives: To evaluate the relationship between diabetic foot disease and QoL over a 2-year period.	Self-administered	Yes	Yes	82%	Self-report bias	Yes
37	Lloyd, C.E. et al.	2020	Switzerland	Cohort	1,616 adults with T2DM aged between 18 and 65 years old	Questionnaires: The PHQ-9, the WHO-5 and the PAID. Main objectives: To identify specific risk factors for the onset of diagnosed depression as well as depressive symptoms in this cohort of individuals with T2DM.	Self-administered	Yes	Yes	Not mentioned	Self-report bias	Yes
38	Sacre, J.W. et al.	2021	Australia	Cross-sectional	470 adults with T2DM aged between 18 and 80 years old	Questionnaires: The Generalised Anxiety Disorder (GAD-7), the PHQ-8, the PAID, and the Confidence in Diabetes Self-Care (CIDS) scale and 12-item Diabetes Support Scale (DSS).	Self-administered (phone and online)	Yes	Yes	96%	Self-report and selection bias	Yes

						Main objectives: To investigate worry about COVID-19 and its perceived impact on QoL and healthcare access among adults with T2DM.						
39	Selenius, J.S. et al.	2020	Finland	Cross-sectional	1,930 adults with T2DM	Questionnaires: The SF-36 and the BDI. Main objectives: To investigate whether the association between the different degrees of impairment in glucose regulation and QoL is modified by the severity and type of depressive symptoms.	Self-administered	Yes	Yes	Not mentioned	Self-report bias	Yes
40	Nicolucci, A. et al.	2021	Italy	Cross-sectional	12,028 adults with T2DM	Questionnaires: The SF-36-Item and the Hypoglycemia Fear Survey-II (HFS-II). Main objectives: To investigate factors associated with QoL in patients with T2DM at initiation of second-line glucose-lowering therapy.	Self-administered	Yes	Yes	Between 69.1% and 72.6%	Self-report and non-response bias	Yes

- This table was organised based on the frequency of citations (from the highly cited article to the least cited article

2.4.2 Study characteristics and QoL measurements

The majority of the studies were cross-sectional 60% (205-228), followed by 22.5% clinical trial (229-237) and 17.5% cohort (238-244); with overall response rates ranging between 40% and 98% among adult patients with T2DM (Figure B.2.2, Appendix B).

The following questionnaires used in the QoL assessment included the Medical Outcomes Study Short Form 36 (SF-36), the Medical Outcomes Short Form 12 (SF-12), the 9-item Patient Health Questionnaire (PHQ-9), the EuroQoL EQ-5D, The World Health Organization Quality of Life-Brief (WHOQOL-BREF), the 17-items Diabetes Distress Scale (DDS-17), the Audit of Diabetes Dependent Quality of Life (ADDQoL19), the Diabetes-Specific Quality of Life (DMQoL) and the Impact of Weight on Quality of Life-Lite (IWQoLLite). Other questionnaires used evaluated the mental health combined with QoL assessment. This included the Beck Depression Inventory, the World Health Organisation - Five Well-Being Index (WHO-5), the Chronic Illness Care (PACIC), the Center for Epidemiologic Studies Depression Scale questionnaires (CES-D), the Generalised Anxiety Disorder (GAD-7), the Problem Areas in Diabetes (PAID) scale, the Confidence in Diabetes Self-Care (CIDS) scale, the 12-item Diabetes Support Scale (DSS), the Hypoglycaemia Fear Survey-II (HFS-II), the Health Care Climate-Short Form (HCC-SF), the Global Satisfaction with Diabetes Treatment (GSDT), the Summary of Diabetes Self-Care Activities measure (SDSCA-6), the Barriers to Medications (BM), the Perceived Social Support (PSS) and The Empowerment Scale-Short Form (DES-SF).

Table 2.2. Summary of quality appraisal for excluded studies

S.N	Authors	Year	Study design	Rationale for exclusion
1	Cykert, D. M., et al.	2017	Cross-sectional	The exposure measured was not clearly defined in a valid and reliable way and the standard criteria used for the measurement of the outcomes was unclear.
2	Rani, M., et al.	2019	Cross-sectional	The study subjects and setting were not clearly described. Confounding factors were not mentioned by the authors.
3	Babenko, A. Y., et al.	2019	Cross-sectional	The methodology provided no details on the study subjects and setting. The study lacked details on confounding factors.
4	Haidari, F., et al.	2017	Cross-sectional	The standard criteria for measuring the outcomes and confounding factors were not clear or identified.
5	Pati, S., et al.	2020	Cross-sectional	The exposure and outcomes variables were not measured in a valid and reliable way.
6	Thapa, S., et al.	2019	Cross-sectional	Confounding factors and strategies used to deal with these were not identified in this study. The methodology did not provide

				clear details on the study participants and setting.
7	Sionti, V., et al.	2019	Cross-sectional	Unclear inclusion criteria, study setting, confounding factors, and statistical analysis.
8	Altınok, A., et al.	2016	Cross-sectional	There were no proper details on the study participant, setting, and any confounding factors.
9	Mikailiūkštienė, A., et al.	2013	Cross-sectional	The standard criteria for the measurement of the outcome variables were unclear and there were no details on the study subjects and setting.
10	Dalal, J., et al.	2020	Cross-sectional	There were no confounding factors identified. Unclear outcomes measurement and statistical analysis.
11	Nyoni, A. M., et al.	2018	Cross-sectional	There were no standard criteria used for measuring the outcomes variables and limited details on the study participants and setting.
12	Olukotun, O., et al.	2022	Cross-sectional	There were no confounding factors identified and the study setting was not clearly mentioned.

13	Sato, M. and Y. Yamazaki	2012	Cross-sectional	The validity and reliability for measuring the outcomes were unclear and there were no confounding factors identified.
14	Walker, R. J., et al.	2014	Cross-sectional	The strategies for dealing with confounding factors as well as what was used as the standard criteria for measuring the outcomes variables were unclear.
15	Baruah, M. P., et al.	2021	Cross-sectional	The exposure and outcomes were not measured in a valid and reliable way. The study setting was unclear and no identification of confounding factors.
16	Hu, F., et al.	2015	Cross-sectional	Unclear inclusion criteria for the studied population and strategies for identifying the confounding factors.
17	Hashimoto, Y., et al.	2020	Cross-sectional	There were unclear inclusion criteria and no appropriate information about identifying the confounding factors.
18	Abraham, A. M., et al.	2020	Randomised clinical trial	There was no true randomization used for assignment of participants to treatment groups. Allocation concealment was not done.

19	Kempf, K. and S. Martin	2013	Randomised clinical trial	The trial design was not appropriate and there was no detailed information about any deviations from the standard trial design accounted for the conduct and analysis of the trial.
20	Ebrahimi, H., et al.	2018	Randomised clinical trial	There was no information as to whether the outcomes assessors were blinded to the intervention or not. Unclear baseline similarity in the two groups. The outcome measurements were not clearly conducted in a reliable way.
21	Costa, M. S. A., et al.	2020	Cohort	Unclear whether the groups or the participants were free of the outcomes or not at the baseline of the study. There were no clear strategies to address the incomplete data.

- This table is based on the JBI quality appraisal checklists.

2.4.3 Main findings

The six top commonly used QoL measurements included the SF-12, which was found in 19 studies (205, 206, 208, 209, 211, 213, 215, 218, 219, 221, 223, 224, 230, 236, 238, 240-243); the SF-36, identified in 16 studies (206, 212, 214, 217, 220, 225, 227-229, 231-235, 237, 239); the EuroQoL EQ-5D, included in 8 studies (207, 211, 214, 225, 230, 241-243); the PHQ-9, found in five studies (205, 210, 230, 236, 244); the WHOQOL-BREF, evaluated in two studies (210, 222) and the ADDQoL19, identified in two studies (212, 216) (Figure B.2.3, Appendix B).

Fifteen (37.5%) studies used only one questionnaire. In this regard, the SF-12, was used as a single questionnaire in seven studies (209, 213, 215, 218, 221, 223, 240), the SF-36 in six studies (220, 231-235), the EuroQoL EQ-5D in one study (207) and the ADDQoL19 in one study (216). However, the remaining reviewed studies (62.5%) used more than one questionnaire.

In terms of mental health measurements, there were four questionnaires that were commonly used which combined with QoL questionnaires namely the WHO-5 in three of the reviewed studies (208, 236, 244), the BDI in three studies (217, 227, 237), the PAID in three studies (226, 236, 244) and lastly the PACIC, found in two studies (208, 219).

Most of the studies (90%) reported using self-administered questionnaires with only four (221, 223, 238, 240) identified to use interviewer mode of administration. Moreover, all of the studies indicated that the questionnaires used were validated, reliable and that they supported different languages.

2.5 Discussion

The present systematic review indicates that the SF-12 questionnaire is the most appropriate and commonly used measurement to assess HRQoL and mental health, followed by the SF-

36, the EuroQoL EQ-5D, the PHQ-9, the WHOQOL-BREF and the ADDQoL19. This questionnaire was used in several studies with different methodological approaches and was confirmed to be validated, reliable, less time-consuming, easy to use and available in many languages (245). Other attributes of the SF-12 questionnaire include that it is a self-administered generic measurement and large-scale, population-based health inventory that has been developed to measure both the physical and mental health aspects of a patient. It is effective and efficient with a completion time of fewer than five minutes. Moreover, it has the exact eight health domains (Physical Functioning, Role Physical, Role Emotional, Mental Health, Bodily Pain, General Health, Vitality and Social Functioning) similar to SF-36 but with one or two items per domain and without any notable statistical difference especially for studies with a large sample size. These were the significant advantages of using SF-12 over SF-36 while the disadvantages were considered as less in representation or comprehensiveness of the content of health measures and lacking of the statistical precision of mental and physical components scores compared to SF-36 (245).

One of the largest Randomised Controlled Trials (RCTs), titled Look AHEAD (Action for Health in Diabetes) conducted on 5,145 people living with overweight or obesity and T2DM, assessed the effect of long-term lifestyle modification on QoL and depression symptoms using the BDI and SF-36 questionnaires as the main measurement for their primary outcomes. Concerns included a shallow response rate by fewer than 40% of patients in the final year of the study, possibly due to the high dropout rate and lengthy QoL questionnaire (237). Another RCT was conducted among 1,922 patients with T2DM to evaluate the effect of two different insulin therapies on QoL using the SF-36 alone. The authors of this study observed that there was a lack of a sleep variable on the questionnaire, which was considered as a study limitation. There was no information relating to the response rate in this study (231). The remaining trials that

were included in the present review used the SF-36 with a response rate between 70%-98%, with the exception of one controlled clinical trial that used the SF-12 combined with different questionnaires and most of which had weaknesses with respect to randomisation, blinding and allocation concealment (229, 230, 232-236).

Another population-based cohort study on adults with T2DM conducted on 1,064 participants to assess the impact of diabetic retinopathy on QoL used the SF-12, where interviewers had the questionnaire administered in either English or another language (238). This was similar to a population-based German cohort study that used the SF-12 to examine the change of QoL in 1,046 patients with T2DM through a face-to-face questionnaire administered at baseline, where the response rate was between 67% to 84% (240). However, most of the other cohort studies included in this review preferred to use the SF-12 as a main questionnaire for their studies (241-243).

A longitudinal cross-sectional study conducted to identify the determinants of poor QoL in 1,826 Chinese patients with T2DM who used the SF-12 over 24 months (through a phone interview) had a response rate between 75.5% and 59.7% (221). This study used a similar methodological approach with another longitudinal cross-sectional study regarding the association between depression and QoL among 1,033 adults with T2DM, addressed by interviews throughout the study using the SF-12 questionnaire alone (223). It has been plausible that the majority of the cross-sectional studies matched with cohort studies in terms of using the SF-12 as their primary questionnaire and through interview mode of administration (205, 206, 208, 209, 211, 213, 215, 218, 219, 224).

2.5.1 Strengthens and limitations

The main strength of this review is that it comprehensively reviewed the body of evidence

that focused on the most common and widely used publications over the last decade. This study identified the most common, widely used efficient and validated HRQoL and/or QoL and mental health questionnaire over a large number of publications for more than a decade in different languages. There are some weaknesses due to potential biases identified from the included studies, especially the self-reported and non-response bias, as well as the differences in response rates. Another weakness is the lack of standard terminology which may possibly cause misleading results. Lastly, the huge heterogeneity in the study designs, methodology and sample size has limited the ability to quantify any differences through a meta-analysis.

2.6 Conclusions

In the backdrop of the growing prevalence of this disease worldwide, there has been limited information on the most efficient and commonly used questionnaire for the patients with T2DM. This review found evidence of the effects of six different QoL and mental health questionnaires. Findings identified the SF-12 as the most validated, time efficient and effective questionnaire that allows cross-culture adaption which can be used in population-based studies across the world. These results encourage the use of SF-12 in adult patients with T2DM as a useful screening measure for identifying and monitoring mental health issues that may assist with target treatment and prevention. The wide range of tools used to assess HRQoL and/or QoL, methodology of administration, clinical research question and limited sample size used by studies hinder direct comparisons in patients with T2DM. Future large multicentre prospective research is recommended to help clarify causality on associations between mental health, QoL and any barriers in people with T2DM involving individuals from different cultural backgrounds.

Chapter 3. Epidemiology, contributing risk factors and complications in patients with type 2 diabetes mellitus: a retrospective cohort study in Jeddah, Saudi Arabia

3.1 Abstract

Aims: To evaluate the prevalence and differences in risk factors among patients with Type 2 Diabetes Mellitus (T2DM)-related complications.

Methods: Retrospective study evaluating age, gender, nationality, glycosylated haemoglobin test (HbA1c) and Body Mass Index (BMI) in patients ≥ 18 years with T2DM between January 2010 to July 2022 from a tertiary referral hospital in Jeddah, Saudi Arabia.

Results: Overall, 3,972 patients had T2DM and 74.7% with T2DM-related complications. Development of T2DM-related complications was 1.7% times greater in males (OR = 1.17; 95% CI: 1.01-1.35, P = 0.028), 28% higher for age > 45 years (OR = 1.28; 95% CI: 1.06-1.55, P = 0.010) and obesity raised the odds by 31% (OR = 1.31; 95% CI: 1.09-1.59, P = 0.004). High HbA1c increased this risk by 2.4 times (OR = 2.39; 95% CI: 1.99-2.86, P = 0.001) and by 2.4-fold for patients with high cholesterol (OR = 2.41; 95% CI: 1.18-4.93, P = 0.015).

Conclusions: The prevalence of T2DM-related complications was high, with an increased likelihood of T2DM-related complications associated with elevated HbA1c, BMI and cholesterol levels. Future studies are needed to reduce and manage these complications early.

3.2 Introduction

Type 2 Diabetes Mellitus (T2DM) is a disorder that is dramatically increasing around the world. T2DM is a combination of reduced insulin with insulin resistance, with subsequent effects on raising the glucose level within the bloodstream. This type of diabetes accounts for 90% of diabetes cases affecting all regions and societies globally (7).

Several risk factors for T2DM may contribute to people developing the disease. This includes genetics, age, family history, lack of good diary habits, gestational diabetes, pre-diabetes, increased Body Mass Index (BMI), sedentary lifestyle, high blood pressure, high lipid profile and ethnicity or race (246).

If left untreated, prolonged hyperglycaemia from T2DM may lead to various types of macrovascular (stroke, ischemic heart attack, coronary heart disease and peripheral vascular disease) and microvascular complications (nephropathy, neuropathy, retinopathy, and foot ulcers). The risk of developing these complications increases with the age and duration of diabetes, which impacts the economic burden and Quality of Life (QoL) on individuals and governments (247). The reported expenditure on those diagnosed with diabetes may reach as much as $4390 per person annually and this increases further for those who are suffering from complications in Australia, while the total annual expenditure on those who have complications in the United States reaches $58 billion compared to $27 billion for treating diabetes only (248, 249).

High glycosylated haemoglobin test (HbA1c) levels may play an essential role in developing T2DM-related complications or even progressively increase the risk of having T2DM-related complications along with high BMI or obesity and other factors (250, 251).

Saudi Arabia is a wide country with a population of more than 32.2 million, and it is expected to report a high prevalence rate of T2DM in the coming decades (252). Overall, one-fourth of the adult population is affected by diabetes, which is further predicted to increase to more than double by 2030 (88).

Among Saudis, the prevalence of concomitant diabetic complications is high, with cardiovascular and renal complications reflected as the most frequent. Many of these patients suffer from multiple complications. Several studies have been published on T2DM and T2DM-related complications in different areas of Saudi Arabia. However, due to heterogeneity, their results are not generalisable to all parts of Saudi Arabia (253, 254).

Therefore, the current study is the first of its kind that aims to investigate the magnitude of T2DM-related complications among a defined population in the city of Jeddah, which is the second largest city in Saudi Arabia. This city has an estimated population of 3.4 million people, with limited studies in this area which highlights the need to bridge the current gap (255).

3.3 Methods

3.3.1 Data source

Using the 10th revision of the International Classification of Diseases (ICD-10) codes, data for this study was retrospectively retrieved between January 2010 to July 2022. Research data were collected from the electronic files of patients attending King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia, and were provided to researchers by the Information Technology Department at KAUH. This is after obtaining the necessary ethical approvals from the research ethics committee and according to the bylaws and rules of the committee. KAUH

is a huge teaching hospital in Saudi Arabia and one of the largest hospitals in Jeddah city, with a capacity of 1,067 beds (256).

The definition of patients with T2DM was based on the ICD-10 code E11 (Type 2 diabetes mellitus) and for without complications it was based on the category E11.9 (Type 2 diabetes mellitus without complication), E11.90 (Non-insulin-dependent diabetes mellitus without complications, not stated as uncontrolled) and E11.91 (Non-insulin-dependent diabetes mellitus without complications, stated as uncontrolled) subdivision codes while the other subdivision codes of T2DM were included in with complications group.

A statistically validated sample (n = 146) of medical files was reviewed to verify and assess additional variables such as marital status, duration of T2DM, cholesterol level, smoking status, blood pressure and type of management based on the research timeline.

3.3.2 Inclusion and exclusion criteria for the study population

The study population consisted of all registered adult Saudi or non-Saudi patients aged 18 years or older. Any duplicate data (n = 140,942), patients coded as E11 only without any subdivision (n = 479), deaths (n = 173) and any missing values (n = 261) were excluded.

3.3.3 Patients' variables

The ICD-10 diagnosis code was used for all patients with information such as age, gender, nationality, BMI and HbA1c results retrieved and included in this study (Table C.3.1, Appendix C). Patients' variables were classified into different categories for nationality. This was stratified into non-Saudis if they were originally from any country and living in Saudi Arabia, while Saudi if they were originally from Saudi Arabia. Other variables included age, categorised as ≤ 45 years and > 45 years old. BMI was calculated as weight (kg) / [height (m)]^2

and then classified as ≤ 24.9 kg/m^2 for a healthy weight, between 25 kg/m^2 to 29.9 kg/m^2 for people living with overweight and ≥ 30 kg/m^2 for people living with obesity. Finally, HbA1c was categorised as ≤ 6.4% for normal, between 6.5% to 7.9% for well-controlled, and ≥ 8% for poorly controlled, all based on Centers for Disease Control and Prevention (CDC) recommendations (257-259).

3.3.4 Statistical analysis

Data were extracted into Microsoft Excel, and all descriptive and analytical statistics were conducted by SPSS version 28 (IBM SPSS Statistics for Windows, Armonk, NY, USA) software. Non-parametric continuous variables were described as the median and Interquartile Range (IQR), defined as the 25th to 75th percentile. Pearson's chi-square test was used to examine differences between categorical variables. Binary logistic regression was performed to estimate the likelihood of having T2DM complications in this study. Missing values that were more than 5% of any variables were excluded from the adjusted binary logistic regression or some of the univariate study analyses. A P-value < 0.05 was considered statistically significant for all analyses and all tests were two-tailed.

3.4 Results

3.4.1 Patient characteristics

A total of 3,972 patients with T2DM were included in this analysis. This cohort was represented mainly by patients that were of Saudi nationality (67.4%). However, almost one-third were non-Saudis expatriates, 1,295 (32.6%). The overall male-to-female ratio was 1:1.6, with a median age of 60 years (IQR: 51-68). For males, the overall median age, BMI, HbA1c, and duration of T2DM was 61 years of age (IQR: 51-68), 28 kg/m^2 (IQR: 24.6-31.1), 7.6% (IQR:

6.7-8.3) and 9.5 years (IQR: 6-18) respectively. For females, this was 56 years of age (IQR: 51-57.5), 29.1 kg/m^2 (IQR: 26.3-34.5), 6.9% (IQR 6.1-8.2), and 9 years (IQR: 5-13) respectively (Table 3.1). There was a significant difference between females and males in terms of BMI and HbA1c (P <0.001). Females were more likely to have an increase in BMI (OR: 0.95; 95% CI: 0.92-0.98; P <0.001) and a decrease in HbA1c (OR: -1.07; 95% CI:1.05-1.08; P <0.001) compared to males. When evaluating patients by gender, nationality and whether they had T2DM-related complications or not, most patients were found to be > 45 years old. This was especially evident among non-Saudi females (P = 0.007) (Figure C.3.1, Appendix C).

All stratified groups (nationality, gender and with or without T2DM-related complications) were found to be people living with obesity (≥ 30 kg/m^2) except for non-Saudi males (P = 0.021), both with and without complications (Figure C.3.2, Appendix C). Interestingly, patients with T2DM-related complications who were Saudi or non-Saudi males or females were considered poorly controlled (≥ 8% HbA1c; P <0.001), while those without T2DM-related complications were found to be well-controlled (≤ 6.4%) or normal (6.5%-7.9%) HbAc1 levels despite their gender and nationality (Figure C.3.3, Appendix C).

Table 3.1. Demographic characteristics of patients with T2DM

Variables		Patients (n = 3,972)		
		N	% out of 146	Total %
Gender	Male	1840		46.3
	Female	2132		53.7
Nationality	Saudi	2677		67.4
	Non-Saudi	1295		32.6
Median age, yrs (IQR)	60 (51-68)			
Median BMI, kg/m^2 (IQR)	29.6 (25.9-34.2)			
Median HbA1c, yrs (IQR)	7.3 (6.3-8.8)			
Median duration of T2DM, yrs (IQR)	9 (5-15)			
T2DM-related complications	No	1006		25.3
	Yes	2966		74.7
Marital status	Unmarried	46	31.5	1.2
	Married	100	68.5	2.5

High cholesterol	No	58	39.7	1.5
	Yes	88	60.3	2.2
High blood pressure	No	41	28.1	1.0
	Yes	105	71.9	2.6
Smoking status	Non-smoker	117	80.1	2.9
	Smoker	29	19.9	0.7
Type of management	Healthy lifestyle only	5	3.4	0.1
	Healthy lifestyle and oral medication	3	2.1	0.1
	Healthy lifestyle and insulin	1	0.7	0.0
	Oral medication only	79	54.1	2.0
	Insulin only	15	10.3	0.4
	Oral medication and insulin	43	29.5	1.1
Admissions	Emergency	112		2.8
	Inpatient	429		10.8
	Outpatient	3431		86.4

Median LOS, days (IQR)	3 (1-3)	

T2DM, type 2 diabetes mellitus; IQR, interquartile range; BMI, body mass index; HbA1c, glycosylated haemoglobin test; LOS, length of stay at the hospital; yrs, years.

