Population Level Outcomes of Advancements in Diabetes Care

Katerina Vivian Kiburg

ORCID: 0000-0002-3894-5793

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The University of Melbourne

Abstract

The development of diabetes-related complications is a major healthcare problem. The overall aim of this thesis is to document trends in the incidence of diabetes-related complications, focusing on those related to cardiovascular and renal disease. Diabetes care has improved significantly over past decades, resulting in improved glycaemic control and an increase in the number of patients achieving various metabolic goals. Indeed, the application of multifactorial, target driven interventions has been shown to reduce the development and progression of diabetes related complications in the clinical trial setting. Furthermore, novel glucose lowering medications have recently been shown to reduce the development of cardiovascular and renal complications in recent clinical trials. It is possible that these recent improvements in diabetes management have contributed to reductions in complications in the general diabetes population. In this thesis I examined changes in rates of diabetes related complications in people with and without diabetes over time in Victoria, Australia.

The research described in this thesis is mainly centred on an analysis of trends in hospital admissions in Victoria, Australia for various diabetes related complications. This thesis shows that there was a significant decline in the cardiovascular outcomes of, incident AMI, stroke and heart failure presentations for patients with type 1 diabetes, type 2 diabetes and without diabetes between 2004 and 2016. The greatest rate of decline was observed in patients with type 2 diabetes, followed by patients with type 1 diabetes.

My research also demonstrates that there was a significant decline in end stage renal disease presentations (separate to those for dialysis and transplantation) for patients with type 1 diabetes, type 2 diabetes or no diabetes. However, rates of admissions for diabetic nephropathy and specifically for dialysis and transplantation remained stable. This lack of translation of a reduction in ESRD presentations to reduced rates of dialysis and transplantation may be due to changes in clinical practices, such as greater access and eligibility for renal replacement programs. The continuing large number of patients with diabetic nephropathy represent an opportunity for the better implementation of best practice guidelines aimed at slowing the development and progression of diabetic kidney disease.

In addition, I was able to show that overall rates of lower extremity amputations (LEA) declined for patients with type 2 diabetes, compared to those with type 1 diabetes who did not experience such a decline. Concerningly, a significant rise was seen in all types of LEA for younger patients with type 1 diabetes, whereas pleasingly, older patients with type 2 diabetes saw a decline in rates of LEA.

While there is a large amount known on the numbers of people that experience cardiovascular events, less is known about the intravascular burden of coronary artery disease in people with and without diabetes. I was able to show a significant increase over time in the burden of coronary artery disease for patients with type 2 diabetes, compared to those without diabetes in whom no change was observed. A key finding was that following adjustment for the use of traditional cardiovascular protective medications such as statins, renin-angiotensin system inhibitors and anti-platelet drugs, there was no significant difference in the extent of intra-coronary artery disease between patients with and without type 2 diabetes. The implication of this finding is that the aggressive use of traditional preventative therapies can greatly help to reduce the excess burden of disease within the coronary arteries of patients with type 2 diabetes.

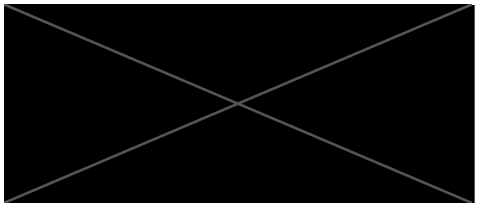
The improvement in rates of traditional diabetes related complications has led to a corresponding increase of non-traditional complications, including malignancies. In the last results chapter of this thesis, I was able to show that for patients with type 2 diabetes and malignancies there was a significantly increased risk of emergency department presentations, inpatient admissions and all-cause mortality compared to patients with malignancies but without diabetes.

This thesis adds to a growing body of evidence of the negative impact of diabetes, on patient outcomes and the importance of risk factor modification and multifactorial interventions. It highlights that although improvements in hospital admission rates for many diabetes related complications are occurring, the overall burden of complications still remains a major public health problem. Unfortunately, my work also shines a light on the changing face of diabetes complications and the potential problems associated with the emergence of non-traditional complications, such as malignancies.

Declaration

This is to certify that this thesis:

i) contains no material that has been accepted for the award of any other degree or diploma in any university of other institution,
ii) comprises only my original work except where indicated in the Preface,
iii) due acknowledgement has been made in the text to all other material used,
iv) is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices



Katerina V. Kiburg, 7th April 2021

Preface

The work presented in this thesis was undertaken at St Vincent's Hospital Melbourne under the principal supervision of Professor Richard MacIsaac, Department of Endocrinology and Diabetes, St Vincent's Hospital and Department of Medicine, University of Melbourne. The work was co-supervised by Professor Vijaya Sundararajan, La Trobe University, Bundoora, Australia.

Others have contributed to the work presented in this thesis as outlined below:

Associate Professor Andrew MacIsaac and Professor Andrew Wilson assisted in the data acquisition and provided expert advice in the interpretation of results for Chapters 3 and 6. Professor Frank Ierino provided expert insights into the results for Chapter 4 and assisted with the final draft of the chapter. Dr Anna Galligan assisted in the interpretation of the results and final discussion in Chapter 5. Dr Sue-Anne McLachan provided expert advice in the design and interpretation of the results in Chapter 7. Dr Sara Vogrin provided statistical advice throughout the duration of the thesis and in Chapter 7.

Chapters 7 has been published in a peer-reviewed journal. Chapter 3 has been accepted into a peer-reviewed journal and Chapter 6 has been submitted for publication in peer-reviewed journal and are currently under review.

These studies were funded by the Department of Endocrinology and Diabetes St Vincent's Hospital Melbourne, St Vincent's Institute and St Vincent's Foundation.

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This thesis would not have been possible without the support and encouragement of a great number of people.

First and foremost, Richard thank you for encouraging me to do a PhD and believing that I was capable of it. I am incredibly grateful for all of your encouragement and support throughout the years. Despite the numerous commitments you have, your dedication to my research is most appreciated and I look forward to many more years of working together.

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To all of the friends I have made in the Department of Endocrinology and Diabetes and The Department of Medicine of which there are too many to name individually but whom I would not have been able to survive this without, thank you very much for all of your support, kindness and coffees throughout this. Varuni, thank you very much for all of your assistance with making my talks and posters aesthetically pleasing, and going for many coffees with me.

Without funding the project would not have been possible, I am most grateful to the Department of Endocrinology and Diabetes St Vincent's Hospital Melbourne, St Vincent's Institute and St Vincent's Foundation for making this PhD possible.

I am incredibly grateful to my parents for always supporting me and pushing me to pursue any opportunity available, thank you mum and dad for supporting me throughout this latest challenge. To my brother, Simon thank you for always being keen to get a drink with me when I need to, and for being able to put things into perspective. To all of my friends who have supported me throughout this, went away for weekends, dinners and kept me sane, this would not have been possible without you.

Finally, to my husband Michael, thank you for everything you have done. I did not plan on doing a PhD during a pandemic and during a lockdown, without all of your love, support and encouragement I would never have been able to complete this thesis (and would have eaten scrambled eggs for 3 years).

List of Publications and Abstracts Relating to this Thesis

Published Articles

Kiburg KV, AI MacIsaac, A Wilson, V Sundararajan, RJ MacIsaac. Changes in hospital admission rates for cardiovascular complications in patients with and without diabetes in Victoria, Australia 2004-2016. Accepted for publication Medical Journal of Australia. 2021 Mar.

Kiburg KV, Ward GM, Vogrin S, Steele K, Mulrooney E, Loh M, McLachlan SA, Sundararajan V, MacIsaac RJ. Impact of type 2 diabetes on hospitalization and mortality in people with malignancy. Diabetic Medicine. 2020 Feb;37(2):362-8.

Articles Submitted for Publication

Kiburg KV, MacIsaac AI, McCluskey GE, Sundararajan V, MacIsaac R. Coronary artery disease as assessed by angiography and the impact of preventative cardiovascular therapies in patients with and without type 2 diabetes. Submitted and under review.

Conference Abstracts

Kiburg KV, Ward GM, Steele K, Mulrooney E, Loh M, McLachlan SA, Sundararajan V & MacIsaac RJ. Characteristics and outcomes for patients with diabetes diagnosed with cancer. Presented at the Australian Diabetes Society – Australian Diabetes Educators Association (ADS-ADEA) Annual Scientific Meeting, Adelaide 2018. Finalist Presidents Young Investigator Award ADS.

Kiburg KV, Ward G, O'Neal D, Santamaria J, Sundararajan V & MacIsaac R. Key factors for achieving glycaemic and lipid targets. Presented at the ADS-ADEA Annual Scientific Meeting, Adelaide 2018. Finalist Clinical Science Poster Award ADS.

Kiburg KV, Ward GM, Vogrin S, Steele K, Mulrooney E, Loh M, McLachlan SA, Sundararajan V & MacIsaac RJ. The impact of a diabetes co-diagnosis on hospitalisation and mortality in patients with malignancy. Presented at the American Diabetes Association (ADA) 79th Scientific Sessions, San Francisco 2019. Diabetes 2019; 68(S1): 1646-P1

Kiburg KV, MacIsaac AI, Santamaria J, Sundararajan V & MacIsaac RJ. Characteristics and features of patients with and without diabetes undergoing coronary angiography. Presented at the ADS-ADEA Annual Scientific Meeting, Sydney 2019.

Kiburg KV, MacIsaac AI, Sundararajan V & MacIsaac RJ. Change in extent of coronary artery disease in people with and without diabetes undergoing coronary angiography. Presented at the ADA 80th Scientific Sessions, Virtual Meeting 2020. Diabetes 2020; 68(S1): 417-P.

Kiburg KV, MacIsaac AI, McCluskey GE, Sundararajan V & MacIsaac RJ. Impact of preventative therapies on the extent of coronary artery disease in people with and without diabetes. Presented at the ADA 80th Scientific Sessions, Virtual Meeting 2020. Diabetes 2020; 68(S1): 416-P.

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Kiburg KV, MacIsaac AI, Wilson A, Sundararajan V & MacIsaac RJ. Changes in Hospital Admission Rates for Cardiovascular Complications in Patients with and without diabetes in Victoria, Australia 2004-2016. Presented at the ADS-ADEA Annual Scientific Meeting, Virtual Meeting 2020. Abstract 72.

Prizes and Awards

2020

- St Vincent's Hospital Research Endowment Fund: "Predicting re-admissions and mortality in patients with and without diabetes and heart failure" - $20,000
- ADS-Abbott ADC Registration Grant - $250
- Eastern Hill Campus Precinct Travel Grant - $185

2019

- St Vincent's Hospital Research Endowment Fund: "The use of a national echocardiogram database to determine the impact of diabetes on the characteristics and outcomes of patients with pulmonary hypertension" - $20,000
- Australian Diabetes ADS ADA Travel Grant - $2,000

2018

- Nominated Junior Investigator Award St Vincent's ACMD Research Week, 2018, Characteristics and outcomes for cancer patients with and without diabetes.
- Nominated Presidents Young Investigator Award Australian Diabetes Association, 2018, *Characteristics and outcomes for cancer patients with and without diabetes.*

List of Other Related Publications Completed During Candidature

Published Articles

Flanagan E, Wright EK, Sparrow MP, Moore GT, Connell WR, De Cruz P, Christensen B, Shelton E, Kamm MA, Ward MG, Dowling D, Brown S, Kashkooli S, Thompson AJ, Ross AL, **Kiburg KV**, Bell SJ. A Single Educational Intervention Improves Pregnancy-Related Knowledge and Emotional Health Among Women with IBD Who Are Pregnant or Wish to Conceive. Inflammatory Bowel Diseases. 2021 March 11:izab021. doi: 10.1093/ibd/izab021. Epub ahead of print. PMID: 33704467.

Gogna R, Jung C, McLachlan K, Balasubramanian K, Hong A, Derbyshire M, **Kiburg KV**, Zacharin M, MacIsaac RJ, Sachithanandan N, Caputo C. Reducing adverse events associated with the glucagon stimulation test for the assessment of growth hormone deficiency in adults with a high prevalence of pituitary hormone deficiencies. Clinical Endocrinology. 2021 Mar 17. doi: 10.1111/cen.14464. Epub ahead of print. PMID: 33728673.

Flanagan E, Wright EK, Hardikar W, Sparrow MP, Connell WR, Kamm MA, De Cruz P, Brown SJ, Thompson A, Greenway A, Westley I, Barclay M, Ross A, **Kiburg KV**, Bell SJ, PICCOLO Study Group. Maternal thiopurine metabolism during pregnancy in inflammatory bowel disease and clearance of thiopurine metabolites and outcomes in exposed neonates. Alimentary Pharmacology & Therapeutics. 2021 Feb 19.

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Ducharlet K, Philip J, **Kiburg K**, Gock H. Renal supportive care, palliative care and end-of-life care: Perceptions of similarities, differences and challenges across Australia and New Zealand. Nephrology. 2020 Sep 29

Seastres RJ, Hutton J, Zordan R, Moore G, Mackelprang J, **Kiburg KV**, Sundararajan V. Long-term effects of homelessness on mortality: a 15-year Australian cohort study. Australian and New Zealand Journal of Public Health. 2020 Dec;44(6):476-81.

Zafari N, Churilov L, Wong LL, Lotfaliany M, Hachem M, **Kiburg KV**, Kong L, Torkamani N, Baxter H, MacIsaac RJ, Ekinci EI. Evaluation of the diagnostic performance of the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation in people with diabetes: A systematic review. Diabetic Medicine. 2020 Aug 18:e14391

Flanagan E, Wright EK, Begun J, Bryant RV, An YK, Ross AL, **Kiburg KV,** Bell SJ. Monitoring Inflammatory Bowel Disease in Pregnancy using Gastrointestinal Ultrasonography. Journal of Crohn's and Colitis. 2020 Apr 28.

Zafari N, Churilov L, MacIsaac RJ, Torkamani N, Baxter H, **Kiburg KV**, Ekinci E. Diagnostic performance of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at estimating glomerular filtration rate in adults with diabetes mellitus: a systematic review and meta-analysis protocol. BMJ open. 2019 Aug 1;9(8):e031558.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

ABS	Australian Bureau of Statistics
ACHI	Australian Classification of Health Interventions
AGE	Advanced glycation end products
ACS	Acute coronary syndrome
AAPC	Average annual percentage change
APC	Annual percentage change
AMI	Acute myocardial infarction
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary artery bypass grafting
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular Disease
CVDL	The Centre for Victorian Data Linkage
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DPP-4	Dippeptidylpeptidase-4
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
GLP-1	Glucagon-like peptide-1
HDL-C	High density lipoprotein-C
HF	Heart Failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HLA	Human leukocyte antigen
HR	Hazard Ratio
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification
IRR	Incident rate ratios
LDL-C	Low-density lipoprotein cholesterol
LEA	Lower extremity amputation
MACE	Myocardial infarction, stroke or CV death
NDI	National Death Index
NDSS	National Diabetes Service Scheme

PCI	Percutaneous coronary intervention
PCSK-9	Proprotein convertase subtilisin/kexin type 9
PH	Pulmonary hypertension
RAS	Renin-angiotensin system
RVD	Right ventricular dysfunction
SD	Standard Deviation
SEIFA	Socio-Economic Indexes for Areas
SES	Socioeconomic status
SGLT-2	Sodium-glucose co-transporter-2
TZD	Thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study
VAED	Victorian Admitted Episode Dataset
VEMD	Victorian Emergency Minimum Dataset
VDI	Victorian Death Index

List of Third-party Copyright Material Included in this Thesis

Citation information for Third-party copyright material	Location of item in thesis	Permission granted
Huebschmann AG, Huxley RR, Kohrt WM, et al. Sex differences in the burden of type 2 diabetes and cardiovascular risk across the life course. Diabetologia 2019:1-12[1].	Figure 1.3 Page 29	Yes, Copyright Springer Nature
Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocrine reviews 2016;37:278-316[2].	Figure 1.4 Page 30	Yes, Copyright Oxford University Press

Chapter 1: Introduction and Literature Review

Diabetes is one of the biggest chronic health disease challenges facing developed countries. In the most recent report from The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) which is a longitudinal population study examining the natural history of diabetes and related complications, the prevalence of diabetes in the general Australian population was estimated to be 7.4%[3]. If rates of diabetes continue to rise at the same rate, this prevalence is predicted to reach 35%(95% CI: 36.6, 38.9) in 2025, which equates to an additional one million cases[4]. This high prevalence of diabetes comes at a great cost to the Australian Government, with $1.50 billion being spent on the management of diabetes across 2008-2009[5]. It is well appreciated that patients with diabetes are at an increased risk of a number of complications and that improvements in glycaemic control translate to a decreased risk of both micro- and macro-vascular complications[6]. As traditional diabetes complications are increasingly well managed, patients with diabetes are living for longer and are now faced with mortality and morbidity from complications not historically associated with diabetes.

There has been a significant decline in excess all-cause mortality observed for both males and females who have either type 1 or 2 diabetes, which is mirrored across the general population that has also seen a decline in all-cause mortality. However, the relative decline in mortality rates of patients with diabetes are experiencing appears to be greater than those without diabetes, suggesting improvements in the management of diabetes related complications are contributing to this accelerated improvement in mortality for patients with diabetes[7-9]. Despite these improvements, patients with diabetes are still at an overall increased risk of all-cause mortality compared to patients without diabetes, with patients with type 1 diabetes at a 3 fold increased risk and patients with type 2 diabetes at a 20 percent increased risk of all-cause mortality[7, 10]. Despite the above, the rate at which patients with diabetes are dying of cardiovascular disease (CVD) has been declining, with mortality rates of other complications, such as cancer, chronic lower respiratory disease, infections and renal disease, rising[7, 11]. This reduction in death from CVD causes has led to an increase in number of years lived for patients with diabetes, but in some cases this has led to an increase in the overall years lived with morbidity for these patients[8]. This change in morbidity and mortality may mean that clinical management of diabetes, and the way in which diabetes prevention and disease monitoring occur may need to be reassessed. Despite the above, diabetes reduces life expectancy by at least 6 years when diagnosed at 40 years and by 4 years when diagnosed at 60 years [4, 12].

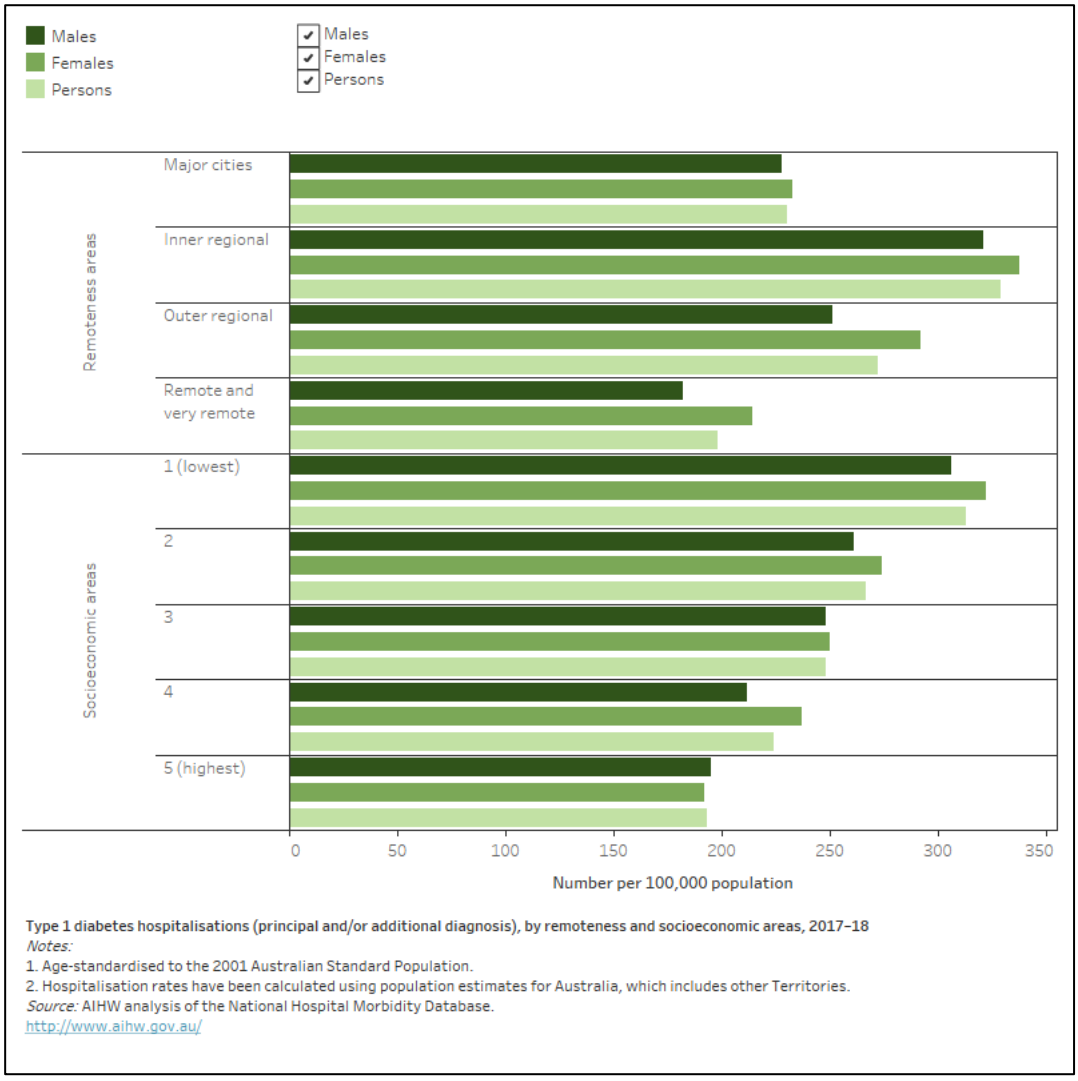
This literature review represents a short summary and synthesis of the major publications related to the development, progression, treatment and epidemiology of diabetes complications.

Introduction to Diabetes and its management

Type 1 Diabetes

Type 1 diabetes affects 5-10% of patients diagnosed with diabetes[13]. In 2018, there were 12 cases per 100,000 population in Australia of type 1 diabetes, this rate has remained relatively stable over the past 20 years[14]. The incidence did not vary between level of remoteness, level of socioeconomic disadvantage or ethnicity/race (Figure 1.1).

Figure 1.1: Incidence of type 1 diabetes, by remoteness and socioeconomic areas.



Source: Australian Institute of Health and Welfare15.

Type 1 diabetes is an autoimmune disease, resulting in the destruction of pancreatic beta cells leading to a decrease in the body's ability to produce insulin, resulting in hyperglycaemia and ketosis. Autoimmune markers include islet cell autoantibodies, autoantibodies to GAD (GAD65), insulin, tyrosine phosphatases (IA-2 and IA-2β) and zinc transporter 8 antibody[13]. Symptoms of hyperglycaemia include polyuria, polydipsia, weight loss and infections. Left untreated type 1 diabetes results in ketoacidosis and ultimately death. Patients require treatment with lifelong exogenous insulin, apart from a small handful of patients that receive a pancreas of islet-cell transplant. Although type 1 diabetes can be diagnosed at any age it is typically diagnosed in childhood or in young adults. There is a known strong association between human leukocyte antigen (HLA) type and the development of type 1 diabetes, with the HLA-DR and HLA-DQ genes known to be associated with an increased risk in the development of type 1 diabetes[16].

1.1.1.1 Management and Management of Type 1 Diabetes

Patients with type 1 diabetes are encouraged to keep their blood glucose levels as close to normal as safely possible in order to minimise the chances of acute complications, including diabetic ketoacidosis (DKA) and severe hypoglycaemia, and the development and progression of long-term diabetes-related complications. The Diabetes Control and Complications Trial (DCCT) was responsible for establishing the importance of glycaemic control on micro and macrovascular outcomes. The DCCT was a multi-centre randomised control trial that compared the effect of standard versus intensive (haemoglobin A1C <6.05% (43mmol/mol)) insulin therapy on early vascular and neurological diabetes-related complications using two separate cohorts. The trial showed a significant reduction in retinopathy, albuminuria and clinical neuropathy in the intensive therapy group[6]. The long-term follow up of the DCCT participants, Epidemiology of Diabetes Interventions and Complications (EDIC), provided evidence that intensive glucose control was able to significantly reduce the long-term complications of nonfatal myocardial infarction, stroke or death from cardiovascular disease by 57% for study participants initially randomised to intensive control that were followed for a mean of 17 years[17].

The impact that glycaemic variability may have on the risk of developing diabetes-related complications, beyond the effect of long-term hyperglycaemia alone, remains controversial[18]. With an analysis of the DCCT/EDIC using multiple imputation for missing data to calculate standard deviation (SD), mean amplitude of glycaemic excursions and M-value, it was found that overall there was no association between

within-day glycaemic variability in the development of microvascular complications beyond standard mean glucose[19]. The introduction of insulin pumps that automate insulin delivery and in some cases are also able to integrate glucose sensors and adjust insulin delivery accordingly has seen an expansion in the insulin delivery options available to patients with type 1 diabetes. Both sensor-augmented pumps and hybrid closed-loop systems have been shown to significantly increase time in range (glucose 70-180mg/dl or 3.9-10mmol/L) in a clinical trial and real world setting[20-22]. A Scottish registry study of over 4,500 people with type 1 diabetes using insulin pump therapy found it was associated with a decrease in haemoglobin A1c, reduced rates of diabetic ketoacidosis and severe hospitalised hypoglycaemia[23]. However, as of yet there have been no large cohort studies using the newer continuous glucose monitoring technology that have followed patients up over time to monitor for long-term diabetes-related complications.

Type 2 Diabetes

Type 2 diabetes is the most common form of diabetes, accounting for 90-95% of diabetes diagnoses[13]. Over 1 million Australian adults were diagnosed with type 2 diabetes in 2017-18[14]. Unlike individuals with type 1 diabetes, it may take a prolonged time period for a diagnosis to be made. Symptoms may not initially be as severe as those seen in patients with type 1 diabetes, and seldom do individuals develop diabetic ketoacidosis. This delay in diagnosis is important as even prior to a patient being diagnosed, and therefore untreated, hyperglycaemia is causing organ damage. The result of this is that people are often not being diagnosed until a serious diabetes-related complication, such as acute myocardial infarction, occurs. This type of diabetes includes a range of individuals who can have relative insulin deficiency and peripheral insulin resistance. Throughout their lifetime individuals may progress to requiring insulin, though this may not always be the case.

1.1.1.2 Management and Treatment of Type 2 Diabetes

Chronic hyperglycaemia is well known to be associated with an increased risk in the development and progression of various diabetes related complications, with meta-analysis showing that for each 1% increase in glycated haemoglobin there was a corresponding 18% increased risk of cardiovascular events, 12-14% of death and 37% increased risk of retinopathy or renal failure[24-26]. Following the results of the UKPDS trial where tight glycaemic control (haemoglobin A1C 7.0% (53 mmol/mol) vs. 7.9% (63 mmol/mol)) was shown to reduce microvascular complications but just failed to significantly reduce rates of myocardial infarction ($p=0.052$)[27]. Therefore, studies were

commenced in patients with Type 2 diabetes to further investigate the effects of intensive glucose control on the development of diabetes related complications, focussing mainly on vascular complications and overall mortality (Table 1.1). Interestingly there was limited benefit associated with intensive control beyond maintaining standard glycaemic control on macrovascular complications, intensive glucose control was associated with an increased risk of hypoglycaemia and weight gain[28, 29]. In The Action to Control Cardiovascular Risk in Type 2 Diabetes (ACCORD) trial intensive control was associated with an increased risk of mortality, which may in part have been due to the intensive-therapy group receiving a greater number of medications from different drug classes. There were also a larger number of people on medications such as Rosiglitazone now known to be associated with an increased risk of AMI and death from cardiovascular causes (91.2% vs 57.5%)[20]. However, the exact mechanisms that resulted in the increased mortality rate in ACCORD for patients randomised to intensive control remain unknown. Of note, there was no increase in mortality in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT) for patients randomised to intensive glycaemic control[30, 31].

Table 1.1: Outcomes for glucose lowering trials

	UKPDS[27]	ACCORD[29]	ADVANCE[31]	VADT[30]
Number of subjects	3,867	10,251	11,140	1,791
Age (years)	53	62	66	60
Duration of diabetes (years)	0	10	8	11.5
History of CV disease (%)	NR	35	32	40
Median HbA1c at baseline (%)	7.0	8.1	7.2	9.4
Duration of follow-up (years)	10	3.5	5	5.6
Achieved median HbA_{1c} for I vs S (%)	7.0 vs 7.9	6.4 vs 7.5	6.3 vs 7.0	6.9 vs 8.5
HR or RR for primary CV outcome (95% CI)	0.84 (0.71 to 1.00) NS	0.90 (0.78 to 1.04) NS	0.94 (0.84 to 1.06) NS	0.88 (0.74 to 1.05) NS
HR or RR for all-cause mortality (95% CI)	0.94 (0.80 to 1.10) NS	1.22 (1.01 to 1.46) p = 0.02	0.93 (0.83 to 1.06) NS	1.07 (0.81 to 1.42) NS

The recommended initial choice of treatment for patients with type 2 diabetes is lifestyle modification, by exercise and diet modification which is universally recommended by most guidelines. Generally if after 3 months patients have failed to reach glycaemic targets, it is recommended that glucose lowering therapy is started, with metformin usually being the first line choice, unless contraindicated[32]. Following the introduction of metformin, it is also recommended that patients should be reviewed every 3-6 months, and if failing to reach glycaemic targets a second line medication may be introduced. Optimising glycaemic targets for individual patients is currently encouraged by leading diabetes societies but the general target for good control remains <7.0% (53mmol/mol).

There are a large number of second-line medication options available, all of which have benefits or side effects which may make them more or less appropriate for specific patients (Table 1.2). As mentioned, metformin is the most widely used first line agent and works by reducing hepatic glucose output which subsequently results in lower fasting glucose levels. The main side effects reported include gastrointestinal upset

and lactic acidosis. Metformin is also unsuitable for patients with an eGFR below 30 mL/min/m^2 [27]. There is also some evidence to suggest that metformin provides cardiovascular protection[33, 34]. Sulfonylureas are a cheap, widely available drug but do have side-effects that need to be considered; the main ones being hypoglycaemia and weight gain[27]. However, they need to be used in caution in people with declining renal function especially as it approaches end stage renal disease. The sulfonylureas gliclazide MR and glimepiride have proven safety cardiovascular safety despite being shown to be associated with an increased risk of hypoglycaemia [31, 35, 36]. Acarbose is a medication with moderate glucose lowering effects that may be useful in treating post-prandial hyperglycaemia. However, the medication is now not widely used due to its side-effect profile (bloating and flatulence) and the availability of other treatment options.

Table 1.2: List of glucose lowering medication

	Mechanism of action	Efficacy	Hypo-glycaemia	Effect on atherosclerotic disease	Effect on HF	Effect on progression of DKD	Side effects	Contraindications
Metformin	Reduces hepatic glucose output	High	No	Benefit	Neutral	Neutral	GI upset Lactic acidosis	Renal impairment (<30 mL/min/m^2) Hepatic impairment
Sulfonylurea	Insulin is released in a glucose independent mechanism	High	Yes	Neutral	Neutral	Neutral	Weight gain	Severe renal/hepatic impairment
Thiazolidinedione	Binds to transcription factor peroxisome proliferator activated receptor PPARϒ and increasing insulin sensitivity	High	No	Potential benefit	Increased risk	Neutral risk	Fluid retention HF Non-axial fractures in women Bladder cancer Weight gain	Black box warning for HF
DPP-4 inhibitors	Decreases inactivation of GLP-1 increasing availability	Inter-mediate	No	Neutral	Potential risk (Saxagliptin)	Neutral	Rash Pancreatitis GI upset	Pancreatitis Hospitalisation due to HF with Saxagliptin

	Mechanism of action	Efficacy	Hypo-glycaemia	Effect on atherosclerotic disease	Effect on HF	Effect on progression of DKD	Side effects	Contraindications
GLP-1 receptor agonists	Increases beta-cell insulin releases, decreases gastric emptying	High	No	Neutral, benefit with (Dulaglutide, Liraglutide, Semaglutide)	Neutral	Potential benefit	Nausea Vomiting Weight loss	Pancreatitis or pancreatic malignancy
SGLT-2 inhibitors	Inhibition of SGLT-2 increases urinary glucose loss	Inter-mediate	No	Benefit with (Empagliflozin, Canagliflozin)	Benefit with (Empagliflozin, Canagliflozin, Dapagliflozin)	Benefit with (Canagliflozin, Empagliflozin, Dapagliflozin)	Dehydration Dizziness Genitourinary infections Ketoacidosis Weight loss	Renal impairment (<45 mL/min/m^2) Avoid use with loop diuretics
Insulin	Direct activation of insulin receptor	Highest	Yes	Neutral	Neutral	Neutral	Hypoglycaemia Weight gain	

*HF: Heart Failure, DKD: Diabetic Kidney Disease

The introduction and subsequent controversy surrounding the potential negative cardiovascular effects of the thiazolidinediones (TZDs) has led to major changes in the way that trials of new glucose lowering medications are conducted with a focus on monitoring the cardiovascular safety of glucose lowering medications in addition to the ability to lower glucose levels. This has resulted in an expansion in the amount of data available on cardiovascular outcomes for patients with diabetes. TZDs were available as pioglitazone, which is currently still available in Australia, and rosiglitazone which is no longer available[37, 38]. They work in lowering glucose by binding to transcription factor peroxisome proliferator activated receptor PPARγ and increasing insulin sensitivity as well as changes in fat metabolism and reductions in free fatty acids[39, 40]. However, these medications have been shown to be associated with an increased risk of fluid retention, heart failure, non-axial fracture in women, bladder cancer and weight gain[41]. Indeed, in 2007 a "black box" warning was added to the TZDs reminding physicians that these medications should not be used in people with heart failure.

Following the above experience with the TZDs, the Federal Drug Administration mandated cardiovascular outcome trials to monitor for any potential adverse outcomes that may be associated with the introduction of new glucose lowering medications (Figure 1.2). The dipeptidylpeptidase-4 inhibitors (DPP-4) inhibitors were the next class of medication to be introduced and underwent the first cardiovascular outcome safety studies. This class of drugs was shown to be mostly cardiovascular and renal neutral for the respective trials[42-46]. This was with the exception of Saxagliptin which was shown to be associated with an increased risk of hospitalisation for heart failure HR: 1.27 95% C.I: (1.07, 1.51)[47]. The major side effects and precautions for this class include pancreatitis, gastrointestinal upset and rash[41]. DPP-4 inhibitors lower glucose by blocking the enzyme DPP that usually metabolises glucagon-like peptide 1 (GLP-1). Therefore DPP-4 inhibitors increase availability of GLP-1 which stimulates beta cell insulin release. The main advantage of this class of medication is that they lower blood glucose levels without hypoglycaemia, are weight neutral and generally well tolerated.

