Diabetes management in low and middle income countries

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Diabetes management in low and middle income countries

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Table of Contents

Abstract I

General declaration IV

Publications IX

Acknowledgements XI

Abbreviations XIV

Chapter 1 1

Introduction 1

Background 3

1.1 Definition of diabetes 5

Diabetes 5

1.1.1 Type 1 diabetes 5

1.1.2 Type 2 diabetes 6

1.1.3 Gestational diabetes 6

1.1.4 Pre-diabetes 6

1.2 Diagnosis of diabetes and pre–diabetes 7

1.3 Prevention or delay of type 2 diabetes 8

1.3.1 Risk factors for type 2 diabetes 10

1.4 Complications of diabetes 11

1.4.1 Microvascular complications of diabetes 12

1.4.2 Macrovascular complications 13

1.4.3 Disability related to diabetes 15

1.5 Management of diabetes 17

1.5.1 Guidelines for the management of diabetes 17

1.5.2 Non-pharmacological management of diabetes 18

1.5.2.3 Diabetes self-management education and support 19

1.5.3 Pharmacological management of diabetes 20

1.6 Delivery of care in diabetes 25

1.6.1 Diabetes management in actual practice, the role of Real World Evidence (RWE) studies 26

1.6.2 The role of nurse prescribers in diabetes management 27

1.7 The aims of this thesis 28
REFERENCES 32
Chapter 2 53
Methods and Materials 53
2.1 Mauritius Non-Communicable Disease Survey 55
2.2.1 Survey population and sampling method 56
2.2.2 Survey procedure and measurements 58
2.2.3 Statistical analysis 64
2.2.4 Ethical approval 66
2.2.1 Data sources 67
2.2.2 General demographic 68
2.2.3 Disease history and complications of diabetes 68
2.2.4 Glycaemic, blood pressure and lipid level control 69
2.2.5 Medications 69
2.2.6 Statistical analysis 70
2.2.7 Ethical approval 70
2.3 The effect of nurse prescribers on HbA1c levels in diabetes; a systematic review and meta-analysis 71
2.3.1 Data sources and searches 71
2.3.2 Search methods for identification of studies 71
2.3.3 Data extraction and quality assessment 72
2.3.4 Statistical analysis 73
REFERENCES 74
Chapter 3 77
Understanding the contributing factors in the association of diabetes with disability 77
3.1 Disability and the burden of diabetes associated with disability 79
Chapter 4 93
Trends of diabetes management in Mauritius 93
REFERENCES 111
Chapter 5 113
Trends of diabetes management outside of North America and Western Europe with respect to glycaemic control 113
5.1 Real world evidence 115

REFERENCES 140
Chapter 6 141
Trends of diabetes management outside of North America and Western Europe with respect to cardiovascular disease control 141
Chapter 7 171
Nurse prescribers and diabetes management 171
REFERENCES 187
Chapter 8 189
Discussion and conclusion 189
8.1 Overview of the main findings 191
8.1.1 Diabetes is associated with higher risk of disability, while diabetes risk factors have a major contribution to this association 191
8.1.2 Reaching glycaemic, blood pressure and lipid targets is challenging for patients with diabetes in LMICs 192
8.1.3 Narrowing in some of the health inequalities in people with diabetes 193
8.1.4 Use of glucose lowering medications has increased and diabetes treatment become more complex and intensive 194
8.1.5 There is a need for research on the effectiveness rather than efficacy of new GLMs at the population level 195
8.1.6 There was an improvement in lipid management from 2006 to 2015 196
8.1.7 Anti-hypertensive treatment approaches shifted from using ACE inhibitors towards using more ARBs 197
8.1.8 Change and inconsistency in the blood pressure targets suggested by guidelines could result in no improvement in hypertension management 197
8.1.9 Nurse-led prescribing services are an alternative approach for glycaemic control where there is limited access to doctor-led services 198
8.2 Strength and limitations 201
8.3 Implications and future direction 203
8.3.1 Clinical implication 203
8.3.2 Public health policy implication 204
8.4 Areas for future research 205
8.5 Conclusion 205
REFERENCES 207
Appendixes 211

Appendix 1: Response rate for Mauritius NCD surveys (2009, 2015 and 1998 cohort)…...212
Appendix 2: Mauritius 2015 non- communicable disease survey…….214
Appendix 3: Real World Evidence data sheet……... 238

List of Tables

Table 1. WHO criteria for the diagnosis of diabetes and pre-diabetes (17) 8

Table 2. Modifiable and non-modifiable risk factors for type 2 diabetes.....8

Table 3. Non-insulin medicines for treatment of type 2 diabetes.....21

Table 4. Insulin type in treatment of diabetes.....23

Table 1. Mauritius Non-Communicable Disease Survey Questionnaire.....58

Table 2. Body mass index classification of obesity by ethnicity.....62

Table 3. Characteristics of clinical services included in the Real World Evidence project 67

List of Figure

Figure 1. The main types of CVD (International Diabetes Federation. Diabetes and cardiovascular disease. Brussels, Belgium: International Diabetes Federation, 2016. www.idf.org/cvd) (80) 15

Abstract

Back ground

The epidemic of diabetes has shown no signs of relenting, with the number of people affected by diabetes expected to reach to 629 million by 2045. Low and middle income countries (LMIC) carry 80% of the burden of diabetes, and more than 60% of all people with diabetes in the world live in Asia. Successful management of diabetes reduces economic loss to people with diabetes and their families, and to health systems and national economies. Given a higher burden of diabetes and the limited data available from LMIC, the aim of this PhD was to understand the impact of diabetes on disability and to explore diabetes management in a number of low-middle income countries.

Methods

First, we assessed the extent to which the association of diabetes with disability is explained by diabetes risk factors and co-morbidities. Then, we examined the trends of diabetes management and therapeutic approaches in a number of LMICs by using both individual level data obtained from surveys and also the Real-World Evidence data obtained from medical records or national registries. Finally, we examined a potential solution to improve diabetes management by studying how implementing nurse prescribers in health care services can potentially improve diabetes management.

Projects

1. Mauritius Non-Communicable Disease survey, 2009 and 2015.
2. Real world evidence project. The data for this project obtained from medical record of patients from 10 clinical services in 9 countries.

3. Systematic review and meta-analysis for the effect of nurse prescribers on glycaemic control in diabetes.

Summary of findings

1. Obesity explained the largest percentage of the relationship between diabetes and disability.
2. In Mauritius, from 2009 to 2015, glycaemic and blood pressure control improved, and total and LDL cholesterol control remained unchanged.
3. The real world study showed that from 2006 to 2015, the proportion of patients with diabetes using glucose lowering medications (GLMs) increased. Therapeutic regimens become more complex and aggressive with increases in triple and insulin therapy and decreases in monotherapy. Despite this, there was no clear and significant improvement in glycaemic control.
4. The real word study also showed that from 2006 to 2015, there was improvement in the management of cholesterol, likely due to a substantial increase in statin use. The proportion of patients with BP>140/90 mmHg increased and antihypertensive treatment shifted from ACE inhibitors to ARBs.
5. The systematic review and meta-analysis showed that when nurses replaced physicians, their outcomes were comparable to those of physicians in regard to glycaemic control.

Conclusion

Weight management should be considered as one of the key factors in reducing disability in patients with diabetes. Therapeutic regimens for control of diabetes become more complex and aggressive, but the majority of people with diabetes had inadequately controlled HbA1c, blood pressure and lipids, stressing the need for further improvements in diabetes management

in LMIC. There may be value in providing nurse-led prescribing services where there is limited access to doctor-led services.

General declaration

Monash University declaration for thesis based or partially based on conjointly published or unpublished work

General declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes three original papers published in peer reviewed journals and two submitted publication. The core theme of the thesis is understanding diabetes management in low and middle income countries. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Department of Diabetes and Population Health at Baker Heart and Diabetes Institute under the supervision of Prof Dianna Magliano, Prof Jonathan Shaw.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of (chapter 3 – 7) my contribution to the work involved the following:

Thesis Chapter	**Publication Title**	**Status** (published, in press, accepted or returned for revision, submitted)	**Nature and extent of candidate's contribution**	**Co-author name(s) Nature and % of Coauthor's contribution**	**Coauthor (s), Monash Student Y/N**
3	The association between type 2 diabetes and disability: what is the contribution of diabetes risk factors and diabetes complications?	Published	80%. Development of survey questionnaire, cleaning, analysing and interpreting the data, conceptualisation and writing of the manuscript, critical revision, corresponding author	***Jonathan E. Shaw , Dianna J. Magliano*** Survey design, conceptualisation, interpretation and approval for the final for publication ***Paul Z. Zimmet, Stefan Söderberg, Sudhir Kowlessur, Maryam Timol, Noorjehan Joonas, Ameena Sorefan, Praneel Gayan, George M.M. Alberti, Jaakko Tuomilehto*** Survey design , reviewing and editing the manuscript ***Digsu N. Koye (4%)*** Reviewed and edited the manuscript	N for all but Digsu N. Koye 4%
4	Meeting American Diabetes Association diabetes management targets: trends in Mauritius	Published	80%. Development of survey questionnaire, cleaning, analysing and interpreting the data, conceptualisation and writing of the manuscript, critical revision, corresponding author	***Jonathan E. Shaw , Dianna J. Magliano*** Survey design, conceptualisation, interpretation and approval for the final for publication ***Paul Z. Zimmet, Stefan Söderberg, Sudhir Kowlessur, Maryam Timol, Noorjehan Joonas, George M.M.***	N for all

				Alberti, Jaakko Tuomilehto Survey design , reviewing and editing the manuscript ***Benjamin J. Shaw*** Data cleaning, reviewing and editing the manuscript	
5	Trends of diabetes management and treatment approaches outside of America and West Europe from 2006 to 2015	Submitted	80%. Research design, extracting and summarizing data from medical record of patients in each individual clinical services, cleaning, analysing and interpreting the data, conceptualisation and writing of the manuscript, critical revision, corresponding author	***Jonathan E. Shaw , Dianna J. Magliano*** Research design, conceptualisation, interpretation and approval for the final for publication ***Stephanie K Tanamas, Filip Surmont, Silver Bahendeka, Chern-En Chiang, Jorge F Elgart, Juan Jose Gagliardino, Sanjay Kalra, Satheesh Krishnamoorthy, Andrea Luk, Hiroshi Maegawa, Ayesha A Motala, Fraser Pirie, Ambady Ramachandran, Khaled Tayeb, Olga Vikulova, Jencia Wong*** Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N for all
6	Cardiovascular disease management in people with diabetes outside of North America and Western	Published	80%. Research design, extracting and summarizing data from medical record of patients in each individual	***Jonathan E. Shaw , Dianna J. Magliano*** Research design, conceptualisation, interpretation and approval for the final for publication	

	Europe in 2006 and 2015		clinical services, cleaning, analysing and interpreting the data, conceptualisation and writing of the manuscript, critical revision, corresponding author	***Stephanie K Tanamas, Filip Surmont, Silver Bahendeka, Chern-En Chiang, Jorge F Elgart, Juan Jose Gagliardino, Sanjay Kalra, Satheesh Krishnamoorthy, Andrea Luk, Hiroshi Maegawa, Ayesha A Motala, Fraser Pirie, Ambady Ramachandran, Khaled Tayeb, Olga Vikulova, Jencia Wong*** Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	
7	The effect of nurse prescribers on glycaemic control in type 2 diabetes: a systematic review and meta-analysis	Published	80%. Conceiving the study, developing search strategy, searching databases, deciding on inclusion of studies, extracting details of selected studies, analysing the data , conceptualisation and writing of the manuscript, critical revision, corresponding author	***Jonathan E. Shaw , Dianna J. Magliano*** Conceiving the study, deciding on inclusion of studies, conceptualisation, reviewing and editing the manuscript, approval for the final for publication ***Digsu N. Koye (5%)*** Extracting details of selected studies, reviewing and editing the manuscript	N for all but Digsu N. Koye 5%

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

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*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Publications

ASSOCIATED PUBLICATIONS, PRESENTATIONS AND AWARDS

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- **Maryam Tabesh**, Dianna J. Magliano, Digsu N Koye, Jonathan E, **The effect of nurse prescribers on glycaemic control in type 2 diabetes: a systematic review and meta-analysis**, International Journal of Nursing Studies. 2018; 78: 37-43.

PRESENTATIONS

- **The association between diabetes and disability: what is the contribution of diabetes risk factors and complications?** International Diabetes Federation congress, December 2017, Abu Dhabi, UAE.

- **The trends of diabetes management and treatment approaches outside of America and West Europe from 2006 to 2015.** International Diabetes Epidemiology Group, December 2017, Abu Dhabi, UAE.

- **Trends of cardiovascular disease management in people with diabetes outside of North America and Western Europe.** International Diabetes Epidemiology Group, December 2017, Abu Dhabi, UAE.

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Abbreviations

AACE/ACE	American Association of Clinical Endocrinologists and American College of Endocrinology
ABC	HbA1c, blood pressure, cholesterol
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACEI	Angiotensin converting enzyme inhibitors
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
ARBs	Angiotensin receptor blockers
ARIC	Atherosclerosis Risk in Communities
AusDiab	Australian Diabetes, Obesity, and Lifestyle Study
BMI	Body mass index
BP	Blood pressure
CABG	Coronary Artery Bypass Grafting
CABG/PCI	Coronary Artery Bypass Grafting/ percutaneous coronary intervention
CCBs	Calcium channel blockers
CENTRAL	Cochrane Central Register of Controlled Trials
CES-D	Centre for Epidemiological Studies Depression Scale
CGM	Continuous Glucose Monitoring
Chol	Cholesterol
CI	Confidence interval
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DASH	Dietary Approaches to Stop Hypertension
DPP4i	Dipeptidyl peptidase-4 inhibitors
DSME/S	Diabetes self-management education and support
EASD	European Association for the Study of Diabetes
ECRHS	The European Community Respiratory Health Survey
EPIC Norfolk	European Prospective Investigation of Cancer and Nutrition
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate

GI	Glycaemic index
GLM	Glucose lowering medication
GLP-1	Glucagon-like peptide-1 receptor
GPAQ	Global Physical Activity Questionnaire
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
HOT	Hypertension Optimal Treatment
HPLC	High performance liquid chromatography
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
Katz	Katz Index of Independence in Activities of Daily Living
LDL	low density protein
LMIC	Lower and middle income countries
MACE	Major adverse cardiac events
MESH	Medical Subject Heading
MENA	Middle East and North Africa
MI	Myocardial infarction
min/week	Minutes per week
mmHg	Millimeters of Mercury
mmol/L	Millimoles per litre
mmol/mol	Millimoles per mole
NCD	Non-Communicable Disease
NPH	Neutral protamine Hagedorn
OGTT	Oral glucose tolerance test
PCI	Percutaneous coronary intervention
PSU	Primary sampling unit
RAAS	Renin-angiotensin-aldosterone system
RCTs	Randomised Clinical Trials
RR	Relative risk
RWE	Real World Evidence
SD	Standard deviation
SE	Standard error

SGLT2 inhibitors	Sodium-glucose transporter 2 inhibitors
TG	Triglycerides
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
WHO	World Health Organization

Chapter 1

Introduction

Background

Diabetes represents both a medical and socio-economic crisis across the globe (1, 2). Despite scientific breakthroughs, and better healthcare facilities, the burden of diabetes continues to increase, especially in middle and low income countries (3, 4). The large burden of diabetes is due mainly to a variety of severe complications associated with long disease duration (4-7).

The International Diabetes Federation (IDF) reported that the number of people affected by diabetes was 425 million in 2017 (3). The epidemic of diabetes has shown no signs of relenting, with the number of people affected by diabetes expected to reach to 629 million by 2045 (3, 8). The large global increase in the number of people affected by diabetes is mainly attributed to the large increase in the diabetes population in specific regions namely Africa, South East Asia, the Middle East and North Africa (MENA) where the numbers of affected people will increase by 156%, 84% and 72%, respectively. Low and middle income countries (LMIC) carry 80% of the burden of diabetes, and more than 60% of all the people with diabetes live in Asia (5). Population growth, aging of the population, rapid urbanisation, unhealthy diet and a sedentary lifestyle are the major contributors to such a large increase in the number of people affected by diabetes in these regions (5).

People with diabetes are at risk of developing a number of disabling complications including cardiovascular disease, renal failure, blindness and lower limb amputation. In recent years, it has been recognised that in addition to these *classical* complications, others conditions, including liver disease, depression and physical disability, are also more common in people with diabetes. Disability is associated with many poor outcomes including loss of employment and productivity, increased use of health services and premature death which impose a substantial burden on healthcare expenditure (9). Without effective strategies to support better management of diabetes, it is likely that there will be large increases in the rates of these complications of diabetes resulting in disability and premature death. Effective approaches are

required to prevent the complications and premature death that can result from diabetes. These approaches include control of risk factors such as blood glucose, blood pressure and cholesterol levels. Successful management of diabetes, reduces economic loss to people with diabetes and their families, and to health systems and national economies (10).

While there is a modest amount of information available from high-income countries concerning trends of diabetes management, there are limited data available in LMIC. Given a higher burden of diabetes and the limited data available from LMIC, the aim of this PhD was to explore diabetes management in some low and middle income countries.

This thesis consists of eight chapters. This first chapter will define diabetes, its risk factors and related complications and the importance of diabetes management in reducing the burden of diabetes. This chapter will also briefly introduce components of diabetes guidelines and explain the parameters needed to be addressed to improve diabetes management. Finally, this chapter will explain the outline and aims of this thesis.

1.1 Definition of diabetes

Diabetes

Diabetes is a serious chronic disease characterised by an elevated level of glucose in the blood. Diabetes is caused by insufficient insulin secretion (a hormone that regulates blood glucose) and/or insulin resistance (the diminished ability of cells to respond to the action of insulin). Symptoms of diabetes include increased thirst, frequent urination, hunger, fatigue and blurred vision, though many people have no symptoms. There are three main types of diabetes – type 1 diabetes, type 2 diabetes and gestational diabetes (GDM). There are some other rare types of diabetes such as monogenic diabetes (resulting from mutations or changes in a single gene) and secondary diabetes (which is a consequence of another medical condition).

1.1.1 Type 1 diabetes

Type 1 diabetes, previously known as juvenile diabetes, is an auto-immune condition in which the immune system is activated to destroy the beta cells in the pancreas, which are responsible for producing insulin. Type 1 diabetes accounts for 5–10% of all cases of diabetes and usually develops among people aged <30 years (1). Patients with type 1 diabetes are dependent on use of insulin for survival. However, some with type 1 (e.g. latent autoimmune diabetes of adults) may survive for several years without insulin. Risk factors for type 1 diabetes are poorly understood but genetic susceptibility, viral infection and having white ethnicity appear to play a role in development of type 1 diabetes.

(11-13).

1.1.2 Type 2 diabetes

Type 2 diabetes, previously known as adult onset diabetes, usually starts with resistance to the effects of insulin and then gradually progresses to a loss of capacity to produce enough insulin in the pancreas (14). Type 2 diabetes is the most common type of diabetes and accounts for 90–95% of all cases of diabetes (1). Risk factors for type 2 diabetes include age, family history of diabetes (15), overweight or obesity (16), lack of physical activity (17), hypertension (18), low levels of high density lipoprotein (HDL), high levels of triglycerides (TG), and a history of cardiovascular disease (19, 20). Type 2 diabetes can be delayed or even prevented by increasing physical activity level, weight management and following a healthy diet (21).

1.1.3 Gestational diabetes

Gestational diabetes is a condition in which a woman develops diabetes during pregnancy. It is estimated that 16.2% of live births to women in 2017 had some form of hyperglycaemia in pregnancy. An estimated 86.4% of those cases were due to GDM (3). GDM usually disappears after childbirth. However, a woman who has had GDM faces a higher risk of developing type 2 diabetes later in life. Risk factors for GDM include age, overweight or obesity, having a history of polycystic ovary syndrome, previously having GDM and a family history of diabetes. GDM is usually treated by exercise, diet and insulin (22).

1.1.4 Pre-diabetes

Pre-diabetes is a condition in which blood glucose levels are higher than normal but still not high enough to be diagnosed as type 2 diabetes (Table 1). Pre-diabetes is the precursor to type 2 diabetes (23). Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are two

forms of pre-diabetes (24). IFG is characterised by reduction in hepatic insulin sensitivity, beta cell dysfunction and elevated glucagon secretion. In IFG, the fasting plasma glucose is 6.1 – 7.0 mmol/l and the 2 hour-plasma glucose is normal (<7.8 mmol/l). IGT is characterised by a reduction in peripheral insulin sensitivity (i.e. in muscles), relatively normal hepatic insulin sensitivity, progressive loss of beta cell function and elevated glucagon secretion. In IGT, the 2 hour-plasma glucose level is above normal (7.8–11.1 mmol/l) as a result of reduced peripheral insulin sensitivity but the fasting plasma glucose is in the non-diabetic range (<7.0 mmol/l). Individuals developing both IFG and IGT exhibit defects in both peripheral and hepatic insulin sensitivity, as well as a progressive loss of beta cell function (25).

1.2 Diagnosis of diabetes and pre–diabetes

The diagnosis of diabetes or pre-diabetes is based on the measurement of fasting plasma glucose, plasma glucose 2-hour after ingestion of a 75g oral glucose load or haemoglobin A1c (HbA1c). Diagnostic criteria for diabetes and pre-diabetes have been debated and updated over decades; the current criteria from the World Health Organization (WHO) are shown in Table 1 (25).

HbA1c reflects average plasma glucose over the previous three months, and is a key measure for assessing glycaemic control. However, it can also be influenced by a number of other factors, including red cell turnover, which can sometimes lead to inaccuracies in HbA1c as an indicator of glycaemic control. After much debate, in 2009, the American Diabetes Association and the WHO included HbA1c cut-points for the diagnosis of diabetes. The cut-point recommended for diagnosis of diabetes is HbA1c ≥6.5% (48 mmol/mol) (8). The ADA also recommended using HbA1c 5.7–6.4% for identifying pre-diabetes. However, some guidelines

for example Australian Diabetes Society guideline do not recommend using HbA1c for identifying pre-diabetes (26).

Table 1. WHO criteria for the diagnosis of diabetes and pre-diabetes (25)

	Fasting plasma glucose		2-hour plasma glucose
Normal glucose tolerance	<6.1 mmol/l	and	<7.8 mmol/l
Impaired fasting glucose	≥6.1 mmol/l and <7.0 mmol/l	and	<7.8 mmol/l
Impaired glucose tolerance	<7.0 mmol/l	and	≥7.8 mmol/l and <11.1 mmol/l
Diabetes	≥7.0 mmol/l	or	≥11.1 mmol/l

1.3 Prevention or delay of type 2 diabetes

Previous studies have demonstrated the effectiveness of lifestyle interventions to reduce incidence of diabetes in people with pre-diabetes (27-31). One study showed significant mortality benefits with early intervention to prevent type 2 diabetes (32). It is also beneficial for society in terms of cost and reduced health care services demand (33). Prevention of diabetes is possible by controlling modifiable risk factors such as diet, physical activity and weight (34, 35). Pharmacological interventions also prevent or delayed type 2 diabetes in those with pre-diabetes (36). Diabetes risk factors are summarized in Table 2 (33) .

Table 2. Modifiable and non-modifiable risk factors for type 2 diabetes

Modifiable risk factors	Non-modifiable risk factors
Overweight (BMI* ≥25 Kg/m^2)	Ethnicity
Central obesity	Family history of Type 2 diabetes
Sedentary life style	Age
Pre diabetes (IGT or IFG)	Gender
Metabolic syndrome	History of gestational diabetes

Hypertension	Polycystic ovary syndrome
Decreased HDL-chol	
Increased TG	
Dietary factors	
Fatty liver	
Reduced/increased sleep	
Intrauterine environment	
Inflammation	

*BMI: Body mass index

The Da Qing Diabetes Prevention Study was conducted in 1986 and was one of the earliest intervention studies aimed at preventing diabetes and was commenced in 1986 among people with IGT in China. Participants received advice on life style change including diet and a physical activity program. The 20-year follow up of this study in 2008 showed that 92% of this high risk population, developed diabetes in the absence of the intervention, and only six years of life style intervention was associated with a 43% reduction in the incidence of diabetes (32). The findings of this study were confirmed with other trials. The Diabetes Prevention Program (DPP) study in the U.S. (27) and Diabetes Prevention Study (DPS) in Finland (30) demonstrated the benefit of lifestyle intervention in reducing risk of diabetes in the IGT population. Both the DPP (27) and DPS (30) studies showed a 58% reduction in the risk of diabetes by using lifestyle interventions.

1.3.1 Risk factors for type 2 diabetes

1.3.1.1 Obesity

The strong positive association between obesity (BMI≥30.0 kg/m^2), overweight (BMI 25.0 – 29.9 kg/m^2) and type 2 diabetes has been consistently reported from cross-sectional and cohort studies (16). Obesity is a major risk factor for type 2 diabetes and the increases in the prevalence and incidence of obesity have mirrored those of diabetes (37-39). A meta-analysis study of 18 prospective cohort studies showed that the relative risk (RR) of developing diabetes was over seven in obese individuals compared to those of normal weight. This meta-analysis also reported that the RR for diabetes was approximately 3 for overweight individuals compared to normal weight persons (16). Obesity is associated with a high risk of developing insulin resistance which may eventually lead to type 2 diabetes. In obese people, there is an increased release of fatty acids, leptin and pro-inflammatory cytokines from adipose tissue which cause insulin resistance (40).

Guidelines recommend annual monitoring for the development of diabetes among those with pre-diabetes. People with pre-diabetes are also suggested to be referred for intensive life style intervention with a focus on weight loss, and increased physical activity level to 150 min/week (8). Reducing energy intake is the main focus of weight loss. Recent evidence also suggested that specific dietary components may have an important role in reducing risk of diabetes (41-44). It has been suggested that consumption of whole grains (45), nuts (46), berries (47) and yogurt (48) are associated with decreased risk of diabetes. In contrast, red meat and sugar-sweetened beverages increased the risk of developing of diabetes (42).

1.3.1.2 Low levels of physical activity and sedentary life style

Low levels of physical activity are associated with the development of diabetes (49, 50). Guidelines recommend moderately-intensive physical activity such as brisk walking for at least 150 min/week for those with a high risk of diabetes. Physical activity increases insulin sensitivity and reduces visceral fat (51, 52). In addition to this, there are more recent studies showing a predominantly sedentary lifestyle is related to diabetes, independent of physical activity levels (53). Recent clinical studies have shown that breaking up prolonged sedentary time has benefits in decreasing post prandial glucose (54, 55) and could potentially decrease the risk of developing type 2 diabetes.

1.4 Complications of diabetes

Type 2 diabetes can cause severe complications, which are generally divided into two groups; macrovascular (due to damage to larger blood vessels) and microvascular (due to damage to small blood vessels) complications (3, 56). Macrovascular complications include myocardial infraction, stroke and peripheral arterial disease (Fig 1). Microvascular complications include retinopathy, nephropathy and neuropathy (57). Diabetes is also associated with other conditions such as diabetic cheiroarthropathy, characterized by thickened skin and limited joint mobility, cataracts, cancer, liver disease, sleep apnoea and depression (58-60). The pathophysiology of how diabetes leads to these complications is complex and still not well understood, however it has been shown that there are direct detrimental effects of high blood glucose levels, hypertension and lipid abnormalities which contribute to the development and progression of diabetes complications. Diabetes complications can be prevented or at least delayed by controlling hyperglycaemia, hypertension and dyslipidaemia. Diabetes screening

programs are recommended for early diagnosis and initiation of treatment before the complications of diabetes develop (3, 61).

1.4.1 Microvascular complications of diabetes

1.4.1.1 Retinopathy (eye damage)

Diabetic retinopathy, in which blood vessels inside the retina at the back of the eye are damaged, is the most common microvascular complication of diabetes and is the leading cause of visual disability and blindness in people with diabetes (62). Retinopathy can affect the peripheral retina, the macula, or both. The risk of developing retinopathy and other microvascular complications of diabetes depends on several risk factors such as duration of diabetes, severity of hyperglycaemia (high blood glucose levels), hypertension and dyslipidemia (63). Hyperglycaemia decreases retinal blood flow, increases inflammation in retinal blood vessel and results in hypoxia and damage to the retina (63).

1.4.1.2 Nephropathy (kidney damage)

Diabetes in the leading cause of end stage kidney disease worldwide. Nephropathy is caused by damage to small blood vessels in the kidney, which can cause the kidneys to be less efficient, or to fail altogether (64). Controlling blood glucose and blood pressure levels are the key factors in preventing or delaying the development of nephropathy (65). It has been shown that using ACE or ARBs can lower the risk of developing diabetes nephropathy (66) .

1.4.1.3 Neuropathy (nerve damage)

Diabetes widely affects the peripheral nerve system and the most common form of diabetic neuropathy is sensory loss or dysfunction in the lower limbs (60). As people with diabetes lose peripheral sensation, trauma to the skin may go unnoticed, which causes ulceration, serious infections and eventually may lead to amputations. Neuropathy may also cause erectile dysfunction and problems in digestion, urination and a number of other autonomic functions. Neuropathy results from multiple risk factors such as prolonged high blood glucose, age, hypertension, dyslipidemia. (61, 62).

1.4.2 Macrovascular complications

Since the Framingham study (63), numerous epidemiological studies have demonstrated the increased risk of cardiovascular disease in patients with diabetes (64, 65). Cardiovascular disease is the largest contributor to the direct and indirect costs of diabetes (66). People with diabetes have double the risk of having cardiovascular disease (CVD) as compared to individuals without diabetes after adjustment for CVD risk factors such as age, obesity, dyslipidemia, hypertension and smoking (67). The Multiple Risk Factor Intervention Trial study reported that those with diabetes have 2–4 higher odds for cardiovascular mortality than those without diabetes (68). These findings have been confirmed by other studies such as Australian Diabetes, Obesity, and Lifestyle Study (AusDiab) (69), the European Prospective Investigation of Cancer and Nutrition (EPIC Norfolk) study (70) and the Atherosclerosis Risk in Communities (ARIC) study (71). A study conducted in Finland showed that an increment of 1 percentage point of HbA1c levels is associated with a 52% increase in CVD mortality in type 1 diabetes and by 7.5% in type 2 diabetes (72). A meta-analysis of observational studies

reported that for each 1 percentage point increase in HbA1c levels the relative risk of developing any cardiovascular event is 1.18 for type 1 diabetes and 1.15 in type 2 diabetes (80).

There is a close interrelation between diabetes and CVD risk factors (81), such as hypertension (82). Nevertheless, epidemiological studies have demonstrated that diabetes itself is an independent risk factor for CVD events. The combination of hyperglycemia, dyslipidemia (high triglycerides (TG), high level of low density protein cholesterol (LDL-chol), low level of high density lipoprotein (HDL-chol)), hypertension, and some other risk factors such as obesity, inflammation, smoking and insulin resistance can injure the vascular endothelium and result in macro vascular events (83, 84). These risk factors contribute in varying degrees to the CVD risk in those with diabetes and the mechanisms by which this occurs is complex and not fully understood. Atherosclerosis, inflammation, oxidative stress, decreased bioavailability of nitric oxide, endothelial cell dysfunction, increased levels of coagulation factors and anti-fibrinolytic proteins, increased platelet activation, are some of the factors explaining the link between diabetes and CVD (85).

Previous studies have shown the efficacy of controlling each individual risk factor in reducing the risk of CVD events in diabetes but if multiple risk factors are addressed simultaneously, there are more substantial decreases in risk of CVD (86).

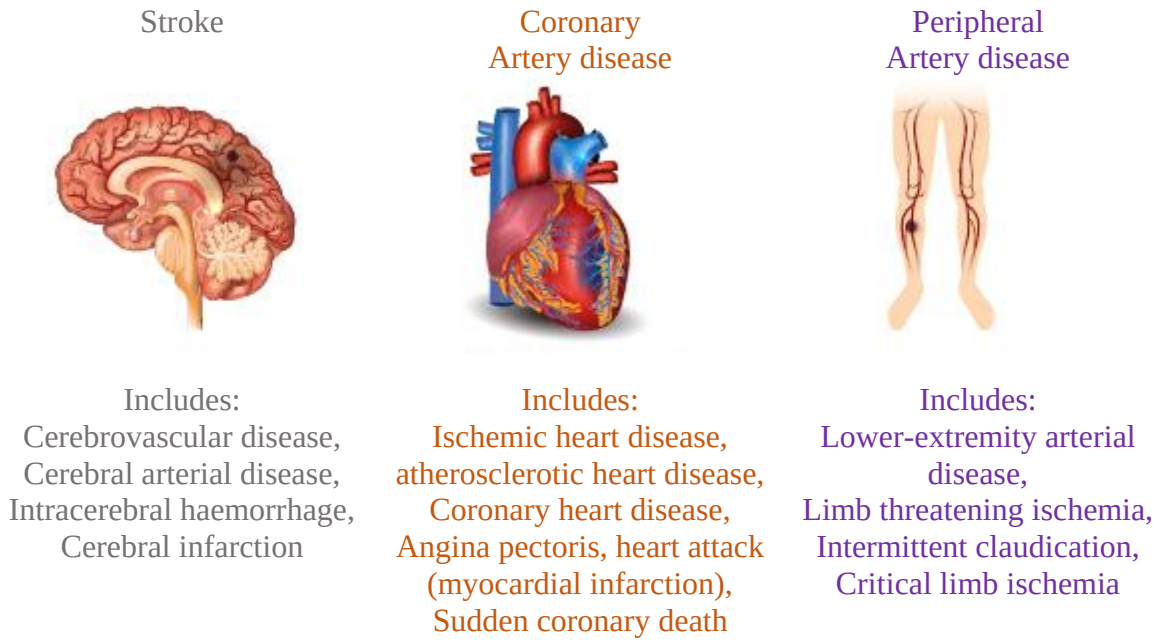

Figure 1. The main types of CVD (International Diabetes Federation. Diabetes and cardiovascular disease. Brussels, Belgium: International Diabetes Federation, 2016. www.idf.org/cvd) (87)

1.4.3 Disability related to diabetes

Recent studies have shown that there are many diseases rather than just classically known complications, which are related to diabetes. One of the newly recognised complications of diabetes which has attracted attention is disability. Disability is associated with many poor outcomes including loss of productivity and employment, difficulty in performing daily self-care activities, increased use of health services, and premature death (9, 88, 89). People with diabetes have a two to three fold higher risk of physical disability (90). The high prevalence of disability among people with diabetes has various causes. Diabetes is strongly associated with disabling diseases such as cardiovascular disease, renal failure, blindness and lower limb amputation (91-95). Furthermore, overweight and obesity are major risk factors for type 2 diabetes and are often associated with impaired mobility (96). Diabetes can cause disability through mechanisms that are linked to restriction in physical mobility (97, 98), decline in

muscle function (99, 100), impairment of the peripheral nervous system (101) and decrease in circulation and respiratory function (102, 103).

Some of the diabetes risk factors such as age and obesity are also associated with disability. The contribution of obesity to the association of disability with diabetes can be explained from different perspectives. First, obesity *per se* is one of the main obstacles to physical mobility (96). Second, obesity is associated with chronic systemic inflammation which is related to insulin resistance. It has been shown that increased level of inflammatory biomarkers and insulin resistance can result in peripheral neuropathy, and reduced muscle strength that leads to disability (104, 105). Other diabetes complications such as stroke and heart attack can directly affect the physical mobility of people with diabetes because of neuromuscular weakness and decline in exercise capacity. Recent studies also highlighted the contribution of some other chronic diseases such as asthma and depression in the association of diabetes with disability (92, 106, 107).

Increasing prevalence of diabetes together with aging of the population is giving rise to a large burden of disability which will affect both individuals and health care systems (108). Effective prevention and treatment programs are necessary to reduce the progression of disability in patients with diabetes. Due to the multifactorial nature of disability, identifying and assessing the risk factors that contribute to the association between diabetes and disability is crucial for developing successful interventions in order to reduce the risk of disability and to improve the quality of life people with diabetes.

1.5 Management of diabetes

Optimal diabetes management can help people with diabetes to live longer and relatively healthily with diabetes. Research is increasingly demonstrating the benefit of diabetes management in reducing morbidity and mortality in diabetes (8).

The primary aim of these interventions is reducing the risk of developing complications of diabetes by controlling blood glucose, blood pressure and lipids. These interventions are usually conducted through a combination of life style change and medications. Lifestyle management is an essential component of diabetes care and includes diet therapy, increasing physical activity, smoking cessation counselling and mental health care. Diabetes self-management education and support (DSME/S) provides the foundation to help people with diabetes to improve daily self-management decisions and to perform self-care activities. DSME is the process of facilitating the knowledge, skill, and ability necessary for diabetes self-care. DSMS refers to the support that is required for implementing and sustaining coping skills and behaviours needed to self-manage on an ongoing basis (118). Screening for complications of diabetes is another important factor for better diabetes management. The longer an individual lives with undiagnosed and untreated diabetes, the worse their complications are likely to be (25).

Diabetes management can be strengthened by applying guidelines or protocols developed by national and international organisations. The aim of these guidelines is to achieve standardized and consistent management approaches for the management of diabetes.

1.5.1 Guidelines for the management of diabetes

There are a number of nationally and internationally recognized, comprehensive guidelines for the prevention, diagnosis and management of diabetes. These diabetes guidelines include those developed by the World Health Organization (WHO) (109), American Diabetes Association (ADA) (8), IDF (87), European Association for the Study of Diabetes (EASD) (110) and American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) (111).

Many countries also develop their own national guidelines according to availability of medications and other interventions (112). The national guidelines are mostly supported by national ministries of health or national diabetes societies/associations or both of each country. Optimal control of plasma glucose, blood pressure, and lipids is central to diabetes management. These are the key factors in reducing morbidity and mortality attributed to diabetes. It has been well established that achieving these targets averts or considerably delays complications of diabetes, enabling people with diabetes to live longer with fewer disabilities and improved quality of life.

1.5.2 Non-pharmacological management of diabetes

Non-pharmacological treatment of diabetes mainly focus on the following aim:

- Interventions to improve lifestyle such as a healthy diet, increased physical activity and smoking cessation.
- Improvement in diabetes self-management such as monitoring blood glucose and foot care

1.5.2.1 Diet

Nutrition therapy is one of the most important and challenging parts of diabetes management. Medical nutrition therapy in patients with diabetes focuses on two aims: first, providing a healthy eating pattern and second, weight loss for those who have obesity or are overweight. The Mediterranean (113), low-carbohydrate, low-glycaemic index (GI) (114), and Dietary Approaches to Stop Hypertension (DASH) diets are among those that have been recommended for people with diabetes (42). The emphasis of the diet should be on whole grains rather that refined grains (115), vegetables, fruits, legumes, low-fat dairy products, lean meats, nuts, and seeds. People with diabetes are recommended to replace the consumption of saturated fat, dietary cholesterol, and trans fat with mono-unsaturated fatty acids such as olive oils (116).

1.5.2.2 Physical activity

Meta-analyses have demonstrated that all types of exercise including aerobic, resistance and combinations are helpful in controlling hyperglycaemia and improving health outcomes (117). Benefits of exercise are similar to those that are achieved by diet and taking medications (117). Physical activity reduces blood glucose, blood pressure and blood cholesterol (118). Furthermore, increased physical activity helps to reduce weight which is associated with reducing risk of CVD (119).

1.5.2.3 Diabetes self-management education and support

Diabetes self-management education and support (DSME/S) provides the foundation to help people with diabetes to improve daily self-management decisions and to perform self-care activities. DSME is the process of facilitating the knowledge, skill, and ability necessary for diabetes self-care. DSMS refers to the support that is required for implementing and sustaining coping skills and behaviours needed to self-manage on an ongoing basis (120). Continuous Glucose Monitoring (CGM) is one of the most important recent advances in diabetes technology for improving diabetes management. CGM provides an insight into glycaemic profiles that can be used to guide treatment and motivate patients with diabetes.

1.5.3 Pharmacological management of diabetes

1.5.3.1 Glycaemic management

There is a strong association between intensive blood glucose control and prevention of complications of diabetes (113-115). HbA1c is the most widely recommended means of assessing overall glycaemic control, and has the advantages of not requiring patients to fast and of reflecting the general glycaemic control in the previous three months. However, self-blood glucose monitoring, fasting plasma glucose, and, more recently, continuous glucose monitoring can each contribute to assessing the levels of glycaemic control. A meta-analysis (121) on four landmark clinical trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD) (60), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) (116), the UK Prospective Diabetes Study (UKPDS) (117) and Veterans Affairs Diabetes Trial (VADT) (118), showed that a lower HbA1c level is associated with reduction

in macro vascular complications of diabetes. The ADVANCE study showed that intensive glycaemic control is renoprotective in people with diabetes (122). Also, the ACCORD study showed the benefit of intensive glycaemic control in reducing risk of retinopathy, but the mortality rate was higher in the intensive glycaemic control group (123, 124).

The optimal glycaemic target recommended by most guidelines for diabetes is to achieve HbA1c< 7.0% (53 mmol/mol) (8). However, targets should be individualized based on duration of diabetes, age, comorbid conditions, known CVD or advanced microvascular complications, hypoglycaemia unawareness, and other individual patient considerations (8).

1.5.3.1.1 Glucose lowering medications

Medications for diabetes can be categorised into insulin and non-insulin medications. The type of medications prescribed for diabetes is based on the type of diabetes, age, severity of disease and related complications and also tolerability of medications (125).

Non- insulin glucose lowering medications

Different classes of glucose lowering medication (GLM) with different mechanisms of action are used to control hyperglycaemia in diabetes (125). In general, they target the following mechanisms:

1) increasing sensitivity of target organs to insulin (Insulin sensitizer);

2) increasing secretion of insulin from the pancreas;

3) decreasing the rate at which glucose is absorbed from the intestinal tract;

4) blocking the re-uptake of glucose in the renal tubules

The majority of these medications are oral hypoglycaemic agents, while glucagon-like peptide-1 receptor (GLP-1) agonists are injectable. Table 3 shows some of the most commonly used non-insulin GLM and their mechanism of action.