Complications were found in 74.7% and almost all patients reviewed were managed on an outpatient basis (86.4%), with only 2.8% managed in the King Abdulaziz University Hospital (KAUH) emergency department. Approximately one out of 10 patients in this study were required to be admitted as an inpatient. The overall median hospital length of stay (LOS) was 3 days (IQR: 1-3) for these patients. The availability of different new classes of medications and their effect on the progression of complications like SGLT2i and GLP1RA were not addressed in this study. Some of the new medications were not affordable to all patients for various reasons, including financial constraints on the university hospital, particularly during the COVID-19 crisis (Table 3.1).

3.4.2 Risk factors and complications

Of those patients who had T2DM-related complications, approximately 52.7% were female compared to 47.3% males (P = 0.028). There was no difference between Saudis (68%) and non-Saudis (32%) in this group relating to complication rates (P = 0.161). Older patients (> 45 years of age) had a greater rate of T2DM-related complications (85.7%) compared to younger patients (P = 0.010) (Table 3.2). Furthermore, risk factors identified for T2DM included BMI and HbA1c with an overall median of 29.6 kg/m^2 (IQR: 25.9-34.2) and 7.3% (IQR: 6.3-8.8) respectively (Table 3.1). For people living with obesity (≥ 30 kg/m^2) with T2DM the median age, BMI and HbA1c duration was 61 years (IQR: 53.5-65.5), 34.3 kg/m^2 (IQR: 31.8-37.1), 7.4% (IQR: 6.4-8.4) and 11 years (IQR: 7-14.5) respectively with no significant difference between BMI categories in relation to age, HbA1c and duration of T2DM. For the uncontrolled people living with diabetes (≥ 8% HbA1c) the median age, BMI and HbAc1 duration were 61 years (IQR: 50-67), 28.9 kg/m^2 (IQR: 26.3-33.5), 9% (IQR: 8.3-10.2) and 11 years (IQR: 8-22)

respectively with a significant difference between the HbA1c levels with respect to age (P <0.001) and duration of T2DM (P = 0.003) only.

Table 3.2. Univariate analysis of T2DM risk factors and the development of T2DM-related complications

Risk Factors		Without complications (n = 1,006)				With complications (n = 2,966)				
		N	Column %	Column % out of 146	Row%	N	Column%	Column % out of 146	Row %	P
Gender	Male	436	43.3		23.7	1404	47.3		76.3	0.028
	Female	570	56.7		26.7	1562	52.7		73.3	
Nationality	Saudi	660	65.6		24.7	2017	68.0		75.3	0.161
	Non-Saudi	346	34.4		26.7	949	32.0		73.3	
Age, yrs	≤ 45	178	17.7		29.5	425	14.3		70.5	0.010
	> 45	828	82.3		24.6	2541	85.7		75.4	
BMI ranges, kg/m^2	≤ 24.9 (Healthy weight)	220	21.9		28.0	567	19.1		72.0	0.001
	25-29.9 (Overweight)	350	34.8		27.6	917	30.9		72.4	
	≥ 30 (Obese)	436	43.3		22.7	1482	50.0		77.3	
HbA1c levels, %	≤ 6.4 (Normal)	377	37.5		33.5	749	25.3		66.5	

	6.5-7.9 (Well-controlled)	370	36.8		27.3	987	33.3		72.7	
	≥ 8 (Poorly controlled)	259	25.7		17.4	1230	41.5		82.6	<0.001
Duration of T2DM, yrs	≤ 5	14	1.4	30.4	34.1	27	0.9	27.0	65.9	
	6-10	14	1.4	30.4	32.6	29	1.0	29.0	67.4	0.848
	> 10	18	1.8	39.1	29.0	44	1.5	44.0	71.0	
Marital status	Unmarried	9	0.9	19.6	19.6	37	1.2	37.0	80.4	
	Married	37	3.7	80.4	37.0	63	2.1	63.0	63.0	0.035
High cholesterol	No	25	2.5	54.3	43.1	33	1.1	33.0	56.9	
	Yes	21	2.1	45.7	23.9	67	2.3	67.0	76.1	0.014
High blood pressure	No	12	1.2	26.1	29.3	29	1.0	29.0	70.7	
	Yes	34	3.4	73.9	32.4	71	2.4	71.0	67.6	0.716
Smoking status	Non-smoker	35	3.5	76.1	29.9	82	2.8	82.0	70.1	
	Smoker	11	1.1	23.9	37.9	18	0.6	18.0	62.1	0.405
Type of management	Healthy lifestyle only	3	0.3	6.5	60.0	2	0.1	2.0	40.0	
	Healthy lifestyle and oral medication	0	0.0	0.0	0.0	3	0.1	3.0	100.0	

	Healthy lifestyle and insulin	0	0.0	0.0	0.0	1	0.0	1.0	100.0
	Oral medication only	36	3.6	78.3	45.6	43	1.4	43.0	54.4
	Insulin only	3	0.3	6.5	20.0	12	0.4	12.0	80.0
	Oral medication and insulin	4	0.4	8.7	9.3	39	1.3	39.0	90.7

T2DM, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycosylated haemoglobin test.

Overall, patients with obesity were 50% more likely to be at risk of having T2DM-related complications than all other patients (P = 0.001). This trend was further emphasised when more patients with T2DM were poorly controlled (41.5%) and had T2DM-related complications compared to patients without T2DM-related complications (P <0.001). Among complicated patients with T2DM, almost half (44%) had T2DM for more than 10 years duration (P = 0.848). In addition, 63% were married (P = 0.035), 67% had high cholesterol (P = 0.014), 71% were hypertensive (P = 0.716), 18% were smokers (P = 0.405) and 39% were taking both oral medication and insulin (Table 3.2).

In the univariate analysis, we found that the risk of developing T2DM-related complications was 17% greater in males compared to females (OR = 1.17; 95% CI: 1.01-1.35, P = 0.028) and that people living with diabetes aged > 45 years were at 28% higher risk (OR = 1.28; 95% CI: 1.06-1.55, P = 0.010) compared to those less than 45 years. Compared to healthy weight patients, living with obesity had a 31% increased risk (OR = 1.31; 95% CI: 1.09-1.59, P = 0.004) of developing T2DM-related complications, whereas people living with poorly controlled diabetes had an almost two and half times higher risk (OR = 2.39; 95% CI: 1.99-2.86, P <0.001). Moreover, we found that married patients with T2DM were less likely to develop T2DM-related complications (OR = -0.41; 95% CI: 0.18-0.95; P = 0.038) than those who were unmarried. In addition, people living with diabetes with high cholesterol were at a greater risk of developing T2DM-related complications (OR = 2.41; CI: 1.18-4.93; P = 0.015) than those without normal cholesterol. However, after controlling for all other variables, multivariable analysis showed that the most significant independent predictors for developing complications from T2DM were gender, BMI and HbA1c (Table 3.3).

Table 3.3. Univariate and adjusted multivariable analysis of gender, nationality, age, BMI, and HbA1c for all patients predicting the risk for the development of T2DM-related complications

Risk factors		Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Male		1.17 (1.01-1.35)	0.028	1.20 (1.03-1.39)	0.015
Saudi		1.11 (0.95-1.29)	0.161	1.14 (0.97-1.33)	0.092
Age > 45 yrs		1.28 (1.06-1.55)	0.010	1.20 (0.98-1.46)	0.064
BMI ranges, kg/m^2	≤ 24.9 (Healthy weight)	(Ref.)			
	25-29.9 (Overweight)	1.01 (0.83-1.24)	0.871	1.04 (0.85-1.28)	0.649
	≥ 30 (Obese)	1.31 (1.09-1.59)	0.004	1.39 (1.14-1.69)	<0.001
HbA1c levels, %	≤ 6.4 (Normal)	(Ref.)			
	6.5-7.9 (Well-controlled)	1.34 (1.13-1.59)	<0.001	1.30 (1.10-1.55)	0.002
	≥ 8 (Poorly controlled)	2.39 (1.99-2.86)	<0.001	2.36 (1.96-2.84)	<0.001
Duration of T2DM, yrs	≤ 5	(Ref.)			
	6-10	1.07 (0.43-2.66)	0.877		

	> 10	1.26 (0.54-2.95)	0.583	
Marital status	Unmarried	(Ref.)		
	Married	-0.41 (0.18-0.95)	0.038	
High cholesterol	No	(Ref.)		
	Yes	2.41 (1.18-4.93)	0.015	
High blood pressure	No	(Ref.)		
	Yes	-0.86 (0.39-1.89)	0.716	
Smoking status	Non-smoker	(Ref.)		
	Smoker	-0.69 (0.29-1.63)	0.407	

OR, odds ratio; CI, confidence interval; T2DM, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycosylated haemoglobin test; yrs, years.

The main types of T2DM-related complications identified included neurological (11.7%), ophthalmic (10.7%), unspecified (10.4%), renal (9.8%), microvascular and foot ulcer complications (7.7%). All risk factor categories were statistically significant (P <0.001) with their T2DM-related complication types except for nationality (Table 3.4).

Table 3.4. T2DM risk factors and associated T2DM-related complications for all patients

Risk factors		Hyperosmolarity and with or without coma complications			Ketoacidosis			Renal complications				Ophthalmic complications			Neurological complications				Circulatory complications				Musculoskeletal, periodontal, dermatological, and hypoglycaemia complications				Microvascular and foot ulcer complications				Unspecified complications				P
		N	Column %	Column % out of 146	Row %	N	Column	Column % out of 146	Row %	N	Column %	Column % out of 146	Row %	N	Column%	Column % out of 146	Row %	N	Column %	Column % out of 146	Row %	N	Column%	Column n % out of 146	Row%	N	Column %	Column % out of 146	Row %	N	Column %	Column % out of 146	Row %	N	Column %	Column n % out of 146	Row %	
Gender	Male	24	40.7		2.2	48	50.0		4.4	148	50.7		13.4	150	47.5		13.6	156	45.0		14.2	102	62.6		9.3	198	45.3		18.0	125	55.1		11.4	150	48.9		13.6	
	Female	35	59.3		3.1	48	50.0		4.2	144	49.3		12.6	166	52.5		14.5	191	55.0		16.7	61	37.4		5.3	239	54.7		20.9	102	44.9		8.9	157	51.1		13.7	0.004
Nationality	Saudi	44	74.6		2.9	57	59.4		3.7	203	69.5		13.2	231	73.1		15.0	246	70.9		16.0	108	66.3		7.0	298	68.2		19.4	147	64.8		9.6	202	65.8		13.2	
	Non-Saudi	15	25.4		2.1	39	40.6		5.5	89	30.5		12.6	85	26.9		12.0	101	29.1		14.3	55	33.7		7.8	139	31.8		19.6	80	35.2		11.3	105	34.2		14.8	0.162
Age, yrs	≤ 45	12	20.3		3.8	36	37.5		11.4	33	11.3		10.5	32	10.1		10.2	44	12.7		14.0	11	6.7		3.5	67	15.3		21.3	27	11.9		8.6	53	17.3		16.8	
	> 45	47	79.7		2.4	60	62.5		3.1	259	88.7		13.4	284	89.9		14.7	303	87.3		15.7	152	93.3		7.9	370	84.7		19.2	200	88.1		10.4	254	82.7		13.2	<0.001
BMI ranges, kg/m²	≤ 24.9 (Healthy weight)	13	22.0		2.8	36	37.5		7.8	50	17.1		10.8	54	17.1		11.7	46	13.3		9.9	42	25.8		9.1	86	19.7		18.6	66	29.1		14.3	70	22.8		15.1	
	25-29.9 (Overweight)	18	30.5		2.6	24	25.0		3.5	78	26.7		11.4	104	32.9		15.2	107	30.8		15.7	53	32.5		7.8	135	30.9		19.8	69	30.4		10.1	95	30.9		13.9	<0.001
	≥ 30 (Obese)	28	47.5		2.6	36	37.5		3.3	164	56.2		14.9	158	50.0		14.4	194	55.9		17.7	68	41.7		6.2	216	49.4		19.7	92	40.5		8.4	142	46.3		12.9	

HbA1c levels, %	≤ 6.4 (Normal)	22	37.3		3.6	18	18.8		2.9	79	27.1		12.8	81	25.6		13.1	103	29.7		16.7	30	18.4		4.9	125	28.6		20.3	49	21.6		7.9	110	35.8		17.8		
	6.5-7.9 (Well-controlled)	18	30.5		2.3	20	20.8		2.6	99	33.9		12.9	114	36.1		14.8	116	33.4		15.1	50	30.7		6.5	174	39.8		22.7	74	32.6		9.6	103	33.6		13.4		<0.001
	≥ 8 (Poorly-controlled)	19	32.2		2.2	58	60.4		6.8	114	39.0		13.3	121	38.3		14.1	128	36.9		14.9	83	50.9		9.7	138	31.6		16.1	104	45.8		12.1	94	30.6		10.9		
Duration of T2DM, yrs	≤ 5	2	3.4	100.0	8.7	2	2.1	66.7	8.7	1	0.3	14.3	4.3	4	1.3	25.0	17.4	3	0.9	18.8	13.0	1	0.6	50.0	4.3	4	0.9	36.4	17.4	2	0.9	33.3	8.7	4	1.3	44.4	17.4		
	6-10	0	0.0	0.0	0.0	1	1.0	33.3	5.6	3	1.0	42.9	16.7	5	1.6	31.3	27.8	3	0.9	18.8	16.7	0	0.0	0.0	0.0	3	0.7	27.3	16.7	1	0.4	16.7	5.6	2	0.7	22.2	11.1		
	> 10	0	0.0	0.0	0.0	0	0.0	0.0	0.0	3	1.0	42.9	9.7	7	2.2	43.8	22.6	10	2.9	62.5	32.3	1	0.6	50.0	3.2	4	0.9	36.4	12.9	3	1.3	50.0	9.7	3	1.0	33.3	9.7		
Marital status	Unmarried	1	1.7	50.0	3.2	3	3.1	100.0	9.7	3	1.0	42.9	9.7	3	0.9	18.8	9.7	9	2.6	56.3	29.0	2	1.2	100.0	6.5	4	0.9	36.4	12.9	1	0.4	16.7	3.2	5	1.6	55.6	16.1		
	Married	1	1.7	50.0	2.4	0	0.0	0.0	0.0	4	1.4	57.1	9.8	13	4.1	81.3	31.7	7	2.0	43.8	17.1	0	0.0	0.0	0.0	7	1.6	63.6	17.1	5	2.2	83.3	12.2	4	1.3	44.4	9.8		
High cholesterol	No	0	0.0	0.0	0.0	1	1.0	33.3	5.0	2	0.7	28.6	10.0	4	1.3	25.0	20.0	3	0.9	18.8	15.0	0	0.0	0.0	0.0	4	0.9	36.4	20.0	2	0.9	33.3	10.0	4	1.3	44.4	20.0		
	Yes	2	3.4	100.0	3.8	2	2.1	66.7	3.8	5	1.7	71.4	9.6	12	3.8	75.0	23.1	13	3.7	81.3	25.0	2	1.2	100.0	3.8	7	1.6	63.6	13.5	4	1.8	66.7	7.7	5	1.6	55.6	9.6		
High blood pressure	No	1	1.7	50.0	4.8	1	1.0	33.3	4.8	2	0.7	28.6	9.5	5	1.6	31.3	23.8	4	1.2	25.0	19.0	0	0.0	0.0	0.0	2	0.5	18.2	9.5	2	0.9	33.3	9.5	4	1.3	44.4	19.0		
	Yes	1	1.7	50.0	2.0	2	2.1	66.7	3.9	5	1.7	71.4	9.8	11	3.5	68.8	21.6	12	3.5	75.0	23.5	2	1.2	100.0	3.9	9	2.1	81.8	17.6	4	1.8	66.7	7.8	5	1.6	55.6	9.8		

Smoking status	Non-smoker	2	3.4	100.0	3.2	3	3.1	100.0	4.8	7	2.4	100.0	11.1	15	4.7	93.8	23.8	15	4.3	93.8	23.8	0	0.0	0.0	0.0	9	2.1	81.8	14.3	5	2.2	83.3	7.9	7	2.3	77.8	11.1
	Smoker	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	1	0.3	6.3	11.1	1	0.3	6.3	11.1	2	1.2	100.0	22.2	2	0.5	18.2	22.2	1	0.4	16.7	11.1	2	0.7	22.2	22.2
Type of management	Healthy lifestyle only	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0
	Healthy lifestyle and oral medication	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	1	0.2	9.1	50.0	1	0.4	16.7	50.0	0	0.0	0.0	0.0
	Healthy lifestyle and insulin	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0
	Oral medication only	1	1.7	50.0	2.9	2	2.1	66.7	5.9	5	1.7	71.4	14.7	8	2.5	50.0	23.5	3	0.9	18.8	8.8	0	0.0	0.0	0.0	7	1.6	63.6	20.6	3	1.3	50.0	8.8	5	1.6	55.6	14.7
	Insulin only	0	0.0	0.0	0.0	0	0.0	0.0	0.0	2	0.7	28.6	20.0	3	0.9	18.8	30.0	3	0.9	18.8	30.0	0	0.0	0.0	0.0	2	0.5	18.2	20.0	0	0.0	0.0	0.0	0	0.0	0.0	0.0
	Oral medication and insulin	1	1.7	50.0	3.8	1	1.0	33.3	3.8	0	0.0	0.0	0.0	5	1.6	31.3	19.2	10	2.9	62.5	38.5	2	1.2	100.0	7.7	1	0.2	9.1	3.8	2	0.9	33.3	7.7	4	1.3	44.4	15.4

T2DM, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycosylated haemoglobin test; yrs, years.

3.5 Discussion

The present study found that the overall prevalence of T2DM-related complications, either microvascular or macrovascular, was 74.7% of the total studied population. The risk of T2DM-related complications was more remarkable in males compared to females as well as patients above 45 years of age. In comparison, a study evaluating the records of 1,111 Saudi participants found that 28% had macrovascular complications, whereas 54.6% had microvascular complications. Most of these patients were females (65.2%); however, males and elderly patients with a mean age of 57.6 years had one or more T2DM-related complications associated with their disease when compared to others. Other factors such as longer duration of diabetes, sedentary lifestyle and lower socioeconomic status were significantly associated with a higher prevalence of all complications (260). Results from a retrospective study conducted on Japanese patients with T2DM showed that 92.9% (22.1% with cardiovascular disease and 35.4% with chronic kidney disease) of 10,151 patients (the mean age was 66±13 years, 60.8% males, the mean of HbA1c was 7.2%±1.1 and the mean of BMI was 25.5kg/m2 ± 4.9) had ≥ 2 comorbid conditions or complications. This finding reflects a very high prevalence which is similar to results from this study in relation to T2DM-related complications. Additionally, this prevalence was also observed in elderly patients and slightly more in males than females (41.9% vs. 43.7%), especially among those who had ≥ 4 comorbid conditions or complications (261).

Another retrospective study (n=6,688) reported increased odds of microvascular and macrovascular complications in patients ≥ 60 years (OR: 5.04; CI: 3.20-7.96 and OR: 24.14; CI: 12.57-46.34) compared to < 40 years, HbA1c ≥ 7% (OR: 1.11; CI: 0.90-1.36 and OR: 1.14; CI:

0.94-1.38) compared to < 7%, which decreased in educated and married patients with T2DM when included in their analysis of independent variables with P ≤ 0.20 (262).

A retrospective cohort study reviewed 365 (52.9% female, mean age was 50 years) patients with T2DM who were regularly followed up within the family medicine clinics at King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia. This cohort found similar results where males were at greater risk of developing T2DM complications compared to females. The overall prevalence of complications in this study was, however, 21.6%. This was lower than the results from the retrospective study in this Chapter, possibly due to the cohort comprising mainly primary healthcare patients. The authors stated that the mean duration of developing complications early was 5.5 years from the time of diagnosis, which is probably a reflection of patients with T2DM visiting their physician every couple of years to avoid any complications (263).

The prevalence of obesity among patients with T2DM was high in this studied population for this chapter, which was reflected more so in females. The risk of T2DM-related complications in patients with obesity with T2DM was 1.4 times higher than healthy weight patients with T2DM (OR: 1.39; 95% CI: 1.14-1.69, P <0.001). A retrospective, cross-sectional study conducted among 346 patients with T2DM in Al-Khobar, Saudi Arabia, found that 62.4% of patients were people living with obesity, with most being more than 61 years of age. In this study, females were positively associated with uncontrolled HbA1c (264). Similarly, work in a different region of Saudi Arabia showed that 57.8% (n = 354) of their patients with T2DM were people living with obesity, with the number of females being more than males (265). This finding was statistically significant in relation to older people living with diabetes and low education levels (264, 265). However, this might be because of genetic factors, bad dietary

habits or physical inactivity. These findings were supported by another study conducted among 1,240 patients with T2DM from a Saudi population. This study found that patients with T2DM with low physical activity were at 4.32 (95% CI: 1.26-14.82, P = 0.001) times higher risk (compared to high physical activity) of developing macrovascular and microvascular complications (266).

The HbA1c is one of the most useful diagnostic tools for diabetes and its complications (267). This is reinforced by findings from this Chapter, that poorly controlled patients with T2DM (HbA1c results more than 8) were at 2.36 (95% CI: 1.967-2.842, P <0.001) times higher risk of developing any type of T2DM-related complications than normal patients with T2DM. Furthermore, the levels of HbA1c might be variable between patients based on their history of diabetes and treatment plan (e.g., tablets only, long or short-term insulin dosage). In a study on 697 patients with T2DM (the mean age of 58 years old) living in Tabuk, Saudi Arabia, approximately 29.8% of patients had complications and 81.5% had poor glycaemic control (the mean of HbA1c was 8.4). This study highlighted that a longer diabetes duration was found to be significantly higher (OR = 1.05; 95% CI: 1.02-1.08, P = 0.003) among patients with poor glycaemic control as well as in patients who used combined treatments compared to insulin only (OR = 4.65; 95% CI: 1.55-13.94, P = 0.006). Interestingly, this study showed no statistically significant association between HbA1c and other risk factors such as BMI, blood pressure, low-density lipoproteins levels, albumin creatinine ratios and urine microalbumin (268).

However, studies with small sample sizes conducted among patients with T2DM within the Saudi population suggested that longer duration of diabetes and high HbA1c were significantly associated with diabetic retinopathy (OR = 5.2; 95% CI: 1.907-14.228; P<0.001 for HbA1c; and OR = 6.9; 95% CI: 0.88-54.00; P = 0.40 for the duration of T2DM), lung function impairment (P

= 0.026 for HbA1c but were not significant for the duration of T2DM), lack of self-awareness and poor cognitive function (P <0.001 for HbA1c and duration of T2DM) which may highlight the importance of raising knowledge about HbA1c and regular monitoring of HbA1c levels along with improvement in quality of life and mental health status (269-272).

Lastly, the massive demand for tertiary healthcare services due to T2DM-related complications might highlight the urgent need for a holistic approach to prevent the complications before they occur, as suggested by a recent study conducted on an Australian population (273).

3.5.1 Strengths and limitations

The strength of this study is that it is one of a few available to evaluate the current burden of diabetes and its complications, as well as the association between risk factors related to T2DM and the likelihood of having complications. Most importantly, this cohort is of a large sample size of patients with T2DM, which is dependent on the ICD-10 standardised diagnostic classification tool. Study limitations include the limited number of variables or risk factors available. This is because it relies on data collected from a hospital-based system, which may be subject to misclassification bias, missing data and may over or underestimate results. It is also limited to single centre hospitals, which may further limit the generalisability of the results to other hospitals.

In conclusion, the overall prevalence of micro and macro complications in patients with T2DM who visited the hospital recently and living within the Saudi population was found to be high. There was a significant difference between the risk factors categories except for the Saudi and Non-Saudi patients regarding T2DM-related complications.