Sodium glucose co-transporter 2 (SGLT-2) inhibitors were introduced following DPP-4 inhibitors and were shown to inhibit sodium-glucose cotransporters which leads to urinary glucose loss and a reduction in blood glucose levels. There have now been a large number of CV outcome safety trials, which have shown a positive effect of different SGLT-2 inhibitors on cardiovascular death, heart failure and the composite end-point of myocardial infarction, stroke or cardiovascular death[48]. SGLT-2 inhibitors are also favourably associated with positive outcomes for renal complications[49-53], with

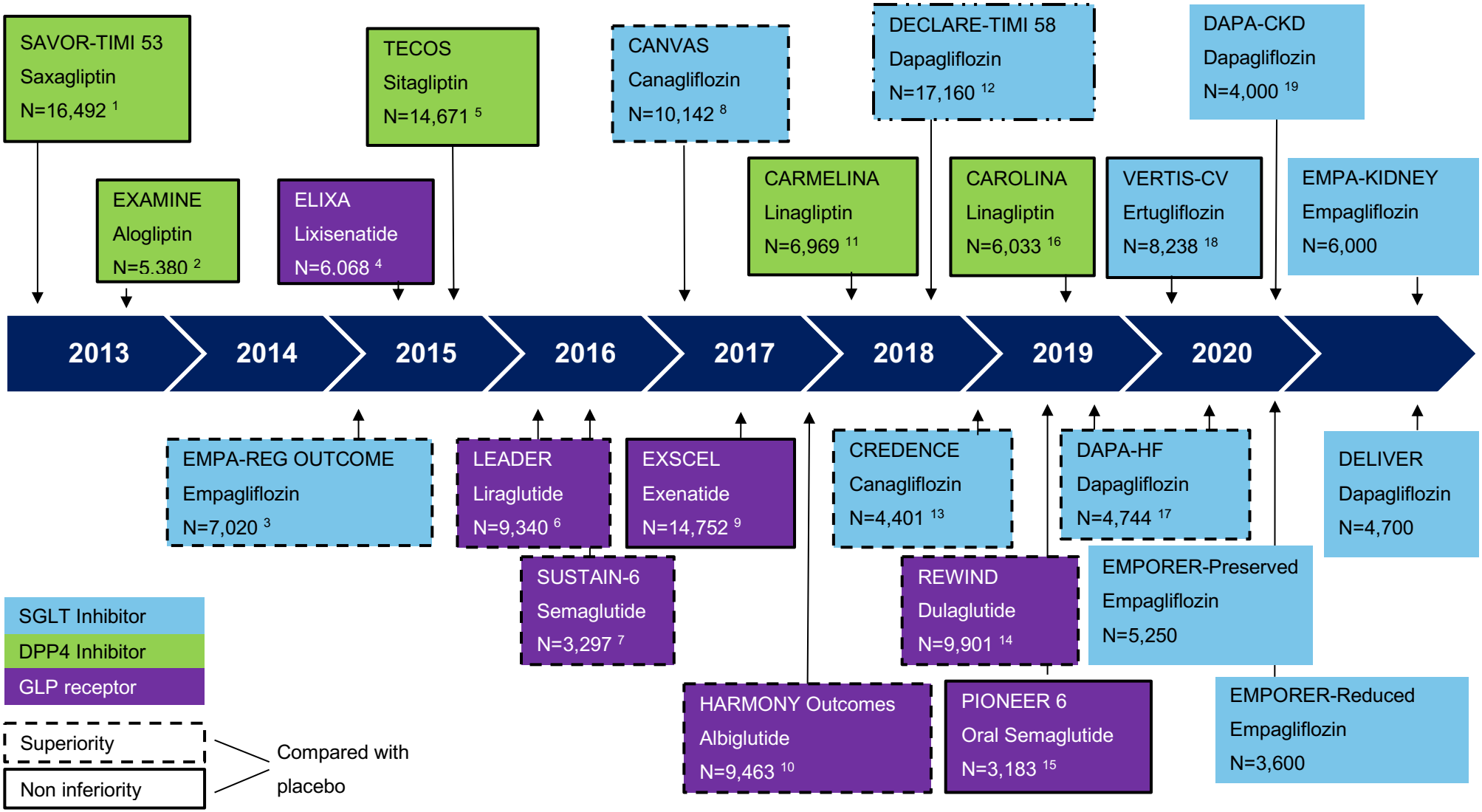
one meta-analysis finding an overall reduction of renal complications with a HR of 0.62: 95% C.I: 0.56, 0.70[48]. Importantly, the SGLT-2 inhibitors slow progression to end stage renal disease There is some heterogeneity within the class for various outcomes, especially MACE (myocardial infarction, stroke or CV death), CV death and composite kidney outcomes suggesting that protective effects may be medication rather than class specific. However, differences in design and the characteristics of patients studied in the various SGLT-2 inhibitor CV kidney trials may also explain the above heterogeneity. Despite these differences the SGLT-2 inhibitor class of medications have consistently been shown to reduce hospitalisations for heart failure. The side effects of SGLT-2 inhibitors include dehydration, infections, ketoacidosis, weight loss and genitourinary infections[41].

Around the same time as SGLT-2 inhibitors were released onto the market, GLP-1 receptor agonists were also introduced. This class of medication is based on the modification of the native GLP-1 to promote its half-life and avoid quick degradation by the DPP-4 enzyme, which in turn results in a stimulation of beta-cell insulin release and a slowing of gastric emptying. They are associated with side effects such as weight loss, nausea and vomiting[41]. Similar to SGLT-2 inhibitors they were shown to be cardioprotective in their cardiovascular outcome trials[43]. Liraglutide, Semaglutide and Dulaglutide have been shown to reduce renal complications and showed a reduction in worsening or new nephropothy[54-56]. The renal effects of the GLP-1 receptor agonists to date, have mainly been related to reductions in albuminuria, but dulaglutide has been shown to reduce renal function loss in the recent REWIND trial[56, 57]. The majority of the patients included in trials so far, with the exception of the REWIND trial, had previous cardiovascular disease, it is possible the GLP-1 receptor agonists will offer primary CV protection in people with diabetes therefore it remains to be seen what primary cardiovascular protection they are able to confer[56].

Although insulin can improve hyperglycaemia in most people, the potential benefits need to weighed against the risks of potential hypoglycaemia and weight gain. There are several options for insulin dosing with basal insulin alone being the most convenient, with the aim to reduce hepatic glucose production and limit hyperglycaemia overnight and between meals[58, 59]. There is also a reduction in the risk of hypoglycaemia compared to short and intermediate acting insulins with longer acting basal insulins such as Degludec and Toujeo[60, 61]. Many individuals will also require short or rapid acting insulin prior to meals in order to reach their individualised glycaemic targets. Premixed insulin is also available and may be appropriate when

both fasting and postprandial glucose levels are elevated. Trials have demonstrated that insulin does not provide any additional protection against complications beyond intensive glucose control[27, 28]. Insulin which was discovered 100 years ago in 1921 is a lifesaving medication in type 1 diabetes through the suppression of hyperglycaemia, ketosis and the promotion of a catabolic state. However, many patients with type 2 diabetes may still need to progress to insulin therapy to maintain good glycaemic control.

Figure 1.2: CVOT safety trials and contemporary cardiovascular-kidney trials



Legend of included studies:

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2. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. New England Journal of Medicine 2013;369:1327-1335[62].

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4. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. New England Journal of Medicine 2015;373:2247-2257[64].

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8. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. New England Journal of Medicine 2017;377:644-657[49].

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11. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. Jama 2019;321:69-79[45].

12. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine 2019;380:347-357[51].

13. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. New England Journal of Medicine 2019;380:2295-2306[68].

14. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. The Lancet 2019;394:121-130[56].

15. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. New England Journal of Medicine 2019;381:841-851[69].

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17. McMurray JJ, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine 2019;381:1995-2008[70].

18. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. New England Journal of Medicine 2020;383:1425-1435[53].

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1.1.1.3 Modifiable Risk factors in the development of type 2 diabetes

Obesity

The term metabolic syndrome describes a number of metabolic risk factors including; obesity, hypertension, dyslipidaemia and insulin resistance which combine to increase the risk of type 2 diabetes and cardiovascular morbidity and mortality[72]. A number of risk factors have been identified in the development of type 2 diabetes of which the most important modifiable risk factor is obesity. Increased body mass index (BMI), waist circumference and waist/hip ratio have all been shown to be associated with the development of type 2 diabetes[73]. Central adiposity appears to be the best predictor of type 2 diabetes [74, 75]. A number of potential mechanisms have been identified to explain this association. Adipocytes in visceral fat compared to subcutaneous are more lipolytic in conditions of increased secretion of pro-inflammatory adipokines and decreased secretion of anti-inflammatory adipokines. This in turn leads to increased insulin resistance, activating inflammatory pathways in adipose tissue, liver and skeletal muscle[72]. Waist circumference is the most practical measure of central adiposity.

Diet

Diet plays an important role in the development or prevention of type 2 diabetes, through its association with obesity and various components of metabolic syndrome. Therefore, a healthy diet represents a significant target for public health lifestyle interventions aimed at reducing the burden of type 2 diabetes in the community. A number of studies have shown an association between an excess consumption of high sugar beverages, processed meat, refined grains and an increased risk for the development of type 2 diabetes. Importantly these associations remain following adjustment for BMI[76]. In addition to increasing risk, certain diets have been associated with a decreased risk of developing type 2 diabetes such as; diets with a low glycaemic index, with low glycaemic load, low in fatty acids, and an increased concentration of cereal fibre and polyunsaturated fatty acids[76].

In particular, the Mediterranean diet has been shown to lower the risk of cardiovascular disease in people at high risk, such as those with diabetes[77]. In the PREDIMED trial the Mediterranean diet with extra-virgin olive oil was investigated for the effect on primary prevention of cardiovascular disease as well as the Mediterranean diet with nuts. Both groups were found to have lower rates of cardiovascular events than those in the reduced-fat diet control group, HR: 0.66 95% CI (0.49, 0.89) for Mediterranean diet with extra-virgin olive oil, HR 0.64 95% CI (0.47, 0.88) Mediterranean diet with nuts[78]. When

the effect of glycaemic index and glycaemic load was examined in over 130,000 individuals across five continents of varying socio-economic status it was found that a high glycaemic index was associated with an increased risk of both major cardiovascular events and death in both participants with or without pre-existing disease[79]. High glycaemic load was also associated with an increased risk of death from cardiovascular causes, however, this was not significant when examined in people with pre-existing cardiovascular disease[79].

Physical Activity

Physical activity level is another modifiable risk factor and target of many public health interventions. The recommended weekly physical activity for Australians is a minimum of 150 minutes of moderate intensity activity. However, in a report by the Australian Institute of Health and Welfare, 56% of all adults did not meet this recommended target, with those in lower socioeconomic areas, of older age or female being less likely to meet physical activity recommendations[80].

In the Look AHEAD trial (Action for Health in Diabetes) the effect of longitudinal change of fat mass, lean mass and waist circumference was examined on the risk of heart failure (HF) and acute myocardial infarction (AMI) in type 2 diabetes over a 4-year follow up period. They found that a decline in fat mass and waist circumference were associated with a lower risk of HF, especially of heart failure with preserved ejection fraction, but not with an AMI[81].

A 2017 Cochrane systematic review of 11 randomised control trials found that diet and exercise was able to reduce or delay the incidence of type 2 diabetes in people with impaired fasting glucose[82]. However, they were not able to examine the impact of diet or exercise independently. As well as simply increasing the amount of exercise undertaken, there is a growing body of evidence supporting the need to reduce the overall sedentary time, which has been shown to be associated with the severity of insulin resistance experienced[83].

Smoking

Smoking is a known risk factor in the development of both type 2 diabetes and its associated complications, with smokers at a 45% increased risk of type 2 diabetes than non-smokers[84]. However, passive smoking has also been shown to be associated with an increased risk of developing type 2 diabetes[85]. The risk between developing type 2

diabetes and smoking appears to be dose dependant with risk increasing as smoking intensity increases[85]. Smoking is thought to increase the risk of type 2 diabetes by increasing insulin resistance and compensatory insulin-secretory responses[86]. Smoking is also known to be associated with greater central fat accumulation which is a known risk factor in the development of type 2 diabetes.

Psychosocial factors

Diabetes distress is a distinct psychological disorder, associated with the high psychological burden resulting from managing a demanding chronic disease, with an estimated prevalence reported to be between 18-45%[87, 88]. Individual's stressors are associated with the burden of managing their diabetes and include: emotional and cognitive distress related to diabetes, interpersonal distress, dosing of medication, monitoring of blood glucose, management of food intake and exercise[32, 89].

The distinct difference between diabetes related distress and general depressive symptoms also relate to their predictive ability. Appropriate management of this condition is important, with diabetes distress potentially directly impacting on an individual's ability to manage their diabetes. This may occur by impacting on medication taking behaviour, dietary habits and exercise which in turn may increase haemoglobin A1C [87, 90].

1.1.1.4 Non-Modifiable Risk factors in the development of type 2 diabetes

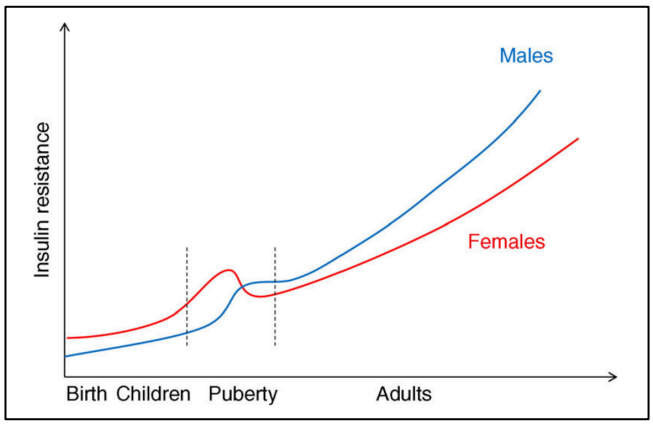
Increasing Age

The past century has seen a dramatic increase in life expectancy for Australians, with individuals born in 2016-18 expected to live 34 years longer than those that were born in 1881-91[91]. This increase in life expectancy has led people to live to an age where they develop type 2 diabetes, develop associated complications and sometimes live with these diabetes related complications for decades. There are several processes through which aging is associated with an increased risk of developing type 2 diabetes; by impairing insulin secretion and enhancing insulin resistance through obesity and sarcopenia[92]. In addition, increased age has been shown to be independently associated with lower physical activity levels, with the number of Australians aged 65 not doing 30 minutes of moderate or vigorous exercise a day over 75%, with this figure increasing further with greater age[80]. Given that Australia has an aging population, the association between age and type 2 diabetes has implications for the incidence of type 2 diabetes and its associated complications.

Sex

In Australia there are differences seen in the prevalence of type 2 diabetes by sex and socioeconomic status, unlike type 1 diabetes. Men are more likely to report a diagnosis of type 2 diabetes compared to women, 6.1% vs 4.6%[14]. However, it appears that this sex difference varies at different ages and across different regions, (Figure 1.3)[2].

Figure 1.3: Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus



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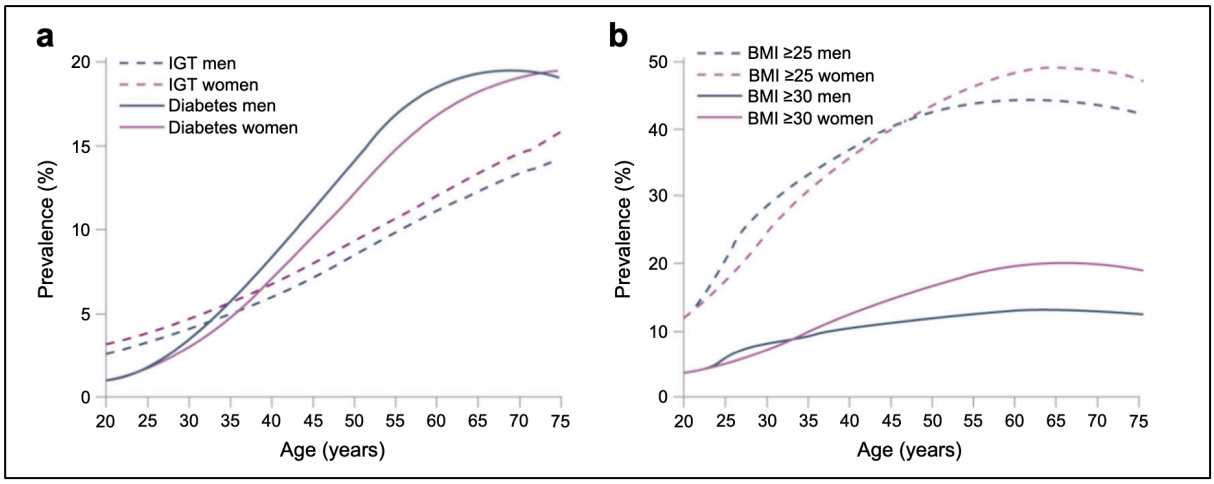
Studies have placed estimates of two-thirds of children and adolescents with type 2 diabetes as being female[93-97]. However, Asian populations have reported the opposite with higher proportions of males being diagnosed with youth onset type 2 diabetes [97, 98]. Throughout midlife, the prevalence of type 2 diabetes tends to be higher in men than in women. This may be in part explained by increased insulin resistance in men and obesity thresholds in women. Hyperinsulinaemic-euglycaemic insulin clamp data suggests that men are more insulin resistant than women throughout midlife[99]. Another hypothesis is the severity in obesity associated with developing type 2 diabetes is increased with women, with one study in the United Kingdom demonstrating that women had a BMI that was 1.8 kg/m^2 higher than males at diagnosis of type 2 diabetes($p<0.01$) following adjustment for age[100]. As people age further there may be a subsequent increase in risk for type 2 diabetes in females due to changes relating to menopause[1]. These include increased visceral fat deposition, leading to insulin resistance and an elevated risk of metabolic syndrome, (Figure 1.4)[1, 101, 102].

Figure 1.4: Sex differences in burden of type 2 diabetes and cardiovascular risk across the life course



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History of diabetes

A family history diabetes has been implicated in an increased risk of developing type 2 diabetes later in life. This may be despite an individual maintaining a healthy lifestyle. There has been evidence from a number of twin and family studies to support this hypothesis[103]. A number of studies have been conducted with the increased availability and decreasing cost of genome-wide association studies with the identification of over 300 genetic variants with a strong association with type 2 diabetes[104]. Given that type 2 diabetes is a complex and polygenic disease, this is likely to only represent a small proportion of the genetic variants associated with it. Estimates so far place the identified loci at ~20% of type 2 diabetes heritability[105]. One study was able to cluster potential susceptibility loci into five major clusters based on their influence on glycaemic phenotypes. One cluster led to changes in insulin sensitivity, the second leading to reduced insulin secretion and fasting hyperglycaemia, the third a defect in insulin processing. The fourth cluster led to a change in insulin processing and secretion, however no change in fasting glucose was detected as a result of these changes. The final cluster contained 20 at risk loci with no clear association to glycaemic traits[106]. Considering the ~80% of unaccounted heritability, this could suggested interaction between susceptible loci and environment[107].

Aboriginal Populations

Several studies have demonstrated an increased prevalence of type 2 diabetes in Aboriginal populations. However, the increased prevalence of type 2 diabetes in Aboriginal populations compared to non-aboriginal populations is not a consistent finding with one systematic review finding differences depending on level of urbanisation[108]. The Australian Indigenous population has one of the highest prevalence of type 2 diabetes, estimated at between 3.5-33.1%, depending on the specific population studied[109, 110]. Following the development of diabetes, Indigenous Australians with type 2 diabetes are hospitalised at 4.3 times the rate as non-Indigenous Australians[14]. Diabetes is listed as a contributing factor in 8% of deaths for Indigenous Australians[111].

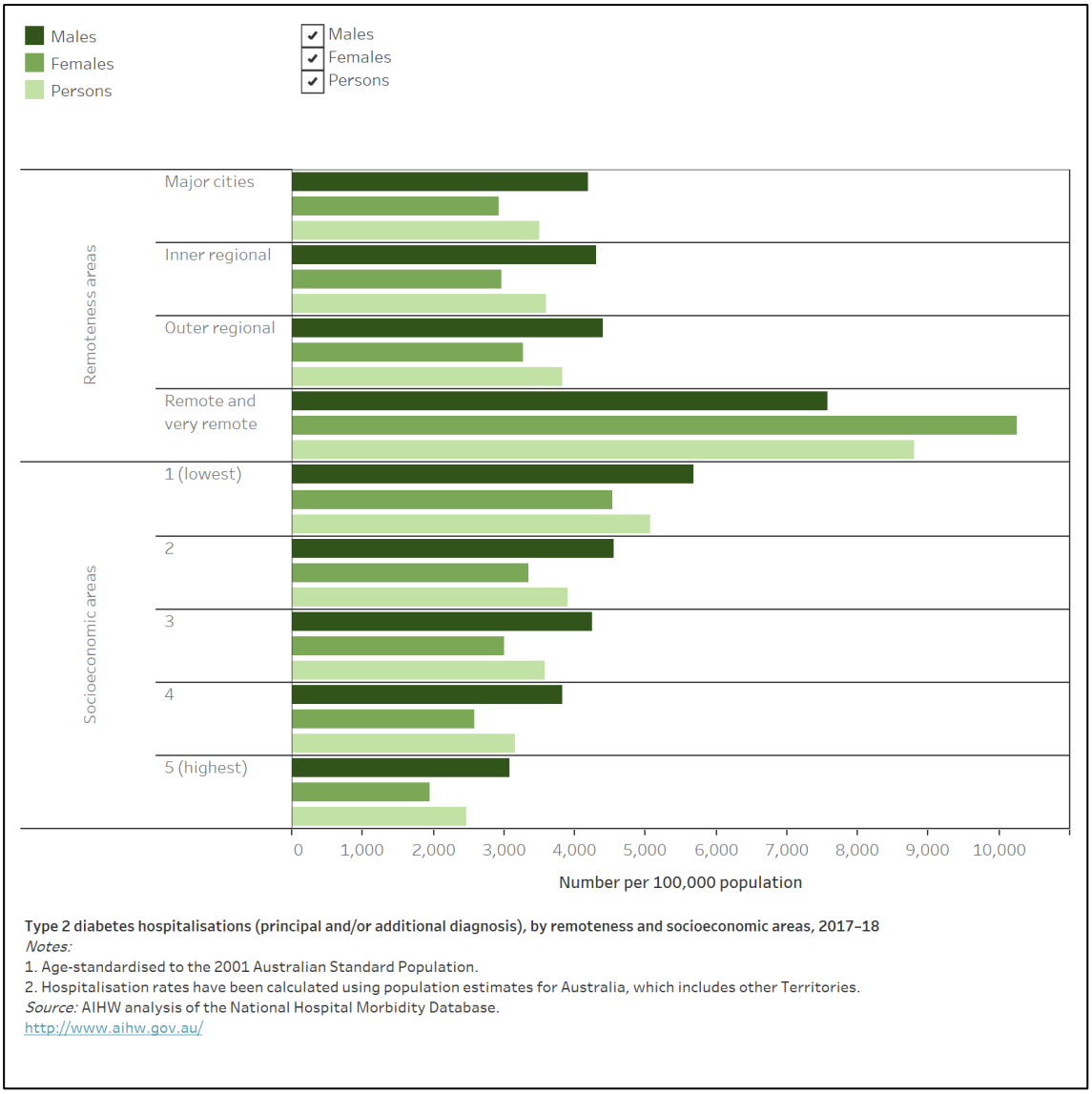
Socioeconomic status

Lower socioeconomic status (SES) has been shown to be an independent risk factor in the development of type 2 diabetes[104]. Within Australia SES is measured by the Australian Bureau of Statistics (ABS) as the Socio-Economic Indexes for Areas (SEIFA) score which is a summary of an area's relative advantage/disadvantage. This index is calculated on information collected at the time of the census such as[112];

- Percentage of low-income households
- Unemployment rate
- Percentage of low-skilled occupants or individuals without qualifications
- Percentage of households without a car
- Percentage of households experiencing overcrowding
- Percentage of individuals under 70 with a disability
- Percentage of children with unemployed parents
- Percentage of people with poor English proficiency

According to estimates by the Australian Institute of Health and Welfare, individuals that were living in the lowest socioeconomic area were twice as likely to develop type 2 diabetes compared to those living in the highest socioeconomic area, (Figure 1.5)[14].

Figure 1.5: Prevalence of self-reported type 2 diabetes, persons 18 and over, by sex, remoteness and socioeconomic areas, 2017-18



Type 2 diabetes hospitalisations (principal and/or additional diagnosis), by remoteness and socioeconomic areas, 2017–18
Notes:
1. Age-standardised to the 2001 Australian Standard Population.
2. Hospitalisation rates have been calculated using population estimates for Australia, which includes other Territories.
Source: AIHW analysis of the National Hospital Morbidity Database.
http://www.aihw.gov.au/

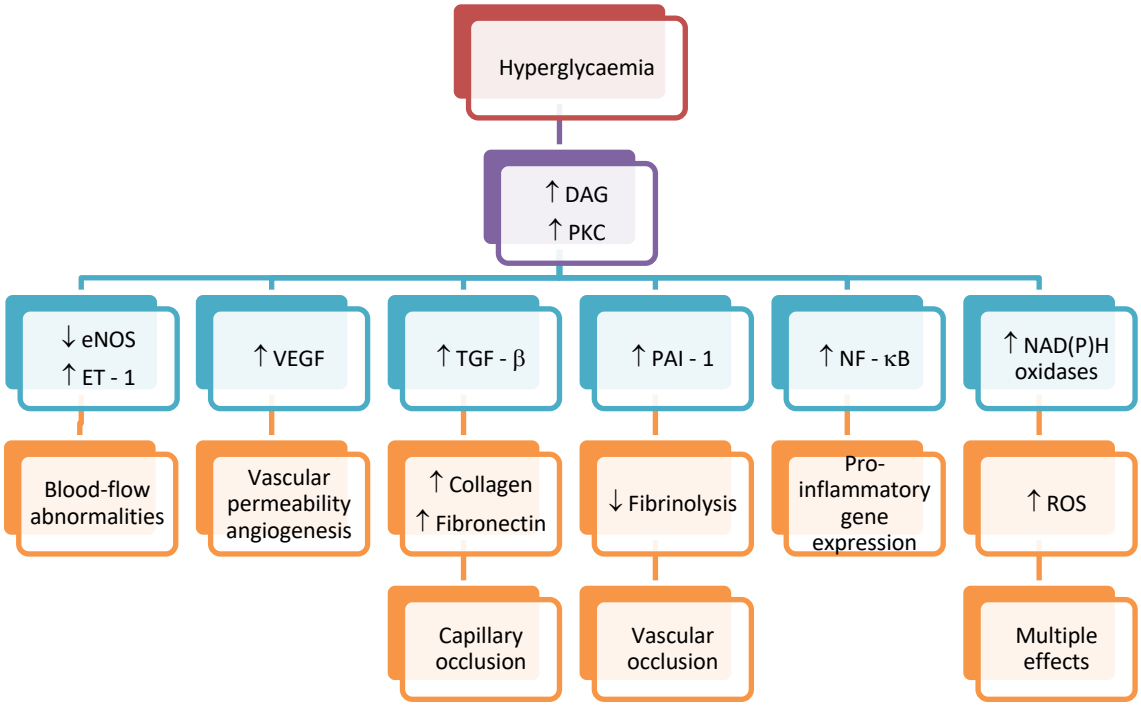
Source: Australian Institute of Health and Welfare[15].

The exact link between SES and the increased risk for development of type 2 diabetes remains to be fully explained. Even after accounting for traditional risk factors such as diet, exercise and obesity, there still remains between 50-77% of excess risk to be explained[113].

The Pathogenesis of Diabetes Related Complications

The micro and macrovascular complications seen in patients with diabetes are in part due to early onset endothelial dysfunction. In patients with diabetes there is an increase in circulating inflammatory markers and oxidative stress, which in turn leads to endothelial dysfunction[114]. There are a number of mediators of this endothelial dysfunction including: nitric oxide, reactive oxygen species, the renin-angiotensin system, endothelin-1, advanced glycation end products (AGE) and inflammation (Figure 1.6)[115-118]. These mediators have a number of deleterious effects on the vascular system including capillary and vascular occlusion, blood-flow abnormalities, pro-inflammatory gene expression, vascular permeability and angiogenesis[118, 119]. All of these mediators combine to increase the rate of macro and microvascular complications.

Figure 1.6: Mechanisms of Diabetic Complications



Adapted from: Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414(6865):813 and Rask-Madsen C, King GL. Vascular complications of diabetes: mechanisms of injury and protective factors. Cell metabolism. 2013;17(1):20-33 [118, 119].

DAG: Diacylglycerol, PKC: Protein kinase C, eNOS: Endothelial nitric oxide synthetase, ET – 1: Endothelin -1. VEGF: Vascular endothelial growth factor, TGF - β: Transforming growth factor - β, PAI -1: Plasminogen activator inhibitor -1, NF - κB: nuclear factor kappa-light-chain-enhancer of activated B cells, NAD(P)H oxidases: Nicotinamide adenine dinucleotide phosphate

Risk Factor Reduction Through Multifactorial Intervention

It is well established that risk factor modification through the optimisation of glycated haemoglobin levels and blood pressure, treatment of microalbuminuria, dietary intervention, exercise and smoking cessation are able to reduce the rates of development and progression of vascular complications[120, 121]. Hyperglycaemia is associated with endothelial dysfunction to which increased thrombogenicity, hypertension and dyslipidaemia contribute. Therefore, effective management and prevention of complications are required to be multifactorial in nature and target blood pressure, lipids and glucose. Best practice guidelines currently involve multifactorial interventions of: glycaemia control, blood pressure control, antiplatelet therapy, lipid control and lifestyle modification to within target ranges[122].

A number of trials, both pharmacological and epidemiological, have suggested that the use of statins and blood pressure (BP) lowering medications are primarily responsible for the risk reduction seen in cardiovascular (CV) events that had been observed in recent times[123-127].The publication of these large influential studies in the 1990's and early 2000's, and the further confirmation of the CV benefits of the above approach in later studies, has led to a drastic increase in the uptake of statins and anti-hypertensive agents, in particular renin-angiotensin system (RAS) inhibitors, for high risk vascular patients with and without diabetes[128-130].

One of the earliest multifactorial risk-factor studies was the Euro Heart Study, which showed that the use of renin-angiotensin-aldosterone system inhibitors, beta-blockers, anti-platelets and statins that were given to 44% of patients with type 2 diabetes was associated with a decrease in all-cause mortality HR: 0.37 (95% CI: 0.20, 0.67) and cardiovascular events HR: 0.61 (95% CI: 0.40, 0.91)[131].

The Steno-2 is one of the most influential diabetes trials of risk factor modification to date showing the impact of target-driven multifactorial therapy. A total of 160 patients with type 2 diabetes were randomised to receive intensive therapy or standard therapy. Those that were randomised to the intensive arm, received a combination of lifestyle counselling as well as target driven haemoglobin A1C, lipid and blood pressure control. They received a combination of renin angiotensin system blockers, statins and aspirin. Following 7.8 years a 50% reduction in micro and macrovascular complications was observed in the intensive group[121]. This benefit in complications persisted onto the 13-year follow up, and a decrease in mortality was seen, with a reduction of 20%[130]. Other

Steno-2 follow up studies have shown a reduction in renal events and heart failure related events[132].

Large scale epidemiological studies have also shown the importance of multifactorial management. One study of over 270,000 patients with type 2 diabetes in Sweden showed that if patients were able to maintain 5 risk factors to within target: haemoglobin A1C, LDL-C, albuminuria, blood pressure and smoking patients were able to reduce their risk of death, myocardial infarction or stroke to equivalent to the general population[133]. However, the risk of heart failure persisted despite adequate control of risk factors. It was hypothesised that it was most likely that cardio-renal mechanisms were contributing as atrial fibrillation, haemoglobin A1C, BMI and poor renal function were very strong predictors of heart failure related events, which may prove hard to modify. This was further supported by Wright et al. who found that even with optimal risk factor control the risk for cardiovascular events, cardiovascular mortality and heart failure was higher in patients with type 2 diabetes compared to those without diabetes[134]. This risk was highest in those with both cardiovascular and renal disease at the commencement of the study.

However, over time, some concern about side-effects has been reported regarding the use of statins, with patients reporting side effects such as myalgia and memory loss[135, 136]. Due to the reported concerns associated with statins, the introduction of newer approaches to treat dyslipidaemia, such as the proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors and ethyl icosapent, will become increasingly important in the treatment and prevention of dyslipidaemia and subsequent cardiovascular events[137, 138].

Guidelines for lipid management vary between various professional societies. Some groups promote specific targets based on risk categories, whereas others propose variability in statin therapy intensity. Both the 2019 European Society of Cardiology (ESC) and 2020 American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guidelines recommend specific targets based on patients risk category[139, 140]. The main difference being that the ESC guidelines also recommend a reduction of at least 50% in LDL-C for those at high to very high risk of CVD[140]. The AACE/ACE guidelines are not specific to diabetes patients and include treatment goals for non-HDL-C, APO-B and triglycerides. They are also based on estimated 10-year risk. With diabetes included as a risk factor, all patients would be considered to be at a minimum high risk or above and would be aiming for a LDL-C

level of below 2.6mmol/L which is the same as the moderate CVD risk category in the ESC guidelines[139, 140]. The American Diabetes Association guidelines are based on primary and secondary prevention and do have specific targets, but rather suggest basing statin therapy intensity based on 10-year risk of CVD in primary prevention. Both the ADA and AACE/ACE guidelines recommend the use of PCSK-9 inhibitors in cases where LDL-C remains above target despite intensive treatment. Although the ESC guidelines recommend the use, they do contain a caveat stating that the role in patients with diabetes remains to be further elucidated[140].

The routine use of aspirin for primary prevention has become a controversial topic with the release of several large-scale randomised control trials both for general and diabetes specific populations. The ASCEND trial found no overall benefit for patients with diabetes, with the prevention of serious vascular events outweighed by the bleeding hazard[109]. This was also described in the ASPREE trial of the general patient population, of which 11% had diabetes, finding no significant benefit for CV events and an increased risk of major haemorrhage[141, 142]. These findings were again supported by a large-scale meta-analysis of over 150,000 patients looking at all-cause mortality and the primary safety outcome of major bleeding, finding no benefit in all-cause mortality[143]. Though this trial initially showed a risk reduction for AMI this was not seen when the analysis was restricted to more contemporary trials. The same risk of major bleeding and intracranial haemorrhage was also reported as in other trials[143]. The release of these trial results has resulted in changes to guidelines, with few now outright recommending their use in primary prevention, and a shift to use an individual base for those at very high risk of CV events[77, 140]. For secondary prevention, despite the risks associated, the risk of adverse events are outweighed by the benefits associated with the reductions seen in CV events, as demonstrated in a meta-analysis by the Antithrombotic Trialists Collaboration demonstrating a reduction of 6.7% compared to 8.2%, $p<0.001$[144].

Traditionally Associated Diabetes Complications

Cardiovascular Disease

Cardiovascular disease is listed as the leading cause of death in people with type 2 diabetes. With a growing number of people diagnosed with diabetes, the number of people living with and dying of CVD is expected to grow[145]. The prevalence of any CVD, including AMI, HF, stroke and peripheral artery disease in adults with diabetes is currently estimated to be 32%[146]. A diagnosis of diabetes incurs a significant financial cost both at the population and individual level with CVD management contributing between 20-49% of the direct cost associated with treating type 2 diabetes[147]. Of growing concern are the number of people being diagnosed with type 2 diabetes at a younger age, placing them at a potentially higher CV risk. This group may warrant particular focus on risk factor modification in order to prevent the development and progression of atherosclerotic CV disease[148].

Changes in practice and technologies available to detect CV disease have improved considerably. Current guidelines recommend only screening patients who are symptomatic or experiencing atypical cardiac symptoms such as unexplained dyspnoea or chest pain, peripheral artery disease or electrogram abnormalities[77]. Guidelines do not support routine screening of asymptomatic individuals, as appropriate intensive risk factor modification has been shown to be equivalent to invasive revascularisation[149]. The values of screening with newer methods such as computed tomography calcium scoring and computed tomography angiography have not yet been proven in asymptomatic patients with diabetes, and need to be balanced with benefit, cost and risks such as exposure to radiation and false positive results. They may however prove to provide further information on CV risk assessment in people with diabetes[150].

1.1.1.5 Acute Myocardial Infarction

Cardiovascular events related to atherosclerotic disease remain a leading preventable cause of death for people with diabetes, with the prevalence of AMI for people with diabetes estimated to be at 10.0% (95% C.I. 7.5, 12.5.)[146, 151]. A significant number of patients are diagnosed with diabetes at the time of their AMI with estimates ranging from 5% upwards, suggesting that patients are living with diabetes for many years and suffering complications before being diagnosed with diabetes[152].