Table 3. Non-insulin medicines for treatment of type 2 diabetes

Type	Mechanism of action and other effects	Other clinical advantages
Older medications for diabetes		
Biguanides	Insulin sensitizer	Minimal risk of hypoglycaemia Lipid lowering effects
Sulfonylureas	Secretagogues	Low cost
α-Glucosidase inhibitors	Delay digestion and absorption of carbohydrates in intestine	Minimal risk of hypoglycaemia Low cost
Meglitinides	Secretagogues	Safe to use in patients with renal failure
Newer medications for diabetes		
DPP4i	Secretagogues/incretin effects	Minimal risk of hypoglycaemia
GLP-1 agonist	Secretagogues/incretin effects	Weight loss Minimal risk of hypoglycaemia Reduce appetite Delayed gastric emptying
Thiazolidinediones	Insulin sensitizer	Lipid lowering effects
SGLT2 inhibitors	Prevent renal reabsorption of glucose and facilitate its excretion in urine	Weight loss Minimal risk of hypoglycaemia

DPP4i: Dipeptidyl peptidase-4 inhibitors
GLP-1 agonist: Glucagon-like peptide-1 receptor agonists
SGLT2i: Sodium-glucose transporter 2 inhibitors

It should be noted that some GLP-1 agonists and SGLT2i, have been shown to reduce blood pressure, risk of cardiovascular events and mortality (126).

Insulin

Insulin is the most commonly used medication for those with type 1 diabetes and gestational diabetes. Insulin is also used for type 2 diabetes when the non-insulin agents fail to control hyperglycaemia. Insulin type is categorised into four groups (127).

Table 4. Insulin type in treatment of diabetes

Type	**Name**	**Onset of action** (length of time before insulin reaches bloodstream)	**Peak** (time period when insulin is most effective)	**Duration** (how long insulin works for)
Rapid-acting	Lispro Glulisine Aspart	10 – 30 minutes	30 minutes - 3 hours	3 – 5 hours
Short-acting	Regular (R)	30 minutes - 1 hour	2 - 5 hours	Up to 12 hours
Intermediate-acting	NPH (N)	1.5 - 4 hours	4 - 12 hours	Up to 24 hours
Long-acting	Plain glargine Lantus U 300 Detemir	0.8 – 4 hours	Minimal peak	Up to 24 hours
Ultra-long acting	Glargine U300 (Degludec)	30 minutes – 1.5 hour	Minimal peak	Up to 42 hours

1.5.3.2 Blood pressure management

Numerous randomised clinical trials have demonstrated the benefit of reducing blood pressure levels <140/90 mmHg to reduce cardiovascular risk in patients with diabetes (128, 129). Thus, ADA guidelines suggest the blood pressure target at <140/90mmHg (8). Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, have been recommended for those individuals at high risk of cardiovascular disease.

Blood pressure management in hypertensive individuals with diabetes has undergone some significant changes over the last 15 years. The ADA target for management of hypertension among patients with type 2 diabetes has changed over time. In 2006, the ADA guideline recommended the blood pressure target at 130/80 mmHg for patients with diabetes. This target was based on several large studies including the Hypertension Optimal Treatment (HOT) study (130), the UKPDS (131) and the ADVANCE study (132), which showed benefit in keeping blood pressure level <130/80 mmHg to reduce cardiovascular events in patients with diabetes. However, more recently a meta-analysis reporting no benefit or even harm when low blood pressure was achieved. This meta-analysis study on patients with type 2 diabetes demonstrated that although the use of intensive versus standard blood pressure targets might cause a small reduction in the risk for stroke, there was no evidence of benefit of intensive targets in reducing risk of mortality or myocardial infarction but rather there was an increased risk of hypotension and other adverse events. Thus, there was a modification to guidelines suggesting a less stringent blood pressure i.e. 140/90 mmHg with emphasis on individualization of blood pressure targets with regards to age and existence of other risk factors. Nevertheless, the American Association of Clinical Endocrinologists/American College of Endocrinology AACE/ACE (111) and IDF (133) still recommended the blood pressure target at <130/80 mmHg.

1.5.3.2.1 Antihypertensive medications

Angiotensin converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARBs), have been considered as the first line treatment in patients with diabetes. Previous studies have demonstrated that both renin-angiotensin-aldosterone system (RAAS) blockers, ACEI and ARBs, are associated with reduced CVD and mortality in patients with diabetes (134, 135).

Calcium channel blockers (CCBs) are usually considered as the first line treatment for elderly with isolated systolic hypertension (136). Diuretics are usually considered as second-line medications for treatment of hypertension in people with diabetes because of adverse effects of this medication on insulin resistance (137-139). Alpha-blockers, beta-blockers and methyldopa are affordable and available antihypertensive medications in LMICs (140, 141).

1.5.3.3 Lipid management

Management of dyslipidaemia, a modifiable risk factor for CVD, is a crucial aspect in multifactorial approaches in reducing risk of CVD in people with diabetes (142). Diabetic dyslipidemia is characterized by increased triglyceride (TG) levels and decreased HDL-chol levels. LDL-chol has the greatest role in progression of atherosclerosis disease and is considered as the primary target of dyslipidaemia treatment (8). Several randomised controlled trials and meta-analyses demonstrated the benefit of using statins in reducing CVD events (143, 144).

1.5.3.3.1 Lipid lowering medications

Statins are cholesterol-lowering drugs, which are highly effective and are the first line medications in the primary and secondary prevention of CVD (145). Several studies have shown benefit of using statins for both primary (143, 146-148) and secondary prevention of CVD in people with diabetes (147, 149). A meta-analysis of 14 randomised clinical trials showed that statin consumption is associated with a 21% decrease risk of vascular events per mmol/L LDL-chol reduction (150). This study showed that this reduction was present irrespective of whether patients had prior cardiovascular disease, or what the baseline LDL-

chol was (up to an LDL-chol level of 2.6 mmol/l). The findings of this triggered the ADA guidelines to consider statin use in patients with diabetes as the primary prevention of CVD, unless very specific exclusion criteria, regardless of baseline LDL-chol levels and prior CVD events (145).

1.6 Delivery of care in diabetes

1.6.1 Diabetes management in actual practice, the role of Real World Evidence (RWE) studies

In the last decades, a considerable effort has been made in introducing new classes of glucose lowering medications and formulating guidelines to improve diabetes management. The main sources for developing guidelines are reliance on the evidence generated by Randomised Clinical Trials (RCTs), which are the gold standard for establishing causation between a therapy and an outcome. In general, RCTs use a rigorous experimental design with the primary aim of exploring the "average" overall benefit and risk of using a therapy in a selected group of patients under ideal and controlled conditions and usually in a short period of time (151, 152).

RCTs have internal validity and a therapy that is found to have biological benefit is considered efficacious. Thus, RCTs are dealing with establishing the efficacy of a new therapy which is valuable in advancing medical knowledge. However, even when findings from RCTs strongly favour the efficacy of a new therapy, this does not mean that the same effect will translate into the actual practice in the "Real World".

There is some concern about how well the therapy may perform in different clinical settings and in a diverse group of patient populations, in terms of age, ethnicity, gender, complications, etc., than those studied in traditional RCTs (153). Furthermore, it is unclear how therapies are best applied within the larger environment of the healthcare delivery system where costs, availability and access to medications become issues for both patients and health care providers. Therefore, the evidence from traditional RCTs, efficacy studies, must generally be supplemented by evidence from observational effectiveness studies to provide a clear and comprehensive understanding of treatment and care of patients with a specific disease such as diabetes (154).

In contrast to RCTs, data from real world evidence studies are usually derived from medical records, registries and pharmacy and health insurance databases. The real world evidence studies use data collected in the ordinary clinical care, not in the research setting.

Real World studies can provide information on the size and nature of the gaps between actual practice and the targets and therapies set out in guidelines. They can also provide a basis for the development of interventions to improve delivery of care. Possible limitations of real world evidence studies are lack of precision in measurements, the absence of information on why clinical decisions are made, and the ability to make clear causal inferences.

Obtaining information on diabetes management requires access to medical records. However, only electronic medical records have the potential to allow extraction of the large amounts of data that are needed for such projects. The availability of such electronic databases has facilitated the reports on diabetes management in North America and Europe. In recent years, the use of such records systems has spread to other parts of the world, allowing projects to examining how patients with diabetes are actually managed outside these two regions.

1.6.2 The role of nurse prescribers in diabetes management

Diabetes guidelines have provided evidence based recommendations to reduce complications of diabetes and provide optimal management of diabetes. Unfortunately, these guidelines are inadequately translated into daily practice and treatment remains substandard in many patients with diabetes (155-167). Increasing the number of people with diabetes imposes a high work load on physicians and can affect the quality of care provided for patients (168). Strategies for successful implementation and the cost effective of translation of guidelines into clinical practice has become a major challenge for health care services, especially in LMICs.

Given the issues above, advanced nursing roles in diabetes and other chronic diseases, and specific skills such as nurse prescribing have evolved and have resulted in nurses taking on roles that have traditionally been performed by doctors. Considering the increase in the global prevalence of diabetes, this extension role of nurses has the potential to reduce the cost of care and increase the quality of care delivered to patients, particularly when doctors are facing high workloads or when there is a shortage of doctors. This is the case in many low income countries, and in rural settings in some communities in high income countries Nurse prescribers can be split into two categories based on their role in prescribing: independent prescribers; and supplementary prescribers who work in a team in collaboration with doctors. While the benefit of extending nursing roles into prescribing with the management of health outcomes such as hypertension in patients with diabetes has been demonstrated by systematic reviews (169), the role of nurse prescribers on glycaemic control has shown inconsistent findings (170-184).

1.7 The aims of this thesis

Although 80% of people with diabetes live in low-income and middle-income countries, and a dramatic increase has been predicted in the population affected by diabetes in these countries, there is a dearth of data about diabetes management from these countries. The complexity of

diabetes management and socio-economic, psychological, behavioural, political, and technological factors that are involved in diabetes management makes it challenging to translate the findings from high income countries to LMICs. Given a higher burden of diabetes in low and middle income countries and little information available from these countries the aims of this PhD thesis were to explore the recently-recognised challenge of disability in diabetes, to determine the level of achievement of diabetes management targets, and to assess the value of nurse prescribers in diabetes. Specifically, the aims were:

To examine the risk factors that contribute to the association of diabetes and disability, and to quantify the contribution of each risk factor to the association between diabetes and disability.

To examine the trends of diabetes management and therapeutic approaches from 2009 to 2015 in one middle income country, namely Mauritius, where approximately 20% of patients have diabetes, by using unit level data obtained from a national survey that was conducted in 2015.

1. To explore trends in diabetes management and achievement of treatment targets between 2006 and 2015 in a number of LMICs by using the Real World Evidence data obtained from medical records or national registries. Specifically, this aim explores trends in medication usage, glycaemic control, blood pressure and lipid control.
2. To examine the role of nurse prescribers in glycaemic control in type 2 diabetes by conducting a systematic review and meta-analysis.

To achieve these aims, we have the following data sources:

1. A study of diabetes management and related complications in Mauritius, entitled the Mauritius Non-Communicable Disease (NCD) survey, 2009 and 2015.
2. Real World Evidence (RWE) project with focus on diabetes management and treatment approaches in nine countries.

3. A systematic review and meta-analysis study on the effect of nurse prescribes on HbA1c levels in diabetes.

Chapter 2 of this thesis describes the methods and materials related to each of the three studies mentioned above.

Chapter 3 of this thesis investigated the risk factors that contribute to the association between diabetes and disability. The findings of this study highlighted the major risk factors that need to be considered and addressed in diabetes management in order to decrease the disability burden of diabetes in LMIC. For this chapter, data from Mauritius 2015 Non- Communicable Disease (NCD) survey, was used.

Chapter 4 examined the trends of diabetes management and therapeutic approaches in the middle income country of Mauritius from 2009 to 2015. Mauritius is a multi-ethnic country and has one of the highest prevalence of diabetes in the world. The high prevalence of diabetes together with the multi-ethnic nature of this country provide a valuable setting in which to understand the factors, including ethnicity, that explain the changes in the trends of diabetes management in recent years. This chapter explored trends in reaching glycaemic, blood pressure and lipid targets according to ADA guidelines and the factors that explain reaching these targets. We also examined trends in using GLM, antihypertensive and lipid lowering drugs in this country. For this chapter we have used data from Mauritius Non-Communicable Disease (NCD) survey, 2015 and compare the result of this survey to a similar survey that was conducted in 2009.

Chapter 5 examined trends in glycaemic control in nine countries including Argentina, Australia, Hong Kong, India, Japan, Russia, Saudi Arabia, South Africa and Uganda from 2006 to 2015. For this chapter we used data from Real-World Evidence project.

Chapter 6 explored CVD management and trends in therapeutic approaches with regards to antihypertensive and lipid lowering medications in people with diabetes in the real world setting. In this chapter, we focused on the trends of CVD management in seven countries including Argentina, Australia, Hong Kong, India, Japan, Saudi Arabia and South Africa from 2006 and 2015. For this chapter we used data from Real-World Evidence project.

Chapter 7 examined a potential solution to improve diabetes management by examining whether implementing nurse prescribers in the health care setting can improve glycaemic control in people with type 2 diabetes. In this chapter, we performed a systematic review and meta-analysis on the clinical trial studies in which nurses have the prescribing role in diabetes management.

Chapter 8 provides a summary and the conclusion of this thesis.

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Chapter 2

Methods and Materials

In this chapter, the methods and materials related to each of the following studies are discussed.

1. Mauritius Non-Communicable Disease (NCD) survey, 2009 and 2015. This study contributed to the publications in chapters 3 and 4 of this thesis.
2. Real-World Evidence (RWE) project. This study contributed to the publications in chapters 5 and 6 of this thesis.
3. A systematic review and meta-analysis study on the effect of nurse prescribers on HbA1c levels in diabetes. This study contribute to publications in chapter 7 of this thesis.

2.1 Mauritius Non-Communicable Disease Survey

Mauritius is a middle-income and multi-ethnic country located in the Indian Ocean with a population of 1.3 million. The population is 68% of South Asian (of Indian origins), 27% African Creoles (predominantly originating in Madagascar, Mozambique, Malawi, Tanzania and Zambia), 3% Chinese and 2% Franco Mauritians (1, 2).

Regular surveys have been conducted every 5 to 6 years in Mauritius, to measure the prevalence of diabetes and related risk factors and complications. Findings from these surveys have demonstrated a dramatic increase in the prevalence of diabetes and related complications parallel with lifestyle change (westernisation) in Mauritius (1-4). A study conducted in 2009 reported a substantial increase in the age-standardized prevalence of diabetes from 13% in 1987 to 21.3% in 2009 (5). In 2015, a survey was conducted in Mauritius by the Mauritius government in collaboration with the Baker IDI Heart and Diabetes Institute, Australia. Chapter 3 of this thesis is based on the 2015, Mauritius, NCD survey and chapter 4 is based on the 2015 and 2009 surveys. The methods and materials of the two surveys were very similar, with any important differences highlighted below.

2.2.1 Survey population and sampling method

2.2.1.1 Survey design

Two different designs were employed during the 2015 survey. A cross-sectional survey of a representative sample of the Mauritian adult population was recruited to address the objectives related to prevalence of diabetes, related risk factors and complications. This sample was known as the Mauritius NCD Survey 2015. Additionally, a sample was recruited from the previous 1998 survey. This is known as the Mauritius 1998 NCD cohort.

2.2.1.2 Sampling frame

Mauritius NCD Survey 2009 and 2015

The target population for both surveys comprised all Mauritian adults aged 18 years and above (according to the Global NCD Framework Indicators).

We followed standard epidemiological sampling procedures for cross-sectional studies. The enumeration and the sampling procedure was performed by the Statistics Department of the Ministry of Health and Quality of Life in Mauritius. In brief, in each survey, Mauritius was divided into 9 districts. Then within each district, the required number of primary sampling units (PSU) (an area representing approximately 300 households) were randomly selected using a simple random sampling method.

To ensure that there was sufficient number of recruited individuals to meet the required sample size, each PSU was formed into a super cluster by selecting two neighbouring clusters to each PSU. This was performed by the supervisor on the field. The selection of neighbouring PSUs

was random and not biased. In each super cluster, enumerators listed names of the all people aged 18 and above. Depending on how many people were required in the supercluster, every second or third person were chosen from the list.

In 2009, a total of 20 main clusters were selected for the whole island. For the 2009 survey, the target sample size was 6800, however 7492 participants were invited to participate in the survey because the research team expected a lower response rate. A similar process was conducted in 2015 but only 11 PSUs were sampled and 4400 people invited to the survey. Among those invited to participate in the survey (n=4400), 3830 participated and thus the overall response rate was 87.0%. The response rate was 84.2% for men and 89.6% for women (Appendix 1).

The Mauritius study was conducted to meet the requirements of the Mauritius Ministry of Health and Quality of Life. In all surveys conducted by the Ministry, there is a legal requirement to have a sample whereby it is possible to conduct analyses by ethnicity. While, the initial sampling led to a representative sample, it was supplemented by additional clusters, Plaine Verte and China town, to allow investigators to analyse data and have a clear understanding of prevalence by ethnic group.

Mauritius 1998 NCD cohort

The 1998 sample was used as the base population for the Mauritius 1998 NCD cohort. For the 2015 follow-up survey, participants were recruited from 9 out of 14 clusters which were used in the year 1998. A list of all participants was obtained and a total of 3570 participants were re-visited. Approximately 2751 individuals were traced and they were all invited to participate in the follow up study. The final sample size was 2069 (overall response rate was 75.2%, 73.9% for men and 76.2% for women).

The study population for chapter 3 of thesis is obtained by merging the sample derived from the Mauritius NCD Survey 2015 and the Mauritius 1998 NCD cohort. Thus, the sample was drawn from 22 clusters in 9 districts.

The study population for chapter 4 of this thesis is taken from the Mauritius NCD Survey 2009 and 2015. The Mauritius 1998 NCD cohort samples are not included in this chapter.

2.2.2 Survey procedure and measurements

All participants gave written informed consent to participate in the survey upon arrival at the testing site. Assessments included a blood and urine sample, anthropometric and blood pressure measurements, and interviewer-administered questionnaires. Participants were moved through the physical examination procedures in a circuit-like manner that took approximately 2–2.5 hours to complete. Participants were asked to remain on site until all tests were performed. Central to the physical examination was the standard two-hour oral glucose tolerance test (OGTT), during which time all other procedures were performed.

A series of interviewer-administered questionnaires were used to collect a range of health and social information Table 2.1. The survey questionnaire is available in appendix 2.

Table 1. Mauritius Non-Communicable Disease Survey Questionnaire

Questionnaire	Source
General demographic	Developed by research team
Physical examination	Developed by research team
Medical history	Developed by research team
Diabetes complications	Developed by research team
Health utilisation, diabetes knowledge, attitude and dietary habits	Developed by research team
Physical activity	Global Physical Activity Questionnaire (GPAQ) (6, 7)
Disability	Katz Index of Independence in Activities of Daily Living (Katz) (8)

Asthma screening questionnaire	The European Community Respiratory Health Survey (ECRHS) (9)
Depression	Centre for Epidemiological Studies Depression Scale (CES-D) (10)

2.2.2.1 General demographic and Medication use

Ethnicity, educational level, type of treatment and medication use were obtained using interviewer-administered questionnaires. The level of education was categorised as primary (0–6 years), secondary (7–12 years), or tertiary (>12 years). Based on self-report ethnicity, participants were categorised as South Asian, African or other. For those with previously diagnosed diabetes, self-report date of diagnosis was obtained. Duration of diabetes was calculated by using the date of diagnosis and the year of the survey, and then categorised into three sub-groups as <5, 5–10 and ≥10 years.

Participants self-reported whether or not they were taking medications for diabetes, hypertension or dyslipidemia, and were asked to specify the names of drugs. Prior to surveys, all study participants were asked to bring their prescription list or a box of their medications to the survey. In both surveys, 2009 and 2015, participants were asked a multiple choice question about their glucose lowering medications: “What is the present treatment for diabetes”. The possible answers were 1) none, 2) diet only, 3) herbal, 4) oral drug 5) insulin and 6) both oral and insulin. This question was followed by an open ended question that asked them to specify the name and dosage of drugs. In 2015, we added another question about how the medication was reported for each study participant - from memory, via a prescription list or via bringing the medications to the survey. In 2015, 49% of medications were confirmed by participants bringing their prescriptions or medications with them to the survey.

2.2.2.2 Blood sampling, oral glucose tolerance test and laboratory procedures

Fasting blood samples and urine samples were collected from all study participants. The second blood sample was collected 2 hours after the 75 g oral glucose load to conduct an OGTT. The OGTT was performed on all participants, except those on insulin or oral hypoglycaemic drugs, those with fasting plasma glucose (FPG)≥13 mmol/l and those who were pregnant or those who failed to fast.

Blood samples were collected by venepuncture after an overnight fast of at least 8 hours. In 2009, blood samples were collected in fluoride/oxalate tubes centrifuged directly after drawing and samples were then tested using a YSI 2300 STAT PLUS instrument on site. In 2015, samples were collected in fluoride/oxalate tubes, kept at 4ºC for 1–3 hours and transferred to a central laboratory (Victoria Hospital in Quatre-Bornes) and assayed using a similar YSI instrument. Glucose stability studies were conducted to confirm that the samples collected for glucose assay reached the laboratory without any deterioration or undergoing red cell lysis (un-published data). All other assays were conducted at Victoria Hospital. Serum triglycerides, total cholesterol, and HDL-chol were measured using enzymatic methods adapted on an automated system (Abbott Architect c8000; Human Diagnostics, Wiesbaden, Germany). LDL-chol was calculated for participants with triglycerides ≤4.52 mmol/L using the Friedewald formula (11). HbA1c was analysed using the high performance liquid chromatography (HPLC) method on the Tosoh G7 automated system (Tosoh Biosciences, Tokyo, Japan).

The diagnostic criteria for diabetes, IGT and IFG were based on the values for venous plasma glucose concentration (fasting and two-hour measurements) outlined in the World Health Organization report on the Diagnosis and Classification of Diabetes (12).

Chronic kidney disease is defined as present when there is impaired kidney function. The standard measure of kidney function is the glomerular filtration rate (GFR) (13). GFR can be

estimated from the results of a blood test ('estimated' GFR or eGFR) and an impaired eGFR is defined as an eGFR of <60 ml/min/1.73m. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (14).

2.2.2.3 Urine collection and laboratory procedures

A morning spot urine sample was taken. Urine creatinine was measured by the modified kinetic Jaffe reaction on the Roche Cobas Integra 400 (Roche Diagnostics, chemistry-analyser, Rotkreuz, Switzerland). Urine albumin was measured by a method based on radioactive label from Immunotech (Beckman Coulter, Villepinte, France).

2.2.2.4 Anthropometry

Height was measured to the nearest 0.5 cm without shoes using a stadiometer. Weight was measured without shoes and excess clothing to the nearest 0.1 kg using a mechanical beam balance and weighing scales. Body mass index (BMI: kg/m^2) was calculated. Waist circumference and hip circumference were measured using a dress-maker's measuring tape applied horizontally. Waist circumference was measured at the mid-point between the iliac crest and the lower margin of the ribs. Hip circumference was recorded as the maximum circumference around the buttocks. Waist and hip circumference were measured to the nearest 0.5 cm.

Overweight and obesity were defined using the WHO classification based on BMI (weight/height^2), and waist circumference (12). The WHO recommends different cut-points depending on ethnicity (Table 2).

Table 2. Body mass index classification of obesity by ethnicity

	BMI (kg/m^2)	
	Europeans including African Creoles	Asian (South Asians)
Normal	<25.0	<23.0
Overweight	25.0–29.9	23.0–24.9
Obese	≥30.0	≥25.0

2.2.2.5 Blood pressure

Blood pressure measurements were performed in a seated position after resting for five minutes or more using an automated blood pressure monitor that was regularly calibrated (Digital Auto Blood Pressure Monitor M7; Omron, Kyoto, Japan). A cuff of suitable size was applied on the participant's exposed upper arm (the arm not used for blood collection), which was supported on a table at heart level. Several cuff sizes were available at all sites. Before blood pressure measurements were taken, the mid arm circumference of the non-dominant arm for the participant was measured with a tape measure. An 'obese' cuff (16x36 cm) was available for use when mid arm circumference >35 cm. Two measurements were taken, with a 1 minute interval between them, and the mean of the two measurements was calculated. If the difference between the first and second measurement was greater than 10 mmHg, for either systolic or diastolic blood pressure, a third measurement was taken, and the mean was calculated from the two closest readings.

Participants who reported having hypertension and taking drug treatment or reported hypertension and had a blood pressure of greater or equal to 140/90 mmHg were classified as hypertensive. Participants who had systolic blood pressure or diastolic blood pressure greater or equal to 140/90 mmHg and not on anti-hypertensive medication were defined as untreated hypertension.

2.2.2.6 Physical activity

Self–reported data on physical activity was collected using the Global Physical Activity Questionnaire (GPAQ) (6). This questionnaire asks about moderate and vigorous physical activity during leisure time and walking, and travelling to and from work. The Ministry of Health and Quality of Life recommend that Mauritians should undertake 30 minutes of exercise each day comprising of brisk walking, jogging, swimming, cycling or dancing (aerobic).

2.2.2.7 Disability

The prevalence of disability was estimated in adults aged greater than or equal to 50 years of age using the Katz questionnaire (8). Disability was defined as difficulty with any of the following: walking across a small room; moving in and out of a chair or bed; bathing or showering; dressing yourself; feeding yourself; using the toilet. Disability scores were derived from the answers to the above questions. For each of above 6 activities, the responses were: 1, no difficulty; 2, a little difficulty; 3, some difficulty; 4, a lot of difficulty.

2.2.2.8 Asthma

The prevalence of asthma-like symptoms was measured using The European Community Respiratory Health Survey (ECRHS) screening questionnaire (9). Asthma-like symptoms were defined as wheezing or whistling in the chest at any time in the last 12 months (Q1) if breathlessness occurred during the wheezing episode (Q1a) and these symptoms occurred in the absence of a cold (Q1b). We also included those who reported current medication for asthma (Q6).

2.2.2.9 Depression

Depression was assessed using the Centre for Epidemiologic Studies Depression Scale (CES-D), which is one of the most common screening tests for identifying depressive symptoms in the general population (10). Major components of depressive symptomology are incorporated into the scale, including depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance. The possible range of the 10-item scale is 0 to 30, and a cut off score of ten or higher indicates the presence of significant depressive symptoms.

2.2.3 Statistical analysis

Analyses were conducted using Stata (version 14; Stata Corp, College Station, TX). For chapter 3 of this thesis, changes in mean values over time were tested using regression models adjusted for age, sex and duration of diabetes. Change in the prevalence of 'ABCs' (A1c, blood pressure, and cholesterol) between the two surveys was analysed by logistic regression, adjusted for age, sex and duration of diabetes, with each ABC domain as the outcome, and the year of the survey as the independent variable. We tested for interactions of sex, ethnicity, education, and duration of diabetes with a change in the proportions of reaching the targets of HbA1c, lipids and blood pressure between 2009 and 2015. We explored effect modification (departure from a multiplicative effect) by performing stratified analysis when the interaction term had a p-value ≤ 0.2. A p-value <0.05 was considered as statistically significant. Serum triglyceride and HDL, HbA1c and fasting plasma glucose levels were log transformed to correct for the skewed distribution and reported as medians (interquartile change). There were very few missing data (maximum number of missing=41, for duration of diabetes), except for type of medication where data were available for 1,007 of the 1,283 participants, who reported they were taking medication.

For chapter 4 of this thesis, differences in general characteristics of the participants, by disability status, were assessed using Pearson's Chi-square test for proportions and Student's t-test for means, as appropriate. We considered interactions to be significant when $p < 0.2$. For all other analyses, a $p < 0.05$ was considered statistically significant.

A series of logistic regression models was used to examine the association between diabetes and disability, with disability as the main outcome of interest. Adjustments were as follows: model 1, adjusted for demographic and behavioural factors including age, sex and education; model 2, adjustments in model 1 plus BMI; model 3, adjustments in model 1 plus history of cardiovascular disease (CVD); model 4, adjustments in model 1 plus asthma-like symptoms; model 5, adjustments in model 1 plus depression; and model 6, adjustments for all variables included in models 1 to 5.

We calculated the percentage of excess odds in model 1 (adjusted for age, sex and education that could be accounted for by risk factor adjustment, using the following formula: (15)

$$100 \times \frac{(OR^{\text{adjusted for age, sex and education}} - OR^{\text{adjusted for age, sex and education + risk factors}})}{(OR^{\text{adjusted for age, sex and education}} - 1)}$$

We used bootstrapping techniques to estimate the uncertainty intervals around the calculation described above. If the confidence interval estimated by bootstrapping was lower than zero or more than 100, we replaced them by zero and >100, respectively. In general, the analyses have not been adjusted for clusters in chapter 3. For chapter 4, we did indeed adjust for clustering but there were no material differences in the results which or without accounting for clustering so we reported the results unadjusted for clustering.

2.2.4 Ethical approval

Written informed consent was obtained from all participants. The survey was approved by the Ethics committee of the Ministry of Health and Quality of Life, Mauritius, Monash University Human Research Ethics Committee (number CF16/22 - 2016000010), and the Alfred Ethics Committee (number 624/15), Australia.

2.2 Real World Evidence project

Chapters 5 and 6 of this thesis are based on a Real World Evidence project. Methods and materials for this project are presented below.

2.2.1 Data sources

Through a series of meetings and personal links, we sought to identify clinical services outside North America and Western Europe that were able to produce clinic-wide or population-wide reports on the provision of care to people with diabetes. We identified ten data sources from nine countries (Argentina, Australia, Hong Kong, India, Japan, Russia, Saudi Arabia, South Africa and Uganda) that captured individual-level information from all patients within a given service or jurisdiction. There were eight specialist care services, one national register and one primary care/specialist care data source (Table 7).

Table 3. Characteristics of clinical services included in the Real World Evidence project

Country	Centre
Argentina	Centro de Endocrinología Experimental y Aplicada
Australia	Baker Heart and Diabetes Institute
Australia	Royal Prince Alfred Hospital,Sydney
Hong Kong (China)	Prince of Wales Hospital
India	Dr. A Ramachandran's Diabetes Hospitals
Japan	Shiga University of Medical Science
Russia	Endocrinology Research Centre Moscow
Saudi Arabia	Diabetes Center at AlNoor Specialist Hospital
South Africa	Inkosi Albert Luthuli Central Hospital
Uganda	San Raphael of St. Francis Nsambya Hospital

Each site extracted data from medical records of all out-patients attending in the years 2006 and 2015, and then summarized their data for each of those years.

All sites used the standard reporting form developed for this project to collect and report data (Appendix 3). Data included demographics; disease history; percentages of those with type 2 diabetes on various classes of GLM, on complexity of regimens (i.e. monotherapy, combination non-insulin therapy or insulin), mean clinic-level laboratory values related to glycaemic and lipids control, blood pressure and complication of diabetes.

2.2.2 General demographic

Each clinical site reported the information regarding the number of patients with diabetes attending each year, gender distribution, mean age and the relevant standard deviations (SDs), as well as the percentage of patients aged >65, >80 and <30 years. Mean BMI and the relevant SDs were also reported. The proportion of patients in each class of BMI (kg/m^2) including (<20.0, 20.0 – 24.9, 25 – 29.9 and ≥30) were also reported by each clinical sites.

2.2.3 Disease history and complications of diabetes

Information was collected about the percentage of those patients diagnosed with type 2 diabetes, mean duration of diabetes and the percentage of those with duration of diabetes >10 years.

Data regarding the complications of diabetes were collected about the percentage with major adverse cardiac events (MACE). MACE were defined as any of history of stroke, myocardial infarction (MI), coronary artery bypass grafting/ percutaneous coronary intervention (CABG/PCI) or cardiovascular death. The proportions of patients with retinopathy, nephropathy and amputation were also reported.

2.2.4 Glycaemic, blood pressure and lipid level control

Each site reported mean HbA1c levels with SDs and the method of HbA1c measurement. The percentage of people who achieved the HbA1c targets of <7.0%, 7.0–7.9%, 8.0–8.9% and ≥9.0% was reported for each site.

Blood pressure was reported as mean systolic/diastolic (mmHg) and the relevant SDs. The following proportions were also collected for evaluating blood pressure management. The proportion with BP > 130/80, > 140/90, >130/80 or on antihypertensive therapy, >140/90 or on antihypertensive therapy, >130/80 and using antihypertensive therapy and >140/90 and using antihypertensive therapy.

Mean total and LDL cholesterol among all diabetes patients as well as among those on statin were also reported.

2.2.5 Medications

Diabetes treatment was classified into five categories: diet only, non-insulin monotherapy, non-insulin dual therapy, non-insulin triple therapy and insulin therapy (with or without other therapies). Information was also collected separately for percentages of patients treated with each class of GLM, including metformin, sulphonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1R agonist), alpha glucosidase inhibitors, sodium-glucose co-transporter-2 (SGLT2) inhibitors, meglitinides and insulin.

Antihypertensive medication were reported in four categories: angiotensin-converting-enzyme inhibitors (ACE inhibitors), calcium channel blockers (CCB), angiotensin II receptor blockers (ARB) and thiazide diuretics. Data were also collected on the percentage of patients using statins and antiplatelet drugs.

2.2.6 Statistical analysis

Analyses were conducted using Stata (version 14; Stata Corp, College Station, TX). We reported continuous variables as mean ± standard deviation and categorical variables as proportions.

2.2.7 Ethical approval

This study was approved by the Monash University Human Research Ethics Committee (number 1441), and the Alfred Ethics Committee (number 64/15) in Australia and the local committees of the participating countries. This study is low risk as there is negligible risk to participants. No direct measurements were made from patients in this study, and only aggregated data was received in Australia, thus no consent form were obtained from participants.

2.3 The effect of nurse prescribers on HbA1c levels in diabetes; a systematic review and meta-analysis

The method and materials discussed here contribute to chapter 7 of this thesis, which is a systematic review and meta-analysis on the effects of nurse prescribers on HbA1c levels in patients with type 2 diabetes.

2.3.1 Data sources and searches

We conducted a systematic search for randomised controlled trials which compared nurse prescriber interventions with usual care in adults aged 18 years or over with a diagnosis of type 2 diabetes. The main outcome measure was change in HbA1c levels.

We included interventions in which nurses were involved in prescribing glucose-lowering medication following protocols or algorithms with or without the direct supervision of a physician. Studies where nurses educated people without prescribing any medication, or those in which nurses provided self-management support only were excluded. The control group was generally defined as the traditional model of care or usual care.

2.3.2 Search methods for identification of studies

The literature search strategy involved Medical Subject Heading (MESH) and text words that include “diabetes” and “nurse” or “nursing practitioners” and “trials”. We searched Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases for randomised controlled trials published between January 1980 and May 2015 and then updated our search on 19th of July 2016. We restricted our search to English language studies because of the cost of

translation. We screened the references of all retrieved articles to identify additional publications. Hand searches identified three more relevant publications for our study.

Two of the authors (Maryam Tabesh and Dianna Magliano) independently selected potentially relevant studies by screening retrieved citations and abstracts from the electronic searches. Each reviewer indicated whether the citation was potentially relevant, clearly not relevant, or did not give sufficient information to make a judgement. If studies were potentially eligible or the reviewer needed more information before a judgement could be made, the full text was retrieved for further review. When the two reviewers disagreed on whether or not the study was to be included or had differing quality assessments, conflict was resolved by discussing with a third reviewer (Jonathan Shaw). This occurred in two instances. In general, we classified studies into two categories regarding the role of nurse in disease management. In one category, nurses supplemented usual care in a team including a doctor, and the comparison arm was a similR team, but without the nurse prescriber. In the other category, the nurse worked independently, and the comparison arm was a doctor working without a nurse. We categorised the studies based on this distinction and analysed these groups separately.

2.3.3 Data extraction and quality assessment

Two authors (Maryam Tabesh and Digsu Koye) independently extracted details of the selected studies and checked the references of all included studies to find other potentially relevant studies. We contacted authors of all the papers included in the study to obtain necessary information not reported in the publication. Extraction of information included: year of publication, mean age of participants in each group, duration of diabetes, duration of follow up, country of origin, ethnicity of participants, presence of diabetes related complications, baseline and follow up HbA1c, sample size, components of intervention and control groups,

types of intervention (nurses worked in a team or work independently) and the nature of the control treatment (physicians only or team work) using a structured data collection form.

We used the Cochrane Collaboration's tool for assessing risk of bias in clinical trials to assess the study quality and reporting bias (16). A score between 6 (high quality) and 0 (low quality) was assigned to each study. Features of trial design included in the score are: the use of random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). We categorised the total score into the following groups: low risk (score 5 or 6), medium risk (score 3 and 4) and high risk of bias (total score less than 3).

2.3.4 Statistical analysis

The pooled effect size of studies and 95% confidence interval (CI) for the differences in the mean between intervention and control groups were calculated using mean and standard deviation (SD) or standard error (SE) from each individual study. When the mean difference in the change of HbA1c (from baseline to study end) was not reported, baseline and follow-up HbA1c were used to calculate it using Revman 5 calculators. Data were pooled and analysed using Revman 5. An effect size of 0.2 was regarded as small, 0.5 as medium, and 0.8 as large (17). The Q test was used to test for significant heterogeneity of effect size among studies. The I^2 (%) statistic was used to quantify the extent of the heterogeneity or proportion of between study variability in effect size that was due to true heterogeneity. The I^2 statistic was interpreted as small, moderate, or large if I^2 was less than 25%, 25% to 50%, or greater than 75%, respectively (16). A random effects model was performed to estimate effect size in the pooled meta-analysis (18). The presence of publication bias was assessed using a funnel plot.

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Chapter 3

Understanding the contributing factors in the association of diabetes with disability

3.1 Disability and the burden of diabetes associated with disability

People with diabetes have a higher risk of developing physical disability (1). The higher risk of disability in people with diabetes is multifactorial and may broadly be explained by existence of complications of diabetes that directly affect physical function (e.g. stroke, amputation and heart failure) and the features of diabetes that may affect neuromuscular function (e.g. hyperglycaemia and hypertension). The higher risk of disability in people with diabetes can also be explained by neuropathy and pain. Patients with painful diabetic neuropathy characteristically present with tingling sensation, numbness, burning, stabbing or deep aching in the feet (21).

Chronic or recurrent pain or discomfort may cause restriction and result in disability in people with diabetes (22). Furthermore, people with diabetes have a five-fold increased risk of falling which can cause mobility decline and activity avoidance (23).

Identifying and assessing the risk factors that contribute to the association between diabetes and disability can provide a basis for developing interventions in order to reduce the risk of disability in people with diabetes and improve their quality of life. Therefore, this chapter of the thesis is focused on identifying the factors that contribute to the association between diabetes and disability. We also quantified the contribution of these factors to this association.

The publication included in this chapter of this thesis comprises results derived from national surveys that were conducted in Mauritius. The study population for this chapter of this thesis is derived by merging the samples derived from both the Mauritius NCD Survey 2015 and the follow up of the Mauritius 1998 NCD cohort in 2015. These studies were conducted by the Ministry of Health and Quality of Life of Mauritius in collaboration with the Baker Heart and

Diabetes Institute, Australia. I was involved in developing survey instruments and data collections forms.

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The main finding of this work is that diabetes is associated with a 67% increased odds of disability. The prevalence of disability was found to be higher among women compared to men (16.4% *vs.* 9.1%). We further found that the association between diabetes and disability was stronger among those with African Creole ethnicity than among South Asians. The association between diabetes and disability was multi-factorial. We found that forty percent of the association of diabetes with disability could be explained by diabetes risk factors and concomitant disease. Among these risk factors, obesity explained the largest percentage of the relationship between diabetes and disability, indicating that weight management might be helpful in controlling disability related to diabetes. These findings provide an important basis for further studies to identify interventions that will reduce the burden of physical disability in people with diabetes.

Declaration for Thesis – Chapter 3

Maryam Tabesh, Jonathan E Shaw, Paul Z Zimmet, Stefan Söderberg, Digsu N Koye, Sudhir Kowlessur, Maryam Timol, Noorjehan Joonas, Ameena Sorefan, Praneel Gayan, George M.M. Alberti, Jaakko Tuomilehto, Dianna J. Magliano, The association between type 2 diabetes and disability: what is the contribution of diabetes risk factors and diabetes complications?, J Diabetes. 2018 Mar 6. doi: 10.1111/1753-0407.12659.

In the case of chapter 2, the nature and extent of my contribution to the work was the following:

Nature of the contribution	Extent of the contribution
Development of survey questionnaire, cleaning, analysing and interpreting the data, conceptualisation and writing of the manuscript, critical revision, corresponding author	80%

The following co-authors contributed to the work. If co-authors are student at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of the contribution	Extent of the contribution (%) for student co-authors only
Jonathan E. Shaw	Survey design, conceptualisation, interpretation and approval for the final for publication	N
Paul Z. Zimmet	Survey design , reviewing and editing the manuscript	N
Stefan Söderberg	Survey design , reviewing and editing the manuscript	N
Digsu N. Koye	Reviewed and edited the manuscript	Y, 4%
Sudhir Kowlessur	Survey design , reviewing and editing the manuscript	N
Maryam Timol	Survey design , reviewing and editing the manuscript	N
Noorjehan Joonas	Survey design , reviewing and editing the manuscript	N
Ameena Sorefan	Survey design , reviewing and editing the manuscript	N
Praneel Gayan	Survey design , reviewing and editing the manuscript	N
George M.M. Alberti	Survey design , reviewing and editing the manuscript	N
Jaakko Tuomilehto	Survey design , reviewing and editing the manuscript	N
Dianna J. Magliano	Survey design, conceptualisation, interpretation and approval for the final for publication	N

The undersigned hereby certify that the above declaration correctly reflects the nature and the extent of the candidate's and co-author's contribution to this work *.

Student Signature	[redacted]	Date: 28/06/2018
Main Supervisor Signature		Date: 28/06/2018

*note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

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ORIGINAL ARTICLE

Association between type 2 diabetes mellitus and disability: What is the contribution of diabetes risk factors and diabetes complications?