3.6 Conclusions

This study found that the prevalence of T2DM-related complications was high among the studied population, along with high HbA1c, high BMI, and high cholesterol. This increased the likelihood of having T2DM-related complications, which were greater than other variables such as gender, age and nationality. In Saudi Arabia, there is an enormous need for future nationwide prospective studies that will include all risk factors to address the probability of developing complications among people with T2DM.

Chapter 4. Health-related quality of life and mental health aspects among people with type 2 diabetes mellitus; with and without diabetes-related complications: a cross-sectional study in Jeddah, Saudi Arabia

4.1 Abstract

Aims: To assess the impact of Health-Related Quality of Life (HRQoL) and mental health aspects in patients with compared to without Type 2 Diabetes Mellitus (T2DM)-related complications and to identify the variables that correlate with increasing this risk.

Methods: A cross-sectional survey using the 12-item Short Form Version 2 (SF-12v2) was performed on patients with T2DM ≥ 18 years from September to December 2022 in Jeddah, Saudi Arabia. This involved the Mental Component Summary (MCS) and the Physical Component Summary (PCS) scores of SF-12v2 and all its health domains. Demographic characteristics and risk factors such as age, gender, nationality, glycosylated haemoglobin test (HbA1c), marital status, education, duration of T2DM, body mass index (BMI) and cholesterol were collected. Data were presented as median, Interquartile Range (IQR), and Odds Ratio (OR) with their corresponding 95% Confidence Intervals (CI).

Results: In total, there were 182 patients with T2DM with a median age of 56 years (IQR: 48-64), BMI 29.6 kg/m^2 (IQR: 25.9-32), HbA1c test was 7% (IQR: 6.5-8%), T2DM duration of 9 years (IQR: 4.7-18) with 60% of patients having diabetic complications. The median MCS score was 52.3 (IQR: 48-55.5) and 46.3 (IQR: 42.9-54.1) for PCS. Females (OR=9.40; 95% CI:1.70-51.83; P=0.010), poorly controlled HbA1c (OR=10.32; 95% CI:1.31-80.81; P=0.026), high cholesterol (OR=8.74; 95% CI:1.79-42.53; P=0.007), long T2DM duration (OR=8.82; 95% CI:1.42-54.78; P=0.019) as well as below average MCS (OR=3.44; 95% CI:1.65-7.18; P=<0.001) and PCS (OR=5; 95% CI:2.49-10.01; P<0.001) increased the risk of complications.

Conclusions: These findings reflect the negative impact on HRQoL and mental health among patients with T2DM, particularly those with complications.

4.2 Introduction

In 2023, Diabetes Mellitus (DM) affects more than half a billion people worldwide and this number is projected to reach 643 and 783 million by 2030 and 2045, respectively. However, the forecasted increase in people with DM is expected to vary in different regions worldwide. For example, the worst will be in Africa, followed by the Middle East and North Africa (MENA), Southeast Asia, as well as South and Central America regions, with an expected increase in the percentage to be 134%, 87%, 68% and 50% respectively (7).

Saudi Arabia is one of the Gulf Cooperation Council (GCC) countries and MENA region countries that currently report very high age-adjusted comparative prevalence rates of DM. This is similar to countries such as Pakistan and Egypt, with rates of 18.7%, 30.8% and 20.9%, respectively (7). When compared to Australia, the prevalence rate of DM in Saudi Arabia is almost three times greater. This is predicted to increase to just over 22% by 2045, which is 2.8 times higher than that expected for Australia for this year. These predictions reflect the enormous current and future magnitude of the problem related to DM in Saudi Arabia, in particular Type 2 Diabetes Mellitus (T2DM), which accounts for the vast majority (over 95%) of diabetes cases worldwide (1, 7).

Over the years, several studies have highlighted the complex bidirectional relationship between DM, Health-Related Quality of Life (HRQoL) and mental health, indicating the importance of all three areas interacting together (78, 79, 89). Evidence has also accumulated regarding the importance of HRQoL and mental health aspects in managing patients with diabetes. This includes identifying the predictors related to worse HRQoL and mental health aspects among patients with T2DM (82, 148). HRQoL becomes worse when associated with T2DM-related complications and their comorbidities, which can be prevented by early

detection as well as changes in lifestyle (1, 7, 148, 274, 275). Currently, there are very few published studies on HRQoL in people with diabetes in the Saudi population, specifically in those with T2DM-related complications (89-91, 274, 276).

Therefore, the current study is the first of its kind that specifically aims to bridge the gap in the available research by assessing the impact of HRQoL and mental health aspects in patients with T2DM-related complications compared to those without T2DM-related complications. It will also identify the variables that correlate with increasing this risk among a defined population at Jeddah city, the second-largest city of Saudi Arabia with a population of 3.4 million (255).

4.3 Methods

4.3.1 Study design and participants

A cross-sectional study was carried out between 1st September to 31st December 2022 on 182 individuals with T2DM attending the outpatients' primary diabetes care clinic at King Abdulaziz University Medical Services Center (KAUMS) and King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia. Patients aged ≥ 18 years who were diagnosed with T2DM and consented to participate were included.

All patients were approached by their treating doctors and were invited voluntarily to participate in the study after the study purpose and aims were explained. Patients were then first interviewed by a trained health professional in a quiet side room, which was located beside the doctors-clinic. Data was then collected by a face-to-face interviewer setting using a predesigned form that included demographic details, various sociodemographic, clinical characteristics, disease characteristics, associated comorbidities, treatment modalities,

participants' awareness about T2DM, T2DM-related complications and related variables. The diagnosis of T2DM and patient complications were ascertained from the patients and confirmed by reviewing their medical record files. The interviewer filled out the predesigned form to help with accuracy. At the same time, the questionnaire was self-administered and filled out by the patient, who was assisted by the interviewer if required. This was followed by participants' responses to questions from the Arabic version of the 12-item Short Form Health Survey Version 2 (SF-12v2) interviewer administered questionnaire which was used as the instrument to assess the influences of T2DM on HRQoL and mental health for this study.

The SF-12v2, a known HRQoL-validated questionnaire consisting of 12 questions measuring eight health domains to assess physical and mental health was used in this study (87, 277). The Physical health-related domains include General Health (GH), i.e., overall health status (excellent, very good, good, fair, or poor), Physical Functioning (PF); i.e., moderate activities such as climbing several flights of stairs or moving a table, Role Physical (RP); i.e., accomplished less than usual or limitation in any kind of work and Body Pain (BP); i.e., pain interfered with regular work. Mental health-related scales include Vitality (VT), i.e., having a lot of energy; Social Functioning (SF), i.e., frequency that health problems interfered with social activities; Role Emotional (RE), i.e., did work or other activities less carefully than usual and Mental Health (MH); i.e., felt calm and peaceful or downhearted and depressed. The instrument has been validated across several chronic diseases and conditions, including numerous studies on people living with T2DM (277, 278).

Since the research in this chapter is primarily aimed to measure the influences of T2DM on HRQoL and mental health aspects of people with T2DM, with and without T2DM-related complications, the translated Arabic 12-item Short Form Version 2 (SF-12v2) questionnaire

was used. This consistent of HRQoL and mental health components, including the Mental Component Summary (MCS) and the Physical Component Summary (PCS) scores. This was based on findings from the recently published systematic review by our research group (87). This will avoid disturbing procedures of clinical care offered to patients since it is brief and can be completed in a much shorter time span than other tools, including the SF-36 summary scores questionnaire, without substantial loss of information (245, 279). In addition, based on a United States general population sample, the SF-12v2 implements a linear *T*-score and *z*-score transformation approach to produce scores for each health domain scale and component summary measures with a mean or benchmark of 50 and a standard deviation of 10. Thus, scores above (towards better health) and below (towards worse health) 50 are considered above and below the general population average according to the user's manual for the SF-12v2 health survey, third edition (280).

4.3.2 Patients' variables

BMI was calculated by the researcher by using the documented measured height and weight that was recorded by a qualified nurse in the clinic. In addition, blood pressure was measured continuously at each visit. A recent (less than 6 month) documented HbA1c was also taken. Participants were divided into non-Saudis who were born outside Saudi Arabia and lived in Saudi Arabia, while Saudis who were born in Saudi Arabia. Other variables included age, which was classified as ≤ 45 years and older than 45 years. BMI was calculated as weight (kg) / [height (m)]^2 and then stratified as healthy at 24.9 kg/m^2, people living with overweight from 25 kg/m^2 to 29.9 kg/m^2, and people living with obesity at 30 kg/m^2. Finally, based on Centers for Disease Control and Prevention (CDC) standards, HbA1c was classified as ≤ 6.4% for normal, 6.5% to 7.9% for well-managed and ≥ 8% for poorly controlled (257-259).

4.3.3 Data entry and statistical analysis

Descriptive and analytical statistics were used to compare variables. Non-parametric continuous variables were presented as the median with interquartile range (IQR), defined as the 25th to 75th percentile to the associated variables in the whole group as well as in both sub-groups, with and without diabetes complications, including the perspectives of patients to their HRQoL and mental health components. Binary logistic regression was performed for the multivariable analysis for possible risk factors and on the SF-12v2 scores for all patients with T2DM to help predict the risk of developing complications. All data are presented as odds ratio (OR) with their corresponding 95% confidence interval (CI). All participant mental health and HRQoL responses were entered into the QualityMetric Incorporated scoring software (PRO CoRE; License Agreement no. QM059531) and other variables were extracted into Microsoft Excel. All analyses were performed using SPSS version 28 (IBM SPSS Statistics for Windows, Armonk, NY, USA) software. All tests were two-tailed and a P-value < 0.05 was considered to be statistically significant.

4.4 Results

4.4.1 Scio-demographic characteristics of participants

In this study, the median age of all enrolled patients (n= 182) was 56 years (IQR: 48-64). Almost two-thirds (67%) were males, the vast majority (96.1%) were married and 57.6% were Saudi nationals. More than two-thirds of patients were educated (69.2%), half were employed (54.4%) and 41.2% had a monthly income of 3,000-5,999 Australian Dollars (AUD). Around half of the studied patients (51.1%) were living with obesity (≥ 30 kg/m^2), HbA1c level was ≥ 6.5% in 77% of patients, 66.5% had T2DM for more than five years and 90.1% had a family history of T2DM. Associated hypertension was reported in 60.4% of all studied patients, high

cholesterol in 69.7%, and 68.1% were smokers. Almost half of all patients were recruited from the primary care centre affiliated with KAU and the remaining were from the tertiary care university hospital (KAUH), 53.2% versus 46.7%. Overall, 50 patients (27.4%) gave a history of previous hospitalisation (Table 4.1).

4.4.2 Participants' awareness about T2DM

Most patients (95.6%) claimed they were knowledgeable about T2DM. In total, 83.5% declared that they regularly attend follow-up care appointments and 90.1% reported their commitment to treatment. However, only 19.2% indicated having regular dietitians' care, 4.4% indicated the importance of mental health support and only 32.45% believed that mental health is affected by T2DM and its related complications (Table 4.1).

Table 4.1. Demographic characteristics of patients with T2DM with the SF-12v2 main components and all health domains score and the univariate analysis

		Without complications (n = 73, 40.1%)			With complications (n = 109, 59.9%)			Overall (n = 182)			
Risk factors		N	%	Median (IQR)	N	%	Median (IQR)	N	%	Median (IQR)	P value
Gender	Male	54	74		68	62.4		122	67		0.103
	Female	19	26		41	37.6		60	32.9		
Age, years				52 (44-59)			61 (53-67)			56 (48-64)	
	≤ 45	21	28.8		16	14.7		37	20.3	41 (36-43)	0.021
	> 45	52	71.2		93	85.3		145	79.6	61 (53-66.5)	
Marital status											
	Unmarried	2	2.7		5	4.6		7	3.8		0.525
	Married	71	97.3		104	95.4		175	96.1		
Nationality											
	Non-Saudi	30	41.1		47	43.1		77	42.3		0.787
	Saudi	43	58.9		62	56.9		105	57.6		
Education status											
	Uneducated	9	12.3		47	43.1		56	30.7		<0.001
	Educated	64	87.7		62	56.9		126	69.2		
Employment status											<0.001
	Unemployed	15	20.5		68	62.4		83	45.6		

	Employed	58	79.5	41	37.6	99	54.4		
Monthly income, AUD	≤ 1,499	7	9.6	30	27.5	37	20.3		
	1,500-2,999	7	9.6	23	21.1	30	16.4		<0.001
	3,000-5,999	39	53.4	36	33	75	41.2		
	≥ 6,000	20	27.4	20	18.3	40	21.9		
BMI, kg^2			30 (26.3-31.8)		29.3 (25.3-32)			29.6 (25.9-32)	
	≤ 24.9	8	11	20	18.7	28	15.3	23.6 (21.4-24.2)	0.398
	25-29.9	26	35.6	35	30.8	61	33.5	27.2 (25.9-28.2)	
	≥ 30	39	53.4	54	50.5	93	51.1	31.9 (30.5-35.1)	
HbA1c, %			6.8 (6-7.1)		7.2 (6.8-8.3)			7 (6.5-8)	
	≤ 6.4	26	35.6	16	14.7	42	23	5.7 (5.5-6.1)	<0.001
	6.5-7.9	36	49.3	52	47.7	88	48.3	7 (6.8-7.1)	
	≥ 8	11	15.1	41	37.6	52	28.5	9 (8.1-10)	
Family history of T2DM	No	9	12.3	9	8.3	18	9.8		0.367
	Yes	64	87.7	100	91.7	164	90.1		
Duration of T2DM, years			6 (3-10)		12 (6-23)			9 (4.7-18)	
	≤ 5	36	49.3	25	22.9	61	33.5	3 (2-5)	<0.001
	5-10	25	34.2	26	23.9	51	28	8 (7-10)	
	> 10	12	16.4	58	53.2	70	38.4	20 (15-30)	

Type of management							
Healthy lifestyle only	0	0	2	1.8	2	1.1	
Healthy lifestyle and oral medication	42	57.5	38	34.9	80	43.9	
Healthy lifestyle and insulin	10	13.7	16	14.7	26	14.2	0.015
Oral medication only	8	11	13	11.9	21	11.5	
Insulin only	12	16.4	24	22	36	19.7	
Oral medication and insulin	0	0	10	9.2	10	5.4	
All	1	1.4	6	5.5	7	3.8	
High blood pressure							
No	36	49.3	36	33	72	39.5	0.028
Yes	37	50.7	73	67	110	60.4	
High cholesterol							
No	39	53.4	16	14.7	55	30.2	<0.001
Yes	34	46.6	93	85.3	127	69.7	
Smoking history							
No	53	72.6	71	65.1	124	68.1	0.289

	Yes	20	27.4	38	34.9	58	31.8	
Regularly follow-up with a physician								
	No	0	0	9	8.3	9	4.9	0.017
	Sometimes	6	8.2	15	13.8	21	11.5	
	Yes	67	91.8	85	78	152	83.5	
Enough treatment knowledge								
	No	0	0	4	3.7	4	2.2	0.204
	Sometimes	1	1.4	3	2.8	4	2.2	
	Yes	72	98.6	102	93.6	174	95.6	
Persistent on treatment								
	No	1	1.4	7	6.4	8	4.4	0.006
	Sometimes	0	0	10	9.2	10	5.4	
	Yes	72	98.6	92	84.4	164	90.1	
Regularly follow-up with a dietician								
	No	24	32.9	56	51.4	80	43.9	0.013
	Sometimes	36	49.3	31	28.4	67	36.8	
	Yes	13	17.8	22	20.2	35	19.2	
Nearby physician clinic								
	No	0	0	3	2.8	3	1.6	0.153
	Sometimes	0	0	0	0	0	0	
	Yes	73	100	106	97.2	179	98.35	

Needs of Mental health support									
	No	59	80.8	78	71.6	137	75.2		0.051
	Sometimes	14	19.2	23	21.1	37	20.3		
	Yes	0	0	8	7.3	8	4.4		
Mental health affected by T2DM and its complications									
	No	34	46.6	36	33	70	38.4		<0.001
	Sometimes	29	39.7	24	22	53	29.1		
	Yes	10	13.7	49	45	59	32.4		
Admit to the hospital (last year)									
	No	69	94.5	63	57.8	132	72.5		<0.001
	Yes	4	5.5	46	42.2	50	27.4		
Type of centre									
	Primary healthcare	51	69.9	46	42.2	97	53.2		<0.001
	Tertiary healthcare	22	30.1	63	57.8	85	46.7		
MCS			54.4 (50.9-57.2)		50.9 (43.8-54.4)			52.3 (48-55.5)	
	Above average	57	78.1	61	56	118	64.8	54.7 (52.5-57.5)	0.002
	Below average	16	21.9	48	44	64	35.1	45.9 (37.4-48.7)	
PCS			52 (46-57.1)		44.3 (41.5-48.5)			46.3 (42.9-54.1)	
	Above average	39	53.4	23	21.1	62	34	56.5 (54-58.6)	<0.001
	Below average	34	46.6	86	78.9	120	65.9	43.8 (41.2-46.2)	

MH			52.7 (52.7-58.4)			52.7 (47-52.7)			52.7 (52.7-54.1)	
	Above average	68	93.2	70	64.2		138	75.8	52.7 (52.7-58.4)	<0.001
	Below average	5	6.8	39	35.8		44	24.1	41.2 (36.9-47)	
RE			45.8 (45.8-56.2)			45.8 (35.4-45.8)			45.8 (40.6-45.8)	
	Above average	32	43.8	12	11		44	24.1	56.2 (51-56.2)	<0.001
	Below average	41	56.2	97	89		138	75.8	45.8 (35.4-45.8)	
SF			48 (48-56.9)			48 (39.1-48)			48 (48-56.9)	
	Above average	30	41.1	21	19.3		51	28	56.9 (56.9-56.9)	0.001
	Below average	43	58.9	88	80.7		131	71.9	48 (39.1-48)	
VT			58 (58.9-58.9)			58.9 (49-58.9)			58.9 (58.9-58.9)	
	Above average	68	93.2	70	64.2		138	75.8	58.9 (58.9-58.9)	<0.001
	Below average	5	6.8	39	35.8		44	24.1	49 (39.2-49)	
GH			57.6 (57.6-63.6)			57.6 (47.7-57.6)			57.6 (57.6-63.6)	
	Above average	67	91.8	73	67		140	76.9	57.6 (57.6-63.6)	<0.001
	Below average	6	8.2	36	33		42	23	47.7 (47.7-47.7)	
BP			57.7 (48.7-57.7)			39.6 (30.6-48.7)			48.7 (30.6-57.7)	
	Above average	46	63	24	22		70	38.4	57.7 (57.7-57.7)	<0.001
	Below average	27	37	85	78		112	61.5	39.6 (30.6-48.7)	
PF			49.1 (33.4-57)			41.3 (41.3-49.1)			41.3 (41.3-57)	
	Above average	34	46.6	26	23.9		60	32.9	57 (57-57)	0.001
	Below average	39	53.4	83	76.1		122	67	41.3 (33.4-41.3)	

RP			49 (49-57.4)		44.7 (40.5-49)			49 (40.5-53.2)	
	Above average	34	46.6	16	14.7	50	27.4	57.4 (53.2-57.4)	<0.001
	Below average	39	53.4	93	85.3	132	72.5	44.7 (40.5-49)	

T2DM, type 2 diabetes mellitus; SF-12v2, the 12-item short form health survey version 2; IQR, interquartile range; SD, standard deviation; BMI, body mass index; HbA1c, glycosylated haemoglobin test; AUD, Australian dollar; MCS, mental component summary; PCS, physical component summary; MH, mental health; RE, role emotional; SF, social functioning; VT, vitality; GH, general health; BP, bodily pain; PF, physical functioning; RP, role physical.

4.4.3 Variables associated with T2DM-related complications

In the univariate analysis, three of the studied socioeconomic factors were significantly associated with T2DM-related complications. This included a lack of education, unemployment and low monthly income. Poor control of T2DM as demonstrated by higher HbA1c levels, longer duration of T2DM, poor compliance to treatment plan and history of previous hospitalisation were significantly associated with the development of complications (Table 4.2). Among the investigated comorbid conditions, only high cholesterol level was significantly (P <0.001) related to complications (n=93; 85.3%) (Table 4.1 and 4.2). More patients with high blood pressure were noted in the complications compared to the uncomplicated group (67% versus 46.6%, P=0.028), as reflected in Tables 4.1 and 4.2. Additionally, a significant association with T2DM-related complications (P<0.001) was noted in those patients who gave a history of previous admission to hospitals and/or had been treated in hospitals and in those who were not aware of the impact of T2DM on their mental health (Table 4.2).

However, after controlling for all other variables, multivariable analysis of possible risk factors for all T2DM patients that predict the risk for the development of T2DM-related complications showed that; female gender (AOR=9.40; 95% CI:1.70-51.83; P=0.010), monthly income 1,500 to 2,999 AUD (AOR=49.17; 95% CI:2.34-1033.20; P=0.012), poorly controlled HbA1c (AOR=9.89; 95% CI: 1.71-57.22; P=0.010), high cholesterol (AOR=8.74; 95% CI:1.79-42.53; P=0.007) and long T2DM duration (AOR=8.82; 95% CI:1.42-54.78; P=0.019) increase the risk of T2DM-related complications (Table 4.2).

Table 4.2. Univariate and multivariable analysis of possible risk factors for all T2DM patients predicting the risk for the development complications

		95% C.I. for OR				95% C.I. for OR		
Risk factor	Unadjusted OR	Lower	Upper	P value	Adjusted OR	Lower	Upper	P value
Female	1.71	0.89	3.28	0.105	9.40	1.70	51.83	0.010
Age, > 45 years	2.34	1.12	4.88	0.023	1.08	0.20	5.79	0.928
Marital status, married	-0.58	0.11	3.10	0.530	-0.23	0.00	67.80	0.618
Nationality, Saudi	-0.92	0.50	1.67	0.787	-0.10	0.01	0.55	0.009
Education status, educated	-0.18	0.08	0.41	<0.001	-0.41	0.05	3.50	0.421
Employment status, employed	-0.15	0.07	0.31	<0.001	-0.41	0.06	2.84	0.372
Monthly income, AUD, ≤ 1,499				0.002				0.076
1,500-2,999	-0.76	0.23	2.49	0.659	49.17	2.34	1033.20	0.012
3,000-5,999	-0.21	0.08	0.55	0.001	8.85	0.51	152.60	0.133
≥ 6,000	-0.23	0.08	0.65	0.006	3.22	0.15	68.93	0.453
BMI, kg^2, ≤ 24.9				0.406				0.900

25-29.9	-0.53	0.20	1.41	0.208	1.31	0.23	7.43	0.757
≥ 30	-0.55	0.22	1.38	0.207	1.51	0.25	9.05	0.647
HbA1c, %, ≤ 6.4				0.001				0.026
6.5-7.9	2.34	1.10	4.98	0.027	9.89	1.71	57.22	0.010
≥ 8	6.05	2.43	15.06	<0.001	10.32	1.31	80.81	0.026
Family history of T2DM, yes	1.56	0.58	4.14	0.370	-0.89	0.13	6.02	0.910
Duration of T2DM, years, ≤ 5				<0.001				0.038
5-10	1.49	0.70	3.16	0.291	4.52	1.02	20.01	0.047
> 10	6.96	3.11	15.55	<0.001	8.82	1.42	54.78	0.019
Healthy lifestyle with oral medication vs. with insulin	1.76	0.71	4.36	0.216	2.30	0.17	30.86	0.529
Oral medication vs. insulin	1.23	0.40	3.77	0.716	-	-	-	-
High blood pressure, yes	1.97	1.07	3.62	0.029	-0.24	0.05	0.99	0.050
High cholesterol, yes	6.66	3.30	13.45	<0.001	8.74	1.79	42.53	0.007
Smoking history, yes	1.41	0.74	2.71	0.290	2.10	0.40	10.93	0.374

Admit to the hospital (last year), yes	12.59	4.28	36.98	<0.001	10.94	0.74	160.54	0.081
Type of centre, tertiary healthcare	3.17	1.69	5.94	<0.001	-0.98	0.06	14.61	0.989

T2DM, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycosylated haemoglobin test; AUD, Australian dollar.