There are a number of reasons associated with cardiovascular pathology why patients with diabetes are thought to have an increased rate of cardiovascular disease including[153]:

- Increased plaque burden
- Increased complexity of lesions and coronary calcification
- A greater extent of coronary ischaemia
- More diffuse disease
- Disease affecting a greater number of vessels[154, 155]
- Vessels that are more significantly affected
- Relatively fewer normal vessels
- Reduced coronary collateral recruitment[156]
- Reduced coronary vasodilatory reserve

As a result of these factors, patients with diabetes and CAD have both poorer short- and long-term outcomes, including survival, compared to patients without diabetes. For patients with diabetes requiring multivessel revascularisation guidelines support coronary artery bypass grafting (CABG) over percutaneous coronary interventions (PCI) given the current available evidence[157, 158]. This was first shown in the BARI trial (Bypass Angioplasty Revascularisation Trial) which showed a doubling in the 5-year mortality in patients with diabetes that underwent PCI compared to those that underwent CABG[159]. This management approach was further reinforced in the FREEDOM (Future REvascularisation Evaluation in patients with Diabetes Mellitus) study which found benefits for survival, nonfatal myocardial infarction or nonfatal stroke for patients with diabetes treated with CABG over PCI with the SYNTAX (Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) study also finding benefits for survival for patients treated with CABG[160, 161].

Although the management of atherosclerotic disease and AMI has progressed over recent years, it appears that these benefits for mortality have not extended to the same degree for patients with diabetes compared to patients without diabetes. This was shown in one large meta-analysis of over 1.6 million patients between 1970 to 2010 with AMI or acute coronary syndrome (ACS)[162]. In this study significant associations between early mortality and mortality 6-12 months post their event persisted over time for patients with diabetes.

There have been a number of changes to how patients with AMI have been diagnosed. These changes in biomarkers and diagnostic criteria may have resulted in a potential increase in the number of cases of patients diagnosed with an AMI in recent years. A consensus document was released by The European Society of Cardiology and The American College of Cardiology in 2000 in order to redefine how AMIs are classified, resulting in an increasingly sensitive diagnostic criteria[163]. The introduction of high-sensitivity troponin assays has allowed for the detection of previously unrecognised AMIs as compared to creatine kinase-MB[164].

There is conflicting literature available as to temporal trends of AMI in patients with diabetes compared to those without diabetes. This may partly be a reflection of differing health services in which these patients are able to receive care and also due to a change in diagnostic criteria over time resulting in a change in cohorts. Gregg et al. found a significant decline in rates of AMI in patients in the US between 1990-2010 and in another study between 1998-2014 this is similar to findings by the US National Health Interview Survey[12, 165]. This is in contrast to findings from countries with health services which may more comparable to Australia such as Scotland, which found although the incidence of AMI had declined for both patients with and without diabetes the increased risk associated with a diagnosis of diabetes had not changed over time[166]. This was confirmed by a local study from Western Australia between 2006-2010, finding no change in the excess risk of AMI associated with a diagnosis of diabetes over time compared to patients without diabetes[167].

1.1.1.6 Non-Haemorrhagic Stroke

A stroke can occur when either an artery supplying blood to the brain is blocked (an ischaemic stroke or cerebral infarction) or when the artery ruptures and bleeds (haemorrhagic stroke). Ischaemic stroke accounts from 80% of strokes[168]. In 2018, 386,900(1.3%) Australians had experienced a stroke. Annually over 80,000 hospitalisations are required for stroke patients, and in cases where CVD is listed as the underlying cause of death, 20% were due to stroke[169]. Diabetes is known to increase the risk of stroke, people with diabetes are at a 2 times increased risk, and nearly 20% of people with diabetes die due to stroke[170, 171].

Diabetes has shown to be an independent predictor of ischaemic stroke[172]. The degree of risk is further heightened by the extent of CAD a patient has. There are a number of factors that result in an increased risk of ischaemic stroke due to diabetes which

include: endothelial dysfunction, increased inflammation and thrombogenesis[173]. These act in combination with well-known atherosclerotic risk factors which occur in higher prevalence in patients with diabetes such as: hypertension and dyslipidaemia[174]. However, a recent epidemiological study has also suggested that it is possible for patients with type 2 diabetes to eliminate their excess risk for death, compared to the general population if they can achieve five risk-factor variables (glycated haemoglobin, low-density lipoprotein cholesterol, systolic blood pressure, albuminuria and smoking status) within target ranges/recommendations[133]. Atrial fibrillation further increases the risk of stroke in patients with diabetes[175].

Epidemiological studies have shown a decline in both the incidence of ischaemic stroke and case fatality in Western countries over the past decades[8, 12, 176-179]. Declines of more than 50% have been observed in Western Australia for patients with type 2 diabetes[179]. Similar trends have been observed in other studies including Gregg et al. in the US[12]. Although the majority of studies have examined first ever stroke, the rate of recurrent stroke has also been shown to be declining as shown by Rautio et al. in Northern Sweden. However, this effect appears to be sex specific as men did not experience a similar significant decline in recurrent stroke[177]. This has been mirrored in the trends found in mortality, although declines in cerebrovascular disease in both patients with and without diabetes have been shown to be significant, the reduction seen in patients with diabetes is almost double that of patients without diabetes[8].

As with many epidemiological studies that rely on administrative datasets there are a number of limitations to consider when interpreting these results, including incomplete follow-up and misclassification of key endpoints. There is also limited information available on risk factors and their control. Davis et al. were one of the few studies that used a population-based sample but one of the limitations was the relatively small number of events and the selection from a relatively small geographic area which potentially may restrict its generalisability[179].

1.1.1.7 Heart Failure

The cardiovascular complications of diabetes have traditionally been grouped into those of coronary artery disease, stroke and peripheral vascular disease. However, in more recent times, heart failure (HF) has emerged as the most common cardiovascular complication of diabetes and represents a particularly high-risk group of patients[180]. It is now well established that a diagnosis of diabetes is associated with an increased risk

of developing heart failure, both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF)[181]. Given the projected increase in prevalence of diabetes, optimal management strategies are critical in preventing the development and progression of HF in people with diabetes from both the personal and population level, and to subsequently reduce the potential impact of diabetes and HF on health systems[4]. It is likely that a diagnosis of diabetes influences morbidity and mortality in patients with either HFrEF or HFpEF.

The past decade has seen the introduction of SGLT-2 inhibitors and GLP-1 receptor agonists, which have been shown to decrease vascular events in patients with diabetes [182-184]. SGLT-2 inhibitors have recently been shown to reduce cardiovascular death and hospitalisation for heart failure in both patients with or without diabetes for patients with HFrEF(DAPA-HF and EMPEROR Trials)[185, 186]. Although GLP-1 receptor agonists have not yet been shown to reduce admission rates for heart failure, it is possible that they may do so indirectly through their ability to cause weight loss, as obesity has been strongly linked with an increased risk of developing HF[187]. As a result of the above trials these classes of medications may play a significant role in the management of HF, as well as controlling hyperglycaemia, in people with and without diabetes. It remains to be seen how the application of these drugs will impact on patients with characteristics that would have excluded them from randomised controlled trials that produced the positive outcomes described above. As mentioned previously, multifactorial interventions as per the Steno-2 trial have also been shown to reduce HF admissions in patients with type 2 diabetes and microalbuminuria.

Chronic Kidney Disease

Diabetes is the leading cause of new cases of end-stage renal disease (ESRD) treated with renal replacement therapy in Australia, with this number increasing over time from 13% in 1991 to 38% in 2012 of all incident renal replacement therapy patients[188]. Diabetes related kidney disease can be defined as persistent albuminuria, proteinuria and/or estimated glomerular filtration rates (eGFR) <60mL/min per 1.73 m2[188]. Both reduced eGFR and the presence of albuminuria are independently associated with an increased risk of progression to ESRD, cardiovascular mortality and all-cause mortality in people with and without diabetes. The greater the extent of abnormality in eGFR or albuminuria the greater the risk of adverse outcome[189].

The United Kingdom Prospective Diabetes Study (UKPDS) found that 25% of people with type 2 diabetes will develop albuminuria within 10 years of diagnosis[190]. With type 2 diabetes increasing the risk of risk of CKD by 50% compared to people without diabetes[3]. A diagnosis of diabetes earlier in life is also associated with an increased risk of developing CKD and progressing to ESRD[190]. There have been significant declines in a number of complications traditionally associated with diabetes. However, studies have suggested that the incidence of ESRD have plateaued or even increased over recent years[12, 191]. The plateau may be in part due to the rise in prevalence of diabetes[3]. It may also represent a change in medical practices, and a greater availability and willingness to actively treat a greater range of individuals with renal replacement therapy who would previously have been considered unsuitable[191]. Furthermore, due to better vascular outcomes for patients with diabetes, more patients may be surviving long enough to progress to ESRD. There may also be a subgroup of people who have been diagnosed with diabetes at a younger age and are now progressing to ESRD and requiring renal replacement therapy at a young age.

Risk factor modification is known to prevent and slow the progression of CKD and ESRD. However, there has been no overall improvement in mean haemoglobin A1C for the past four years for people attending specialist centres (8.1% (6.5 mmol/mol) in 2010, 8.3% (6.7 mmol/mol) in 2012 and 8.2% (6.6 mmol/mol) in 2014)[192]. In regard to risk factor modification, people with diabetes were more likely to have abnormal levels, ≥1.0 mmol/L, of high density lipoprotein-C (HDL-C) compared to people without diabetes (48.6% vs. 21.7%) and higher levels, ≥2.0 mmol/L, of triglycerides (31.5% vs. 12.5) as measured in the Australian Health Survey Data[193].

The importance of multifactorial risk factor modification was highlighted in the long-term follow-up of the Steno-2 participants with microalbuminuria which showed that intensive glycaemic was able to significantly reduce the progression to macroalbuminuria and slow the rate in decline of GFR. The combined endpoint of ESRD and death was also significantly different over this 21 year up period (HR: 0.53 95% CI 0.35, 0.80)[194].

Further exploration is required to enable up to date reporting on the total number of people both with and without diabetes that develop ESRD and decide to progress to renal replacement therapy and those who don't, in order to judge the impact of clinical practice guidelines and the introduction of newer medications.

Diabetic Foot Ulceration and Lower Extremity Amputation

Diabetic foot is a chronic complication of diabetes that results in lesions of the deep tissue and is associated with neurological disorders and varying degrees of peripheral vascular disease of the lower limbs[195]. There are a range of diabetes related foot complications including ulceration, deformity, ischaemia, infection and Charcot's neuroarthropathy.

Diabetic foot is often multi-factorial with peripheral neuropathy, peripheral artery disease, foot deformity, trauma, infection, impaired healing and difficulties with self-care all leading to ulceration, failure to heal and subsequent potential amputation. The most common causes of foot ulceration are peripheral neuropathy, foot deformity and external trauma[196]. The best outcomes for patients with diabetic foot ulcers have shown to be delivered by multi-disciplinary teams comprised of; medical, surgical, podiatric, nursing and orthotic specialities[195]. These teams are able to address the systemic factors that impair the healing of diabetic foot ulcers such as; hyperglycaemia, cardiovascular disease, peripheral vascular disease, bacterial infections and abnormal plantar pressures[195]. The medical management includes offloading, treatment of infection and debridement. Surgery is often required for the treatment of infected ulcers and revascularisation of the limb[195, 197]. Two risk factors have been identified for the recurrence of ulcers, the location of the index ulcer, planter hallux ulcers being high risk, and the diagnosis of peripheral vascular disease[198]. There has been some concern regarding the association between risk of below-knee amputations and SGLT-2 inhibitors. However, a recent multicentre observational study found no association[199].

One of the leading risk factors, peripheral artery disease (PAD), is estimated to affect up to 30% of patients with diabetes and is also associated with an increased risk of cardiovascular events and lower extremity amputations[200]. With high rates of PAD there is a need for a cost-effective, easy test which is currently the ankle-brachial index (ABI). However, there is evidence that compared to the general population this is reduced in patients with diabetes. Although it has a high specificity (0.87, 95% CI: 0.48, 0.71) there is a low sensitivity (0.60, 95% CI: 0.48, 0.71) compared to angiography and colour duplex ultrasound[201]. Once disease is established and symptomatic, treatments are restricted to invasive making the early intervention and optimisation of risk factors even more important[195, 200].

The Australian Burden of Disease Study identified 12,300(1.7% of people with diabetes) admissions for diabetes-related lower limb amputation in 2011[202]. It has been estimated that worldwide every 30 seconds a lower limb is amputated due to diabetes, and that 50-70% of all lower extremity amputations are related to diabetes[203, 204]. Estimates have shown that Australia has one of the lowest incidences of diabetes foot in the world, 3.0% (95% CI: 0.9-5.0%) compared to North America with the highest 13.0% (95% CI: 10.0-15.9%) in a meta-analysis[205]. However, there have been concerns raised with poor screening processes for diabetes foot in Australia. The National Diabetic Foot Disease Management Program of Australia set a regular foot examination screening target of 80%. However actual rates of screening are significantly less than these targets, reported to be 50%[206, 207].

There is conflicting evidence on trends in the incidence of diabetic foot and lower extremity amputations, with very little current evidence available for Australia. This variation may in part be due to methodological differences, variations in healthcare systems and differences in how healthcare is delivered[208]. Harding et al. reported an initial period of decline for lower extremity amputation patients with type 1 and type 2 diabetes between 2000-2015 in the US. However, this period of progress plateaued[209]. Wu et al. reported an overall decline in rates of hospitalisations for lower extremity amputation in Hong Kong between 2001-2016[210]. This is in contrast to Aziz et al. who found no change between 2014-2017 in rates of admission for lower extremity amputation[211]. An Australian study by Kurowski et al. conducted between 2000-2010 showed that rates of first instance of lower extremity amputation in Western Australia declined for patients with type 1 and type 2 diabetes. However, recurrent minor amputations increased significantly for patients with type 2 diabetes[212]. Further research is required to establish information on local contemporary trends.

Diabetic Retinopathy

Diabetic retinopathy is a vascular complication that is specific to patients with type 1 or type 2 diabetes and the risk of developing it is proportional to the duration of diabetes and level of glycaemic control. Diabetic nephropathy is the leading cause of new blindness in adults aged 20-74 in developed countries, with other eye conditions also more likely to occur in people with diabetes[146]. As well as duration of diabetes other factors such as: long term hyperglycaemia, nephropathy, hypertension and dyslipidaemia are also associated with an increased risk of diabetic retinopathy[213].

However, studies have shown that tight glycaemic control is able to prevent or slow the progression of diabetic retinopathy[213].

A number of studies have reported on the prevalence of diabetic retinopathy and diabetic macular oedema which range depending on the type of diabetes an individual is diagnosed with and the region the study was conducted in. One pooled-analysis found estimates for diabetic retinopathy of 35%, proliferative diabetic retinopathy of 7% and vision-threatening diabetic retinopathy of 10%[214]. They found estimated for patients with type 1 diabetes to be significantly higher than those with type 2 diabetes. There are few studies that have examined nationwide trends in the incidence of diabetic retinopathy over time. Those that have, have found differing results by type of diabetes, with declines in more severe diabetic retinopathy reported over time for patients with type 1 diabetes[215, 216]. Data regarding type 2 diabetes is conflicting, one study by Cugate et al. in Australia found an increase in any form of diabetic retinopathy. However rates of moderate to severe diabetic retinopathy and proliferative diabetic retinopathy decreased more recently[217]. An English study by Mathur et al. found a decrease in rates of diabetic retinopathy for patients with type 1 diabetes, and stable rates for patients with type 2 diabetes. However, they also reported an increase in screening for diabetic retinopathy for patients with type 2 diabetes compared to stable rates for patients with type 1 diabetes which may go some way to explaining these changes[216].

Interestingly for patients with pre-existing diabetes and retinopathy, retinopathy can temporarily worsen in the setting of rapid improvements in glucose control as shown in the DCCT. A worsening of retinopathy has also been reported in the SUSTAIN-6 trial of Semaglutide[218]. Currently there is no evidence of a direct limit between Semaglutide or any GLP-1 receptor agonist with a worsening of diabetic retinopathy[219]. A number of studies have now supported vascular endothelial growth factor (VEGF) as a key cytokine in the pathophysiology of diabetic retinopathy which has led to a number of new treatment options, including bevacizumab and ranibizumab[220, 221]. These have shown some promising results in restoring normal anatomy and vision loss due to macular oedema[222, 223].

Emerging Complications Associated with Diabetes

As patients with diabetes have received improved glycaemic control and have had better access to advancements in medical care, rates of the traditional complications of diabetes such as lower extremity amputations, acute complications related to diabetes, CVD, all-cause mortality and CVD mortality have declined[224]. However, as people survive longer other complications such as: cancer, chronic obstructive pulmonary disease and non-alcoholic fatty liver disease are becoming more prevalent. Recent literature has suggested that despite the decline in mortality for traditional complications, there has been no change in cancer mortality for patients with diabetes[9]. Despite the recent shift in types of complications seen in patients with diabetes there is little literature available on outcomes other than mortality for patients with and without diabetes. The decline in all-cause and CVD related mortality may be leading to a proportional increase in other forms of morbidity, with clear implications for future policy and resource allocation planning.

Cancer

Epidemiological studies have suggested that patients with diabetes are at an increased risk of developing and dying of cancer compared to patients without diabetes. However, these studies have often been conducted in different populations. The large number of studies in this area have been summarised in recent reviews[225-227]. Whilst there is a strong association between diabetes and cancer, the strength of association depends on the type of cancer being examined, with an increased risk of the development of liver, pancreatic and gallbladder cancers in patients with diabetes[228]. A meta-analysis has shown that patients with diabetes were at an increased risk of developing cancer compared to those without diabetes (HR: 1.19 for men and HR: 1.27 in women), after adjusting for relevant covariates[229]. With increasing rates of diabetes in the community this has clear relevance to future cancer rates. Apart from prevalence studies there has been little information regarding the impact of diabetes on clinical outcomes such as emergency department presentation rates, inpatient admission rates and length of hospital inpatient stay for patients with diabetes compared to patients without diabetes. Following the development of cancer, diabetes has also shown to be predictive of mortality in certain types of cancers. The greatest association between mortality and diabetes has been observed in cancers of the colon, endometrium, liver, pancreas and female breast[230, 231].

There are a number of possible explanations for the observed association between the increased risk of mortality and a diagnosis of diabetes. Cancer patients with diabetes may have increased tumour cell proliferation and may be at an increased risk of metastasis due to a physiological environment of hyperinsulinemia of hyperglycaemia[232]. It may be that high insulin or insulin like growth factor may also promote cancer cell and tumour cell growth[232]. Another potential pathway is acute exposure to hyperglycaemia, leading to increased endothelial cell permeability. Reactive oxidative species are produced at an increased rate and cause structural changes in the basement membrane which may increase the chances of metastasis[233]. There may also be difference in the way that patients with diabetes are managed clinically compared to patients without diabetes[232, 234]. Patients with diabetes are more likely to present with comorbid conditions such as ischaemic heart disease and chronic kidney disease which may lead to less aggressive cancer treatment affecting their survival. It may also be that patients with diabetes have a poorer response to cancer therapies, which includes increased infection risk and intraoperative mortality[235, 236]. There is conflicting literature surrounding the effect of diabetes on diagnosis stage, with the SEER database identifying that women over the age of 67 with pre-existing diabetes were at a 17% increased risk of being diagnosed with late stage breast cancer compared to women without diabetes[237]. However, a meta-analysis found that stage of cancer was not significantly associated with a diagnosis of diabetes[231]. A diagnosis of cancer may also mean that the management of a patients glycaemia and blood pressure is not prioritised, which has shown to have long-term impacts on morbidity and mortality for patients with diabetes[133].

Pulmonary Hypertension

It is increasingly recognised that a diagnosis of diabetes increases the risk of developing heart failure, and more specifically HFpEF[181]. However, the impact of a diagnosis of diabetes on the risk for developing pulmonary hypertension (PH) has not been well documented. One study has shown an increased risk in the development of PH for patients with type 2 diabetes. However, this finding was no longer significant following the adjustment for other explanatory variables and the competing risk of death[238]. However, this study was limited by the small number of cases of PH (n=49, 3.8% of patients with type 2 diabetes). The risk of developing HFpEF and PH seems to be independent of other cardiac conditions commonly associated with a diagnosis of diabetes, such as coronary artery disease, congestive heart failure and hypertension [239]. Of growing interest is the association of PH with right ventricular dysfunction (RVD)

and HFpEF. In the past HFpEF was primarily thought to involve the left ventricle. However, now it is appreciated that RVD is highly prevalent in HFpEF and that it is also associated with an increased risk of adverse outcomes [240].

Although the current classification of PH does not include hyperglycaemia and insulin resistance as causes of PH, these conditions have been shown to be an independent predictor in the development of HFpEF and PH [241]. One multicentre study of PH patients in America which assessed all newly diagnosed PH patients for diabetes found a prevalence of 26% (107 of 415 PH patients), which is significantly higher than the estimated prevalence of diabetes in the general population of America [239]. The exact mechanism behind this increased risk has yet to be defined, however it is thought that that pulmonary vascular tone may be less responsive to vasodilating substances in patients with diabetes [242].

Several animal studies have demonstrated that diabetes may increase the risk of PH by causing left-heart dysfunction through the effect of hyperglycaemia on pulmonary vasculature. It has been shown that patients with diabetes and HFpEF often develop aortic stiffening, adverse haemodynamic profiles and a greater degree of left ventricular hypertrophy compared to patients without diabetes [181]. It has also been suggested that patients with diabetes may have higher right atrial pressures, suggesting stiffer right ventricles and higher levels of diastolic dysfunction, which may be similar to the impact of insulin resistance on the left ventricle[243].

It is proposed that RVD in HFpEF is mainly due to PH, with left ventricular diastolic dysfunction and a decrease in left atrial compliance due to HFpEF leading to an increase in load on the pulmonary venous system and pulmonary pressure. There are a number of general risk factors that have been identified in HFpEF and PH, including; older age, hypertension, coronary heart disease, atrial fibrillation, obesity, left atrial dilation and diabetes [244]. Epidemiological studies of HFpEF have shown varying prevalence of PH, with estimates ranging from 36% to 83% [245]. This variation in estimates may be due to a number of factors including the type of studies these estimates are based on. For example, clinical trials may exclude patients with severe stages of HFpEF, whereas community-based studies may allow any patient with HFpEF to be included. These clinical trials often exclude patients based on co-morbidities such as renal dysfunction and pulmonary disease which are known to be strongly associated with PH.

There is a lack of evidence into the development and outcomes for patients with RVD. However, a number of smaller studies have shown that patients with HFpEF and PH show an increase in severity of symptoms including reduced VO2-max and increased hospitalisation rates for HF and mortality [246, 247]. Despite advances in treatment options and patient support options, survival remains poor, with just under 50% of patients surviving 7 years following diagnosis in one study [248]. This lack of evidence has been highlighted by the Association of the European Society of Cardiology which published a position statement addressing the importance of further study in the area in order to improve the treatment and management of these patients [245]. Given the prevalence of diabetes in the community and plausible contributions to HFpEF and RVD, further exploration of the role of diabetes in outcomes of patients with PH will help to guide future therapeutic interventions. Of note, the SGLT-2 inhibitor empagliflozin has been recently shown to reduce mortality, right ventricle systolic pressure and maladaptive pulmonary modelling in a PH rat model[249].

Alzheimer's disease and Dementia

Growing evidence has shown that diabetes increases the risk of late-life cognitive decline, vascular dementia and Alzheimer's disease[250-252]. There is now also evidence that even high normal levels of glucose are associated with cognitive impairment later in life. However, intensive glycaemic control in randomised control trials has failed to show a reduction in the rate of cognitive decline[253]. The risk of vascular dementia in patients with diabetes appears to be sex specific with one meta-analysis demonstrating a 19% increased risk for women[252]. There are also region-specific differences for Alzheimer's disease with the highest risk seen in Eastern populations[251]. There are a number of potential mechanisms behind this association. Insulin resistance has been shown to be associated with brain atrophy in middle age. High fasting blood glucose has also been linked with reduced hippocampal microstructure in older adults and hippocampal atrophy in adults greater than 60 years without diabetes[254, 255].

Osteoporosis

There is a known increased risk of fractures in patients with type 1 and type 2 diabetes. In people with type 1 diabetes, the risk of hip fracture is 6-times higher than the general population and 2.5 times than that of the population with type 2 diabetes[256]. There have been a number of potential causes identified, with diabetes known to be associated with an increased risk of hypoglycaemic events and falls. The use of insulin for men has also been associated with an increased risk of more falls[257]. This may be explained

by the higher severity of disease in those that require insulin, with associated increases to their risk of having peripheral neuropathy and retinopathy, thereby increasing their risk of falls. Bone mineral density is known to be decreased in patients with diabetes with this decrease being greatest in patients with type 1 diabetes (a decrease of 22-37%), while patients with type 2 diabetes have a 5-10% reduction when compared to age-matched non-diabetic populations[258, 259]. Following a diagnosis of diabetes, β-cell function declines, as does glucose control. This in turn is believed to promote a state of increased oxidative stress, inflammation and the production of reactive oxygen species and advanced glycated end products leading to organ damage and increasing the risk of developing complications[260]. These processes lead to the compromise of bone collagen and mineralisation and bone strength. Obesity and bone marrow fat also act to impair bone health[261, 262]. The medications used in diabetes management also have different effects on bone mineral density and fracture risk, with metformin and incretin-based medications considered neutral. Thiazolidinediones are known to increase the risk of fracture[256]. The effects of SGLT-2 inhibitors on bone quality and fracture risk remains to be fully defined[263]. Given the high life-time risk of a fracture and global disease burden due to osteoporosis and the high incidence of diabetes, the best management and avoidance of osteoporosis is crucial.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease marked by persistent respiratory symptoms and limitations in airflow. Both diabetes and COPD are leading cases of morbidity and mortality and are commonly associated with each other[264, 265]. There is also evidence of an association between decreased lung function and diabetes with a meta-analysis showing a linear inverse relationship between each 10% increase of FEV1% and FVC% lowering the risk of type 2 diabetes by 13% and 12% respectively[266]. One study estimating that 10% of patients admitted with diabetes also had a diagnosis of COPD[267]. Patients with diabetes are also at an increased risk of severe exacerbations and death due to COPD compared to patients without diabetes[264]. In patients with type 1 diabetes, reduced elastic recoil and diffusion capacity have both been reported, potentially due to glycosylation of lung connective tissue and pulmonary microangiopathy[268]. Previous studies have shown that there is a vicious cycle between diabetes and COPD, with inflammatory markers and oxidative stress leading to an increased risk of diabetes which in turn leads to hyperglycaemia and the production of reactive oxygen species which activate inflammation mediators, increasing glucose intolerance[266]. Further evidence has found

that insulin resistance in COPD patients is linked with inflammation markers such as C-reactive protein, interleukin-6 and tumour necrosis factor-alpha[269, 270]. Some of the medications used in the management of COPD have also been linked to hyperglycaemia and weight gain, such as prednisolone[271, 272]. As many people survive or avoid what would have been the traditional diabetes related complications such as an AMI or stroke, they now survive to develop and die of other chronic diseases such as COPD[178]. This has been reflected in research by Gregg et al. who found a significant increase in the number of people dying of chronic lower respiratory disease between 1988-2015, with an average 10-year difference off 0.2(95% CI: 0.0, 0.3) in the HR compared to people without diabetes for whom no significant difference was observed[8].

Contemporary Concepts Regarding the Development of Diabetes Related Complications

Of concern is the growing number of younger adults and even children that are being diagnosed with type 2 diabetes, referred to as young-onset type 2 diabetes. This trend correlates with an increase in rates childhood obesity. Of particular concern with this type of diabetes is the increase in exposure to hyperglycaemia over an individual's lifetime and subsequent risk in the development of diabetes associated complications. Rates of youth-onset type 2 diabetes appear to have remained stable over the past decade in the UK, with those developing youth-onset type 2 diabetes having higher cardiometabolic risk factors compared to those diagnosed with type 2 diabetes later in life[148]. Several studies have now demonstrated that patients with young-onset type 2 diabetes are at an increased risk of mortality, primarily due to cardiovascular disease, compared to patients with type 1 diabetes[148, 273]. One recent meta-analysis showed that each 1-year lived with type 2 diabetes was associated with a 4% increase in all-cause mortality, 3% increase in macrovascular disease and 5% increase in microvascular disease[274]. This group potentially represents a group which warrants greater attention to better metabolic control and provides opportunity for early intervention to prevent potential complications and associated morbidity and mortality.

There are known differences in clinical presentations and trajectory for type 2 diabetes. Recent years have seen a number of studies try and identify clusters within type 2 diabetes based on ethnicity, age of diagnosis, BMI, HDL-C, C-peptide, homeostasis model assessment 2 estimates and other relevant factors[275-277]. Each of these clusters has been identified in separate cohorts and however they are not always able to be

translated to different cohorts due to lack of standardised variables available, and different characteristics within race/ethnicities[275]. The stratification of these clusters has shown a difference in risk for complications and risk factors such as CKD and coronary artery calcium score[275, 276, 278]. The identification and stratification of clusters within type 2 diabetes may allow for the targeting of interventions and therapies to groups that are of particularly high-risk and may gain the most benefit from these interventions, especially in environments that are resource poor.

The other relatively new diabetes phenotype of concern is patients with type 1 diabetes that also have features of the metabolic syndrome, so called double diabetes. There is some difficulty in the diagnosis of double diabetes which relies on the presence of clinical features of insulin resistance. Currently literature suggests the diagnosis of double diagnosis be based on family history of type 2 diabetes, weight gain/obesity and metabolic syndrome and atypical features for type 1 diabetes, such as not initially being insulin dependent or features of insulin resistance[279-281]. The prevalence of metabolic syndrome is estimated to be 30% in Australian patients with type 1 diabetes[282]. This is another group of patients with diabetes that appear to be at high risk for the development of diabetes related complications. It is thought that a potential mechanism behind this risk may be that the insulin resistance and peripheral hyperinsulinemia that are seen in type 1 diabetes is exaggerated in double diabetes, This chronic hyperglycaemia and lipid partitioning leads to increased rates of atherosclerosis and premature rates of cardiovascular disease and other diabetes related complications[280].

Recent Trends in Diabetes Related Complications and Mortality

There is a growing and ever-changing body of literature available documenting the trends in diabetes related complications and mortality. Whilst overall trends of most diabetes related complications appear to be declining (Table 1.3), there is some evidence to suggest that there may be a rise in complications including LEA in younger age groups[283]. Overall in high income countries mortality appears to be decline alongside complications[284].

These trends are influenced by a number of factors which need to be taken into account when interpreting and comparing results between studies which may at times be conflicting. These include the different types of data sources used (administrative, registry or surveys), the standardised definitions of both diabetes and complications

and the location of the study and differing health services available to individuals and health practices.

Table 1.3: Summary of Available Literature on Changes in Diabetes Related Complications

Author, publication year	Years reported	Location	Origin of data source	Type of data	Diabetes definition	Complication reported on	Change in rates reported
Aziz et al, 2020[211]	2014-2017	Austria	Austrian Health Insurance database	Health Insurance	Clinical diagnosis (ICD) plus treatment	Major LEA	→
van den Berge et al, 2018[285]	1985-2008	The Netherlands	Prospective hospital registry	Registry	Treatment	Heart failure	↓*
de Boer et al, 2011[286]	1988-1994, 1999-2004, 2005-2008	USA	National Health and Nutritional Examination Survey	Survey	Glucose (HbA1c) plus treatment	Albuminuria	↓
						Impaired GFR (60 mL/min/1.73 m2)	↑
Burrows et al, 2020[287]	2000-2016	USA	U.S. Renal Data System	Registry	Clinical diagnosis	ESRD in American Indians, Blacks and Hispanics	↓*
Davis et al. 2020[179]	1993-1996, 2008-2011	Fremantle, Australia	Fremantle Diabetes Study, Hospital Morbidity Data Collection, Death Registrations	Registry, Administrative	Clinical diagnosis (ICD)	AMI	↓*
						Stroke	↓*
						HF	↓*
						LEA	↓
						CVD Death	↓*
						All-cause mortality	↓*

Author, publication year	Years reported	Location	Origin of data source	Type of data	Diabetes definition	Complication reported on	Change in rates reported
Fox et al, 2004[288]	1950-1995	USA	Framingham Heart Study	Registry	Glucose level or treatment	CVD Composite of AMI, CVD death, stroke	↓*
Geiss et al, 2019[289]	2000-2015	USA	National Inpatient Sample and NHIS	Administrative, Survey	Clinical diagnosis (ICD)	LEA	Recent (2009) ↑*
Gregg et al, 2014[12]	1990-2010	USA	NHIS, National Health Discharge Survey, U.S. Renal Data System, U.S. National Vital Statistics System	Survey, Administrative, Registry	Clinical diagnosis (ICD)	LEA	↓
						AMI	↓*
						Stroke	↓
						ESRD	↓
Harding et al, 2016[9]	2000-2011	Australia	NDSS, NDI	Registry, Administrative	Clinical diagnosis (ICD)	All-cause mortality	↓*
Kennon et al, 2012[290]	2004-2008	Scotland	Scottish Morbidity Record, Scottish Care Information-Diabetes Collaboration National Diabetes Register	Administrative, Registry	Clinical diagnosis	LEA	↓*
Lind et al, 2013[291]	1996-2009	Ontario, Canada and UK	Healthcare database and The Health Improvement Network (THIN)	Administrative	Clinical diagnosis, treatment and laboratory	All-cause mortality	↓*
Nedkoff et al, 2014[167]	1998-2010	Western Australia	Hospital Morbidity Data System and Mortality Registrations	Administrative	Clinical diagnosis (ICD)	AMI	↓*
						CHD	↓*

Author, publication year	Years reported	Location	Origin of data source	Type of data	Diabetes definition	Complication reported on	Change in rates reported
Read et al, 2019[166]	2006-2015	Scotland	Scottish Morbidity Record, Scottish Care Information-Diabetes	Administrative, Registry	Clinical diagnosis, age at diagnosis, prescription data	AMI	↓*

Thesis Aims

Given the available evidence and identified gaps in knowledge this thesis aimed examined:

1. Changes in Hospital Admission Rates for Cardiovascular Complications in Patients with and without diabetes in Victoria, Australia 2004-2016 (Chapter 3)
2. Trends in rates of kidney disease in people with type 1, type 2 diabetes and without diabetes in Victoria, Australia 2009-2016 (Chapter 4)
3. Temporal trends in lower extremity amputations and 12-month mortality in people with diabetes in Victoria, Australia 2004-2016 (Chapter 5)
4. Change in extent of coronary artery disease and impact of preventative therapies in people with and without diabetes undergoing coronary angiography (Chapter 6)
5. The impact of type 2 diabetes on hospitalisation and mortality in people with malignancy (Chapter 7)

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Chapter 2: Methods

Publications included within this thesis are from analyses conducted using a number of data sources: the Victorian Admitted Episode Dataset (VAED), The Victorian Death Index (VDI), The National Diabetes Service Scheme (NDSS) and a number of smaller hospital level data sources. Specific details that relate to each publication are provided in later chapters.

Ethics and Governance

St Vincent's Hospital Melbourne Human Research Ethics Committee and Research Governance Unit provided ethics approval for the conduct of the studies (HREC/18/SVHM/146 Chapters 3-6) and (LRR 176/18 Chapter 7). I was responsible for the writing of the ethics applications and for the process of submission of applications to the ethics committee.

Data Sources

Victorian Admitted Episode Dataset

Victorian hospital discharge data are maintained by Victorian Department of Health and Human Services[1]. These data sets contain demographic and clinical information on each episode of patient care. Diagnostic information is coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM)[2] and procedural information according to the Australian Classification of Health Interventions (ACHI)[3]. For discharge data, coding occurs at the conclusion of a patient's hospitalisation when experienced clinical coders, record the diagnoses and procedures relevant to the episode and review the entire medical record[4]. Independent audits of Victorian coded hospital administrative data has shown to be to a high level of reliability and adherence to coding standards[4].