Highlights
- Diabetes is associated with 67% increased odds of disability.
- The prevalence of disability is higher among women than men.
- Forty per cent of the association of diabetes with disability can be explained by risk factors and concomitant disease.
- Obesity explained the largest percentage of the relationship between diabetes and disability, indicating that weight management may be helpful in controlling disability related to diabetes.

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Abstract

Background: The aim of this study was to evaluate the association between type 2 diabetes and disability in Mauritius and to assess the extent to which the effect of diabetes is explained by diabetes risk factors and concomitant complications.

Methods: Data from a national survey in the multiethnic nation of Mauritius, which comprises South Asians and African Creoles, were analyzed. Disability was measured using the Katz activities of daily living questionnaire in participants aged >50 years.

Results: Among 3692 participants, 487 (13.2%) had some level of disability. Diabetes was associated with significantly higher risk of disability (odds ratio [OR] 1.67; 95% confidence interval [CI] 1.34–2.08). After adjusting for demographic, behavioral, and metabolic factors, as well as comorbidities, disability was significantly associated with diabetes among African Creoles (OR 2.03; 95% CI 1.16–3.56), but not South Asians (OR 1.27; 95% CI 0.98–1.66). Obesity explained much of the association between diabetes and disability (excess percentage of risk: 26.3% in South Asians and 12.1% in African Creoles). Obesity, history of cardiovascular disease (CVD), asthma-like symptoms, and depression together explained 46.5% and 29.0% of the excess risk in South Asians and African Creoles, respectively.

Conclusions: Diabetes is associated with a 67% increased risk of disability. Diabetes risk factors and comorbidities explain more of the association between diabetes and disability among South Asians than Africans. Obesity and history of CVD explained the largest percentage of the relationship

between diabetes and disability, indicating that weight and CVD management may be helpful in controlling disability related to diabetes.

Keywords: disability, ethnic differences, Mauritius, obesity, type 2 diabetes.

Introduction

The increasing prevalence of diabetes together with aging of the population may give rise to a large burden of disability that will affect both individuals and healthcare systems.[1] Disability is associated with many poor outcomes, including loss of employment and productivity, difficulty in performing daily self-care activities, increased use of health services, and premature death.[2–4] People with diabetes have a two- to threefold higher risk of physical disability.[5]

The high prevalence of disability among people with diabetes has various causes. Diabetes is strongly associated with disabling diseases such as cardiovascular disease (CVD), renal failure, blindness, and lower limb amputation.[1,6–10] Furthermore, overweight and obesity are major risk factors for type 2 diabetes and are often associated with impaired mobility.[11]

Although the relationship between disability and diabetes is well described,[5] little is known about how risk factors for diabetes and complications of diabetes contribute to this association. Koye et al.[12] showed that body mass index (BMI) and cardiometabolic risk factors (hypertension, prior CVD, impaired glomerular filtration rate [GFR], triglycerides, and high-density lipoprotein cholesterol [HDL-C]) together explained 65% of the excess odds of disability among Australians aged >60 years. Gregg et al.[3] reported that among the older US population, comorbidities and diabetes risk factors together contributed to 68% and 58% of the excess odds of disability in women and men, respectively.

We have not been able to identify any study that examined the contribution of diabetes risk factors and concomitant complications to the association between diabetes and disability among South Asians and Africans. In addition, previous studies have not specifically examined the role of ethnicity in the association between diabetes and disability. The younger age of onset of diabetes and the various levels of adiposity in South Asians than other ethnicities suggest the possibility of a different relationship between diabetes and disability in terms of strength and contributory factors to this association.[13] Understanding the factors that explain the association between diabetes and disability may provide insight into strategies to reduce the burden of disability and its related cost, as well as to improve the quality of life among people with diabetes.

Mauritius is multi-ethnic nation with a population of 1.3 million people comprising diverse ethnicities, including South Asians (Indian origin), Creoles of mainly African origin, and Chinese. In 2009, the prevalence of diabetes was 22.3% among men and 20.2% among women, which is one of the highest in the world in terms of prevalence of diabetes.[14] The high prevalence of diabetes and concomitant diseases, together with ethnic diversity, makes Mauritius an ideal setting in which to investigate the association of disability with diabetes in different ethnic groups in a middle-income country. If the relationship and the factors explaining the association between diabetes and disability differ by ethnicity or gender, then the interventions implemented may be different for each ethnic or gender subgroup.

Thus, the aim of the present study was to evaluate the association between diabetes and disability in the total population as well as in the ethnic subgroups, and to assess the extent to which the association of diabetes is explained by risk factors that may be specific to an ethnicity for diabetes and comorbidities of diabetes. This information may be valuable in evaluating specific management or interventions.

Methods

Survey design

The Mauritius Non-Communicable Disease (NCD) survey was conducted in 2015 by the Ministry of Health and Quality of Life in Mauritius. The aim of that national population-based survey was to measure the prevalence of NCDs and explore the risk factors and complications related to these diseases.[14] One of the aims of the survey was to understand the association of chronic disease such as diabetes with disability. Mauritius was divided into nine districts to ensure geographical and ethnic representation. Index clusters (24 in total) were randomly selected from each of the districts. Each index cluster was assigned two neighboring clusters to create a "super-cluster". From these super-clusters, one in three households was randomly chosen and one adult per household was randomly selected to participate in the survey. In total, 7151 individuals were invited to participate in the survey, with 5898 agreeing to take part in the survey, giving a response rate of 82%.

Written informed consent was obtained from all participants. The survey was approved by the Ethics Committee of the Ministry of Health and Quality of Life in Mauritius and the Monash University Human Research Ethics Committee (no. CF16/22-2016000010) and Alfred Ethics Committee (no. 624/15) in Australia.

Data collection and samples

The methodology of the survey, data collection, and laboratory tests have been described elsewhere.[14] Briefly, the assessments included a blood sample, anthropometric and blood pressure measurements, and interviewer-administered questionnaires. An oral glucose tolerance test (OGTT) was conducted, except on those with previously diagnosed diabetes. Participants self-reported their demographic information, ethnicity, educational level, smoking status, medical history, and medication usage. Based on self-report of ethnicity, participants were categorized as South Asian, African Creoles, or other ethnicities.

Measurements and laboratory tests

Body mass index (BMI) was calculated by dividing the weight (kg) by height squared (m^2). Blood pressure was measured three times using an automated blood pressure monitor (Digital Auto Blood Pressure Monitor M7; Omron, Kyoto, Japan), and the three readings were averaged.

Blood samples were collected by venepuncture after an overnight fast of at least 8 h. For glucose testing, blood samples were collected into fluoride-oxalate tubes. For HbA1c testing, samples were collected into EDTA tubes and assayed on a Tosoh G8 automated system using HPLC (Tosoh Biosciences, Tokyo, Japan). Serum triglycerides, total cholesterol, and HDL-C were measured using enzymatic methods adapted on an automated system (Abbott Architect c8000; Human Diagnostics, Wiesbaden, Germany). Low-density lipoprotein cholesterol (LDL-C) was calculated for participants with triglycerides ≤4.52 mmol/L using the Friedewald formula.[15]

Definition of diabetes and other diseases

Diabetes was defined as self-report of previously diagnosed diabetes and confirmed by fasting plasma glucose (FPG) ≥7.0 mmol/L or 2-h plasma glucose (2hPG) ≥11.1 mmol/L after a 75-g glucose load, or by self-report of the use of insulin or oral glucose-lowering medications.[16] Newly diagnosed diabetes was defined as FPG ≥7.0 mmol/L or 2hPG after a 75-g glucose load ≥11.1 mmol/L among people without previously diagnosed diabetes. Participants were classified as having impaired glucose tolerance (IGT) if FPG was <7.0 mmol/L and 2hPG was between 7.8 and 11.1 mmol/L. Impaired fasting glucose (IFG) was defined as FPG 6.1–6.9 mmol/L and 2hPG <7.8 mmol/L.[16] The term "prediabetes" was used in this analysis for either IFG or IGT or combined IFG and IGT.

Depression was assessed using the Center for Epidemiologic Studies–Depression (CES-D) scale.[17] The prevalence of asthma-like symptoms was measured using the European Community Respiratory Health Survey (ECRHS) screening questionnaire.[18] Impaired GFR was defined as having estimated GFR (eGFR) <60 mL/min per 1.73 m^2, and was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[19] Dyslipidemia was defined as LDL-C ≥ 2.59 mmol/L or triglycerides ≥2.0 mmol/L or HDL-C < 1.03 mmol/L for men and < 1.29 mmol/L for women or a self-report of using lipid-lowering drugs regardless of the lipid values.

Outcome assessment

Disability was estimated in adults aged ≥50 years using the Katz index of independence in activities of daily living (ADL) questionnaire.[20] This instrument rates adequacy of performance in six major ADL living, namely walking, bathing, transferring, toileting, dressing, and eating. Each of the activities were graded using a four-point scale as follows: 1, no difficulty; 2, a little difficulty; 3, some difficulty; 4, a lot of difficulty. Disability was defined as a response of at least a little difficulty to any of the Katz ADL items.

Statistical analysis

Statistical analyses were performed using STATA version 14 (StataCorp, College Station, TX, USA). The significance of differences in the general characteristics of participants, by disability status, was assessed using Pearson's Chi-squared test for proportions and Student's *t*-test for mean values, as appropriate. Interactions were considered to be significant when $P < 0.2$. For all other analyses, two-tailed $P < 0.05$ was considered significant.

A series of logistic regression models was used to examine the association between diabetes and disability, with disability as the main outcome of interest. Adjustments were as follows: Model 1, adjusted for demographic and behavioral factors, including age, sex, and education; Model 2, adjusted for all factors in Model 1 plus BMI; Model 3, adjusted for all factors in Model 1 plus a history of CVD; Model 4, adjusted for all factors in Model 1 plus asthma-like symptoms; Model

5, adjusted for all factors in Model 1 plus depression; and Model 6, adjusted for all variables included in Models 1–5.

The percentage of excess odds in Model 1 (adjusted for age, sex, and education) that could be accounted for by risk factor adjustment was calculated using the following formula:[21]

$$\%Excess\ odds = \frac{(OR_{ASE} - OR_{ASE+RF})}{OR_{ASE} - 1} \times 100$$

where OR_{ASE} is the odds ratio (OR) adjusted for age, sex, and education and OR_{ASE+RF} is the OR adjusted for age, sex, education, and risk factors.

Bootstrapping techniques were used to estimate the uncertainty intervals around the calculation described above. If the confidence intervals estimated by bootstrapping were lower than 0 or more than 100, we replaced them with 0 and > 100, respectively.

Results

Participant characteristics

Among 3701 participants aged ≥50 years, 3692 completed the Katz ADL questionnaire (99.7%) and 487 participants were categorized as having disability. Table 1 shows the characteristics of participants according to disability status. The prevalence of disability in the total population aged ≥50 years was 13.2% (95% confidence interval [CI] 12.1–14.3), with a significantly higher prevalence among women (16.4%; 95% CI 14.8–18.0) than men (9.1%; 95% CI 7.8–10.6). Participants with disability had a significantly lower level of education and higher BMI, waist circumference, and systolic blood pressure than those without disability. Those with disability also had a greater burden of chronic diseases and other conditions, such as depression, history of CVD, hyperlipidemia and impaired eGFR (Table 1). The prevalence of each individual component of the disability index, stratified by ethnicity, is given in Table S1, available as Supplementary Material to this paper.

Table 1 General characteristics of the study population according to disability status

	Disability status		
	Disabled	Not disabled	*P*-value
% Subjects	13.2 (487)	86.8 (3205)	
Age (years)	62.1 ± 8.0	67.0 ± 9.2	<0.001
Men	30.6 (149)	46.3 (1483)	<0.001
Ethnicity			0.008
South Asian	79.3 (386)	74.5 (2387)	
African	18.1 (88)	19.7 (631)	
Other	2.7 (13)	5.9 (187)	
Education			<0.001
Primary (0–6 years)	72.2 (307)	51.0 (1548)	
Secondary (6–12 years)	26.1 (111)	41.0 (1244)	
Tertiary (>12 years)	1.6 (7)	8.0 (244)	
Smoking status			0.27
Current smoker	22.8 (34)	25.8 (383)	
Ex-smoker	23.5 (35)	18.2 (270)	
Never smoker	53.7 (80)	56.0 (830)	
Diabetes status			<0.001
Normoglycemia	23.6 (107)	36.1 (1124)	
Prediabetes	16.5 (75)	20.3 (632)	
Diabetes	59.9 (272)	43.6 (1359)	
HbA1c	7.2 (1.7)	6.9 (1.7)	0.004
BMI (kg/m^2)	27.4 ± 5.6	25.9 ± 4.6	<0.001
Men	25.5 ± 5.1	25.1 ± 4.0	0.27
Women	28.2 ± 5.6	26.6 ± 4.9	<0.001
Waist circumference (cm)			
Men	94.1 ± 13.0	91.5 ± 10.8	0.011
Women	92.9 ± 11.7	89.0 ± 10.7	<0.001
Blood pressure (mmHg)			
Systolic	136.0 ± 23.7	133.0 ± 22.5	0.008
Diastolic	80.0 ± 11.7	81.0 ± 11.9	0.280
Hyperlipidemia	81.3 (396)	77.0 (2496)	0.035
Asthma	20.7 (101)	8.1 (257)	<0.001
Depression	28.2 (133)	11.0 (347)	<0.001
History of CVD	24.6 (119)	11.7 (373)	<0.001
eGFR <60 mL/min per 1.73 m^2	25.5 (124)	12.0 (384)	<0.001

Data are given as the mean ± SD or as percentage (*n*).
BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

Association between diabetes and disability

A series of logistic regression analyses was performed and adjusted for potential risk factors in a stepwise manner to understand how these risk factors may confound the association between diabetes and disability (Table 2). Potential risk factors were defined as those variables that were significantly associated with disability in the multivariate analysis. Although hypertension, dyslipidemia, and e-GFR were significantly associated with disability in univariate analyses (Table 1), the association of these variables with disability was attenuated and lost significance in the multivariate analysis. Therefore, to make models parsimonious and to facilitate making reliable conclusions as to which individual variables are genuinely contributing to the association between diabetes and disability, these variables were not included in the final logistic regression model.

In Model 1, adjusted for age, sex and education, diabetes was associated with increased odds of disability in the total population (OR 1.67; 95% CI 1.34–2.08). With further adjustment in Model 2 (adjusted for BMI), Model 3 (adjusted for history of CVD), Model

Table 2 Odds ratios for the association of diabetes with disability, stratified by ethnicity

	Total population		South Asians		Africans	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Model 1	1.67 (1.34–2.08)	<0.001	1.52 (1.19–1.95)	0.001	2.57 (1.53–4.34)	<0.001
Model 2	1.50 (1.19–1.88)	<0.001	1.36 (1.05–1.76)	0.018	2.30 (1.33–3.95)	0.003
Model 3	1.54 (1.23–1.93)	<0.001	1.40 (1.09–1.81)	0.008	2.39 (1.41–4.06)	0.001
Model 4	1.66 (1.33–2.07)	<0.001	1.52 (1.18–1.95)	0.001	2.51 (1.48–4.26)	0.001
Model 5	1.61 (1.28–2.01)	<0.001	1.48 (1.14–1.90)	0.003	2.40 (1.40–4.12)	0.001
Model 6	1.34 (1.06–1.70)	0.01	1.27 (0.98–1.66)	0.07	2.03 (1.16–3.56)	0.01

Model 1: adjusted for age, sex and education.
Model 2: adjusted for all factors in Model 1 plus body mass index (BMI).
Model 3: adjusted for all factors in Model 1 plus a history of cardiovascular disease (CVD).
Model 4: adjusted for all factors in Model 1 plus asthma.
Model 5: adjusted for all factors in Model 1 plus depression.
Model 6: adjusted for all factors in Model 1 plus BMI, history of CVD, asthma, and depression.
OR, odds ratio; CI, confidence interval.

4 (adjusted for asthma), and Model 5 (adjusted for depression) the odds of disability remained significantly higher among people with diabetes. In the fully adjusted model, Model 6, the odds of disability was 34% higher among people with than without diabetes (OR 1.34; 95% CI 1.06–1.70).

Contribution of potential risk factors for diabetes to the association between diabetes and disability

To quantify the contribution of risk factors to the association of disability with diabetes, the percentage of excess odds of disability related to diabetes in each model was calculated and compared with the base model, which was adjusted for age, sex and education (Table 3). Body mass index explained much of the association between diabetes and disability. A history of CVD explained 15.8% of the excess odds of disability related to diabetes, whereas asthma and depression explained 1.8% and 7.9% of these associations, respectively. Collectively, all the potential factors included in the logistic regression analysis explained 42.0% of the association of diabetes with disability.

In a further analysis, the association between obesity and disability among those with and without diabetes was assessed. In both the diabetes and non-diabetes groups, there was a significant association between obesity and disability, indicating a direct association of obesity with disability.

Interactions of ethnicity and sex in the association between diabetes and disability

The relationship between diabetes and disability was seen in both ethnic groups, but it was somewhat stronger among African Creoles than South Asians (OR 2.57 [95% CI 1.53–4.34] and 1.52 [95% CI 1.19–1.95], respectively; Table 2). The association between diabetes and disability remained significant after adjustment for each group of risk factors in Models 1–5. Adjusting for all risk factors in Model 6 attenuated the association of disability with diabetes among South Asians to become non-significant (OR 1.27; 95% CI 0.98–1.66), whereas in African Creoles the association remained significant (OR 2.03; 95% CI 1.16–3.56). There was no interaction of sex in the association between diabetes and disability.

With regard to the risk factors contributing to the association between diabetes and disability, BMI explained 26.3% and 12.1% of the association between diabetes and disability among South Asians and African Creoles, respectively. The contribution of a history

Table 3 Effect of separately controlling for risk factors on the percentage of excess odds of disability associated with diabetes

	% Excess odds accounted for by risk factor adjustment (95% CI)		
Model	Total population	South Asians	Africans
Model 1	Base model	Base model	Base model
Model 2	21.7 (9.9–37.1)	26.3 (10.3–63.4)	12.1 (0.5–30.6)
Model 3	15.8 (8.0–31.5)	19.0 (8.2–54.8)	7.8 (0.0–22.7)
Model 4	1.8 (0.0–9.7)	0.83 (0.0–11.6)	2.7 (0.0–16.0)
Model 5	7.9 (0.0–11.6)	7.5 (0.0–16.1)	7.4 (0.0–16.7)
Model 6	42.0 (17.5–76.7)	46.5 (18.7–100)	29.0 (0.0–67.8)

Model 1: adjusted for age, sex and education.
Model 2: adjusted for all factors in Model 1 plus body mass index (BMI).
Model 3: adjusted for all factors in Model 1 plus a history of cardiovascular disease (CVD).
Model 4: adjusted for all factors in Model 1 plus asthma.
Model 5: adjusted for all factors in Model 1 plus depression.
Model 6: adjusted for all factors in Model 1 plus BMI, history of CVD, asthma, and depression.
CI, confidence interval.

Table 4 General characteristics of the study population stratified by ethnicity

	South Asians			Africans		
	Disabled	Not disabled	*P*-value	Disabled	Not disabled	*P*-value
% Subjects	13.9 (386)	86.1 (2386)		12.2 (88)	87.8 (631)	
Age (years)	66.9 ± 9.1	61.8 ± 7.8	<0.001	66.6 ± 9.5	62.6 ± 9.0	<0.001
Men	30.3 (117)	46.9 (1120)	<0.001	28.4 (25)	43.3 (273)	0.009
Education			<0.001			0.001
Primary	72.9 (1407)	52.2 (1167)		75.9 (63)	54.8 (337)	
Secondary	38.1 (976)	39.9 (892)		22.9 (19)	41.6 (256)	
Tertiary	7.0 (180)	7.8 (175)		1.2 (1)	5.6 (22)	
Smoking status			0.76			0.85
Current smoker	19.7 (23)	25.7 (288)		36.0 (9)	31.9 (87)	
Ex-smoker	24.8 (29)	17.1 (191)		20.0 (5)	24.5 (67)	
Never smoker	55.6 (65)	57.2 (641)		44.0 (11)	43.6 (119)	
Diabetes status			<0.001			<0.001
Normoglycemia	25.6 (92)	35.1 (816)		14.6 (12)	35.8 (219)	
Prediabetes	16.1 (58)	20.0 (465)		15.8 (13)	20.5 (125)	
Diabetes	58.3 (210)	44.8 (1041)		69.5 (57)	43.7 (267)	
HbA1c	7.1 (1.6)	7.0 (1.6)	0.19	7.6 (1.8)	6.9 (1.8)	0.002
BMI (kg/m^2)	27.1 ± 5.5	25.8 ± 4.4	<0.001	29.5 ± 5.5	27.0 ± 5.0	<0.001
Men	25.0 ± 4.9	25.1 ± 4.0	0.796	28.3 ± 5.7	25.7 ± 4.2	0.009
Women	27.9 ± 5.5	26.4 ± 4.7	<0.001	29.9 ± 5.4	27.8 ± 5.2	0.007
Waist circumference (cm)						
Men	93.0 ± 12.8	91.9 ± 10.7	0.323	99.6 ± 13.5	92.1 ± 10.9	0.003
Women	92.5 ± 11.6	88.8 ± 10.5	<0.001	96.2 ± 11.3	91.3 ± 10.7	0.001
Hypertension	69.4 (268)	55.9 (1333)	<0.001	75.9 (66)	66.5 (419)	0.082
Dyslipidemia	80.3 (310)	77.2 (1844)	0.18	86.4 (76)	79.1 (499)	0.11
Asthma	21.0 (81)	8.5 (202)	<0.001	21.6 (19)	8.2 (52)	<0.001
Depression	27.3 (102)	11.3 (265)	<0.001	36.9 (31)	12.2 (76)	<0.001
History of CVD	25.1 (96)	11.6 (276)	<0.001	21.6 (19)	13.6 (85)	<0.001
eGFR <60 mL/min per 1.73 m^2	27.5 (106)	13.7 (327)	<0.001	19.3 (17)	7.6 (48)	<0.001
Stroke	21.1 (20)	9.5 (26)	0.004	36.8 (7)	9.52 (8)	0.005

Data are given as the mean ± SD or as percentage (*n*). *P*-values were calculated using Chi-squared tests for categorical variables and one-way ANOVA for continuous variables.
BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

of CVD to the association between diabetes and disability was 19.0% among South Asians and 7.8% among African Creoles, whereas the contribution of depression was 7.5% and 7.4% for South Asians and African Creoles, respectively. The contribution of asthma to the association between diabetes and disability was negligible (0.8% for South Asians and 2.7% for African Creoles).

To explore why ethnic subgroups may have differed from each other with regard to the strength of the association between diabetes and disability, we examined the characteristics of participants stratified according to ethnicity (Table 4). Among people aged ≥50 years, the prevalence of diabetes was similar among South Asians (34.5%) and Africans Creoles (33.4%). In addition, the prevalence of disability among those aged ≥50 years was similar between African Creoles and South Asians (12.2% and 13.9%, respectively). The prevalence of each individual component of the disability index was similar between African Creoles and South Asians (Table S1). However, among women aged >70 years, South Asians were more likely to be classified as having disability than were African Creoles (36.1% vs 24.5%, respectively; $P = 0.03$). In both ethnic groups, the disabled people were more likely to be female, have lower education, and a higher prevalence of chronic disease, including asthma-like symptoms, depression, and a history of CVD, and impaired eGFR than non-disabled people.

The association of disability with other factors such as age, BMI, education, history of CVD, asthma-like symptoms, depression, and history of stroke was similar between South Asians and African Creoles (Table 4). There was strong and significant collinearity between diabetes status and HbA1c levels, thus HbA1c was not added to the models. Nevertheless, there was no significant difference in mean HbA1c levels among those with diabetes of African descent compared with South Asians with diabetes (8.3% vs 8.2%, respectively; $P = 0.29$).

Discussion

In this representative sample of adults aged ≥50 years in the multi-ethnic country of Mauritius, we demonstrated that diabetes was associated with a 67% increased risk of disability. We further observed that high BMI and a history of CVD explain a large proportion of the association between diabetes and disability.

Previous studies that examined the association between diabetes and disability were mostly conducted in developed countries, and among Europid population.[3,22,23] Studies in Hong Kong, Japan, and Taiwan also showed a positive association between diabetes and disability.[24–26] Although the majority of previous studies demonstrated a relationship between diabetes and disability,[5] there are inconsistencies reported as to which risk factors may mediate this association.

The contribution of obesity to the association of disability with diabetes can be explained from different perspectives: obesity per se is one key cause of immobility[11] and hence disability. This was confirmed by the significant association between obesity and disability in the non-diabetic groups in the present study. Further, because obesity is considered to be one of the major risk factors for type 2 diabetes, some of the extent to which obesity appears to explain the diabetes–disability association may actually be a direct effect of diabetes in people in whom diabetes was caused by obesity. Given the present study was a cross-sectional study, causal pathways cannot be established, but it is likely that obesity is related to disability via several pathways.

The Australian Diabetes, Obesity and Lifestyle (AusDiab) study showed that the association between diabetes and disability was attenuated and became non-significant after adjusting for risk factors for diabetes, and for comorbidities of diabetes.[12] Similar to the findings of the present study, in the AusDiab study BMI explained much of the association between diabetes and disability.[12] A study conducted among older Americans reported that risk of disability associated with diabetes was reduced by 52% in women when they accounted for coronary heart disease (CHD) together with BMI.[3] Similarly, adjustment for stroke and CHD reduced the risk of disability by 23% in men.[3] Maggi et al.[22] demonstrated sex disparity among Italians in the association between diabetes and disability, finding that adjusting for age, education, and BMI resulted in a significant association between diabetes and disability among women, but not men. In both sexes, BMI and CVD together explained much of the association between diabetes and disability, with a 19% reduction in excess odds of disability among women and a 12% reduction in excess odds among men.[22] In contrast with the findings of Maggi et al.,[22] two studies from East Asia demonstrated significant associations between diabetes and disability among men, but not women.[24,26] In the present study, we did not observe any difference in the association between diabetes and disability by sex.

In the present study, adjustment for risk factors partially attenuated the strength of the association between diabetes and disability, suggesting that the residual association between diabetes and disability may be explained by other unmeasured factors. It should be noted that the present study used a cross-sectional study design that does not allow us to assess causality (i.e. high BMI is one of the risk factors for disability, whereas disability per se can lead to high BMI by reducing physical activity levels).

We observed that the relationship between diabetes and disability may be different between African Creoles and South Asians. However, further studies are needed to confirm this. The possible differences between ethnic subgroups in the association of diabetes with disability may be explained by genetic and environmental factors such as lifestyle. Previous studies have shown that, compared with other ethnicities, older Africans have a higher percentage of intramuscular adipose tissue, which may indicate that metabolic insults such as diabetes have a greater effect on muscle function.[27,28]

In the present study we showed that the possible ethnic difference was not due to the difference in HbA1c, educational level, age, BMI, history of CVD, smoking status, history of stroke, or ethnic differences in reporting of disability. The *P*-value for the interaction between diabetes and ethnicity for disability was 0.06, but the confidence intervals for the ethnic-specific ORs overlapped. Thus, we are unable to make a robust conclusion that the association of diabetes with disability differs by ethnicity. However, the borderline significant *P*-value for the interaction suggests the possibility of some differences between South Asians and Africans in the association between diabetes and disability, and that further studies are required to examine this finding. The present study sheds light on the potential existence of ethnic disparity in the association between diabetes and disability, but further studies are required to confirm this finding.

The strength of the present study is the nationally representative sample and high response rate. Asthma-like symptoms and depression were evaluated in the survey by validated questionnaires rather than relying on the self-reported presence of disease. The present study is limited by its observational cross-sectional design and lack of an objective measurement to assess disability. Furthermore, because the main aim of the present study was to understand the association between diabetes and

disability, rather than presenting prevalence, we did not weight the samples. A further limitation of the present study is that people with severe disability or cognitive deficits would have been less likely to attend the survey. Because the present survey was not designed a priori for the exploration of the association between diabetes and disability, some factors that may contribute to this association were not examined in the study.

Conclusion

We found that diabetes is associated with a 67% increased odds of disability, and that this association may differ by ethnicity. The association between diabetes and disability is multifactorial. Body mass index explains much of the association, indicating weight management as one of the possible strategies in preventing disability associated with diabetes. However, control of hyperglycemia and other factors may also have a role to play. These findings provide an important basis for further studies to identify interventions that will reduce the burden of physical disability in people with diabetes.

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Disclosure

No potential conflicts of interest relevant to this article are reported.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Prevalence of different components of disability stratified by ethnicity and among those with diabetes.

Supplementary Table: Prevalence of different components of disability stratified by ethnicity and among those with diabetes

	Total population		Diabetes
	South Asians	**Africans**	
N	2773	719	1628
Walking	3.8 (105)	3.3 (24)	5.1 (83)
Bathing or showering	5.6 (155)	4.3 (31)	6.7 (109)
Moving in and out of a chair or bed (transferring)	11.4 (316)	10.1 (73)	14.0 (220)
Using a toilet	5.1 (140)	5.1 (37)	6.8 (110)
Dressing	4.6 (129)	3.5 (25)	5.8 (95)
Eating	2.1 (57)	1.0 (7)	2.1 (34)

Data are percentage (n)

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Chapter 4

Trends of diabetes management in Mauritius

It has been well established that controlling glycaemia, blood pressure and lipids are critical in preventing or delaying morbidity and mortality in people with diabetes. Guidelines have advocated for regular assessment of the treatment targets for HbA1c, blood pressure and lipids often known as the ‘‘ABC’’ goals in diabetes management (1). Despite a considerable effort in formulating these guidelines, translating guidelines into clinical practice remains challenging.

Despite the high diabetes prevalence in low and middle income countries, studies examining quality of diabetes management according to the ABC goals are rare in these countries. Mauritius is a multi-ethnic, middle-income country with a high diabetes prevalence. In Mauritius, the government has conducted serial NCD surveys, starting in 1987 and repeating every 5–6 years, thus this is an ideal place to assess the trends of diabetes management at the population level using two independent samples. Furthermore, the multi-ethnic nature of this country will allow us to examine whether or not there is any differences in diabetes management among different ethnic groups.

The publication included in this chapter comprises the results derived by comparing the data obtained from two national surveys, the 2009 and 2015 Mauritius NCD Surveys. These surveys were conducted by the Ministry of Health and Quality of Life of Mauritius in collaboration with the Baker Heart and Diabetes Institute, Australia. I was involved in developing survey instruments and data collections forms.

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The main finding of this work is that in 2015 compared to 2009, control of glycaemia and blood pressure improved, and total and LDL cholesterol control remained unchanged. We also observed that the use of glucose-, blood pressure- and LDL cholesterol-lowering medication was greater in 2015 than in 2009.

There was better control of glycaemia and blood pressure in some subgroups in 2015 compared to 2009. Better control of HbA1c was mainly observed in subgroups where control was poorest in 2009, such as women and those with only a primary level of education as compared to men and those with higher levels of education, respectively. This was also true for blood pressure levels, where there was better control of blood pressure among South Asians compared to African Creoles. Given that the African Creoles are generally the most disadvantaged ethnic group in Mauritius, improved blood pressure control in these subgroups might indicate a narrowing in some of the health inequalities in people with diabetes.

In the journal review process of this paper, several reviewers indicated that they believed that following a cohort was a superior design to assessing two independent surveys. However, comparing the results of independent cross-sectional surveys at two different time-points is the appropriate strategy to explore how diabetes management changes at the population level over a specific period of time. The alternative approach of following members of a cohort of people with diabetes over the same time period has several limitations. First, in the first wave of the study, some people would have been referred to medical care, on the basis of abnormal results, leading to a study effect on their findings at follow-up. Second, when we follow the same people in a cohort study, diabetes duration and age would have automatically increased during the study period, whereas in the independent random samples derived from the general population, the characteristics of the sample would reflect the characteristics of the real populations in each year of the study. Third, no one with recently diagnosed diabetes could be in the follow-up examination of a cohort, so excluding an important sub-group.

Although we observed clear improvement in glucose and blood pressure levels of patients with diabetes, the proportion of participants reaching the targets is still far from optimal. The proportion of participants reaching all three ABC targets (HbA1c<7%, LDL<2.59 mmol/L and blood pressure<140/90 mmHg) was 2.9% in 2009 and 6.7% in 2015. Using the blood pressure

target of <130/80 mmHg, the proportion of people reaching all three targets was only 1.6% in 2009 and 5% in 2015. While these findings are encouraging and indicating improvement in some aspects of diabetes management, the majority of people with diabetes still had inadequately controlled HbA1c, blood pressure and lipids. The DBP was 0.6 mmHg higher in 2015 compared to 2009. This was statistically significantly higher than in 2009, but unlikely to be of any clinical relevance. The failure to fall, when SBP fell might reflect an increasing clinical focus on achieving systolic, rather than diastolic, targets.

Successful diabetes management includes more than just pharmaceutical therapy, and requires a systematic approach for supporting patients and improving the health care system. Diabetes self-management education and ongoing diabetes self-management support are two main strategies that are associated with better control of glucose and greater satisfaction of patients with diabetes.

Taking and managing medications, active self-monitoring of glucose and blood pressure levels, foot health, participating in eye and renal screening and assessing mental health are important components of diabetes self-management. Diabetes self-management also requires behavioural changes related to physical activity, dietary habits and weight management.

Further to diabetes self-management, improving the health care system is one of the most effective strategies to improve diabetes management. Such changes may include implementing more intensive management strategies, applying evidence-based guidelines, educating patients, implementing electronic health record tools, reducing financial barriers and out of pocket costs related to education, prevention and medications.

Quality improvement programs are among the successful and cost –effective strategies that are associated with improvement diabetes outcomes. The aim of the quality improvement strategies are to achieve significant improvement in the structure, processes or outcomes of

care for people with diabetes by means of organizational or structural changes. Quality improvement strategies emphasize team work and can involve the combined effort of health care system, clinicians, patients and even their families.

Declaration for Thesis – Chapter 4

Maryam Tabesh, Jonathan E. Shaw, Paul Z. Zimmet, Stefan Soderberg, Sudhir Kowlessur, Maryam Timol, Noorjehan Joonas, George M.M. Alberti, Jaakko Tuomilehto, Benjamin J. Shaw, Dianna J. Magliano, Meeting American Diabetes Association diabetes management targets: trends in Mauritius, Diebet Med. 2017; 34(12):1719-27.

In the case of chapter 3, the nature and extent of my contribution to the work was the following:

Nature of the contribution	Extent of the contribution
Development of survey questionnaire, cleaning, analysing and interpreting the data, conceptualisation and writing of the manuscript, critical revision, corresponding author	80%

The following co-authors contributed to the work. If co-authors are student at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of the contribution	Extent of the contribution (%) for student co-authors only
Jonathan E. Shaw	Survey design, conceptualisation, interpretation and approval for the final for publication	N
Paul Z. Zimmet	Survey design , reviewing and editing the manuscript	N
Stefan Söderberg	Survey design , reviewing and editing the manuscript	N
Sudhir Kowlessur	Survey design , reviewing and editing the manuscript	N
Maryam Timol	Survey design , reviewing and editing the manuscript	N
Noorjehan Joonas	Survey design , reviewing and editing the manuscript	N
George M.M. Alberti	Survey design , reviewing and editing the manuscript	N
Jaakko Tuomilehto	Survey design , reviewing and editing the manuscript	N
Benjamin J. Shaw	Data cleaning, reviewing and editing the manuscript	N
Dianna J. Magliano	Survey design, conceptualisation, interpretation and approval for the final for publication	N

The undersigned hereby certify that the above declaration correctly reflects the nature and the extent of the candidate's and co-author's contribution to this work *.

Student Signature	[redacted]	Date: 28/06/2018
Main Supervisor Signature	[redacted]	Date: 28/06/2018

*note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

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Research: Epidemiology

Meeting American Diabetes Association diabetes management targets: trends in Mauritius

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Aims To examine the proportion of people with diabetes in the multi-ethnic country of Mauritius meeting American Diabetes Association targets in 2009 and 2015.

Methods Data from independent population-based samples of 858 and 656 adults with diagnosed diabetes in 2009 and 2015, respectively, were analysed with regard to recommended American Diabetes Association targets for HbA_{1c}, blood pressure and LDL cholesterol.

Results In 2015 compared with 2009, the proportion of people achieving American Diabetes Association targets for glycaemic control in Mauritius was higher in women ($P \leq 0.01$) and in those with only a primary education level ($P=0.07$), but not in men or people with a higher level of education. Achievement of blood pressure <140/90 mmHg was higher in 2015 compared with 2009 (60% vs 42%) in people of South Asian ethnicity ($P<0.001$), but not in those of African ethnicity ($P=0.16$). The percentages of people with LDL cholesterol <2.59 mmol/l were 42.1% and 50.4%, in 2009 and 2015, respectively ($P=0.27$). Better control of HbA_{1c} and blood pressure was observed in groups in which that control was poorest in 2009. The use of glucose-, blood pressure- and LDL cholesterol-lowering medication was higher in 2015 than in 2009.

Conclusions In certain subgroups, namely women, those with poorer education and those of South Asian ethnicity, whose target achievement was the poorest in 2009, control of glycaemia and blood pressure was better in 2015 as compared with 2009. While these findings are encouraging, further work is required to improve outcomes.

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Introduction

Type 2 diabetes represents a substantial human, social and economic burden, especially in low- and middle-income countries [1]. Previous studies in Mauritius, a rapidly developing economic nation with a mixed ethnic population of South Asian, African Creole and Chinese people, have demonstrated a substantial increase in the prevalence of diabetes over 22 years [2,3]. The age-standardized prevalence of diabetes was 13.0% in 1987 and increased to 21.3% in 2009 in people aged 25–74 years [2]. Given this high prevalence of diabetes, appropriate management of diabetes is important to prevent the development of high rates of diabetes complications.

Metabolic control of Type 2 diabetes involves addressing three key areas: glycaemia, blood pressure and lipid levels. The American Diabetes Association (ADA) 2016 guidelines recommend that most adults with diabetes should achieve an HbA_{1c} concentration <53 mmol/mol (7.0%), blood pressure <140/90 mm Hg, and LDL cholesterol <2.59 mmol/l [4]. These recommendations are in line with those developed in many other countries [5]. In 2009, the ADA recommendation for adequate control of blood pressure was <130/80 mmHg [6–8], while the other targets were the same for both 2009 and 2015.

Over the last two decades, the proportion of those with diabetes who met the [Hb]A_{1c}, blood pressure and cholesterol, or 'ABC', goals have increased in many countries

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What's new?

- This study in Mauritius is one of the first assessments of the trends in the achievement of treatment targets among people with diabetes in a lower- or middle-income country.
- In Mauritius, the control of glycaemia and blood pressure was better in 2015, compared with the year 2009.
- From 2009 to 2015, no significant differences were observed in levels of total cholesterol and LDL cholesterol.
- In Mauritius, the majority of people with diabetes continue to have inadequately controlled HbA_{1c}, blood pressure and lipids, highlighting the need for further improvements in diabetes management.

[9,10]. Despite the high diabetes prevalence in low- and middle-income countries, studies examining the status and quality of diabetes management according to ABC goals are rare in these countries [9,11–13].

Because Mauritius has regular national health surveys (usually every 5 years), and has a multi-ethnic population with a high diabetes prevalence, it is an ideal place to assess the trends in the proportions of people with diabetes attaining the ADA ABC targets at the population level.

Research design and methods

Survey design

Mauritius is a country in the Indian Ocean with a population of 1.3 million people, and comprises different ethnicities, including South Asian, African (Creole) and Chinese. Non-communicable disease surveys were conducted in 2009 and 2015 by the Ministry of Health and Quality of Life in collaboration with several international research institutions [14,15]. The two survey populations were selected independently of each other using cluster-based sampling (Appendix S1). The response rates for the 2009 and 2015 surveys were 85% and 87%, respectively. Written informed consent was obtained from all participants in both surveys. Both surveys were approved by the ethics committee of the Ministry of Health and Quality of Life, Mauritius. The present study was also approved by Monash University Human Research Ethics Committee and the Alfred Ethics Committee, Australia.

Data collection and samples

To collect demographic, medication use and medical history information, identical questionnaires were used in both 2009 and 2015. The date on which participants were first diagnosed with diabetes, ethnicity, educational level, type of treatment and medication use were obtained using interviewer-administered surveys. The level of education was categorized as primary (0–6 years' of education), secondary (7–12 years), or tertiary (>12 years). Based on self-report ethnicity, participants were categorized as South Asian, African or other. Duration of diabetes was categorized into three subgroups as <5, 5–10 and ≥10 years. Participants self-reported whether or not they were taking medications for diabetes, hypertension or hyperlipidaemia, and were asked to specify the names of drugs. In 2015, 49% of medications were confirmed by participants bringing their prescriptions or medications with them to the survey.

The present analysis included all men and non-pregnant women aged 20–75 years with previously diagnosed diabetes. Diabetes was defined as self-report of a previous diagnosis of diabetes, and was confirmed by either fasting plasma glucose ≥7.0 mmol/l or 2-h plasma glucose after a 75-g glucose load ≥11.1 mmol/l, or use of glucose-lowering medications. The 2-h glucose tolerance test was not conducted among those participants who were on glucose-lowering medications.

Measurements and laboratory tests

Weight was measured with the participant in light clothing, using a mechanical beam balance in 2009 and using electronic scales in 2015. Height was measured using a stadiometer in both surveys. BMI was calculated by dividing the weight (kg) by the square of the height (m). Participants were defined as overweight or obese if the BMI was ≥25 and ≥30 kg/m^2, respectively, in African participants, and ≥23 and ≥27 kg/m^2 in South Asian and Chinese participants [16]. Blood pressure was measured three times using an automated blood pressure monitor (Omron Digital Auto Blood Pressure Monitor SEM-1 in 2009 and Omron Digital Auto Blood Pressure M7 in 2015) by a trained operator. All three measurements were averaged to give a mean blood pressure.