4.4.4 SF-12v2 questionnaire scores associated with T2DM-related complications

Overall, the median of the MCS score and PCS score among the ones with T2DM-related complications were 50.9 (IQR: 43.8-54.4) and 44.3 (IQR: 41.5-48.5), respectively, compared to 54.4 (IQR: 50.9-57.2) and 52 (IQR: 46-57.1) respectively in the subgroup without T2DM-related complications. However, both the MCS and PCS scores were significantly lower in the ones with T2DM-related complications (P=0.002 and P<0.001). Similarly, all of the components, including mental health, role emotional, social functioning, vitality, general health, bodily pain, physical functioning and role physical scores, were significantly lower in those with T2DM-related complications (Table 4.1). In univariate analysis, all SF-12v2 summary components and health domains had below-average scores and were statistically significantly associated with an increased risk of T2DM-related complications. The multivariable analysis showed that below-average PCS (AOR=5; 95% CI:2.49-10.01; P<0.001), MCS (AOR=3.44; 95% CI:1.65-7.18; P<0.001), and RE (AOR=2.69; 95% CI: 1.05-6.90; P=0.039) have increased the risk of T2DM-related complications (Table 4.3).

4.4.5 T2DM-related complications associated with SF-12v2 summary component score

There was a significant influence of the T2DM-related complications on the MCS (OR=2.80; 95% CI:1.433-5.48; P=0.003) and PCS (OR=4.28; 95% CI:2.23-8.22; P<0.001) compared to without complications, but in regards to having more than one T2DM-related complication compared to only one complication, it was shown that only PCS (OR=3.95; 95% CI:1.34-11.60; P=0.012) was statistically significant influenced by T2DM-related complications (Table 4.4).

Table 4.3. Univariate and multivariable analysis of below average SF-12v2 scores for all T2DM patients predicting the risk for the development complications

		95% C.I. for OR				95% C.I. for OR		
SF-12v2 score	Unadjusted OR	Lower	Upper	P value	Adjusted OR	Lower	Upper	P value
MCS	2.80	1.43	5.48	0.003	3.44	1.65	7.18	<0.001
PCS	4.28	2.23	8.22	<0.001	5.00	2.49	10.00	<0.001
MH	7.57	2.81	20.37	<0.001	2.47	0.71	8.50	0.151
RE	6.30	2.95	13.45	<0.001	2.69	1.05	6.90	0.039
SF	2.92	1.50	5.69	0.002	1.49	0.64	3.48	0.347
V	7.57	2.81	20.37	<0.001	3.26	0.90	11.77	0.071
GH	5.50	2.18	13.89	<0.001	1.80	0.57	5.64	0.309
BP	6.03	3.12	11.63	<0.001	1.37	0.55	3.38	0.487
PF	2.78	1.47	5.26	0.002	2.32	0.97	5.56	0.057
RP	5.06	2.51	10.22	<0.001	1.98	0.82	4.80	0.128

T2DM, type 2 diabetes mellitus; SF-12v2, the 12-item short form health survey version 2; MCS, mental component summary; PCS, physical component summary; MH, mental health; RE, role emotional; SF, social functioning; VT, vitality; GH, general health; BP, bodily pain; PF, physical functioning; RP, role physical.

Table 4.4. Univariate analysis of having complications for all T2DM patients predicting the risk for development below average SF-12v2 scores

	Unadjusted OR	95% C.I. for OR				95% C.I. for OR		
Risk factor	MCS	Lower	Upper	P value	Unadjusted OR PCS	Lower	Upper	P value
Complication, yes	2.80	1.43	5.48	0.003	4.28	2.23	8.22	<0.001
Single vs multiple complications	1.56	0.73	3.35	0.249	3.95	1.34	11.60	0.012

T2DM, type 2 diabetes mellitus; SF-12v2, the 12-item short form health survey version 2; MCS, mental component summary; PCS, physical component summary.

4.4.6 T2DM-related complications pattern among participants

Around six out of ten enrolled patients reported having T2DM-related complications (59.9%) versus (40.1%) without complications (Table 4.1). The most common complication reported among the studied group was neuropathy, followed by retinopathy, cardiovascular diseases and diabetic foot disorders in 38.5%, 12.8%, 1.8% and 0.9% of patients, respectively. Multiple complications were reported more with retinopathy, neuropathy and foot disorders in 15.6% of patients, followed by retinopathy and neuropathy in 12.8% and retinopathy, neuropathy and nephropathy in 10.1% (Figure 4.1).

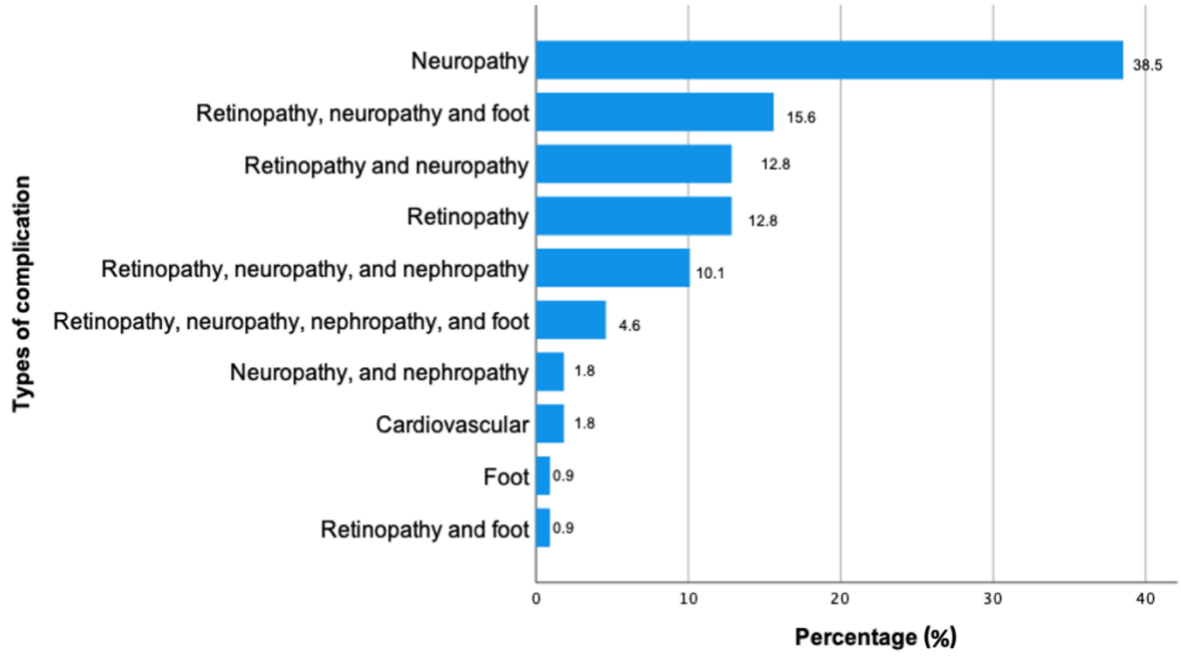


Figure 4.1. Types of T2DM-related complications

4.5 Discussion

Studies that addressed the correlations between T2DM and its related complications on HRQoL and mental health aspects are limited in numbers and heterogeneous in nature. Despite this, there is overwhelming evidence that lifestyle changes can help prevent T2DM-

related complications and the long-term benefits for the management of T2DM, as well as improving HRQoL and mental health aspects of people with T2DM (78, 79, 148, 150, 275).

In this study, almost six out of ten enrolled patients reported T2DM-related complications (59.9%) versus (40.1%) without complications. This percentage of complications lies in the middle of previous studies that reported a 72.6% percentage of complications among patients of a similar cross-sectional study conducted in five Primary Health Care (PHC) centres in the Al-Khobar area in Saudi Arabia (274). Another study conducted in the southern region of Saudi Arabia in patients with T2DM reported a 39.2% complication rate (276). The wide range of complication rates between studies highlights the heterogenicity in the studied populations' characteristics and the different methodologies used by investigators, which may explain some of the discrepancies between previous studies across the world, including Saudi Arabia. For example, in the latter Saudi study, 40% of their enrolled patients were recently diagnosed with DM (less than one year ago), whereas 66.5% of the participants in this cross-sectional survey had T2DM for more than five years and the median duration of T2DM was nine years (4.7-18) (276) (Table 4.1).

The most common complication reported in this study was diabetic neuropathy in 38.5% of the studied group. This is similar to the magnitude reported in a recent systematic review and meta-analysis that showed a high percentage of patients with diabetic neuropathy (39%) (281). This is also similar to another cross-sectional Saudi study that showed a rate of 44.1% with neuropathy (282). Other complications were less common, including retinopathy, cardiovascular diseases and diabetic foot disorders (Figure 4.1).

4.5.1 Variables associated with T2DM-related complications

Among the studied socioeconomic variables that correlate with T2DM-related complications, this study found that a lack of education, unemployment and low monthly income were significantly associated with having T2DM-related complications (Table 4.3). These findings coincide with other previous studies (89, 274). Similarly, poor control of T2DM as demonstrated by higher HbA1c levels, longer duration of T2DM, poor compliance to treatment plans and history of previous hospitalisation were significantly associated with the development of complications (276, 283).

Among the investigated comorbid conditions, high cholesterol level was the only significant ($P<0.001$) variable associated with complications in 85.3% of the patients. In this cross-sectional study, more patients with high blood pressure were noted in the complications group (67%) compared to (46.6%) in the non-complicated group; however, this was not found to be significant ($P=0.028$) (Table 4.3). These percentages are comparable to those reported in a large Japanese study that reviewed the electronic medical records of 10,151 patients with T2DM (261). This study found that dyslipidaemia (84.7%) and hypertension (75.1%) were the most prevalent comorbid conditions among Japanese patients with T2DM in a real-world setting (261). Another large retrospective study that reviewed 1,389,016 eligible patients with T2DM in the USA using the Quintiles Electronic Medical Record database demonstrated that the vast majority of patients (97.5%) had at least one comorbid condition and 88.5% had at least two (283). These results indicate the need for a comprehensive approach to patient management.

Additionally, a significant association with T2DM-related complications was noted in those patients who had a history of previous admission to hospitals and/or had been treated in

hospitals (Table 4.3). This highlights the need for high demand for hospital services due to T2DM-related complications (especially macrovascular complications) (273). This is further emphasised in a recent Australian study stating the importance of preventing and properly managing T2DM-related complications (273).

A significant association with T2DM-related complications was also noted in those who were not aware of the negative impacts of T2DM on their mental health (Table 4.3). Concerns about the low self-awareness and poor knowledge about various negative impacts on T2DM control and consequently on different aspects of patient health among people with T2DM were recently raised in a few Saudi studies (272, 284, 285). A recent systematic review highlighted the need for increased knowledge and awareness among patients with diabetes in the Saudi Arabia population by integrating patients' education into existing healthcare systems and processes (286). This will better inform patients, families and communities about this pandemic chronic non-communicable disease (286).

The univariate and multivariable analysis in this chapter identified possible risk factors that may predict the risk for the development of T2DM-related complications (this included low monthly income, poorly controlled HbA1c, female gender, high cholesterol and long T2DM duration). These results were found to be similar in several other previous studies in Saudi Arabia and elsewhere (89-91, 93, 96, 268, 274-276) (Tables 4.3 and 4.4). Again, direct comparisons between studies have not been feasible due to the vast differences in methodological designs, sample size, heterogeneity and populations used.

In a world that faces severe economic crises in both high- and low-income countries, it is not surprising that low-income patients have negative impacts on all aspects of health, including mental health and access to care of patients with some non-communicable diseases including

T2DM (287). Results from this chapter show that, a low monthly income of T2DM patients (1,500-2,999 AUD) was at the top of the list of all risk factors that predict the risk of T2DM-related complications. Interestingly, findings reflect that the impact of low monthly income on complications was harsher than the one reported in a similar study from Lebanon, an Arab low income country, as the OR was 3.4, much lower than what was identified by this research (288).

4.5.2 SF-12v2 questionnaire scores associated with T2DM-related complications

The median MCS and PCS score among patients with T2DM-related complications were 50.9 (IQR: 43.8-54.4) and 44.3 (IQR: 41.5-48.5) respectively, compared to 54.4 (IQR: 50.9-57.2) and 52 (IQR: 46-57.1) in the subgroup without T2DM-related complications. The MCS and PCS scores were significantly lower in patients with T2DM-related complications (Table 4.2). The PCS score was worse than the MCS score among all patients with T2DM. This finding is similar in both those with and without T2DM-related complications. The relatively better MCS score may be attributed to other influencing factors in the local culture, such as religiosity, that positively influenced HRQoL in some populations, which is also highlighted in other studies in Saudi Arabia and Malaysia (106, 289).

Overall, results from this chapter supports the findings of previous work from various regions of Saudi Arabia, the GCC and other MENA countries, as well as the rest of the world, as it shows that T2DM impairs the overall HRQoL and mental health aspects of patients living with T2DM and that the level of impairment may not be the same across studies due to the discrepancies and huge heterogenicity among cohorts (78, 79, 82, 89-91, 93, 94, 96, 102, 148, 150, 274-278, 290-292). Therefore, it may be hard to discuss all the studies and to compare their results and/or generalise their findings without taking into consideration all the

contributing variables. This includes socio-demographics of the studies' populations, including local communities in countries with different populations ethnic, social, economic and cultural backgrounds, as well as the different designs/settings/methodologies of the studies, diverse HRQoL measurements tools used and various aspects of QoL covered. However, the predictors of HRQoL among patients with T2DM in Saudi Arabia were similar to those in other countries around the world, indicating that patients with T2DM share several standard features (292). Collectively, research from this chapter share concerns with other investigators about major methodological and reporting flaws among previous studies that may limit the validity and generalisability of their findings (152).

Yet, findings from this cross-sectional study shows that the worse impact is associated with T2DM-related complications when both the MCS and PCS scores were lower than the average, as well as all of the health domain scores, which concur with other studies from Saudi Arabia and adjacent GCC countries with similar backgrounds. For example, a study from the United Arab Emirates demonstrated that HRQoL in Emirati patients with diabetes was significantly associated with the presence of diabetes-related complications, glycaemic control, and age of the patient (Tables 4.2, 4.3, and 4.4) (92). These findings highlight the need for more multidimensional and multisectoral research to strengthen the evidence base and accumulate more accurate knowledge on the negative influences of T2DM on HRQoL. This will help confront the epidemic of T2DM in Saudi Arabia and across the world, particularly in countries that already report the highest prevalence rates of T2DM and its complications in countries such as Saudi Arabia and its adjacent GCC countries (284).

4.5.3 Strengths and limitations

This study is among the few to explore the prevalence and types of T2DM-related complications in Saudi Arabia. In addition, it was possible to correlate risk factors with these complications and measure the impact of T2DM on HRQoL and mental health aspects among people with T2DM, specifically those with T2DM-related complications. This was performed using the QoL and mental health components, including the MCS and the PCS scores. Another strength is the use of the SF-12v2 as a research instrument, which was self-administered and filled by the patient who was assisted by the interviewer occasionally, whenever needed.

Limitations included the cross-sectional study design and relatively small sample size, which limited the number of T2DM patients from two outpatient healthcare centres in one city of Saudi Arabia, Jeddah. However, this limitation is applied to most of the available studies carried out in Saudi Arabia (284). Secondly, the study sample was convenient and therefore it was not possible to determine the response rate among the studied population, which may have resulted in nonresponse bias.

4.6 Conclusions

In conclusion, results from this study showed that almost six out of ten of the enrolled patients reported having T2DM-related complications, with diabetic neuropathy being the most common. Possible risk factors to predict the development of T2DM-related complications were female gender, low monthly income, poorly controlled HbA1c, high cholesterol and long T2DM duration. Findings also showed that MCS and PCS scores were significantly lower in those patients with T2DM-related complications across all the MCS and PCS components.

Future country-wide Saudi studies are recommended to assess the magnitude of T2DM-related complications and measure the influences of T2DM on HRQoL and mental health among all people with T2DM, specifically those with T2DM-related complications. Results of such studies will hopefully reflect positively on guiding better individualised interventions that target both T2DM care, HRQoL and mental health aspects among all patients with T2DM, with and without complications.

Chapter 5. Physicians' perspectives on health-related quality of life and mental health aspects of people with type 2 diabetes mellitus: a cross-sectional study in Jeddah, Saudi Arabia

5.1 Abstract

Aims: To explore the physicians' knowledge, awareness and perspectives on Health-Related Quality of Life (HRQoL) and mental health aspects of people with Type 2 Diabetes Mellitus (T2DM) in Jeddah, Saudi Arabia.

Methods: A cross-sectional survey study was conducted over a three-month period (October to December 2022) on 54 physicians. Physicians were requested to respond to a 12-item researcher designed, self-administered survey questionnaire that explored their perspectives regarding the importance of their patients' general, physical and mental health aspects using the 12-item Short Form Health Survey Version 2 (SF-12v2).

Results: Overall, 85.2% of physicians were male, with almost two-thirds (64.8%) practising in one medical and more than two-thirds (35%.2%) in the surgical specialties. Most physicians (57.4%) were consultants, which was also reflected in both subgroup specialties (54.3% versus 63.2%, respectively). The majority of physicians (83.3%) asked their patients about their general health; however, only 18.5% responded positively to questions about emotional problems. There was a low positive response to questions relating to the emotional component, such as feeling "calm and peaceful" (38.9%) and "feeling a lot of energy" (35.2%). This was even lower (25.9%) for questions related to mental health.

Conclusions: This study indicates the need for future well-designed, multidimensional, and multisectoral research studies that will help broaden knowledge about the magnitude of the current problem. This may improve overall general, physical and mental health by enhancing patient level of care, adherence to health care plans and reducing long-term complications.

5.2 Introduction

Diabetes mellitus (DM) is the most chronic metabolic disorder and one of the fastest-growing global health emergencies of the 21st century; it has reached alarming levels and Type 2 Diabetes Mellitus (T2DM) accounts for the vast majority (over 90%) of DM cases worldwide and is usually associated with high mortality, morbidity, poor general health, as well as low levels of Health-Related Quality of Life (HRQoL) and mental health (1).

A complex bidirectional relationship between T2DM, HRQoL, and mental health has already been addressed in previous studies, indicating that the three of them interact and influence each other (78, 79, 88). Evidence has also accumulated about the importance of evaluating HRQoL and mental health aspects in the day-to-day management of patients with diabetes, including early identification of predictors that relate to worse HRQoL and mental health aspects among all patients with T2DM, specifically those patients with T2DM-related complications (82, 89). The evidence also indicated that lifestyle changes can help prevent complications and improve the overall long-term management of T2DM (93, 148).

However, a smaller number of studies explored the knowledge, awareness, practices and perspectives of physicians and/or other healthcare providers regarding the overall management of their patients with T2DM (293-295). In contrast, very few studies explored physicians' perspectives regarding their patients' HRQoL and mental health, as well as the challenges and difficulties they meet during the regular healthcare of their patients with T2DM (296, 297).

This present study aimed to explore the physicians' knowledge, awareness and perspectives on their patients' HRQoL and mental health aspects among people with T2DM in Jeddah, Saudi Arabia.

5.3 Methods

5.3.1 Study design and participants

A cross-sectional survey was carried out over a three-month period (October to December 2022) on a convenient sample of 54 physicians in Jeddah, the second-largest city in Saudi Arabia. Physicians were recruited using the snowball sampling method (a recruitment technique in which research participants are asked to assist researchers in identifying other potential subjects) to explore their knowledge, awareness and perspectives on HRQoL and mental health aspects of people with T2DM. All enrolled physicians practising in a public and/or private healthcare hospital in Jeddah that provided healthcare to patients diagnosed with T2DM from all medical, surgical specialties/subspecialties and family medicine physicians were eligible and invited to participate. Only physicians who speak English, licensed specialists in Jeddah and regularly care for T2DM and/or T2DM-related complications as part of their regular practice were invited to participate to the current study.

5.3.2 Study procedures

At the beginning of the data collection processing, the researcher-designed and self-administered survey questionnaire was piloted and tested on a subsample of participants to ensure effectiveness, clarity, and accuracy of the questionnaire. After accepting the invitation of the principal investigator, physicians were sent an online link to their emails or phones that took them to an online page (through Microsoft Forms) that displayed a three-section form to be filled out by each participant. Participants were first asked to consent to join the study and then given personal identification data. They were then requested to provide a response to a researcher designed data collection form (through Microsoft Forms) regarding physicians' demographic characteristics, seniority level, length of experience per year, specialty,

workplace, size of clinical practice per hospital beds, average number of patients per week, percentage of patients who have most of their diabetes care in the physicians' practice place. In addition, physicians were asked to report their perceptions regarding encouraging patients to attend diabetic educational seminars, type of secondary healthcare support referral, how they base their decisions and types of used protocols/guidelines, types of challenges met in practice and their perspectives on preferable approaches to improve patients' mental health and quality of life.

Finally, participants were then requested to answer a 12-item researcher-designed, self-administered survey questionnaire that explored their perspectives regarding the importance of their patients' general, physical and mental health aspects. The questions were derived with modifications, from the well-known 12-item Short Form Health Survey Version 2 (SF-12v2) questionnaire that consists of 12 questions that measure eight health domains to assess physical and mental health (General Health (GH), Physical Functioning (PF), Role Physical (RP), Body Pain (BP), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH)).

In general, Questions (Q) from 1 to 5 and 8 are considered as related to the physical component and Q6, Q7, Q9, Q10, Q11, and Q12 are considered as related to the mental component in the survey (Table 5.3).

5.3.3 Data entry and statistical analysis

Data were extracted into Microsoft Excel, and all descriptive and analytical statistics were conducted using SPSS version 28 (IBM SPSS Statistics for Windows, Armonk, NY, USA) software. Non-parametric continuous variable was described as the median and Interquartile Range (IQR), defined as the 25^{th} to 75^{th} percentile to the associated variable.

5.4 Results

5.4.1 Physicians' demographic characteristics

In this study, the overall median age of physicians was 55 years (IQR: 51-59). The majority (85.2%) of the studied participants were males, who predominated in both the medical (82.9%) and surgical (89.5%) subgroups, respectively. Almost two-thirds of participants (64.8%) were practising in one of the medical specialties, whereas 35.1% were in the surgical specialties (Table 5.1).

5.4.2 Physicians' practice characteristics (seniority, experience, specialty, working place, practice volume)

Most participants were at the consultant level (57.4%), which was applied to both subgroups (54.3% and 63.2%), respectively. The majority (85.2%) had ≥ 5 years of field experience. The common specialties in the medical group were internal medicine (31.4%), followed by nephrology (14.3%) and endocrinology (11.4%), whereas the common surgical specialties were vascular surgery (68.4%), general surgery (21.1%) followed by podiatry (10.5%). Only, (11.4%) were practising family medicine or psychiatry. Half of all participants were working in the private sector and more than four-fifths (87%) were in hospitals with bed capacity of ≥ 100 beds. The vast majority (94.4%) of participants reviewed > 10 patients per week and claim that > 24.1% of their patients have most of their diabetes care in their practice place (Table 5.1).