Victorian Death Index

The registry of Birth, Deaths and Marriages contains a record of all deaths that occur within Victoria. Commonly the death registration is done by a funeral director and a medical practitioner is responsible for completing the Medical Certificate with the cause of death. The Victorian Death Index is available from January 1994 and contains date of birth, death, age at death, non-coded ICD-10-AM cause of death as recorded by the

medical practitioner, sex, number of siblings, marital status, number and age of children and last residence of the deceased[1].

The National Diabetes Service Scheme

The National Diabetes Services Scheme (NDSS) was established in 1987 by the Australian Government and is administered by Diabetes Australia, including over 1.3 million registrants[5]. It provides subsidised diabetes supplies such as testing strips, syringes and other needs, to registered individuals and is free to all eligible individuals. It includes information about the type of diabetes an individual was diagnosed with type 1, type 2, gestational diabetes or other, but does not include information about individuals with pre-diabetes or impaired glucose tolerance. Between 80-90% of Australians with known diabetes are registered on the NDSS[6]. The registration process requires a medical professional to sign off regarding a patient's diabetes status.

The Australian Census of Population and Housing

The Australian Census of Population and Housing is conducted every 5 years by the Australian Bureau of Statistics and is a compulsory survey of every Australian resident and overseas resident on the night. It includes demographic, social and economic data. Total numbers of people without diabetes were obtained from the publicly available Australian Census of Population and Housing.

Data Linkage

The Centre for Victorian Data Linkage (CVDL) conducts data linkage in Victoria and was established in 2009. It uses a mix of deterministic data linkage and fuzzy matching. Deterministic matches occur when fields match exactly across different records such as date of birth and sex. Fuzzy matching allows slight variation in names and dates resulting in a reduction in the number of false negatives[1].

Statistical Analysis

A range of statistical analysis approaches were used throughout this thesis with a summary of these provided below.

Joinpoint regression was used in chapters 3-5 in order to assess changes in trends over time, this statistical method has been used in a number of iconic diabetes epidemiological trials[7-9]. Joinpoint regression software is available for download from the Surveillance Research Program of the U.S. National Cancer Institute[10]. The program takes the available data and finds the line of best fit for the years, it then also tests whether a multi-segmented line would be a significantly better fit than a straight or less-segmented line[11]. These lines are joined at points called join points, where each Joinpoint marks a statistically significant change ($p = 0.05$). The Joinpoint software uses a Monte Carlo Permutation Method for the tests of significance.

Once line segments are established, the estimated annual percent change is used to describe and test the significance of trends in the model. The annual average percentage change (AAPC) and 95% confidence intervals are calculated as a weighted average from the annual percentage annual percentage change (APC) and 95% confidence intervals where the AAPC represents the entire study periods and APC represents each segmented line identified. If no join points are identified the APC is equal to the AAPC.

Chapter 3 - Changes in Hospital Admission Rates for Cardiovascular Complications in Patients with and without diabetes in Victoria, Australia 2004-2016

Aim

To identify changes for incident admissions for AMI, stroke and heart failure in patients with type 1, type 2 diabetes or no diabetes.

Data Sources

The VAED between 1999-2016 with linkage provided by the CVDL, NDSS and Australian Census, (Figure 2.1).

Statistical Analysis

The total number of each admission for AMI, HF and stroke were obtained through ICD-10-AM codes through the VAED, these admission numbers for each year by type 1 diabetes or type 2 diabetes were divided by the total number of NDSS registrants for each year with either type 1 diabetes or type 2 diabetes.

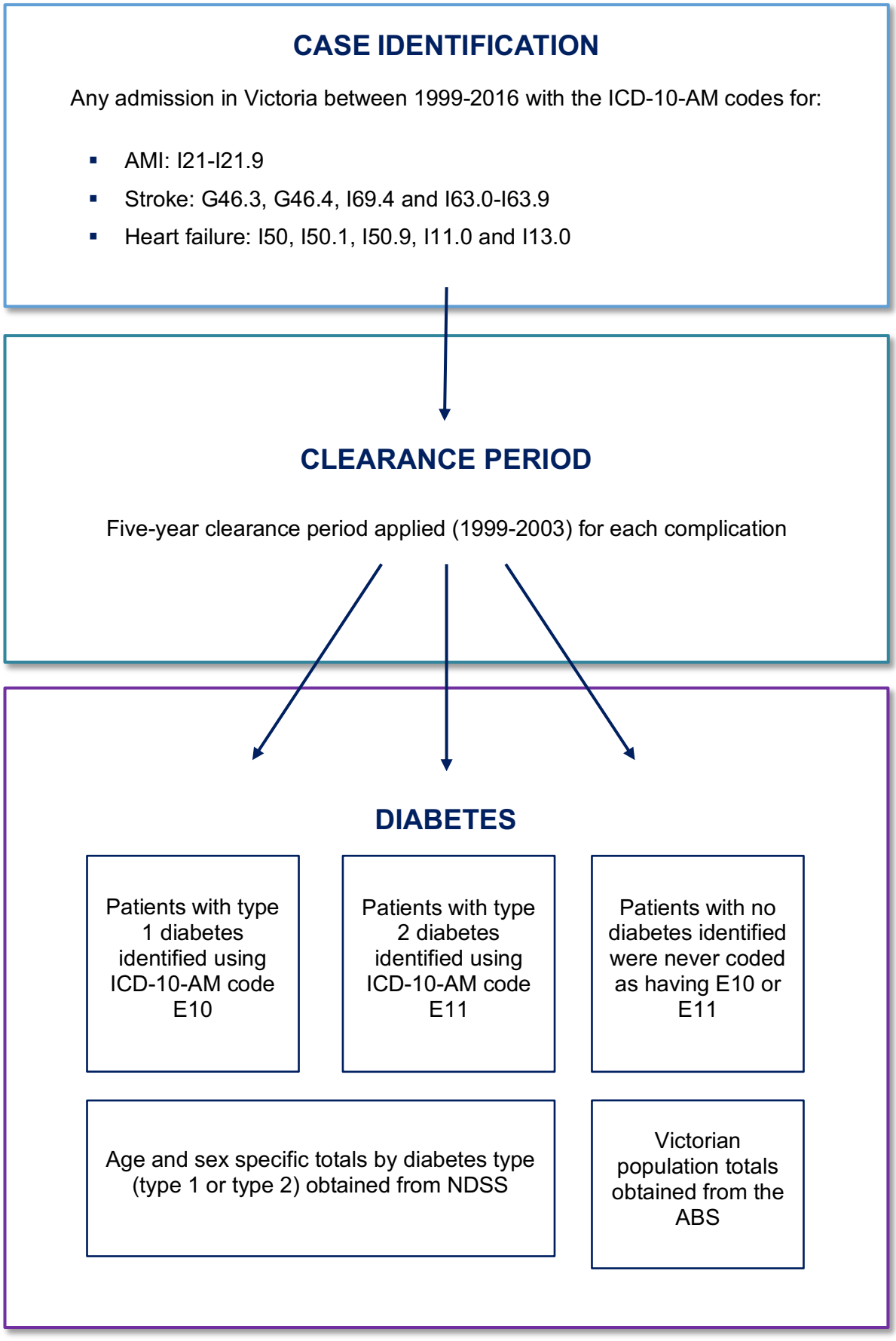
The number of patients admitted for each CV complications without diabetes were divided by the total Victorian population obtained from the Australian Census less the total NDSS registrants for that year to obtain the number of admissions per 10,000 per year.

Rates for AMI, HF and stroke admissions were calculated per 10,000 between 2004 and 2016 by diabetes type and no diabetes and were standardized by applying age and sex specific rates obtained from the NDSS and ABS using the *dstdize* command in STATA.

Poisson regression models adjusted by age group and sex were fitted in order to examine changes over time, with an offset variable included to account for changes in the prevalence of diabetes over the observational period of the study.

Changes in rates over time were then analysed by Joinpoint regression (version 4.7.0.0, Statistical Methodology and Applications Branch and Data Modeling Branch, Surveillance Research Program, National Cancer Institute)[11].

Figure 2.1: Chapter 3 data linkage and case identification



Chapter 4 - Trends in rates of kidney disease in people with type 1, type 2 diabetes and without diabetes in Victoria, Australia 2009-2016

Aim

To identify changes in the rates of diabetic nephropathy, end stage renal disease and dialysis or kidney transplantation in patients with type 1 or type 2 diabetes.

Data Sources

The VAED between 2004-2016, NDSS and Australian Census with linkage provided by the CVDL (Figure 2.2).

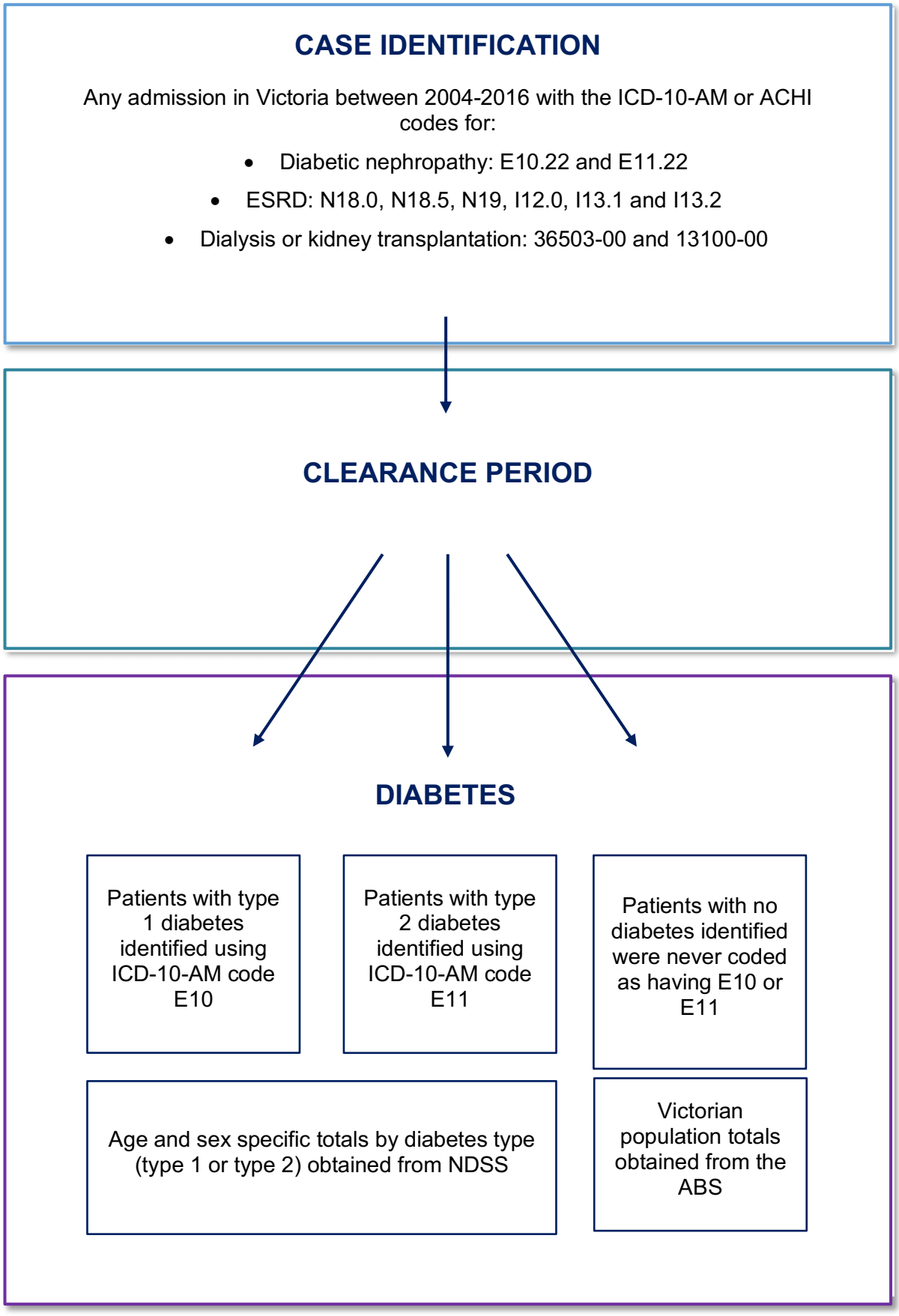
Statistical Analysis

The total number of cases of patients with diabetic nephropathy, end-stage renal disease, dialysis or kidney transplantation with and without diabetes were obtained through ICD-10-AM codes or ACHI codes for kidney disease and diabetes diagnosis (Figure 2.2). This was then divided by the total number of NDSS registrants for either type 1 diabetes or type 2 diabetes, and for patients with no diabetes the total Victorian population obtained from the Australian Census less the total NDSS registrants for that year.

Standardised rates were calculated, and diabetes specific rates observed in the NDSS and ABS populations and expressed per 10,000 adults with 95% confidence intervals (using the STATA command *dstdize*).

Poisson regression models adjusted by age group and sex were fitted in order to examine changes over time. Incident rate ratios were calculated to examine change in rates of admission from 2009 to each subsequent year stratified by diabetes type. Incident rate ratios were also calculated for patients with and without diabetes stratified by year in order to assess any change in risk of admission over time. Changes in rates over time were then analysed by Joinpoint regression[11].

Figure 2.2: Chapter 4 data linkage and case identification



Chapter 5 - Temporal trends in lower extremity amputations and mortality in people with diabetes in Victoria, Australia 2002-2016

Aim

To describe the incidence, mortality and trends over time in minor and major lower extremity amputations in patients with type 1 or type 2 diabetes.

Data Sources

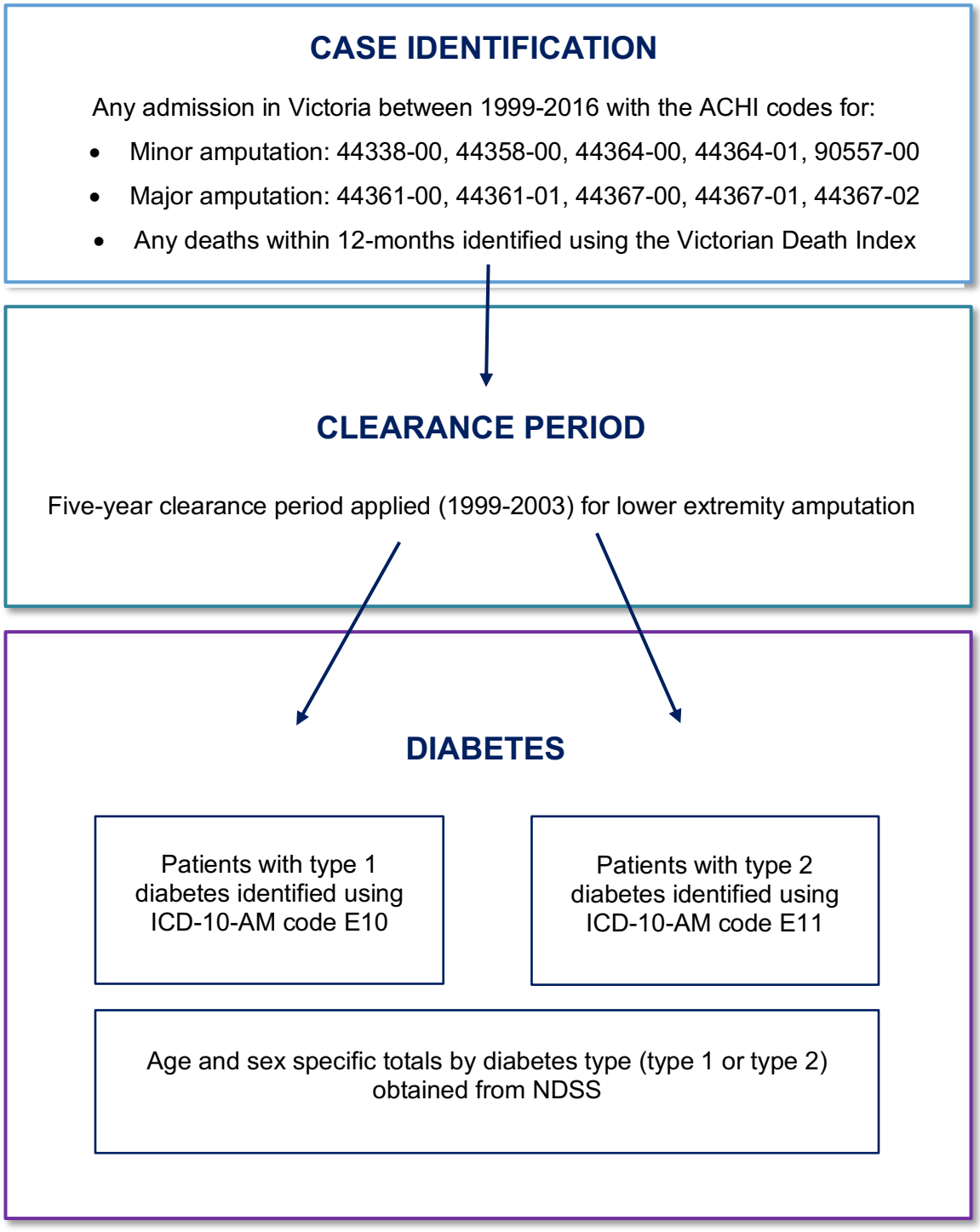
The VAED and Victorian Death Index between 1999-2016, with linkage provided by the CVDL, (Figure 2.3).

Statistical Analysis

Total numbers of patients per year with lower extremity amputations and with diabetes were obtained through ICD-10-AM codes for diabetes and ACHI codes for lower extremity amputations diagnosis. This was then divided by the total number of NDSS registrants for either type 1 diabetes or type 2 diabetes. Standardised rates were calculated by sex, age and diabetes specific rates observed in the NDSS population and expressed per 10,000 adults with 95% confidence intervals.

Poisson regression models adjusted by age group and sex were fitted in order to examine changes over time, with total numbers of patients with diabetes obtained from the NDSS included as an offset variable. Incident rate ratios were calculated to examine changes in rates of admission from 2004 to each subsequent year stratified by diabetes type. In order to assess trends in admission rates over time, we used Joinpoint regression software.

Figure 2.3: Chapter 5 data linkage and case identification



Chapter 6 - Change in extent of coronary artery disease and impact of preventative therapies in people with and without diabetes undergoing coronary angiography

Aim

To evaluate coronary artery burden of atherosclerotic disease in patients with and without type 2 diabetes in a real-world setting and its possible modification by preventative therapies.

Data Sources

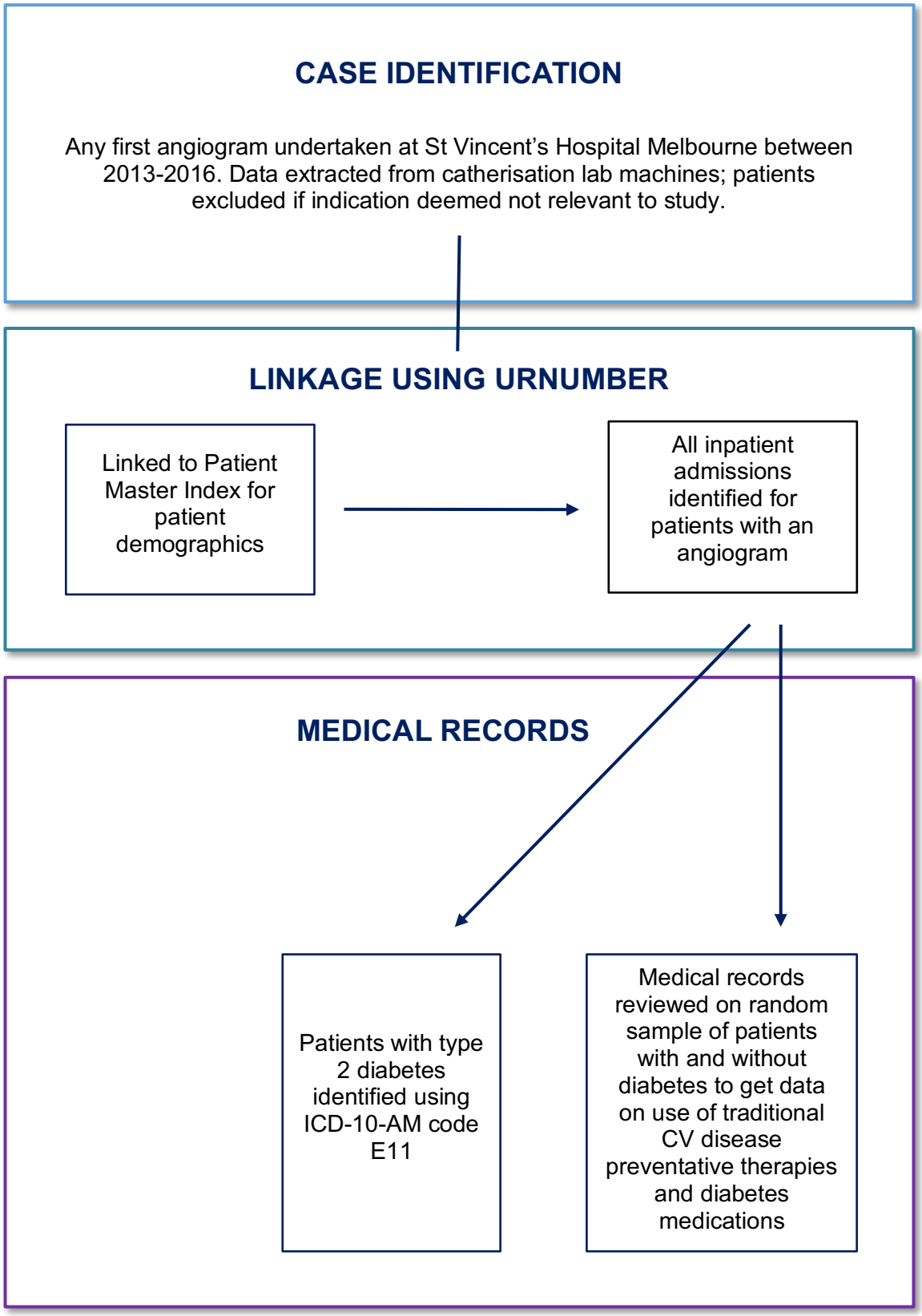
Coronary angiography and hospital discharge data between 2013 and 2019. A manual chart review was conducted for medication use, (Figure 2.4).

Statistical Analysis

Propensity scores were used in two ways: to match and to inverse probability weight One propensity score was developed to identify a 1:1 matched sample of patients with and without type 2 diabetes in the time analysis (the time cohort) and a second propensity score was developed to inverse probability weight the sub-sample which underwent chart review for their medication use.

An ordinal logistic regression model stratified by type 2 diabetes status was fitted to estimate effect of type 2 diabetes on the severity of coronary artery disease over time in years in the matched sample, the time cohort. A separate ordinal logistic regression model was fitted to estimate the average treatment effect among the treated on the random sample of patents who had their charts reviewed for medication use, the medication cohort.

Figure 2.4: Chapter 6 data linkage and case identification



Chapter 7 - The impact of type 2 diabetes on hospitalisation and mortality in people with malignancy

Aim

To assess the impact of type 2 diabetes on all-cause mortality, number of emergency department presentations, length of any hospital stay and inpatient admission.

Data Sources

Clinically coded hospital data and manually conducted chart review, (Figure 2.5).

Statistical Analysis

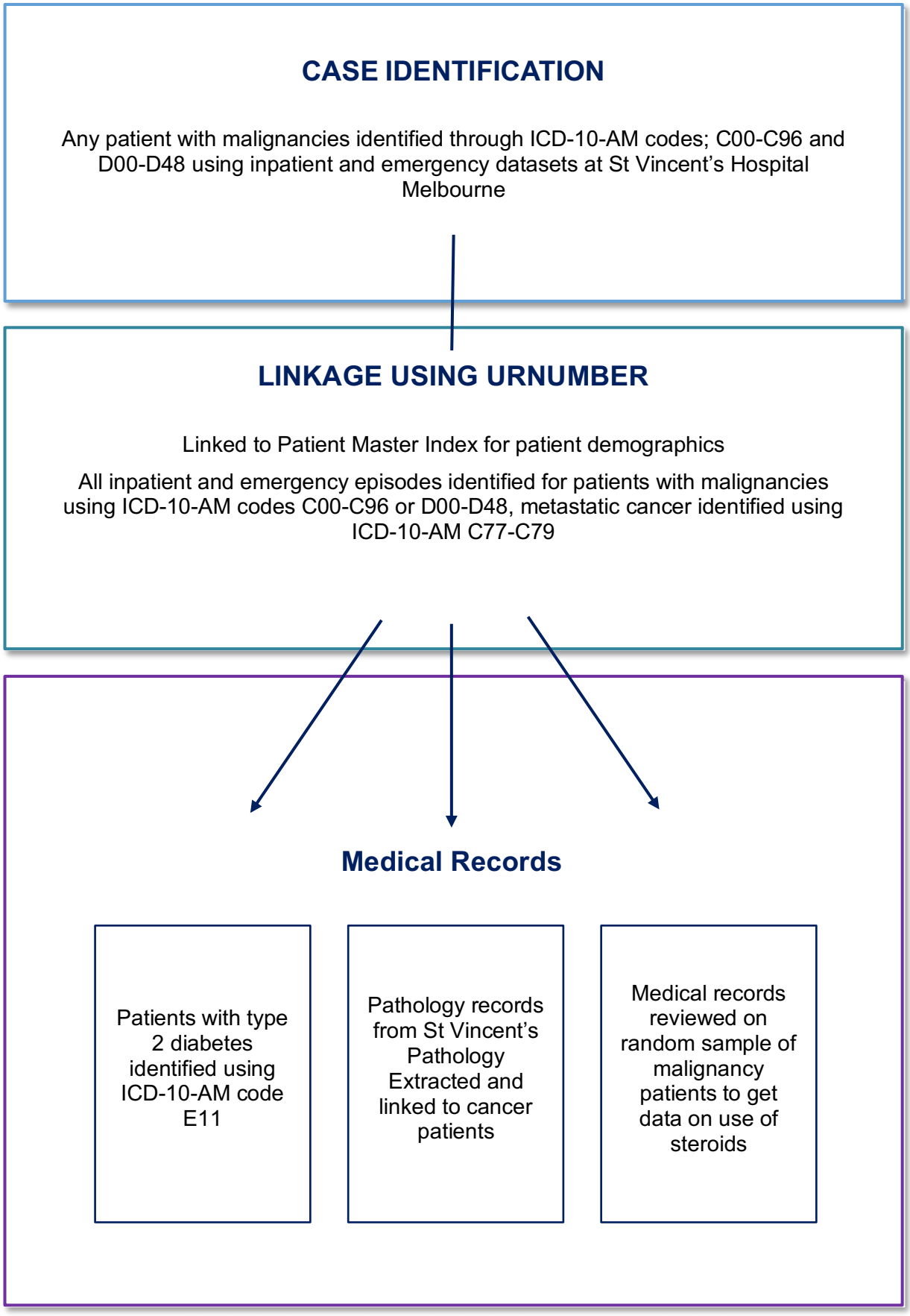
Multivariate Cox regression models were used to estimate the effect of diabetes on all-cause mortality. Truncated negative binomial regression models were used to assess the impact of diabetes on length of hospital inpatient stay and Prentice–Williams–Peterson total time models were used to assess the effect of diabetes on the number of emergency department presentations and inpatient admissions following an individual's index admission of presentation.

An additional set of analysis were done with propensity scores for the above outcomes. In order to address the non-balanced nature of this patient cohort we estimated a propensity score for each patient. This score was based on their demographic and clinical characteristics including age, gender, history of ischaemic heart disease, BMI category, type of cancer, smoking history, Charlson comorbidity score and whether the patient had metastatic cancer. This score was then used to weight the analysis as described later. The propensity score model estimating the probability of having diabetes was fitted using logistic regression with 17 categorical covariates [12].

The average treatment effect on the treated was evaluated by giving all treated patients a weight of 1, whereas all patients all patients that are untreated are untreated are weighted by the odds receiving the treatment [13].

Balance between the treatment groups for all of the covariates included in the model used to develop the propensity score was assessed using the standardised difference[14]. A sensitivity analysis was conducted with a sample trimmed at the 5th centile [15].

Figure 2.5: Chapter 7 data linkage and case identification



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Chapter 3: Changes in Hospital Admission Rates for Cardiovascular Complications in Patients with and without diabetes in Victoria, Australia 2004-2016

Abstract

Background

There are few large, contemporary studies assessing incidence trends for hospitalisations associated with acute myocardial infarction (AMI), stroke and heart failure in patients with type 1 diabetes or type 2 diabetes that have also included an appropriate comparator population of patients without diabetes.

Methods

Using state-wide hospital discharge data for Victoria, Australia, we calculated age- and sex- adjusted admission rates for incident AMI, stroke and heart failure between 2004 and 2016 for patients without diabetes (WoD), type 1 diabetes (T1D) or type 2 diabetes (T2D). Joinpoint regression was used to identify changes in linear trends which were described as average annual percentage change (AAPC).

Findings

For 382,107 incident admissions. The sample consisted of 278,991 (73%) admissions WoD, 3,645 (1.0%) T1D and 99,471 (26%) T2D patients. Significant AAPC decreases for incident AMI: -5% (WoD), -8% (T1D) and -11% (T2D): stroke, -2% (WoD), -7% (T1D) and -12% (T2D): and heart failure, -3% (WoD), -10% (T1D) and -9% (T2D) were observed across the 12 years.

Interpretation

Cardiovascular related admissions to Victorian hospitals declined between 2004 and 2016 for all groups of patients, with rates of decline for patients with diabetes surpassing those for patients without diabetes.

Introduction

Intensive metabolic control reduces the incidence and progression of diabetes related micro- and macrovascular complications[1-3]. Despite this, people with diabetes still

remain at an excess risk for the development of cardiovascular (CV) disease compared with people without diabetes[4]. However, recent studies have suggested that the incidence rates for CV disease are generally declining at a greater rate for people with diabetes compared to those without diabetes[5,6]. One of the major limitations of these studies has been that they have generally failed to compare outcomes between people with type 1 diabetes (T1D), type 2 diabetes (T2D) and those without diabetes (WoD). There is also a lack of contemporary, comprehensive and large studies that have assessed outcomes for major CV complications including acute myocardial infarction (AMI), stroke and heart failure in the one study. This represents a significant knowledge gap, as heart failure is now emerging as an important CV complication of diabetes[4,7].

We have therefore evaluated trends in admission rates for incident hospitalisations for the CV outcomes of AMI, stroke and heart failure using state-wide hospital discharge data from Victoria, Australia for WoD, T1D and T2D patients over a 12-year period between 2004 and 2016.

Design and Methods

Data Sources

Hospital discharge data from the Victorian Admitted Episode Dataset was obtained between 1999 and 2016 to allow for a five-year clearance period and a 12-year observational period as described below. Diagnostic information was coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM)[8].

Total numbers of patients diagnosed with T1D or T2D were obtained through the National Diabetes Services Scheme (NDSS), which captures 80-90% of Australians with known diabetes[9]. Total numbers of people WoD were obtained from the publicly available Australian Census of Population and Housing available from the Australian Bureau of Statistics[10].

Definitions

We identified incident cases for three CV complications of diabetes: AMI, stroke and heart failure. The specific codes were as follows: AMI ICD-10-AM codes: I21-I21.9, stroke ICD-10-AM codes: G46.3, G46.4, I69.4 and I63.0-I63.9 and heart failure ICD-10-AM codes: I50, I50.1, I50.9, I11.0 and I13.0. A diagnosis of diabetes was established

using ICD-10-AM codes E10.0-E10.9 for T1D and E11.0-E11.9 for T2D in the hospital discharge data (supplementary Table 1). Incident cases were established by ensuring that in the previous five years (1999-2003) there were no admissions for the same complication.

Statistical Analysis

We calculated rates for each CV related admission per 10,000 population from 2004 to 2016 stratified by diabetes type. The total number of admissions for each CV complication together with the diabetes status of patients was obtained with the case definitions above. These admission numbers for T1D or T2D patients were then divided by the total number of NDSS registrants with either T1D or T2D. For WoD patients, the total Victorian population obtained from the Australian Census less the total NDSS registrants for that year was used as the denominator, to obtain admissions per 10,000 population per year.

Poisson regression models adjusted by age group and sex (as shown in Table 1, Descriptive characteristics by diabetes status) were fitted in order to examine changes over time, with total numbers of people with and without diabetes included as an offset in the model as derived from the NDSS and ABS.

From the above we calculated incident rate ratios (IRR) (relative to 2003) for each of the CV complications per year stratified by the three groups of patients according to their diabetes status. These changes were then analysed by Joinpoint regression (version 4.7.0.0, Statistical Methodology and Applications Branch and Data Modelling Branch, Surveillance Research Program, National Cancer Institute). The benefit of this analysis method is that it allows for the identification of changes in rates in different CV complications in different years. Beginning with one straight overall line for the time period, permutation tests were then used to identify points where linear trends changed significantly ($p<0.05$) in either direction or magnitude. Then up to 3 joinpoints were added to the model to identify significant changes in the slope[11]. Each trend segment was described by an annual percentage change (APC) and the trend for the entire study period (2004-2016) described by the average annual percentage change (AAPC), a summary measure of the trend accounting for each trend segment.

Finally, we assessed changes in the admission rates for T1D and T2D patients for the three CV complications compared to that for patients WoD. To achieve this, we

calculated incident rate ratios (IRR) per year for T1D and T2D patients as compared to patients WoD.

Analysis was done using STATA version 15.1 (StataCorp, College Station, TX). This study was approved by the St Vincent's Hospital Melbourne Human Research Ethics Committee (HREC/18/SVHM/146).

Results

Our study sample consisted of 382,107 patients with 131,515 AMI, 70,264 stroke, and 189,748 heart failure admissions between 2004 and 2016. The study population consisted of 278,991 (73%) WoD, 3,645 (1%) T1D and 99,471 (26%) T2D patients. For patients WoD there were 114,965 AMI, 52,320 stroke and 135,524 heart failure admissions; for T1D patients there were 1,272 AMI, 504 stroke and 1,393 heart failure admissions; and for T2D patients there were 15,278 AMI, 17,440 stroke and 52,831 heart failure admissions. The characteristics of the population at the time of incident admission, separated by diabetes status are shown in Table 1. In summary, T2D patients were more likely to be older and T1D patients with diabetes were more likely to be male compared to patients WoD.

The annual event rates (per 10,000 population) for the three outcomes of interest for WoD, T1D and T2D patients are shown in Supplementary Table 2 and summarised in Table 2. When rates in 2016 were compared with those in 2004, AMI admissions decreased by 26% (WoD), 12% (T1D) and 53% (T2D); stroke admissions decreased by 13% (WoD), 30% (T1D) and 47% (T2D) and heart failure admissions by 26% (WoD), 47% (T1D) and 41% (T2D) patients (Figure 1)

Trends expressed as AAPCs from 2004 for the three CV complications groups for the three groups of patients are also shown in Table 2. For AMI admission rates, the AAPC for T1D patients decreased significantly between 2004-2016; AAPC -7.7 (95% CI -13.4, -1.5), with two separate APC trends identified between 2005-2009 and 2009-2016. There was also a reduction in admissions for T2D patients across the entire study duration of 2004-2016 with an AAPC of -11.4 (95% CI -13.0, -9.9). Patients WoD also experienced a decrease in AAPC for AMI admissions across the studies duration, however, this was not as large as those seen in patients with diabetes; AAPC -5.0 (95% CI -6.7, -3.4).