Blood samples were collected by venepuncture after an overnight fast of at least 8 h (hours since last meal was self-reported). In 2009, blood samples were collected in fluoride/oxalate tubes centrifuged directly after drawing and samples were then tested using a YSI 2300 STAT PLUS instrument on site. In 2015, samples were collected in fluoride/oxalate tubes, kept at 4°C for 1–3 hours and transferred to a central laboratory (Victoria Hospital in Quatre-Bornes) and assayed using a similar YSI instrument. Glucose stability studies were conducted to confirm that the samples collected for glucose assay reached the laboratory without any deterioration or undergoing glycolysis (Appendix S1). For HbA_{1c} testing, samples were collected in EDTA tubes and assayed on a Tosoh G7 automated system using high-performance liquid chromatography, in both 2009 and 2015. Serum triglycerides, total cholesterol and HDL cholesterol were measured using enzymatic methods adapted on the automated system

of Targa 3000+ Biotechnica equipment and Abbott Architect c8000 in 2009 and 2015, respectively. LDL cholesterol was calculated on participants with triglycerides ≤4.52 mmol/l, using the Friedewald formula [17].

Statistical methods

Statistical analysis was performed using STATA (version 14; Stata Corp, College Station, TX, USA). Changes in mean values over time were tested using regression models adjusted for age, sex and duration of diabetes. Change in the prevalence of 'ABCs' between the two surveys was analysed by logistic regression, adjusted for age, sex and duration of diabetes, with each ABC domain as the outcome, and the year of the survey as the independent variable. We tested for interactions of sex, ethnicity, education, and duration of diabetes with a change in the proportions reaching the targets of HbA_{1c}, lipids and blood pressure between 2009 and 2015. We explored effect measure modification (departure from a multiplicative effect) by performing stratified analysis when the interaction term had a *P* value ≤0.2. *P* values <0.05 were taken to indicate statistical significance. Serum triglyceride, HDL cholesterol, HbA_{1c} and fasting plasma glucose levels were log transformed to correct for the skewed distribution and reported as medians (interquartile range). There were very few missing data (maximum number of missing =41, for duration of diabetes), except for type of medication, where data were available for 1007 of the 1283 participants who reported they were taking medication.

Results

Population characteristics

Characteristics of the study populations are shown in Figure 1. The generalizability of the survey to the total population of Mauritius is described in the Appendix. The age- and sex-standardized prevalence of Type 2 diabetes in the Mauritian population aged 18–74 years was estimated at 20.5% in 2009 and 19.2% in 2015. The total study population comprised 1514 people with known diabetes, 858 from 2009 and 656 from 2015 (Table 1). Overall, characteristics of the participants were similar in both surveys, but there were more people aged >55 years in

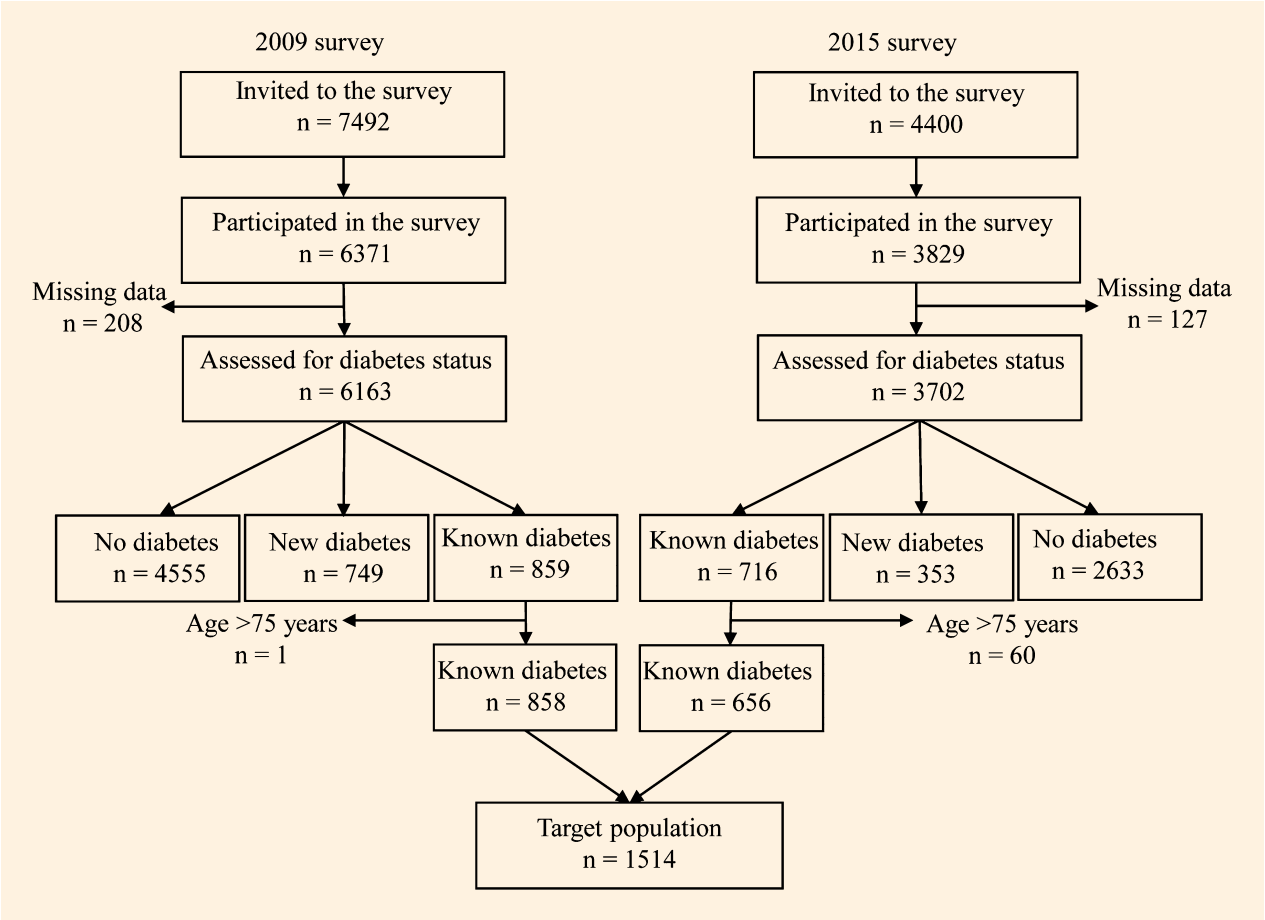

FIGURE 1 Flow chart of the study population in the 2009 and 2015 surveys.

Table 1 Comparisons of clinical characteristics in people with diagnosed diabetes in 2009 and in 2015

	2009	2015	*P**
Number of participants	858	656	
Gender, % (*n*)			0.28
Men	47.3 (406)	44.5 (292)	
Women	52.7 (452)	55.5 (364)	
Median (IQR) age, years	57.0 (50.0 to 63.0)	59.9 (53.9 to 65.9)	<0.001†
Ethnicity, % (*n*)			0.78
South Asian	77.2 (662)	75.6 (496)	
African (Creole)	19.5 (167)	20.7 (136)	
Other (mostly Chinese)	3.4 (29)	3.7 (24)	
Mean ± SD BMI, kg/m^2	26.6 ± 4.6	27.3 ± 4.9	0.01
BMI‡, % (*n*)			0.37
Normal	19.7 (168)	17.4 (114)	
Overweight	38.1 (325)	37.2 (244)	
Obese	42.3 (361)	45.4 (298)	
Median (IQR) duration of diabetes, years	5.0 (2.0 to 10.0)	6.8 (3.2 to 12.9)	<0.001†
Duration of diabetes, % (*n*)			0.53
<5 years	44.4 (366)	38.4 (236)	
5–10 years	22.7 (187)	23.6 (145)	
≥10 years	32.9 (271)	38.1 (234)	
Total§, *N*	824	615	
Education, % (*n*)			0.03
Primary school education or no education	64.2 (546)	57.9 (380)	
Secondary school education	32.3 (275)	39.0 (256)	
Tertiary education	3.5 (30)	3.1 (20)	
Biochemical markers			
Median (IQR) fasting plasma glucose, mmol/l			
Men	9.1 (7.4 to 11.7)	8.4 (7.0 to 10.6)	0.033†
Women	9.9 (7.9 to 12.8)	8.3 (6.7 to 10.9)	<0.001†
Total	9.5 (7.7 to 12.4)	8.3 (8.8 to 10.8)	<0.001†
Median (IQR) HbA_{1c}			
Men			0.278†
mmol/mol	97.2 (53.0 to 86.9)	63.9 (54.1 to 80.3)	
%	8.3 (7.0 to 10.1)	8.0 (7.1 to 9.5)	
Women			<0.001†
mmol/mol	77.0 (60.7 to 97.8)	65.0 (54.0 to 83.6)	
%	9.2 (7.7 to 11.1)	8.1 (7.1 to 9.8)	
Total			<0.001†
mmol/mol	72.7 (57.4 to 92.4)	63.9 (54.1 to 82.5)	
%	8.8 (7.4 to 10.6)	8.0 (7.1 to 9.7)	
HbA_{1c}, % (*n*)			0.12
<53 mmol/mol (<7%)	18.4 (158)	21.8 (143)	
53–63.9 mmol/mol (7–7.9%)	16.7 (143)	25.5 (167)	
64– 74.9 mmol/mol (8–8.9%)	17.5 (150)	18.3 (120)	
≥75 mmol/mol) ≥9%	47.4 (407)	34.5 (226)	
Mean ± SD total cholesterol, mmol/l	5.0 ± 1.3	4.9 ±1.2	0.72
Median (IQR) HDL cholesterol, mmol/l	1.3 (1.1 to 1.6)	1.3 (1.1 to 1.5)	0.117†
Mean ± SD LDL cholesterol¶, mmol/l	2.9 ± 0.9	2.8 ± 0.9	0.50
Median (IQR) triglycerides, mmol/l	1.4 (1.0 to 1.8)	1.5 (1.1 to 2.1)	<0.001†
Clinical markers			
Mean ± SD systolic BP, mmHg	146.2 ± 91.5	135.5 ± 85.5	<0.001
Mean ± SD diastolic BP, mmHg	80.9 ± 11.9	81.5 ± 11.8	0.03
Medication, % (*n*)			
Glucose-lowering			
Monotherapy	33.0 (283)	40.2 (264)	0.002
Dual or triple therapy	15.0 (129)	23.8 (156)	<0.001
Insulin	10.8 (93)	12.5 (82)	0.85
Total§, *N*	505	502	
Antihypertensive	30.9 (265)	52.1 (342)	<0.001
Statin	19.2 (165)	37.8 (248)	<0.001
Smoker, % (*n*)			
Men	30.7 (124)	22.3 (65)	0.12
Women	2.0 (9)	1.7 (6)	0.84

BP, blood pressure; IQR, interquartile range.
**P* values calculated by regression model for continuous outcomes and logistic regression model for dichotomous outcomes adjusted for age, sex and duration of diabetes, except for duration which is adjusted only for age and sex, and age which is adjusted only for sex and duration of diabetes. *P* values for categorical variables were calculated using the chi-squared test.
†*P* values are calculated using a *t*-test after log transforming variables.
‡BMI thresholds were ethnic-specific.
§When the variable has >10 participants with missing data, the sample size is reported.
¶Calculated only using those participants with triglycerides ≤ 4.52 mmol/l.

2015 (P<0.001). Compared with 2009, the median age and mean BMI were higher, and the median duration of diabetes was longer in 2015. The proportion of smokers in men was 30.7% in 2009 and 22.3% in 2015 (P=0.007). Very few women smoked in either survey.

Median fasting plasma glucose levels were lower in both men (P=0.03) and women (P<0.001) in 2015 than in 2009, and the median HbA_{1c} was significantly lower in women (P<0.001) but not in men (P=0.27; Table 1). Serum HDL cholesterol and LDL cholesterol levels did not change significantly from 2009 to 2015, but the median triglyceride level was higher by 0.1 mmol/l in 2015 (P<0.001). Mean systolic blood pressure was lower in 2015 compared with 2009.

Medication

Overall, glucose-lowering medication use was higher in 2015 compared with 2009 (Table 1). The proportion of participants on monotherapy was 33% in 2009 and 40% in 2015 (P=0.002). Of the 1283 participants who reported they were taking glucose-lowering medication, 1007 provided details on the type or brand name of such drugs. The percentage of participants on dual or triple therapy was also higher in 2015 compared with 2009 (P<0.001). The proportion of people on insulin therapy was not significantly different between the two surveys. Metformin use was higher in 2015 (66%) compared with 2009 (43%; P<0.001). Statin use was higher in 2015 (37%) compared with 2009 (19%; P<0.001). In participants aged >50 years, statin use was 21.8% and 40.2% in 2009 and 2015, respectively (P<0.001). Use of anti-hypertensive medication was 30.9% in 2009 and 52.1% in 2015 (P<0.001).

Achievement of targets

Glycaemic control

In 2009, only 23% of men and 15% of women achieved the ADA target of HbA_{1c} <53 mmol/mol (<7%; Table 2). These proportions reached ~22% in 2015 in both men (P=0.45) and women (P=0.01). Among women, achievement of each of the three HbA_{1c} targets of 53 mmol/mol (<7%), 64 mmol/mol (<8%) and 75 mmol/mol (<9%) was higher in 2015 as compared with 2009. While, such differences were not observed in men (P values for the interactions with sex at the three HbA_{1c} thresholds ≤0.03). In 2015 compared with 2009, the proportion of participants reaching the HbA_{1c} target <64 mmol/mol (<8%) was significantly higher in those with primary or no formal education, but not in those with secondary and tertiary levels of education (P value for the interactions = 0.10). Among people with <5 years' diabetes duration and also those with >10 years', HbA_{1c} targets of <64 mmol/mol (<8%) and <9% (<75 mmol/mol) were achieved more often in 2015 than in 2009.

Blood pressure

The proportion of participants reaching the blood pressure target <140/90 mmHg was significantly higher in 2015 (57.9%) compared with 2009 (42.1%; Table 3). There was a significant interaction of ethnicity and reaching blood pressure target (P value for interaction =0.09). In 2015, the proportion who reached the blood pressure target <140/90 was higher among South Asian participants (P<0.001) but not in the African subgroup (P=0.16). Achievement of the lower blood pressure target of <130/80 mmHg was 22.6% and 33.0% in 2009 and 2015, respectively (P<0.001).

LDL cholesterol

The proportion of people reaching the ADA target of LDL cholesterol <2.59 mmol/l was not different between 2009 and 2015 (P=0.14). In 2015, >50% of men and 60% of women still had LDL cholesterol levels >2.59 mmol/l (Table 3).

All three ABC targets

The proportion of participants reaching all three ABC targets [HbA_{1c} <53 mmol/mol (<7%), LDL cholesterol <2.59 mmol/l and blood pressure <140/90 mmHg] was 2.9% in 2009 and 6.7% in 2015 (P=0.002). Using the blood pressure target of <130/80 mmHg, the proportion of people reaching all three targets was only 1.6% in 2009 and 5% in 2015 (P<0.001).

Discussion

The major findings of this study were that, in people with diabetes in Mauritius, the glycaemic control and blood pressure control was better in 2015 than in 2009, while there was no difference in mean LDL cholesterol levels. The proportion achieving HbA_{1c} <64 mmol/mol (<8.0%) and <75 mmol/mol (<9.0%) and blood pressure <140/90 mmHg (and 130/80 mmHg) was higher in 2015 than in 2009.

It is important to note that higher achievement rates of ABC targets were primarily observed in groups with the poorest control in 2009. This was particularly true for glycaemic control of HbA_{1c} <64 mmol/mol (<8.0%) and HbA_{1c} <75 mmol/mol (<9.0%), but not at the target level of HbA_{1c} <53 mmol/mol (<7.0%). Furthermore, significantly better control of glycaemia was seen in women in the year 2015, but not in men. In 2009, women had a higher median level of HbA_{1c} than men. The improvements we observed in HbA_{1c} levels in people with a lower level of education may indicate a narrowing of some of the health inequalities in people with Type 2 diabetes since 2009, which is encouraging. The higher proportion of people achieving targets in 2015 was paralleled by a greater use of medications for these three conditions, but it is not possible to ascertain to what extent medications or other factors led to the observed improvements. the proportion of people who reached the ABC targets specified by ADA, however, is still suboptimal,

Table 2 The prevalence of those with diabetes achieving various targets for glycaemic control HbA_{1c} levels in 2009 and 2015

	2009	2015	*P** (2009 vs 2015)	*P*† interaction
Number of participants	858	656		
HbA_{1c} <53 mmol/mol				
Total	18.6 (16.1 to 21.3)	21.8 (18.8 to 25.1)	0.21	
Gender				0.022
Men	22.9 (19.0 to 27.3)	21.6 (17.2 to 26.7)	0.45	
Women	14.7 (11.7 to 18.3)	22.0 (18.0 to 26.5)	0.01	
Ethnicity				0.517
South Asian	17.4 (14.7 to 20.5)	21.4 (18.0 to 25.2)	0.25	
African (creole)	19.9 (14.4 to 26.7)	22.1 (15.8 to 29.9)	0.52	
Other (mostly Chinese)	37.9 (21.6 to 57.6)	29.2 (13.7 to 51.5)	0.65	
Education				0.227
Primary school or no education†	16.7 (13.8 to 20.0)	22.1 (18.2 to 26.6)	0.07	
Secondary school	20.6 (16.2 to 25.9)	21.5 (16.8 to 27.0)	0.91	
Tertiary education	33.3 (18.2 to 52.8)	20.0 (7.0 to 45.3)	0.53	
Duration of diabetes				0.059
<5 years	23.5 (19.4 to 28.1)	30.5 (24.9 to 36.7)	0.19	
5–10 years	20.8 (15.6 to 27.3)	15.2 (10.1 to 22.1)	0.15	
≥10 years	10.8 (7.6 to 15.2)	17.5 (13.1 to 23.0)	0.09	
HbA_{1c} <64 mmol/mol				
Total	35.1 (31.9 to 38.3)	47.2 (43.4 to 51.1)	<0.001	
Gender				0.016
Men	42.8 (38.1 to 47.7)	48.6 (42.9 to 54.4)	0.24	
Women	28.1 (24.1 to 32.4)	46.1 (41.1 to 51.3)	<0.001	
Ethnicity				0.210
South Asian	34.6 (31.0 to 38.3)	48.0 (43.6 to 52.4)	<0.001	
African (Creole)	33.5 (26.7 to 41.1)	45.6 (37.3 to 54.1)	0.01	
Other (mostly Chinese)	55.2 (36.1 to 72.8)	41.7 (22.9 to 63.1)	0.75	
Education				0.102
Primary school or no education†	32.8 (29.0 to 36.8)	48.9 (43.9 to 54.0)	<0.001	
Secondary school	38.2 (32.6 to 44.1)	44.1 (38.1 to 50.3)	0.23	
Tertiary education	50.0 (31.9 to 68.1)	55.0 (31.8 to 76.2)	0.53	
Duration of diabetes				0.074
<5 years	43.2 (38.2 to 48.3)	60.6 (54.2 to 66.7)	<0.001	
5–10 years	38.0 (31.2 to 45.2)	40.0 (32.3 to 48.3)	0.74	
≥10 years	22.5 (17.9 to 27.9)	39.3 (33.2 to 45.8)	<0.001	
HbA_{1c} <75 mmol/mol				
Total	53.0 (49.6 to 56.3)	65.5 (61.8 to 69.1)	<0.001	
Gender				0.030
Men	59.7 (54.8 to 64.4)	66.4 (60.8 to 71.6)	0.17	
Women	47.0 (42.4 to 51.6)	64.8 (59.8 to 69.6)	<0.001	
Ethnicity				0.587
South Asian	52.9 (49.1 to 56.7)	65.7 (61.4 to 69.8)	<0.001	
African (Creole)	50.0 (42.4 to 57.6)	64.0 (55.4 to 71.7)	0.005	
Other (mostly Chinese)	72.4 (52.5 to 86.2)	70.8 (48.4 to 86.2)	0.98	
Education				0.278
Primary school or no education‡	50.2 (46.0 to 54.4)	64.7 (59.8 to 69.4)	<0.001	
Secondary school	57.0 (51.0 to 62.8)	65.6 (60.0 to 71.2)	0.15	
Tertiary education	63.3 (44.0 to 79.2)	80.0 (54.6 to 93.0)	0.08	
Duration of diabetes§				0.192
<5 years	60.0 (54.8 to 64.9)	75.8 (70.0 to 80.9)	<0.001	
5–10 years	55.1 (47.8 to 62.1)	60.0 (51.7 to 67.7)	0.43	
≥10 years	41.4 (35.6 to 47.4)	60.2 (53.8 to 66.4)	<0.001	

Data are expressed as percentage (95% CI).
**P* value calculated by logistic regression model adjusted for age, sex and duration of diabetes. †*P* values are interactions of sex, ethnicity, education, and duration of diabetes with a change in the proportions of reaching the HbA_{1c} targets between 2009 and 2015. ‡0 to 6 years of education. §Data were available on 1439 participants; for other variables the number of missing is <10.

with 95% of people with diabetes not attaining all three ABC targets in 2015.

As compared with other studies, the proportion of participants with HbA_{1c} <53 mmol/mol (<7%) is lower in Mauritius. In 2009 in Mauritius, <20% of the participants had HbA_{1c} <53 mmol/mol (<7%), while in a US study this proportion was >50% in the time period of 2007 to 2010 [19]. While the percentage of participants reaching the HbA_{1c} target <53 mmol/mol (<7%) did increase to 21.8% in 2015 in Mauritius, it is still lower than other countries where such data are available [9].

The percentage of participants reaching the blood pressure targets <130/80 mmHg and <140/90 mmHg in Mauritius was higher or at least similar to clinic-based studies

Table 3 Prevalence of those with diabetes achieving American Diabetes Association targets for blood pressure and lipid levels in 2009 and 2015

	2009	2015	*P** (2009 vs 2015)	*P*† interaction
Number of participants	858	656		
Blood pressure < 140/90 mmHg				
Total	42.1 (38.8 to 45.5)	57.9 (54.0 to 61.6)	<0.001	
Gender				0.094
Men	41.4 (36.7 to 46.3)	59.2 (53.5 to 64.8)	<0.001	
Women	42.8 (38.3 to 47.4)	56.7 (51.6 to 61.8)	<0.001	
Ethnicity				0.095
South Asian	42.2 (38.5 to 46.0)	60.2 (55.8 to 64.4)	<0.001	
African (Creole)	43.7 (36.3 to 51.4)	47.8 (39.4 to 56.3)	0.16	
Other (mostly Chinese)	31.0 (16.3 to 51.0)	66.7 (44.5 to 83.3)	0.02	
Education				0.442
Primary school or no education‡	40.3 (36.2 to 44.5)	54.5 (49.4 to 59.4)	<0.001	
Secondary school	44.7 (38.9 to 50.7)	63.5 (57.4 to 69.2)	<0.001	
Tertiary education	50.0 (27.7 to 72.3)	50.0 (27.7 to 72.3)	0.55	
Duration of diabetes				0.211
<5 years	51.2 (43.6 to 53.9)	58.0 (51.6 to 64.2)	0.001	
5–10 years	38.5 (31.7 to 45.7)	60.7 (52.4 to 68.4)	<0.001	
≥10 years	38.0 (32.4 to 44.0)	54.9 (48.5 to 61.2)	<0.001	
LDL cholesterol <2.59 mmol/l				
Total	36.7 (33.5 to 40.0)	42.9 (39.1 to 46.8)	0.14	
Gender				0.714
Men	42.1 (37.3 to 47.1)	50.4 (44.4 to 56.3)	0.27	
Women	32.0 (27.8 to 36.5)	37.1 (32.3 to 42.3)	0.35	
Ethnicity				0.481
South Asian	37.9 (34.3 to 41.8)	42.8 (38.4 to 47.3)	0.72	
African (Creole)	33.9 (27.0 to 41.6)	44.3 (36.0 to 53.0)	0.046	
Other (mostly Chinese)	24.1 (11.4 to 44.0)	36.4 (18.2 to 59.5)	0.46	
Education				0.945
Primary school or no education‡	34.8 (31.0 to 39.0)	41.1 (36.1 to 46.2)	0.21	
Secondary school	39.4 (33.6 to 45.4)	44.7 (38.6 to 51.0)	0.58	
Tertiary education	48.3 (30.1 to 67.0)	55.5 (30.9 to 77.8)	0.75	
Duration of diabetes§				0.510
<5 years	35.7 (30.8 to 40.8)	38.6 (32.4 to 45.1)	0.69	
5–10 years	32.0 (25.5 to 39.3)	41.1 (33.2 to 49.6)	0.13	
≥10 years	42.5 (36.6 to 48.5)	46.7 (40.2 to 53.2)	0.72	

Data are expressed as percentage (95% CI).
*P value calculated by logistic regression model adjusted for age, sex and duration of diabetes
†P-values are interactions of sex, ethnicity, education, and duration of diabetes with a change in the proportions of reaching the lipids and blood pressure targets between 2009 and 2015.
‡0 to 6 years of education
§Data were available on 1439 participants; for other variables the number of missing is < 10.

conducted in Poland [20], Taiwan [9], India [13] Iran [11] and Singapore [13]; however, better blood pressure control was reported in population-based data from the USA [19]. While blood pressure control improved in other ethnicities, no improvement was observed among Africans in Mauritius. Previous studies also report ethnic disparity in blood pressure control among people with Type 2 diabetes. In a cohort study conducted in the UK, blood pressure increased significantly in people of Afro-Caribbean ethnicity as compared to those of white European ethnicity over 9 years [13]. These differences may be attributable to genetic or epigenetic differences, access to healthcare, different diets, different smoking levels and other lifestyle factors.

Better control of blood pressure and glycaemia in people with diabetes in Mauritius in 2015 is likely to be partially attributable to more widespread use of medication, although for glycaemia it is notable that the increase was mainly in the use of oral medication, not insulin. Increasing public awareness about diabetes and changing lifestyle might also contribute to this improvement. Another contributor to better control of blood pressure and glycaemia may have been the addition of diabetes nurse educators in several clinics. In May 2014, 58 diabetes nurses were introduced to selected diabetes clinics in Mauritius to help to educate people about a healthy lifestyle, including diet and physical activity and to teach people how to improve self-management of diabetes and encourage the adherence to medication.

A meta-analysis showed that involving nurses in chronic disease management improved blood pressure and glycaemia in Type 2 diabetes [21]. There are some other approaches that might result in improved diabetes management in Mauritius, such as introducing awareness campaigns and improved healthcare structure, improving diabetes self-management, educating healthcare professionals and

identifying or developing additional resources to improve diabetes management.

The change in triglyceride levels may have been attributable to the higher BMI in 2015 [22]. The reason that LDL levels were not lower in 2015 is not clear. Statin use did indeed increase from 19.2% to 37.8%, but we do not have data on adherence; poor adherence to statin therapy may have contributed to this lack of change in LDL cholesterol levels [23].

The 3.4% increase in the proportion of participants who attained all three ABC targets set out by the ADA is lower but similar to other countries [4]. For example, a national survey in Taiwan showed that the attainment of all ABC goals increased by 4.3% from 2006 to 2011 [9]. Studies in the US population indicated achievement of all three targets has improved in the previous two decades [10,19,24–26].

The Swedish quality register of diabetes (n=384 124) reported that the proportion of people with controlled HbA_{1c}, blood pressure and lipids improved markedly from 1996 to 2015 in both specialist and primary care clinics [27]. A study in seven Asian populations (n=3687) in 2007–2009 reported that 5.4% of participants reached all three ABC targets [13]. Among those with diabetes from Hong Kong, it was reported that 12% achieved ADA targets, while those from India had the lowest proportion meeting ABC targets at 1.9%. Comparing our results with those from other published studies, Mauritius had the lowest rate of attainment of ABC targets in 2009 at 1.6%, which is similar to the Indian study [13].

A strength of the present study was the nationally representative sample with high response rates, which allowed us to generalize the results to the whole diabetes population of Mauritius. Limitations include the fact that there were differences in some general characteristics of the participants such as age, duration of diabetes and BMI in the two surveys, which might have affected the outcomes. Second, adherence to medication was not assessed, and we relied on self-reported medication use. Third, this analysis did not evaluate lifestyle change, such as patterns of dietary intake and levels of physical activity of participants.

The present study is one of the first assessments of trends in management target achievement among people with diabetes in a lower- or middle-income country. Using two population-based independent survey samples, we found that in 2015 compared with 2009, control of glycaemia and blood pressure was better, and total and LDL cholesterol control remained unchanged. While we cannot define the reasons for this favourable trend, it occurred in parallel with higher rates of medication use. Better control of HbA_{1c} was mainly observed in groups where control was poorest in 2009, perhaps indicating a narrowing in some of the health inequalities in people with diabetes. Nevertheless, the majority of people with diabetes still had inadequately controlled HbA_{1c}, blood pressure and lipids, stressing the need for further improvements in diabetes management in Mauritius.

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Competing interests

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Survey sampling method, generalizability of the study population, and glucose stability study.

Appendix

Survey sampling method

We have followed the standard epidemiological sampling procedures for cross-sectional studies. Both surveys are representative samples of the total population. In each survey, Mauritius was divided into nine districts to ensure geographical representation. The sample drawn from each district was proportional to the population size of the district (according to census data). Within each district, an *index* primary sampling unit (PSU) (an area representing approximately 300 households) was chosen randomly proportional to size of the PSU and then combined with two nearby PSU to form a *main* cluster.

In 2009, a total of 20 main clusters were selected for the whole island. In each of the 20 main clusters, a selection of 1 in 3 households was made to have on average 320 households per main cluster. In each household selected, only one person was randomly chosen to give an approximate survey sample size of 7492 subjects for the whole island. A similar process was conducted in 2015 but only 11 PSUs were sampled and 4400 people invited to the survey. In both samples, two additional PSUs were selected in the district of Port Louis (China town and Plaine Verte) to ensure that Chinese participants and those of Muslim descent were adequately represented. So, the surveys were ethnic and gender representative of the population of Mauritius.

Generalizability of the study population with respect to gender and ethnicity

This study is generalizable to the whole population of Mauritius with respect to gender and ethnic distribution. Both surveys are generalizable with respect to gender to the nearest census data, 2008 census data for 2009 survey and 2014 census data for 2015 survey.

Table1. Census data in 2008 compared to 2009 survey data by age groups

	% Male		**% Female**	
Age groups	2008 census	2009 survey	2008 census	2009 survey
20-40	50.0	44.7	50.0	55.3
40-60	49.6	47.0	50.4	53.0
60-75	45.0	43.0	55.0	57.0

Table 2. Census data in 2015 compared to 2015 survey data by age groups

	% Male		**% Female**	
Age groups	2014 census	2015 survey	2014 census	2015 survey
20-40	50.5	44.7	49.5	55.3
40-60	50.0	45.0	50.0	55.0
60-75	46.0	46.0	54.0	54.0

According to the data that is reported by the government of Mauritius, the last census which officially captured population data by ethnicity was in 1972. However, in the various censuses after 1972, namely 1983, 1990, 2000 and 2011, estimates are available by religious groups as follows: 55% Hindu, 17% Muslim, 25% Creole and 3% Chinese. Hindus and Muslims have a South Asian background and are categorised as South Asians (72%).

Table 3. Ethnic distribution of the 2009 and 2015 surveys population compared to 2011 census data

	2011 Census data	**2009 survey**	**2015 survey**
Indian origin	72%	73.7 %	71 %
Creole	25%	23 %	21.5 %
Chinese	3%	3 %	6 %
Others	-	0.3 %	1.5 %

Glucose stability study

In the surveys, blood was collected into fluoride oxalate tubes, stored in cool boxes immediately after blood was taken, and sent to the laboratory within 3 hours of collection. We performed a sub-study in 2015 to examine whether there was any effect on glucose concentration of delaying glucose measurement for up to three hours. These samples were transported to the laboratory immediately in cool boxes, and assayed 1, 2 and 3 hours after collection. The mean plasma glucose was 7.7 mmol/l for each of the three time points.

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Chapter 5

Trends of diabetes management outside of North America and Western Europe with respect to glycaemic control

5.1 Real world evidence

In chapter 4, we compared diabetes management between 2009 and 2015 in the middle-income country of Mauritius using individual level data obtained from two nationally representative surveys. Even though that study shows improvement in some aspects of diabetes management, it was demonstrated that only a small fraction of adults met the established guidelines for control of ABCs for diabetes. The question then arises as to why these evidence based guidelines (with a great potential to improve diabetes outcomes) remain inconsistently and inadequately implemented in actual practice.

Although surveys are one of the appropriate approaches to describing the characteristic of the study population, they are prone to bias such as volunteer bias, as those who agree to participate in a study may have different characteristics to those who do not choose to participate. In addition, surveys are prone to recall bias because when participants self-report information, they might inaccurately remember details. An alternative approach to understanding diabetes management which avoids many of these biases is to use real world data. Real world data is usually obtained from registries or medical records of patients within specific clinical services. Electronic medical records have the potential to allow extraction of large amounts of objective data. While individual services are not necessarily representative of the population within which they are located, they provide information on all patients and therefore remove volunteer and recall bias.

The availability of such electronic databases has facilitated reports on diabetes management in North America and West Europe. In recent years, the use of such records systems has also occurred in other parts of the world, allowing projects examining how patients with diabetes are managed in terms of their risk factors to be undertaken.

Therefore, in chapters 5 and 6 of this thesis, we use real world evidence data obtained from medical records and national registries of patients with diabetes. This chapter of the thesis focusses on the trends of diabetes management from 2006 to 2015 in ten data sources from nine countries including Argentina, Australia, Hong Kong, India, Japan, Russia, Saudi Arabia, South Africa and Uganda. Furthermore, this chapter specifically focuses on the trends of using each class of glucose lowering medication, including metformin, sulphonylureas, meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1R agonist), alpha glucosidase inhibitors, sodium-glucose co-transporter-2 (SGLT2) inhibitors, and insulin.

The main finding of this work is that in most clinical services, the use of monotherapy decreased and diabetes management shifted towards more complex treatment such as triple therapy, and increased use of insulin. Glycaemic control changed very little between 2006 and 2015. Therefore, such changes in medication utilization were not associated with improvement in glycaemic control. We also found that metformin was the most popular prescribed medication followed by sulphonylureas, which is in line with diabetes guidelines. Use of new classes of GLM such as DPP4 inhibitors, GLP-1R agonist and SGLT2 inhibitors increased in many sites, but there were some sites where these new medications for treatment of diabetes were not available.

Lack of improvement in glycaemic control despite prescription of more complex medication regimens could be related to inadequate prescription, poor adherence to such medications and higher costs associated with new drugs. Our findings highlight the need for more research to be performed with a focus on the effectiveness of new GLMs. Appropriate prescription and adherence to treatment, also need to be addressed in future studies.

Declaration for Thesis – Chapter 5

Maryam Tabesh, Dianna J Magliano, Stephanie K Tanamas, Filip Surmont, Silver Bahendeka, Chern-En Chiang, Jorge F Elgart, Juan Jose Gagliardino, Sanjay Kalra, Satheesh Krishnamoorthy, Andrea Luk, Hiroshi Maegawa, Ayesha A Motala, Fraser Pirie, Ambady Ramachandran, Khaled Tayeb, Olga Vikulova, Jencia Wong, Jonathan E Shaw, Trends of diabetes management and treatment approaches outside of America and West Europe from 2006 to 2015.

In the case of chapter 4, the nature and extent of my contribution to the work was the following:

Nature of the contribution	Extent of the contribution
Research design, extracting and summarizing data from medical record of patients in each individual clinical services, cleaning, analysing and interpreting the data, conceptualisation and writing of the manuscript, critical revision, corresponding author	70%

The following co-authors contributed to the work. If co-authors are student at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of the contribution	Extent of the contribution (%) for student co-authors only
Dianna J. Magliano	Research design, conceptualisation, interpretation and approval for the final for publication	N
Stephanie K. Tanamas	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Filip Surmont	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Silver Bahendeka	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Chern-En Chiang	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Jorge F. Elgart	Extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Juan Jose Gagliardino	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Sanjay Kalra	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Satheesh Krishnamoorthy	Extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N

Andrea Luk	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Hiroshi Maegawa	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Ayesha A. Motala	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Fraser Pirie	Extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Ambady Ramachandran	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Khaled Tayeb	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Olga Vikulova	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Jencia Wong	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Jonathan E. Shaw	Research design, conceptualisation, interpretation and approval for the final for publication	N

The undersigned hereby certify that the above declaration correctly reflects the nature and the extent of the candidate's and co-author's contribution to this work *.

Student Signature	[redacted]	Date: 28/06/2018
Main Supervisor Signature	[redacted]	Date: 28/06/2018

*note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Trends of diabetes management and treatment approaches outside of North America and West Europe from 2006 to 2015

Running title: Diabetes management in the real world

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Abstract

Background:

The impact of introducing new classes of glucose-lowering medication (GLM) on diabetes management remains unclear, especially outside North America and Western Europe. Therefore, we aimed to analyse trends in glycaemic control and the usage of new and old GLMs in people with type 2 diabetes from 2006 to 2015.

Methods:

Summary data from clinical services from nine countries outside North America and Western Europe were collected and pooled for statistical analysis. Each site summarized individual level data from out-patient medical records for 2006 and 2015. Data included: demographics; HbA1c and fasting plasma glucose levels; and the proportions of patients taking GLM as monotherapy, combination therapy and/or insulin.

Results:

Between 2006 and 2015, glycaemic control remained stable, although body mass index (BMI) and duration of diabetes increased. The proportion of people on GLM increased, and the therapeutic regimens became more complex. There were increases in the use of insulin and triple therapy, while monotherapy, particularly in relation to sulphonylureas, decreased. Despite the introduction of new GLMs, such as DPP-4 inhibitors, insulin use increased over time.

Conclusions:

There was no clear evidence that the use of new classes of GLMs was associated with improvements in glycaemic control or reduced the reliance on insulin. These findings were consistent across a range of economic and geographic settings.

Highlights

- Diabetes treatment became more complex with increased use of insulin and triple therapy and decreases in monotherapy.
- Despite the intensification in GLM and increased use of newer agents, there was no evidence of improved glycaemic control.
- Lack of improvement in glycaemic control despite more complex medication regimens could be related to inadequate prescription or poor adherence to prescribed medications and to limited access to more expensive new drugs.

Keywords

Diabetes, glycaemic control, management, treatment, glucose lowering medications, low-middle income countries

1. Introduction

Based on the most recent International Diabetes Federation (IDF) report, the number of people with diabetes will increase from 425 million people in 2017 to 629 million by 2045 (1). The prevalence of diabetes is increasing at a greater rate in some regions, such as Asia and the Middle East compared to the western world (1, 2). Furthermore, approximately 80% of people with diabetes reside in low- and middle- income countries (LMIC), representing a huge economic burden to these nations (3).

The importance of glycaemic control in preventing and delaying the progression of diabetes complications is well established (4-6). Despite considerable efforts undertaken in introducing new classes of glucose lowering medications (GLM) and formulating guidelines for the use of these therapies to optimise glycaemic control (7), little is known about how this is actually put into practice in the different healthcare settings around the world and whether their introduction has led to significant improvement in glycaemic control.

A modest amount of information on the use of medications and the achievement of treatment targets is now available from large databases in North America and in Western Europe (8-12). In the United Kingdom General Practice Research Database, increasingly aggressive management of diabetes was reflected by a substantial increase in the prescription of GLM between 2000 and 2006 (13). Similarly, there was a substantial increase in GLM use in Portugal and Holland from 2004 to 2013 (14).

Much less is known about how treatment is actually delivered in other parts of the world. This information is important to obtain as it describes the size and nature of the gap between actual practice, and the targets and therapies set out in guidelines. It can also provide a basis for the development of interventions to improve delivery of care to people with diabetes. Obtaining large-scale information on diabetes management requires systematic access to clinical records,

which is facilitated by the use of electronic medical records. The availability of such electronic databases has facilitated reporting on diabetes management in North America and Western Europe. In recent years, the use of such record systems has spread to other parts of the world, allowing the exploration of how patients with diabetes are actually managed.

This Real World Evidence (RWE) study has identified a series of data sources around the world, outside North America and Western Europe, that captured individual patient-level information from all people within a given service or jurisdiction. Data sources included clinical services using either paper or electronic medical records, and regional or national registries. While individual services are not necessarily representative of the population within which they are located, their medical records provide data on all patients within that service and remove volunteer bias (15). Given the high burden of diabetes and limited information on delivery of care, the aim of this study was to use data from RWE to describe and compare trends in glucose-lowering medication use between 2006 and 2015 across different parts of the world.

2. Methods

Through a series of meetings and personal links, we sought to identify clinical services outside North America and Western Europe that were able to produce clinic-wide or population-wide reports on the provision of care to people with diabetes. We identified ten data sources from nine countries (Argentina, Australia, Hong Kong, India, Japan, Russia, Saudi Arabia, South Africa and Uganda) that captured individual-level information from all patients within a given service or jurisdiction. There were eight specialist care services, one national register and one primary care/specialist care data source. Each site extracted data from medical records of all out-patients attending in the years 2006 and 2015, and then summarized their data for each of those years. All sites used the same questionnaire developed for this project to collect and

report data. Data included demographics; disease history; percentages of those with type 2 diabetes on various classes of GLM, on complexity of regimens (i.e. monotherapy, combination non-insulin therapy or insulin) and mean clinic-level laboratory values related to glycaemic control. Each site reported mean HbA1c levels with standard deviations and the method of HbA1c measurement. The percentage of people who achieved the HbA1c targets of <7.0% (53 mmol/mol), 7.0-7.9% (53-63 mmol/mol), 8.0-8.9% (64-74 mmol/mol) and ≥9.0% (75 mmol/mol) was reported for each site. Diabetes treatment was classified into five categories: diet only, non-insulin monotherapy, non-insulin dual therapy, non-insulin triple therapy and insulin therapy (with or without other therapies). Information was also collected separately for percentages of patients treated with each class of GLM including metformin, sulphonylureas, meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1R agonist), alpha glucosidase inhibitors, Sodium-glucose co-transporter-2 (SGLT2) inhibitors, and insulin. Analyses were conducted using Stata (version 14; Stata Corp, College Station, TX). We reported continuous variables as mean ± standard deviation (SD) and categorical variables as proportions. This study was approved by the Alfred Hospital Research Ethics Committee as well as local committees of the participating countries.