Table 5.1. Physicians' demographic characteristics

		Medical (n=35)			Surgical (n=19)			Total (n=54)	
		N	%	Row %	N	%	Row %	N	%
Gender	Female	6	17.1	75	2	10.5	25	8	14.8
	Male	29	82.9	63	17	89.5	37	46	85.2
Level of seniority	Specialist	16	45.7	69.6	7	36.8	30.4	23	42.6
	Consultant	19	54.3	61.3	12	63.2	38.7	31	57.4
Length of experience per years	< 5	7	20	87.5	1	5.3	12.5	8	14.8
	5-10	5	14.3	55.6	4	21.1	44.4	9	16.7
	> 10	23	65.7	62.2	14	73.7	37.8	37	68.5
Specialty	Internal medicine	11	31.4	100		N/A		11	20.4
	General surgery		N/A		4	21.1	100	4	7.4
	Endocrinology	4	11.4	100				4	7.4
	Nephrology	5	14.3	100				5	9.3
	Neurology	4	11.4	100		N/A		4	7.4
	Ophthalmology	1	2.9	100				1	1.9
	Family medicine	4	11.4	100				4	7.4

	Podiatry		N/A		2	10.5	100	2	3.7
	Anaesthesia	2	5.7	100		N/A		2	3.7
	Psychiatry	4	11.4	100				4	7.4
	Vascular surgery		N/A		13	68.4	100	13	24.1
Type of workplace	Public hospital	7	20	41.2	10	52.6	58.8	17	31.5
	Private hospital	22	62.9	81.5	5	26.3	18.5	27	50
	Public and private hospital	6	17.1	60	4	21.1	40	10	18.5
Size of clinical practice per hospital beds	< 100	7	20	100	0	0	0	7	13
	100-500	22	62.9	75.9	7	36.8	24.1	29	53.7
	> 500	6	17.1	33.3	12	63.2	66.7	18	33.3
Average patients per week	5-10	1	2.9	33.3	2	10.5	66.7	3	5.6
	> 10	34	97.1	66.7	17	89.5	33.3	51	94.4
Percentage of patients have most of their diabetes care in physicians' practice place	< 30	4	11.4	66.7	2	10.5	33.3	6	11.1
	30-90	24	68.6	68.6	11	57.9	31.4	35	64.8
	> 90	7	20	53.8	6	31.6	46.2	13	24.1

5.4.3 Physicians' perspectives regarding patients' education, referral to mental health, protocols/guidelines, challenges met, suggestions for improving patients' mental health and HRQoL

When asked about their encouragement of patients to attend health educational seminars, only 18.5% answered "Yes" they do, whereas a higher percentage (59.3%) answered "No". With regards to referral to mental health care, only 51.9% of all participants claimed they do (more likely in medical than surgical specialties, 67.9% versus 32.1%, respectively). Almost two-thirds (66.7%) of participants answered "Yes" that they base their decision on protocols/guidelines, whereas the other third answered "sometimes" or "No" in 13% and 20.3%, respectively (Table 5.2).

International protocols/guidelines were used more than local ones (31.5% versus 5.6%) and the most common pattern is to base decisions of referral to other disciplines based on international and local protocols/guidelines (42.6%). Two-thirds of participants indicated that the main challenges they face in daily practice are limited time allocated for patients' visits and lack of resources. Finally, when asked about their perspectives on preferred approaches to improve patients' mental health and HRQoL, only 20.4% indicated the need for hospital-based support, 13% referred to psychiatrist and cognitive therapy, 11.1% community based support, 9.3% individualised support and almost half of participants indicated the need for all of the previous approaches (Table 5.2).

Table 5.2. Physicians' practice characteristics (seniority, experience, specialty, working place, practice volume) and other related questions

		Medical (n=35)			Surgical (n=19)			Total (n=54)	
		N	%	Row %	N	%	Row %	N	%
Encourage the patients to attend diabetic seminar	No	20	57.1	62.5	12	63.2	37.5	32	59.3
	Sometimes	8	22.9	66.7	4	21.1	33.3	12	22.2
	Yes	7	20	70	3	15.8	30	10	18.5
Type of secondary healthcare support referral	Elective care only	0	0	0	0	0	0	0	0
	Emergency and elective care	11	31.4	73.3	4	21.1	26.7	15	27.8
	Emergency care only	5	14.3	45.5	6	31.6	54.5	11	20.4
	Mental health care only	19	54.3	67.9	9	47.4	32.1	28	51.9
	All	0	0	0	0	0	0	0	0
Decision based on any protocol or guidelines	No	10	28.6	90.9	1	5.3	9.1	11	20.4
	Sometimes	4	11.4	57.1	3	15.8	42.9	7	13
	Yes	21	60	58.3	15	78.9	41.7	36	66.7
Type of used protocol	Local	2	8	66.7	1	5.6	33.3	3	5.6

	International	11	44	64.7	6	33.3	35.3	17	31.5
	Both	12	48	52.2	11	61.1	47.8	23	42.6
Type of challenges	Limited time	15	42.9	71.4	6	31.6	28.6	21	38.9
	Lack of resources	9	25.7	50	9	47.4	50	18	33.3
	Difficult to find proper care support	7	20	70	3	15.8	30	10	18.5
	All	4	11.4	80	1	5.3	20	5	9.3
Preferable strategies to improve patients' mental health and quality of life	Individual support	3	8.6	100	0	0	0	3	5.6
	Community-based support	5	14.3	83.3	1	5.3	16.7	6	11.1
	Hospital-based support	5	14.3	45.5	6	31.6	54.5	11	20.4
	Referral to psychiatrist and cognitive therapy	6	17.1	85.7	1	5.3	14.3	7	13
	All	16	45.7	59.3	11	57.9	40.7	27	50

5.4.4 Physicians' perspectives regarding their patients' mental health and HRQoL, including physical and emotional health problems

The details of physicians' responses to the 12 questions in the questionnaire are demonstrated in Table 5.3. The majority of physicians (83.3%) asked their patients about their general health (Q1); however, when it comes to asking about patients' activities that they might do during a typical day and related limitations in these activities (Q2), like moving a table, pushing a vacuum cleaner, bowling or playing golf; only 29.6% of the studied physician answered "Yes". Similar percentages (31.5%), (31.5%) and (29.6%) were reported to questions (3, 4, and 5) regarding climbing several flights of stairs, accomplishing less than they would like and limitations in the kind of work or other activities (Table 5.3).

In contradiction, when physicians were asked about asking their patients, during the past four weeks, if they had problems with their work or other regular daily activities as a result of any emotional issues (such as feeling depressed or anxious), only 18.5% responded positively to (Q6) related to accomplishing less than they would like and 14.8% asked patients about working or doing activities less carefully than usual, (Q7). However, a higher percentage (46.3%) was noted regarding asking patients how much the pain interfered with their patients' normal work (Q8). Low percentages were also noted with regards to questions related to the role of emotional components, including feelings such as feeling "calm & peaceful" (Q9) and "feeling a lot of energy" (Q10), as only 38.9% and 35.2%, respectively, answered "Yes" to these two questions. A much lower percentage (25.9%) was noted (Q11) that relates to mental health (feeling downhearted and blue). Finally, 35% of participants answered "Yes" to the questionnaire's last question (Q12) related to the social role among patients with T2DM (Table 5.3).

Table 5.3. Physicians' perspectives regarding their patients' mental health and health-related quality of life

		Medical (n=35)			Surgical (n=19)			Total (n=54)	
		N	%	Row %	N	%	Row %	N	%
Q1- Do you ask your patient with diabetes about their general health?	No	1	2.9	100	0	0	0	1	1.9
	Sometimes	6	17.1	75	2	10.5	25	8	14.8
	Yes	28	80	62.2	17	89.5	37.8	45	83.3
The following questions are about their activities they might do during a typical day. Does their health now limit them in these activities? If so, do you ask them about these questions?									
Q2- Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	No	8	22.9	66.7	4	21.1	33.3	12	22.2
	Sometimes	15	42.9	57.7	11	57.9	42.3	26	48.1
	Yes	12	34.3	75	4	21.1	25	16	29.6
Q3- Climbing several flights of stairs.	No	11	31.4	78.6	3	15.8	21.4	14	25.9
	Sometimes	14	40	60.9	9	47.4	39.1	23	42.6
	Yes	10	28.6	58.8	7	36.8	41.2	17	31.5

During the past 4 weeks, have you asked your patient with diabetes if they had any of the following problems with their work or other regular daily activities as a result of their physical health due to suffering from Type 2 Diabetes Mellitus?									
Q4- Accomplished less than they would like.	No	10	28.6	76.9	3	15.8	23.1	13	24.1
	Sometimes	15	42.9	62.5	9	47.4	37.5	24	44.4
	Yes	10	28.6	58.8	7	36.8	41.2	17	31.5
Q5- Were limited in the kind of work or other activities.	No	10	28.6	90.9	1	5.3	9.1	11	20.4
	Sometimes	16	45.7	59.3	11	57.9	40.7	27	50
	Yes	9	25.7	56.3	7	36.8	43.8	16	29.6
During the past 4 weeks, have you asked your patient with diabetes if they had any of the following problems with their work or other regular daily activities as a result of any emotional problems due to suffering from Type 2 Diabetes Mellitus (such as feeling depressed or anxious)?									
Q6- Accomplished less than they would like.	No	8	22.9	61.5	5	26.3	38.5	13	24.1
	Sometimes	19	54.3	61.3	12	63.2	38.7	31	57.4

	Yes	8	22.9	80	2	10.5	20	10	18.5
Q7- Did they work or do activities less carefully than usual?	No	10	28.6	71.4	4	21.1	28.6	14	25.9
	Sometimes	20	57.1	62.5	12	63.2	37.5	32	59.3
	Yes	5	14.3	62.5	3	15.8	37.5	8	14.8
Q8- During the past 4 weeks, have you asked your patient with diabetes about how much did the pain interfere with their normal work due to suffering from T2DM?	No	10	28.6	100	0	0	0	10	18.5
	Sometimes	13	37.1	68.4	6	31.6	31.6	19	35.2
	Yes	12	34.3	48	13	68.4	52	25	46.3
These questions relate to how your patient with diabetes was <u>feeling</u> during the <u>past 4 weeks</u>.									
Q9- Do you ask them: have you felt calm & peaceful?	No	7	20	53.8	6	31.6	46.2	13	24.1
	Sometimes	13	37.1	65	7	36.8	35	20	37
	Yes	15	42.9	71.4	6	31.6	28.6	21	38.9
Q10- Do you ask them: did you have a lot of energy?	No	10	28.6	62.5	6	31.6	37.5	16	29.6
	Sometimes	11	31.4	57.9	8	42.1	42.1	19	35.2

	Yes	14	40	73.7	5	26.3	26.3	19	35.2
Q11- Do you ask them: have you felt down-hearted and blue?	No	13	37.1	56.5	10	52.6	43.5	23	42.6
	Sometimes	13	37.1	76.5	4	21.1	23.5	17	31.5
	Yes	9	25.7	64.3	5	26.3	35.7	14	25.9
Q12- During the past 4 weeks, have you asked your patient with diabetes about how much of the time has their physical health or emotional problems affected by Type 2 Diabetes Mellitus and interfered with their social activities (like visiting friends, relatives, etc.)?	No	12	34.3	52.2	11	57.9	47.8	23	42.6
	Sometimes	10	28.6	83.3	2	10.5	16.7	12	22.2
	Yes	13	37.1	68.4	6	31.6	31.6	19	35.2

5.5 Discussion

Numerous studies, including work from the cross-sectional survey from chapter 4 in this thesis evaluating HRQoL and mental health aspects among people with T2DM, with and without diabetes-related complications in Jeddah, Saudi Arabia, explored the burden of T2DM on HRQoL and mental health aspects among people with T2DM (82, 89, 93, 148). Research from this chapter investigated the burden of T2DM on HRQoL and mental health aspects from a physicians' perspective. It is one of the very few studies that has attempted to examine the awareness, practices and perspectives of physicians who care for people with T2DM by exploring the importance of assessing HRQoL and mental health aspects among patients during daily management. This was performed by using a researcher-designed data collection form and a 12-item researcher constructed, self-administered survey questionnaire.

In view of the unavailability of a validated, reliable tool that is specially constructed to explore the physicians' perspectives, this study opted to use a self-constructed tool, similar to the other researchers who used different self-constructed research tools to explore knowledge, awareness, practices and perspectives of physicians and/or other health care providers regarding the overall management of their patients with T2DM; and also to other investigators who specifically explored physicians' perspectives regarding their patients' HRQoL and mental health (293-300). Furthermore, the present study uses a research instrument based on or inspired by the same instrument (SF-12v2) used previously in this thesis to examine the influence of T2DM on HRQoL and mental health aspects among people with T2DM, specifically those with T2DM-related complications, which was found to be one of the most common and validated instruments to evaluate HRQoL and mental health in patients with T2DM by earlier work in this thesis (87).

The current studied sample was a convenience sample of physicians in various (medical and surgical) specialties/ sub-specialties privileged in managing people with T2DM, with or without T2DM-related complications. It involved males and females; however, a higher percentage of males was noted (85.2% versus 14.8%) in the whole sample, with most participants experienced at a consultant level. It also included physicians in the public and private sectors, as both sectors usually provide services to Saudi patients. Most of the participants were practising in well-sized hospitals and, therefore, were managing considerable numbers of patients with diabetes, with or without related complications, who were receiving their care in the same facility (Table 5.1).

Evidence is growing regarding the negative impacts of T2DM on several aspects of general, physical, HRQoL and mental health aspects of people with T2DM (301-303). On the other end, mental health problems adversely affect many aspects of patients' daily lives with regard to their general, physical and self-adherence to a diabetes care plan (302). Given this, healthcare providers, specifically physicians, are supposed to be fully aware of their expected roles in early diagnosis of mental health issues that may affect diabetes care and HRQoL among their patients, and vice versa, regardless of their specialty.

Several clinical practical guides for healthcare professionals working with people with T2DM who experience emotional difficulties have offered strategies and tools for how to recognise and have conversations about emotional problems with patients, as well as for providing appropriate support (301-305). In this regard, the Saudi Diabetes Clinical Practice Guidelines (SDCPG) recommended referral to a mental health provider in certain circumstances like anxiety, depressive symptoms, fears of hypoglycaemia, eating disorder, suspected mental illness, cognitive impairment, impaired diabetes self-care and before and after obesity surgery

(305). However, very few studies explored the perspectives of physicians about their norms in this regard and their perspectives about challenges and difficulties met during the day-to-day management of their patients, including their attitude towards referring their patients to mental health services, health education and support groups activities in the same health facilities, using protocols/guidelines and suggestions for improving patients' mental health, if any. This is in addition to, exploring physicians' perspectives regarding assessing their patients' HRQoL mental health aspects.

Recognition and understanding of physicians' challenges when treating diabetes patients' physical, social and emotional difficulties are essential for developing programmatic interventions (297). Therefore, this study is one of the few studies that attempted to bridge the present information gaps about these aspects by exploring the physicians' knowledge, awareness and perspectives towards their patients' HRQoL and mental health aspects among people with T2DM, in Jeddah, the second largest city in Saudi Arabia.

Positive findings from this study include physicians' awareness when using different protocols and/or guidelines to base their decisions on managing people with T2DM in their practices, as almost two-thirds (66.7%) of studied participants answered "Yes" they do. In contrast, regarding referral to mental health care, only 51.9% of all participants answered "Yes" more likely in medical than surgical specialties (67.9% versus 32.1%, respectively). Also, when explicitly asked about their perspectives on preferred approaches to improve patients' mental health and HRQoL, only 13% would consider referral of their patients to psychiatry and cognitive therapy services (Table 5.2).

With regards to physicians' responses to the 12 questions regarding their patients' mental health and HRQoL, physicians did better in the physical domain compared to the mental one.

Among the 12 answers, the best positive response of participants was on Q1, which relates to the physical health-related domain, as most physicians (83.3%) answered “Yes” when they asked their patients about their general health. This was followed by Q8, which relates to pain interference with their patients’ normal work, as 46.3% of participants indicated that they did ask about that (Table 5.3).

In contrast, the lowest responses were on the vitality questions of the mental domain that relate to emotional problems (Q6 and Q7); only 18.5% and 14.8% answered “Yes” (Table 5.3). The responses to the remaining questions were suboptimal as the percentages of those physicians who answered “Yes” were modest and ranged between 25.9% and 38.9% (Table 5.3). Overall, the lower percentages were more associated with their response to the mental domain questions (Table 5.3). In terms of the difficulties met, two-thirds of participants indicated that the main challenges they face in daily practice are limited time allocated for patients’ visits and lack of resources (Table 5.2).

Several causes may be responsible for these results, such as the importance of HRQoL and mental health not being commonly taught. Physicians need to be better educated in this area to decrease this gap. In addition, the focus should also be on the availability of educational courses and/or include the importance of HRQoL and mental health among aspects and review of patients with T2DM in current guidelines (293-296). This may highlight the need to evaluate patients during clinic hours.

5.5.1 Strengths and limitations

The main strength of this study is that all of the invited physicians agreed to participate. This study is also among the few that explored the physicians’ knowledge, awareness and perspectives on HRQoL and mental health aspects of people living with T2DM (295-297, 300).

Another strength is the inclusion of a self-constructed tool based on the SF-12v2 health survey, which covered HRQoL and mental health domains. The simplicity of the questions may help reduce the risk of bias and variability in the answers and interpretations. The studied sample involved good numbers and representation of senior and experienced physicians who were practising in various related medical and surgical specialties and not limited to one specialty. This ensured a more comprehensive representation of caring physicians from different related medical and surgical specialties practising in public and private sector hospitals.

Nevertheless, the present study has some limitations. One of the main limitations of this study is the small sample size. The second is the use of an unvalidated self-reported questionnaire for data collection, which could be subjected to a potential source of bias. However, this may be minimal since it was specifically built for the purpose of the study. The third, it is a descriptive cross-sectional survey study on a convenience sample, which means that it was limited to physicians working in one city of Saudi Arabia. Therefore, it may limit the generalisability of the findings. Despite these limitations, which are commonly demonstrated with these types of study designs relating to this topic, it has provided the essential characteristics and preliminary evidence and has identified gaps that will be essential for improvement and future planning (296-298, 300).

5.6 Conclusions

The findings from this study demonstrate several gaps in knowledge and suboptimum practices towards HRQoL and mental health aspects among the studied physicians during their regular care for people with T2DM. Therefore, there is a great need for more extensive, well-designed, multidimensional and multisectoral research studies to accumulate greater knowledge about the perspectives of all related healthcare providers, including physicians, to

identify the magnitude of the current problems, challenges met during regular healthcare of propel with T2DM; specifically, in dealing with the physical and emotional burden on T2DM patients. Such studies will consequently outline implementation plans for mitigating the current difficulties and challenges met during regular health care of people with T2DM.

Chapter 6. Overall discussion

6.1 Main findings

The primary focus of the current PhD thesis was to explore the bidirectional relationship between epidemiological factors, Health-Related Quality of Life (HRQoL) and mental health aspects of individuals diagnosed with Type 2 Diabetes Mellitus (T2DM) within a cohort of patients receiving care at primary care clinics and a tertiary care hospital in Jeddah, Saudi Arabia. Furthermore, this thesis aimed to gather insights from physicians providing care to people living with T2DM based on their current practices to help define the current gaps in their care and consequently propose comprehensive approaches that aim at enhancing their patients' HRQoL and mental health, specifically in those with associated T2DM-related complications.

At the conceptualisation of this research project, it was assumed that the expected findings from the various intended studies of this research project would hopefully inform healthcare policymakers in outlining strategies, health promotion evidence-based initiatives and guidelines to improve and provide better care to patients with diabetes, specifically in those with complications. Furthermore, it will help practising physicians in various specialties who deal with patients diagnosed with T2DM, focusing on the importance of adopting better care that is directed to improving patients' HRQoL and mental health patterns. This is based on the findings of the conducted studies in this thesis. It was also assumed that the findings of the extensive comprehensive review of the available previous related studies (**Chapter 1**), as well as of the other four conducted studies in this thesis (**Chapters 2-5**), reflect directly on improving HRQoL and mental health aspects of people with T2DM both directly and indirectly by decreasing T2DM related complication rates, improving quality of life and reducing the soaring economic impacts of T2DM on patients, their families, particularly in those with

complications. At the same time, it will reduce the economic burden of the disease on governments and healthcare systems (**Chapter 1**), not only in Saudi Arabia and its adjacent Gulf countries but also in other countries that steadily report high prevalence rates of T2DM and its complications worldwide.

To achieve these goals, **Chapter 1** consisted of an extensive literature review on T2DM, HRQoL and mental health aspects to identify gaps in the existing global research. It identified the magnitude of the problem in different countries around the world, particularly those that report high prevalence rates, like Saudi Arabia. Additionally, previous studies on governments' measurement, guidelines and health promotion initiatives in different countries were extensively reviewed in this Chapter. **Chapter 1** concluded the current economic burden of diabetes on governments, health systems, insurers and the entire community, as well as on people living with diabetes and their families. In particular, those expenses that relate to individuals' HRQoL and their mental health aspects. Key findings from this work (**Chapter 1**) identified gaps in the available literature and the need for more robust nationwide studies to address further the former concerns, particularly in countries that report, and are expected to report, higher prevalence rates of T2DM in the near future. In particular, Saudi Arabia and the adjacent Gulf countries share similar cultural, ethnic and economic backgrounds in terms of this disease and its impact on HRQoL and mental health problems.

Chapter 2 included a systematic review that assessed and analysed the methodological quality of commonly used tools for measuring HRQoL and mental health in T2DM patients. The aim was to identify the most appropriate measurement tools that could be used in the two intended studies described in **Chapters 4 and 5.** This was done by exploring both patients' and physicians' knowledge, awareness and perspectives on the impact of HRQoL and mental

health aspects in individuals with T2DM. Interestingly, this updated review demonstrated that the 12-item Short Form Health Survey (SF-12) questionnaire is the most appropriate instrument for evaluating QoL and/or HRQoL and mental health, followed by the Medical Outcomes Short Form 36 (SF-36). Accordingly, results from this chapter identified the SF-12 questionnaire as the most appropriate and preferred research instrument for these survey studies (**Chapters 4 and 5**). This was based on the findings of this systematic review due to its widespread use, validation, good reliability, ease of administration and availability in multiple languages. These factors made this a practical quality metrics tool for studying both patients and physicians in diverse settings.

Chapter 3 was a retrospective cohort study conducted in Jeddah, the second largest city in Saudi Arabia, to primarily assess the magnitude of T2DM problems among a defined population of patients with T2DM in Jeddah. This is performed by investigating the prevalence of T2DM-related complications, including the differences in the associated contributing risk factors among patients with and without T2DM-related complications. Interestingly, findings from this work revealed that almost three-quarters (74.7%) of the studied population experienced T2DM-related complications, whether they were microvascular or macrovascular. Results highlighted that the likelihood of complications was notably higher for males and those over 45 years of age. Additionally, patients living with obesity (≥ 30 kg/m^2) with T2DM were found to have a 1.4 times higher risk of developing T2DM-related complications compared to those with a healthy weight. Patients with poorly controlled T2DM, who had HbA1c levels exceeding 8%, faced a 2.36 times greater risk of developing T2DM-related complications compared to patients with normal HbA1c levels. In addition, the HbA1c levels varied among patients based on their diabetes history and treatment regimen. This chapter provided deeper insights into the burden of the T2DM-related complications

group and added to the current literature for patients with T2DM-related complications in Saudi Arabia. It highlighted the need to focus more on those patients with complications, which was explored further in **Chapters 4 and 5**.