An analysis of admission rates for stroke by diabetes status showed that T1D patients experienced a significant decrease between 2004-2016, with an AAPC of -7.2 (95% CI -12.2, -1.9). Three separate linear trends were identified for T2DM patients: between 2005-2011; a significant decrease of -14.7 (95% CI -17.6, -11.7), over 2011-2014, a non-significant increase of 5.8 (95% CI -19.0, 38.2) and between 2014-2016, a significant decline of -26.1 (95% CI -39.8, -9.2). For WoD patients, two trends were observed: between 2005-2014 a significant decline of -4.1 (95% CI -5.8, -2.3) followed by a non-significant increase of 9.6 (95% CI -10.2, 34.4) between 2014-2016 (Table 2).

A significant decline was seen across all groups in rates of admissions for heart failure between 2004 and 2016 with the greatest decline seen in T1D patients with, AAPC -10.3 (95% CI -14.1, -6.4), followed by T2D patients, AAPC -9.2 (95% CI -11.0, -7.3) and then WoD diabetes, AAPC -2.8 (95% CI -4.1, -1.5) (Table 2).

As shown in table 3 T1D and T2D patients experienced a narrowing of IRR as compared to WoD patients between 2004 and 2016 for AMI, stroke and heart failure admissions (see also supplementary tables 3-5). This finding signifies that the rate of decline in admissions for all CV complications was occurring at a faster rate in patients with diabetes compared to patients WoD. The greatest reductions were seen for T2D patients with a difference the IRR over time for AMI of IRR 4.95 (95% CI 4.63, 5.3), stroke IRR 5.30 (95% CI 4.78, 5.87) and heart failure of IRR 4.76 (95% CI 4.49, 5.09) being observed. T1D patients also experienced reductions compared to patients WoD with a decline of IRR 0.93 (95% CI 0.88, 0.98) for AMI, IRR 1.50 (95% CI 1.35, 1.67) for stroke and IRR 2.19 (95% CI 2.06, 2.32) for heart failure occurring over the observational period of the study.

Discussion

Our analysis shows a significant decline in the incident occurrence of AMI, stroke and heart failure for 382,107 patients admitted to Victorian hospitals in Australia over a 12-year observational period commencing from 2004. Of relevance to this study, the AAPC decrease in the above CV outcomes were particularly evident in T1D and T2D patients and occurred at a 2-5-fold greater rate than for patients WoD. However, despite greater decreases in rates over time of CV complications rates of complications in T1D and T2D still exceed those WoD in 2016. Importantly, we show that admissions for heart failure decrease in a linear fashion during the observational period of our study for T1D and T2D patients. Heart failure is now emerging as an important CV

complication of diabetes and it should be noted that absolute numbers of admissions for heart failure greatly exceeded that for AMI or stroke in patients with diabetes between 2004 and 2016.

A preliminary report for the USA has suggested that rates of AMI and stroke increased by approximately 25% between 2010 and 2015, following a significant decrease in these admissions, as originally reported between 1995 and 2010(12). In our study, there was no evidence of a significant increase in AAPC for any of the CV outcomes we assessed during the observational period up to 2016. However, event rates appeared to plateau after 2010 as shown in Figure 1.

Factors accounting for a relatively greater decline in CV outcomes for people with diabetes compared to those without diabetes remain to be fully elucidated. However, patients with diabetes are generally considered as high-risk CV patients compared to those without diabetes and are being treated more aggressively, benefiting from specialist intervention with greater room for risk factor improvement with multifactorial target driven interventions. The suggestion that patients with diabetes are increasingly being recognised as a high-risk group and treated more aggressively would also be supported by studies that show that the proportion of adults with diabetes reaching glycaemic and blood pressure targets has increased significantly between 1999-2010(13). Other factors related to healthcare provision, such as the earlier detection of diabetes, the earlier screening for complications and overall better integration of care for people with diabetes should also be considered as factors contributing to the declining admission rates that we report.

There were a number of limitations with this study. Utilisation of hospital discharge coding data meant that information was not available on metabolic control or medication use. Therefore, a major weakness of our study was that we were not able to assess whether CV risk factor modification and the uptake of certain medications accounted for the changes in admission rates for AMI, stroke and heart failure. Given the time frame of our study, it is very unlikely that the use of medications belonging to the sodium glucose co-transporter 2 (SGLT-2) inhibitor and glucagon like peptide-1 receptor agonist (GLP-1RAs) class influenced the trends we report. Coding changes also took place which affected how diabetes was coded in 2008 and 2012. For principal diagnosis this meant that in 2010 a causal relationship was required between the principal diagnosis of diabetes and complication diagnosis. There have also been changes to how diabetes has been classified as a comorbidity, prior to 2008 a single

blood glucose measurement was enough to classify someone as having diabetes. From 2008 treatment of a patient's diabetes was required in order to code a patient as having diabetes therefore coded inpatient episodes may more accurately represent the documented conditions treated. However, the data may also allow for less surveillance of comorbidities using diabetes codes. This was mirrored in our results which showed a decline in total number of patients coded with both T1D and T2D in 2008 and 2011, followed by an increase in 2012(14). We also lacked information on the duration of diabetes for patients with hospital coded diabetes. Despite the coding changes, there were still differences in AMI, stroke and HF rates for T1D and T2D compared to patients WoD which may mean the dual coding of diabetes and these diabetes related complications may not have changed substantially.

Another limitation to consider is that patients may have presented with a complication prior to 1998. In that situation, these cases would have been counted as an incident admission in our analysis as they would not have fallen into our 5-year clearance period. As patients in this group would be at a very high risk for further admissions, the inclusion of these cases could possibly exaggerate the admission rates that we reported over the observational period of our study. Although we calculated age- and sex- adjusted rates for each diabetes related complication per 10,000 from 2004 to 2016 using data supplied by the Australian NDSS, which requires a medical professional to sign off regarding a patient's diabetes status, and Victorian census data as the denominator, hospital coding data was used to determine diabetes status associated with each of the complications that we assessed. This approach may have resulted in some error regarding the ascertainment of diabetes status during a patient's hospital stay.

The limitations of this study are offset by the strengths of the study which included the fact that it was a large, state-wide study including all patients admitted in Victoria, Australia with a population age and gender composition similar to other developed countries. Our study also had a long observation follow up period of 12 years and reports on outcomes for T1D and T2D patients and a comparison group consisting of WoD patients and includes a conservative 5-year clearance period in order to establish incident cases. Despite the above, it is possible the findings we report may still only apply to trends in admission rates for patients attending Victorian hospitals.

Although improvements in CV outcomes over recent times for patients with diabetes are welcomed, it should be noted that in relative terms, those with diabetes still remain

at an exaggerated risk for developing CV disease compared to people without diabetes. However, in an analysis from the state of Western Australia it suggests that rates of stroke admissions for people with type 2 diabetes may no longer be different from that of people without diabetes[15]. Reductions in CV event rates for people with diabetes in Australia also appear to be translated into better survival rates as age standardised mortality rates for CV disease have been shown to decrease people with either type 1 or type 2 diabetes from 2000 to 2011[16]. Regardless of these encouraging results, the absolute number of diabetes related admissions is expected to increase, given the increasing prevalence of diabetes in the community[17]. In addition, any relative decrease in admission rates for CV complications may also be offset by the development of newly recognised complications of diabetes such as malignancies and age related disabilities[18,19].

Conclusion

Overall, rates of admissions to Victorian hospitals for CV disease in patients with diabetes declined between 2004 and 2016 and that these rates of decline surpassed those seen in patients without diabetes. Furthermore, whilst the results we report are very encouraging, the increasing prevalence of diabetes suggests that a substantial gap in admission rates for patients with diabetes compared to patients without diabetes will continue for the foreseeable future.

Declaration of interest

We declare no competing interests.

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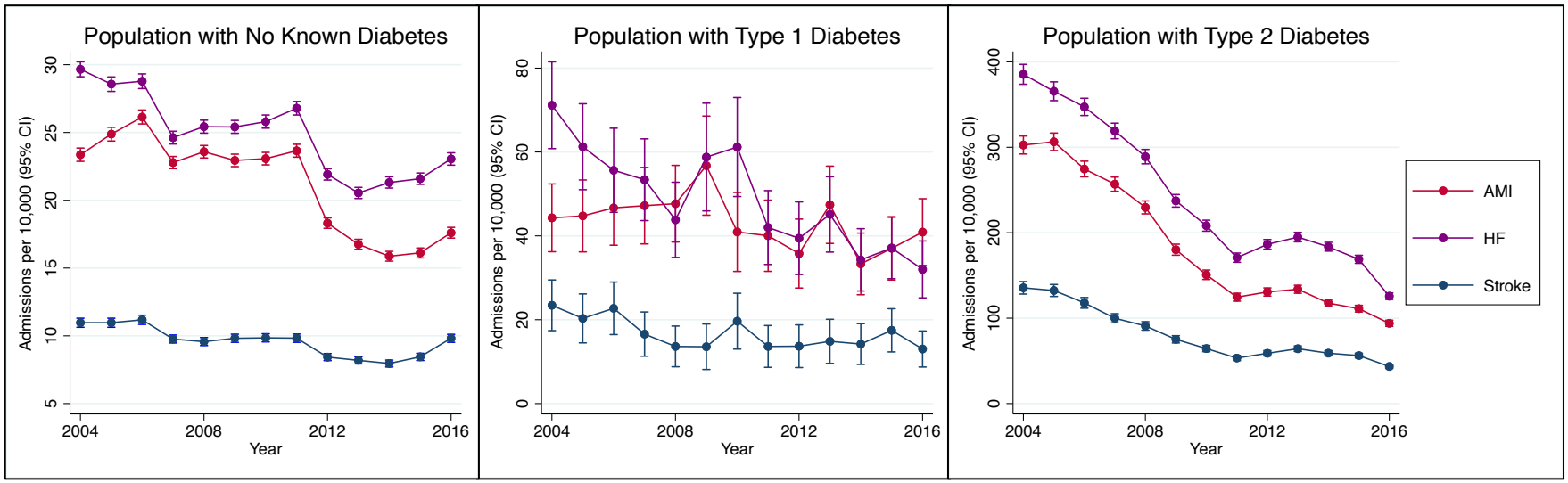
Tables

Table 3.4: Age and gender by diabetes status at time of incident admission

	No known diabetes	Type 1 Diabetes	Type 2 Diabetes
n	278,991 (73.0%)	3,645 (1.0%)	99,471 (26.0%)
Age group			
16-20	0.1	0.2	<1
21-29	0.7	3.0	0.1
30-39	1.9	8.4	0.5
40-49	5.3	14.0	2.7
50-59	10.3	18.2	9.1
60-69	15.4	18.4	19.2
70-79	23.2	19.9	31.6
80+	43.2	17.8	36.8
Sex			
Male	54.1	55.8	57.2

Data shown as % for categorical variables

Figure 3.6: Trends in hospital admission rates for cardiovascular outcomes for patients by diabetes status



Age and sex adjusted

Abbreviations: HF – Heart Failure, AMI – Acute myocardial infarction

‡Please note the difference in the scale used in the y-axis for the populations with no known diabetes, type 1 diabetes and type 2 diabetes

Table 3.5: Average annual percentage change (AAPC) and annual percent change (APC) for cardiovascular outcomes

	Diabetes Status	Total admissions	Overall trend*	Initial Trend*		Subsequent Trends*		Event rate (95% CI) (per 10,000 adults)*	
			AAPC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	2004	2016
AMI	No Diabetes	114,965	-5.0(-6.7, -3.4)					23.36(22.87, 23.85)	17.60(17.21, 18.00)
	Type 1 Diabetes	1,272	-7.7(-13.4, -1.5)	2005-2009	7(-9.7, 22.8)	2009-2016	-15.1(-21.3, -8.7)	44.30(36.22, 52.38)	40.90(32.95, 48.86)
	Type 2 Diabetes	15,278	-11.4(-13.0, -9.9)					302.69(292.16, 313.23)	93.96(90.35, 97.58)
Stroke	No Diabetes	52,320	-1.7(-4.9, 1.5)	2005-2014	-4.1(-5.8, -2.3)	2014-2016	9.6(-10.2, 33.8)	10.97(10.63, 11.30)	9.82(9.52, 10.11)
	Type 1 Diabetes	504	-7.2(-12.2, -1.9)					23.44(17.40, 29.48)	13.02(8.72, 17.32)
	Type 2 Diabetes	17,440	-11.9(-17.0, -6.5)	2005-2011	-14.7(-17.6, -11.7)	2011-2014	5.8(-19.0, 38.2)	135.5(128.18, 142.82)	43.43(41.06, 45.79)
						2014-2016	-26.1(-39.8, -9.2)		
HF	No Diabetes	135,524	-2.8(-4.1, -1.5)					29.66(29.11, 30.21)	23.05(22.59, 23.50)
	Type 1 Diabetes	1,393	-10.3(-14.1, -6.4)					71.16(60.81, 81.5)	32(25.22, 38.78)
	Type 2 Diabetes	52,831	-9.2(-11.0, -7.3)					385.42(373.79, 397.04)	125.71(121.85, 129.57)

*Adjusted for age and sex, AMI – Acute myocardial infarction, HF – Heart Failure

Table 3.6: Rate Ratios (95% CI) in hospital admission rates by diabetes status compared to patients without diabetes

	Type 1 Diabetes			Type 2 Diabetes		
	Change	2004	2016	Change	2004	2016
AMI	0.93 (0.88, 0.98)	2.14 (1.95, 2.35)	1.21 (1.07, 1.37)	4.95 (4.63, 5.3)	7.97 (7.35, 8.65)	3.02 (2.72, 3.35)
Stroke	1.50 (1.35, 1.67)	2.32 (2.04, 2.64)	0.82 (0.69, 0.97)	5.30 (4.78, 5.87)	7.34 (6.54, 8.22)	2.04 (1.78, 2.35)
HF	2.19 (2.06, 2.32)	2.96 (2.75, 3.18)	0.77 (0.69, 0.86)	4.76 (4.49, 5.09)	7.50 (7.02, 8.02)	2.74 (2.53, 2.98)

*Adjusted for age and sex, AMI – Acute myocardial infarction, HF – Heart Failure

Supplementary Tables

Supplementary Table 1 – ICD-10-AM codes used for case definition

Condition	Code (ICD-10-AM)	Description
Acute Myocardial Infarct		
	I21	Acute myocardial infarction
	I210	Acute transmural MI of anterior wall
	I211	Acute transmural MI of inferior wall
	I212	Acute transmural MI of other sites
	I213	Acute transmural MI of unspecified site
	I214	Acute subendocardial MI
	I219	Acute myocardial infarction unspecified
Heart Failure		
	I50	Heart failure
	I500	Congestive heart failure
	I501	Left ventricular failure
	I509	Heart failure unspecified
	I110	Hypertensive heart disease with (congestive) heart failure
	I130	Hypertensive heart and kidney disease with (congestive) heart failure

Condition	Code (ICD-10-AM)	Description
Non-Haemorrhagic Stroke		
	G463	Brain stem stroke syndrome
	G464	Cerebellar stroke syndrome
	I694	Sequelae of stroke not haem or infarct
	I630	Cerebral infarction due to thrombosis of precerebral arteries
	I631	Cerebral infarction due to embolism of precerebral arteries
	I632	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
	I633	Cerebral infarction due to thrombosis of cerebral arteries
	I634	Cerebral infarction due to embolism of cerebral arteries
	I635	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
	I636	Cerebral infarction due to cerebral venous thrombosis, nonpyrogenic
	I638	Other cerebral infarction
	I639	Cerebral infarction, unspecified

Supplementary Table 2 - Events per 10,000 for index admission for patients with no known diabetes, type 1 diabetes and type 2 diabetes.

Year	AMI	Stroke	Heart Failure
No known diabetes			
	n=114,965	n=52,320	n=135,524
2004	23.36 (22.87, 23.85)	10.97 (10.63, 11.30)	29.66 (29.11, 30.21)
2005	24.88 (24.37, 25.38)	10.97 (10.63, 11.30)	28.57 (28.03, 29.10)
2006	26.14 (25.63, 26.66)	11.18 (10.84, 11.52)	28.78 (28.24, 29.32)
2007	22.78 (22.33, 23.23)	9.76 (9.47, 10.06	24.62 (24.15, 25.09)
2008	23.58 (23.12, 24.04)	9.57 (9.57, 9.28)	25.43 (24.95, 25.91)
2009	22.94 (22.48, 23.40)	9.82 (9.52, 10.12)	25.41 (24.94, 25.89)
2010	23.07 (22.61, 23.53)	9.85 (9.55, 10.15)	25.8 (25.32, 26.29)
2011	23.65 (23.18, 24.13)	9.83 (9.52, 10.13)	26.79 (26.29, 27.29)
2012	18.31 (17.93, 18.70)	8.43 (8.17, 8.69)	21.91 (21.49, 22.32)
2013	16.75 (16.38, 17.12)	8.19 (7.93, 8.43)	20.54 (20.13, 20.95)
2014	15.87 (15.51, 16.23)	7.96 (7.70, 8.21)	21.31 (20.90, 21.73)
2015	16.12 (15.75, 16.48)	8.45 (8.18, 8.71)	21.59 (21.17, 22.01)
2016	17.60 (17.21, 18.00)	9.82 (9.52, 10.11)	23.05 (22.59, 23.50)
Year	**AMI**	**Stroke**	**Heart Failure**
Type 1 Diabetes			
	n=1,272	n=504	n=1,393
2004	44.30 (36.22, 52.38)	23.44 (17.40, 29.48)	71.16 (60.81, 81.50)
2005	44.76 (36.18, 53.33)	20.32 (14.48, 26.15)	61.26 (51.01, 71.50)
2006	46.68 (37.77, 55.58)	22.72 (16.46, 28.98)	55.65 (45.62, 65.68)
2007	47.20 (38.08, 56.32)	16.57 (11.30, 21.85)	53.39 (43.65, 63.14)
2008	47.67 (38.53, 56.81)	13.63 (8.78, 18.49)	43.83 (34.86, 52.79)
2009	56.75 (44.93, 68.57)	13.56 (8.13, 18.98)	58.79 (45.95, 71.64)
2010	40.93 (31.51, 50.35)	19.65 (13.0, 26.31)	61.18 (49.38, 72.99)
2011	40.03 (31.53, 48.53)	13.63 (8.64, 18.61)	41.99 (33.18, 50.79)
2012	35.78 (27.56, 44.00)	13.68 (8.59, 18.77)	39.43 (30.77, 48.10)
2013	47.41 (38.19, 56.63)	14.85 (9.59, 20.11)	45.11 (36.13, 54.10)
2014	33.31 (25.96, 40.66)	14.20 (9.34, 19.06)	34.28 (26.85, 41.71)
2015	37.03 (29.48, 44.57)	17.47 (12.32, 22.62)	37.11 (29.77, 44.44)
2016	40.90 (32.95, 48.86)	13.02 (8.72, 17.32)	32.00 (25.22, 38.78)

Year	AMI	Stroke	Heart Failure
Type 2 Diabetes			
	n=15,278	n=17,440	n=52,831
2004	302.69 (292.16, 313.23)	135.50 (128.18, 142.82)	385.42 (373.79, 397.04)
2005	306.42 (296.19, 316.65)	132.39 (125.40, 139.38)	365.59 (354.62, 376.56)
2006	274.57 (265.42, 283.73)	117.91 (111.67, 124.14)	347.29 (337.20, 357.38)
2007	256.81 (248.50, 265.12)	99.90 (94.54, 105.25)	319.13 (310.04, 328.23)
2008	229.66 (222.06, 237.26)	90.93 (85.99, 95.86)	289.07 (280.67, 297.47)
2009	180.15 (173.70, 186.60)	75.22 (70.96, 79.48)	237.35 (230.04, 244.67)
2010	150.77 (145.23, 156.31)	64.40 (60.71, 68.08)	208.25 (201.81, 214.70)
2011	124.54 (119.88, 129.20)	53.32 (50.24, 56.40)	170.78 (165.38, 176.19)
2012	130.65 (125.90, 135.40)	58.89 (55.66, 62.12)	186.41 (180.80, 192.02)
2013	133.84 (129.15, 138.53)	64.23 (60.94, 67.52)	194.9 (189.32, 200.48)
2014	117.66 (113.47, 121.86)	59.01 (56.01, 62.00)	183.58 (178.43, 188.73)
2015	111.11 (107.20, 115.03)	56.21 (53.42, 59.00)	168.87 (164.15, 173.58)
2016	93.96 (90.35, 97.58)	43.43 (41.06, 45.79)	125.71 (121.85, 129.57)

Supplementary Table 3 – Rate Ratios (95% CI) for patients with diabetes compared to no known diabetes for hospitalisations for acute myocardial infarction

Year	Type 1 Diabetes	Type 2 Diabetes
2004	2.14 (1.95, 2.35)	7.97 (7.35, 8.65)
2005	1.95 (1.79, 2.14)	7.82 (7.24, 8.46)
2006	1.97 (1.80, 2.15)	6.49 (6.01, 7.01)
2007	2.60 (2.37, 2.85)	7.16 (6.59, 7.78)
2008	2.13 (1.95, 2.34)	6.17 (5.68, 6.70)
2009	3.28 (3.00, 3.59)	5.10 (4.69, 5.56)
2010	2.24 (2.04, 2.46)	4.17 (3.83, 4.55)
2011	1.92 (1.75, 2.11)	3.32 (3.04, 3.62)
2012	1.84 (1.65, 2.05)	4.46 (4.05, 4.92)
2013	2.68 (2.40, 2.99)	5.16 (4.66, 5.71)
2014	1.45 (1.28, 1.64)	4.49 (4.04, 4.99)
2015	1.66 (1.47, 1.87)	4.16 (3.74, 4.63)
2016	1.21 (1.07, 1.37)	3.02 (2.72, 3.35)

Supplementary Table 4 - Rate Ratios (95% CI) for patients with diabetes compared to no known diabetes for hospitalisations for stroke

Year	Type 1 Diabetes	Type 2 Diabetes
2004	2.32 (2.04, 2.64)	7.34 (6.54, 8.22)
2005	2.01 (1.77, 2.30)	7.20 (6.42, 8.07)
2006	2.17 (1.91, 2.47)	6.44 (5.74, 7.21)
2007	1.52 (1.31, 1.77)	6.18 (5.46, 6.70)
2008	1.19 (1.02, 1.40)	5.95 (5.25, 6.74)
2009	1.19 (1.02, 1.39)	4.69 (4.13, 5.33)
2010	2.52 (2.20, 2.88)	3.95 (3.47, 4.49)
2011	1.45 (1.24, 1.68)	3.18 (2.79, 3.63)
2012	1.70 (1.45, 1.99)	4.25 (3.70, 4.89)
2013	1.63 (1.39, 1.92)	4.71 (4.10, 5.42)
2014	1.25 (1.06, 1.49)	4.35 (3.77, 5.02)
2015	1.46 (1.24, 1.72)	3.75 (3.25, 4.32)
2016	0.82 (0.69, 0.97)	2.04 (1.78, 2.35)

Supplementary Table 5 – Rate Ratios (95% CI) for patients with diabetes compared to no known diabetes for hospitalisations for heart failure

Year	Type 1 Diabetes	Type 2 Diabetes
2004	2.96 (2.75, 3.18)	7.50 (7.02, 8.02)
2005	2.80 (2.60, 3.02)	7.47 (6.98, 7.99)
2006	2.59 (2.41, 2.79)	6.99 (6.53, 7.48)
2007	2.60 (2.40, 2.82)	7.59 (7.05, 8.16)
2008	1.83 (1.68, 1.99)	6.66 (6.19, 7.16)
2009	3.35 (3.10, 3.62)	5.52 (5.13, 5.95)
2010	2.84 (2.62, 3.07)	4.61 (4.28, 4.96)
2011	1.63 (1.50, 1.78)	3.62 (3.36, 3.90)
2012	1.94 (1.77, 2.12)	4.88 (4.51, 5.29)
2013	1.99 (1.81, 2.18)	5.47 (5.04, 5.94)
2014	1.37 (1.25, 1.52)	4.84 (4.46, 5.25)
2015	1.38 (1.25, 1.52)	4.37 (4.03, 4.75)
2016	0.77 (0.69, 0.86)	2.74 (2.53, 2.98)

Chapter 4: Trends in rates of kidney disease in people with type 1, type 2 diabetes and without diabetes in Victoria, Australia 2009-2016.

Abstract

Background:

Chronic kidney disease (CKD) is one of the leading causes of morbidity and mortality worldwide, with people that have diabetes being at particular risk of progressive CKD. There is a lack of studies that have assessed incidence trends for admissions for the separate diagnosis of end stage renal disease (ESRD) (excluding renal replacement therapies) or dialysis or transplantation in patients with type 1 diabetes (T1DM) or type 2 diabetes (T2DM) that have also included an appropriate comparator population of patients without diabetes.

Methods**:**

Through the use of Victorian hospital discharge data, we calculated age- and sex-adjusted admission rates for incident cases of ESRD (without dialysis and transplantation) and dialysis or transplantation for patients without diabetes, and those with T1DM or T2DM between 2009 and 2016. Incident cases of known diabetic nephropathy for patients with T1DM or T2DM were also calculated. The use of Joinpoint regression enabled the identification of changes in linear trends and were described as average annual percentage change (AAPC).

Findings:

Of the 76,639 patients identified with any kidney disease 2,271(3%) had T1DM and 58,666(77%) had T2DM. The majority of patients with diabetes had diabetic nephropathy. Significant declines in rates of ESRD hospital admissions were seen in all groups: -6% (no diabetes), -23% (T1DM) and -24% (T2DM). The same significant reductions were not observed in rates for dialysis or transplantation (for all three groups of patients), and for admissions for diabetic nephropathy in patients with T1DM or T2DM.

Interpretation:

Rates of admissions for ESRD (for patients not undertaking renal replacement therapy) declined significantly between 2009 to 2016 in Victorian hospitals, with the greatest rates seen in patients with diabetes. In contrast, rates of admissions for dialysis or transplantation for patients with or without diabetes have not altered over the 8 years as have admissions for diabetic nephropathy. The factors resulting in the above trends remain to be determined.

Introduction

Chronic kidney disease (CKD) is one of the leading causes of morbidity and mortality worldwide and is associated with significant health cost burden. This substantial cost is in large due to the cost associated with providing renal replacement therapy, with the number of people receiving therapy worldwide currently exceeding 2.5 million and projected to exceed 5.4 million in 2030[1]. Prevalence studies have estimated that 16% of adults in Australia have some level of kidney damage[2]. The presence of CKD is also known to increase the risk of cardiovascular disease and known to further add to the risk of complications that are already associated with a diagnosis of hypertension and diabetes[3]. The leading cause of CKD in Australia is diabetes with 36% of all new cases of CKD in recent times being attributed to diabetes, compared to 17% in 1994. The other common causes of CKD in Australia are currently glomerulonephritis (18%), hypertension (14%) and polycystic kidney disease (8%)[4]. Furthermore, diabetes is the leading cause of new cases of ESRD treated with renal replacement therapy in Australia, with this number (percentage of all ESRD cases) increasing over time from 13% in 1991 to 38% in 2012[5].

Risk factor modification is known to prevent and slow the progression of CKD and ESRD as well as other complications traditionally associated with diabetes including acute myocardial infarction, stroke and amputation[6]. The control of blood pressure, especially with the use of renin-angiotensin system inhibitors (both through angiotensin converting enzyme inhibitors and angiotensin II receptor blockers) has been shown to be effective in slowing the progression to ESRD in patients with and without diabetes and in some cases has resulting in an improvement in kidney function[7, 8].

Internationally, significant declines have been observed in rates of diabetes related complications, however, ESRD has seen the smallest decline[9]. This may be the results of people surviving longer than previously and hence living longer with diabetes, and

increasing the risk of developing ESRD [10]. Furthermore cardio-renal risk factor modification in patients with diabetes appears to be more difficult to achieve than in people without diabetes. People with diabetes were more likely to have elevated blood pressure (>140/70mm/Hg) compared to the overall Australian population as measured in the Australian Health Survey Data and Australian National Diabetes Audit (27.3% vs 22.8%)[11, 12]. In addition, fewer than 50% of high risk diabetes patients were meeting the stringent recommendation of blood pressure control, ≤130/80mm/Hg [11].

The excess risk of ESRD attributed to diabetes has been well documented and some recent reports have suggested that there are non-significant changes in trends for dialysis and transplantation in people with T1DM and indigenous Australians with T2DM. Less well documented is the underlying large subgroup of patients with CKD that do not progress to require or elect to undergo dialysis or transplantation and are therefore not registered with the Australia and New Zealand Dialysis and Transplant Registry[5, 13, 14]. Most studies have that have reported on trends in ESRD in people with diabetes have used the hard clinical endpoint of acceptance onto renal replacement programs. However, this approach may fail to capture the true prevalence of ESRD as patients with kidney failure may not progress to dialysis or transplantation. Patients may not access dialysis or transplantation due to patient preference or may not survive due to high rates of high mortality from causes such as cardiovascular disease whilst waiting for access[15].

To negate the above potential problem, we calculated rates of admission for ESRD (excluding dialysis and transplantation) and those for dialysis and transplantation as separate diagnoses. Furthermore, hospital admission rates for diabetic nephropathy (pre-ESRD or transplant/dialysis) have not been well documented. The aim of this study was therefore to assess trends in rates of ESRD and dialysis or transplantation in people with type 1, type 2 or no diabetes, plus those for diabetic nephropathy over time in Victorian hospitalised patients.

Design and Methods

Data Sources

Hospital discharge data was obtained for 13 years between 2004 and 2016 to allow for a five-year clearance period and 8-year observational period. Diagnostic information was coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM)[16] and

procedural information according to the Australian Classification of Health Interventions (ACHI)[17].

Total numbers of people diagnosed with T1DM or T2DM were obtained through the Australian National Diabetes Service Scheme (NDSS), which captures 80-90% of Australians with known diabetes[18]. Total numbers of people without diabetes were obtained from the publicly available Australian Census of Population and Housing available from the Australian Bureau of Statistics (ABS)[19].

Definitions

We identified incident cases of diabetic nephropathy (ICD-10-AM codes: E10.21, E10.22, E11.21, E and E11.22), ESRD (ICD-10-AM codes: N18.0, N18.5, N19, I12.0, I13.1 and I13.2) (Supplementary Data) and dialysis or kidney transplantation (ACHI codes: 36503-00, 13100-00). A diagnosis of diabetes was established using ICD-10-AM codes E10.0-E10.9 for T1DM and E11.0-E11.9 for T2DM. All patients that were classified under procedural codes of dialysis and transplantation were required to have diagnostic codes. Each complication per individual was counted once. Incident cases were established by ensuring that in the clearance period (2004-2008) there were no admissions for the same complication.

Statistical Analysis

We calculated rates per 10,000 from 2009 to 2016 stratified by diabetes type. The total cases of patients with ESRD and with diabetes was obtained through ICD-10-AM codes or ACHI codes for ESRD diagnosis and diabetes diagnosis. This was then divided by the total number of NDSS registrants for either T1DM or T2DM, and for patients with no diabetes the total Victorian population obtained from the Australian Census less the total NDSS registrants for that year. Standardised rates were calculated by sex, age and diabetes specific rates observed in the NDSS and ABS populations and expressed per 10,000 adults with 95% confidence intervals (using the STATA command *dstdize*). Poisson regression models adjusted by age group (as expressed in table 1) and sex were fitted in order to examine changes over time, allowing for adjustment in possible changes in the prevalence of diabetes, as derived from the NDSS data. Incident rate ratios were calculated to examine change in rates of admission from 2009 to each subsequent year stratified by diabetes type and used in the below mentioned Joinpoint regression. Incident rate ratios were also calculated for patients with and without diabetes stratified by year in order to assess any change in

risk of admission over time. Analysis was done using STATA version 15.1 (StataCorp, College Station, TX).

In order to assess trends in admission rates over time, we used Joinpoint regression software (version 4.7.0.0, Statistical Methodology and Applications Branch and Data Modelling Branch, Surveillance Research Program, National Cancer Institute). Beginning with one straight overall line for the time period, permutation tests were then used to identify points where linear trends changed significantly ($p<0.05$) in either direction or magnitude. Then up to 3 joinpoints were added to the model to identify significant changes in the slope[20]. Each trend segment was described by an annual percentage change (APC) and the trend for the entire study period (2009-2016) described by the average annual percentage change (AAPC), a summary measure of the trend accounting for each trend segment.

This study was approved by the St Vincent's Hospital Melbourne Human Research Ethics Committee (HREC/18/SVHM/146).

Results

A total of 75,639 patients were identified with CKD between 2009 and 2016, of these 2,273 had T1DM and 58,666 had T2DM, noting that this included patients' admissions coded as diabetic nephropathy. Their characteristics at first known admission are described in Table 1. For patients without diabetes there were 14,727 ESRD and 2,657 dialysis or transplantation admissions, for patients with T1DM there were 2,164 diabetic nephropathy, 618 ESRD and 274 dialysis or transplantation admissions, and for T2DM there were 55,889 diabetic nephropathy, 11,650 ESRD and 1,678 dialysis or transplantation admissions. The characteristics of the populations at the time of their first known admissions separated by diabetes type: no diabetes, T1DM or T2DM and kidney disease are shown in Table 1.

In summary, for any type of kidney disease both patients with and without diabetes were more likely to be male. Patients with T1DM were more likely to develop ESRD and require dialysis or transplantation at a younger age than patients without diabetes and patients with T2DM. Patients with T1DM were also more likely to develop diabetic nephropathy than patients with T2DM.

An analysis of admission rates for ESRD (excluding dialysis or transplantation) by diabetes status showed that patients with no diabetes experienced a significant decrease during the study period, AAPC -6.2 (95% CI -12.0, -0.1). Patients with T1DM also experienced a significant decline AAPC -22.7 (95% CI –36.5, -6.0). Two separate non-significant trends were observed, between 2010-2014, APC -7.8 (95% CI -31.6, 24.3) followed by 2014-2016 -45.8 (95% CI -82.8, 71.7). Patients with T2DM experienced a significant overall decrease with an AAPC of -23.5 (95% CI -34.9, -10.0), two non-significant trends were also identified between 2010-2014, APC -3.2 (95% CI -24.7, 24.3) and 2014-2016, APC -52.2 (-81.3, 22.6).

For patients without diabetes a non-significant decrease was observed in rates of dialysis or transplantation, AAPC -0.5 (95% CI -6.8, 6.2) with there being no significant change in presentation rates for patients with T2DM with an AAPC of 3.2 (95% -8.2, 17.1) and for patients with T1DM a non-significant decrease in was observed, AAPC -8.0 (95% CI -15.7, 0.3).

As shown in Table 2, when rates for diabetic nephropathy for patients with T1DM and T2DM were expressed as average annual percentage change AAPC, no significant decrease was observed for either group between 2009-2016, AAPC -19.0 (95% CI -44.0, 17.2) and AAPC -19.9 (95% CI -33.2, 16.1), respectively. For patients with T1DM two non-significant trends were observed between 2010-2013, APC 16.7 (95% CI -59.2, 234.3) and 2013-2016 APC -43.6 (-83.6, 93.0).

Discussion

Our analysis of hospital admissions for 75,639 patients (3% with T1DM and 78% with T2DM) shows a significant decline in ESRD (excluding dialysis or transplantation) for patients with T1DM, T2DM or no diabetes admitted to Victorian hospitals in Australian over a 14-year period commencing in 2009, with the decline being most pronounced in patients with T1DM or T2DM. However, we did not find a significant change in admissions for same day dialysis or transplantation for all three groups of patients. For T1DM and T2DM patients there was also no significant decrease in rates of admissions coded for diabetic nephropathy observed over time. This lack of decline suggests that there has been no change in the large number of patients living with diabetic nephropathy, in fact this likely represents an under-reporting of diabetic nephropathy as a large number of patients would be unaware of this diagnosis. This suggests that

despite the decline in ESRD, that we report, there is still a large number of people that may potentially progress to ESRD and require dialysis or transplantation.