3. Results

3.1. Study population

We used data from 10 clinical services in 9 countries, which included 4,591,840 patients with diabetes. Among these, more than 90% were categorised as type 2 diabetes (Table 1). The sample size varied from 291 in Japan, to 3,677,976 in Russia. Most of the sites were providers of secondary care, either in a hospital or in specialist out-patient practice. There was heterogeneity in the characteristics of study participants between sites. In most sites,

approximately half of the study populations were men, but in Russia and South Africa the majority of participants were women. The mean age ranged from 46 to 73 years. The mean age of the participants was nearly five years higher in 2015 compared to 2006 in Russia, Saudi Arabia and Uganda, while in Japan mean age increased from 63 to 73 years in this time period. For all other centres, the mean age was similar in 2006 and 2015. The mean duration of diabetes increased by ≥3 years in Australia (Melbourne and Sydney) and Hong Kong and decreased by 2.2 years in India. For other sites the change in duration of diabetes was <2 years.

3.2. Medication

Generally, the proportion of patients on either monotherapy or dual therapy decreased, while utilization of insulin and triple therapy increased over time (Figure 1A). Insulin utilization increased in 8 out of 10 sites. We observed a shift from diet therapy to monotherapy in Russia and Hong Kong. In other countries there was a shift from monotherapy and dual therapy towards triple and insulin therapy. In Japan, there was a decrease in mono-, dual and insulin therapy and an increase in triple therapy in parallel with an improvement in glycaemic control. The proportion of patients in each class of GLM in non-insulin regimens is presented in Table 2. The number of treatment options used in different countries varied; Australia, Hong Kong, and India used all of the new classes of glucose lowering medications by 2015. In Saudi Arabia, South Africa and Uganda, GLP-1R agonists and meglitinides were not prescribed. In Uganda, GLM was limited to metformin, sulphonylureas, alpha glucosidase inhibitors and insulin. In 2006, DPP-4 inhibitors were not available in any of the clinical services but many sites were using these medications by 2015. After approval of the first SGLT2 inhibitor in 2013, three countries, namely Australia, Hong Kong and India, started using this class. Use of SGLT2 inhibitors, increased by less than 5 percentage points in Australia and Hong Kong and by 16.8 percentage points in India.

Metformin was the most popular GLM in all sites. The proportion of people on metformin as monotherapy or any non-insulin combination therapy with metformin increased substantially in South Africa (from 33.6 to 72.0%), Uganda (from 37.9 to 81.0%), Russia (from 14.5 to 56.4%) and India (from 59.3 to 90.6%). In other sites, this proportion increased, but to a lesser degree, except for Australia and Saudi Arabia where there was a decline in metformin use as monotherapy or non-insulin combination therapy. The proportion of patients on alpha glycoside inhibitors decreased in all sites except for India and Japan.

The proportion of people on sulphonylurea monotherapy decreased in all sites from 2006 to 2015. However, sulphonylurea use in combination with other non-insulin drugs increased in India, Russia, South Africa and Uganda, and decreased at the remaining sites. Thus, sulphonylureas remained the second most commonly used diabetes treatment in all sites in 2015. There was virtually no use of DPP-4 inhibitors in 2006. By 2015, DPP-4 inhibitors were used by less than 5% of the patients in Argentina, Russia and South Africa, and remained unused in Uganda. In contrast, over 40% of the populations in Japan and India were using DPP-4 inhibitors in 2015. The proportion of using DPP-4 inhibitors was 15% and 20% in the two Australian sites in 2015. In Japan and India, the proportion of people on meglitinide increased from 2006 to 2015. Three sites, namely Uganda, South Africa and Saudi Arabia, did not use GLP-1R agonists for treatment of diabetes. In all other sites, the use of GLP-1R agonists increased, with the increase ranging from 0.07 percentage points in Russia to nearly 10 percentage points in Australia (Melbourne).

3.3. Glycaemic control

In 2015 compared to 2006, mean HbA1c was higher in five sites, including Argentina, Australia (both sites), Saudi Arabia and Hong Kong, while in four sites there was a decline in HbA1c, ranging from 0.3 percentage points in India to 0.7 percentage points in South Africa

(Figure 1B). Table 1 shows that BMI increased in three of the five sites where HbA1c increased, as well as in two of the four sites where HbA1c fell; age increased in two of the five sites where HbA1c increased, as well as in two of the four sites where HbA1c fell; and diabetes duration increased in four out of the five sites where HbA1c increased, as well as in two of the four sites where HbA1c fell. Figure 1 shows no consistent relationship between change in complexity of therapy and change in HbA1c.

In 2006, Hong Kong, Saudi Arabia, Australia and Russia had the highest proportion of patients with HbA1c<7.0% (53 mmol/mol) compared to other countries (Table 1). However, the proportion reaching this target (as well as the proportion <9.0%) fell in all of these sites, except Russia, by 2015, indicating a decline in reaching the glycaemic target in those countries with the best glycaemic control in 2006. The proportion of patients who reached the target of HbA1c<7.0% (53 mmol/mol) increased in Argentina, India, Japan, Russia and South Africa. Among all the clinical services, South Africa had the poorest glycaemic control with only 10% and 17% in 2006 and 2015, respectively, reaching the target of HbA1c<7.0% (53 mmol/mol). South Africa also had the highest proportion of people with HbA1c≥9% (75 mmol/mol), 57% in 2006 and 44% in 2015. In 2015, Russia and Japan compared to other countries, had better glycaemic control with 45% and 47% of patients reaching the target of HbA1c<7.0% (53 mmol/mol). Japan had the lowest proportion of patients with HbA1c≥9.0% (75 mmol/mol), 9.4% and 6.5% in 2006 and 2015, respectively. There were insufficient data on HbA1c in Uganda. The method of measuring HbA1c was reported by seven sites. The method of measuring HbA1c varied between different sites but in each clinical service the method did not change between 2006 and 2015. Some clinical sites received results for HbA1c from a number of different laboratories, and so it was not possible to identify changes in methods.

4. Discussion

This study provides real-world information on glycaemic control and the status of diabetes treatment on more than four million people with diabetes from nine countries. In this study, while there was heterogeneity between countries in terms of diabetes management, a number of similar patterns were observed in most countries in medication use. In general, glycaemic control changed very little between 2006 and 2015, while there was an increase in BMI and duration of diabetes in most sites. In most clinical services, monotherapy decreased and diabetes management shifted towards more complex treatment such as triple therapy, and there was increased use of insulin. Nevertheless, such changes in medication utilization were not associated with improvement in glycaemic control.

There are several possible reasons why we saw little improvement in glycaemic control: a) patients attending the clinics in 2015 tended to have a greater BMI and diabetes duration than did those in 2006. However, this did not occur in all centres, and there was no consistent relationship between these factors and change in glycaemic control. Indeed, in 50% of the centres where HbA1c fell, there was an increase in diabetes duration; b) the lack of improvement in glycaemic control despite more complex medication regimens could be related to inadequate prescription and/or poor adherence to prescribed medications. Unfortunately, we did not have data on actual medication usage, only on the medications listed in medical records, so could not assess adherence properly; c) the HbA1c measuring methodology varied among sites and some of them received data from several laboratories. Nevertheless similar methods of measuring HbA1c in each clinical site over time, and the constant targets of HbA1c<7% (53 mmol/mol) during the study period limited the effect of variation on HbA1c measuring methods on glycaemic change. Thus, even when the HbA1c assay methodology was not uniform, the fact that the target remained constant should minimise the impact of assay changes on achieved HbA1c levels; d) if adherence is a major barrier to achieving good glycaemic control, it is unlikely to be mainly affected by the availability of additional classes of drugs. A

recent real-world study demonstrated that poor adherence to diabetes medication is one of the key factors explaining the high proportion of patients who fail to achieve glycaemic targets suggested by guidelines (16) and e) more recent diabetes guidelines emphasise the importance of an individualised approach for diabetes management in which higher HbA1c targets are used for some groups of patients (older or with multiple comorbidities), and so this approach might have contributed to a failure to see an improvement in glycaemic control in this study. However, if that was a major cause for the lack of significant improvement in glycaemic control, it might be expected that treatment complexity would not increase over time. Since we observed increasing treatment complexity, it seems unlikely that higher HbA1c targets were being used for significant numbers of patients.

In this study, metformin was the most commonly prescribed GLM in most clinical services and this is in line with most guidelines for diabetes management (17). Sulphonylureas as the second line of diabetes treatment were also prescribed widely in all sites. However, prescriptions of sulphonylureas, particularly as monotherapy, decreased and were replaced by other drugs such as DPP-4 inhibitors. A meta-analysis of 14 clinical trials showed that DPP-4 inhibitors resulted in similar glycaemic control compared to sulphonylureas, but with lower body weight and lower incidence of hypoglycaemia (18). It might have, therefore, been anticipated that the increased acceptability of DPP-4 inhibitors would lead to better effectiveness through increased adherence, but we saw no evidence of better glycaemic control.

One of the advantages of the newer classes of GLM is that they might potentially avoid or delay the use of insulin. However, we saw no evidence to suggest that this has actually been a consequence of the introduction of such drugs. For example, of the four sites in which DPP-4 inhibitor use rose to 20% or more of the population, only one (Japan) had a reduction in the use of insulin. Notably, Japan had the largest increase in DPP-4 inhibitor use (50 percentage points), suggesting that a very large increase in use of such agents may be required to influence

insulin therapy. However, in India, where DPP4 inhibitor use rose by 41 percentage points, insulin use also increased.

A number of strengths and limitations of the study should be considered in interpreting the findings. We obtained real-world information about glycaemic control and treatment patterns in the management of diabetes in nine different countries. Our data include some countries that have a large number of people with diabetes, and for which there is currently very little information. Data were obtained from either national registries or medical records which eliminates volunteer and recall bias. However, generalising the results of this study to the health system of each country should be done very cautiously, because the majority of data were obtained from specialist care services. Furthermore, the variability in the nature of the services at the different sites might also influence the findings. This study is also limited by its cross-sectional design which does not allow to determine cause and effect, i.e. we do not know whether the increasing complexity of medication, with no improvement in HbA1c, should be interpreted as an appropriate response to increasing complexity of patients or as a failure of increasing complexity to improve glycaemic control. Furthermore, we had no data on medication adherence and our results focused only on drugs as listed in the medical record. There were no data on HbA1c levels in Uganda, thus we were not able to assess the glycaemic control in that country.

5. Conclusion

This real world study showed that from 2006 to 2015, the proportion of patients with diabetes using GLMs increased. Therapeutic regimens become more complex and aggressive with increases in triple and insulin therapy and decreases in monotherapy. Despite this, there was

no clear and significant improvement in glycaemic control. Lack of improvement in glycaemic control despite prescription of more complex medication regimens could be related to inadequate prescription, poor adherence to such prescriptions and higher costs of new drugs. Our findings highlight the need for more research to be performed using a population-based design with a focus on the effectiveness of new GLMs. Appropriate prescription and adherence to treatment, as the major causes of treatment failure, also need to be addressed in future studies.

6. Acknowledgements

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7. Conflicts of interest

This study was supported by AstraZeneca.

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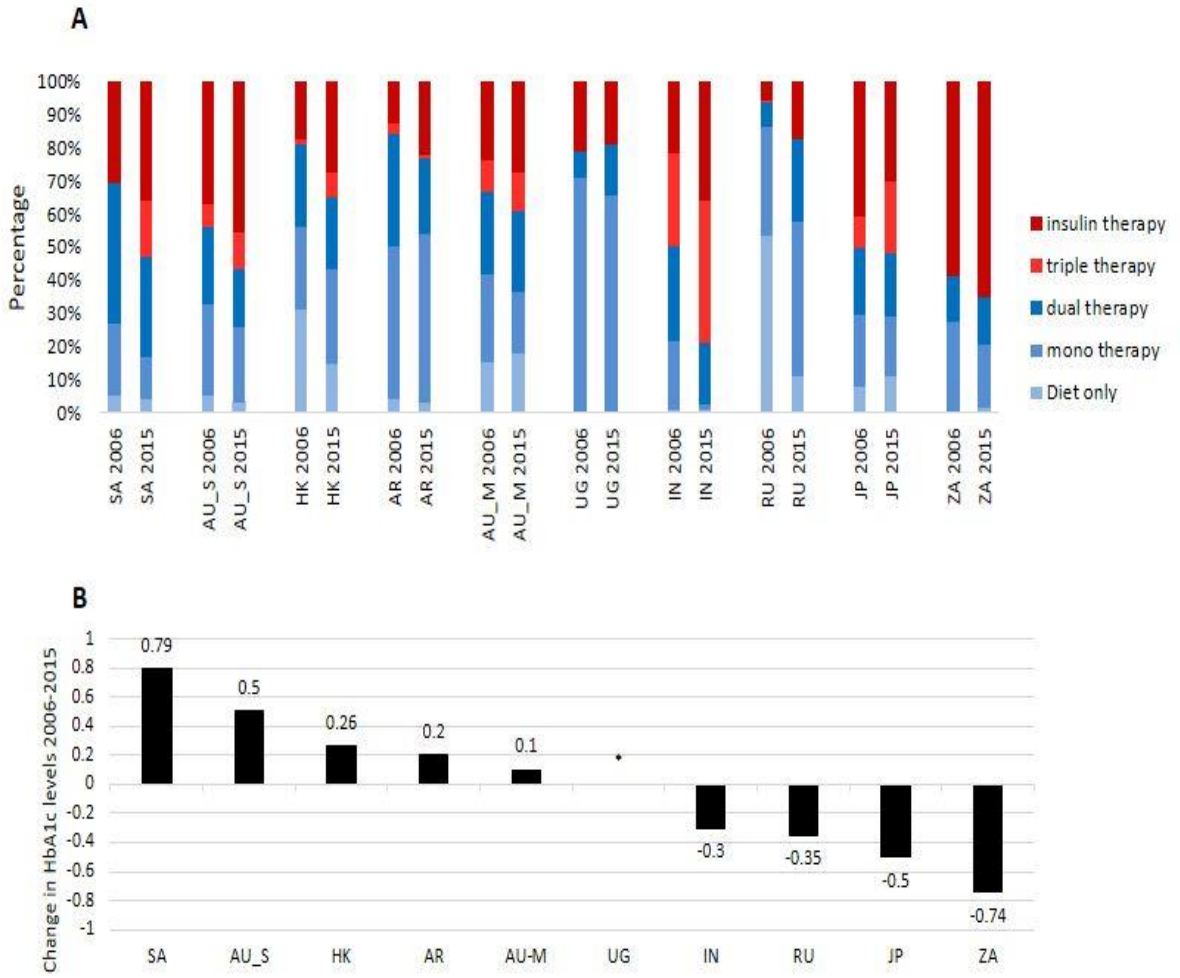

Fig 1.

A-Complexity of glucose lowering medication regimens in people with type 2 diabetes stratified by clinical service

B- Percentage point change in HbA1c levels from 2006 to 2015 in people with type 2 diabetes stratified by clinical service

AR: Argentina, AU_M: Australia, Melbourne, AU_S: Australia, Sydney, HK: Hong Kong, IN: India, JP: Japan, RU: Russia, SA: Saudi Arabia, UG: Uganda, ZA: South Africa

* Insufficient data

Table 1. Characteristics of people with type 2 diabetes in 2006 and 2015 stratified by clinical service

Country (Centre)	Year	Centre description*	Sample size	Age (years)	Sex, % men (n)	BMI (kg/m^2)	Duration of diabetes (years)	Type 2 diabetes, %	HbA1c (%)			
									<7	7-8	8-9	≥9
Argentina (Centro de Endocrinología Experimental y Aplicada)												
	2006	Sp	2,403	58.1 (11.1)	48.4 (1163)	30.1 (5.4)	9.3 (9.0)	92.1	36.5	24.1	18.8	20.7
	2015	Pr (26%) / Sp (74%)	2,534	54.7 (9.9)	49.6 (1258)	32.1 (6.4)	8.9 (7.2)	94.1	40.0	18.3	14.1	26.6
Australia (Baker Heart and Diabetes Institute)												
	2006	Sp	4,080	61.7 (15.6)	57.2 (2331)	29.8 (6.0)	9.8 (9.8)	80.5	37.0	31.7	17.6	13.8
	2015	Sp	4,059	61.8 (15.7)	60.6 (2459)	29.7 (5.8)	13.8 (10.4)	77.5	30.3	35.2	19.6	14.8
Australia (Royal Prince Alfred Hospital (*complications clinic cohort*))												
	2006	Sp	1,406	60.3 (13.6)	58.2 (818)	30.7 (6.3)	11.2 (8.4)	90.6	41.9	30.6	15.2	12.3
	2015	Sp	1,351	59.6 (15.3)	59.5 (804)	30.2 (6.4)	14.2 (10.2)	79.6	27.9	29.8	20.2	22.1
Hong Kong (Prince of Wales Hospital)												
	2006	Sp	788	58.5 (12.9)	49.2 (388)	25.7 (4.2)	6.6 (7.1)	98.6	48.6	24.2	10.5	16.7
	2015	Sp	2,043	59.9 (12.0)	54.2 (1108)	26.2 (4.8)	11.3 (8.8)	96.6	36.9	30.4	18.3	14.4
India (Dr. A Ramachandran's Diabetes Hospitals)												
	2006	Sp	6,022	58.0 (12.0)	58.4 (3214)	26.9 (4.5)	13.7 (9.3)	97.0	22.7	26.0	18.9	32.4
	2015	Sp	13,348	54.0 (13.0)	59.5 (7945)	27.5 (4.8)	11.5 (9.3)	84.4	30.2	24.4	17.5	27.8
Japan (Shiga University of Medical Science *(outpatient data)*)												
	2006	Sp	384	63.0 (11.0)	53.9 (207)	24.0 (3.8)	18.0 (10.0)	92.2	27.9	34.9	24.2	9.4
	2015	Sp	291	73.0 (5.0)	59.8 (174)	23.5 (3.5)	17.0 (11.0)	89.2	47.1	37.5	8.3	6.5
Russia (Endocrinology Research Centre Moscow)												
	2006	NR	871,777	62.4 (13.4)	26.6 (231,893)	30.4 (6)	7.2 (7.6)	90.9	38.2	27.3	17.4	17.1
	2015	NR	3,677,976	67.5 (11.3)	29.5 (1,086,341)	31.2 (10.0)	8.2 (6.6)	93.9	45.0	31.0	12.0	11.0
Saudi Arabia (Diabetes Center at AlNoor Specialist Hospital)												
	2006	Sp	383	53.5 (16.8)	41.5 (159)	31.3 (5.6)	8.9 (7.7)	100.0	41.0	21.2	13.3	24.6
	2015	Sp	276	56.4 (12.1)	51.4 (142)	31.7 (6.7)	9.6 (8.8)	100.0	23.2	23.2	18.8	34.8
South Africa (Inkosi Albert Luthuli Central Hospital, Durban)												
	2006	Sp	601	49.3 (17.5)	34.6 (208)	30.2 (7.3)	13.2 (11.0)	77.7	10.3	13.8	18.7	57.2
	2015	Sp	681	46.5 (20.4)	36.4 (248)	29.9 (7.5)	14.0 (10.3)	59.3	17.2	21.3	17.2	44.3
Uganda (San Raphael of St. Francis Nsambya Hospital)												
	2006	Sp	1,128	50.7 (14.5)	38.7 (437)	26.4 (6.0)	5.3 (5.8)	94.9	-	-	-	-
	2015	Sp	309	55.1 (10.1)	42.1 (130)	26.9 (5.7)	6.9 (6.6)	97.1	-	-	-	-

Data presented as mean (SD) or percentage (n).

Pr: Primary care

Sp: Specialist care

NR: National register

* Specialist care includes hospital settings for diabetes care (secondary care, tertiary care and teaching hospitals)

- Data not available

Table 2. Glucose lowering medication (in non-insulin regimens) utilization in people with type 2 diabetes in 2006 and 2015 stratified by clinical service

T2DM		Metformin			Sulphonylurea			DPP-4 i			GLP-1R agonist			α-glucosidase i			Meglitinide			SGLT2i		
(n)		Mono	≥Dual	Total	Mono	≥Dual	Total	Mono	≥Dual	Total	Mono	≥Dual	Total	Mono	≥Dual	Total	Mono	≥Dual	Total	Mono	≥Dual	Total
Argentina																						
2006	2214	24.7	40.5	65.2	20.3	35.4	55.7	0	0	0	0	0	0	0.2	0.7	0.9	0.6	2.3	2.9	0	0	0
2015	2384	48.1	39.7	87.8	2.5	22.9	25.4	0.3	2.4	2.7	0.4	0.26	0.3	0	0	0	0	0	0	N/A	N/A	N/A
Australia, Melbourne																						
2006	3284	17.8	31.9	49.7	8.2	32.2	40.4	0	0	0	0	0.03	0.03	0	0.6	0.6	0.1	0.5	0.6	0	0	0
2015	3144	13.0	30.7	43.7	3.5	23.0	26.5	1.3	18.9	20.2	0.9	9.1	10.0	0	0.1	0.4	0.03	0	0.03	1.0	1.0	2.0
Australia, Sydney																						
2006	1274	23.1	29.6	52.7	4.0	26.0	30.0	0	0	0	0	0	0	0	1.7	1.7	0.08	0.22	0.3	0	0	0
2015	1075	15.5	24.0	39.5	1.5	23.2	24.7	5.5	9.2	14.7	0	4.1	4.1	0	0.93	0.93	0	0	0	0	4.7	4.7
Hong Kong																						
2006	760	12.1	34.1	46.2	12.5	33.2	45.7	0	0	0	0	0	0	0.26	2.77	3.03	0	0.26	0.26	0	0	0
2015	1965	30.2	39.0	69.2	6.5	30.6	37.1	2.3	17.2	19.4	0.1	0.77	0.87	0.05	0.31	0.36	0	0	0	0	0.81	0.81
India																						
2006	5337	5.9	53.4	59.3	13.5	57.9	71.4	0.04	0.4	0.4	0	0	0	0.48	20.42	20.9	0.02	0.15	0.17	0	0	0
2015	11259	0.04	90.6	90.6	0.7	76.5	77.2	0.1	40.8	40.9	0.14	2.66	2.82	0.1	22.1	22.2	0	21.2	21.2	0.09	16.71	16.80
Japan																						
2006	354	1.7	18.6	20.3	13.6	27.1	40.7	0	0	0	0	0	0	2.3	11.3	13.6	2.3	3.3	5.6	0	0	0
2015	291	5.8	34.4	40.2	2.1	30.2	32.3	6.9	43.3	50.2	1.0	1.7	2.7	1.4	17.8	19.2	2.1	4.8	6.9	0	0	0
Russia																						
2006	792185	5.3	9.2	14.5	26.8	10.8	37.5	0	0.01	0.01	0	0	0	0.03	0.05	0.08	0.57	0.5	1.07	0	0	0
2015	3453292	24.4	32.0	56.4	21.6	30.0	51.6	0.3	1.99	2.29	0.01	0.06	0.07	0.01	0.02	0.03	0.25	0.24	0.49	0	0	0
Saudi Arabia																						
2006	383	15.7	42.3	58.0	6.5	42.3	48.8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2015	276	9.8	41.6	51.4	1.5	42.4	43.8	1.5	26.8	28.3	0	0	0	0	0	0	0	0	0	0	0	0
South Africa																						
2006	467	20.1	13.5	33.6	6.9	13.4	20.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2015	404	15.3	56.7	72.0	3.5	27.7	31.2	0	0.7	0.7	0	0	0	0	0	0	0	0	0	0	0	0
Uganda																						
2006	1070	29.6	8.3	37.9	42.7	8.3	51.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2015	300	66.0	15.0	81.0	0	15.0	15.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Data presented as numbers or percentages

T2DM: type 2 diabetes, N/A: data not available, DPP-4 i: DPP-4 inhibitors, GLP-1R agonist: Glucagon-like peptide-1 agonist, Alpha-glucosidase i: alpha glucosidase inhibitor, SGLT2i: Sodium-glucose co-transporter-2 inhibitors

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Chapter 6

Trends of diabetes management outside of North America and Western Europe with respect to cardiovascular disease control

Cardiovascular disease management is an indispensable part of diabetes management, thus in this chapter we explore trends in using antihypertensive and lipid lowering medications from 2006 to 2015 using data from the Real World Evidence project.

For antihypertensive medications, we specifically focussed on four classes of medications including angiotensin-converting-enzyme inhibitors (ACE inhibitors), calcium channel blockers (CCB), angiotensin II receptor blockers (ARB) and thiazide diuretics. For lipid lowering medications, we focused on statins. We also explored the change in using antiplatelet drugs such as aspirin.

The main finding of this work is that from 2006 to 2015, there was an improvement in cholesterol levels. This improvement in cholesterol levels was simultaneous to an increase in the proportion of patients using statins. The proportion of patients on anti-hypertensive medications decreased slightly or remained unchanged with concomitant increases in the proportion of patients with BP>140/90 mmHg in most sites. This can be explained by changing the blood pressure target from 130/80 to 140/90 during the study period. Anti-hypertensive treatment patterns shifted from predominantly using ACE inhibitors towards using more ARB medications. Nevertheless, the change to newer anti-hypertensive drugs was not associated with improvement in blood pressure levels.

Declaration for Thesis – Chapter 6

Maryam Tabesh, Dianna J Magliano, Stephanie K Tanamas, Filip Surmont, Silver Bahendeka, Chern-En Chiang, Jorge F Elgart, Juan Jose Gagliardino, Sanjay Kalra, Satheesh Krishnamoorthy, Andrea Luk, Hiroshi Maegawa, Ayesha A Motala, Fraser Pirie, Ambady Ramachandran, Khaled Tayeb, Olga Vikulova, Jencia Wong, Jonathan E Shaw, Cardiovascular disease management in people with diabetes outside of North America and Western Europe in 2006 and 2015.

In the case of chapter 5, the nature and extent of my contribution to the work was the following:

Nature of the contribution	Extent of the contribution
Research design, extracting and summarizing data from medical record of patients in each individual clinical services, cleaning, analysing and interpreting the data, conceptualisation and writing of the manuscript, critical revision, corresponding author	70%

The following co-authors contributed to the work. If co-authors are student at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of the contribution	Extent of the contribution (%) for student co-authors only
Dianna J. Magliano	Research design, conceptualisation, interpretation and approval for the final for publication	N
Stephanie K. Tanamas	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Filip Surmont	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Silver Bahendeka	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
Chern-En Chiang	Research design, extracting and summarizing data from medical record of patients in each individual clinical services, reviewing and editing the manuscript	N
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Jonathan E. Shaw	Research design, conceptualisation, interpretation and approval for the final for publication	N

The undersigned hereby certify that the above declaration correctly reflects the nature and the extent of the candidate's and co-author's contribution to this work *.

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Main Supervisor Signature		Date: 28/06/2018

*note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Title: Cardiovascular disease management in people with diabetes outside of North America and Western Europe in 2006 and 2015

Short Running title: Cardiovascular disease management in the real world

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Conflict of interest

This study was supported by AstraZeneca.

Bulleted novelty statement

- Mean total cholesterol levels fell in people with diabetes simultaneous with increase in statin use.

- The percentage with blood pressure>140/90 mmHg increased, which may reflect the change in the blood pressure targets from ≤130/80 mmHg to ≤140/90 mmHg that occurred between 2006 and 2015.

- Anti-hypertensive treatment approaches shifted towards using more angiotensin II receptor blockers (ARBs) with a simultaneous decline in the use of angiotensin-converting-enzyme (ACE) inhibitors.

    - While improved control of high cholesterol in people with diabetes were encouraging, further efforts are required to improve hypertension management in people with diabetes.

Abstract

Background

Optimal treatment of cardiovascular disease is essential to decrease mortality among people with diabetes, but information is limited on how actual treatment relates to guidelines. We aimed to analyse changes in therapeutic approaches to antihypertensive and lipid lowering medications in people with type 2 diabetes from 2006 and 2015.

Methods

Summary data from clinical services from seven countries outside of North America and Western Europe were collected from 39,684 participants. Each site summarized individual-level data from out-patient medical records for 2006 and 2015. Data included: demographic information, blood pressure, total cholesterol levels and percentages on statins, antihypertensive medication (angiotensin-converting-enzyme inhibitors [ACE inhibitors], calcium channel blockers [CCB], angiotensin II receptor blockers [ARB], thiazide diuretics) and antiplatelet drugs.

Results

From 2006 to 2015, mean cholesterol levels decreased in 6/8 sites (range from -0.5 to -0.2) while the proportion with blood pressure levels >140/90 mmHg increased in 7/8 sites. Decreases in cholesterol levels paralleled increases in statin use (range from 3.1 to 47.0 percentage points). Overall, utilization of antihypertensive medication did not change. However, there was an increase in the usage of ARBs and a decline in ACE inhibitors. The percentage of individuals receiving CCBs and aspirin remained unchanged.

Conclusions

Our findings indicate that control of cholesterol levels improved and coincided with increased use of statins. The percentage with blood pressure >140/90 mmHg was higher in 2015 than in 2006. Hypertension treatment shifted from using ACE inhibitors to ARBs. Despite the

potentially greater tolerability of ARBs, there was no associated improvement in blood pressure levels.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity among people with diabetes, and is the main contributor to health costs related to diabetes (1, 2). Numerous randomised clinical trials have demonstrated the benefits of blood pressure (BP) and dyslipidaemia treatment in preventing or delaying complications of diabetes, including CVD. CVD management has therefore been emphasized as an indispensable part of diabetes management by most guidelines (1-7).

There are several reports on cardiovascular risk management in people with diabetes from North America and Western Europe (8, 9). The National Health and Nutrition Examination Surveys (NHANES) demonstrated a decline in the prevalence of hypertension from 64% to 37%, and in the prevalence of high cholesterol levels from 72% to 55% among adults with diabetes in the U.S. between 1971 and 2000 (8). The Health Survey for England (HSE) reported a linear decline in cholesterol levels parallel to an increase in the proportion of people with diabetes on lipid lowering drugs (2.2 to 47.4%) between 1994 and 2009 (9). The HSE also reported a significant decline in both systolic and diastolic blood pressure and an increase in the use of antihypertensive drugs (9).

There is limited information about how hypertension and dyslipidaemia treatment are actually delivered outside of North American and Western Europe. These data are important because they show how targets translate into practice and how change in treatment approaches and targets are reflected in actual practice. Such information will also provide a basis for establishing interventions to improve delivery of diabetes care with a focus on reducing the risk of CVD in people with diabetes.

Obtaining data on treatment approaches in diabetes requires access to medical records. However, only electronic medical records have the potential to allow extraction of the large amounts of objective data that are needed for such projects. The availability of such electronic

databases has facilitated the reports on diabetes management in North America and Western Europe. In recent years, the use of such records systems has spread to other parts of the world, allowing for the development of projects to examine/investigate how people with diabetes are actually managed, including the Real World Experience (RWE) project described here.

The Real World Experience (RWE) project has identified a series of data sources around the world, outside North America and Western Europe. These electronic data sources captured individual-level information from all people with diabetes attending specific clinical services. Given the fact that there is not enough information about treatment of dyslipidemia and hypertension outside of North America and Western Europe, the aim of this study was to explore changes in antihypertensive and lipid lowering and antiplatelet medications, as well as in blood pressure and cholesterol target achievement in people with diabetes from 2006 and 2015, outside of North America and Western Europe.

Methods

Through a series of meetings and personal links, we sought to identify clinical services outside of North America and Western Europe that were able to produce clinic-wide or population-wide reports on the provision of care to people with diabetes. We identified eight data sources from seven countries (Argentina, Australia, Hong Kong, India, Japan, Saudi Arabia and South Africa) that captured individual-level information from all individuals with type 2 diabetes within a given service or jurisdiction. This study is a retrospective study in which we extracted and summarized data from all individuals with diabetes aged>18 years attending each of the eight clinical services. In this study, we did not select a representative sample from a population, instead we included all the individuals from each site, which provides a level of high internal validity. Since the population for this study consists of all individuals in each

clinical service and was not a selected sample, it was not appropriate to conduct a test of significance. P-values are used to indicate the probability that the findings in a selected sample truly reflect the population from which the sample was drawn. This paper reports whole of population data for each service (like a census), and therefore statistical tests relating to sampling are not relevant. To make it easy to interpret the changes in each clinic, we have reported changes over time as greater or less than 5%, as an indicator of a meaningful change. There were seven specialist care services and one primary care/specialist care data source. Each site extracted and summarised data from medical records of all out-patients attending in the years 2006 and 2015, using a standardised data reporting form developed for this project to collect and report data. Data included demographics, disease history, diabetic complications, blood pressure, cholesterol levels, and antihypertensive, lipid lowering and antiplatelet medications. For those participants who had more than one laboratory result or measurement during the year, the result closest to the middle of the year was chosen (30th June). If there was more than one result with the same date, the average of the two was taken. If there were two or more results with different dates equidistant to the middle of the year, the value was chosen depending on the quarter it was in, in the order of: 2nd quarter, 3rd quarter, 4th quarter, 1st quarter.

The percentage of people who reached the targets of BP≤140/90 and ≤130/80 mmHg and the percentage of people on antihypertensive therapy were reported by each site. Hypertension was defined as BP>140/90 mmHg or on antihypertensive medications. To understand how well those with hypertension were managed, the percentage of those with BP above target who were not on antihypertensive medications was also reported. Information was also collected separately for proportions of each class of antihypertensive medication including ACE

inhibitors, ARBs, thiazide diuretics and CCBs. The proportion of people using statins and antiplatelet medications were also reported by each site.

Analyses were conducted using Stata (version 14; Stata Corp, College Station, TX). We reported continuous variables as mean ± standard deviation (SD) and categorical variables as proportions. As this was an analysis of data already collected for clinical purposes, and since no individual level data left any clinical sites, no consent was obtained from participants, and some sites did not require local ethics approval. The study was approved by the Monash University Human Research Ethics Committee (number 1441), and the Alfred Ethics Committee (number 64/15) in Australia and in some of the sites, as required by local guidelines.

Results

Study population

For the purpose of this analysis, the RWE study includes 39,684 participants with diabetes from eight clinical sites in seven different countries (Table 1). All participants received specialist care services except Argentina where 26% and 74% of the participants were treated in primary care in 2006 and 2015, respectively. There was heterogeneity in the characteristics of study participants between sites. Sample size varied from 291 in Japan, to 13,348 in India. The mean age of the population with diabetes ranged from 46 to 73 years. From 2006 to 2015, the mean age of the population decreased by more than 5% in Argentina, India and South Africa, and increased by more than 5% in Saudi Arabia and Japan. The BMI changed by less than 5% in all sites except Argentina, where BMI rose by 7%. The duration of diabetes decreased by nearly one year in three centres (Argentina, India and Japan), but rose in the other clinics. The increase in duration of diabetes ranged from 0.8 years in in South Africa to 4.7 years in Hong Kong. Mean HbA1c increased by >5% in Australia (Sydney) and Saudi Arabia, decreased by >5% in Japan and South Africa, and changed by less than 5% in the other sites.

Management of Dyslipidemia

There was a decline (≥5%) in mean cholesterol level among people with diabetes in 6/8 clinical sites (range -0.5 to -0.2 mmol/mol) and no change (<5%) in the two Australian clinical sites, from 2006 to 2015 (Figure 1A). This improvement was accompanied by a large increase in statin use during the study period (range from 3.1 to 47 percentage points) (Figure 1B). However, the magnitude of reduction in mean cholesterol levels differed by site (Figure 1A). Argentina, Japan, Saudi Arabia and South Africa showed the highest proportion of people with high cholesterol in 2006 and 2015. The greatest reductions in mean cholesterol levels were mainly observed in those sites with the highest mean cholesterol levels in 2006 (Argentina, Hong Kong, Japan, Saudi Arabia and South Africa). In each site, at least half of the population with diabetes was on statin therapy in 2015 (Table 2).

Management of hypertension

In 2015, South Africa and Japan had the highest prevalence of hypertension, defined as BP ≥140/90 or on antihypertensive medication (Table 2). There was an increase in the proportion of people with BP≥140/90 mmHg (range 1.4 to 21.3 percentage points) in all sites except for Australia (Sydney) where there was a 13.8 percentage point reduction in the percentage of people with BP>140/90 (Figure 2A). Use of antihypertensive medications declined in Argentina, Australia (Melbourne) and South Africa (range -13.1 to -7.3 percentage points), increased in Australia (Sydney), Hong Kong and Saudi Arabia (range 4.3 to 6.1 percentage points), and remained unchanged (<5%) in India and Japan (Figure 2B).

There was no improvement in mean systolic blood pressure over time except for Argentina and Australia (Sydney), with 5 mmHg and 7 mmHg decreases in mean systolic blood pressure,

respectively (Table 2). Mean systolic blood pressure increased in Japan (132 to 140 mmHg) and Saudi Arabia (127 to 134 mmHg), while in other clinics, there was no change in mean systolic blood pressure (Table 2).

From 2006 to 2015, the prevalence of hypertension, defined as either using antihypertensive medications or having BP >140/90 mmHg, decreased in Australia (Sydney) (-11.3 percentage points), increased in Japan, Hong Kong and South Africa (range 7.7 to 11.8 percentage points) and remained unchanged (change <5%) in other sites. The prevalence of un-treated hypertension increased in Australia (Melbourne), Hong Kong, Saudi Arabia and South Africa (range 5.5 to 16.9 percentage points) and remain unchanged (change <5%) in other sites.

The proportion of people in each class of antihypertensive medications is presented in Table 3. ACE inhibitors were the most commonly prescribed antihypertensive medication in most sites, followed by CCBs and ARBs. While there was no increase in the total proportion of people on antihypertensive treatment, there was a change in the type of medications used. There was a reduction in the proportion of people on ACE inhibitors from 2006 to 2015. Simultaneously, utilization of ARBs increased. Furthermore, we observed a huge variability in the use of ARBs and ACE inhibitors between sites. For example, the prescription of ARBs among people with diabetes varied from 4.0% in South Africa to 35.0% in Australia (Melbourne) in 2006; this heterogeneity in ARBs usage persisted in 2015, when 14.2% and 45.0% used ARBs in South Africa and Japan, respectively. Of note, the heterogeneity in use of ACE inhibitors persisted from 2006 (from 4.7% in India - 56.1% in South Africa) to 2015 (from 3.2% in India - 60.7% in Argentina). For other types of medication, such as statin and antiplatelet agents, we did not observe such heterogeneity in the prescription rates between sites.

There was a mixed pattern for use of other antihypertensive medications such as thiazide diuretics and CCBs in different sites. Between 2006 and 2015, prescription of thiazide diuretics increased in Argentina, India and Japan and decreased in Australia (Melbourne), Saudi Arabia and South Africa. Utilization of CCBs decreased by 14% in South Africa and fluctuated within 5 percentage points in other sites. Prescription of aspirin and other antiplatelet medications decreased in three sites, namely Australia (Sydney), Saudi Arabia and South Africa (range -11.8 to -7.5 percentage points), increased in Australia (Melbourne) (9.7 percentage points) and remain unchanged (change <5%) in India and Hong Kong (Table 3).

Table 4 shows the prevalence of complications of diabetes in 2006 and 2015 in people with diabetes. We did not observe any relationship between complications rates and change in medications.

Discussion

This study provides information on CVD management in more than 39,000 people with type 2 diabetes from seven different countries. Despite the existence of heterogeneity between countries in terms of cardiovascular risk management, similar changes can be observed in treatment approaches. In general, mean cholesterol levels decreased in the study population in line with increase in statin use. In addition, lower cholesterol levels among those on statins likely reflects the use of higher doses and of more potent statins. The proportion of people on anti-hypertensive medications decreased slightly or remained unchanged with concomitant increases in the proportion of people with BP>140/90 mmHg in most sites. Anti-hypertensive treatment patterns shifted from predominantly using ACE inhibitors towards using more ARB medications. Nevertheless, the change to newer hypertension drugs was not associated with improvement in blood pressure levels.

The benefit of statin use both for primary and secondary prevention of CVD events in people with diabetes is well-established and extensively investigated (10). The American Diabetes Association (ADA) guidelines recommend a lower LDL-cholesterol target (<1.8 mmol/l) for people with diabetes and a concomitant cardiovascular event than the general population (<2.6 mmo/l) (11). The results of our study are consistent with those reported by the HSE, which showed that from 1994 to 2009, total cholesterol levels declined in people with diabetes from 6.1 mmol/l to 4.5 mmol/l, in parallel with an increase in prescription of statins from 2.2% to 47.4% (9). A study on people with diabetes from Taiwan also showed a three-fold increase in statin use in a seven year period (12). Similar to our findings, a study conducted in persons with type 2 diabetes in the US showed a substantial increase in statin use (from 4.2% in 1988 to 51.4% in 2010), accompanied by substantial improvement in the percentage of people achieving the LDL-cholesterol target of <2.6 mmol/l from 9.9% to 56.2% (13).

Our study shows that nearly 80% of the people with BP>140/90 mmHg were on antihypertensive medication. Reasons for failing to achieve the BP target despite receiving treatment for hypertension may include poor adherence (14, 15), inadequate efficacy of antihypertensive medications, side effects of drugs and variability in blood pressure measurement. Blood pressure management in hypertensive individuals with diabetes has undergone some significant changes over the last decade. The ADA targets for management of hypertension among people with type 2 diabetes has changed over time. In 2006, the ADA guidelines recommended the blood pressure target at 130/80 mmHg for people with diabetes. This target was based on several large studies such as the Hypertension Optimal Treatment (HOT) study and the United Kingdom Prospective Diabetes Study (UKPDS), which showed that maintaining blood pressure levels below 130/80 mmHg reduced cardiovascular events in

people with diabetes. However, the pooled analysis of mortality risk associated with the use of intensive blood pressure targets vs. standard targets in people with type 2 diabetes reported no benefit or even harm when the lower blood pressure targets were achieved (16). This meta-analysis demonstrated that although the use of intensive versus standard blood pressure targets might cause a small reduction in the risk for stroke, there was no evidence of benefit of intensive targets in reducing risk of mortality or myocardial infarction, but rather there was an increased risk of hypotension and other adverse events (16). Thus, there has been a modification to recent guidelines recommending a less stringent blood pressure target i.e. 140/90 mmHg, with emphasis on individualization of blood pressure management with regard to age and existence of other risk factors. Another explanation for lack of improvement in blood pressure control is the variability in BP targets suggested by different guidelines. The ADA guidelines recommend the blood pressure target at <140/90 mmHg (17) for people with diabetes, while the American Association of Clinical Endocrinologists/American College of Endocrinology AACE/ACE (4) and IDF (1) recommended the blood pressure target at <130/80 mmHg. National guidelines for Australia and Japan also recommended the blood pressure target at <130/80 mmHg in 2015 (18, 19). Despite the fact that the only changes to targets have been in regard to 130/80 mmHg, it is concerning that the percentage of people with BP >140/90 mmHg increased in all but one site. This suggests that raising BP targets from 130/80 to 140/90 can have the undesired effect of increasing the number of people failing to achieve the 140/90 target, and this should be considered in future guideline deliberations.