Chapter 4 was a cross-sectional survey conducted in Jeddah that aimed to examine the impact of HRQoL and mental health aspects among a well-defined population of T2DM patients with and without T2DM-related complications. This Chapter used the measurement tool that was identified to be the most suitable in **Chapter 2**, namely the SF-12 questionnaire. **Chapter 4** was based on the findings from **Chapter 3**, which identified the burden of T2DM-related complications among these patients. Additionally, the study aimed to identify other variables that relate to socioeconomic factors and comorbid conditions that are associated with an increased risk of complications. This included socioeconomic variables such as lack of education, unemployment and low monthly income, which were all significantly associated with the presence of T2DM-related complications. These findings reflect the need to focus on the social and economic disadvantaged

Over the years, there has been a growing emphasis on population-based health outcomes, value-based care and social determinants of health. **Chapter 4** highlighted the essential areas requiring improvement. The results emphasised the importance of addressing and improving these determinants at individual, organisational and policy levels to reduce T2DM-related complications and enhance outcomes. Furthermore, among the comorbid conditions examined, high cholesterol levels were the only significant variable associated with complications in 85.3% of the patients. Interestingly, with regards to HRQoL and mental health aspects in patients with T2DM, this Chapter showed that all summary components and health domains of the SF-12v2 questionnaire had below-average scores. In addition, in the univariate

analysis, they were significantly associated with an increased risk of T2DM-related complications. However, in the multivariable analysis, only below-average scores in Physical Component Summary (PCS), Mental Component Summary (MCS) and Role Emotional (RE) domains were found to have an increased risk of T2DM-related complications. Overall, this study highlighted the importance of considering socioeconomic factors and comorbid conditions in influencing the risk of developing T2DM-related complications in these patients.

Chapter 5 was a cross-sectional survey study that aimed to investigate the knowledge, awareness and perspectives of practising physicians regarding the HRQoL and mental health aspects of people living with T2DM. The questions used were similar to those asked of patients who participated in the **Chapter 4** study. The reason for this was to obtain physician insight and perspective. It was performed in Jeddah, the same city in which the patient survey was conducted. Findings from this work revealed that most physicians (83.3%) inquired about their patients' overall health status. However, when it came to addressing emotional issues such as depression or anxiety, only 18.5% of physicians responded affirmatively. This study also highlighted low percentages of physicians asking their patients about their emotional well-being, including feelings of calmness, peacefulness and energy, as only 38.9% and 35.2% of physicians responded positively to these questions, respectively. Furthermore, a significantly lower percentage (25.9%) of physicians addressed mental health concerns, such as feelings of sadness or melancholy among their patients. **Chapter 5** concluded with a “call for action” for future well-designed, multidimensional and multisectoral research studies to accumulate greater knowledge about the magnitude of the current problem and how to bridge the current gaps in the care of people with T2DM. Furthermore, the findings from **Chapters 5 and 4** linked together in terms of emphasising the importance of narrowing the gap between the patients and their physicians, increasing patient-physician engagement,

increasing the comprehensiveness of management or care and delivering a deeper understanding of the social, economic and structural determinants of HRQoL and mental health.

6.2 Strengths and limitations

The main strength of this thesis is that it was designed to identify the current research gaps in the literature, particularly in relation to Saudi Arabia and Gulf Cooperation Council (GCC) countries (**Chapter 1**). This also included Middle East and North Africa (MENA) and other countries with similar cultural and socioeconomic backgrounds. This is particularly important when the impact of T2DM on HRQoL and mental health aspects of patients with T2DM-related complications was evaluated.

The comprehensive systematic review of the overall body of evidence pertaining to commonly used measurement research tools for HRQoL and mental health in the past decade (**Chapter 2**) provides strong evidence of the most appropriate tool to use. Furthermore, this thesis addressed the scarcity of studies that assessed the current burden of diabetes and its complications. It correlated the contributing risk factors for T2DM and the likelihood of developing complications, particularly within a large cohort of patients with T2DM, using specifically the recent 10th Revision of the International Classification of Diseases (ICD-10) diagnostic classification system (**Chapter 3**). In **Chapter 3**, de-identified data was limited in capacity to be cross-checked with patient records to ensure patient anonymity was maintained. The data from **Chapter 3** reflects the continuity of care, so the patient is receiving the same healthcare service from the same clinician for a long time, which is certainly a strength and reflects the real-life situation. Furthermore, due to the nature of the study design further work may be required to confirm these findings.

In addition, and as elaborated in **Chapter 4**, the study stands out for its unique approach in linking risk factors to T2DM-related complications and the HRQoL and mental health aspects among the studied individuals with T2DM, with interest in correlating these variables with complications. This was performed through face-to-face assessments using a structured and validated questionnaire conducted by trained healthcare professionals in primary and tertiary healthcare centres. Moreover, the novelty of the **Chapter 5** study is that it is the first to investigate the knowledge, awareness and perspectives of physicians regarding the HRQoL and mental health aspects of people with T2DM. It used a structured self-administered survey questionnaire that was modified and based on the SF-12v2 questionnaire, which covered HRQoL and mental health domains. The questions were aligned and similar to those asked to patients who participated in the preceded **Chapter 4** patients' study. In addition, the **Chapter 5** study ensured a comprehensive representation of healthcare providers across different health sectors. It included a sample of senior physicians who represent several medical and surgical specialties that deal with patients with T2DM who work in Jeddah, the second largest city of Saudi Arabia.

Like other previous studies, current studies in this thesis have their limitations. For example, the systematic review study in **Chapter 2** has notable potential biases such as self-reported, non-response and variations in response rates. Additionally, the absence of standardised terminology could lead to potentially misleading outcomes. The **Chapter 3** study is constrained to some extent by the number of variables or risk factors available. This is primarily due to the reliance on data obtained from a hospital-based system, which is susceptible to the possibility of misclassification bias (the information was reliant on ICD-10-AM), missing data and potential over or underestimation of results. This is a common

limitation that is often seen in retrospective studies along with other limitations. For example, this type of study design does not allow for inferences to be drawn on causality.

Limitations in the **Chapter 4** study include the utilisation of a cross-sectional study design and a relatively small sample size, as recruitment was restricted to two outpatient healthcare centres in Jeddah, which may not reflect the general population. Lastly, one of the primary limitations of this survey study in **Chapter 5** is the use of an unvalidated self-reported questionnaire for data collection, which may introduce a potential source of bias. Moreover, being a descriptive cross-sectional study on a convenience sample is subject to inherent limitations. This includes the inability to follow up with participants over time. Despite this, it led to an excellent response rate and it was useful to use as findings provided preliminary evidence to help us understand the issues that would be relevant in future planning for both more advanced studies and in closing the gaps for improvement. This is particularly important since there is not too much data or evidence available to explore this in more detail in Jeddah, Saudi Arabia.

6.3 Implications and future directions

Chapter 4 of this thesis aimed to measure the variables that influence the impact of T2DM on HRQoL and mental health aspects among people with T2DM, with and without T2DM-related complications, using the SF-12v2 questionnaire. During the same period, the use of this tool was extended from the patients' perspective to explore their physicians' viewpoint about the influence of T2DM on HRQoL and mental health aspects among people with T2DM. This included physicians' perspectives regarding the difficulties and challenges met during their regular care of patients to ensure that there is a more comprehensive and multifaceted approach to the problem (**Chapter 5**).

As indicated in the previous chapters (**Chapters 4 and 5**), findings from both studies demonstrated problems about the negative impacts of T2DM on HRQoL and mental health aspects among the studied patients with T2DM. This was in addition to concerns regarding the current sub-optimum practices among attending physicians. This included the reluctance of the studied group of physicians to refer patients with mental issues to mental healthcare providers. These findings highlight the need for more work to be performed in this area in terms of improving the current diabetes care, including regular HRQoL and mental health assessment among people with T2DM (**Chapters 4 and 5**). These current practices of the studied group of physicians were, to some extent, in contradiction to the recommendations of several diabetes guidelines such as Clinical Practice Guides (CPGs), Best Practice Guidelines (BPGs) and American Diabetes Association (ADA). This includes the Saudi Diabetes Clinical Practice Guidelines (SDCPG), which recommends referral to mental health providers in certain circumstances like anxiety and depressive symptoms, fears of hypoglycaemia, eating disorders, suspected mental illness, cognitive impairment, impaired diabetes self-care, and before and after obesity surgery (156, 161).

Some examples of these sub-optimum practices are mentioned in **Chapter 5**. Here, when physicians were questioned about the referral of their patients with T2DM to mental health care, only 51.9% of all participants responded positively by answering “Yes”. Also, when explicitly asked about their perspectives on preferred approaches to improve patients’ mental health and HRQoL, only 13% considered referral of their patients to psychiatry and cognitive therapy services. The current thesis studies indicate the need to explore the perspectives of patients and healthcare providers to ensure better outcomes of all interventions and/or programs, including patients’ satisfaction in primary care settings (306). At the hospital level, a recent study discussed the efforts of 18 governmental hospitals in Saudi Arabia, which have

been enrolled in a collaborative improvement project to advance care among all the chronic illness clinics, including diabetes. This work indicated that a collaborative multilevel approach using evidence base care minimises variation and enables standardisation of care management plans by a multidisciplinary team leading to a noticeable improvement in all key performance indicators (307).

Findings from these projects support the recommendations from this thesis, as previously discussed in **Chapters 4 and 5**. However, further strategies and approaches should be introduced to deal with HRQoL and mental health issues in people with diabetes. In this regard, numerous strategies, initiatives, interventions and programs have been promoted and assessed to measure the magnitude of their effects on improving HRQoL and mental health aspects. Work from this thesis reinforces the importance and need for early periodic mental health screening among patients diagnosed with T2DM and T2DM-related complications. This will ensure that patients are not disadvantaged and that optimum treatment is received. This will hopefully decrease both the microvascular and macrovascular complications of diabetes. It will also help with patient compliance with their treatment and care, improve outcomes, ensure better quality of life and will decrease economic impact. Other studies in patients with severe mental illness and complications of T2DM have shown that they receive suboptimal treatment when compared to the general population. Periodic screening was also suggested by these investigators (308-310). At a global level, studies have indicated the need for an increase in interventions to improve the HRQoL of patients with diabetes. This includes translating evidence from clinical interventions to community interventions and by developing collaborative research between developed and developing countries. Both community and family based interventions as well as those focused on lifestyle and utilisation of digital technologies would be helpful (311). In addition, findings from a recent meta-analysis found

that health behaviour interventions may help improve the HRQoL of people with T2DM over the short term (312).

Undoubtedly, such goals may not be achieved without government support and efforts such as identifying those individuals to be at high-risk of developing T2DM early. This will subsequently outline government policy measures that may be similar to that on sugar taxes and regulatory measures applied in the preschool setting for children and adolescents (313). To achieve this, a bundle of strategies in conjunction with communication methods using evidence-based population-level prevention strategies have been recommended (313, 314). For example, prevention strategies through the National Diabetes Prevention Program have been recognised in the United States, suggesting a need for a multi-tiered approach which involves appropriate risk targeting and whole-population efforts to slow down the global diabetes epidemic (314). In addition, governments should support health education activities and increase efforts to raise awareness among patients, physicians and other healthcare providers on various aspects of T2DM care. This is particularly important in countries with high prevalence rates of diabetes. More nationwide efforts focusing on diabetes education directed to the public, patients with diabetes, their families as well as healthcare providers are needed (315, 316). The Australian National Diabetes Strategy 2021-2030 is an example of an excellent government initiative which aims to outline the national response to diabetes. The Strategy states seven high-level goals with areas for action that cover prevention, awareness, early detection and management of diabetes. It highlights the populations impacted and the research agenda (317). Another Australian government initiative is National Diabetes Services Scheme (NDSS) which provides subsidised products and support services to individuals with diabetes who register with the scheme (318).

Improving the mental health of individuals with diabetes requires a holistic approach to care. It should recognise the interplay between psychosocial and physiological factors in the development of mental health symptoms among people with diabetes. Consequently, and as mentioned earlier, early screening is suggested, followed by treatment. This will help mitigate the impact on diabetes self-management as well as on developing a major mental disorder (311, 312, 319-321). It also requires a collaborative care model, with diabetes and mental health expertise effectively integrated to offer patients the best of both worlds. This may require a psychologist to be a member of the team or to at least to be available for referral and consultation, preferably in a same healthcare facility (322).

Among future directions for screening and monitoring of this disease, comes the need for more research that aims to test innovative approaches to case-finding. The use of Artificial Intelligence (AI) and adaptive computerised testing is one approach. These methods may help to differentiate a persons' risk for mental illness and therefore offer or help clinicians provide a more personalised intervention for the evolving patients' needs (322, 323). Other recent advancements that demonstrated promising future applications, include 'digital phenotyping' through Ecological Momentary Assessments (EMA) and smartphone technology. These technologies are encouraged to be used by the patients for monitoring their wellbeing and mental health states daily (324). Evidence-based psychological interventions have been developed for a range of psychological problems. These include Internet-based and Mobile based Interventions (IMIs), which should also be explored, as integrating IMIs will help provide better diabetes care and psychological support to a larger group of people with diabetes (325). Recently, diabetes-specific self-guided Cognitive Behavioural Therapy (CBT) applications were offered to assist people with diabetes in facing mild symptoms of psychological distress and fatigue (326). A recent study confirmed the feasibility of MyDiaMate which is a diabetes-

specific self-guided app for adults trying to preserve or improve their psychological health (326). Overall, user experiences were positive, however, investigators indicated the need for further research in terms of tailoring the content to individual needs and preferences in order to enhance uptake, usage and appreciation (326).

In regards to future directions, further research is needed to support new studies that aim to explore the translation of clinical interventions to prevent diabetes into community care. This may help physicians overcome the time-consuming problem caused by routine assessment of their patients with diabetes about HRQoL and mental health mentioned in **Chapter 5**. Further studies are also needed to assess optimal approaches to promoting effective decision-making, coping and adherence, as well as more interdisciplinary studies that consider ecological models to develop a roadmap for policies and diabetes management recommendations (327).

In addition, as highlighted in **Chapter 4**, further work is needed to help reduce diabetes-related health disparities among disadvantaged groups, minorities and low socioeconomic groups. Future research is also needed to understand how patients with diabetes, including family members and providers, use technology to assist in diabetes prevention and achieve their management goals. Furthermore, there is a need for industry-academia partnerships to create empirically supported and scalable applications to effectively handle increasing users, transactions and data volume without performance issues. It should also contain proven behavioural strategies that are appropriate for target users (327). Such innovative approaches are just some examples of the precision medicine strategies that have been discussed in a recent consensus report that presented views of the American Diabetes Association (ADA) Precision Medicine in Diabetes Initiative. This was in collaboration with the European

Association for the Study of Diabetes (EASD) on the development of tools for the application of precision medicine to people with diabetes (328).

In summary, the World Health Organisation (WHO) highlighted that health promotion equates to going beyond healthcare. Therefore, it puts health on the agenda of decision-makers in all sectors and at all categories. This is one way of directing them to be aware of the detrimental health impact of their decisions and to accept their responsibilities for health. Accordingly, the health promotion policy combines diverse but complementary strategies, including legislation, fiscal measures, taxation and organisational change (329). In addition, health promotion is supposed to create supportive environments for people, strengthen community actions and support personal and social development. This can be achieved by providing information, education for health and enhancing life skills that will enable individuals to learn throughout life to prepare themselves for all of its phases and to cope with any chronic illness including diabetes. Caring, holism and ecology are essential in establishing strategies for health promotion. Therefore, those involved should take as a guiding principle that, in each phase of planning, implementation and evaluation of health promotion activities with equal partnerships (329). Moreover, all health promotion and wellness initiatives need to take into consideration adults with Intellectual and Developmental Disabilities (IDD) among people with T2DM. Reasonable adjustments should be provided to address this population’s cognitive impairments and communication difficulties (330).

Nevertheless, challenges in access to diabetes specialists and educators and inadequate motivational support for proper disease self-management contribute to poor control of diabetes and worse HRQoL in people with diabetes. This is especially true as high patient volumes and low reimbursement rates limit physicians' time spent on lifestyle behaviour

counselling. These barriers to optimum diabetes care have subsequently led to high rates of T2DM-related complications, driving healthcare costs up and simultaneously decreasing the HRQoL and mental health among people with diabetes (331). The high lifetime cost of treating T2DM highlights the importance of potential long-term governments' return on investment of interventions to prevent or delay T2DM, specifically T2DM-related long-term complications (332). Therefore, there is a need to have better insight into diabetes care costs, particularly into the expenses attached to T2DM and the association with an individuals' HRQoL and mental health aspects (167-170, 333).

However, there are significant opportunities to achieve better efficiency in diabetes care and increase patient involvement in diabetes self-management by adopting recent advancements in healthcare delivery technologies like smartphone applications, telemedicine, m-health, device connectivity, machine-learning technology and AI (331).

6.4 Conclusions and recommendations

In this thesis, the potential risk factors for predicting the development of T2DM-related complications are gender, age (above 45), low monthly income or socioeconomic status, poorly controlled HbA1c, long duration of T2DM, high cholesterol levels, and high BMI. This research project also revealed that both MCS and PCS scores related to HRQoL and mental health were notably lower in individuals with T2DM-related complications across all components of MCS and PCS. In addition, numerous deficiencies in knowledge and unsatisfactory approaches towards HRQoL and mental health aspects were also observed among the studied caring physicians of individuals with T2DM. Concerns about the quality of current care that relates to HRQoL and mental health provided to patients with T2DM were addressed by both patients and physicians who participated in the current studies.

The outcomes of the current research project revealed the need for more government measures, innovative programs and health promotion interventions/initiatives at all levels of care that collectively aim to bridge the current gaps in care provided to people living with T2DM. This is particularly important in those countries that report high prevalence rates of diabetes and are projected to do so over coming decades across the world including the low and middle-income countries. Without government support, establishing diabetes registries, which are essential tools for disease surveillance and health planning, as well as outlining national diabetes plans that apply whole-population approaches such as socioeconomic policies, healthy food promotion, environmental/systems changes, and awareness-raising programs, may not be attainable. Plans should prioritise personalised interventions that address all aspects of care, including HRQoL and mental health in all T2DM patients, with and without complications.

In terms of research, there is a need for comprehensive, well-structured, multidimensional and multisectoral research initiatives to enhance our understanding of the perspectives of related healthcare providers, including physicians. In addition, the extent of the existing challenges and shortcomings encountered in the routine care of individuals with T2DM, particularly addressing the physical and emotional burdens faced by T2DM patients' needs to be determined. Future population-based epidemiological research studies should aim to formulate updated strategies and policies that translate the current clinical interventions into community-based and family-based ones. They should also incorporate the recent effective technologies in health promotion and education of people with T2DM such as the web-based self-management programmes and other behavioural interventions to ensure the optimal integration of technology. This may help contain the growing health expenditure on caring for patients with T2DM in both those with and without T2DM-related complications. Future

nationwide prospective studies should also focus on evaluating the prevalence of T2DM-related complications and on assessing the impacts of T2DM on HRQoL and mental health among all individuals with T2DM and vice versa. This is particularly important in those patients with complications or when management targets are not met.

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Appendices

Appendix A: Ethical approval

KINGDOM OF SAUDI ARABIA
Ministry of Higher Education
KING ABDULAZIZ UNIVERSITY
Faculty of Medicine

المملكة العربية السعودية
وزارة التعليم العالي
جامعة الملك عبد العزيز
كلية الطب

Ref.F.M : ..... الرقم : .....
Date : / / التاريخ : / / ١٤هـ
Encl : ..... المرفقات : .....

UNIT OF BIOMEDICAL ETHICS
Research Ethics Committee (REC)
NCBE Registration No: (HA-02-J-008)

TO: Principal Investigator & Local Supervisor: Dr. Rajaa Al-Raddadi **From: Professor. Hasan Alzahrani**
(Associate Professor, Community Medicine, Faculty of Medicine)
External-Principal-Supervisor: Prof. Kerry Hitos **External-Co-Principal-Supervisor: Prof. John Fletcher**
First-Investigator: Dr. Owiss H. Alzahrani (PhD Student, Community Medicine, University of Sydney)
Date: Thursday, June 23, 2022 **CC: Vice-Dean, Academic Affairs & Monitoring Committee, REC File**
Title: "
"
(Reference No 324-22) Non-Intervention (Cross Sectional, Retrospective Record Review)

Application for Research Form, Detailed Proposal, CVs, Data Collection Sheet/research instrument.

1. The PI and investigators are responsible to get necessary academic/administrative approvals, according to bylaws, and they must get the administrative approval from any organization collaborators outside KAU and/or KAUH.
2. The approval of conduct of this study will be automatically suspended after 06 months in case of no submission of " Continuing Review Progress Report Form " to be reviewed by REC- Monitoring Committee.
3. The investigators will conduct the study under the direct supervision of Dr. Rajaa Al-Raddadi.
4. Any amendments to the already approved protocol or any element of the submitted documents should NOT be undertaken without prior notification of REC, and further approval by REC of any modifications.
5. Final Report: After completion of the study, a final report must be forwarded to the REC.
6. The PI must provide to REC a conclusion abstract and the manuscript before publication.
7. Biological samples: No biological samples to be shipped outside the Kingdom of Saudi Arabia without prior REC approval.
8. All biological samples collected for the purpose of this research must be stored in the KAU/KAUH related repository.
9. Participant incentives: No financial compensation or gifts to be given to participants without prior REC approval.
10. This REC approved research study must not contradict with any Saudi law including, but not limited to, the Saudi Law of Ethics of Research on Living Creatures and its Implementing Regulations. And is expected to adhere to all regulations issued by the National Committee of Bioethics (NCBE) - King Abdul Aziz City for Science and Technology.

Kindly note that the committee does not disclose names of any of its members, however we confirm compliance with the above mentioned Saudi National Committee sections. The committee is also fully compliant with the regulations as they relate to Ethics Committees and the conditions and principles of good clinical practice. Research Ethics Committee (REC) is based on the Good Clinical Practice (GCP) Guidelines. Please note that this approval is valid for one year commencing from the date of this letter.