Rates of ESRD may be declining due to secondary prevention through better attention to risk factor modification, in particular, better blood pressure control and the use of other renal protective management strategies. This may be related to an increase in the use of angiotensin receptor blockers and angiotensin converting enzyme inhibitors which are known to reduce rates of albuminuria and in high risk renal patients slow progression to ESRD[21]. The increased availability and uptake of sodium-glucose cotransporter 2 (SGLT-2) inhibitors which have been shown to be associated with slower progression of kidney disease and kidney events[22]. However, the use of SGLT-2 inhibitors would not have been widespread yet, given the known renal-protective effects further declines may be expected in the future. The factors related to the failure of the above decline in ESRD not being translated into a significant decline in rates of patients entering renal replacement programs await to be fully explained, as discussed below.

There is conflicting literature available on temporal trends in rates of development of kidney disease and its consequences. This may partly be a reflection of differing health services and eligibility for dialysis and transplantation in which patients are able to receive care and also due to a change in diagnostic criteria over time resulting in a change in cohorts. A large part of the variation in trends for patients with T2DM is thought to be due to the management of patients diabetes, with different regions having different rates of kidney disease due to varying adoption of best practice guidelines in patients diabetes management[23].

Overall, our results are similar to those of Koye et al. which looked at an Australian population with diabetes, in regards to transplantation and dialysis[13]. In that study, the incidence rates for dialysis and transplantation for T1DM remained stable between 2002 to 2013. We also showed that rates of admissions for dialysis and transplantation did not change significantly between 2009-2016. Whereas, for patients with T2DM Koye et al. showed a significant increase, which appear to be driven by an increase in dialysis in non-indigenous people, particularly in those with early-onset T2DM[13]. In contrast we showed that rates of dialysis and transplantation in T2DM patients remained stable between 2009-2016. This difference may in part be driven by our more contemporary study period. We also report on ESRD and dialysis and transplantation separately, so it is possible that whilst ESRD is declining, more patients are entering

dialysis and transplantations programs to negate the expected decline that may possibly be expected to follow a decrease in ESRD presentations. Koye et al. included all of Australia which may include a higher risk group of Indigenous Australians which may not be captured in Victorian data used in our study.

Despite the findings of this study, rates of treatment for ESRD (dialysis and/or transplantation) have been reported to decline in certain populations. A recent study from Finland has shown that the cumulative risk of ESRD (onset of renal replacement therapy) has declined during the past five decades[24]. A study from the United States has also shown that ESRD (defined as people registered under the United States Renal Data System) in people with diabetes has declined in racial and ethnic minority populations but not in whites[25]. These results appear to be more consistent with the results we report for trends in ESRD excluding dialysis and transplantation with the differences between our findings and those of the above studies remaining to be fully explained.

There were a number of limitations with this study. As we utilized hospital discharge coding data, information was not available on metabolic control or medication use. Nor was there biochemical information available on renal function, in order to classify the degree of renal impairment, this meant we used coding in order to classify an individual's stage of kidney disease. Therefore, a major weakness of our study was that we were not able to assess whether renal risk factor modification and the uptake of certain medications accounted for the changes in admission rates. Coding changes also took place which affected how diabetes was coded in 2012. This was mirrored in our results which showed a decline in total number of patients coded with both T1DM and T2DM in 2011, followed by an increase in 2012[26].

Another limitation to consider is that patients may have presented with a complication prior to 2004. In that situation, these cases they would have been counted as an incident admission in our analysis as they would not have fallen into our 5-year clearance period. As patients in this group would be at a very high risk for further admissions, the inclusion these cases could possibly exaggerate the admission rates that we reported over our observational period. Although we calculated age- and sex-specific rates for each diabetes related complication per 10,000 from 2009 to 2016 using data supplied by the Australian NDSS, which requires a medical professional to sign off regarding a patient's diabetes status, and Victorian census data as the denominator, hospital coding data was used to determine diabetes status associated

with each of the complications that we assessed. This approach may have resulted in some error regarding the ascertainment of diabetes status during a patient's hospital stay. We also lacked information on the duration of diabetes for patients with hospital coded diabetes. Furthermore, as this was a study based on patients admitted to hospital, the results cannot be extrapolated to rates of development of complications that are managed in the community.

The limitations of this study are offset by the strengths of the study which included the fact that it was a large state-wide study including all patients admitted to both public and private hospitals in Victoria, Australia with a population age and gender composition similar to other developed countries. Our study also had a long observation follow up period of 8 years that concluded in 2016 and reports on outcomes for patients with T1DM and T2DM and a comparison group consisting of patients without diabetes. A comparison with a group of patients without diabetes was lacking in the last major study examining rates of dialysis and transplantation in Australian patients with diabetes[13]. It also reports on patients that chose not to or were unable to undergo haemodialysis or transplantation that are otherwise not captured on studies using the Australia and New Zealand Dialysis and Transplant Registry and includes patients that were coded as being diagnosed with diabetic nephropathy. To negate this potential problem rates of admissions for ESRD excluding dialysis and transplantation and those for dialysis and transplantation were calculated separately. Possibly, the above findings, as mentioned above, are reflected by the decrease in ESRD rates found in this study and that the lack of change in patients entering renal replacement programs is related more to changes in care practices, such as when to commence dialysis and individuals dying of other causes such as cardiovascular disease while waiting for access to renal replacement programs and transplantation[15].

Conclusion

Rates of ESRD as assessed by hospital coding that examines this outcome separately to that of dialysis and transplantation, have declined in Victorian hospitals for patients with and without diabetes between 2009 and 2016 with the greatest declines seen in patients with diabetes. However, the large number of patients we report with diabetic nephropathy is of concern as they may progress to more severe kidney disease and require a greater level of intervention and care in the future. This study reports no significant change in rates of admissions for dialysis and transplantations. This finding may relate to more patients being eligible and an overall greater access to renal

replacement programs, which in turn has possibly negated the expected flow on effect of decreases in ESRD presentations.

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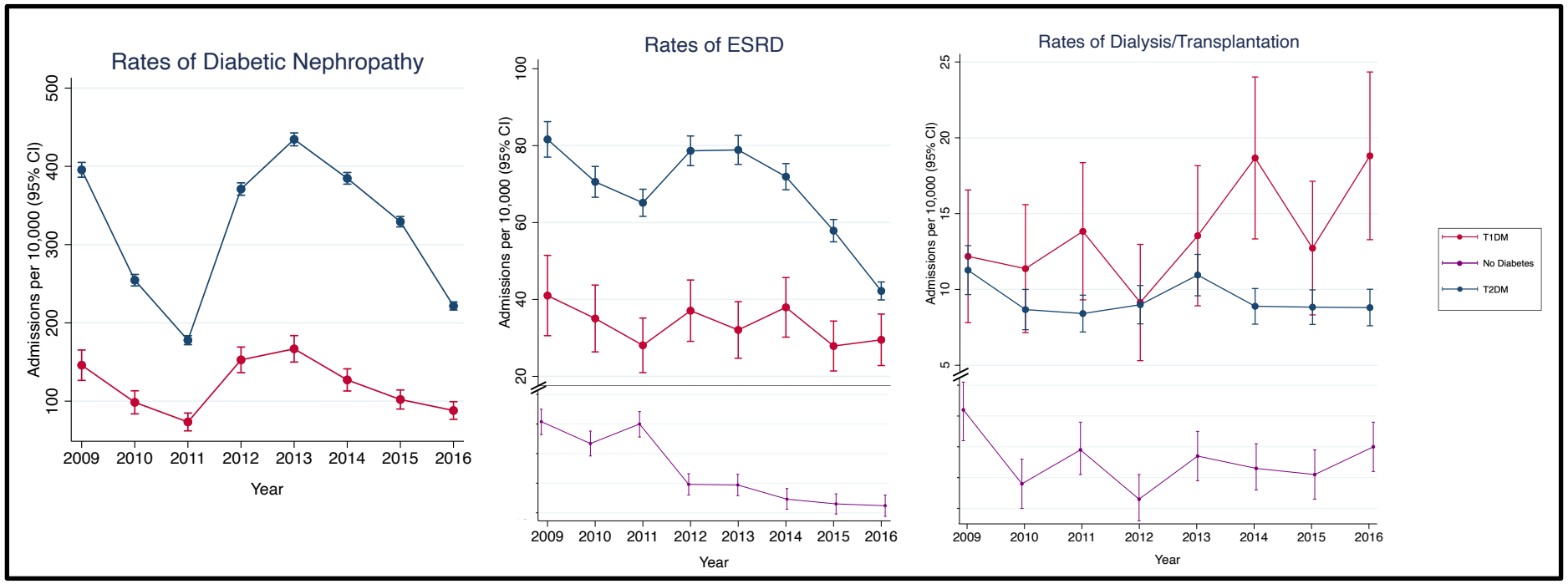
Tables

Table 4.7: Age and gender by diabetes status at time of incident admission

	No known diabetes n=14,700		**T1DM n=2,273**			**T2DM n=58,666**		
	ESRD	Dialysis or Transplantation	Diabetic Nephropathy	ESRD	Dialysis or Transplantation	Diabetic Nephropathy	ESRD	Dialysis or Transplantation
No. of Patients	14727	2657	2164	618	274	55889	11650	1678
Sex								
Male	8074 (54.8%)	1661 (62.5%)	1131 (52.3%)	329 (53.2%)	152 (55.5%)	32009 (57.3%)	6763 (58.1%)	1152 (68.7%)
Female	6653 (45.2%)	996 (37.5%)	1033 (47.7%)	289 (46.8%)	122 (44.5%)	23880 (42.7%)	4887 (41.9%)	526 (31.3%)
Age at Incident Admission								
16-20	55 (0.4%)	27 (1.0%)	18 (0.8%)	3 (0.5%)	1 (0.4%)	2 (<1%)	0 (0.0%)	0 (0.0%)
21-29	265 (1.8%)	172 (6.5%)	161 (7.4%)	29 (4.7%)	15 (5.5%)	68 (0.1%)	15 (0.1%)	3 (0.2%)
30-39	456 (3.1%)	275 (10.4%)	300 (13.9%)	109 (17.6%)	71 (25.9%)	264 (0.5%)	73 (0.6%)	32 (1.9%)
40-49	760 (5.2%)	451 (17.0%)	338 (15.6%)	137 (22.2%)	78 (28.5%)	1122 (2.0%)	286 (2.5%)	107 (6.4%)
50-59	1129 (7.7%)	531 (20.0%)	399 (18.4%)	132 (21.4%)	66 (24.1%)	3725 (6.7%)	1014 (8.7%)	342 (20.4%)
60-69	1762 (12.0%)	593 (22.3%)	355 (16.4%)	96 (15.5%)	33 (12.0%)	9799 (17.5%)	2087 (17.9%)	530 (31.6%)
70-79	2754 (18.7%)	399 (15.0%)	344 (15.9%)	57 (9.2%)	10 (3.6%)	18267 (32.7%)	3594 (30.8%)	508 (30.3%)
80+	7546 (51.2%)	209 (7.9%)	249 (11.5%)	55 (8.9%)	0 (0.0%)	22642 (40.5%)	4581 (39.3%)	156 (9.3%)

Abbreviations: ESRD, end-stage renal disease; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus.

Figure 4.7: Trends in hospital admission rates for kidney disease for patients by diabetes status



Age and sex adjusted
*Change in coding practices were relevant
‡Please note the break in axis

Table 4.8: Average annual percentage change (AAPC) and annual percent change (APC) for kidney disease

	Diabetes Status	Standardised event rate (95% CI) (per 10,000 adults)*		Overall trend*	Initial Trend*		Subsequent Trend*	
		2009	2016	AAPC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
Diabetic Nephropathy	T1DM	146.0 (126.6, 165.4)	88.1 (76.7, 99.4)	-19.0 (-44.0, 17.2)	2010-2013	16.7 (-59.2, 234.3)	2013-2016	-43.6 (-83.6, 93.0)
	T2DM	395.6 (386.1, 405.1)	221.6 (216.4, 226.8)	-11.9 (-33.2, 16.1)				
ESRD	No Diabetes	5.0 (4.8, 5.3)	3.6 (3.4, 3.8)	-6.2 (-12.0, -0.1)				
	T1DM	41.0 (30.6, 51.5)	29.5 (22.8, 36.2)	-22.7 (-36.5, -6.0)	2010-2014	-7.8 (-31.6, 24.3)	2014-2016	-45.8 (-82.8, 71.1)
	T2DM	65.6 (81.6, 86.2)	42.2 (39.9, 44.6)	-23.5 (-34.9, -10.0)	2010-2014	-3.2 (-24.7, 24.3)	2014-2016	-52.2 (-81.3, 22.6)
Dialysis/ Transplant	No Diabetes	0.9 (0.8, 1.0)	0.8 (0.7, 0.9)	-0.5 (-6.8, 6.2)				
	T1DM	12.2 (7.8, 16.6)	18.8 (13.3, 24.3)	3.7 (-8.2, 17.1)				
	T2DM	11.3 (9.7, 12.9)	8.8 (7.6, 10.0)	-8.0 (-15.7, 0.3)				

Abbreviations: ESRD, end-stage renal disease; AAPC, average annual percentage change; APC, annual percentage change; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus. *Adjusted for age and sex

Supplementary Tables

Supplementary Table 1 – ICD-10-AM and ACHI codes used for case definition

Condition	Code ICD-10-AM or ACHI	Description
Kidney Disease		
Dialysis/Transplantation	3650300	Kidney Transplantation
	1310000	Haemodialysis (same-day admission)
End stage renal disease	N180	End-stage renal disease
	N185	Chronic kidney disease, stage 5
	N19	Unspecified kidney failure
	I120	Hypertensive kidney dis w kidney failure
	I131	Hypertensive heart and kidney disease with kidney failure
	I132	Hypertensive heart and kidney disease with both (congestive) heart failure and kidney failure
Diabetic Nephropathy	E10.21 E11.21	Type 1 or 2 diabetes mellitus with incipient diabetic nephropathy
	E10.22 E11.22	Type 1 or 2 diabetes mellitus with established diabetic nephropathy

ICD-10-AM Definition of Diabetic Nephropathy

The use of the codes for diabetic nephropathy E1-.21 is when diabetes documented in notes of the coding admission with the following conditions:

- chronic kidney disease:
    - stage 1
    - stage 2
- glomerular:
    - basement-membrane thickening
    - mesangial expansion
- incipient nephropathy (early)(mild)(reversible)
- microalbuminuria:
    - constant
    - persistent
- tubulo-interstitial changes

The use of E1-.22 is when diabetes documented with the following conditions:

- advanced kidney disease
- chronic kidney:
    - disease >= stage 3
    - failure
    - impairment
- end-stage kidney disease
- glomerulosclerosis:
    - diffuse
    - intracapillary
    - nodular
- Kimmelstiel-Wilson (disease)(lesion)
- macroalbuminuria
- nephropathy (advanced)(NOS)(progressive)
- nephrosis
- nephrotic syndrome
- proteinuria:
    - fixed
    - persistent

Chapter 5: Temporal trends in lower extremity amputations and 12-month mortality in people with diabetes in Victoria, Australia 2004-2016

Abstract

Background

Lower extremity amputations (LEA) are a major source of morbidity and mortality both at an individual and community level with patients with diabetes being at a particularly high risk. There is a lack of studies that have assessed trends in admissions for any LEA, minor LEA, major LEA and mortality 12-months following LEA in patients with type 1 diabetes (T1DM) or type 2 diabetes (T2DM).

Methods

Through the use of Victorian hospital discharge data, we calculated age- and sex- adjusted admission rates for incident cases of any LEA, minor LEA, major LEA and 12-month mortality following any LEA for patients with T1DM or T2DM between 2004 and 2016. A sex and age specific analysis was also conducted. The use of Joinpoint regression enabled the identification of changes in linear trends and were described as average annual percentage change (AAPC).

Findings

A total of 10,406 patients were identified that underwent an LEA between 2004-2016 that had either T1DM (8%) or T2DM (92%). Significant declines in rates of overall LEA were seen for patients with T2DM (-38%) which was not observed in patients with T1DM. Patients with T2DM experienced significant declines in minor LEA (-3%), major LEA (-12%) and 12-month mortality (-4%) This was in contrast to patients with T1DM who had stable rates in all categories except for minor LEA, which rose (17%). Concerningly, younger patients with T1DM experienced a significant rise in any LEA in more recent years (2009-2016). In contrast, older patients with T2DM experienced significant declines for any LEA.

Interpretation

There were significant differences in LEA trends seen by type of diabetes and age group. Patients with T2DM experienced a decline in LEA (both minor and major) between 2004 and

2016, an outcome that was particularly evident in older patients. In contrast, younger patients with T1DM appear to be experiencing an increase in LEA rates during the above time period. Whilst our results are welcome news for patients with T2DM, better primary prevention strategies, targeting the detection and prevention of diabetic foot ulcers are critical interventions that need to be improved to further reduce LEA rates, especially in younger patients with T1DM.

Introduction

It has been estimated that worldwide a lower limb is amputated every 30 seconds due to diabetes, and that 50-70% of all lower extremity amputations (LEA) are related to diabetes[1, 2]. The Australian Burden of Disease Study identified 12,300 admissions for diabetes-related LEA in 2011[3]. LEA is a source of major morbidity and mortality and comes with a significant monetary cost both at an individual and community level[4]. Recent studies have shown that although there may be an overall decline or plateau in rates of LEA, there may be increases observed in specific subgroups of amputations, this trend was particularly evident in younger patients with diabetes[5]. Furthermore, in the small amount of literature available looking at mortality, 12-month mortality post LEA is alarmingly high, ranging between 1-29%[6, 7]. The aim of this study was to assess trends in LEA using state-wide linked hospital admission data. Trends were examined for all LEA, minor LEA, major LEA and mortality 12-months following an LEA in patients with type 1 diabetes (T1DM) or type 2 diabetes (T2DM) between 2004 and 2016.

Methods

Study Design and Population

Data for this study was obtained from the Centre for Victorian Data Linkage which links hospital discharge data and mortality records. Hospital discharge data was obtained for 17 years between 1999 and 2016 to allow for a five-year clearance period and 12-year observational period. Diagnostic information was coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM)[8] and procedural information according to the Australian Classification of Health Interventions (ACHI)[9]. Total numbers of people diagnosed with T1DM or T2DM were obtained through the National Diabetes Service Scheme (NDSS), which captures 80-90% of Australians with known diabetes[10].

LEA Hospitalisations

Patients who underwent a LEA in the linked dataset from Victoria were identified, a minor amputation was defined as an amputation distal to the ankle joint with ACHI codes: 44338-00, 44358-00, 44364-00, 44364-01, 90557-00. Major amputations were those through or proximal to the ankle joint, 44361-00, 44361-01, 44367-00, 44367-01, 44367-02. To prevent an overestimation of LEA rates due to planned multistep procedures that could span weeks or months, the highest-level amputation per year was included per patient. A diagnosis of diabetes was established using ICD-10-AM codes E10.0-E10.9 for T1DM and E11.0-E11.9 for T2DM. Identification of comorbidities was based on a patients hospitalisation history and used the following ICD-10-AM codes: peripheral vascular disease (I70-I79), coronary heart disease (I20-I25), chronic kidney disease (based on the Charlson Comorbidity definition)[11], hypertension (I10, I11, I13, I15), cerebrovascular disease (I60-I69, G54), heart failure (I50) and atrial fibrillation (I48)[12]. Incident cases were established by ensuring that in the clearance period (1999-2003) there were no admissions for the same complication.

Statistical Analysis

Baseline characteristics were compared for patients with T1DM and T2DM using the chi-squared test at the first known admission for any LEA. Total numbers of patients per year with LEA and with diabetes were obtained through ICD-10-AM codes for diabetes and ACHI codes for LEA diagnosis. This was then divided by the total number of NDSS registrants for either T1DM or T2DM. Standardised rates were calculated by sex, age and diabetes specific rates observed in the NDSS population and expressed per 10,000 adults with 95% confidence intervals (using the STATA command *dstdize*). Poisson regression models adjusted by age group and sex were fitted in order to examine changes over time, with total numbers of patients with diabetes obtained from the NDSS included as an offset variable. Incident rate ratios (IRR) were calculated to examine changes in rates of admission from 2004 to each subsequent year stratified by diabetes type and used in the below mentioned Joinpoint regression. Analysis was done using STATA version 15.1 (StataCorp, College Station, TX).

In order to assess trends in admission rates over time, we used Joinpoint regression software (version 4.7.0.0, Statistical Methodology and Applications Branch and Data Modelling Branch, Surveillance Research Program, National Cancer Institute). Beginning with one straight overall line for the time period, permutation tests were then used to identify points where linear trends changed significantly ($p<0.05$) in either direction or magnitude. Then up to 3 joinpoints were added to the model to identify significant changes in the slope,

if available[13]. Each trend segment was described by an annual percentage change (APC) and the trend for the entire study period (2004-2016) described by the average annual percentage change (AAPC), a summary measure of the trend accounting for each trend segment.

This study was approved by the St Vincent's Hospital Melbourne Human Research Ethics Committee (HREC/18/SVHM/146).

Results

There were a total of 10,404 LEA performed in 589 (8%) patients with T1DM and 6,715 (92%) patients with T2DM in Victoria during 2004 to 2016. Patients with T2DM were significantly more likely to be male and older at the time of their first known admission for a LEA compared to patients with T1DM (Table 1). Patients with T2DM were also significantly more likely to present with comorbid conditions including peripheral vascular disease, coronary heart disease, hypertension, heart failure and atrial fibrillation compared to patients with T1DM (Table 1). However, chronic kidney disease was more common in patients with T1DM (54%) compared to patients with T2DM (49%), p=0.04 (Table 1).

Any lower extremity amputation

Rates of LEA in patients with T1DM increased from 23.3 (95% CI 17.3, 29.3) in 2004 to 36.1 (95% CI 28.7, 43.5) per 10,000 in 2016. However, this trend was not significant when examined using Joinpoint analysis; AAPC 2.9 (95% CI -0.2, 6.0) (Figure 1, Table 2). For patients with T2DM there was a significant reduction in overall rates of LEA; AAPC -4.9 (95% CI -6.8, -3.0).

Minor lower extremity amputation

A significant rise in rates of minor LEA was seen for patients with T1DM with 16.6 (95% CI 11.5, 21.7) cases observed in 2004 and 30.0 (95% CI 23.3, 36.8) per 10,000 in 2016 resulting in a significant increase in AAPC of 3.7 (95% CI 0.4, 7.1) observed during the above time period (Table 2). This change was the opposite to rates seen in patients with T2DM who experienced a significant reduction with 38.3 (95% CI 34.3, 42.2) cases in 2004 and 25.0 (95% CI 23.0, 26.9) cases per 10,000 in 2016, resulting in a significant decrease in AAPC of -3.0 (95% -5.0, -1.0) (Table 2).

Major lower extremity amputation

For patients with T1DM a small number (n=182) of major LEA were observed over the study period with no significant changes observed, 6.6 (95% CI 3.4, 9.8) cases in 2004 and 6.1 (95% CI 3.0, 9.2) cases in 2016 per 10,000 (Table 2). For patients with T2DM a significant reduction was also seen in rates of major LEA, between 2004 and 2016 rates decreased from 15.5 (95% CI 13.0, 18.0) to 4.8 (95% CI 4.0, 6.0) per 10,000. A significant AAPC of -11.5 (95% CI -13.6, -9.3) was also observed in patients with T2DM during the above time period (Table 2).

Mortality in 12 months following amputation

A total of 18 deaths over the 13-year study period in the 12 months following any LEA were identified in patients with T1DM between 2004-2016 from a total 934 procedures (1.9%) (Table 3). A non-significant AAPC decrease was observed, -3.9 (95% CI -11.6, 4.4) during the above time period. For patients with T2DM, 595 deaths were identified in the 12 months following a LEA, resulting in 6.3% dying within 12 months of their procedure. When changes over time were examined using Joinpoint analysis a significant decline in mortality for patients with T2DM was observed with an AAPC of -4.2 (95% CI -6.4, -1.9) between 2004-2016 (Table 3).

Age and sex specific rates

Females with T1DM experienced a significant increase in rates of LEA, AAPC 5.1 (95% CI 0.5, 9.9), in contrast both men and women with T2DM experienced a significant decline over the same period; AAPC -4.5 (95% CI -6.3, -2.6) and -6.1 (95% CI -8.7, -3.4), respectively (Table 4). When stratified by age group (< 60 or ≥60), there was an increase in rates in the younger age group for patients with T1DM, for any LEA in more recent years, i.e., 2009-2016, APC 14.2 (95% CI 7.2, 21.6), minor LEA for the entire study period AAPC 7.4 (95% CI 3.2, 11.8) and for major LEA between 2009-2016, APC 15.4 (95% CI 5.7, 26.0). In contrast older patients with T2DM experienced significant declines in rates of any LEA, AAPC -4.8 (95% CI -6.6, -2.9), minor LEA, AAPC -2.6 (95% CI -4.5, -0.6) and major LEA, AAPC -11.9 (95% CI -14.0, -9.8) (Table 4).

Discussion

Our analysis of hospital discharge data for the state of Victoria, Australia over a 12-year study period between 2004-2016 for 10,406 LEA in patients with T1DM or T2DM showed significant differences in trends by type of diabetes, stage of amputation, sex and age group.

Patients with T2DM experienced a significant decline in overall rates of LEA, in contrast patients with T1DM did not. These overall rates for LEA reflected in minor LEA, patients with T2DM experienced a significant decline, with an AAPC of -38%, and patients with T1DM a significant increase, AAPC of 17%. In addition, for patients with T2DM a significant decline was observed in rates of major LEA, AAPC -12%. No significant trends were observed in patients with T1DM for major LEA. Similar trends for LEAs were also observed in 12-month mortality rates with no significant trends observed in T1DM, whereas patients with T2DM experienced a significant decline in mortality with an AAPC of -4%.

Significant differences were observed when trends were examined by sex, age group and diabetes type. When rates of any LEA were examined by sex, females with T1DM experienced a significant increase, AAPC 5%, in contrast to females with T2DM who experienced a significant decline, AAPC of -6%. The only significant trend observed for overall rates of LEA in men was for T2DM, AAPC -4.5%. Concerningly rates of all types of LEA were observed to rise for younger patients (<60) with T1DM, with a significant rise for any LEA between 2009-2016 with an AAPC of 14%. This increase was due to a significant rise in both minor (AAPC 7%) and major (AAPC 15%) amputations during the above observations period. This is in contrast to older patients (≥60) with T2DM who experienced declines in rates of any LEA (AAPC -5%), minor LEA (AAPC -3%) and major LEA (AAPC -12%).

There is conflicting evidence on trends in the incidence of diabetic foot and LEA, with very little current evidence available for Australia. An Australian study by Kurowski et al. conducted between 2000-2010 showed that rates of first instance of LEA in Western Australia declined for patients with T1DM and T2DM. However, similar to our results they showed recurrent minor amputations increased significantly for patients with T2DM[12]. Recently, a study following participants from the community-based Fremantle Diabetes Study phases 1 and phase 2 has shown that incident diabetes-related foot ulcers increased between 1993 and 2011 for patients with T2DM. This increase was particularly evident in younger patients highlighting that the burden of diabetic foot disease appears to have shifted to younger age-groups. No information on amputation rates was provided in the above study[14].

Harding et al. reported an initial period of decline for LEA patients with T1DM and T2DM between 2000-2015 in the U.S. However, this trend for improvement may have plateaued in recent times[15]. Wu et al. reported an overall decline in rates of hospitalisations for LEA in Hong Kong between 2001-2016[6]. This is in contrast to Aziz et al. who found no change

between 2014-2017 in rates of admission for LEA[16]. Geiss et al. examined trends by age group and also found an increase in rates of minor LEA in younger patients. The increase in major LEA that we report in younger patients are slightly less than that reported by Geiss et al.[5]. We report concerningly high rates of 1-year mortality following LEA, especially for T2DM. There is limited literature available on mortality rates following LEA, however our findings are consistent in their high rates with previous publications. In contrast to findings by Wu et al., we did find a decline over time in rates which were similar to results found by a nationwide study in Spain over a similar time period[6, 7]. This variation may in part be due to methodological differences, variations in healthcare systems and differences in how healthcare is delivered[17].

There are differing theories why rates of LEA may be significantly different between subgroups. Minor LEA may be increasing due to a change in clinical practices in an attempt to avoid major LEA. However, our results concerning younger patients with T1DM suggest that rates of major LEA may also be rising. It may be that there are more rudimentary aspects in the prevention of LEA that are being neglected in the above population, such as glycaemic control, cardiovascular risk factor modification and the early detection and treatment of foot ulcers[18]. One of the relevant areas of concern locally is the poor screening processes for diabetes foot in Australia. The National Diabetic Foot Disease Management Program of Australia set a regular foot examination screening target of 80%. However, actual rates of screening are significantly less than these targets, reported to be around 50%[19, 20]. One report from the U.S. found an increase in the total annual foot examinations between 1999-2010 with an increase from 65% to 71%. However, this same report noted that younger adults were less likely than older adults to receive preventative care and therapies which would seem consistent with the outcomes we observe in our results[21]. In Australia patients are able to apply through their General Practitioner. To be placed on a “care-plan”, this results in patients being eligible to receive 6 visits with a podiatrist subsidised by Medicare (the Australian tax funded universal health coverage system). It may be that older adults are more willing to participate in the above models of care and have greater access to General Practitioners and therefore are more likely to receive podiatry care. The importance of access to diabetic foot care was highlighted in a recent meta-analysis, with significant improvements found in overall and major rates of LEA for those with improved access to structured diabetic foot care[22].

There were a number of limitations associated with this study, including that we lacked information on the medication use or metabolic control due to the use of routinely collected hospital discharge data. This also meant that we were unable to assess the impact that the

introduction of newer medications such as the SGLT-2 inhibitors which are known to be cardio- and renal-protective but with some concern surrounding increased risk of LEA, a concern which is possibly abating in more recent times[23]. There were also changes in coding practices which resulted in changes in how diabetes was coded in 2008 and 2012. This was evident in our data which showed a decline in the number of patients that were coded with both T1DM and T2DM in 2008 followed by an increase in 2012 and may have impacted on the severity of the population diagnosed with diabetes[24]. In addition, we were unable to separate causes for LEA from those related to the development of peripheral vascular disease or neuropathy.

The limitations of this study are offset by its strengths which included that it was a large, state-wide study including all patients with diabetes admitted in Victoria, Australia which has a similar age and sex composition to many other developed countries. It also included a prolonged follow up duration (13-years) in order to detect any potential changes in trends over time. Analysis was stratified by type of diabetes, and then further by sex and age groups (< 60 or ≥60), this revealed important trends and allowed for comparisons between the above groups of patients.

Conclusion

These results show a mix of outcomes for LEA depending on type of diabetes and age group. Encouragingly, we detected a significant decrease in LEA rates for patients with T2DM. Concerningly, younger patients with T1DM appear to be driving up an increase in LEA. The exact causes behind this rise are unknown. However, better primary prevention in terms of glycaemic control, cardiovascular prevention and early detection and prevention of foot ulcers targeting younger patients with T1DM may help stabilise and reverse this trend in the future and will also have a positive impact on other diabetes related complications.

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Tables

Table 5.9: Patient characteristics by diabetes status at time of incident admission

	T1DM	T2DM	p-value
	589 (8%)	6715 (92%)	
Sex			
Male	377 (64.0%)	4793 (71.4%)	<0.001
Female	212 (36.0%)	1922 (28.6%)	
Age Group			
21-29	25 (4.2%)	6 (0.1%)	<0.001
30-39	57 (9.7%)	66 (1.0%)	
40-49	115 (19.5%)	335 (5.0%)	
50-59	137 (23.3%)	997 (14.8%)	
60-69	108 (18.3%)	1689 (25.2%)	
70-79	88 (14.9%)	1971 (29.4%)	
80+	59 (10.0%)	1651 (24.6%)	
Comorbidities			
Peripheral vascular disease	304 (51.6%)	3917 (58.3%)	<0.01
Coronary heart disease	178 (30.2%)	2365 (35.2%)	0.02
Chronic kidney disease	316 (53.7%)	3300 (49.1%)	0.04
Hypertension	384 (65.2%)	4857 (72.3%)	<0.001
Cerebrovascular disease	98 (16.6%)	1144 (17.0%)	0.81
Heart Failure	133 (22.6%)	2282 (34.0%)	<0.001
Atrial Fibrillation	79 (13.4%)	1672 (24.9%)	<0.001

Abbreviations: T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus

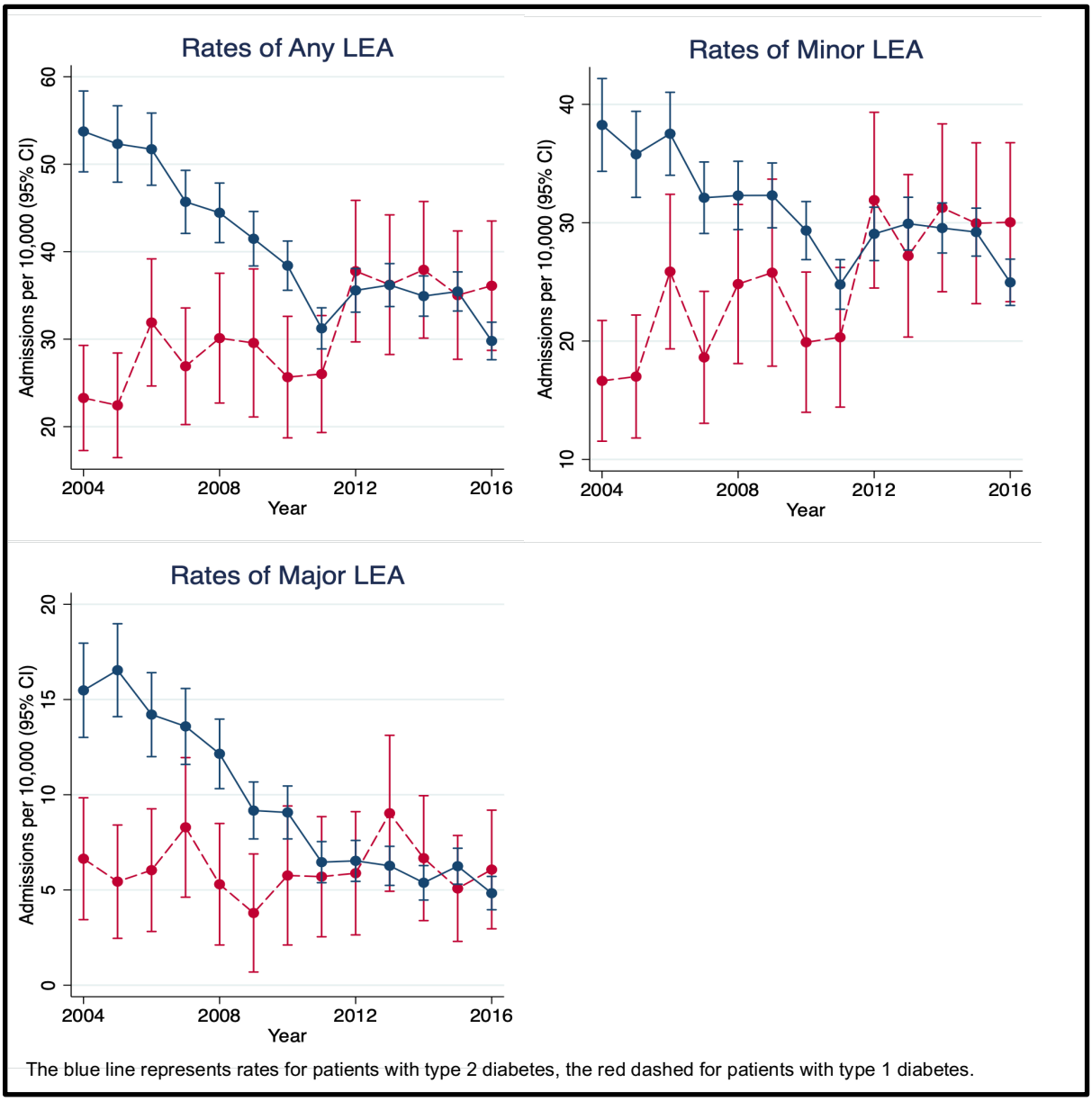
Table 5.10: Trends in rates of LEA in Victoria, Australia

	Diabetes Type	Total number of admissions	Standardised event rate (95% CI) (per 10,000 adults)		Overall trend*
			2004	2016	AAPC (95% CI)
Any LEA	T1DM	934	23.28 (17.27, 29.29)	36.11 (28.72, 43.51)	2.9 (-0.2, 6.0)
	T2DM	9,470	53.75 (49.13, 58.37)	29.8 (27.65, 31.94)	-4.9 (-6.8, -3.0)
Minor LEA	T1DM	752	16.64 (11.54, 21.74)	30.04 (23.33, 36.76)	3.7 (0.4, 7.1)
	T2DM	7,427	38.26 (34.34, 42.18)	24.96 (23.01, 26.92)	-3.0 (-5.0, -1.0)
Major LEA	T1DM	182	6.64 (3.44, 9.84)	6.07 (2.96, 9.19)	-0.4 (-5.5, 5.0)
	T2DM	2,043	15.48 (13.01, 17.96)	4.83 (3.96, 5.71)	-11.5 (-13.6, -9.3)

Abbreviations: AAPC, average annual percentage change; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus

*Adjusted for age and sex

Figure 5.8: Trends in hospital admission rates for LEA for patients by diabetes status



The blue line represents rates for patients with type 2 diabetes, the red dashed for patients with type 1 diabetes.