In this study, ACE inhibitors were the most popular antihypertensive medication in most sites which is consistent with most guidelines. Nevertheless, we observed a shift from prescription of ACE inhibitors to ARBs from 2006 to 2015. According to guidelines (20, 21), ACE inhibitors and ARBs (if intolerant to ACE inhibitors) are the first line antihypertensive

medications for people with diabetes. CCBs, thiazides and thiazide-like diuretics are recommended as the second line of treatment when patients fail to reach the target with first line drugs. Meta-analyses directly comparing ACE inhibitors and ARBs found that both had similar effects in reducing mortality and cardiovascular events (22). However, ARBs have a better side effect than ACE inhibitors in regard to cough, which is reported in 44% in those on ACE inhibitors compared to only 4% for those on ARBs (23).

One of the reasons for the heterogeneity in prescribing antihypertensive medications between sites is the number of different classes of antihypertensive medications available. Thus, health professionals have a range of antihypertensive medications available and will choose each of them based on the availability, cost, side effects, tolerability and local guidelines.

One of the barriers for improving diabetes management is the high cost of medications. One solution for antihypertensive medication could be use of those cheaper medications such as methyldopa, alpha blockers, and beta blockers. Furthermore, it has been shown that the intensification of therapy in patients with uncontrolled type 2 diabetes (T2D) is often inappropriately delayed. The failure of clinician to intensify therapy when clinically indicated or poor management of diabetes, clinical inertia, is associated with poor outcomes of diabetes.

The ADA recommended low-dose aspirin for secondary prevention of cerebrovascular and cardiovascular events (24), and for primary prevention for those with high risk of CVD. The high risk group includes men and women with diabetes aged ≥50 years who have at least one additional major risk factor (family history of premature atherosclerotic cardiovascular disease, hypertension, dyslipidemia, smoking, or albuminuria) and are not at increased risk of bleeding. In our study, usage of anti-platelet therapy was generally below 50% and the change between 2006 and 2015 was variable. A recent population based study in the US showed a slight decrease in the prevalence of aspirin use for both primary and secondary CVD prevention from 2012 to 2015 (25). Potential reasons for the variability in aspirin use in our study include the

controversy in recent years regarding the benefit of aspirin use among those without prior CVD events. Two studies published in 2008 and 2009, showed no clear benefit of aspirin in the primary prevention of CVD events in people with diabetes (29, 30). Furthermore, the Antithrombotic Trialists' (ATT) collaborators, in an individual patient-level meta-analysis in 2009, showed some evidence of sex disparity in that aspirin significantly reduced stroke only in women; in contrast, aspirin reduced the risk of atherosclerotic cardiovascular disease only in men (26).

The strengths of our study include the large sample size and the non-trial setting that the data represent. Clinical trials are conducted under strict conditions which do not necessarily represent real world situations where people with diabetes are managed less rigorously. While individual services are not necessarily representative of the population within which they are located, they provide information on all attending individuals, thus removing volunteer bias. Using data from medical records, our study observed management in real world settings. The aggregate nature of the data we collected is a limitation to our study, as it prevents the analysis of relationships between change in medication use, risk factors and change in blood pressure and lipid levels at an individual level. We also cannot claim causality because the study does not have a longitudinal design and we used aggregate data, not individual level data. Our study is also limited by the selection of the sites, which may not be representative of diabetes and CVD management in each country. The goal of this study was to explore real world experience about CVD management. It is likely that any change we see in our eight clinics may be similar to other clinics in each country. We believe that this is the first step to understand any change at the population level, however we acknowledge the limitation of this study regarding generalizability of this study to the whole population of each country. The number of clinical

services involved in this study is relatively small, and further research should be performed with population-based designs and in more locations. Adherence to treatment, as one of the likely causes of treatment failure, also needs to be addressed in future studies.

Conclusion

This study showed that from 2006 to 2015, there was improvement in the management of cholesterol, likely due to a substantial increase in statin use. The proportion of people with BP>140/90 mmHg increased and antihypertensive treatment shifted from ACE inhibitors to ARBs. Such increase in the proportion of those with BP>140/90 has occurred concomitant to the increase the in blood pressure targets from 130/80 mmHg to 140/90 mmHg in international guidelines.

Table 1. Characteristics of people with type 2 diabetes in 2006 and 2015 stratified by clinical service

Country (Centre)	Year	N	Age (years)	Male % (n)	Obese %	HbA1c	BMI (kg/m^2)	Duration of diabetes (years)
Argentina (Centro de Endocrinología Experimental y Aplicada)								
	2006	2,146	58.1 (11.1)	48.4 (1039)	45.2	7.7 (1.8)	30.1 (5.4)	9.3 (9.0)
	2015	1,828	54.7 (9.9)	49.6 (907)	55.4	7.9 (2.1)	32.1 (6.4)	8.9 (7.2)
Australia (Baker Heart and Diabetes Institute, Melbourne)								
	2006	4,080	61.7 (15.6)	57.2 (2331)	43.2	7.6 (1.4)	29.8 (6.0)	9.8 (9.8)
	2015	4,059	61.8 (15.7)	60.6 (2459)	42.9	7.7 (1.4)	29.7 (5.8)	13.8 (10.4)
Australia (Royal Prince Alfred Hospital,Sydney)								
	2006	1,406	60.3 (13.6)	58.2 (818)	48.6	7.5 (1.5)	30.7 (6.3)	11.2 (8.4)
	2015	1,351	59.6 (15.3)	59.5 (804)	45.3	8.0 (1.7)	30.2 (6.4)	14.2 (10.2)
Hong Kong (Prince of Wales Hospital)								
	2006	788	58.5 (12.9)	49.2 (388)	14.8	7.4 (1.6)	25.7 (4.3)	6.6 (7.1)
	2015	2,043	59.9 (12.0)	54.2 (1108)	17.8	7.6 (1.4)	26.2 (4.8)	11.3 (8.8)
India (Dr. A Ramachandran's Diabetes Hospitals)								
	2006	6,022	58.0 (12.0)	58.4 (3516)	21.2	8.4 (1.8)	26.9 (4.5)	13.7 (9.3)
	2015	13,348	54.0 (13.0)	59.5 (7945)	25.6	8.1 (1.7)	27.5 (4.8)	11.5 (9.3)
Japan (Shiga University of Medical Science)								
	2006	384	63.0 (11.0)	53.9 (207)	7.8	7.7 (1.1)	24.0 (3.8)	18.0 (10.0)
	2015	291	73.0 (5.0)	59.8 (174)	8.9	7.2 (1.0)	23.5 (3.5)	17.0 (11.0)
Saudi Arabia (Diabetes Center at AlNoor Specialist Hospital)								
	2006	383	53.5 (16.8)	41.5 (159)	59.1	7.6 (2.1)	31.3 (5.6)	8.9 (7.7)
	2015	276	56.4 (12.1)	51.4 (142)	58.0	8.4 (1.8)	31.7 (6.7)	9.6 (8.8)
South Africa (Inkosi Albert Luthuli Central Hospital)								
	2006	601	49.3 (17.5)	34.6 (208)	44.6	9.7 (2.5)	30.2 (7.3)	13.2 (11.0)
	2015	681	46.5 (20.4)	36.4 (248)	46.1	9.0 (2.3)	29.9 (7.5)	14.0 (10.3)

Data presented as mean (SD) or percentage

Table 2. Hypertension and dyslipidemia management in people with type 2 diabetes in 2006 and 2015 stratified by clinical service

							Prevalence of abnormal blood pressure					
			Cholesterol mmol/l		Blood pressure (mmHg)		Above target		Hypertension*		Un-treated hypertension**	
Country (Centre)	Year	N	Population statins	Total population	Systolic BP	Diastolic BP	>130/80	>140/90	>130/80	>140/90	>130/80	>140/90
Argentina												
	2006	2,146	5.2 (1.1)	5.5 (1.1)	132.4 (15.9)	80.1 (9.7)	22.8	5.2	68.4	65.5	11.5	10.7
	2015	1,828	4.9 (1.1)	5.1 (1.1)	128.9 (16.3)	78.2 (11.0)	17.6	6.9	63.3	61.1	17.6	13.0
Australia (Melbourne)												
	2006	4,080	4.3 (1.1)	4.1 (1.1)	129.8 (16.7)	74.1 (9.2)	40.1	18.9	75.0	70.8	18.1	12.0
	2015	4,059	4.4 (1.7)	4.2 (1.7)	133.5 (17.2)	75.5 (11.2)	63.1	33.5	77.9	68.1	31.2	24.3
Australia (Sydney)												
	2006	1,406	4.5 (1.1)	4.3 (1.1)	130 (17.0)	74.0 (10.0)	49.3	23.6	83.4	77.3	18.3	12.7
	2015	1,351	4.3 (1.9)	4.1 (1.9)	123 (15.1)	70.7 (9.3)	26.0	9.8	70.2	66.0	16.9	10.7
Hong Kong												
	2006	788	4.8 (1.1)	4.4 (1.1)	130.6 (19.9)	73.6 (10.9)	51.9	29.1	74.0	64.1	31.1	21.4
	2015	2,043	4.3 (0.9)	4.1 (0.9)	133.6 (18.7)	73.7 (11.5)	57.3	32.3	78.8	71.8	28.8	26.9
India												
	2006	6,022	4.4 (1.0)	4.4 (1.0)	132.0 (15.0)	81.0 (6.0)	62.3	12.8	62.3	12.8	48.7	38.5
	2015	13,348	4.2 (1.2)	4.2 (1.1)	130.0 (17.0)	81.0 (8.0)	52.8	15.8	52.8	15.8	45.9	35.7
Japan												
	2006	384	5.1 (0.8)	5.1 (0.8)	132.0 (16.0)	72.0 (10.0)	57.3	28.9	75.0	65.9	32.0	33.3
	2015	291	4.8 (0.8)	4.6 (0.9)	140.0 (16.0)	76.0 (12.0)	74.5	50.2	87.6	77.7	42.0	36.3
Saudi Arabia												
	2006	383	5.0 (1.3)	5.2 (1.6)	127.3 (79.3)	79.3 (8.7)	30.8	13.6	50.4	43.3	26.3	7.7
	2015	276	4.7 (1.2)	4.7 (1.3)	134.5 (63.4)	76.7 (7.8)	42.3	20.6	65.2	52.5	39.2	24.6
South Africa												
	2006	601	4.9 (1.2)	5.1 (1.2)	133.4 (19.9)	76.1 (10.2)	52.7	31.0	80.0	75.0	11.6	4.3
	2015	681	4.4 (1.2)	4.4 (1.2)	131.0 (16.0)	74.0 (11.0)	55.5	48.0	95.5	79.4	28.3	17.5

Data presented as mean (SD) or percentage

* The percentage of those with BP above target or on antihypertensive medications

** The percentage of those with BP above target who were not on antihypertensive medications

Table 3. Prevalence of use of cardiovascular disease drug classes in people with diabetes in 2006 and in 2015 stratified by site

Country	Year	N	ARBs	ACEi	Thiazides	CCBs	Statins	Anti platelet
Argentina								
	2006	2,146	8.9 (190)	52.4 (1124)	14.4 (310)	11.7 (252)	30.9 (664)	-
	2015	1,828	17.3 (317)	60.7 (1109)	16.1 (295)	12.7 (232)	52.0 (951)	35.9 (656)
Australia (M)								
	2006	4,080	35.0 (1429)	33.9 (1383)	26.0 (1061)	26.0 (1059)	54.1 (2207)	21.0 (857)
	2015	4,059	33.7 (1370)	22.0 (382)	25.7 (1042)	23.1 (937)	61.0 (2477)	30.7 (1247)
Australia (S)								
	2006	1,406	32.9 (452)	37.9 (522)	16.3 (227)	21.6 (297)	59.0 (153)	38.5 (529)
	2015	1,351	38.7 (489)	25.1 (318)	N/A	26.1 (330)	71.0 (161)	31.0 (396)
Hong Kong								
	2006	788	5.1 (40)	35.2 (277)	N/A	29.7 (234)	23.5 (185)	19.0 (150)
	2015	2,043	18.4 (377)	30.8 (629)	3.1 (8.3)	35.4 (724)	54.8 (1119)	23.2 (474)
India								
	2006	6,022	19.6 (1077)	4.7 (258)	9.0 (439)	16.8 (925)	24.9 (1371)	18.1 (996)
	2015	13,348	27.3 (3649)	3.2 (426)	9.4 (1248)	15.6 (2081)	51.2 (6831)	21.4 (2862)
Japan								
	2006	384	27.3 (105)	18.8 (72)	14.8 (57)	29.7 (114)	39.8 (153)	33.6 (129)
	2015	291	45.0 (131)	7.9 (23)	17.5 (51)	32.6 (95)	55.3 (161)	28.9 (84)
Saudi Arabia								
	2006	383	5.2 (20)	30.3 (116)	9.4 (36)	14.6 (56)	49.3 (189)	70.8 (271)
	2015	276	20.3 (56)	24.6 (68)	8.3 (23)	18.5 (51)	64.1 (177)	59.1 (163)
South Africa								
	2006	601	4.0 (24)	56.1 (337)	36.4 (219)	47.6 (286)	50.1 (301)	49.1 (295)
	2015	681	14.2 (97)	42.3 (288)	22.6 (154)	33.8 (230)	53.2 (362)	37.3 (254)

Data presented as numbers or percentages (n)
N/A: Not available
ARB: angiotensin II receptor blockers; ACE: angiotensin-converting-enzyme inhibitors, CCBs: calcium channel blockers

Table 4. Prevalence of complications of diabetes in people with diabetes in 2006 and in 2015 stratified by site

Country (Centre)	Year	Retinopathy (%)	total	eGFR<60 ml/min/1.73 m2	total	MACE event	total
Argentina							
	2006	20.6 (111)	538	9.5 (120)	1262	14.7 (191)	1296
	2015	10.4 (201)	1942	10.9 (172)	1578	19.6 (411)	2096
Australia (Melboure)							
	2006	22.6 (921)	4080	34.8 (596)	1703	19.4 (790)	4080
	2015	21.9 (889)	4059	33.7 (621)	1843	19.5 (793)	4059
Australia (Sydney)							
	2006	23.5 (322)	1373	23.5 (210)	892	24.4 (338)	1388
	2015	19.4 (167)	861	21 (272)	1294	-	-
Hong Kong							
	2006	27.9 (220)	788	10.7 (84)	786	11.5 (91)	788
	2015	22.9 (466)	2038	17.7 (361)	2036	18.8 (385)	2039
India							
	2006	-	-	10.9 (487)	4473	15.6 (877)	5503
	2015	-	-	13.0 (1308)	10037	-	-
Japan							
	2006	30.7 (118)	384	24.0 (92)	384	7.8 (30)	384
	2015	36 (107)	291	23.4 (68)	291	14.4 (42)	291
Saudi Arabia							
	2006	9.5 (36)	381	12.4 (46)	370	24.8 (95)	383
	2015	13.1 (36)	275	24.3 (67)	276	20.6 (57)	276
South Africa	2006	1.5 (9)	601	17.9 (103)	574	1 (6)	601
	2015	15.1 (103)	681	13.6 (83)	610	13.5 (92)	681

- Data is not available

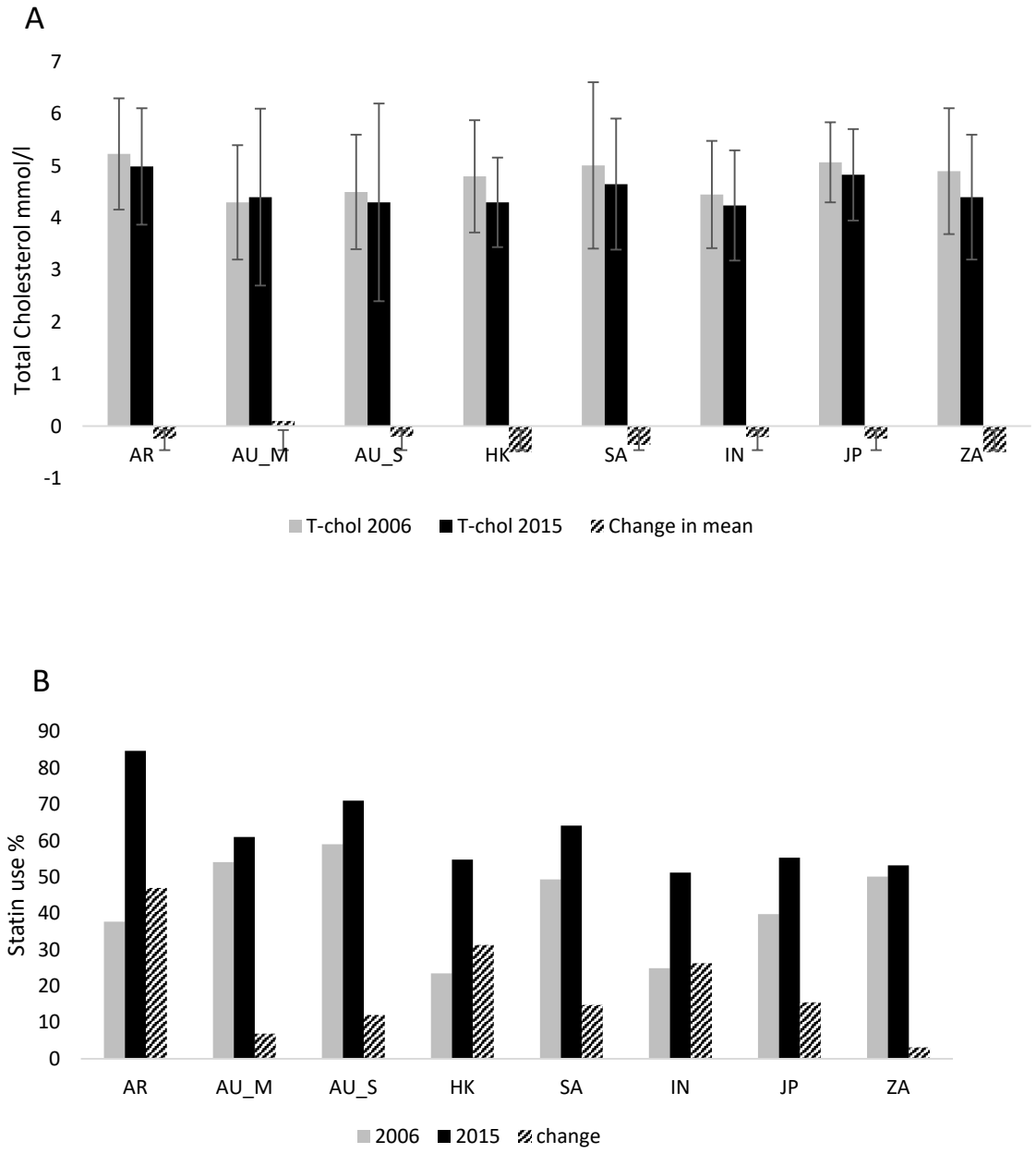

Figure 1.

A) Mean total cholesterol in 2006 and 2015, and change (mmol/l) from 2006 to 2015.

B) Prevalence of statin use in 2006 and 2015, and percentage point change from 2006 to 2015

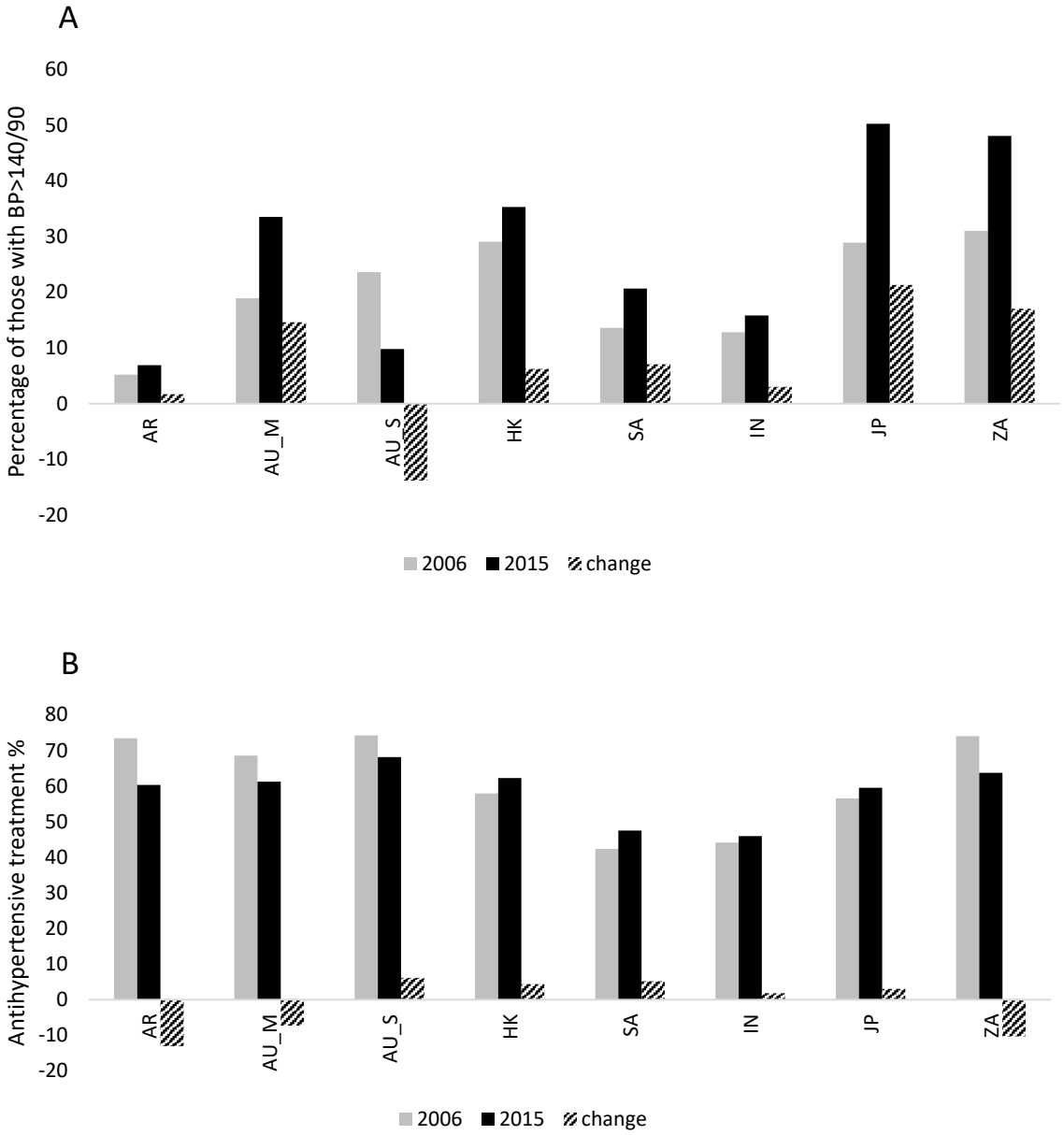

Figure 2.

A) Prevalence of patients with BP>140/90 in 2006 and 2015, and percentage point change from 2006 to 2015.

B) Prevalence of antihypertensive medications use in 2006 and 2015, and percentage point change from 2006 to 2015

AH: antihypertensive medications

AR: Argentina; AU_M: Australia, Melbourne; AU_S: Australia, Sydney; HK: Hong Kong; SA: Saudi Arabia; IN: India; JP: Japan; ZA: South Africa

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Chapter 7

Nurse prescribers and diabetes management

Examining trends of diabetes management using both individual level data obtained from surveys and the real world evidence derived from a number of countries demonstrated poor diabetes control, particularly with regards to glycaemic control in patients with diabetes. These findings highlighted the need for developing strategies to improve glycaemic control in patients with diabetes.

Nurse-led diabetes clinics are an innovative way of potentially improving diabetes management (1-14). Nurse-led diabetic clinics are varied in terms of structure and work delegations. In traditional models of nursing care in diabetes, nurses have the role of providing patient support and education, often with a specific focus on the administration of insulin. In recent years, some clinics have expanded the role of nurses to include the prescribing and monitoring of drug therapy (15). In such settings, nurses work as substitutes for, or to complement, physicians in the management of diabetes. The main aim of this model of care is to enable patients to access safe and effective health care in a timely manner. In this chapter, we conducted a systematic review and meta-analysis to examine whether nurse prescribers can improve HbA1c levels in patients with diabetes.

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Nine RCTs were identified and included in this study. The main finding of this work is that adding nurse prescribers to a usual care health team did not improve glycaemic control. However, when nurse prescribers were compared directly to physician prescribers, they achieved equally good glycaemic outcomes. This finding may be valuable in LMICs, where there is a shortage of doctors or resources. Thus, nurses can take on the responsibility of prescribing following algorithms and protocols.

Declaration for Thesis – Chapter 7

Maryam Tabesh, Dianna J. Magliano, Digsu N Koye, Jonathan E, The effect of nurse prescribers on glycaemic control in type 2 diabetes: a systematic review and meta-analysis, International Journal of Nursing Studies. 2018; 78: 37-43.

In the case of chapter 6, the nature and extent of my contribution to the work was the following:

Nature of the contribution	Extent of the contribution
Conceiving the study, developing search strategy, searching databases, deciding on inclusion of studies, extracting details of selected studies, analysing the data , conceptualisation and writing of the manuscript, critical revision, corresponding author	80%

The following co-authors contributed to the work. If co-authors are student at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of the contribution	Extent of the contribution (%) for student co-authors only
Dianna J. Magliano	Conceiving the study, searching databases, deciding on inclusion of studies, conceptualisation, reviewing and editing the manuscript, approval for the final for publication	N
Digsu N. Koye	Extracting details of selected studies, reviewing and editing the manuscript	Y, 5%
Jonathan E. Shaw	Conceiving the study, deciding on inclusion of studies, conceptualisation, reviewing and editing the manuscript, approval for the final for publication	N

The undersigned hereby certify that the above declaration correctly reflects the nature and the extent of the candidate's and co-author's contribution to this work *.

Student Signature	[redacted]	Date: 28/06/2018
Main Supervisor Signature		Date: 28/06/2018

*note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

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The effect of nurse prescribers on glycaemic control in type 2 diabetes: A systematic review and *meta*-analysis

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ABSTRACT

Background: The creation of advanced nursing roles in diabetes management, with specific skills such as nurse prescribing, has resulted in nurses taking on roles that have traditionally been associated with doctors.
Objectives: We aimed to examine the effectiveness of nurse-led clinics, in which nurses were involved in prescribing, on haemoglobin A1c (HbA1c) among people with type 2 diabetes.
Methods: We systematically searched the literature, Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and Allied Health Literature database guide (CINAHL) databases, to identify randomised controlled trials (RCTs) assessing the effect of nurse prescribers on HbA1c. We focused on randomised controlled trials which compared nurse prescriber interventions with usual care in adults aged 18 years or over with a diagnosis of type 2 diabetes. The main outcome measure was change in HbA1c levels. We performed a random effects model *meta*-analysis to assess the pooled effect size of the intervention. Studies were divided into two groups according to the role of nurses in the intervention. In one group, the nurses supplemented a team, as an add-on to usual care; in the other group, they worked independently, and were compared directly to a doctor.
Results: Nine RCTs were identified and included in this study. All studies were from developed countries, with a medium risk of bias and a moderate heterogeneity between studies. In the five RCTs in which nurse prescribers supplemented a team, there was no significant difference in change of HbA1c compared to usual care (-0.34 percentage points; 95% CI: −0.71, 0.02). In the four RCTs in which nurses replaced doctors, the outcomes of nurse prescribers were comparable to those of doctors. No data on adverse events were available.
Conclusion: There was no clear evidence of benefit on glycaemic control, when nurses who undertake prescribing work alongside a doctor and other practitioners. However, in those studies in which nurses replaced physicians, the glycaemic control was comparable between nurses and doctors. Therefore, there may be value in providing nurse-led prescribing services where there is limited access to doctor-led services.

What is already known about the topic?

- The creation of advanced nursing roles in diabetes management, with specific skills such as nurse prescribing, has resulted in nurses taking on roles that have traditionally been associated with doctors.
- The effect of nurse prescribers on glycaemic control has been evaluated in randomised clinical trial studies and showed inconsistent findings.

What this paper adds

- Nurse prescribers can be split into two types based on their role in prescribing: independent prescribers and supplementary prescribers who work in a team in collaboration with doctors.
- When nurses replaced doctors the result was comparable to that of doctors, thus there is value in implementing nurses, when there is limited access to doctors.
- There is no evidence of benefit on glycaemic control when nurse prescribers work as a supplementary prescribers.

1. Introduction

In 2015, the International Diabetes Federation (IDF) estimated that one in 11 adults had diabetes and around 46% of adults with diabetes were undiagnosed (IDF, 2015). Diabetes imposes a high burden of disease on developing countries which are experiencing rapid health transition (Boutayeb, 2006). Four out of five individuals with diabetes now live in poor countries, with the largest numbers being of working

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age (IDF, 2015). With a rapidly increasing population and limited health care resources, there has been a challenge in diabetes management (Blonde, 2005). Nurse-led diabetes clinics are an innovative way of potentially improving diabetes management (Allen et al., 2011, Aubert et al., 1998, Bilous et al., 2011, Cardenas-Valladolid et al., 2012, Davidson et al., 2006, De Pue et al., 2013, Denver et al., 2003, Ercanfang et al., 2010, Jutterstrom et al., 2016, Lenz et al., 2002, Scain et al., 2007, Smith et al., 2004, So et al., 2003, Vrijhoef et al., 2002). Nurse-led diabetic clinics are varied in terms of structure and work delegations. In traditional models of nursing care in diabetes, nurses have the role of providing patient support and education, often with a specific focus on the administration of insulin. In recent years, some clinics have expanded the role of nurses to include the prescribing and monitoring of drug therapy (Carey and Courtenay, 2007). In such settings, nurses work as substitutes for, or to complement, physicians in the management of diabetes. The main aim of this model of care is to enable patients to access safe and effective health care in a timely manner. Prescribing of medication involves initiation, stopping or changing the dosage of medications. Nurse prescribers can operate within a number of frameworks, ranging from relative freedom in regard to all the aspects of prescribing, including drug selection, to protocols that limit their role to specific drugs and very specific indications. Both regulatory environments and training are relevant to the framework adopted in any particular setting.

Findings from systematic reviews have demonstrated a beneficial role of nurses in improving management of chronic diseases including diabetes (Rosemann, 2014, Tshiananga et al., 2012, Welch et al., 2010). However, these studies do not focus on nurse prescribers but describe the positive role of nurses on chronic disease management. In these settings, nurses facilitate continuity of care which is an important component of chronic disease management. It has been suggested that nurses can provide as high quality care as general practitioners (GPs) in the provision of first contact and ongoing care for patients (Arts et al., 2012, Sibbald et al., 2006).

A *meta*-analysis conducted in 2010 examining the effect of nurse case management interventions on glycaemic control reported a clinically significant improvement in blood glucose control as measured by HbA1c (Welch et al., 2010). Another systematic review conducted by Clark et al. (2010) demonstrated that nurse-led interventions, using structured algorithms for care, were associated with reduced levels of cardiovascular disease (CVD) risk factors, such as high blood pressure in diabetes. A *meta*-analysis by Martinez-Gonzalez et al. (2014) demonstrated no significant differences between nurse-led care and physician-led care in reducing HbA1c levels. This *meta*-analysis is limited in several ways. Firstly, it only included four studies reporting changes in HbA1c, and secondly it assessed the value of a broader intervention to reduce HbA1c including studies where nurses were not involved in prescribing and thus cannot provide clear evidence of the efficacy of nurse prescribers in the management of diabetes.

While the limited evidence which exists may suggest a role for nurses in the management of chronic diseases, it is unclear whether nurse-led clinics, whereby nurses are actually involved in prescribing, can improve diabetes management. We performed a systematic literature review and a *meta*-analysis to determine whether nurse prescribers are efficacious in the management of type 2 diabetes, using HbA1c as an objective marker of glycaemic control.

2. Methods

2.1. Data sources and searches

We conducted a systematic search for randomised controlled trials which compared nurse prescriber interventions with usual care in adults aged 18 years or over with a diagnosis of type 2 diabetes. The main outcome measure was change in HbA1c levels.

We included interventions in which nurses were involved in prescribing glucose-lowering medication following protocols or algorithms with or without the direct supervision of a physician. Studies where nurses educated people without prescribing any medication, or those in which nurses provided self-management support only were excluded. The control group was generally defined as the traditional model of care or usual care. The usual care group receive their ongoing treatment provided by their physicians, who might either work alone or in a team including other health care staff (Table 2).

2.2. Search methods for identification of studies

The literature search strategy involved Medical Subject Heading (MESH) and text words that include “diabetes” and “nurse” or “nursing practitioners” and “trials”, supplementary table. We searched Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and Allied Health Literature database guide (CINAHL) databases for randomised controlled trials published between January 1980 and May 2015 and then updated our search on 19th of July 2016. We restricted our search for English language studies because of the cost of translation. We screened the references of all retrieved articles to identify additional publications. Hand searches identified three more relevant publications for our study.

Two of the authors (MT and DJM) independently selected potentially relevant studies by screening retrieved citations and abstracts from the electronic searches. Each reviewer indicated whether the citation was potentially relevant, was clearly not relevant, or did not give sufficient information to make a judgement. If studies were potentially eligible or the reviewer needed more information before a judgement could be made, the full text was retrieved for further review. When the two reviewers disagreed on whether or not the study was to be included or had differing quality assessments, conflict was resolved by discussing with a third reviewer (JES). This occurred in two instances. In general, we classified studies into two categories regarding the role of nurse in disease management. In one category, nurses supplemented usual care in a team including a doctor, and the comparison arm was the same team, but without the nurse. In the other category, the nurse worked independently, and the comparison arm was a doctor working without a nurse. We categorised the studies based on this distinction and analysed these groups separately.

2.3. Data extraction and quality assessment

Two authors (MT and DNK) independently extracted details of the selected studies and checked the references of all included studies to find other potentially relevant studies. We contacted authors of all the papers included in the study to obtain necessary information not reported in the publication. Extraction of information included: year of publication, mean age of participants in each group, duration of diabetes, duration of follow up, country of origin, ethnicity of participants, presence of diabetes related complications, baseline and follow up HbA1c, sample size, components of intervention and control groups, types of intervention (nurses worked in a team or work independently) and the nature of the control treatment (physicians only or team work) using a structured data collection form.

We used the Cochrane collaboration’s tool for assessing risk of bias in clinical trials to assess the study quality and reporting bias (Higgins et al., 2003). A score between 6 (high quality) and 0 (low quality) was assigned for each study. Features of trial design included in the score are: the use of random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). We categorised the total score into the following groups: low risk (score 5 or 6), medium risk (score 3 and 4) and high risk of bias (total score less than 3).

2.4. Data analysis

The pooled effect size of studies and 95% confidence interval (CI) for the differences in the mean between intervention and control groups were calculated using mean and standard deviation (SD) or standard error (SE) from each individual study. The SDs reported in the study conducted by Taylor et al. are too small to be credible, and were therefore assumed to be SEs from which we calculated the SD using Revman 5. When the mean difference in the change of HbA1c (from baseline to study end) was not reported, baseline and follow-up HbA1c were used to calculate it using Revman 5 calculators. Data were pooled and analysed using Revman 5. An effect size of 0.2 was regarded as small, 0.5 as medium, and 0.8 as large (Cohen et al., 2012). The Q test was used to test for significant heterogeneity of effect size among studies. The I^2 (%) statistic was used to quantify the extent of the heterogeneity or proportion of between study variability in effect size that was due to true heterogeneity. The I^2 statistic was interpreted as small, moderate, or large if I^2 was less than 25%, 25% to 50%, or greater than 75%, respectively (Higgins et al., 2003). A random effects model was performed to estimate effect size in the pooled *meta*-analysis (Gabbay et al., 2006). The presence of publication bias was assessed using a funnel plot.

3. Results

3.1. Characteristic of selected studies

We initially identified 148 full texts, from which 9 studies fulfilled the inclusion and exclusion criteria for the systematic review (an overview of the methodology of the literature review is presented as PRISMA flow diagram in Fig. 1 (Gabbay et al., 2006, Houweling et al., 2011, Houweling et al., 2009, Ishani et al., 2011, Krein et al., 2004, Lenz et al., 2002, Litaker et al., 2003, Taylor et al., 2003, Welch et al., 2011). Among these studies, 7 provided either mean change or baseline and follow up HbA1c levels, thus these 7 studies were included in the meta analysis. The remaining two studies provided comment on changes in glycaemic control, but without any data from which to calculate the change in HbA1c. Table 1 shows the summary of studies included in the systematic review. The total participant sample size was 1974, ranging from 46 to 556 per study. Baseline mean HbA1c was between 7.4 and 9.5%. The duration of follow-up varied between 6 and 18 months, with six of the studies having a duration of 12 months. Among nine studies that included in the systematic review, seven studies were conducted in the U.S. and two in The Netherlands. Studies were published between 2004 and 2011. One study was focused only on people of Hispanic ethnicity (Lenz et al., 2002). In terms of type of intervention (Table 2), in four studies, nurses worked independently following an algorithm or a medical framework without the direct supervision of general practitioners (Houweling et al., 2009, Houweling et al., 2011, Ishani et al., 2011, Lenz et al., 2002). In the remaining five studies, the nurse was part of a team, which also included a doctor and other healthcare professionals (Gabbay et al., 2006, Welch et al., 2011), or a doctor alone (Krein et al., 2004, Litaker et al., 2003, Taylor et al., 2003). In five studies, the intervention was designed to be more intensive than usual care, providing more frequent contact with the health care team (Gabbay et al., 2006, Krein et al., 2004, Litaker et al., 2003, Taylor et al., 2003, Welch et al., 2011). Two studies were conducted specifically among those with concomitant complications such as hypertension and dyslipidaemia (Litaker et al., 2003, Taylor et al., 2003). In three studies, the main intervention was prescribing medication following algorithms (Houweling et al., 2009, Houweling et al., 2011, Lenz et al., 2002), while in the six other studies, in addition to prescribing role, nurses had other responsibilities such as life style modification, improving self-management of diabetes and management of hypertension (Gabbay et al., 2006, Ishani et al., 2011, Krein et al., 2004, Litaker et al., 2003, Taylor et al., 2003, Welch et al., 2011).

3.2. The effect of nurse prescribers on glycaemic control

The systematic review comprised nine studies, of which only seven studies were included in the *meta*-analysis as two studies did not report the change in HbA1c or the baseline and follow-up HbA1c (Fig. 2). The overall, pooled effect of the interventions on HbA1c for studies where nurses worked with doctors showed a trend towards reduction of HbA1c levels in nurse prescribing group, but the differences was not statistically significant (difference = (-0.34 percentage points [95% CI: −0.71, 0.02]) (−3.7 mmol/mol [95% CI: −7.8, 0.2])). Those studies in which nurses replaced doctors showed a comparable effect of nurses compared to doctors on HbA1c reduction (difference = (−0.31 percentage points [95% CI: −0.77, 0.15]) (−3.4 mmol/mol [95% CI: −8.4, 1.6])). In both groups, the heterogeneity was moderate with I^2 = 60% and I^2 = 54% for the first and second groups, respectively.

In the two studies which reported both 6-month and 12-month HbA1c levels (Gabbay et al., 2006, Houweling et al., 2009), the findings at 6 months were similar to those at 12 months.

We performed subgroup analysis according to: location of the study; ethnicity of the participants; baseline HbA1c; quality of the study and the duration of follow up.

These analyses did not demonstrate any significant differences between subgroups, but the small number of studies limits the power to detect such subgroup differences.

3.3. Risk of bias assessment

Overall, study quality in the trials was only moderate. All studies were randomised at the individual level, which provides more precise results compared to randomisation at practice level. Blinding of outcome assessment, attrition bias and reporting bias was adequate, but in one study (Taylor et al., 2003) the relevant information could not be ascertained from the manuscript. Only three studies were assessed as adequate in the use of random sequence generation (Gabbay et al., 2006, Welch et al., 2011) and only two for allocation concealment (Houweling et al., 2009, Welch et al., 2011); there were three studies for which allocation concealment was not well described (Ishani et al., 2011, Krein et al., 2004, Litaker et al., 2003). A funnel plot of standard error over individual effect size of the studies showed the presence of publication bias suggesting that results from studies favouring usual care may not have been published.

3.4. Description of studies that were not included in the meta-analysis

The two studies which were not included in the *meta*-analysis were designed to compare the effectiveness of nurse practitioners with physicians where both had the same level of authority (Ishani et al., 2011, Lenz et al., 2002). Neither reported any significant differences in mean HbA1c levels between nurses and doctors, but in the study of Ishani et al. the percentage of people achieving HbA1c < 7% (< 53 mmol/mol) was significantly higher in the nurse prescribers group compared to the usual physician model of care (Ishani et al., 2011).

4. Discussion

We systematically reviewed published evidence for the effectiveness of nurses who were involved in prescribing medications, on diabetes management, and identified nine randomised controlled trials, seven of which were suitable for inclusion into a *meta*-analysis. Across all study types, we found no statistically significant difference in glycaemic control in the nurse prescriber groups compared to usual care.