Professor Hasan Alzahrani

Chairman of the Research Ethics Committee

Rehab.T.Halawani

ص. ب ٨٠٢٠٥ جدة ٢١٥٨٩ برقياً : «جامعة عبدالعزيز» تلكس ٦٠١١٤١ كايوني إس جيه فاكس : ٦٤٠٠٨٥٥ ☎ : ٦٩٥٢٤٤٦/٦٩٥٢٠٦٣
P.o. Box 80205 Jeddah 21589 Cable : "Jameatabdulaziz" Telex : 601141 Kauni SJ Fax. : 6400855 ☎ : 6952446/6952063

Figure B.2.1. Total of included publications per year and study location

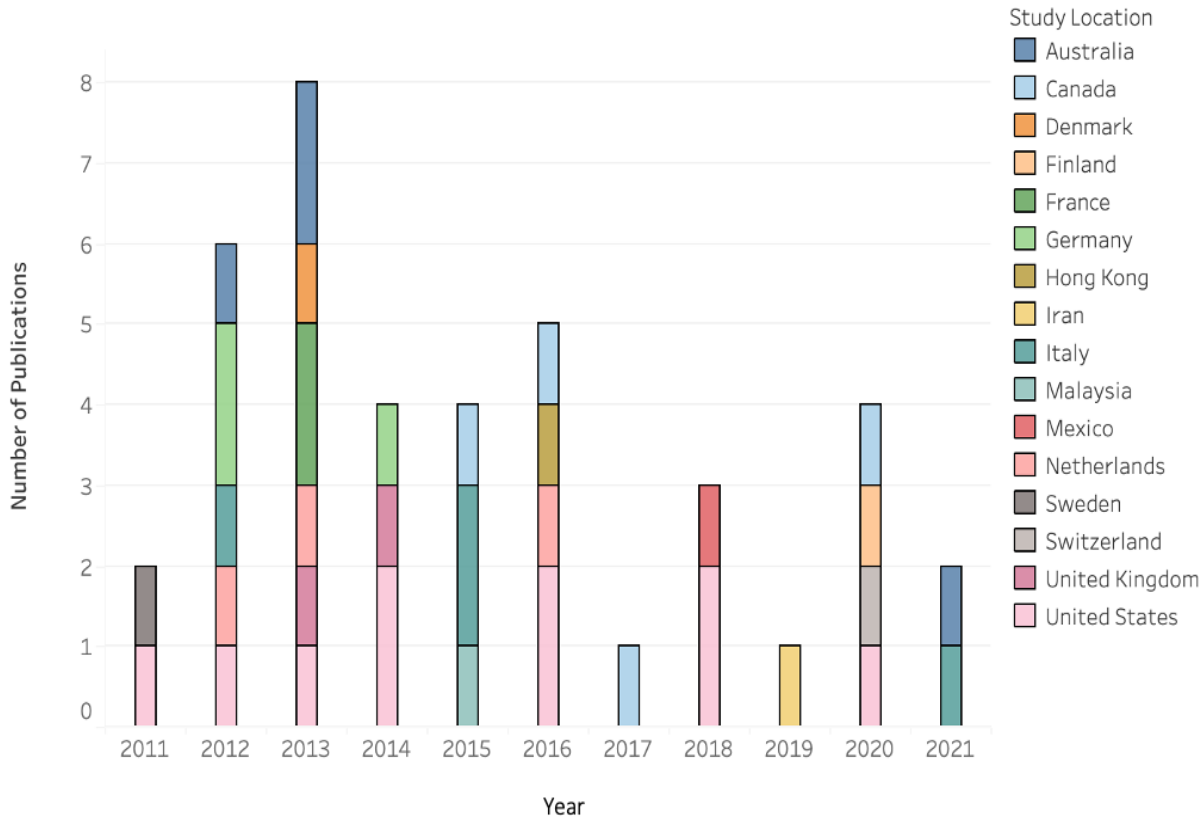

Figure B.2.2. Study design and mood of administration per number of included studies

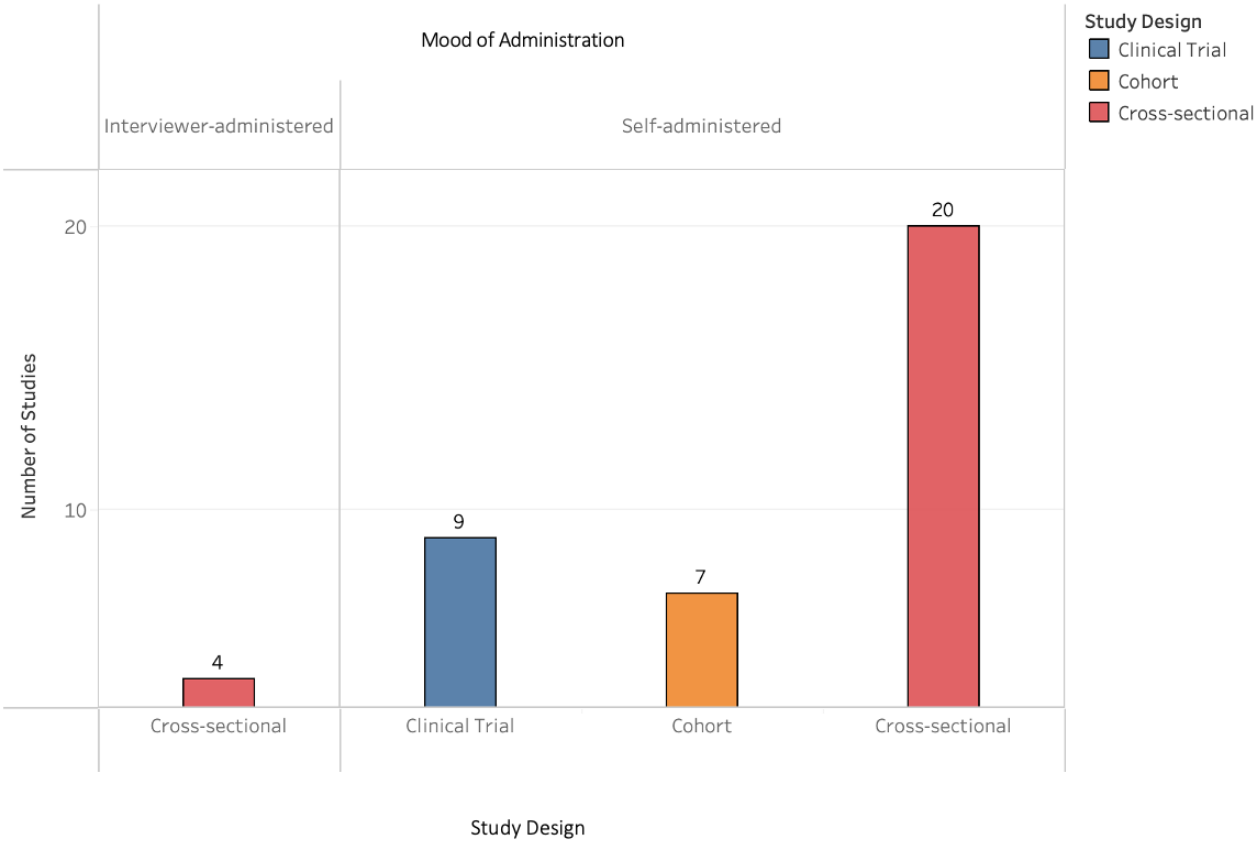

Figure B.2.3. Top commonly used questionnaires with how many times used in the included studies

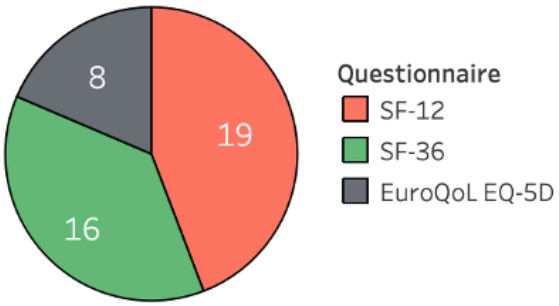

Figure C.3.1. The overall comparison between age groups by gender, nationality, and with or without complications

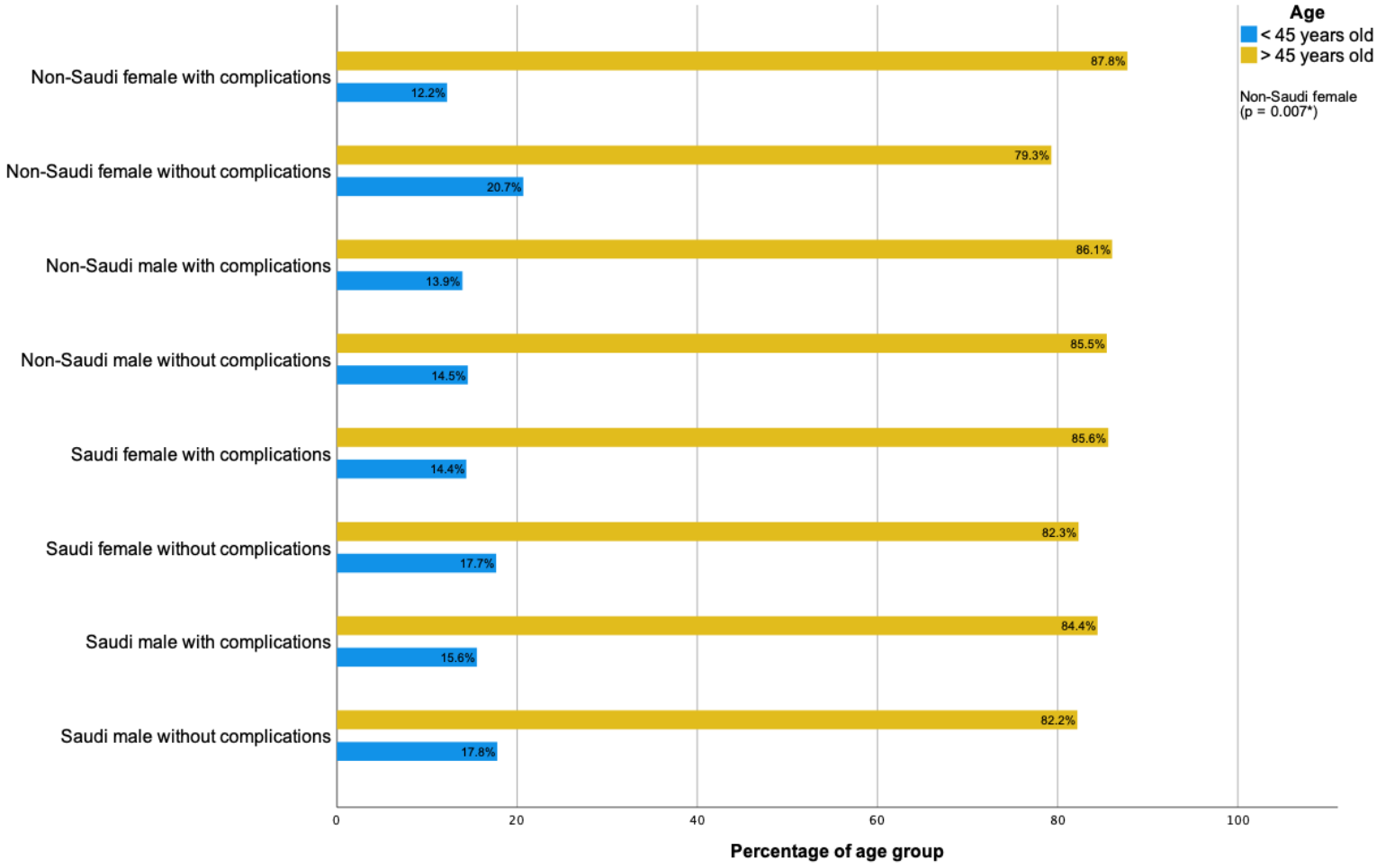

Figure C.3.2. The overall comparison between BMI ranges by gender, nationality, and with or without complications

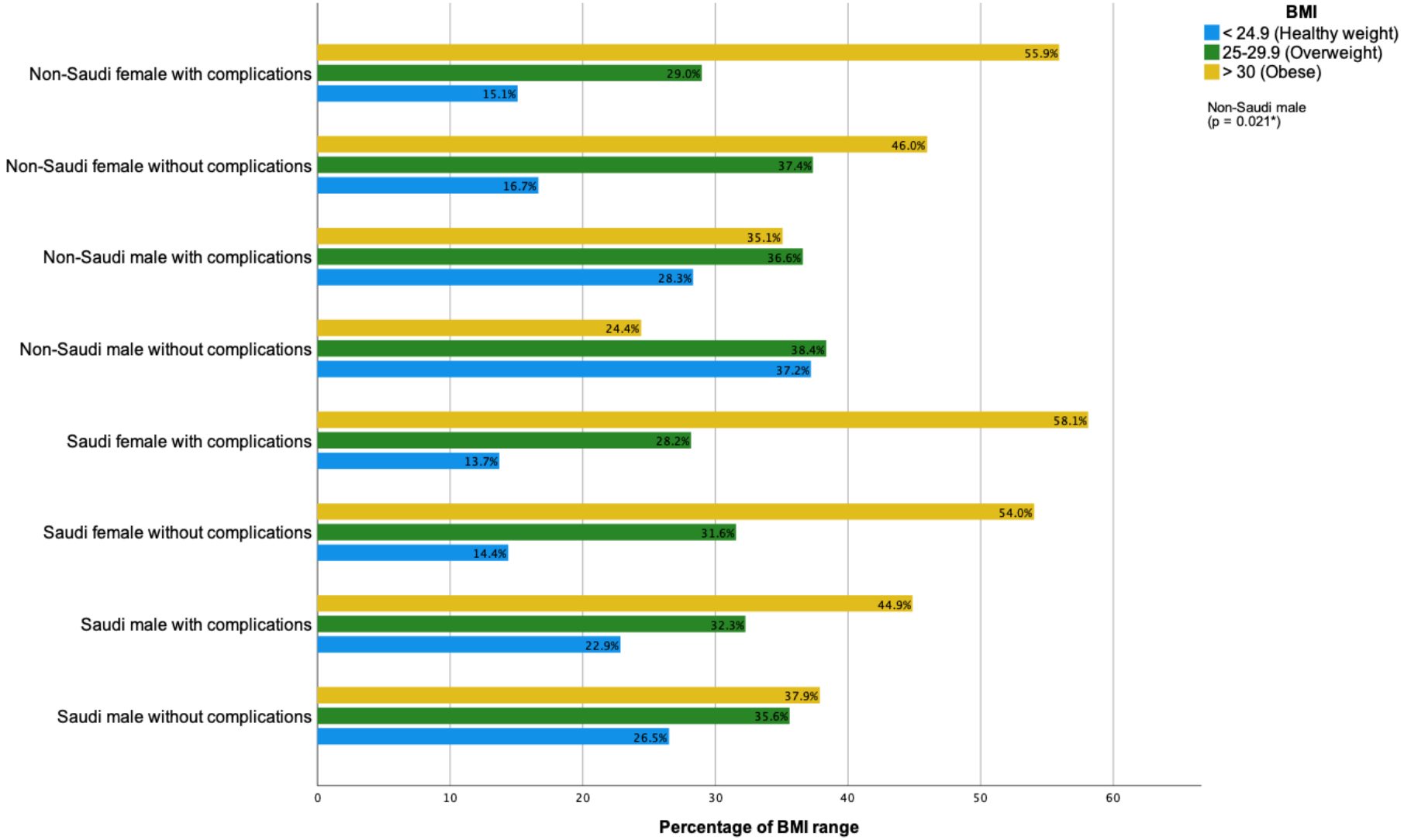

Figure C.3.3. The overall comparison between HbA1c level by gender, nationality, and with or without complications

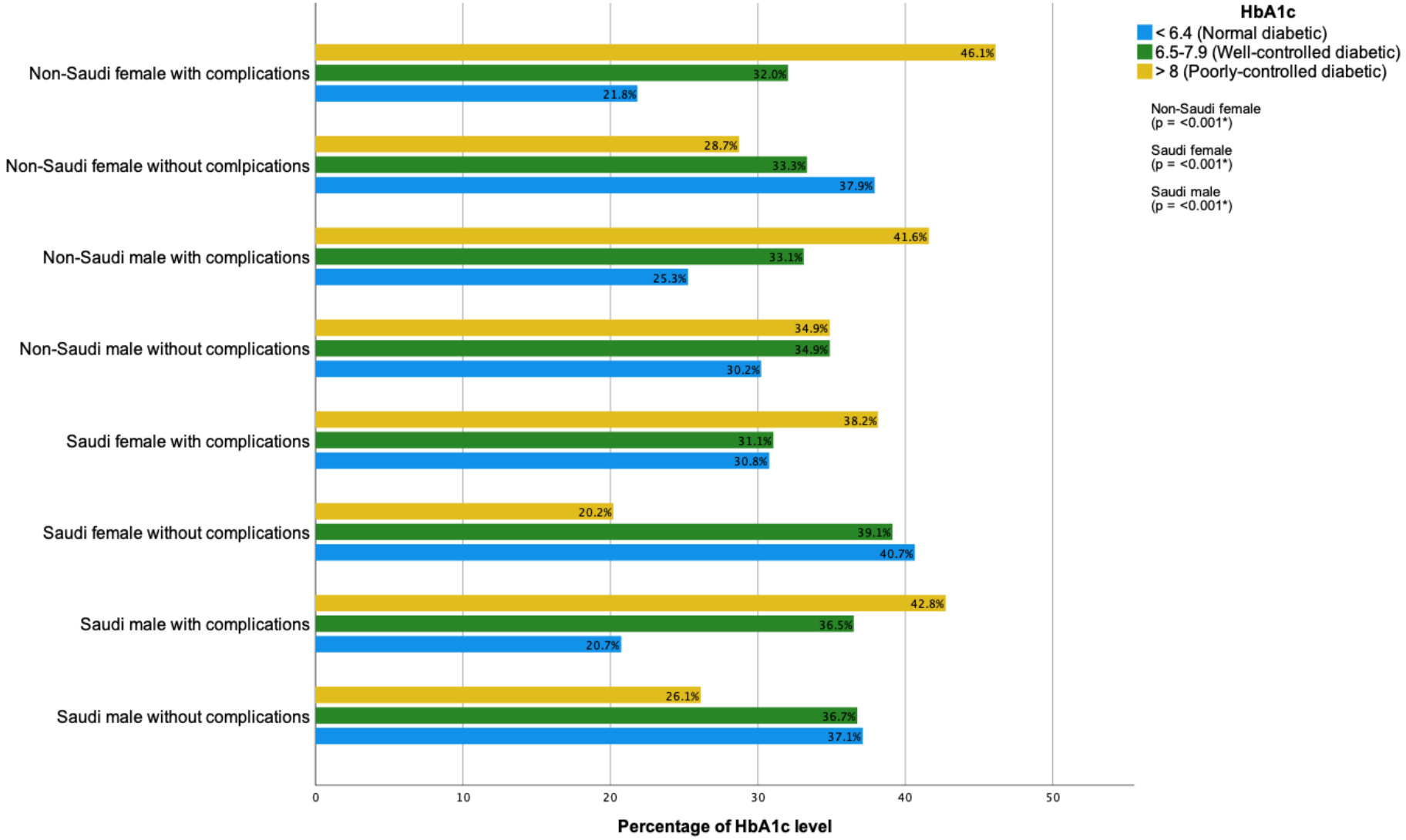

Table C.3.1. The total of ICD-10 codes used to retrieve the data and to differentiate between with or without complications

ICD-10 Codes	Code Description	no.	(%)
E11.00	Non-insulin-dependent diabetes mellitus with coma, not stated as uncontrolled	27	(0.7)
E11.01	Type 2 diabetes mellitus with hyperosmolarity without nonketotic hyperglycaemic-hyperosmolar coma [NKHHC]	28	(0.7)
E11.02	Type 2 diabetes mellitus with hyperosmolarity with coma	4	(0.1)
E11.11	Type 2 diabetes mellitus with ketoacidosis, without coma	74	(1.9)
E11.12	Type 2 diabetes mellitus with ketoacidosis, with coma	4	(0.1)
E11.13	Type 2 diabetes mellitus with lactic acidosis, without coma	6	(0.2)
E11.14	Type 2 diabetes mellitus with lactic acidosis, with coma	3	(0.1)
E11.15	Type 2 diabetes mellitus with ketoacidosis, with lactic acidosis, without coma	6	(0.2)
E11.16	Type 2 diabetes mellitus with ketoacidosis, with lactic acidosis, with coma	3	(0.1)
E11.20	Type 2 diabetes mellitus with renal complication, unspecified	116	(2.9)
E11.21	Type 2 diabetes mellitus with incipient diabetic nephropathy	81	(2)
E11.22	Type 2 diabetes mellitus with established diabetic nephropathy	63	(1.6)
E11.23	Type 2 diabetes mellitus with advanced renal disease	13	(0.3)

E11.29	Type 2 diabetes mellitus with other specified kidney complication	19	(0.5)
E11.30	Type 2 diabetes mellitus with ophthalmic complication, unspecified	82	(2.1)
E11.31	Type 2 diabetes mellitus with background retinopathy	46	(1.2)
E11.32	Type 2 diabetes mellitus with preproliferative retinopathy	8	(0.2)
E11.33	Type 2 diabetes mellitus with proliferative retinopathy	11	(0.3)
E11.34	Type 2 diabetes mellitus with other retinopathy	96	(2.4)
E11.35	Type 2 diabetes mellitus with advanced ophthalmic disease	2	(0.1)
E11.36	Type 2 diabetes mellitus with diabetic cataract	53	(1.3)
E11.39	Type 2 diabetes mellitus with other specified ophthalmic complication	18	(0.5)
E11.40	Type 2 diabetes mellitus with unspecified neuropathy	246	(6.2)
E11.41	Type 2 diabetes mellitus with diabetic mononeuropathy	21	(0.5)
E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy	47	(1.2)
E11.43	Type 2 diabetes mellitus with diabetic autonomic neuropathy	8	(0.2)
E11.49	Type 2 diabetes mellitus with other specified neurological complication	25	(0.6)
E11.50	Type 2 diabetes mellitus with circulatory complication, unspecified	76	(1.9)
E11.51	Type 2 diabetes mellitus with peripheral angiopathy, without gangrene	7	(0.2)

E11.52	Type 2 diabetes mellitus with peripheral angiopathy, with gangrene	19	(0.5)
E11.53	Type 2 diabetes mellitus with diabetic cardiomyopathy	30	(0.8)
E11.59	Type 2 diabetes mellitus with other specified circulatory complication	31	(0.8)
E11.60	Non-insulin-dependent diabetes mellitus with other specified complications, not stated as uncontrolled	46	(1.2)
E11.61	Type 2 diabetes mellitus with specified diabetic musculoskeletal and connective tissue complication	84	(2.1)
E11.62	Type 2 diabetes mellitus with specified skin and subcutaneous tissue complication	10	(0.3)
E11.63	Type 2 diabetes mellitus with specified periodontal complication	1	(0.0)
E11.64	Type 2 diabetes mellitus with hypoglycaemia	45	(1.1)
E11.65	Type 2 diabetes mellitus with poor control	722	(18.2)
E11.69	Type 2 diabetes mellitus with other specified complication	251	(6.3)
E11.70	Non-insulin-dependent diabetes mellitus with multiple complications, not stated as uncontrolled	70	(1.8)
E11.71	Type 2 diabetes mellitus with multiple microvascular or other specified nonvascular complications	14	(0.4)
E11.72	Type 2 diabetes mellitus with features of insulin resistance	31	(0.8)
E11.73	Type 2 diabetes mellitus with foot ulcer due to multiple causes	112	(2.8)
E11.8	Type 2 diabetes mellitus with unspecified complication	289	(7.3)

E11.80	Non-insulin-dependent diabetes mellitus with unspecified complications, not stated as uncontrolled	7	(0.2)
E11.81	Non-insulin-dependent diabetes mellitus with unspecified complications, stated as uncontrolled	11	(0.3)
E11.9*	Type 2 diabetes mellitus without complication	954	(24)
E11.90*	Non-insulin-dependent diabetes mellitus without complications, not stated as uncontrolled	31	(0.8)
E11.91*	Non-insulin-dependent diabetes mellitus without complications, stated as uncontrolled	21	(0.5)

*This code included in without complication group; ICD-10, international classification of diseases 10th revision; no, total number.

Alzahrani *et al.*
Health and Quality of Life Outcomes (2023) 21:27
https://doi.org/10.1186/s12955-023-02111-3

Health and Quality of Life Outcomes

REVIEW Open Access

Quality of life and mental health measurements among patients with type 2 diabetes mellitus: a systematic review

Owiss Alzahrani[1,2,3*], John P. Fletcher[1,2] and Kerry Hitos[1,2]

Abstract

Background Over the past few decades the benefits of assessing Quality of Life (QoL) and mental health in patients with Type 2 Diabetes Mellitus (T2DM) have steadily increased with limited studies relating to the most useful method to assess these patients. This study aims to identify, review, summarise, and evaluate the methodological quality for the most validated commonly used health-related QoL and mental health assessment measurements in diabetic patients.

Methods All original articles published on PubMed, MedLine, OVID, The Cochrane Register, Web of Science Conference Proceedings and Scopus databases were systematically reviewed between 2011 and 2022. A search strategy was developed for each database using all possible combinations of the following keywords: "type 2 diabetes mellitus", "quality of life", mental health", and "questionnaires". Studies conducted on patients with T2DM of ≥ 18 years with or without other clinical illnesses were included. Articles designed as a literature or systematic review conducted on either children or adolescents, healthy adults and/or with a small sample size were excluded.