Table 5.11: Mortality by diabetes type and year

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
Type 1 Diabetes														
Total number of deaths within 12 months of any LEA	3	2	2	1	2	0	1	0	1	3	0	1	2	18
Any LEA	59	55	76	64	65	56	56	60	85	80	91	88	99	934
% Mortality	5.09%	3.64%	2.63%	1.56%	3.08%	0%	1.79%	0%	1.78%	3.75%	0%	1.34%	2.02%	1.93%
Type 2 Diabetes														
Total number of deaths within 12 months of any LEA	40	49	46	52	44	40	45	51	50	38	42	51	47	595

Any LEA	538	571	619	628	667	692	721	676	779	830	880	963	906	9,470
% Mortality	7.44%	8.58%	7.43%	8.28%	6.60%	5.78%	6.24%	7.54%	6.42%	4.58%	4.77%	5.30%	5.19%	6.28%

Table 5.12: Average annual percentage change (AAPC) and annual percent change (APC) for LEA rates

	Sub-group	Total admissions	Standardised event rate (95% CI) (per 10,000 adults)		Overall trend	Initial trend		Subsequent trend	
			2004	2016	AAPC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
T1DM									
Sex									
Any LEA	Male	622	28.87 (19.59, 38.15)	44.13 (32.85, 55.42)	1.6 (-1.5, 4.8)				
	Female	312	17.18 (9.75, 24.61)	27.36 (17.99, 36.72)	5.1 (0.5, 9.9)				
Minor Lea	Male	504	21.00 (12.98, 29.02)	38.29 (27.77, 48.76)	2.7 (-0.8, 6.3)				
	Female	248	11.88 (5.80, 17.96)	21.07 (12.94, 29.19)	5.5 (1.3, 9.9)				
Major LEA	Male	118	7.87 (3.18, 12.57)	5.87 (1.70, 10.03)	-2.8 (-8.2, 3.1)				
	Female	64	5.30 (1.00, 9.59)	6.29 (1.62, 10.96)	2.3 (-4.6, 9.6)				
Age-group (years)									
Any LEA	< 60	533	13.20 (7.92, 18.48)	35.62 (26.77, 44.47)	5.4 (-0.5, 11.6)	2005-2009	-8.4 (-21.7, 7.2)	2009-2016	14.2 (7.2, 21.6)
	≥60	401	49.55 (33.17, 65.93)	36.63 (24.81, 48.44)	-0.6 (-5.3, 4.3)				
Minor Lea	< 60	433	11.00 (6.18, 15.82)	29.27 (21.25, 37.29)	7.4 (3.2, 11.8)				
	≥60	319	31.16 (18.16, 44.17)	32.70 (21.53, 43.87)	0.3 (-4.5, 5.3)				
Major LEA	< 60	100	2.20 (0.04, 4.36)	6.35 (2.60, 10.10)	1.9 (-5.8, 10.3)	2005-2009	-17.9 (-33.9, 1.3)	2009-2016	15.4 (5.7, 26.0)
	≥60	82	18.39 (8.40, 28.38)	3.93 (0.07, 7.79)	-3.4 (-13.2, 7.6)				

	Sub-group	Total admissions	Standardised event rate (95% CI) (per 10,000 adults)		Overall trend	Initial trend		Subsequent trend	
			2004	2016	AAPC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
T2DM									
Sex									
Any LEA	Male	6,905	69.50 (62.30, 76.70)	41.84 (38.40, 45.28)	-4.5 (-6.3, -2.6)				
	Female	2,565	35.78 (30.27, 41.29)	16.06 (13.68, 18.44)	-6.1 (-8.7, -3.4)				
Minor Lea	Male	5,445	50.97 (44.77, 57.18)	35.33 (32.18, 38.48)	-2.6 (-4.5, -0.5)				
	Female	1,982	23.76 (19.26, 28.26)	13.14 (10.98, 15.30)	-4.1 (-6.7, -1.5)				
Major LEA	Male	1,460	18.53 (14.84, 22.21)	6.51 (5.12, 7.91)	-11.1 (-13.2, -8.9)				
	Female	583	12.01 (8.81, 15.22)	2.92 (1.92, 3.91)	-12.4 (-15.7, -8.9)				
Age-group (years)									
Any LEA	< 60	1,974	17.92 (14.49, 21.34)	25.22 (21.73, 28.71)	3.3 (-1.1, 8.0)	2005-2014	-1.5 (-4.0, 1.1)	2014-2016	28.0 (-2.0, 67.0)
	≥60	7,496	74.43 (67.44, 84.41)	35.84 (33.20, 38.48)	-4.8 (-6.6, -2.9)				
Minor Lea	< 60	1,619	14.00 (10.97, 17.03)	20.30 (17.17, 23.43)	3.4 (-1.0, 7.9)	2005-2014	-0.7 (-3.2, 1.8)	2014-2016	24.1 (-4.4, 61.1)
	≥60	5,808	51.45 (45.63, 57.27)	30.80 (28.35, 33.25)	-2.6 (-4.5, -0.6)				
Major LEA	< 60	355	3.92 (2.32, 5.52)	4.92 (3.37, 6.46)	3.1 (-6.6, 13.7)	2005-2014	-4.9 (-10.4, 1.0)	2014-2016	47.7 (-18.5, 167.8)
	≥60	1,688	22.98 (19.09, 26.86)	5.04 (4.05, 6.03)	-11.9 (-14.0, -9.8)				

Chapter 6: Coronary artery disease as assessed by angiography and the impact of preventative cardiovascular therapies in patients with and without type 2 diabetes.

Abstract

Background

Although it is known that patients with Type 2 Diabetes Mellitus (T2DM) are at an increased risk of coronary artery disease (CAD), the actual coronary artery burden of atherosclerotic disease in patients with and without T2DM in a real-world setting and its possible modification by preventative therapies has not been extensively documented.

Methods

Merged coronary angiography and hospital discharge data between 2013 and 2019 were obtained for analysis and a random sub-sample of patient charts were reviewed for medication use. Propensity scores were estimated using logistic regression models and used to match patients, looking at the effect of severity of CAD over time in years in an ordinal logistic regression model. A separate propensity score was estimated and used to inverse probability weight the ordinal logistic regression looking at the effect of medication use on CAD severity in patients with and without T2DM.

Results

From 3,016 patients in the coronary angiography database, 1,421 with T2DM and 1,421 without T2DM were matched on propensity score. T2DM patients had more extensive CAD in 2018 compared to 2013 ((adjusted odds ratio) adjOR: 2.06 95% C.I. 1.38, 2.07), but this risk appeared to be attenuated in 2019. In contrast, there was no effect of time on CAD burden in patients without diabetes. In the sub-sample of 760 patients who underwent a chart review of their medication use, there were 367(48%) with T2DM. For patients with T2DM 69.8% reported taking statins, 64.0% RAS inhibitors and 64.0% anti-platelet drugs. This was significantly higher than patients without diabetes of whom 46.6% reported taking statins, 49.0% RAS inhibitors and 49.9% anti-platelet drugs. As in the full matched sample patients with diabetes had more extensive CAD disease (adjOR: 1.32 95% C.I. 1.01, 1.74). However, after

adjustment for the use of RAS inhibitors, statins and anticoagulants there was no difference in extent of CAD between patients with and without diabetes (adjOR: 1.14 95% C.I. 0.85, 1.53).

Conclusions

Although patients with diabetes have a greater extent of CAD in comparison to those without T2DM, preventative medication use decreases this CAD burden significantly.

Introduction

Patients with diabetes are known to be at an increased risk for developing coronary artery disease (CAD) compared to patients with normoglycaemia. A number of studies over the past decades have shown that the management of cardiometabolic risk factors including hyperglycaemia, dyslipidaemia, and hypertension through intensive multifactorial interventions reduce the development and progression of diabetes related macrovascular complications[1-5]. Despite this, cardiovascular (CV) disease continues to be the leading cause of death for adult patients with type 2 diabetes mellitus (T2DM) and represents a substantial economic burden to both the patient and population[6, 7]. Whilst there have been a large number of clinical studies documenting the relatively poorer CV outcomes for patients with diabetes, there have been few studies that have examined the impact of diabetes on coronary artery anatomy. In particular, the extent of CAD involvement for patients with and without diabetes and the impact of traditional CV disease preventative therapies on disease within the coronary arteries, as assessed by angiography, has not been well characterised over the past 10 years. We have therefore evaluated the severity of CAD based on coronary angiogram for patients with and without T2DM admitted to a tertiary hospital in Australia over the seven-year period between 2013 and 2019.

Methods

Settings and Data Sources

All patient coronary angiography and hospital discharge data at a large Australian tertiary referral hospital between 2013 and 2019 were obtained and merged using the hospital record number. A random stratified sample of these patient charts were reviewed for medication use (renin-angiotensin system (RAS) inhibitors, statins, anti-platelet drugs and medications related to diabetes management), with 50% of charts selected based on T2DM diagnosis (figure 1). Diagnostic information is coded

according to the International Statistical Classification of Diseases and Related Health Problems, Australian Modification (ICD-10-AM)[8].

Case Definition

A patient's first known angiogram at the hospital was included. Indication for angiography was based on the original classification by treating cardiologist and included: chest pain, history of an acute coronary event, breathlessness, positive non-invasive test and other indications for angiogram which could not be directly linked atherosclerotic disease. The sample was restricted to angiograms for the above indication and excluded angiograms performed for the following indications: acute pulmonary oedema, aortic aneurysm, arrhythmia, cardiac arrest, cardiomyopathy, congenital heart defect, endocarditis, myocarditis, positive CT coronary angiogram, previous myocardial infarction, previous stent, pulmonary hypertension, research study patients, transplant work-up or valvular disease. A diagnosis of T2DM was established using ICD-10-AM codes E11.0 to E11.9. Angiograms for patients with a diagnosis of type 1 diabetes using ICD-10-AM codes E10 were excluded.

Main Outcome

The primary outcome was the extent of CAD based on the original classification by treating cardiologists: no disease, mild disease, moderate disease or severe disease. Although grading of the extent of CAD was at the discretion of the treating cardiologist patients with mild disease had minor coronary disease without any evidence of significant vessel stenosis, those with moderate disease had at least one vessel with greater than 50% stenosis, and those with severe disease had two or three vessels with greater than 50% stenosis.

Statistical Analysis

To reduce potential confounding factors in the sample we used the propensity score in two ways: to match and to inverse probability weight The propensity scores were estimated using logistic regression models and included baseline patient characteristics (age, gender, country of birth (Australian y/n), English spoken (y/n), indication for angiogram, year of coronary angiogram, Socio-Economic Indexes for Areas (SEIFA) index (a measure of relative socio-economic disadvantage) and Elixhauser comorbidities (a measure of patients disease burden using hospital administrative data))[9]. Standardized differences were calculated for each baseline patient characteristic variable, with all standardised differences being <0.1. One

propensity score was developed to identify a 1:1 matched sample of patients with and without T2DM in the time analysis (the time cohort) and a second propensity score was developed to inverse probability weight the sub-sample which underwent chart review for their medication use (the medication cohort, see figure 1).

Continuous variables are presented as median (interquartile range) and categorical variables as total number and percentage (%). Patient characteristics by diabetes status were compared using Wilcoxon rank-sum test for continuous variables and Pearson's χ^2 for categorical variables.

An ordinal logistic regression model stratified by T2DM status was fitted to estimate effect of T2DM on the severity of CAD (none, mild, moderate or severe) over time in years in the matched sample, the time cohort. A separate ordinal logistic regression model was fitted to estimate the average treatment effect among the treated on the random sample of patents who had their charts reviewed for medication use, the medication cohort[10]. All analyses were conducted using STATA version 16.1 (StataCorp, College Station, TX).

Ethics Approval

This study was approved by the St Vincent's Hospital Melbourne Human Research Ethics Committee (HREC/18/SVHM/146).

Results

Baseline patient characteristics of the study population are shown in supplementary table 1. Of first angiograms 1,572 (27.2%) had T2DM. Patients with T2DM were significantly older, less likely to be born in Australia, less likely to speak English and had greater numbers of co-morbid conditions than those without T2DM. There were no significant differences in the indication for coronary angiography in patients with and without T2DM: chest pain, 22% vs 22%; history of Acute Coronary Event (ACS); 9% vs 10%, breathlessness, 8% vs 9%; positive non-invasive test, 36% vs 33% and other, 26% vs 27%, respectively.

Time Cohort

Following propensity score matching, there were 1,421 matched pairs of patients (table 1). The median age of patients was 67.3 years (IQR 59.0, 74.7) and 63.2% (1,796) were male. As expected, in the matched cohort there were no significant differences for any of the covariates between patients with and without diabetes.

Supplementary table 2 lists the extent of CAD over time. Figure 2 shows the change in extent of CAD in both patients with and without T2DM over the period of the study. In the ordinal logistic regression, an increasing risk of more extensive CAD was observed between 2013 and 2018 (OR: 2.06 95% C.I. 1.38, 3.09) (table 2) for patients with diabetes. However, this risk appeared to be attenuated in 2019 with no significant change in severity of CAD in 2013 compared with 2019 (OR: 1.37 95% C.I. 0.91, 2.07) (table 2). No consistent significant effect of time on CAD burden in patients without diabetes was found (table 2).

Medication Cohort

Of the 760 patients with medication details available 367 (48.0%) also had a diagnosis of T2DM. Following propensity score weighting no significant differences between any patient covariates persisted (table 3).

When diabetes medications use was examined, metformin was the most frequently reported (66.5%), followed by other medications, which included thiazolidinediones and sulfonylureas (36.8%) and insulin (23.4%). Very few patients reported taking medications belonging to the relatively newer classes of glucoses lowering medications, the sodium-glucose transport-2 (SGLT-2) inhibitors (4.9%) or glucagon-like peptide-1 (GLP-1) receptor agonists (3.3%) (supplementary table 3). Patients with T2DM were more likely to take all of the traditional CV disease preventative therapies than patients without T2DM (supplementary table 3). The greatest difference in medication use between patients with and without T2DM was seen for the use of statins, 69.8% compared to 46.6% ($p<0.001$), respectively. Patients with T2DM were also more likely to be prescribed RAS inhibitors compared to those without T2DM, 64.0% versus 49.0% ($p<0.001$), respectively. There was also a small but significant difference in the rates of anti-platelet drug use in patients with and without T2DM, 64.0% versus to 49.9% ($p=0.05$), respectively.

Of patients with T2DM, 78.2% (n=287) had evidence of angiographic CAD compared with 70.2% (n=276) of patients without T2DM, p<0.01 (supplementary table 4). In the unweighted ordinal logistic regression model patients with T2DM were significantly more likely to have extensive CAD than patients without T2DM (OR: 1.32 95% CI: 1.01, 1.74). Both increasing age (OR: 1.06 95% CI: 1.04, 1.07) and being male (OR: 1.80 95% CI: 1.36, 2.38) were also associated with more extensive CAD in patients with information about medication use (table 4). Following propensity score weighting and adjustment for the use of statins, anti-platelet drugs and RAS inhibitors no significant difference in extent of CAD was seen between patients with and without T2DM (OR: 1.14 95% CI: 0.85, 1.53). In the multivariate regression model both age and being male were still associated with more extensive CAD. The use of anti-platelet drugs was also associated with more extensive CAD (OR: 2.64 95% CI: 1.93, 3.61) (table 4).

Discussion

We found that T2DM patients have a greater burden of CAD as assessed by angiography compared to those without diabetes. Interestingly we also found that T2DM patients had more extensive CAD as assessed by angiograms performed in 2018 compared to 2003, but that possibly this trend was attenuated in 2019. The above finds need to be put into the context of a possible change in the indication or thresholds for performing coronary angiograms in people with T2DM over the observational period of the study. However, possibly the most important finding from our study is that despite a greater use of CV protective medications by patients with T2DM, the extent of disease within the coronary arteries, as assessed by angiography, was still greater in patients with T2DM compared to those without T2DM. However, after adjustment for medication use, we found that there was no longer any difference in the extent of CAD between patients with and without T2DM. These findings highlight the exaggerated risk that patients with T2DM are still at for developing CAD. However, they also suggest that with the greater application of traditional CV disease preventative therapies, it may be possible to reduce the extent of the CAD burden in patients with to that seen in patients without T2DM.

Of the 367 patients with T2DM and medication details available, 78% (n=287) had evidence of angiographic disease. This rate was less in patients without T2DM, of which 70% (n=276) had evidence of angiographic CAD. In our unadjusted ordinal logistic regression model, prior to accounting for the use of preventative medications, patients with T2DM were significantly more likely (by 32%) to have more extensive

CAD than patients without T2DM (OR: 1.32 95% CI: 1.01, 1.74). Following adjustment for the use of statins, RAS inhibitors and anti-platelet drugs this significant difference in extent of CAD no longer persisted between patients with and without T2DM (OR: 1.14 95% CI: 0.85, 1.53).

When comparing the use of traditional CV disease preventative therapies between patients with and without T2DM; statins, RAS inhibitors and anti-platelet drugs were significantly more likely to taken by patients with T2DM. The increase in medication use for patients with T2DM compared to those without T2DM was 23% for statins, 14% for RAS inhibiting agents and 7% for anti-platelet agents. All of these differences for the uptake of CV preventative medication in patients with T2DM compared to those without T2DM were statistically significant. Whist these results are encouraging, our results also emphasise that more aggressive uptake and use of CV protective medications, possibly earlier after a diagnosis of T2DM is made, is still required to reduce the gap between the heightened risk for more severe CAD in patients with T2DM compared to those without T2DM. Unfortunately, we lacked information on achieved lipid or blood pressure measurements to gauge whether targeting the above medications to achieve certain biochemical or clinical parameters influenced the results we report.

It is well established that risk factor modification through the optimisation of glycated haemoglobin levels and blood pressure, treatment of microalbuminuria, dietary intervention, exercise and smoking cessation are able to reduce the risk in the development and progression of vascular complications[4, 11]. Our findings appear to be broadly consistent with those of a recent large epidemiological study which has also suggested that it is possible for patients with T2DM to eliminate their excess risk for acute myocardial infarction compared to the general population if they can achieve five risk-factor variables (glycated haemoglobin, low-density lipoprotein cholesterol, systolic blood pressure, albuminuria and smoking status) within target ranges/recommendations[5].

A number of trials, both pharmacological and epidemiological, have suggested that the use of statins and blood pressure (BP) lowering medications are primarily responsible for the risk for CV events that had been observed in recent times[12-16].The publication of these large influential studies in the 1990's and early 2000's and the further confirmation of the CV benefits of the above approach in later studies has led to a drastic increase in the uptake of statins and anti-hypertensive agents, in particular RAS inhibitors, for both high risk vascular patients with and without T2DM[17-19]. However,

over time, some concern about side-effects has been reported regarding the use of statins[20]. If patients had been ceasing statins due to this concern, we would have expected to see the effect equally across both patients with and without diabetes. Given the reported side effects associated with statins, the wider use of newer approaches to treat dyslipidaemia such as the PCSK-9 inhibitors and possibly, ethyl icosapent, may result in a further decrease in the CAD burden in both patients with and without diabetes[21].

Targets for optimising BP lowering therapy in patients with and without diabetes still remain to be optimally defined and indeed and there has been a relaxing of BP targets for patients with diabetes over the last 10 years[22].However, RAS inhibiting agents are often prescribed for the cardio-renal effects in addition to their use a BP lowering agents. Unfortunately, the design of our study did not allow us to follow any temporal trends in number of patients with and without T2DM taking these agents. Furthermore, the value of aspirin therapy as a primary CV preventive agent, when offset by potential adverse events, has also been called into question in recent times. Whether this issue has differential affected the use of aspirin therapy in patients with and without diabetes remains to be examined.

Our analysis of patients admitted for their first coronary angiogram at a single tertiary hospital shows that the extent of CAD being detected on coronary angiogram was greater over time in patients with T2DM. This was in contrast to patients without T2DM where no significant effect on time on CAD extent was demonstrated. These findings appear to be contrary to reports of reduced rates for myocardial infarctions over recent years for patients with and without diabetes, with relative rate reductions appearing to be being larger in patients with T2DM[23]. It is therefore, important to emphasise that the results we report are not based on clinical events or outcomes but rather on findings from a coronary angiogram. It is possible that the initial increase in severity of CAD burden seen in our study for patients with T2DM may represent improved CAD screening over recent years rather than suboptimal application of preventative therapies to slow disease progression within the coronary arteries. A lower threshold for performing a coronary angiogram may also exist for patients with T2DM given the appreciated higher risk of CAD a diagnosis of T2DM confers and a higher appreciation of asymptomatic CAD in patients with T2DM[24]. Possibly, wider use of medications such as SGLT-2 inhibitors and GLP-1 receptor agonists which have been shown to have CV protective effects will result in improvements in CAD burden following 2019 for patients

with diabetes, however a longer duration of follow-up will be required to confirm whether the attenuation of severity in CAD is a true finding[25-28].

There were a number of limitations with this study. As we utilised hospital discharge coding data, information was not available on metabolic control or duration of diabetes. Therefore, we are unable to account for the effect that these preventative medications may have had on patient's risk profile. There may also be a small number of patients that may have incorrectly been classified as having either having had or not had T2DM[29]. However, the prevalence of diabetes that we found in our study of 28% is consistent with other local studies[30]. Another limitation to consider is that this study relied on individual cardiologists reporting on the indication for angiogram and the extent of CAD without a prospective set of criteria for grading the extent of CAD; however, this is balanced by the large number of experienced cardiologists reporting results. As patients with and without T2DM were assessed in an identical fashion, it is unlikely that the extent of CAD would have been recorded disproportionately for the two groups of patients. We report on the first recorded angiogram at our hospital, it is therefore possible that a patient may have received an angiogram or coronary invasive procedure previously at a different hospital. In this case, these patients may be considered to be high risk to warrant a second angiogram, and this may occur more frequently in patients with T2DM. If this was the case, these patients would almost certainly be classified as high-risk vascular patients and hence been more likely to be further investigated with another angiogram at our hospital. It is presumed that the above scenario occurred more frequently in patients with diabetes given their known exaggerated risk for CAD that this group is at.

These limitations are counterbalanced by the strengths of the study which include a large number of coronary angiograms from both patients with and without diabetes over a seven-year period. As it was an observational study, propensity scores were used in the regressions in order to include as many coronary angiogram results from patients with diabetes as possible allowing for a representative analysis.

Conclusion

Our findings show that the extent of disease within the coronary arteries of patients with T2DM still remains more severe compared to those without T2DM. However, it is possible that this excess burden of disease can potentially be attenuated to the levels seen in patients without T2DM by the more aggressive uptake of traditional CV protective medications. There results support those of a recent large epidemiological study that suggested that aggressive risk factor modification in patients with T2DM can eliminate the excess risk for myocardial infarction compared with that of the general population[5].

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Tables

Figure 6.9: Flow chart of cohort numbers

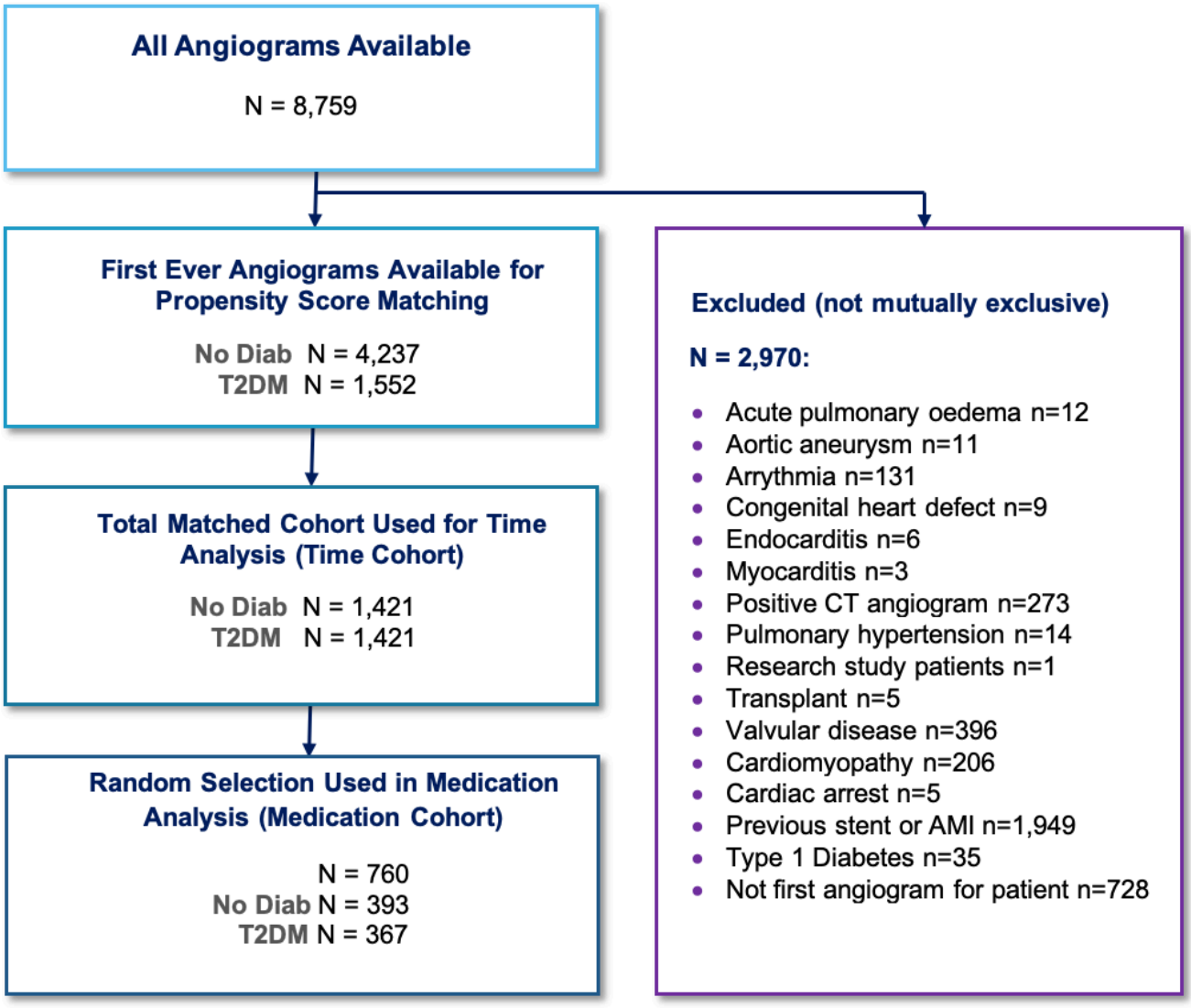

Table 6.13: Patient demographics for the time cohort

Characteristics	No Diabetes (n=1,421)	T2DM (n=1,421)	Standardised Difference	p-value
Age, median (IQR)	67.6 (58.8, 75.5)	67.0 (59.1, 73.7)	1.9%	0.22
Gender (Male)	921 (64.8%)	875 (61.6%)	6.7%	0.07
Country of Birth				
Non-Australian	435 (30.6%)	432 (30.4%)	0.5%	0.80
Australian	933 (65.7%)	929 (65.4%)	0.6%	
Unknown	53 (3.7%)	60 (4.2%)	2.5%	
Language Spoken				
English	1253 (88.2%)	1253 (88.2%)	0.0%	0.93
Not English	121 (8.5%)	124 (8.7%)	0.8%	
Unknown	47 (3.3%)	44 (3.1%)	1.2%	
SEIFA* Index, median (IQR)	6.0 (4.0, 7.0)	6.0 (4.0, 7.0)	0.7%	0.57
Stage of Chronic kidney disease (CKD)				
No known CKD	1343 (94.5%)	1333 (93.8%)	3.0%	0.96
CKD stage 2	6 (0.4%)	5 (0.4%)	1.1%	
CKD stage 3	41 (2.9%)	45 (3.2%)	1.6%	
CKD stage 4	15 (1.1%)	18 (1.3%)	2.0%	
CKD stage 5	12 (0.8%)	15 (1.1%)	2.2%	
CKD stage unknown	4 (0.3%)	5 (0.4%)	1.3%	
Indication for Angiogram				
Chest pain	317 (22.3%)	315 (22.2%)	0.2%	1.00
History of Acute Coronary Event	120 (8.4%)	121 (8.5%)		
Breathlessness	115 (8.1%)	119 (8.4%)		
Positive Non-Invasive Test	504 (35.5%)	506 (35.6%)		
Other	365 (25.7%)	360 (25.3%)		
Year of Angiogram				
2013	141 (9.9%)	147 (10.3%)	2.0%	0.95
2014	210 (14.8%)	207 (14.6%)		
2015	208 (14.6%)	206 (14.5%)		
2016	209 (14.7%)	220 (15.5%)		
2017	229 (16.1%)	242 (17.0%)		
2018	226 (15.9%)	209 (14.7%)		
2019	198 (13.9%)	190 (13.4%)		
Valvular disease	140 (9.9%)	145 (10.2%)	1.2%	0.75
Peripheral vascular disorders	30 (2.1%)	34 (2.4%)	1.9%	0.61
Congestive heart failure	133 (9.4%)	135 (9.5%)	0.5%	0.90
Cardiac arrhythmia	103 (7.2%)	107 (7.5%)	1.1%	0.77
Hypertension	201 (14.1%)	190 (13.4%)	2.2%	0.55

*Other Elixhauser comorbidities matched included pulmonary circulation disorders, other neurological disorders, chronic obstructive pulmonary disease, renal failure, liver disease, metastatic cancer, solid tumour without metastasis, rheumatoid arthritis/collagen vascular disease, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anaemia, deficiency anaemia, alcohol abuse and depression

Figure 6.10: Extent of CAD for patients with and without diabetes of time cohort

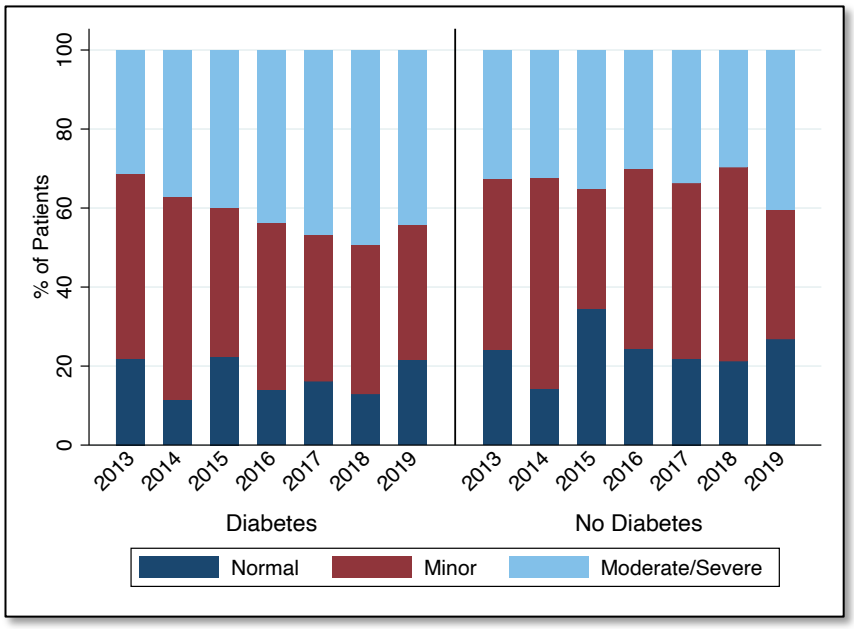

Table 6.14: Ordinal logistic regression model for extent of CAD in the time cohort

	No Diabetes		T2DM	
Extent of CAD	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age	1.05 (1.05, 1.06)	<0.001	1.04 (1.03, 1.05)	<0.001
Gender (Male)	2.44 (1.97, 3.01)	<0.001	2.21 (1.80, 2.72)	<0.001
Study Year				
2013	Reference		Reference	
2014	1.09 (0.73, 1.63)	0.66	1.49 (1.00, 2.21)	0.05
2015	0.85 (0.56, 1.28)	0.43	1.30 (0.87, 1.94)	0.20
2016	0.95 (0.63, 1.42)	0.79	1.60 (1.08, 2.38)	0.02
2017	1.07 (0.72, 1.58)	0.75	1.77 (1.20, 2.61)	<0.001
2018	0.94 (0.63, 1.40)	0.76	2.06 (1.38, 3.09)	<0.001
2019	1.19 (0.78, 1.80)	0.42	1.37 (0.91, 2.07)	0.13

Table 6.15: Patient Demographics for the medication cohort

Characteristics	No Diabetes (n=393)	T2DM (n=397)	Standardised Difference	p-value
Age, median (IQR)	63.9 (54.4, 73.0)	66.6 (59.9, 72.7)	0.5%	0.95
Gender (Male)	230 (58.5%)	224 (61.0%)	1.5%	0.84
Country of Birth				
Non-Australian	92 (23.4%)	108 (29.4%)	0.7%	0.85
Australian	289 (73.5%)	239 (65.1%)	0.2%	
Unknown	12 (3.1%)	20 (5.4%)	2.1%	
Language Spoken	6.0 (4.0, 7.0)	6.0 (4.0, 7.0)	1.2%	0.88
English				
Not English	381 (96.9%)	337 (91.8%)	0.3%	0.97
Unknown	1 (0.3%)	2 (0.5%)	4.9%	
SEIFA* Index, median (IQR)	5 (1.3%)	21 (5.7%)	4.0%	
Stage of Chronic kidney disease (CKD)	2 (0.5%)	3 (0.8%)	1.5	
No known CKD	4 (1.0%)	4 (1.1%)	1.0%	
CKD stage 2				
CKD stage 3	93 (23.7%)	91 (24.8%)	0.6%	0.94
CKD stage 4	45 (11.5%)	42 (11.4%)		
CKD stage 5	42 (10.7%)	32 (8.7%)		
CKD stage unknown	144 (36.6%)	146 (39.8%)		
Indication for Angiogram	69 (17.6%)	56 (15.3%)		
Chest pain				
History of Acute Coronary Event	57 (14.5%)	37 (10.1%)	1.6%	0.84
Breathlessness	46 (11.7%)	50 (13.6%)		
Positive Non-Invasive Test	53 (13.5%)	56 (15.3%)		
Other	54 (13.7%)	56 (15.3%)		
Year of Angiogram	60 (15.3%)	55 (15.0%)		
2013	60 (15.3%)	51 (13.9%)		
2014	63 (16.0%)	62 (16.9%)		
2015	39 (9.9%)	25 (6.8%)	2.6%	0.77
2016	14 (3.6%)	5 (1.4%)	4.3%	0.71
2017	32 (8.1%)	23 (6.3%)	<0.01%	1.00
2018	31 (7.9%)	27 (7.4%)	0.9%	0.91
2019	41 (10.4%)	53 (14.4%)	1.4%	0.86
Valvular disease	63.9 (54.4, 73.0)	66.6 (59.9, 72.7)	0.5%	0.95
Peripheral vascular disorders	230 (58.5%)	224 (61.0%)	1.5%	0.84
Congestive heart failure				
Cardiac arrhythmia	92 (23.4%)	108 (29.4%)	0.7%	0.85
Hypertension	289 (73.5%)	239 (65.1%)	0.2%	

*Other Elixhauser comorbidities matched included pulmonary circulation disorders, chronic obstructive pulmonary disease, renal failure, liver disease, solid tumour without metastasis, coagulopathy, weight loss, fluid and electrolyte disorders, deficiency anaemia and alcohol abuse.