Although nurses were involved in prescribing medications in all studies, the way the interventions were carried out differed. First, the scope of practice of nurse prescribers can vary in regard to the degree of independence. In the studies presented here, the nurses all worked within well-defined protocols for the use of drugs. Second, nurses can

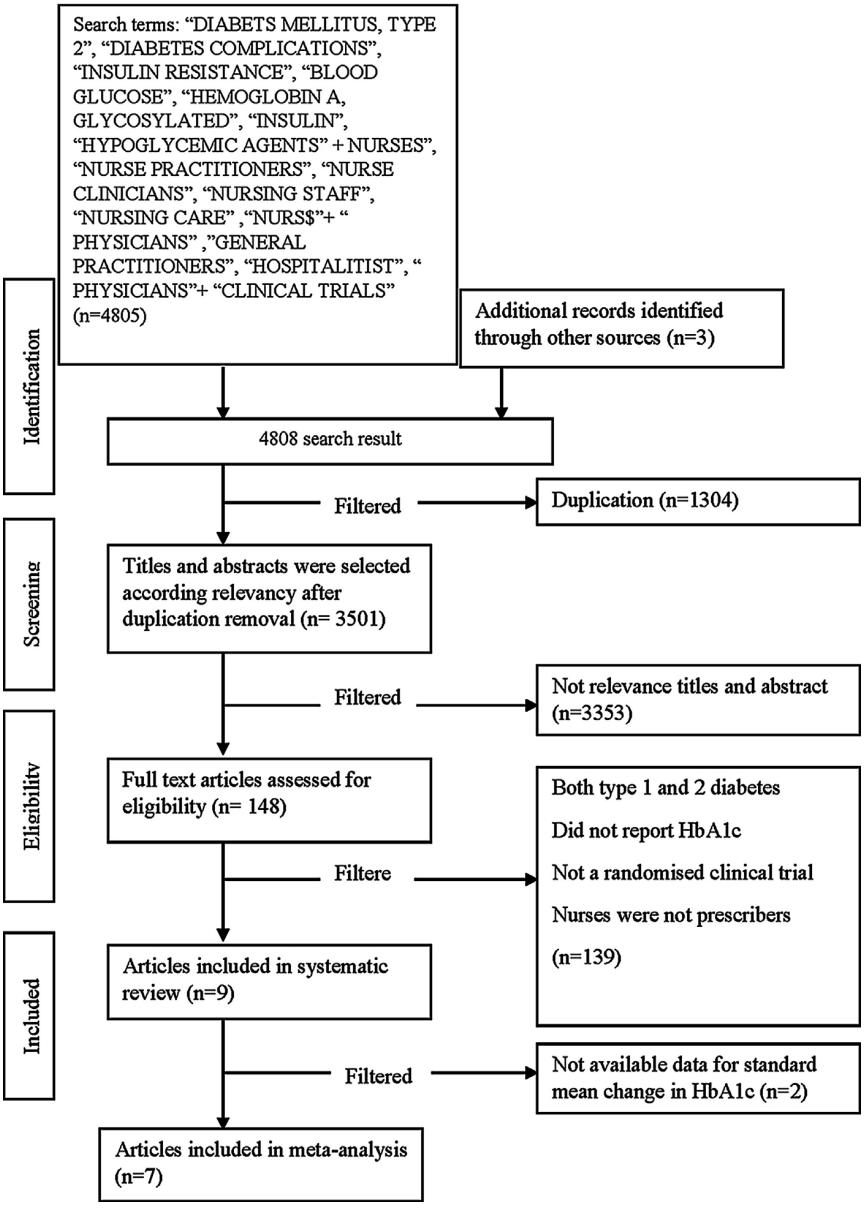

Fig. 1. PRISMA Flow diagram- study selection process.

Table 1
Characteristics of studies included in the systematic review.

First Author (year)	N	Characteristics of Study participants	Follow-up (month)	Country	Baseline HbA1c%	
					Intervention	Control
Nurses worked in a team						
Gabbay (2006)	332	-Type 2 diabetes (95%) −Age > 18	12	U.S.	7.46 ± 1.4	7.36 ± 1.5
Krein (2004)	246	-Type 2 diabetes −HbA1c > 7.5% −Age > 18	18	U.S.	9.3 ± 1.5	9.2 ± 1.4
Litaker (2003)	157	-Type 2 diabetes −Hypertension (Stages I–II) −No organ complications	12	U.S.	8.4 ± 1.4	8.5 ± 1.6
Taylor (2003)	169	-Type 2 diabetes − Aged ≥18 −HbA1c > 10% −One of hypertension, dyslipidaemia or CVD	12	U.S.	9.5 ± 0.3	9.5 ± 0.3
Welch (2011)	46	-Type 2 diabetes −Hispanic −Duration of diabetes > 1 year −HbA1c 7.5–14%	12	U.S.	8.5 ± 1.0	9.0 ± 1.2
Nurses worked independently						
Houweling (2009)	93	-Type 2 diabetes with no treatable comorbidity	12	NL	8.9 ± 1.2	8.6 ± 1.3
Houweling (2011)	230	-Type 2 diabetes	14	NL	7.6 ± 1.3	7.4 ± 1.3
Ishani (2011)	556	-Diabetic patients −Blood pressure > 140/90 (mmHg), HbA1c > 9.0%, or LDL > 100 mg/dL	12	U.S.	8.0 ± 1.6	7.8 ± 1.5
Lenz (2002)	145	-Type 2 diabetes −Hispanic (90.3%)	6	U.S.	–	–

N=Number of participants, U.S. = United States, CVD = Cardiovascular Disease, NL = The Netherland.

Table 2
Intervention and control conditions in studies included in the systematic review.

Author	Intervention team	Interventions	Control
Gabbay (2006)	- Nurse case managers (NCM) - Primary care physicians (PCP) - Diabetes nurse educators - Dieticians	- Following therapeutic recommendations based on ADA guidelines - Behavioural goal setting - Establishing individualized care plan - Providing patient self-management education - Phone calls - Order protocol-driven laboratory tests - Tracking the outcomes	- Ongoing usual care provided by PCPs
Krein (2004)	- Nurse case managers - Primary care providers	- Identifying and initiating medication and dose changes based on medication treatment algorithms - Scheduling follow-ups - Encourage patient self-management, including diet and exercise - Helping with appointment scheduling - Monitoring home glucose and blood pressure levels	- Usual care from PCPs
Litaker (2003)	- Nurse practitioners - Primary care physicians	- Developing treatment regimens using clinical practice algorithms and incorporating patient preferences - Assessing treatment adherence - Education on disease self-management strategies - Regular monitoring and feedback delivering	- Usual care from PCPs
Taylor (2003)	- Nurse case managers - Physicians	- Using treatment algorithms developed based on national guidelines to titrate patient's medication - 90 min meeting with patients to review care and develop self-management program - 1 to 2 h group sessions weekly for four weeks - Follow-up telephone calls until 52 weeks	- Usual care from PCPs - Receiving diabetes pamphlets
Welch (2011)	- Diabetes nurses - Clinical support staff - Primary care providers	- Initiate or increase diabetes medications by contacting doctors as needed - Explore diabetes self-management behaviours and barriers to facilitate diabetes education - One hour diabetes care visits conducted by a diabetes nurse and dietician team	- Usual care from PCPs - One hour diabetes care visits conducted by a diabetes nurse and dietician team
Houweling (2009)	- Nurse specialist in diabetes (NSDs)	- Prescribing medication based on the guidelines from the Dutch College of General Practitioners and those from the Dutch Diabetes Federation - Order laboratory tests	- Standard care by internist - Nurse educator
Houweling (2011)	- Practice nurses (PNs)	- Prescribing 14 different medications and adjusting dosages for a further 30 - The PNs were specifically not permitted to prescribe insulin, but were able to adjust the dosage - Order laboratory tests	- Usual care from PCPs
Ishani (2011)	- Nurse case managers	- Making adjustments to the patients' medications according to the study protocol using a therapeutic algorithm - Established lifestyle modification goals including weight loss, physical activity	- Usual care from PCPs
Lenz (2002)	- Nurse practitioners	- Providing care with the same authority to that of medical doctors to prescribe medication	- Usual care from PCPs

ADA = American Diabetes Association.
PCPs = Primary care physicians.

either work as independent practitioners, or as an addition to, and in combination with, doctors. The former role is usually aimed at improving cost and efficiency, while the latter form of nursing care is usually aimed at increasing the quality of care. These two different categories led to different aims of the studies. In those studies where nurses solely provide care for patients, the aim of the studies was to show that nurses could achieve outcomes that are at least as good as those achieved by physicians. These interventions may be valuable when there is shortage of doctors or the resources are limited, and our findings support the potential for nurses to undertake such a role, without any loss of benefit for glycaemic control. In those studies which tested nurses working in partnership with doctors as a supplementary aspect of care, the aim was to improve the patient's outcome by adding nurses who could prescribe medication into the primary health care systems. We found no evidence that such improvements could be achieved, though there was a non-significant trend towards better HbA1c.

Thre were two studies in which the intervention included nurse prescribers, primary care providers and dieticians or nurse educators (Gabbay et al., 2006, Welch et al., 2011). There were five studies in which the intervention group received more intensive care compared to the control group (Gabbay et al., 2006, Krein et al., 2004, Litaker et al., 2003, Taylor et al., 2003, Welch et al., 2011). Thus, participants in the intervention group had more visists with nurses, more follow-up calls, and were more likely to be referred to dieticians or educators as appropriate or were contacted more often by their health providers compared to those who followed the usual model of care. The multidisciplinary nature of the intervention in these studies provide evidence that if nurse prescribers, as just one part of the multidiciplenary intervention, can not provide evidence of improvement in HbA1c levels we would not expected to see any improvement when they replaced doctors and work alone. This finding is supported by non-significant improvement in HbA1c levels in those studies where nurses worked indipendently. In addition, the result of this study cannot be attributed to the difference in the way that nurses and doctors follow an algorithm. It is because none of the interventions included providing

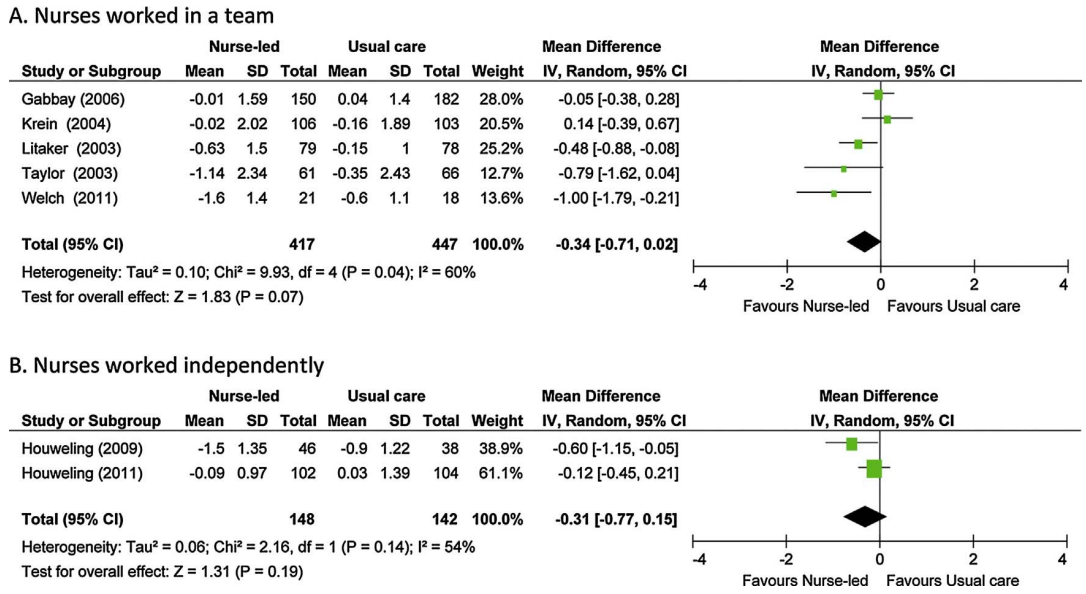

Fig. 2. Forest plot of the effect size for the impact of nurse prescribers comparing to usual care on HbA1c levels using random effects model.
A: Nurses worked in a team; B: Nurses worked independently.

algorithms for usual model of care, while in all intervention arms, nurses followed algorithms or protocols for prescribing medications.

There were four studies in which nurse prescribers worked independently of doctors, and were compared directly to a doctor-led service without a nurse prescriber. All four studies showed that the glycaemic control achieved by nurses was comparable to that achieved by doctors (Houweling et al., 2009, Houweling et al., 2011, Ishani et al., 2011, Lenz et al., 2002). Among this group, in two studies from Netherlands (conducted by the same author), the nurses followed a detailed treatment plan based on the Dutch College of General Practitioners and those from Dutch Diabetes Federation (Wiersma et al., 1999). In these studies, nurses were allowed to prescribe 14 different medications and to adjust dosage for a further 30 medications. They were also allowed to order laboratory tests. However, the study arms were not designed to differ in regard to the overall intensity of management or to the use of other healthcare professionals. Thus, these four studies provide robust evidence that standardised care delivered by nurse prescribers following detailed protocols is a good alternative to usual care delivered by doctors.

Existence of moderate heterogeneity between studies and the presence of publication bias in reporting the effects of the nurse prescribers on glycaemic control indicates that the efficacy of the nurse prescribers clinics on diabetes management needs to be interpreted with caution. It should also be noted that all studies were performed in two countries – the USA and Netherlands, with no studies from developing countries, where the majority of people with diabetes live and where a shortage of physicians results in a heavy workload and poor glycaemic control. Further studies are needed to elucidate the potential role of nurses on diabetes management, particularly in developing countries.

Previous studies showed that nurses are superior to physicians, with respect to health care cost (Arts et al., 2012, Potera, 2012). Therefore nurse-led clinics with the authority to prescribe medications may be a good alternative to the usual model of care particularly when there is limited access to physicians or where the cost is high. Furthermore, other *meta*-analyses have demonstrated the positive effect of nurses on diabetes related complications such as hypertension (Clark et al., 2010, Martinez-Gonzalez et al., 2014). It is possible that nurses could be efficacious in improving diabetes concomitant complications such as hypertension as well as glycaemic control.

There are a number of strengths to our systematic review. First, this is the first systematic review evaluating the effect of those nurse-led clinics where nurses were involved in prescribing medication. We conducted a systematic search for all RCTs from 1980 to 2016 and contacted all authors to obtain or clarify further information where needed.

There are also some limitations to this study. First, two studies failed to report change in HbA1c or provide the baseline and final HbA1c to enable us to calculate the effect size. Thus, we discussed these studies in a narrative sense but were unable to include them in the *meta*-analysis. Reassuringly, they had similar qualitative findings to the two studies with the relevant data. Second, the number of intervention studies was small, and studies varied in many aspects including sample size, study protocols and also the components of usual care delivered in different settings. Third, the inherent difficulties in blinding nurses and other staff affected the quality score of the study by causing concealment bias. Fourth, there was no reporting of adverse events, particularly hypoglycaemia, minimisation of which is an important component of diabetes care, and may have varied between study arms. Fifth, all studies were conducted in two developed countries. Sixth, extensive training and support was provided to the nurses to facilitate their role in prescribing. If this had not been provided, the results may have been different. Last, the legal and cultural implications of nurses prescribing medications vary considerably around the world, and might mean that in some settings there is very limited acceptability of this by other health professionals and by patients. Consequently, applying the findings of this study to other countries may have limitations.

5. Conclusion

This systematic review and *meta*-analysis showed that adding nurse prescribers to a usual care health team did not improve glycaemic control. However, when nurse prescribers were compared directly to physician prescribers, they achieved equally good glycaemic outcomes. This finding may be valuable in the situation where there is a shortage of doctors or resources and nurses can take on the responsibility of prescribing following algorithms and protocols. This intervention merits assessment in resource-limited settings, where it could substantially increase the reach of diabetes services.

Conflict of interest

None declared.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijnurstu.2017.08.018.

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Supplementary table: Search strategy for Medline

	Mesh terms or key terms	Number of articles
1	exp Diabetes Mellitus, Type 2/	90791
2	exp Diabetes Complications/	106411
3	diabet*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	458292
4	exp Insulin Resistance/	58135
5	Blood Glucose/	132806
6	Hemoglobin A, Glycosylated/	24027
7	insulin*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	319266
8	exp Hypoglycemic Agents/	199511
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	703978
10	nurses/ or nurse clinicians/ or exp nurse practitioners/ or exp nurses, community health/ or nurses, public health/ or exp nursing staff/	106446
11	exp Nursing Care/	119313
12	nurs$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	555097
13	10 or 11 or 12	555600
14	physicians/ or general practitioners/ or hospitalists/ or physicians, family/ or physicians, primary care/ or physicians, women/	87037
15	exp General Practitioners/	2398
16	(family physician* or doctor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	96446
17	14 or 15 or 16	167998

18	exp Primary Health Care/	83284
19	exp Patient Care Team/	56289
20	exp Ambulatory Care Facilities/	44772
21	House Calls/	2543
22	Subacute Care/	755
23	(outpatient adj (clinic* or department*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	34367
24	(house call* or home visit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7133
25	titration clinic*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	15
26	exp Patient Care Management/	554546
27	exp Patient Care Planning/	53123
28	exp patient education/	71963
29	exp patient participation/	18654
30	exp ambulatory care information systems/	1159
31	exp feedback/	43439
32	exp Decision Making, Computer-Assisted/ or exp Decision Support Systems, Clinical/	105083
33	exp reminder systems/	2396
34	exp practice guidelines/	84901
35	exp Guideline/	26234
36	exp medical audit/	15356
37	exp medical records/	89744
38	"outcome and process assessment".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	22352

39	(remind* or motiv* or counsel* or self manage* or uncontrol*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	242252
40	((Patient* or program*) adj3 (educat* or manage* or train* or teach*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	282474
41	Patient Care/	7528
42	Guideline Adherence/	22480
43	exp Ambulatory Care/	46507
44	exp Behavior Therapy/	54697
45	Counseling/	28597
46	Motivation/	51241
47	health promotion/	55486
48	exp health education/	138586
49	(reward* or incentive*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	55685
50	self care/	24622
51	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50	1537745
52	13 or 17	706092
53	9 and 51 and 52	6702
54	randomized controlled trial.pt.	392215
55	controlled clinical trial.pt.	89261
56	Randomized Controlled Trial/	392215
57	Random Allocation/	83051
58	Double-Blind Method/	129734
59	Single-Blind Method/	20321

60	clinical trial.pt.	492871
61	exp Clinical Trial/	806250
62	Placebos/	32869
63	placebo$.ti,ab.	156347
64	random$.ti,ab.	683180
65	Research Design/	80693
66	randomly.ti,ab.	205011
67	54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66	1322923
68	animal/ not humans.sh.	3934731
69	53 and 67	1200
70	69 not 68	1200
71	limit 70 to (english language and yr="1980 -Current")	1139

Appendix 1. A description of training that nurses received in the intervention group

Author	Year	Type of training that nurses have received
Houweling	2009	Nurses were trained to follow a detailed treatment and management protocol aimed at optimising glycaemia, blood pressure, and lipid profile. These protocols are based on the guidelines from the Dutch College of General Practitioners and those from the Dutch Diabetes Federation.
Litaker	2003	Nurse training preceded the study enrolment phase with instruction by the investigator team on rationale for and application of treatment algorithms to patient care.
Houweling	2011	One week of training on a detailed treatment and management protocol aimed at optimising glucose, blood pressure and lipid profile regulation and eye and foot care in patients with diabetes. The protocol was based on the guidelines published by the Dutch College of General Practitioners and on those from the Dutch Diabetes Federation.
Gabbay	2006	Registered nurses were trained at the Penn State Diabetes Centre through a series of seminars with a dietician, a certified diabetes nurse educator and an endocrinologist. The nurse implemented specific diabetes management algorithms under the supervision of the patient's primary care physician.
Welch	2011	No information.
Lenz	2002	No information
Taylor	2003	The nurse-care managers, selected for having extensive experience in managing lipids and hypertension, underwent several days of training on the Kaiser Permanente protocols for diabetes and cholesterol. For hypertension and depression, nurse care managers attended diabetes group classes and shadowed some of the diabetes care managers and physicians treating patients with diabetes before beginning the project.
Ishani	2011	No information

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Chapter 8

Discussion and conclusion

8.1 Overview of the main findings

This thesis had three main objectives. First, to understand the contribution of diabetes risk factors in association between diabetes and disability. Second, to explore diabetes management in LMICs and third, to review potential strategies to improve diabetes management in LMICs. The key findings of each chapter are summarised below.

8.1.1 Diabetes is associated with higher risk of disability, while diabetes risk factors have a major contribution to this association

Chapter 3 shows that diabetes is associated with a 67% increased risk of disability. We investigated the contribution of several risk factors such as age, sex, education, BMI, history of cardiovascular disease (CVD), asthma-like symptoms and depression to the association between diabetes and disability. We showed that the prevalence of disability is higher in women as compared to men. We have also shown that the total contribution of the risk factors mentioned above to the association between diabetes and disability was 40%. Among the risk factors, high BMI and history of CVD explain a large proportion of the association between diabetes and disability. The contribution of obesity in the association of disability with diabetes can be explained from different perspectives; obesity *per se* is one of the main cause of immobility, as obese people have difficulties in walking and transferring (1). Furthermore, obesity causes chronic systemic inflammation which is related to insulin resistance (2) . It has been shown that increased level of inflammatory biomarkers and insulin resistance can result in peripheral neuropathy, and lower muscle strength which may then lead to disability. Having a history of CVD can directly affect the physical mobility of people with diabetes.

Chapter three also provides some evidence that the association between diabetes and disability differs by ethnicity. We observed a stronger association between diabetes and disability among

African Creoles than among South Asians. Ethnic disparity in the association of diabetes with disability and in contributory risk factors to this association may be explained by genetic and environmental factors such as lifestyle. Sarcopenia, which is characterized by decreased muscle mass, is associated with less functional performance and increased risk of physical disability (3). Previous studies showed that in Africans there is more intramuscular fat than in other ethnicities, and that this contributes both to sarcopenia and to whole body insulin resistance, leading to a strong association between diabetes and muscle weakness (4-6). In other ethnicities, where impaired beta cell function or hepatic insulin resistance may be more prominent causes of diabetes, the link between diabetes and muscle function might be expected to be weaker.

Another factor explains these results might be related to cultural differences between African Creoles and South Asians. In this study, participants self-reported their disability, and thus it is possible that cultural differences relating to the perceived importance of being independent in older age may affect their response in the questionnaire. However, we could not find support for this as there was relatively similar prevalence of disability among South Asians and African Creoles. This study is one of the first studies to provide evidence regarding the existence of ethnic disparity in the association between diabetes and disability. The role of ethnicity in association between diabetes and disability needs to be explored in futures studies.

8.1.2 Reaching glycaemic, blood pressure and lipid targets is challenging for patients with diabetes in LMICs

Chapter four of this thesis reported one of the first assessments of trends in target achievement among people with diabetes in a LMIC namely Mauritius. The main finding of this study is that the proportion of participants reaching all three ABC targets (HbA1c<7% (<53

mmol/mol), LDL<2.59 mmol/L (100 mg/dL) and blood pressure<140/90 mmHg) was only 2.9% in 2009 and reached 6.7% in 2015. Using the blood pressure target of <130/80 mmHg, the proportion of people reaching all three targets was only 1.6% in 2009 and 5% in 2015.

Despite the fact that the proportion of participants reaching all three ABC targets of ADA in Mauritius is far from that recommended by guidelines, these proportions are comparable to other countries (7). For example, a national survey in Taiwan showed that the attainment of all ABC goals increased by 4.1% in 2006 to 8.6% in 2011 (8). Studies in high income countries such as the US also revealed that only a small proportion of patients with diabetes are able to reach to all three ABC targets (9-13). A study based on the National Health and Nutrition Examination Survey data showed that the proportion of participants reaching all ABC targets was 7.0% in 1999 and increased to 12.2% in 2006 (9). Increases in the percentage of patients who reach the targets highlighted the increasing efforts to pursue optimal treatment of diabetes in different countries. Nevertheless, the very small proportion of people meeting all ABC targets in a variety of studies also indicated that meeting the ABC targets is very challenging for patients with diabetes.

8.1.3 Narrowing in some of the health inequalities in people with diabetes

In chapter four, we have shown that over a 6-year period (from 2009 to 2015) in Mauritius, glycaemic and blood pressure control improved, and total and LDL cholesterol control remained unchanged. Improvements in HbA1c levels were mainly observed where the control was the poorest in 2009. Significant improvement in glycaemic control was seen in women but not in men. At baseline, women had a higher mean level of HbA1c than men. We also observed improvements in HbA1c in people with a lower education but not in those with a higher level of education. All of these findings indicate a narrowing of health inequalities since 2009, which

might reflect the higher focus of intervention in those groups with poor control of glycaemia at baseline and also greater efficiency of interventions on those groups with poor control of HbA1c than those with HbA1c close to targets.

Improvement in blood pressure and glycaemia in people with diabetes in Mauritius can be attributed to three factors. First, increasing use of medication, though for glycaemia, it is notable that the increase was mainly in the use of oral medication, not insulin. Second, increasing public awareness about diabetes and changing life style, and third, the addition of diabetes nurse educators in a number of clinics throughout the country, as discussed in chapter four.

8.1.4 Use of glucose lowering medications has increased and diabetes treatment become more complex and intensive

In chapter four, where we used data from two national surveys in Mauritius, we observed an increase in the proportion of patients using GLMs over time. In chapter five, we extended this work by also looking at different types of GLMs in a number of countries using real world evidence data.

Both survey and the real world evidence data demonstrated increases in the proportion of patients using glucose lowering medications. In chapter five we specifically explored the trends in treatment pattern of eight classes of glucose lowering medications (including metformin, sulphonylureas, meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1R agonist), alpha glucosidase inhibitors, sodium-glucose co-transporter-2 (SGLT2) inhibitors) and insulin from 2006 to 2015.

Our findings indicate that, first, there was a consistent pattern in all 10 countries which demonstrated that treatment patterns have become more aggressive and complex with increased use of triple therapy and insulin and decreased mono and diet therapy. Second, there was significant uptake in use of new classes of glucose lowering medications such as DPP-4 inhibitors, GLP-1R agonists and sodium-glucose co-transporter-2 inhibitors in many sites. However, some countries are still not using these medications for treatment of diabetes. Third, metformin was the most popular glucose lowering medications, followed by sulphonylureas, which is in line with international diabetes guidelines.

Although diabetes treatment was in line with diabetes guidelines and treatment patterns have become more aggressive and complex, we did not observe improvement in glycaemic control. Lack of improvement in glycaemic control could be related to inadequate prescription, poor adherence to such prescriptions and higher costs of new drugs. Moreover, it is suggesting that the current patterns of use of GLMs and antihypertensive medications are not addressing the underlying problems in diabetes. It should be noted that different countries with varying health care systems might experience different pattern in diabetes control. For example in the Mauritius study, we have observed improvement in glycaemia at least in some sub-groups which might be related to increase in knowledge and applying nurse educators in the health care system of the country.

8.1.5 There is a need for research on the effectiveness rather than efficacy of new GLMs at the population level

While most studies are now focusing on proving efficacy of new drugs using clinical trials, there are fewer studies that have examined the effectiveness of new drugs at the population level. Also there are few studies evaluating whether the introduction of new classes of

medications has resulted in improvement in glycaemic control at the population level. We emphasize the need for more studies using real world evidence with a focus on adherence to and effectiveness of new drugs.

It is also worth mentioning that most of the diabetes guidelines are based on RCTs or meta-analyses derived from those RCTs. A considerable effort has been made into developing evidence based guidelines, but most guidelines consider study design and the internal validity of the studies to define high quality evidence, which makes RCTs rank higher than observational studies irrespective of sample size, study conduct and the generalizability of such studies to the total population (14). Considering the fact that guidelines are expected to be applicable for general populations, the evidence based resources used to develop for guidelines are recommended to obtain not only form RCTs, but also from observational studies. The reason is that observational studies provide more realistic and achievable targets than those obtained from RCTs.

8.1.6 There was an improvement in lipid management from 2006 to 2015

Chapter six demonstrated a decline in mean cholesterol levels in line with an increase in statin use across the countries from 2006 to 2015. The greatest reductions in mean cholesterol levels were mainly observed in those sites with the highest mean cholesterol levels in 2006. In recent years, most studies have indicated increased use of statins and decreases in cholesterol levels. The increase in the use of statins and decrease in cholesterol levels reflects the benefit of statin use both for primary and secondary prevention of CVD events in patients with diabetes.

8.1.7 Anti-hypertensive treatment approaches shifted from using ACE inhibitors towards using more ARBs

In chapter six we have shown that ACE inhibitors were the most popular antihypertensive medication in most sites which is consistent with most guidelines. We also observed a shift from prescription of ACE inhibitors to ARBs from 2006 to 2015. According to guidelines (15, 16), ACE inhibitors and ARBs (if intolerant to ACE inhibitors) are the first line antihypertensive medications for patients with diabetes. Meta-analyses directly comparing ACE inhibitors and ARBs found that both had similar effects in reducing mortality and cardiovascular events (17). However, ARBs have a better side effect profile than ACE inhibitors in regard to cough, which is reported in 44% in those on ACE inhibitors compared to only 4% for those on ARBs (18). Thus, an increase in use of ARBs can be probably explained by the fewer side effects caused by this class of medication as compared to ACE inhibitors.

8.1.8 Change and inconsistency in the blood pressure targets suggested by guidelines could result in no improvement in hypertension management

Blood pressure management in hypertensive individuals with diabetes has undergone some significant changes over the last decade. The ADA targets for management of hypertension among patients with type 2 diabetes has changed over time. In 2006, the ADA guidelines recommended the blood pressure target at 130/80 mmHg for patients with diabetes which was based on several large studies demonstrating that maintaining blood pressure levels below 130/80 mmHg reduced cardiovascular events in patients with diabetes. Then, a meta-analysis of mortality risk associated with the use of intensive blood pressure targets vs. standard targets in patients with type 2 diabetes reported no benefit or even harm when the lower blood pressure targets were achieved (19). Thus, there was a modification to recent guidelines recommending

a less stringent blood pressure target i.e. 140/90 mmHg, with emphasis on individualisation of blood pressure management with regard to age and existence of other risk factors. We believe that such change in the blood pressure targets has resulted in lack of improvement in the proportion of patients with BP<140/90 mmHg. Despite the fact that the only changes to targets have been in regard to 130/80 mmHg, it is concerning that the percentage of people with BP >140/90 mmHg increased in most countries. This suggests that raising BP targets from 130/80 to 140/90 can have the undesired effect of increasing the number of people failing to achieve the 140/90 target, and this should be considered in future guideline deliberations.

Another explanation for lack of improvement in blood pressure control is the variability in BP targets suggested by different guidelines. The ADA guidelines recommend the blood pressure target at <140/90 mmHg (20) for patients with diabetes, while the American Association of Clinical Endocrinologists/American College of Endocrinology AACE/ACE (21) and IDF (1) recommended the blood pressure target at <130/80 mmHg. National guidelines for Australia and Japan also recommended the blood pressure target at <130/80 mmHg in 2015 (22, 23).

8.1.9 Nurse-led prescribing services are an alternative approach for glycaemic control where there is limited access to doctor-led services

In chapters four and five we have shown that controlling glycaemia is one of the major challenges in diabetes management in LMICs. One of the reasons for that issue is shortage of health care resources in LMICs. In chapter seven, we examined whether implementing nurse prescribers in the health care systems could potentially improve glycaemic control in diabetes patients. We reported that when nurse prescribers were compared directly to physician prescribers, they achieved equally good glycaemic outcomes. This finding may be valuable in the situation where there is a shortage of doctors or resources and nurses can take on the

responsibility of prescribing following algorithms and protocols. Of note, one of the limitations of this study was that all the clinical trials were conducted in high income countries, so although the findings may be most appealing for implementing in LMICs, no studies have tested it in the LMICs yet. The finding of this study suggesting that applying nurse prescribers can be one of the potential ways to improve diabetes outcomes and improving diabetes care particularly in those group with poor control of diabetes such as African Creoles. From 2014, 58 diabetes nurses were introduced to selected diabetes clinics in Mauritius with focus on educating people about a healthy lifestyle and improving self-management of diabetes. While, those nurses did not have the role of prescribing but we observed improvement in glycaemic control and blood pressure in Mauritius. Therefore, there is potential to see more improvement in diabetes control by applying nurse prescribers in Mauritius.

8.1.10 Potential cost-effective strategies to improve diabetes management

There are several cost-effective strategies that are associated with improvement in diabetes management. Quality improvement strategies are strongly associated with improving diabetes management and usually target health care system, health care providers and patients. QI strategies that target the health care system include any changes to the health system in diagnosis, treatment or follow-up. This include changes in the referral system, applying evidence-based guidelines and reducing financial barriers. One of the cost-effective strategies, particularly applicable in LMICs, could be adding a team member such as nurse, pharmacist, nutritionist, podiatrist, implementing a multidisciplinary team and expansion of professional role for example a nurse or pharmacist becoming involve in monitoring of the patient or adjusting drug regimens. Pharmacists are considered to be the most accessible health care providers, as no appointments are required to see them. As such, they are well placed to play a significant role in the care of patients with type 2 diabetes. Pharmacies provide a range of products/services such as prescription and non-prescription medication, blood glucose meters

and testing strips, needles and swabs, dietary supplements, medication review, vaccination, unit dose dispensing, needle exchange, point of care testing and disposal of unwanted medicines (24). A systematic review and meta-analysis has shown that pharmacist-led self-management interventions are beneficial for diabetes patients by improving HbA1c levels, blood pressure, BMI, and self-management skills (25). It has also been shown that pharmacist interventions have positive influence on metabolic control, medication adherence, and quality of life of patients with type 2 diabetes (26). Dieticians also play an essential role in effective management of diabetes. Their roles include helping in controlling weight, creating a meal plan, tracking blood glucose and counting carbohydrates and reading food labels. Some high income countries are now taking advantage in applying diabetes nurse educators in improving diabetes income. Diabetes nurse educators' responsibilities include identifying barriers to care, care coordination and transition, nutrition therapy, medication therapy and management, hypoglycaemia management and prevention, monitoring glycaemic control, and professional education (27, 28). Diabetes educators play a key leadership role in creating interdisciplinary teams and providing diabetes self-management education and support. Diabetes self-management education and diabetes self-management support are two critical elements of diabetes care which are cost-effective and are strongly associated with decreasing the complications of diabetes. The aim of DSME is to facilitate the knowledge, skill, and ability necessary for diabetes self-care. The main aim of DSMS is to provide ongoing support for people with diabetes in order to implement and sustain the behaviours needed to manage their diabetes (29).

Further to the changes to the health care systems, there are some other strategies that target the health care providers which mainly focus on educating the clinicians (30).

Clinical inertia and diabetes management

One of the main challenges in diabetes management is clinical inertia. Clinical inertia is defined as the failure to establish appropriate targets and intensification of treatment to achieve treatment goals. One systematic review has shown that the median time to initiate treatment intensification after HbA1c is above the target is more than a year (31).

8.2 Strength and limitations

The strengths and limitations pertaining to each study are summarised in the respective sections of each individual publication. Here, I will discuss the limitations and key strengths of each of the three main data sources used for this thesis.

Chapters three and four were based on national surveys conducted in Mauritius. Given the careful sampling strategies and high response rates, these population based studies are representative samples of Mauritius population. There were several limitations that should be acknowledged. There were differences in some general characteristics of the participants, such as duration of diabetes and BMI in the two surveys (2009 and 2015), that might have affected the outcomes. In addition, adherence to medication was not assessed in this study, and we relied on self-reported medication use. A further limitation of this study was that people with severe disability or major cognitive deficits would have been less likely to attend the survey, which might have resulted in selection bias.

The real world evidence study was one of the first studies looking at trends of diabetes management and use of medications in low and middle-income countries. Our data includes some countries that have a large number of people with diabetes, and for which there is currently very little information. The strengths of our study include the large sample size and the non-trial setting that the data represents. Clinical trials are conducted under strict conditions which do not necessarily represent real world situations where patients are managed less

rigorously. While individual services are not necessarily representative of the population within which they are located, they provide information on all attending patients, thus removing volunteer bias.

The aggregate nature of the data in the real world evidence study we collected is a limitation to our study, as it prohibits analysis of relationships between change in medication use, risk factors and change in HbA1c, blood pressure and lipid levels. We also cannot claim causality because the study does not have a longitudinal design and we used aggregate data not individual level data. In addition, generalising the results of this study to the health system of each country should be done very cautiously, because the majority of data was obtained from specialist care services. Furthermore, the variability in the nature of the services at the different sites might also influence the findings.

The systematic review and meta-analysis on the effect of nurse prescribers on glycaemic control was the first systematic review to evaluate the effect of those nurse-led clinics where nurses were involved in prescribing medication. We conducted a comprehensive systematic search in different data bases for all RCTs from 1980 to 2016. However, this study has some limitations. First, two studies failed to report change in HbA1c or provide the baseline and final HbA1c to enable us to calculate the effect size. Second, the number of intervention studies was small, and studies varied in many aspects including sample size, study protocols and also the components of usual care delivered in different settings. Third, the inherent difficulties in blinding nurses and other staff affected the quality of the studies by causing concealment bias. Fourth, all studies were conducted in two developed countries. Last, the legal and cultural implications of nurses prescribing medications vary considerably around the world, and may mean that in some settings there is very limited acceptability of this by other health professionals and by patients. Consequently, applying the findings of this study to other countries may be limited.

8.3 Implications and future direction

There are several clinical and public health implications from this work, along with implications for researchers. These are discussed below.

8.3.1 Clinical implication

This thesis has provided substantive evidence that people with diabetes have a higher risk of disability as compared to those without diabetes. This suggests that an evaluation of the disability status of diabetes patients could be included in the routine care that patients are receiving currently. It has been shown that obesity has a major contribution to the association between diabetes and disability, which suggests that weight management is one of the strategies which can reduce disability and improve the quality of life of people with diabetes. This thesis provides some evidence on the existence of ethnic disparity in the association between disability and diabetes with higher risk among those with African Creole ethnicity as compared to South Asians. Thus, from a clinical perspective, people with diabetes who are of African descent might have a higher risk of disability and this should be considered in treatment patterns and controlling risk factors for this group of patients.

The real world evidence study showed that increased complexity of therapy was not matched by a clear reduction in HbA1c levels which possibly can be explained by lack of adherence in prescribed medications. Thus, understanding the barriers for adherence of medications should be considered in treatment of patients with diabetes. One of the disadvantages of new glucose lowering medications is high cost, which also should be considered as one of the reasons for lack of adherence to medications among patients with diabetes. Therefore, it is suggested that the health care team consider all the barriers for adherence of medications and discuss the issues

of cost with patients when deciding about the prescription. This is particularly true for LIMCs, where cost might be one of the major issues for patients.

8.3.2 Public health policy implication

One of the major implications of this thesis is that there is a large gap between diabetes guidelines and real practice.

We recommend that policy makers, government and health care providers focus on improving the understanding of what causes this gap, and on identifying cost-effective measures of closing the gap. This includes strategies for ensuring that people with diabetes have access to healthcare professionals who can provide appropriate and evidence-based advice, and understanding the barriers to good medication adherence and developing strategies to improve adherence.

The increase in the risk of disability in people with diabetes also suggests that evaluating and preventing disability in patients with diabetes has to be added to diabetes guidelines. We also suggest that weight is one of the main contributors to this association, thus interventions targeting weight loss may be useful in reducing disability in patients with diabetes which may directly and indirectly reduce the costs of diabetes for both individuals and health care systems.

The survey in Mauritius has shown narrowing in health inequalities. This is encouraging as indicating that national policies are attempting to tackle health inequalities and narrow the gap between different groups.

We have shown that using nurse prescribers offer an alternative method of controlling glycaemia when there is shortage of doctors' forces. Thus, government and policy makers could take advantage of implementing nurse prescribers for controlling HbA1c where there is limited access to doctors' care.

8.4 Areas for future research

Although more than 80% of people with diabetes are living in LMICs, there is a dearth of data from these areas which makes it challenging to define needs and prioritise decisions. This is particularly challenging for those factors such as medication adherence which is highly affected by socio-economic status, access to health care and many other factors that vary considerably between high income countries and LMICs. Therefore studies from high income countries are not applicable to LMICs.

We recommend more research to be performed using a population-based design with a focus on the effectiveness of new diabetes drugs. Future research should focus on exploring the gap between the efficacy and the effectiveness of new drugs.

We recommended more research on the clinical relevance and applicability of the evidence used for developing guidelines and providing evidence on optimising diabetes management at the population level. We emphasize the need for more research in LMICs with regard to improving diabetes management, and identifying treatment barriers.

8.5 Conclusion

This body of work has added to the current evidence-base in the association between diabetes and disability and the factors that contribute to this association. These findings provide a basis for screening and suitable interventions in order to prevent disability in people with diabetes.

Furthermore, this thesis sheds lights on the translation of diabetes guidelines into actual practice. The gap between the real practice and the recommendation from guidelines may be attributable to poor adherence and also the high cost of new drugs.

We have shown that an alternative model of care, nurse prescribers, obtain similar glycaemic control in patients with diabetes. This finding may be of particular relevance where there is a shortage of doctors or the cost of care is an issue.