Results A total of 489 articles were identified in all of the electronic medical databases. Of these articles, 40 were shown to meet our eligibility criteria to be included in this systematic review. Approximately, 60% of these studies were cross-sectional, 22.5% were clinical trials, and 17.5% of cohort studies. The top commonly used QoL measurements are the SF-12 identified in 19 studies, the SF-36, included in 16 studies, and the EuroQoL EQ-5D, found in 8 studies. Fifteen (37.5%) studies used only one questionnaire, while the remaining reviewed (62.5%) used more than one questionnaire. Finally, the majority (90%) of studies reported using self-administered questionnaires and only 4 used interviewer mode of administration.

Conclusion Our evidence highlights that the commonly used questionnaire to evaluate the QoL and mental health is the SF-12 followed by SF-36. Both of these questionnaires are validated, reliable and supported in different languages. Moreover, using single or combined questionnaires as well as the mode of administration depends on the clinical research question and aim of the study.

Keywords Type 2 Diabetes Mellitus, Quality of life, Mental health, Systematic review, Questionnaires

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Abstract

Background: Diabetes Mellitus is one of the most common diseases worldwide and is a major cause of morbidity and mortality. Type 2 Diabetes, where its hallmark is insulin resistance, which constitutes most cases. Although usually related to modifiable risk factors, such as obesity, poor diet, and a sedentary lifestyle, insulin resistance can have genetic causes. Here we present one of the rare causes of insulin resistance.

Case Summary: A 21-year-old- Saudi male patient with a long-standing history of deafness, bilateral visual impairment, a seizure disorder, and depression, presented to the emergency department with a 3-week history of polyuria, polydipsia, and weight loss. He was found to have significant hyperglycemia, managed initially with insulin infusion, then transitioned to subcutaneous insulin injections. Because he was requiring high doses of insulin, along with the presence of acanthosis nigricans, insulin resistance was suspected. Putting together his insulin resistance and chronic history of syndromic features, Alström syndrome (ALMS) was entertained. Genetic testing ordered and revealed a mutation in the ALMS1 gene which is consistent with Alström syndrome. Patient was then started on insulin sensitizers with tapering down of his insulin with good response.

Conclusion: Insulin resistance should be suspected if insulin requirement is high and if acanthosis nigricans is present. Alström syndrome is one of the rare causes of insulin resistance. Affected individuals will usually have insulin-resistance diabetes by a young age and have associated blindness and deafness by the time of diagnosis. Insulin sensitizers are an important part of the treatment.

Keywords: Insulin resistance, Diabetes Mellitus, Blindness, Hearing loss, Alström syndrome.
Abbreviations: ALMS - Alström syndrome

Funding and Conflicts of Interest

Conflict of Interest: The authors do not have any conflict of interest and this research did not receive any specific grant from 4funding agencies in the public, commercial, or not-for-profit sectors.

doi:10.1016/j.metabol.2023.155418

0011

The Effect of Coenzyme Q10 Supplementation on Insulin Resistance in Overweight/Obese Women with Polycystic Ovary Syndrome

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[b]I.K. Akhunbaev Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan;
[c]Beihua University, Jilin, China

Abstract

Introduction: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive age women. PCOS is associated with dyslipidemia, obesity, diabetes, hypertension, metabolic syndrome, and insulin resistance (IR), which contributes to the development of cardiovascular diseases. Coenzyme Q10 (CoQ10) is a benzoquinone that helps in the elimination of free radicals, and inhibition of lipid–protein oxidation.

Objective: To evaluate the effect of CoQ10 supplementation on IR in obese women with PCOS.

Materials and methods: For comparative analysis, the 82 obese women aged 18-40 years with and without the diagnosis of PCOS were divided into two groups: group 1 (obese with PCOS, n = 41); group 2 (obese without PCOS, n = 41), and underwent supplementation with CoQ10 100mg/day orally for eight weeks. Obesity was characterized by body mass index (cutoff point ≥ 30.0 kg/m²). All statistical analyses were performed by SPSS software.

Results: The analyzes of the pre-and post-intervention Group 1 parameters showed significant differences in association with the mass (92.5 vs. 88.8 kg; p=0.006), 120-minute glucose (135 vs. 118.3 mg/dL; p=0.003), insulin (15.6 vs. 11.5 μUI/mL; p=0.000), Homeostasis Model Assessment of IR (4.12 vs. 3.16; p=0.000) and quantitative insulin-sensitivity check index (0.28 vs. 0.29; p=0.000). Additionally, significant changes were observed in follicle-stimulating hormone (6.6 vs. 5.8 IU/mL; p=0.003), luteinizing hormone (6.8 vs. 5.1 IU/mL; p=0.000), testosterone (29.6 vs. 19.1 ng/dL; p=0.000), and progesterone (0.25 vs. 0.40 ng/dL; p=0.000).

Conclusion: Intervention with CoQ10 promotes beneficial effects in association with the main metabolic and hormonal changes in PCOS and obesity.

Keywords: Polycystic Ovary Syndrome; Insulin Resistance; Coenzyme Q10; Obesity
Abbreviations: Polycystic ovary syndrome (PCOS); insulin resistance (IR); Coenzyme Q10 (CoQ10)

Funding and Conflicts of Interest

No financial support was received for the study and the authors declare no conflicts of interest.

doi:10.1016/j.metabol.2023.155419

0012

Quality of Life and Mental Health Measurements Among Patients with Type 2 Diabetes Mellitus: A Systematic Review

Owiss Alzahrani[a,b,c], John P. Fletcher[a,b], Kerry Hitos[a,b]

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[b]The University of Sydney, Westmead Clinical School, Sydney, Australia
[c]Department of Community Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Abstract

Background: Over the past few decades the benefits of assessing Quality of Life (QoL) and mental health in patients with Type 2 Diabetes Mellitus (T2DM) have steadily increased with limited studies relating to the most useful method to assess these patients. This study aims to identify, review, summarise, and evaluate the methodological quality for the most validated commonly used QoL and mental health assessment measurements in diabetic patients.

Methods: All original articles published on the PubMed, MedLine, OVID, The Cochrane Register, Web of Science Conference Proceedings and Scopus databases were systematically reviewed between 2011 and 2022.

Results: Total of 489 articles were identified in all the electronic medical databases. Of these articles, 40 were shown to meet our eligibility criteria to be included in this systematic review. Approximately, 60% of these studies were cross-sectional, 22.5% were clinical trial, and 17.5% of cohort design the top commonly used QoL measurements included the SF-12 identified in 19 studies, the SF-36, included in 16 studies, and the EuroQoL EQ-5D, found in 8 studies. Fifteen (37.5%) studies used only one questionnaire, while the remaining reviewed (62.5%) used more than one questionnaire. The majority (90%) of studies reported using self-administered questionnaires and only 4 used interviewer mode of administration.

Conclusion: Our evidence highlights that the commonly used questionnaire to evaluate the QoL and mental health is the SF-12

Method: Current literature was reviewed following a search strategy in EMBASE, CINAHL and PsycInfo databases, using controlled vocabulary and free text search terms. Concepts focused on T1D and DE/ED and limited to English language, published in the last 10 years.

An expert panel of clinicians with significant clinical and research experience in ED/DE and diabetes was established, with national representation of the Diabetes Multidisciplinary Team (Endocrinologists, General Paediatrician, Psychiatry specialising in Eating Disorders, Psychology, Dietitian, Credentialed Diabetes Educator) and consumers. The panel reached a consensus based on their clinical experience and literature search. Extensive peer review, consumer engagement/review was undertaken.

Results: The Guideline was completed in August 2022 and presented at National Conferences (Australian Diabetes Society 2021, Australasian Paediatric Endocrine Group 2022, Australian Paediatric Society-International Society for Paediatric and Adolescent Diabetes 2022). It has been endorsed and published (Clinical Excellence Queensland and Australia New Zealand Paediatric Endocrinology and Diabetes Society in 2022).

Conclusion: With this Guideline, there is now a document with a systematic approach to provide meaningful care that can be adapted locally. The Guideline has received much interest, is endorsed and published in Australia. It is seeking greater awareness globally.

Reference(s)

[1] Clery *et al.* Systematic review and meta-analysis of the efficacy of interventions for people with T1D and DE. *Diabet Med* 2017;34(12):1667.

Diabetes Research and Clinical Practice 209S1 (2024) 111463
https://doi.org/10.1016/j.diabres.2024.111463

IDF23-0304

Contributing Risk Factors and Complications in Patients with Type 2 Diabetes Mellitus: A Retrospective Cohort Study

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Background: Prolonged hyperglycaemia and other risk factors increase the probability of neurological, ophthalmic, renal and foot ulcer complications in patients with Type 2 Diabetes Mellitus (T2DM) impacting quality of life and healthcare costs. Despite this, little is known in terms of prevalence, risk factors and complications in Saudi Arabia.

Aim: To evaluate the prevalence and differences in risk factors among patients with T2DM with and without diabetic-related complications.

Method: Age, gender, nationality, glycosylated haemoglobin test (HbA1c), and Body Mass Index (BMI) were collected retrospectively from patients with T2DM between January 2010 to July 2022 in all patients ≥ 18 years. The 10th revision of the International Classification of Diseases (ICD-10) codes was used to retrieve data from a tertiary referral hospital in Jeddah, Saudi Arabia.

Results: In total, there were 3,972 patients with T2DM and 74.7% with diabetic-related complications. Of these, 52.7% were females (P = 0.028) and 85.7% were > 45 years of age (P = 0.010). Compared to uncomplicated patients, males had a 17% greater likelihood of suffering from diabetic-related complications (OR = 1.17; 95% CI: 1.01–1.35, P = 0.028). Patients of > 45 years (compared to ≤ 45 years) had a 28% greater risk of complications (OR = 1.28; 95% CI: 1.06–1.55, P = 0.010). Obesity increased the risk by 31% (OR = 1.31; 95% CI: 1.09–1.59, P = 0.004) compared to healthy-weight people. Patients with poorly controlled HbA1c (compared to well-controlled) had a 2.4 times greater risk (OR = 2.39; 95% CI: 1.99–2.86, P = 0.001). Furthermore, high cholesterol levels increased this risk by almost two-and-a-half fold (OR = 2.41; 95% CI: 1.18–4.93, P = 0.015) compared to normal levels.

Conclusion: Our prevalence of T2DM complications was high, with a significantly increased likelihood of macro or micro complications associated with high HbA1c, BMI, and cholesterol levels in patients with T2DM. Future studies are needed to identify and manage these complications early to reduce the healthcare burden of this disease.

Diabetes Research and Clinical Practice 209S1 (2024) 111464
https://doi.org/10.1016/j.diabres.2024.111464

IDF23-0305

Comparison of Physician Perspective with Quality of Life and Mental Health Aspects in Type 2 Diabetes Mellitus Patients

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Background: Type 2 Diabetes Mellitus (T2DM) is linked to numerous complications impacting Quality of Life (QoL), mental health, long-term management and healthcare costs. There are limited studies on how to assess, manage and improve the outcomes of these patients in Saudi Arabia.

Aim: To measure the effect of QoL and mental health components among patients with T2DM with and without complications as well as the physician's perspective.

Method: A cross-sectional survey using the 12-item Short Form Version 2 (SF-12v2) consisting of QoL and mental health components was performed on diabetic patients ≥ 18 years from September to December 2022. This involved the Mental Component (MCS) and the Physical Component Summary (PCS) scores. A pre-designed and self-reported questionnaire based on perspectives and knowledge was distributed to primary health-care physicians managing and treating patients with T2DM in Jeddah, Saudi Arabia.

Results: In total, 182 patients and 54 physicians were included. Median age was 56 years ((Interquartile Range (IQR): 48–64), BMI 29.6 kg/m^2 (IQR: 25.9–32), HbA1c test was 7% (IQR: 6.5–8%), T2DM duration of 9 years (IQR: 4.7–18) with 60% of patients

Quality of Life and Mental Health Measurements Among Patients with Type 2 Diabetes Mellitus: A Systematic Review

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Background

• Over the past few decades the benefits of assessing Quality of Life (QoL) and mental health in patients with Type 2 Diabetes Mellitus (T2DM) have steadily increased. There have been limited studies relating to the most useful method to assess QoL these patients.

Aims

• To identify, review, summarise, and evaluate the methodological quality for the most validated commonly used QoL and mental health assessment measurements in diabetic patients.

Methods

• All original articles published in PubMed, MedLine, OVID, The Cochrane Register, Web of Science Conference Proceedings and Scopus databases were systematically reviewed between 2011 and 2022.

Results

• Total of 489 articles were identified. Of these, 40 met our eligibility criteria. (Figure 1)

• Approximately, 60% of these studies were cross-sectional, 22.5% were clinical trial, and 17.5% of cohort design. (Figure 2)

• The top commonly used QoL measurements included the SF-12 identified in 19 studies, the SF-36, included in 16 studies, and the EuroQoL EQ-5D, found in 8 studies. (Figure 3)

• Fifteen (37.5%) studies used only one questionnaire, while the remaining (62.5%) reviewed used more than one questionnaire.

• The majority (90%) of studies reported using self-administered questionnaires and only 4 used interviewer mode of administration. (Figure 2)

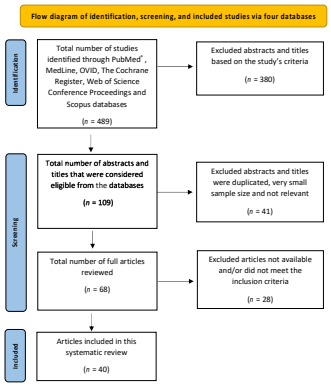


Figure 1: Total of included publications per year and study location.

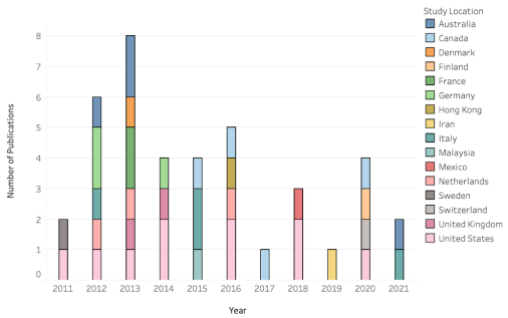
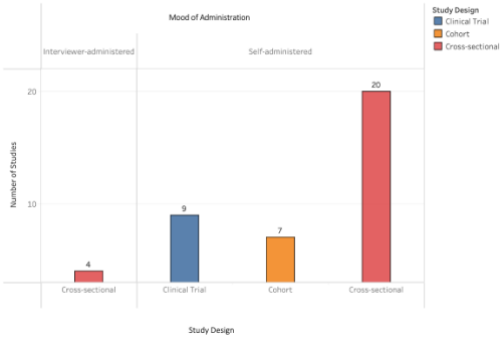


Figure 2: Study design and mood of administration per number of included studies.

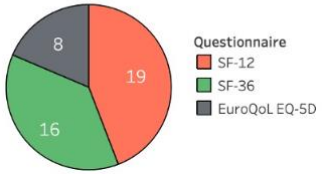


Conclusion

• Our evidence highlights that the commonly used questionnaire to evaluate the QoL and mental health is the SF-12 followed by SF-36. (Figure 3)

• Using a single or combined questionnaire together with the mode of administration is dependent on the clinical research question and aim of the study.

Figure 3: Top commonly used questionnaires with how many times used in the included studies for each questionnaire.



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Contributing Risk Factors and Complications in Patients with Type 2 Diabetes Mellitus: A Retrospective Cohort Study

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(Abstract number: IDF23-0304)

Background

- Several risk factors for Type 2 Diabetes Mellitus (T2DM) may contribute to people developing the disease, such as genetics, age, family history, poor dietary habits, gestational diabetes, pre-diabetes, increased Body Mass Index (BMI), sedentary lifestyle, high blood pressure, high lipid profile, and ethnicity.[1]
- Prolonged hyperglycaemia and other risk factors increase the probability of micro and macro complications in patients with T2DM, which impacts quality of life and healthcare costs.[2]

Aims

To evaluate the prevalence and differences in risk factors among patients with T2DM with and without diabetic-related complications in King Abdulaziz University Hospital, Jeddah, Saudi Arabia.

Methods

- The 10th revision of the International Classification of Diseases (ICD-10) codes was used to retrieve data from a tertiary referral hospital in Jeddah, Saudi Arabia.
- Age, gender, nationality, glycosylated haemoglobin test (HbA1c), and BMI were collected retrospectively from patients with T2DM between January 2010 to July 2022 in all patients ≥ 18 years.
- The data were extracted into Microsoft Excel, and all descriptive and analytical statistics were conducted by SPSS v 28 (IBM, SPSS, USA). Data were presented as Odds Ratio (OR) with 95% Confidence Interval (CI). A P-value < 0.05 was considered statistically significant for all analyses, and all tests were two-tailed.

Results

- In total, there were 3,972 patients with T2DM and 74.7% with diabetic-related complications. Of these, 52.7% were females (P = 0.028), and 85.7% were > 45 years of age (P = 0.010).
- Compared to uncomplicated patients, males had a 17% greater likelihood of suffering from diabetic-related complications (OR = 1.17; 95% CI: 1.01-1.35, P = 0.028).
- Patients of > 45 years (compared to ≤ 45 years) had a 28% greater risk of complications (OR = 1.28; 95% CI: 1.06-1.55, P = 0.010).
- Obesity (BMI ≥ 30 kg/m^2) increased the risk by 31% (OR = 1.31; 95% CI: 1.09-1.59, P = 0.004) compared to healthy-weight people.
- Patients with poorly controlled HbA1c (≥ 8% compared to well-controlled 6.5%-7.9%) had a 2.4 times greater risk (OR = 2.39; 95% CI: 1.99-2.86, P = 0.001).
- High cholesterol levels increased this risk by almost two-and-a-half fold (OR = 2.41; 95% CI: 1.18-4.93, P = 0.015) compared to normal levels (Table 1). Other risk factors such as blood pressure (P = 0.716), smoking status (P = 0.407), and duration of T2DM (P = 0.583) had no significant effect on complications.

Table 1. Univariate and adjusted multivariable analysis of gender, nationality, age, BMI, and HbA1c for all patients predicting the risk for the development of T2DM complications

Risk factors		Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Male		1.17 (1.01-1.35)	0.028	1.20 (1.03-1.39)	0.015
Saudi		1.11 (0.95-1.29)	0.161	1.14 (0.97-1.33)	0.092
Age > 45 yrs		1.28 (1.06-1.55)	0.010	1.20 (0.98-1.46)	0.064
BMI ranges, kg/m^2	≤ 24.9	(Ref.)			
	25-29.9	1.01 (0.83-1.24)	0.871	1.04 (0.85-1.28)	0.649
	≥ 30	1.31 (1.09-1.59)	0.004	1.39 (1.14-1.69)	<0.001
HbA1c levels, %	≤ 6.4	(Ref.)			
	6.5-7.9	1.34 (1.13-1.59)	<0.001	1.30 (1.10-1.55)	0.002
	≥ 8	2.39 (1.99-2.86)	<0.001	2.36 (1.96-2.84)	<0.001

OR, odds ratio; CI, confidence interval; T2DM, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycosylated haemoglobin test; yrs, years.

Conclusion

- Our prevalence of T2DM complications was high, with a significantly increased likelihood of macro or micro complications associated with uncontrolled HbA1c, BMI, and cholesterol levels in these patients.
- Future studies are needed to identify and manage these complications early to reduce the healthcare burden of this disease.

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Background

Type 2 Diabetes Mellitus (T2DM) is linked to numerous complications impacting Quality of Life (QoL), mental health, long-term management and healthcare costs.[123] There are limited studies on how to assess, manage and improve the outcomes of these patients in Saudi Arabia.

Aims

To measure the effect of QoL and mental health components among patients with T2DM with and without complications as well as the physician's perspective.

Methods

- A cross-sectional survey using the 12-item Short Form Version 2 (SF-12v2) consisting of QoL and mental health components was performed on diabetic patients ≥ 18 years from September to December 2022. This involved the Mental Component (MCS) and the Physical Component Summary (PCS) scores.
- A pre-designed and self-reported questionnaire based on perspectives and knowledge was distributed to primary healthcare physicians managing and treating patients with T2DM in Jeddah, Saudi Arabia.
- The data were extracted into Microsoft Excel, and all descriptive and analytical statistics were conducted by SPSS v 28 (IBM, SPSS, USA). Data were presented as Median, Interquartile Range (IQR) and Odds Ratio (OR) with 95% Confidence Interval (CI). A P-value < 0.05 was considered statistically significant for all analyses, and all tests were two-tailed.

Results

- In total, 182 patients and 54 physicians were included. Median age of the patients was 56 years (IQR: 48-64), BMI 29.6 kg/m^2 (IQR: 25.9-32), HbA1c test was 7% (IQR: 6.5-8%), T2DM duration of 9 years (IQR: 4.7-18) with 60% of patients having diabetic complications.
- Median MCS score was 52.3 (IQR: 48-55.5), and 46.3 (IQR: 42.9-54.1) for PCS.
- Variables associated with increasing the risk of complications included:
  i. Female gender (OR=9.40; 95% CI:1.70-51.83; P=0.010)
  ii. Poorly controlled HbA1c (OR=10.32; 95% CI:1.31-80.81; P=0.026)
  iii. High cholesterol (OR=8.74; 95% CI:1.79-42.53; P=0.007)
  iv. Long T2DM duration (OR=8.82; 95% CI:1.42-54.78; P=0.019)
  v. MCS below-average score (OR=3.44; 95% CI:1.65-7.18; P=<0.001)
  vi. PCS below-average score (OR=5; 95% CI:2.49-10.01; P<0.001) (Table 1)
- Physicians responded unfavourably to the physical 2.23 (SD=0.47) and mental health component questions 1.97 (SD=0.57).

Table 1. Univariate and adjusted multivariate analysis of SF-12v2 scores for all T2DM patients predicting the risk for the development complications

	Unadjusted	95% C.I. for OR			Adjusted	95% C.I. for OR		
SF-12v2 score	OR	Lower	Upper	P	OR	Lower	Upper	P
MCS, below average	2.803	1.433	5.485	0.003	3.447	1.653	7.187	<0.001
PCS, below average	4.289	2.238	8.22	0.000	5.002	2.499	10.01	<0.001
MH, below average	7.577	2.818	20.372	0.000	2.472	0.718	8.504	0.151
RE, below average	6.309	2.959	13.454	0.000	2.694	1.051	6.902	0.039
SF, below average	2.924	1.502	5.692	0.002	1.499	0.645	3.483	0.347
V, below average	7.577	2.818	20.372	0.000	3.263	0.904	11.774	0.071
GH, below average	5.507	2.182	13.897	0.000	1.807	0.578	5.648	0.309
BP, below average	6.034	3.129	11.634	0.000	1.375	0.559	3.382	0.487
PF, below average	2.783	1.472	5.261	0.002	2.327	0.974	5.561	0.057
RP, below average	5.067	2.511	10.225	0.000	1.984	0.820	4.800	0.128

T2DM, type 2 diabetes mellitus; SF-12v2, the 12-item short form health survey version 2; MCS, mental component summary; PCS, physical component summary; MH, mental health; RE, role emotional; SF, social functioning; VT, vitality; GH, general health; BP, bodily pain; PF, physical functioning; RP, role physical.

Conclusion

- Our findings reflect the negative impact on QoL and mental health among patients with T2DM, particularly those with complications.
- Establishing a multidisciplinary approach that improves physician awareness and includes HRQOL and mental health assessment as part of routine management is essential.

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