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Appendixes

Appendix 1: Response rate for Mauritius NCD surveys (2009, 2015 and 1998 cohort)

Appendix 2: Mauritius 2015 non- communicable disease survey

Appendix 3: Real World Evidence data sheet

Appendix 1_ Response rate for Mauritius 2009, 2015 and 1998 cohort surveys

Table 1. Response rate for Mauritius 2009 NCD survey

SURVEY CLUSTER	**INVITED**			**PARTICIPATED**			**RESPONSE RATE**		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Rose_Belle	159	162	321	110	143	253	69.2	88.3	78.8
Quatre_Soeurs	184	191	375	132	166	298	71.7	86.9	79.5
Tranquebar	163	177	340	127	144	271	77.9	81.4	79.7
China_Town	87	88	175	66	76	142	75.9	86.4	81.1
Quatre_Bornes	174	201	375	132	173	305	75.9	86.1	81.3
Terre_Rouge	170	205	375	138	169	307	81.2	82.4	81.9
Petit_Verger	184	175	359	140	156	296	76.1	89.1	82.5
Bambous	178	169	347	129	158	287	72.5	93.5	82.7
Floreal	178	197	375	134	178	312	75.3	90.4	83.2
La_Sourdine	182	193	375	141	172	313	77.5	89.1	83.5
Bel_Air	183	192	375	135	180	315	73.8	93.8	84.0
Chemin_Grenier	182	193	375	143	172	315	78.6	89.1	84.0
Plaines_Des_Roches	195	180	375	154	165	319	79.0	91.7	85.1
Plaines_Verte	102	97	199	79	92	171	77.5	94.8	85.9
Pamplemousses	192	193	385	146	187	333	76.0	96.9	86.5
La_Caverne	161	182	343	133	165	298	82.6	90.7	86.9
Roches_Noires	183	192	375	155	172	327	84.7	89.6	87.2
Mare_Gravier	143	177	320	135	145	280	94.4	81.9	87.5
Coromandel	163	147	310	128	146	274	78.5	99.3	88.4
Lallmatie	195	200	395	162	198	360	83.1	99.0	91.1
Engrais_Martial	142	160	302	131	156	287	92.3	97.5	95.0
Cite_Vallijee	166	155	321	154	154	308	92.8	99.4	96.0
TOTAL	**3666**	**3826**	**7492**	**2904**	**3467**	**6371**	**79.2**	**90.6**	**85.0**

Appendix 1_ Response rate for Mauritius 2009, 2015 and 1998 cohort surveys

Table 2. Response rate for Mauritius 2015 NCD survey

SURVEY CLUSTER	INVITED			PARTICIPATED			RESPONSE RATE		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Pamplemouses	168	250	418	160	246	406	95.5	98.4	97.1
Plaine Verte	130	150	280	124	140	264	95.4	93.3	94.3
Vallée des Prêtres	155	166	321	122	147	269	78.7	88.6	83.8
China Town	101	110	211	98	107	205	97.0	97.3	97.2
Goodlands	178	168	346	100	129	229	56.2	77.4	66.5
Bel Air	176	177	353	134	145	279	76.1	81.9	79.0
Mahebourg	167	171	338	157	165	322	94.	96.5	95.3
Rivière des Anguilles	167	200	367	154	194	348	92.2	97.0	94.8
Henrietta	160	170	330	152	154	306	95.0	90.6	92.7
Curepipe	161	220	381	151	209	360	93.8	95.0	94.4
Rose Hill	173	172	345	154	152	306	89.0	88.4	88.7
Petit Paquet	182	185	367	134	177	311	73.6	95.7	84.7
Petite Rivière	150	193	343	101	123	224	67.3	63.7	65.3
TOTAL	**2068**	**2332**	**4400**	**1741**	**2089**	**3829**	**84.2**	**89.6**	**87.0**

Table 3. Response rate for Mauritius 1998 NCD cohort

SURVEY CLUSTER	INVITED			PARTICIPATED			RESPONSE RATE		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Triolet	208	259	467	143	172	315	68.8	66.4	67.5
Rivière du Poste	135	162	297	101	122	223	74.8	75.3	75.1
Petit Raffray	128	209	337	93	142	235	72.7	67.9	69.7
Phoenix	105	139	244	77	115	192	73.3	82.7	78.7
Cité Vallijee	92	137	229	72	106	178	78.3	77.4	77.7
Rose Belle	153	181	334	132	157	289	86.3	86.7	86.5
Plaine Verte	112	118	230	83	89	172	74.1	75.4	74.8
Mangalkhan	98	160	258	64	130	194	65.0	81.3	75.2
Belvedère	169	186	355	122	149	271	72.2	80.1	76.3
TOTAL	**1200**	**1551**	**2751**	**887**	**1182**	**2069**	**73.9**	**76.2**	**75.2**

1

MAURITIUS 2015 NON-COMMUNICABLE DISEASES SURVEY
ENGLISH

SECTION 1: General demographics (all participants)

Have you participated in a previous survey?
No ☐ Don't know ☐
Yes ☐ if yes, which year?.....

SURVEY No. ☐☐☐☐☐☐

Site name:.....

Survey Site No: ☐☐ Team.....

1. Demography

Surname ....

Given name(s) .....

Maiden name: ……..... Gender Male 1

Address (Street)..... Female 2

(Locality).....

National Identity Number

☐☐☐☐☐☐☐☐☐☐☐☐☐

Day Month Year

Date of birth: ☐☐ ☐☐ ☐☐☐☐

If date of birth is not known, what is the estimated age of participant? ☐☐

Ethnic group: Hindu **1** Muslim **2** Creole **3** Chinese **4** Others **5** *Specify:* ..... ☐

2. Glucose tolerance status: How many hours since last food or drink (except water)? Hours. ☐☐

Women

2a. Are you currently pregnant?

1) Yes
2) No
3) Don't Know ☐

2b. Have you ever been told by a doctor or a nurse that you have diabetes?

1) Yes **➔(Go to Q2c)**
2) No **➔(Go to blood pressure test)** ☐

Men **(NB: There is no Q2a for Men)**

2b. Have you ever been told by a doctor or a nurse that you have diabetes?

1) Yes **➔ (Go to Q3a)**
2) No **➔(Go to blood pressure test)** ☐

3a.How old were you when you were first told that you had diabetes?

(Enter age in years in box) **➔ Go to Q4** ☐☐

Women

2c. Was your diabetes first diagnosed when you were pregnant?

1) Yes **➔(Go to Q2d)**
2) No **➔ (Go to Q3a)** ☐

2d. Has a doctor ever told you that diabetes continued immediately after the end of any pregnancy?

1) Yes **➔(Go to Q3b)**
2) No **➔(Go to Q2e)** ☐

2e. Has a doctor ever told you that diabetes developed again at a time that you were not pregnant?

1) Yes **➔(Go to Q3c)**
2) No **➔(Go to Q3d)** ☐

3a. How old were you when you were first told that you had diabetes?

Enter age in years in box **➔(Go to Q4)** ☐☐

3b.How old were you at the end of that pregnancy?

Enter age in years in box **➔(Go to Q4)** ☐☐

3c. How old were you when you were told that your diabetes had come back?

Enter age in years in box **➔(Go to Q4)** ☐☐

3d. Do you still have diabetes?

1) Yes **➔(Go to Q4)**
2) No **➔(If No, go to blood pressure test)** ☐

4. What is your present treatment for diabetes

None	1
Diet only	2
Herbal	3
Tablet	4
Insulin	5
Tablet & Insulin	6

☐

Proceed to Blood Pressure Station and then Blood Collection Station

5. Blood pressure

Cuff Size
Normal = 1
Obese = 2

1st Reading: Systolic (mmHg) ☐☐☐

Diastolic ☐☐☐

Pulse ☐☐☐

2nd Reading: Systolic (mmHg) ☐☐☐

Diastolic ☐☐☐

Pulse ☐☐☐

3rd Reading: Systolic (mmHg) ☐☐☐

Diastolic ☐☐☐

Pulse ☐☐☐

6. FASTING PLASMA GLUCOSE (mmol/l) ☐☐.☐

NB: the OGTT is NOT PERFORMED if either 1, 2, 3, or 4 are true

1. If fasting glucose > 13 mmol/L
2. Participant has known diabetes AND taking oral medication
3. Participant is taking insulin
4. If the woman is pregnant.

7. TWO HOUR PLASMA GLUCOSE (mmol/l) ☐☐.☐

CHECKLIST

Fasting specimen ☐

2-hour specimen ☐

Urine collected ☐

Glucose load given (1=Yes, 2=No) ☐

If No, please indicate why below

Fasting glucose > 13 mmol/L ☐

Diabetes (Known DM and on medication) ☐

Pregnant ☐

Time glucose given ☐☐☐☐

Time 2 hour sample taken ☐☐☐☐

4

SECTION 2: Physical Examination (all participants)

1. Physical examination

Obs-ID

Height(cm)

Weight(kg)

2. Waist

1) Waist (cm) 2) Waist (cm) 3) Waist (cm)

1) Hip (cm) 2) Hip (cm) 3) Hip (cm)

Obs-ID

3. ECG

Completed

Not completed

Not applicable (age <35)

SECTION 3: Medical history (all participants)

Obs No: ☐☐☐

1. Medical history A

a) Has a doctor ever told you that you have **high blood pressure**?

Yes 1
No 2
Don't know 3 ☐

b) If yes, are you currently taking drugs for high blood pressure?

Yes 1
No 2
Don't know 3 ☐

c) Please, specify……

d) Has a doctor ever told you that you have high cholesterol?

Yes 1
No 2
Don't know 3 ☐

e) If yes, are you currently taking drugs for high cholesterol?

Yes 1
No 2
Don't know 3 ☐

f) Please specify……

g) Have you ever suffered from or experienced a stroke or any heart problems. Heart problems include angina, heart attack, heart bypass operation, an angioplasty or stent?

Yes 1
No 2 (**Skip to Medical History B)**
Don't know 3 ☐

h) Have you ever been told by a doctor or nurse that you have **angina** (chest pain during physical activity relieved by nitroglycerin)?

Yes 1
No 2
Don't know 3 ☐

i) Have you ever been told by a doctor or nurse that you have had a heart attack (myocardial infarction due to coronary artery disease)?

Yes 1
No 2
Don't know 3 ☐
If yes, ***Enter the year in box***. ☐☐☐☐

j) Have you ever been told by a doctor or nurse that you have had a stroke (brain infarction or brain hemorrhage)?

Yes 1
No 2
Don't know 3
If yes, ***Enter the year in box***.

k) Have you ever had a heart bypass (coronary) operation (includes coronary bypass)?

Yes 1
No 2
Don't know 3
If yes, ***Enter the year in box***.

l) Have you ever had a coronary angiography with stent (includes 'coronary angioplasty', 'coronary stent', 'balloon')?

Yes 1
No 2
Don't know 3
If yes, ***Enter the year in box***.

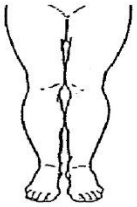
2. Medical history B

a) Have you had a lower limb (leg) amputation?

Yes 1
No 2

a) Specify level (indicate on diagram with a cross).

Above knee 1
Below knee 2
Toes 3



b) Are you currently or have been previously undergoing kidney dialysis?

Yes 1
No 2
Don't know 3

c) Have you had a kidney transplant?

Yes 1
No 2
Don't know 3
If yes, ***Enter the year in box***.

3. Cancer

a) Have you ever had cancer?

Yes 1
No 2 (**Skip to Q 4)** ☐

b) If yes, which if the following cancers have you had?

Breast ☐
Ovary ☐
Endometrium ☐
Cervix ☐
Prostate ☐
Colon ☐
Skin ☐
Lung ☐

c) Any other, specify ……Other ☐

4. Family History

a) Has anyone in your family ever had **diabetes**?

Yes 1
No 2
Don't know 3 ☐

b) If yes, please put a tick for each affected relative.

Mother ☐ Father ☐ Brother ☐ Sister ☐ Daughter ☐ Son ☐ Other ☐

c) Has anyone in your family had any heart or stroke problems?

Yes 1
No 2
Don't know 3 ☐

d) If yes, please specify which family members and the age of onset in the family member?

Example: If 3 of your sisters had heart attacks at the age of 35 (first column), 42 (second column) and 58 (second column) respectively, you have to put one tick in the first and two ticks in the second columns.

relative	Age groups		
	< 40 years	40-60 years	>60 years
Example: sister	✓	✓ ✓	
Grand-parents			
Mother			
Father			
Brother			
Sister			
Child			
Other			

5. CIGARETTE SMOKING

a) Do you smoke cigarettes, cigar or pipe?

Never	1 (Go to question 6)
Ex-smoker (for ≥ 3 mths)	2 (Go to question 5b)
Currently a smoker	3 (Go to question 5b)

b) For **current** and **Ex-smokers**, how many cigarettes, cigar or pipe do/did you smoke?

Number: _____per day

Number: _____per week

c) What year did you start smoking?

d) For **Ex-smokers only,** What year did you quit smoking?

6. ALCOHOL

a) How often do you drink (beer, wine or spirits e.g. Rhum)?

Never	1 (**Skip to Question 6**)
Ex-drinker (for > 6 mths)	2
Once/week or less often	3
2-3 days per week	4
4 or more days/week	5

b) How many alcoholic drinks (beer, wine or spirits e.g. Rhum) do you drink per day on average?

(1 drink = glass of beer or glass of wine or "nip" or spirits)

(1 bottle of beer = 2 drinks)

None	1
≤ 2 per day	2
3-4 per day	3
5 per day	4
≥ 5 per day	5

c) What kind of alcohol did you most commonly drink? (mark more than one if required)

Beer	1
Wine	2
Rhum//Whisky/other spirits	3
Combination	4

7. TV VIEWING

We are also interested in finding out about the time that people spend sitting as part of their everyday lives. This part of the survey is about particular activities you did over the last week whilst sitting. We want you to recall the time over the week not one day.

For the activity listed, answer two questions:

1. *During the last week, how much time in total did you spend on each activity on **week days** (possibly Mon-Fri)?*
2. *During the last week, how much time in total did you spend on each activity on **non-week days (weekends)** (possibly Sat-Sun)?*

Please estimate the total time during the last week that you spent sitting for watching TV or DVDs or playing games on the computer/TV or using a computer for non-work purposes (e.g. surfing the internet). This is when it was the main activity that you were doing; for example you would not include time when the television was switched on and you were preparing a meal.

Week days **(In hours and / or minutes)**

Hours ☐☐

Minutes ☐☐

Weekend **(In hours and / or minutes)**

Hours ☐☐

Minutes ☐☐

8. Education

a) Level of education achieved

None	1
Primary (Up to Std V)	2
Primary CPE	3
Secondary (Form I – IV)	4
Secondary SC	5
Secondary HSC	6
Tertiary	7

☐

b)Total number of years of full time education Years ☐☐

9. Occupation

a) What is your main occupation group? ☐

MANAGERS AND ADMINISTRATORS Magistrate, Farm Manager, General Manager, Director of Nursing, School Principal	1
PROFESSIONALS Scientist, Doctor, Registered Nurse, Allied Health Professional, Teacher, Artist, Engineer, Accountant	2
ASSOCIATE PROFESSIONALS Technician, Manager, Youth Worker, Police Officer, Program Administrator	3
TRADESPERSONS AND RELATED WORKERS Hairdresser, Gardener, Florist, Mechanic, Machinist, Cook	4
CLERICAL AND SERVICE WORKERS I Secretary, Personal Assistant, Flight Attendant, Law Clerk	5
CLERICAL, SALES AND SERVICE WORKERS II Typist, Word Processing/Data Entry Operator, Receptionist, Child Care Worker, Nursing Assistant, Hospitality Worker, Sales Clerk	6
CLERICAL, SALES AND SERVICE WORKERS III Filing/Mail Clerk, Parking Inspector, Sales Assistant, Telemarketer, Housekeeper	7
INTERMEDIATE PRODUCTION AND TRANSPORT WORKERS Sewing Machinist, Machine Operator, Bus Driver	8
LABOURERS AND RELATED WORKERS Cleaner, Factory Worker, General Farm Hand, Fast Food Cook	9
STUDENT	10

b) If unemployed / housewife / retired

please specify previous occupation.....

c) If housewife, please indicate the occupation of husband

……

10. Monthly family income

Less than Rs 6500	1
Rs 6500 – 12999	2
Rs 13000 – 19999	3
Rs 20000 – 29999	4
>30,0000	5
Don't know	6

☐

11. Have you taken ANY prescription medications in the last 3 months for at least 2 weeks?

1) Yes ➔ (If Yes, Go to Q12)
2) No ➔ (If No, go to section 4)

☐

12. For each medication, please write the name of your medication, the number of tablets, capsules, doses of liquids or insulin you have taken each day and the strength of the medication below (please include all medications):

Name of tablet / capsule / liquid/ insulin	**TOTAL number of tablets / capsules / doses of liquid/ number of injections per day**	**Strength of each tablet / capsule / dose of liquid/ units per day**
Example: Metformin	*2*	*500 mg*
Example: Mixtard 30/70	*2*	*28 unit*

13. Have you taken aspirin (this includes Aspirin, Loprin, Astrix, Cartia, Aspin and Glyprin) regularly during the last 3 months for at least 2 weeks?

1) Yes
2) No

☐

11

14. How did the participant produce the list of medication (you can choose more than one option)? 1) Self report 2) Brought in medications 3) Brought in a list	☐

SECTION 4: Health utilisation, diabetes knowledge, attitudes and dietary habits (all participants)

OBS. ID ☐☐☐

A. Health service utilization

1. a) Have you ever attended any Mobile Clinic?

Yes 1
No 2
Don't know 3 ☐

b) If yes, specify where

In your locality 1
At your worksite 2
Other …… 3 ☐

2. How many times in the last 12 months did you visit a doctor? ☐☐☐

3. How many nights have you spent in hospital or private clinics in the last 12 months? ☐☐☐

B. Health Attitudes (all participants)

1. How would you grade your current health?

Excellent 1 ☐
Good 2 ☐
Average 3 ☐
Poor 4 ☐

C. Dietary habits (all participants)

1. Are you a .....?

Vegeterian (do not eat meat or fish) 1
Non-vegeterian 2 ☐

2. How many units of fruit do you eat daily?

Half 1
One 2
Two 3
More than two 4
None 5 ☐

3. How often do you eat pulses (dry peas, dry beans, lentils and chickpeas. Pulses do not include fresh green beans or peas) ?

Once daily 1
Twice daily 2
Once per week 3
2-3 times per week 4
Once a month 5 ☐

4. How often do you eat fish?

Once weekly	1
More than twice weekly	2
Once a month	3
Don't eat fish	4

5. How often do you eat wholemeal flour in the form of faratha/chapatti/bread?

Daily	1
2-3 times per week	2
Rarely	3
Don't eat	4

6. How frequently, on average do you eat meals or snacks at restaurants, café or in street (which were not prepared at home)?

Never	1
Not more than once per month	2
Not more than once per week	3
2 - 3 days per week	4
Most days of the week	5
Don't know	6

7. What type of fat do you (or the household cook) use most often for cooking?

Ration Oil	1
Unsaturated oil (e.g. soyabean, sunflower, olive oil)	2
Ghee	3
Margarine (unspecified)	4
Margarine (polyunsaturated)	5
Other, specify	6

8. How is your food usually cooked?

Boiled	1	
Baked	2	Meat .....
Fried	3	Fish .....
Steamed	4	Rice .....
Braised (Roussi / Fricassé)	5	Eggs.....
Other (specify… …….)	6	Vegetables .....

9. *How many portions of vegetables (cooked/raw; including salads) do you usually have daily with your main meals?

None	1	Lunch
One	2	
Two	3	
More than two	4	Dinner

10. Do you use any of the following "special products"?

a.	Yes	1
b.	No	2
c.	Don't know	3

Vitamin/Mineral Supplement
Dietary Herbal Products (La Tisane)
Low calorie product (artificial sweeteners, diet soft drinks, diabetic jams)
Protein supplements/high protein powder
High-fibre foods (wholemeal bread, high fibre breakfast cereals.)

* It is assumed that a normal portion of each vegetable is consumed. For example, if the participant reports eating two vegetables, then he is eating two 'serves' of vegetables.

SECTION 5:
A : Global Physical Activity Questionnaire (GPAQ) (all participants)

OBS-ID ☐☐

Next I am going to ask you about the time you spend doing different types of physical activity in a typical week. Please answer these questions even if you do not consider yourself to be a physically active person.
Think first about the time you spend doing work. Think of work as the things that you have to do such as paid or unpaid work, study/training, household chores, harvesting food/crops, fishing or hunting for food, seeking employment. *[Insert other examples if needed]*. In answering the following questions 'vigorous-intensity activities' are activities that require hard physical effort and cause large increases in breathing or heart rate, 'moderate-intensity activities' are activities that require moderate physical effort and cause small increases in breathing or heart rate.

	Questions	Response	
Activity at work			
1	Does your work involve vigorous-intensity activity that causes large increases in breathing or heart rate like *[carrying or lifting heavy loads, digging or construction work*] for at least 10 minutes continuously? *(USE SHOWCARD)*	Yes 1 No 2 *If No, go to Q 4*	☐
2	In a typical week, on how many days do you do vigorous-intensity activities as part of your work?	Number of days	☐
3	How much time do you spend doing vigorous-intensity activities at work on a typical day?	Hours : minutes	hrs mins ☐☐ ☐☐
4	Does your work involve moderate-intensity activity that causes small increases in breathing or heart rate such as brisk walking *[or carrying light loads*] for at least 10 minutes continuously? *(USE SHOWCARD)*	Yes 1 No 2 *If No, go to Q7*	☐
5	In a typical week, on how many days do you do moderate-intensity activities as part of your work?	Number of days	☐
6	How much time do you spend doing moderate-intensity activities at work on a typical day?	Hours : minutes	hrs mins ☐☐ ☐☐
Travel to and from places			
The next questions exclude the physical activities at work that you have already mentioned. Now I would like to ask you about the usual way you travel to and from places. For example to work, for shopping, to market, to place of worship. [insert other examples if needed]			
7	Do you walk or use a bicycle (*pedal cycle*) for at least 10 minutes continuously to get to and from places?	Yes 1 No 2 *If No, go to Q 10*	☐
8	In a typical week, on how many days do you walk or bicycle for at least 10 minutes continuously to get to and from places?	Number of days	☐
9	How much time do you spend walking or bicycling for travel on a typical day?	Hours : minutes	hrs mins ☐☐ ☐☐

Recreational activities			
The next questions exclude the work and transport activities that you have already mentioned. Now I would like to ask you about sports, fitness and recreational activities (leisure), [insert relevant terms].			
10	Do you do any vigorous-intensity sports, fitness or recreational (*leisure*) activities that cause large increases in breathing or heart rate like [*running or football,]* for at least 10 minutes continuously? *(USE SHOWCARD)*	Yes 1 No 2 *If No, go to Q 13*	☐
11	In a typical week, on how many days do you do vigorous-intensity sports, fitness or recreational (*leisure*) activities?	Number of days	☐
12	How much time do you spend doing vigorous-intensity sports, fitness or recreational activities on a typical day?	Hours : minutes	hrs ☐☐ mins ☐☐
13	Do you do any moderate-intensity sports, fitness or recreational *(leisure*) activities that causes a small increase in breathing or heart rate such as brisk walking,(*cycling, swimming, volleyball*)for at least 10 minutes continuously? *(USE SHOWCARD)*	Yes 1 No 2 *If No, go to Q16*	☐
14	In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational (*leisure*) activities?	Number of days	☐
15	How much time do you spend doing moderate-intensity sports, fitness or recreational (*leisure*) activities on a typical day?	Hours : minutes	hrs ☐☐ mins ☐☐
Sedentary behavior			
The following question is about sitting or reclining at work, at home, getting to and from places, or with friends including time spent [sitting at a desk, sitting with friends, travelling in car, bus, train, reading, playing cards or watching television], but do not include time spent sleeping. *(USE SHOWCARD)*			
16	How much time do you usually spend sitting or reclining on a typical day?	Hours : minutes	hrs ☐☐ mins ☐☐

SECTION 6: Independence in Activities of Daily Living Questionnaire (Katz). Complete on those ≥50 years of age only

1. During the past month, how much difficulty have you had walking across a small room because of your health? **1)** No difficulty **2)** A little difficulty **3)** Some difficulty **4)** A lot of difficulty **5)** Unable to do the activity	☐
2. During the past month, how much difficulty have you had bathing or showering because of your health? **1)** No difficulty **2)** A little difficulty **3)** Some difficulty **4)** A lot of difficulty **5)** Unable to do the activity	☐
3. During the past month, how much difficulty have you had moving in and out of a chair or bed because of your health? **1)** No difficulty **2)** A little difficulty **3)** Some difficulty **4)** A lot of difficulty **5)** Unable to do the activity	☐
4. During the past month, how much difficulty have you had using the toilet because of your health? **1)** No difficulty **2)** A little difficulty **3)** Some difficulty **4)** A lot of difficulty **5)** Unable to do the activity	☐
5. During the past month, how much difficulty have you had dressing yourself because of your health? **1)** No difficulty **2)** A little difficulty **3)** Some difficulty **4)** A lot of difficulty **5)** Unable to do the activity	☐
6. During the past month, how much difficulty have you had feeding yourself because of your health? **1)** No difficulty **2)** A little difficulty **3)** Some difficulty **4)** A lot of difficulty **5)** Unable to do the activity	☐

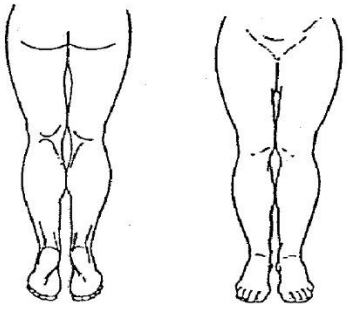
SECTION 7-Diabetes Complications Questions and examination *(Known Diabetes only)*

Signs and symptoms in feet and legs 1. a) Have you ever had a foot ulcer (defined as - full thickness skin break below the malleoli for more than 1 week)? Yes 1 No 2 Don't know 3 b) Site (toe, ball of foot, ankle etc) please specify……..		☐
2.	If yes, when did the ulcer develop? In the last month 1 In the last year 2 In the last 3 years 3 More than 3 years ago 4	☐
3.	Do you have any pain or discomfort in your legs or feet? Yes 1 No 2 Don't know 3 **If no, go on to foot examination Q13**	☐
4.	How would you describe the pain or discomfort? (Mark all types of pain) Burning/ numb/ tingling 2 Aching/ cramp-like/ tired 1 Other 0 (score only the highest scoring symptom)	☐
5.	When is the pain the worst? During the night 2 Day and night the same 1 During the day 0	☐
6.	Does the pain ever wake you up at night? Yes 1 No 0	☐
7.	Do any of the following help or reduce the pain? Walking 2 Standing 1 Sitting down or lying down 0	☐

8. Where do you get this pain or discomfort?

Feet	2
Knee to ankle	1
Anywhere else	0

a) Mark the place(s) with an "x" on the diagram.



9. Do you ever get a pain or discomfort in your leg(s) when you walk?

Yes	1
No	2
I am unable to walk	3

If no, got to Q 13

10. Does this pain ever begin when you are standing still or sitting?

Yes	1
No	2
Don't know	3

11. Do you get this pain if you walk uphill or when walking in a hurry?

Yes	1
No	2
Don't know	3

12. What happens to this pain if you stand still?

1 Usually continues for more than 10 minutes
2 Usually disappears in 10 minutes or less

13. FOOT EXAMINATION

a) Is a foot ulcer present?

Yes	1
No	2

b). Where is the ulcer located?……

14. Pressure perception threshold
No 0, Yes 1

	Left	Right
Great toe		
1st met head		
5th met head		

Total score out of 6 ☐

Section 8: Asthma Screening Questionnaire

TO ANSWER THE QUESTIONS PLEASE CHOOSE THE APPROPRIATE BOX IF YOU ARE UNSURE OF THE ANSWER PLEASE CHOOSE 'NO'

1. Have you had wheezing or whistling in your chest at any time in the last 12 months? Yes 1 No 2 (Go to Q2) a) Have you been at all breathless when the wheezing noise was present? Yes 1 No 2 b) Have you had this wheezing or whistling when you did not have a cold? Yes 1 No 2	☐ ☐ ☐
2. Have you woken up with a feeling of tightness in your chest at any time in the last 12 months? Yes 1 No 2	☐
3. Have you been woken by an attack of shortness of breath at any time in the last 12 months? Yes 1 No 2	☐
4. Have you been woken by an attack of coughing at any time in the last 12 months? Yes 1 No 2	☐
5. Have you had an attack of asthma in the last 12 months? Yes 1 No 2	☐
6. Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma? Yes 1 No 2	☐
7. Do you have any nasal allergies including hay fever? Yes 1 No 2	☐

Section 9: Centre for Epidemiology Studies Short Depression Scale: How you are feeling?

Below is a list of some of your recent feelings and behaviours. Please indicate how often you have felt this way during the past week, by ticking the appropriate box.

1. During the past week, were you bothered by things that don't usually bother you? SCORE 0 Rarely or none of the time (less than 1 day) 1 Some or a little of the time (1-2 days) 2 Occasionally or a moderate amount of the time (3-4 days) 3 Most or all of the time (5-7 days)	☐
2. During the past week, did you have trouble keeping your mind on what you were doing? SCORE 0 Rarely or none of the time (less than 1 day) 1 Some or a little of the time (1-2 days) 2 Occasionally or a moderate amount of the time (3-4 days) 3 Most or all of the time (5-7 days)	☐
3. During the past week, did you feel depressed? SCORE 0 Rarely or none of the time (less than 1 day) 1 Some or a little of the time (1-2 days) 2 Occasionally or a moderate amount of the time (3-4 days) 3 Most or all of the time (5-7 days)	☐
4. During the past week, did you feel everything you did was an effort? SCORE 0 Rarely or none of the time (less than 1 day) 1 Some or a little of the time (1-2 days) 2 Occasionally or a moderate amount of the time (3-4 days) 3 Most or all of the time (5-7 days)	☐
5. During the past week, did you feel hopeful about the future? SCORE 0 Rarely or none of the time (less than 1 day) 1 Some or a little of the time (1-2 days) 2 Occasionally or a moderate amount of the time (3-4 days) 3 Most or all of the time (5-7 days)	☐
6. During the past week, did you feel afraid? SCORE 0 Rarely or none of the time (less than 1 day) 1 Some or a little of the time (1-2 days) 2 Occasionally or a moderate amount of the time (3-4 days) 3 Most or all of the time (5-7 days)	☐

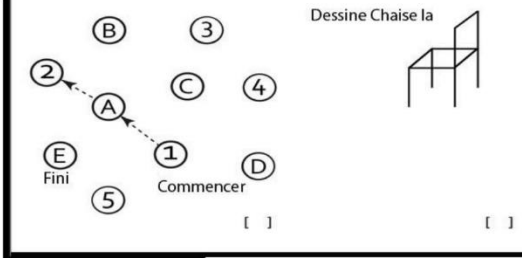
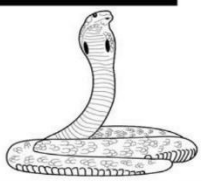
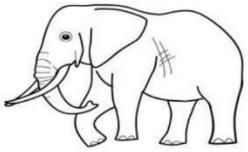
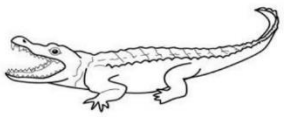
7. During the past week, was your sleep restless? SCORE 0 Rarely or none of the time (less than 1 day) 1 Some or a little of the time (1-2 days) 2 Occasionally or a moderate amount of the time (3-4 days) 3 Most or all of the time (5-7 days)	☐
8. During the past week, were you happy? SCORE 0 Rarely or none of the time (less than 1 day) 1 Some or a little of the time (1-2 days) 2 Occasionally or a moderate amount of the time (3-4 days) 3 Most or all of the time (5-7 days)	☐
9. During the past week, did you feel lonely? SCORE 0 Rarely or none of the time (less than 1 day) 1 Some or a little of the time (1-2 days) 2 Occasionally or a moderate amount of the time (3-4 days) 3 Most or all of the time (5-7 days)	☐
10. During the past week, did you feel that you could not get 'going'? SCORE 0 Rarely or none of the time (less than 1 day) 1 Some or a little of the time (1-2 days) 2 Occasionally or a moderate amount of the time (3-4 days) 3 Most or all of the time (5-7 days)	☐

Section 1: Cognitive Assessment (Creole)

MONTREAL COGNITIVE ASSESSMENT (MOCA)

VERSION 7.2 CREOLE (Adapated from French Version)

NOM: Date de naissance:
Nivo education: Date:
Sex:

POINTS		
	VISUOPATIAL/EXECUTIF  Dessine Chaise la [ ] [ ]	Dessine Reveille (9 h 10 min) **(3 points)** [ ] Contour [ ] Chiffres [ ] Aiguilles	_/5
	DIRE KI ZANIMO SA    [ ] [ ] [ ]		_/3
	MEMOIRE lire ban mots la, participant bizin redire en 2 fois Meme si premiere reponse la bon, bizin redire ene deuxieme fois Relire li apres 5 minutes	1ERE essai / 2ème essai: LAMAIN, NYLON, ZARDIN PUBLIC, CAROTTE, ZAUNE	Pa pu gagne point
	ATTENTION Dire sa banne numero (***1 numero la par second***) Participant la bizin dire sa banne numero la en lordre [ ] 8 1 5 2 4 Participantla bizin redire sa banne numero la commence par dernier [ ] 2 4 7		_/2
	Dire banne alphabet. participant la bizin tap so la main quand li tan alphabet a. Pas pu gagne point si ena 2 faute [ ] FBACMNAAJKLBAFAKDEAAAJAMOFAAB		_/1
	Commence avec 70 retire 7 graduellment allez meme [ ] 63 [ ] 56 [ ] 49 [ ] 42 [ ] 35 4-5 BON CALCULE RETIRER = **3POINT**, 2-3 BON CALCULE = **2POINT**, 1 BON = **1 POINT**, 0 BON CALCULE =**0POINT**		_/3
	LANGUAGE **Dire encore ene nouvo fois:** La police ine reusi arrete sa voleur loto gris la. [ ] Zeleve la ine bliyer so banne livre ek crayon dan so lecole [ ]		_/2
	Regularite language: dire maximum mot commence par R dan ene minute [ ] (N 11 mots)		_/1
	RESUMER Ki ena an commune entre: **(1) ex: ene banane ek zorange = *fruit*** [ ] **(2) lili - latable** [ ] **(3) lettre - telephone** [ ]		_/2
	RAPPEL Bizin rapel mot la SANS INDICES: LAMAIN [ ], NYLON [ ], ZARDIN PUBLIC [ ], CAROTTE [ ], ZAUNE [ ] **OPTIONNEL** Indice avek ene sel example Indice avek beaucoup example	Pou gagne point seulement pu seki ine donne bon response sans indice	_/5
	ORIENTATION [ ] Date [ ] Mois [ ] Année [ ] Jour [ ] Endroit [ ] Ville		_/6

Normal ≥ 26/30 TOTAL _/30

Azute 1 point si nivo leducation ≤ 12 ans

FINAL CHECK BEFORE PARTICIPANT LEAVES TESTING SITE

PROCEDURES COMPLETED. Tick (√) as appropriate. OBS – ID

Blood Specimen Fasting	
Blood Specimen 2 hrs	
Urine Specimen	
ECG	

Diabetes Complications (known and newly diagnosed diabetes)

Pain & foot questions ☐ Foot exam ☐

Questionnaires (tick if completed)	**Verified by**
Section 1:General demographics	☐ ☐ ☐ ☐
Section 2: Physical examination (Height, Weight, Waist)	☐ ☐ ☐ ☐
Section 3: Medical history	☐ ☐ ☐ ☐
Section 4: Health utilisation, diabetes knowledge, attitudes and dietary habits (all participants)	☐ ☐ ☐ ☐
Section 5: Physical activity (GPAQ) Independence	☐ ☐ ☐ ☐
Section 6: Activities of Daily Living Questionnaire (Katz) ≥50 years only	☐ ☐ ☐ ☐
Section 7: (A & B): Diabetes complications (Known diabetes only)	☐ ☐ ☐ ☐
Section 8: Asthma Screening Questionnaire	☐ ☐ ☐ ☐
Section 9: Depression Questionnaire	☐ ☐ ☐ ☐
Section 10: Montreal Cognitive assessment (MOCA)	☐ ☐ ☐ ☐

Real World Evidence data sheet

Site name _____

	Data to be collected	Specific description	2006	2012	2015
General information & demographics	site description	Primary care, specialist care, hospital care (primary-secondary-tertiary), teaching hospital			
	Site location	Urban or rural			
	Clinic size	Number of diabetic patients attending during the year			
		Number of in-patients included			
	sex	% (n/N) male			
	age	mean (SD) (N)			
		% > 65y (n/N)			
		% > 80y (n/N)			
		% < 30y (n/N)			
	BMI	mean (SD) (N)			
		% <20 (n/N)			
		% 20.0-24.9 (n/N)			
		% 25.0-29.9 (n/N)			
		% ≥30 (n/N)			
Disease history	% type 2 diabetes	% (n/N) of patients managed as type 2 diabetes			
	duration of diabetes	Mean (SD) (N)			
		%> 10 years duration (n/N)			
	MACE events	% (n/N) MACE defined as any of history of stroke, MI or CABG/PCI, cardiovascular death.			
	retinopathy	% (n/N) with recorded retinal exam in the year			
		% (n/N) any retinopathy			
		% (n/N) of patients with retinopathy that ever received laser treatment			
	Nephropathy	% (n/N) with urinary albumin result in the year			
		% (n/N) with urinary protein result in the year			
		% (n/N) with urinary albumin or protein result in the year			
		% (n/N) of patients with microalbuminuria, or macroalbuminuria or proteinuria (based on biochemistry results that year)			
		% (n/N) of patients with microalbuminuria, or macroalbuminuria or proteinuria (based on			

		diagnosis or problem lists)*			
		Definition of microalbuminuria			
	amputation	% (n/N) of patients with any amputation			
	blood pressure	Percent (n/N) on antihypertensive therapy*			
		Mean SBP (SD) (N)			
		Mean DBP (SD) (N)			
		%> 130/80 (n/N)			
		% >130/80 OR on antihypertensive therapy (n/N)			
		% of those with >130/80 on antihypertensive therapy (n/N)			
		%> 140/90 (n/N)			
		% >140/90 OR on antihypertensive therapy (n/N)			
		% of those with >140/90 on antihypertensive therapy (n/N)			
Diabetes Medication (among people with type 2 diabetes)	diet and lifestyle	% of T2 population (n/N) on diet and lifestyle alone			
	Non insulin drugs (exclude anyone on insulin from the numerator, but keep them in the denominator for data on all non-insulin therapies)	% of T2 population (n/N) on monotherapy			
		% of T2 population (n/N) on dual therapy			
		% of T2 population (n/N) on three or more therapies			
	sulphonylureas	% of T2 population (n/N) on SU alone or in any combination			
		% of T2 population (n/N) on monotherapy with SU			
		% of T2 population (n/N) on dual therapy with SU			
	Meglitinides (eg repaglinide)	% of T2 population (n/N) on meglitinide alone or in any combination			
		% of T2 population (n/N) on monotherapy with meglitinide			
		% of T2 population (n/N) on dual therapy with meglitinide			
	metformin	% of T2 population (n/N) on metformin alone or in any combination			
		% of T2 population (n/N) on monotherapy with metformin			
		% of T2 population (n/N) on dual therapy with metformin			
	Alpha glucosidase inhibitor (AGI) eg acarbose	% of T2 population (n/N) on AGI alone or in any combination			
		% of T2 population (n/N) on monotherapy with AGI			

		% of T2 population (n/N) on dual therapy with AGI			
	DPP-IV inhibitors	% of T2 population (n/N) on DPP4i alone or in any combination			
		% of T2 population (n/N) on monotherapy with DPP4i			
		% of T2 population (n/N) on dual therapy with DPP4i			
	GLP-1 agonists	% of T2 population (n/N) on GLP-1 alone or in any combination			
		% of T2 population (n/N) on monotherapy with GLP-1			
		% of T2 population (n/N) on dual therapy with GLP-1			
	SGLT2 inhibitors	% of T2 population (n/N) on SGLT2i alone or in any combination			
		% of T2 population (n/N) on monotherapy with SGLT2i			
		% of T2 population (n/N) on dual therapy with SGLT2i			
	insulin	% of T2 population (n/N) on any insulin			
		% of T2 population (n/N) on any insulin as monotherapy			
		% of T2 population (n/N) on basal insulin (no short-acting or pre-mixed insulin, but can be with other agents)			
		% of T2 population (n/N) on pre-mixed insulin (with or without other agents or insulins)			
		% of T2 population (n/N) on short-acting insulin (with or without other agents or insulins)			
Concomitant medication	angiotensin receptor blocker (ARB)	% (n/N) of patients			
	angiotensin converting enzyme blocker	% (n/N) of patients			
	thiazides	% (n/N) of patients			
	calcium channel blockers	% (n/N) of patients			
	statins	% (n/N) of patients			
	aspirin or other anti-platelet agent	% (n/N) of patients			
Laboratory values	HbA1c	Method			
		Mean number per patient per yr (N)			
		Mean value (SD) (N)			
		% <7.0 (n/N)			
		% 7.0-7.9 (n/N)			

		% 8.0-8.9 (n/N)			
		% ≥9.0 (n/N)			
	fasting glucose	Mean value (SD) (N)			
	eGFR	Method of eGFR calculation			
		Mean (SD) (N)			
		% <60 (n/N)			
	serum creatinine	Mean (SD) (N)			
	total cholesterol	Mean (SD) (N)			
		Mean among those on statins (SD) (N)			
	LDL cholesterol	Mean (SD) (N)			
		Mean among those on statins (SD) (N)			

Notes
- Each patient should contribute a single value for each parameter in each year. Thus, the mean HbA1c is not the mean of all values measured in the clinic that year, but the mean after extracting a single value for each patient. Ideally, the single value should be the one closest to the mid-point of the year (June 30), but other methods (eg the 1st, the last, a random value) are also acceptable.
- For mean values, please supply the number of individual patients contributing to the mean (ie after excluding those with missing values).
- All percentages should be calculated among those with available data, rather than from the whole population.
- Determination and recording of the denominator for percentage calculations is very important. For parameters based on a value for everyone (e.g. age, HbA1c), the denominator is the total number of people with a recorded value. For parameters where only a numerator is collected (e.g. MACE event on a problem list), the denominator is the total population, or the sub-population for whom that type of data is potentially available (e.g. those who have completed a specific data collection form).
- Diabetes medication should be determined only among those with type 2 diabetes. Exclude type 1, LADA, GDM and secondary diabetes

*Antihypertensive therapy is defined as use of any of ACEI, ARB, beta blocker, thiazide or thiazide-like diuretic, calcium antagonist, centrally-acting anti-hypertensive.