Table 6.16: Extent of CAD for the medication cohort

Unadjusted Ordinal logistic regression model		
	Odds Ratio (95% CI)	p-value
Diabetes	1.32 (1.01, 1.74)	0.04
Age	1.06 (1.04, 1.07)	<0.001
Gender (Male)	1.80 (1.36, 2.38)	<0.001
Adjusted Ordinal Logistic regression model following propensity score matching		
Diabetes	1.14 (0.85, 1.53)	0.39
Age	1.05 (1.03, 1.06)	<0.001
Gender (Male)	1.76 (1.30, 2.39)	<0.001
Statin (Yes)	1.15 (0.84, 1.59)	0.38
Antiplatelet Drug (Yes)	2.64 (1.93, 3.61)	<0.001
RAS Inhibitor (Yes)	1.37 (1.01, 1.86)	0.04

Supplementary Tables

Supplementary Table 1: Baseline Patient Demographics

Characteristics	No Diabetes (n=4,212)	T2DM (n=1,577)	p-value
Age, median (IQR)	65.0 (55.8-72.9)	67.4 (59.7-74.1)	<0.001
Gender (Male)	2,568 (61.0%)	986 (62.5%)	0.28
Country of Birth			
Non-Australian	957 (22.7%)	504 (32.0%)	<0.001
Australian	3,087 (73.3%)	992 (62.9%)	
Unknown	168 (4.0%)	81 (5.1%)	
Language Spoken			
English	3,854 (91.5%)	156 (9.9%)	<0.001
Not English	192 (4.6%)	1,329 (84.3%)	
Unknown	166 (3.9%)	92 (5.8%)	
SEIFA* Index, median (IQR)	6.0 (4.0-7.0)	6.0 (4.0-7.0)	0.43
Stage of Chronic kidney disease (CKD)			
No known CKD	4,092 (97.2%)	1,422 (90.2%)	<0.001
CKD stage 1	0 (0.0%)	1 (0.1%)	
CKD stage 2	8 (0.2%)	8 (0.5%)	
CKD stage 3	62 (1.5%)	91 (5.8%)	
CKD stage 4	23 (0.5%)	22 (1.4%)	
CKD stage 5	20 (0.5%)	23 (1.5%)	
CKD stage unknown	7 (0.2%)	10 (0.6%)	
Indication for Angiogram			
Chest pain	916 (21.7%)	344 (21.8%)	0.11
History of Acute Coronary Event	414 (9.8%)	134 (8.5%)	
Breathlessness	379 (9.0%)	128 (8.1%)	
Positive Non-Invasive Test	1,373 (32.6%)	566 (35.9%)	
Other	1,130 (26.8%)	405 (25.7%)	
Year of Angiogram			
2013	607 (14.4%)	160 (10.1%)	<0.001
2014	589 (14.0%)	246 (15.6%)	
2015	591 (14.0%)	234 (14.8%)	
2016	589 (14.0%)	239 (15.2%)	
2017	650 (15.4%)	274 (17.4%)	
2018	621 (14.7%)	219 (13.9%)	
2019	565 (13.4%)	205 (13.0%)	
Valvular disease	405 (9.6%)	164 (10.4%)	0.37

Characteristics	No Diabetes (n=4,212)	T2DM (n=1,577)	p-value
Pulmonary circulation disorders	45 (1.1%)	21 (1.3%)	0.41
Peripheral vascular disorders	111 (2.6%)	36 (2.3%)	0.51
Other neurological disorders	12 (0.3%)	2 (0.1%)	0.38
Chronic obstructive pulmonary disease	19 (0.5%)	7 (0.4%)	1.00
Hypothyroidism	0 (0.0%)	1 (0.1%)	0.27
Renal Failure	59 (1.4%)	81 (5.1%)	<0.001
Liver Disease	53 (1.3%)	17 (1.1%)	0.69
Peptic ulcer disease, excluding bleeding	1 (0.0%)	1 (0.1%)	0.47
HIV/AIDS	1 (0.0%)	0 (0.0%)	1.00
Lymphoma	0 (0.0%)	3 (0.2%)	0.02
Metastatic Cancer	3 (0.1%)	2 (0.1%)	0.62
Solid tumour without metastasis	13 (0.3%)	9 (0.6%)	0.15
Rheumatoid arthritis/collagen vascular disease	11 (0.3%)	4 (0.3%)	1.00
Coagulopathy	17 (0.4%)	5 (0.3%)	0.81
Obesity	4 (0.1%)	6 (0.4%)	0.03
Weight loss	30 (0.7%)	13 (0.8%)	0.73
Fluid and electrolyte disorders	122 (2.9%)	60 (3.8%)	0.09
Blood loss anaemia	2 (0.0%)	2 (0.1%)	0.30
Deficiency anaemia	18 (0.4%)	19 (1.2%)	<0.01
Alcohol abuse	42 (1.0%)	6 (0.4%)	0.02
Drug abuse	13 (0.3%)	1 (0.1%)	0.13
Psychoses	2 (0.0%)	1 (0.1%)	1.00
Depression	19 (0.5%)	4 (0.3%)	0.35
Congestive heart failure	393 (9.3%)	157 (10.0%)	0.48
Cardiac arrhythmia	433 (10.3%)	123 (7.8%)	<0.01
Hypertension	381 (9.0%)	240 (15.2%)	<0.001

*Socio-economic Indexes for Areas

Supplementary Table 2: Extent of CAD for patients with and without diabetes derived from the time cohort

	No T2DM* (n=1,421)			T2DM (n=1,421)		
Study Year	Normal	Minor	Moderate/ Severe	Normal	Minor	Moderate/ Severe
2013	34 (24.1%)	61 (43.3%)	46 (32.6%)	32 (21.8%)	69 (46.9%)	46 (31.3%)
2014	30 (14.3%)	112 (53.3%)	68 (32.4%)	24 (11.6%)	106 (51.2%)	77 (37.2%)
2015	72 (34.6%)	63 (30.3%)	73 (35.1%)	46 (22.3%)	78 (37.9%)	82 (39.8%)
2016	51 (24.4%)	95 (45.5%)	63 (30.1%)	31 (14.1%)	93 (42.3%)	96 (43.6%)
2017	50 (21.8%)	102 (44.5%)	77 (33.6%)	39 (16.1%)	90 (37.2%)	113 (46.7%)
2018	48 (21.2%)	111 (49.1%)	67 (29.6%)	27 (12.9%)	79 (37.8%)	103 (49.3%)
2019	53 (26.8%)	65 (32.8%)	80 (40.4%)	41 (21.6%)	65 (34.2%)	84 (44.2%)
Total	338 (23.8%)	609 (42.9%)	474 (33.4%)	240 (16.9%)	580 (40.8%)	601 (42.3%)

*Type 2 Diabetes Mellitus

Supplementary Table 3: Medication use in patients with and without diabetes for the medication cohort

Medication	No T2DM* (n=393)	T2DM (n=367)	p-value
Statin (Yes)	183 (46.6%)	256 (69.8%)	<0.001
Antiplatelet Drug (Yes)	239 (60.8%)	248 (67.6%)	0.05
RAS Inhibitor (Yes)	196 (49.9%)	235 (64.0%)	<0.001
Metformin (Yes)	N/A	244 (66.5%)	
Other (Yes)	N/A	135 (36.8%)	
Diet Only (Yes)	N/A	67 (18.3%)	
Insulin (Yes)	N/A	86 (23.4%)	
SGLT2 Inhibitors (Yes)	N/A	18 (4.9%)	
GLP1 Receptor Agonists (Yes)	N/A	12 (3.3%)	

*Type 2 Diabetes Mellitus

Supplementary Table 4: Extent of CAD by diabetes status for the medication cohort

Extent of CAD	No Diabetes (n=393)	T2DM (n=367)	p-value
Normal	117 (29.8%)	80 (21.8%)	<0.01
Minor	183 (46.6%)	168 (45.8%)	
Moderate/Severe	93 (23.7%)	119 (32.4%)	

Chapter 7: The impact of type 2 diabetes on hospitalisation and mortality in people with malignancy

Abstract

Aim/hypothesis

There is a growing appreciation for the increased risk of incidence and mortality for malignancies in people with a co-diagnosis of diabetes. We aimed to compare the characteristics and outcomes for people with malignancies with and without a co-diagnosis of diabetes.

Methods

Emergency department and hospital discharge data from a single centre between 1 Jan 2015 and 31 Dec 2017 were used to identify people with a diagnosis of a malignancy and diabetes. Multivariate Cox-regression models were used to estimate the effect of diabetes on all-cause mortality. A truncated negative binomial regression model was used to assess the impact of diabetes on length of hospital inpatient stay. Prentice, Williams and Peterson Total Time (PWP-TT) models were used to assess the effect of diabetes on number of Emergency Department re-presentations and inpatient re-admissions.

Results

Of 7,004 people identified with malignancies, 1,195 (17.1%) were also diagnosed with diabetes. A diagnosis of diabetes was associated with an increased number of inpatient re-admissions (adjusted Hazard Ratio (adjHR): 1.13, 95% CI: 1.03, 1.24), increased number of emergency department re-presentations (adjHR: 1.13, 95% CI: 1.05, 1.22) and increased length of stay (adjIRR: 1.14, 95% C.I: 1.04, 1.25). A co-diagnosis of diabetes was also associated with a 48% increased risk of all-cause mortality (adjHR: 1.48, 95%CI: 1.22-1.76).

Conclusions

People with malignancies and diabetes had significantly higher numbers of emergency department presentations, inpatient admissions, length of hospital stay and higher rates of all-cause mortality compared to people with a malignancy without diabetes.

Introduction

The link between diabetes and a rising incidence of malignancies is increasingly being recognised. A recent meta-analysis of over 20 million people has shown that men with diabetes were at a 19% increased risk (RR: 1.19, 95% CI: 1.13, 1.25), whilst women were at a 27% increased risk (RR: 1.27, 95% CI: 1.21, 1.32) of developing a malignancy[1]. This increased risk for developing a malignancy may be related to malignancy type, with pancreatic, liver and gallbladder malignancies reported to be more common in people with diabetes[2]. Furthermore, it has been suggested that people with malignancies and diabetes have increased mortality rates compared to those without diabetes[3-6]. One study has estimated that there is up to a 219% increased risk of mortality for people with malignancies and diabetes compared to people without diabetes, depending on type of malignancy and gender[6].

A number of hypotheses have been put forward to explain the increased prevalence and adverse outcomes of malignancies in people with diabetes[7]. The mechanisms linking diabetes and increased rates of malignancy are not fully understood but hyperinsulinemia and hyperglycaemia have been implicated in increased cell proliferation. Also, once a malignancy develops, high levels of insulin and insulin like growth factors may possibly promote malignant cell and tumour growth, and metastasis[8-10]. In addition, the development and progression of a malignancy may possibly be influenced by various classes of glucose lowering medications. People on metformin may have a decreased risk of malignancy development and mortality, whereas therapies such as sulfonylureas, glitazones, incretin modifiers and insulin may possibly increase the risk of developing a malignancy[11-15].

Apart from incidence and mortality studies, there is little information regarding the impact of diabetes on other clinical outcomes, such as length of hospital stay, hospital admission rates and Emergency Department presentations, for people with a malignancy. Therefore, the aims of this study were to explore the impact a diagnosis of diabetes in people with a malignancy had on clinical outcomes, including length of stay, hospital admission rates, Emergency Department presentations and mortality after adjustment for relevant covariates following index admission.

Research Design and Methods

Study Design

This was a hospital wide retrospective cohort study comparing the characteristics and outcomes of people with a diagnosis of a malignancy with and without diabetes over a 3-year period.

Case Identification

Clinically coded data were used to identify all people who attended the Emergency Department or were admitted as an inpatient at an Australian tertiary referral hospital between 1/1/2015 and 31/12/2017. People were selected using the following codes from the International Classifications of Diseases, version 10, Australian Modification (ICD-10-AM): C00-C96 or D00-D48 for malignancies, C77-C79 for metastatic cancer and E11 for type 2 diabetes[16]. Patients that were classified as having type 1 diabetes or intermediate hyperglycaemia were excluded due to the heterogenous nature of the group.

Outcome measures

The main outcome was all-cause mortality (n=633). The date of death was based on information available in the hospital electronic database. Other outcomes of interest included number of Emergency Department presentations (n=9,916), length of any hospital stay and inpatient admission rates (n=9,029).

Chart review to assess steroid use

As steroids are often part of malignancy treatment and are a risk factor for hyperglycaemia, the temporal relationship between malignancy diagnosis, steroid use and diabetes diagnosis required further investigation as no information on steroid use was available in the databases used in this study. Therefore, in order to investigate the potential difference in steroid use between people with and without diabetes a chart review was conducted. Our preliminary results suggested that people with heamatological and lymphoid malignancies and diabetes were particularly at an increased risk of mortality. Hence, in addition to the above chart review, we specifically reviewed all clinical records of people with diabetes and these diagnoses (N=110) to assess the possible influence of steroid use on hyperglycaemia and the outcomes of interest of this study.

Statistical analysis

Normality was assessed visually using normal probability plots. Normally distributed continuous variables are presented as mean ± standard deviation (SD), non-normally distributed continuous variables are presented as median and interquartile range (IQR) and categorical variables as total number and percentage (%). Patient characteristics by diabetes status were compared using independent sample t-tests for continuous variables, Pearson's χ^2 for categorical variables and Wilcoxen rank-sum test for variables without a normal distribution.

Three different approaches were taken to fit models for mortality, length of hospital stay and hospital utilisation numbers: 1) multivariate Cox-regression model were used to estimate the effect of diabetes on all-cause mortality; 2) truncated negative binomial regression model were used to assess the impact of diabetes on length of hospital inpatient stay; and 3) Prentice, Williams and Peterson Total Time (PWP-TT) models were used to assess the effect of diabetes on the number of Emergency Department presentations and inpatient admissions following a patients index admission of presentation[17]. All models accounted for baseline characteristics of subjects including age, gender, diabetes, ischaemic heart disease, chronic kidney disease, body mass index (kg/m2) (BMI) less than 18.5, 18.5-25 and greater than 25, type of malignancy, metastatic disease, and, for the length of stay model, vital status at discharge. The proportional hazards assumption was assessed visually using log-log plots for individual covariates. The presence of multicollinearity was assessed by the variance inflation factor. Propensity scores were estimated to evaluate the average treatment effect of the treated for the above outcomes as an additional analysis (Supplementary table 6, 7 Supplementary figure 1).

As mentioned above, two chart reviews were conducted; one to examine potential difference in steroid use in people with and without diabetes and another to examine the temporal relationship between diabetes and malignancy diagnosis for people with lymphoid and haematological malignancies (a group of people with a high proportion of steroid use).

Ethics

Ethics approval of this study was granted by the St Vincent's Hospital Melbourne ethics committee (LNR 176/18)

Results

A total of 7,004 people were identified with a diagnosis of a malignancy that attended our hospital between 1/1/2015 and 31/12/2017, of whom 1,195 (17.1%) also had a diagnosis of diabetes (Table 1). People with diabetes were more likely to be male, older, have ischaemic heart disease, chronic kidney disease and a BMI of greater than 25 kg/m2, compared to those without diabetes (Table 1).

People with diabetes were more likely to have certain types of malignancies compared to those without diabetes. In particular, malignant neoplasms of the respiratory, intrathoracic organs, digestive organs, ill-defined, secondary and unspecified sites were more common (Table 2). In contrast, malignancies of the eye, brain and other parts of the central nervous system were less common in people with diabetes compared to those without diabetes.

Our overall chart review suggested that for our cohort of people with malignancy, there was no significant difference in steroid use between people with and without diabetes (25% vs. 23% p=0.74).

People with malignancies and diabetes had significantly higher numbers of Emergency Department presentations, inpatient admissions and increased length of hospital stay compared to people without diabetes (Table 3). Analysis of the data showed that the Cox-regression models for all-cause mortality, Emergency Department re-presentations and inpatient re-admissions fulfilled the proportional hazards assumption and no multicollinearity existed. A PWP-TT model was then used to investigate possible factors, in addition to diabetes status, that were associated with increased numbers of Emergency Department re-presentations and inpatient re-admissions in the cohort. The model revealed that the risk for subsequent hospitalisation following an index admission for people with a diagnosis of diabetes compared to people without diabetes was increased by 14% (HR: 1.14, 95% CI: 1.04, 1.25) (Supplementary table 1). We also found that certain malignancy types were associated with more hospital admissions (Supplementary table 1). A similar relationship between diabetes (HR: 1.19, 95% CI: 1.11, 1.28), and malignancy type was also seen for the risk of Emergency Department re-presentations (Supplementary table 2).

Factors that influenced inpatient length of hospital stay were further assessed using a truncated negative binomial regression model. This model confirmed that diabetes was an independently and significantly associated with an increased length of hospital stay (IRR: 1.14, 95% CI: 1.04, 1. 25). This model also showed type of malignancy, BMI greater than 25

kg/m2 and Charlson comorbidity score was associated with an increased length of hospital stay (Supplementary table 3). Following adjustment for covariates, the expected length of hospital stay for people with diabetes compared to those without diabetes was 4.98 days (95% CI 4.49, 5.46) vs 4.36 days (95% CI 4.06, 4.66).

A univariate Cox-regression model showed a strong and statistically significant increased risk of all-cause mortality for people with malignancy and diabetes compared to those without diabetes, (HR: 1.99, 95% CI: 1.67, 2.37). A Kaplan Meier curve illustrating this relationship is shown in figure 1. The increased risk of death for people with a malignancy and diabetes compared to those without diabetes still remained significant when assessed by a multivariate Cox-regression analysis (HR: 1.48, 95% C.I: 1.23, 1.77) (Supplementary table 4). This analysis also revealed that increasing age, end stage kidney disease, metastatic disease, Charlson comorbidity score and type of malignancy were significantly associated with an increased risk for mortality. A low BMI (less than 18.5kg/m2) was also found to be associated with an increased risk of all-cause mortality (HR: 1.45, 95% C.I: 0.99, 2.12).

Results obtained using propensity score weighting were similar to those obtained in the original analyses for all-cause mortality, emergency department re-presentation, inpatient re-admission and increased length of stay. The results were similar in the trimmed sample (Supplementary table 8).

We investigated the relationship between different types of malignancy and risk of all-cause mortality in people with and without diabetes. Due to the limited number of deaths for each type of malignancy, the analysis was limited to people with malignant neoplasms of the digestive, respiratory and intrathoracic organs and lymphoid and haematological malignancies. The only significant difference for mortality associated with a diagnosis of diabetes was seen in those with lymphoid and haematological malignancies. For people with lymphoid and haematological malignancies, a co-diagnosis of diabetes was associated with an 127% increased risk for mortality (HR: 2.27, 95% C.I: 1.41, 3.66) (Supplementary table 5). Our chart review of people with lymphoid and haematological malignancies suggested that the diagnosis of diabetes in these people was not influenced by steroid use. For this group of people only 9% (10/110) were classified as having diabetes after the commencement of steroid therapy during the course of their malignancy treatment. It was hypothesised that diabetes may merely be a marker of more severe pancreatic cancer, for this reason we conducted sensitivity analysis where we excluded all cases of pancreatic cancer from the survival analysis, this resulted in 43 people with diabetes and 55 people

without diabetes being excluded and a change in the hazard ratio from (HR: 1.40 95% C.I: 1.00, 1.97) to (HR: 1.44 95% C.I: 1.01, 2.05) which remained significant.

Discussion

Our findings support the hypothesis that a co-diagnosis of type 2 diabetes and malignancy is associated with a number of adverse outcomes, including increased number of emergency department re-presentations, hospital re-admissions, length of stay and all-cause mortality compared to people with malignancies without diabetes. Our analysis was adjusted for covariates that could potentially influence the above outcomes, including age, gender, ischaemic heart disease, chronic kidney disease, type of malignancy, smoking status, Charlson comorbidity score, metastatic disease and BMI (kg/m2). Even following adjustment for covariates, the adverse effect of a diagnosis of diabetes persisted. Furthermore, in our multivariate cox survival analysis, a co-diagnosis of diabetes remained a statistically significant risk factor for all-cause mortality (HR:1.48, 95% C.I: 1.23, 1.77). Malignancy type was also influenced by the presence of diabetes. We found a higher prevalence of malignant neoplasms of the respiratory, intrathoracic organs, digestive organs, ill-defined, secondary and unspecified sites in people with diabetes compared with those without diabetes. In contrast, malignancies of the eye, brain and other parts of the central nervous system were less prevalent in people with malignancy and diabetes compared to those without diabetes.

The hazard ratio for all-cause mortality in people with malignancies and diabetes that we report is comparable to the increased risk reported in other studies for people with diabetes (HR range 1.26-3.87)[3,5,18,19]. Due to sample size limitations, a malignancy type-specific analysis was only possible for lymphoid and haematological malignancies. For these malignancies, we found an increased mortality rate for a co-diagnosis of diabetes of approximately 130% (HR: 2.27, 95% C.I: 1.41, 3.65) Previous studies have reported inconsistent findings regarding the association between diabetes and mortality for people with lymphoid and haematological malignancies. One study has suggested that the adverse relationship between diabetes and blood malignancies is restricted to people with lymphoma[18]. The differences we report in regard to diabetes, cancer type and mortality may be explained by the different populations and the methods of statistical analysis used in different studies. Our chart analysis suggested that the use of steroids was unlikely to influence this relationship between diabetes and all-cause mortality with lymphoid and haematological malignancies.

The association between a BMI below 18.5kg/m2 and increased all-cause mortality is not unexpected given that people who are severely unwell are likely to have lower BMIs. There may also be differences in the type and intensity of malignancy treatment for people with and without diabetes, that could contribute to the observed increase in mortality for people with malignancy and diabetes. It is possible that elderly people with diabetes and a high burden of other comorbidities may have received treatment with an intended palliative rather than curative outcome[20]. Our results relate to people who already have cancer, weight gain has been showed to increase the risk of developing cancer[9,21,22].

A strength of this study was the focus on outcomes other than mortality, which has not been previously explored in this setting. We were able to demonstrate that people with malignancies and diabetes are at a significantly increased risk of inpatient re-admission, Emergency Department re-presentation and increased length of hospital stay. The models used to explore the above relationships were adjusted for relevant covariates that also took into account comorbidities that are more common in people with diabetes. We found that people with diabetes were at significantly increased risk of inpatient re-admission (HR: 1.10, 95% C.I. 1.00, 1.20) and Emergency Department re-presentations (HR: 1.12, 95% C.I: 1.04, 1.20) compared to those without diabetes. The above relationships were derived utilising a PWP-TT model which allows for the adjustment of an individual's baseline risk to increase as their number of admissions or presentations increases[17]. This is achieved through the stratification by number of previous failure events a patient experienced. Although the hazard ratios for risk of inpatient and emergency department is modest, given the large cost, both financial and in resources, associated with hospital attendance and admission any increase in admission rates most likely have a significant negative impact on healthcare costs. We also report length of stay was significantly increased for people with malignancy and diabetes compared to those without diabetes (IRR: 1.14, 95% C.I: 1.04, 1.25), which equates to 4.98 days (95% CI 4.49, 5.46) vs 4.36 days (95% CI 4.06, 4.66) for people with and without diabetes and a malignancy. As ICD-10-AM codes were used to select malignancy admitted episodes their admission may not necessarily be related to their malignancy treatment, there were also a number of same day admissions which resulted in an overall short length of stay.

There were a number of limitations associated with this study. Although this study was only from a single site, it represents outcomes for people of a large tertiary referral and university teaching hospital with a state-wide catchment area. However, we acknowledge that our results may not be generalizable to other regions where treatment and management of malignancies and/or diabetes may differ. The small number of deaths limited our analysis for

this outcome by malignancy type. The relatively short follow-up period of three years may also present a potential limitation. As this was an observational study, any relationship that we described for outcomes in people with malignancy and diabetes compared to those without diabetes should only be inferred as describing an association, rather than establishing causation.

The ICD-10-AM based case selection of both malignancies and diabetes could potentially represent an underestimation of the prevalence of these two diagnoses. We report a slightly lower prevalence of diabetes (17%) compared with a previous inpatient survey of hospitals including our centre, which reported a diabetes prevalence of 25%[23]. It is possible that those with milder forms of diabetes were less likely to be captured which may have resulted in an over-estimate in the relationship between diabetes and cancer outcomes.

In addition, the clinically coded hospital data used for this analysis lacked information on date of diabetes and malignancy diagnosis, a deficit which we attempted to account for through our chart reviews. We did not have information on medication use and were therefore unable to adjust analysis for this potential confounder. We also acknowledge the limitation that mortality rates were obtained from our hospital database and not from a central registry and did not have information on cause of death. This means that it is likely that there is an under-estimation of the event rates, both in terms of hospitalisation and deaths.

These limitations are counterbalanced by the strengths of this study which include the large sample size, the availability of detailed pathology and anthropometric data, comprehensive information on BMI and comorbidities on all people which has been lacking in other studies[6].

Conclusion

In summary, this study shows that people with malignancies and diabetes have a significantly higher number of Emergency Department re-presentations, inpatient re-admission, longer length of hospital stay, and higher rates of all-cause mortality compared to people with malignancy without diabetes. Given that the number of people with diabetes is increasing throughout the world, the above findings may have implications for future healthcare planning. Further work is needed to explore the mechanisms that explain the adverse relationship between malignancy and a co-diagnosis diabetes.

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Tables

Table 7.17: Patient characteristics by diabetes status at time of incident admission

Baseline characteristics (n=7004)	No Diabetes	Diabetes	Logistic regression OR (95% C.I)	p-value
N (%)	5809 (82.9)	1195 (17.1)		
Gender (Male)	3229 (55.6%)	746 (62.5%)	1.38 (1.27, 1.49)	<0.001
Age at first admission (years), median (IQR)	64.0 (51.0, 74.0)	72.0 (65.0, 79.0)	1.04 (1.04, 1.05)	<0.001
Chronic Kidney Disease (CKD)				<0.001
No known CKD	5716 (98.4%)	1129 (94.5%)	BASELINE	
CKD stage 1	0 (0.0%)	1 (0.1%)	N/A	
CKD stage 2	7 (0.1%)	5 (0.4%)	N/A	
CKD stage 3	34 (0.6%)	35 (2.9%)	6.09 (3.74, 9.93)	
CKD stage 4	24 (0.4%)	11 (0.9%)	2.54 (1.23, 5.25)	
CKD stage 5	28 (0.5%)	14 (1.2%)	2.23 (1.10, 4.55)	<0.001
Ischaemic Heart Disease (IHD)	57 (1.0%)	49 (4.1%)	4.32 (2.93, 6.35)	<0.001
BMI				
< 18.5kg/m2	161 (2.8%)	20 (1.7%)	BASELINE	
18.5-25kg/m2	1277 (22.0%)	206 (17.2%)	1.46 (1.13, 1.91)	
> 25kg/m2	4371 (75.2%)	969 (81.1%)	1.67 (1.29, 2.15)	<0.001
Death	451 (7.8%)	182 (15.2%)	2.14 (1.77, 2.57)	<0.001

CKD: Chronic kidney disease, IHD: Ischaemic heart disease, BMI: Body mass index (kg/m2)

Table 7.18: Malignancy type at death or final admission by diabetes status, by individual patient

	No Diabetes	Diabetes	p-value
N =	5809 (82.9)	1195 (17.1)	
Malignant neoplasms of breast	253 (4.4%)	45 (3.8%)	0.36
Malignant neoplasms of eye, brain and other parts of CNS	380 (6.5%)	49 (4.1%)	0.001
Malignant neoplasms of ill-defined, secondary and unspecified sites	1280 (22.0%)	316 (26.4%)	<0.001
Malignant neoplasms of lymphoid, haematopoietic and related tissues	391 (6.7%)	78 (6.5%)	0.80
Malignant neoplasms of skin, lip and oral cavity and in-situ and benign neoplasm	1447 (24.9%)	279 (23.3%)	0.25
Malignant neoplasms of respiratory, intrathoracic organs or digestive organs	1045 (18.0%)	339 (28.4%)	<0.001
Malignant neoplasms of bone, articular cartilage, mesothelial or soft tissue	254 (4.4%)	48 (4.0%)	0.58
Malignant neoplasms of Genito urinary tract	395 (6.8%)	94 (7.9%)	0.19

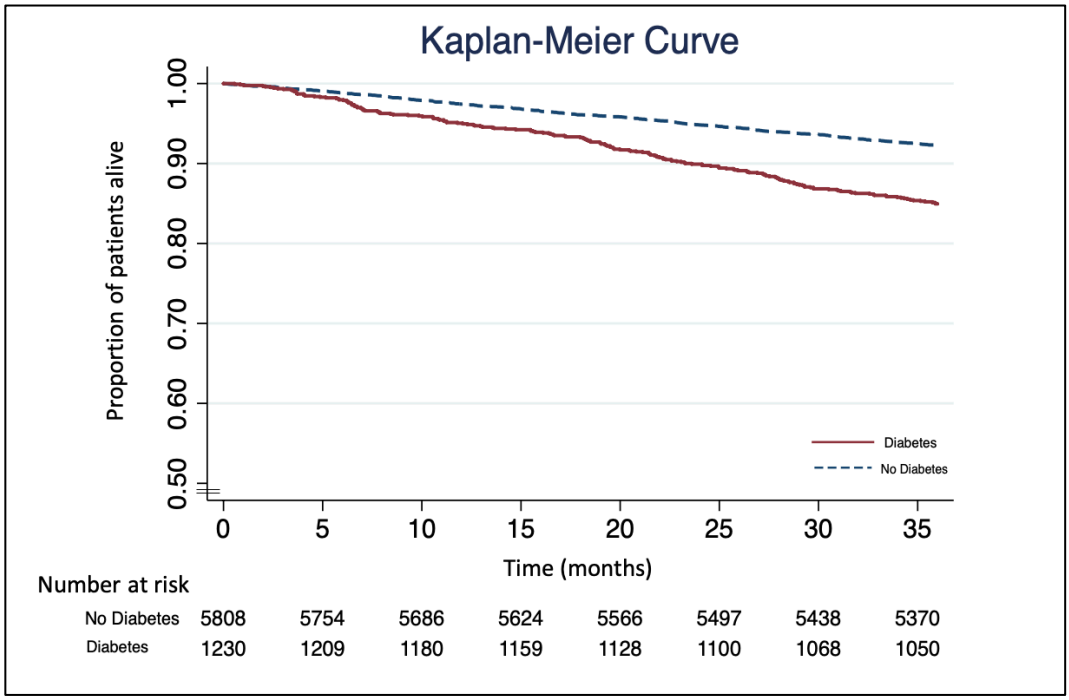
CNS: Central nervous system

Table 7.19: Hospital presentations and length of stay, by presentation

Baseline characteristics (n=7004)	No Diabetes	Diabetes	Univariate Hazard Ratio	p-value *
Total	12776	3398		
Number of ED+ presentations, median (IQR)	2.0 (1.0, 3.0)	3.0 (2.0, 5.0)	1.19 (1.11, 1.27)	<0.001
Number of inpatient admissions, median (IQR)	1.0 (1.0, 2.0)	2.0 (1.0, 3.0)	1.10 (1.01, 1.20)	<0.001
Length of stay (days), median (IQR)	4.0 (1.0, 9.0)	5.0 (2.0, 11.0)	1.38 (1.31, 1.46)	<0.001

* Using Wilcoxon-Rank sum test, + Emergency Department

Figure 7.11: Trends in hospital admission rates for cardiovascular outcomes for patients by diabetes status



Supplementary Tables

Supplementary Table 1: Balance of baseline covariates between patients with and without diabetes in weighted sample

	Weighted Sample ATT		
	No Diabetes (%)	Diabetes (%)	Standardised difference
N (weighted sum)	12,775	3,394	--
Age Group			
< 55	6.6%	6.4%	0.008
55 – 75	50.8	51.0	-0.003
> 75	42.6	42.6	-0.000
Sex (male)	66.4	66.7	-0.007
IHD*	5.0	5.7	-0.033
CKD# Stage			
No known CKD	95.5	95.2	0.016
CKD stage 2	0.2	0.2	0.000
CKD stage 3	1.8	2.0	-0.012
CKD stage 4	1.0	1.1	-0.004
CKD stage 5	1.4	1.5	-0.011
Malignant neoplasm of			
Malignant neoplasm of the breast	2.6	2.5	0.002
Malignant neoplasm of the eye, brain and other parts of CNS+	2.3	2.3	-0.002
Malignant neoplasms ill-defined, secondary and unspecified sites	17.0	18.0	-0.019
Malignant neoplasms of lymphoid, haematopoietic and related tissues	6.4	6.4	0.000
Malignant neoplasms of skin, lip and oral cavity and in-situ and benign neoplasms	17.0	17.0	0.002
Malignant neoplasms of respiratory of intrathoracic organs	7.0	7.0	0.000
Malignant neoplasms of digestive organs	14.1	14.3	-0.007
Malignant neoplasms of bone, articular cartilage, mesothelial or soft tissue	0.9	1.0	-0.007
Malignant neoplasms of Genito-urinary tract	6.0	6.0	-0.001

	Weighted Sample ATT		
	No Diabetes (%)	Diabetes (%)	Standardised difference
Metastatic cancer	33.0	33.0	-0.013
Smoker	37.6	38.5	-0.018
BMI category•			
< 18.5 kg/m2	2.1	2.1	0.001
18.5 – 25 kg/m2	50.9	51.6	-0.014
25 – 30 kg/m2	25.1	24.0	0.026
> 30 kg/m2	21.9	22.3	-0.011
Charlson Comorbidity score			
1	89.4	89.4	-0.001
2	5.1	5.2	-0.007
3	3.5	3.1	0.022
4	1.2	1.1	0.012
5	0.1	0.2	-0.035
6	0.3	0.4	-0.017
7	0.0	0.2	-0.046

Supplementary Table 2: Distribution of ATT weights

	Mean (SD)	Median (IQR)	Minimum	99th Percentile	Maximum
Diabetes	1 (0)	1 (1, 1)	1	1	1
No Diabetes	1 (0.93)	0.90 (0.29, 1.25)	0.08	4.32	15.11
All combined	1 (0.83)	1 (0.61, 1.15)	0.08	3.95	15.11

ATT = average treatment effect in treated

Supplementary Table 3: Inpatient Admissions (PWP-TT model)

Year	Hazard Ratio	P>|z|	95% CI	
Diabetes	1.10	0.05	1.00	1.20
Age Group				
< 55	REFERENCE			
55 – 75	0.89	0.03	0.81	0.99
> 75	1.03	0.65	0.92	1.15
Sex (male)	1.05	0.24	0.97	1.15
IHD*	1.04	0.76	0.79	1.37
CKD# Stage				
No known CKD	REFERENCE			
CKD stage 2	0.73	0.73	0.73	0.73
CKD stage 3	1.20	1.20	1.20	1.20
CKD stage 4	1.14	1.14	1.14	1.14
CKD stage 5	1.16	1.16	1.16	1.16
Malignant neoplasm of				
Malignant neoplasm of the breast	0.97	0.81	0.75	1.25
Malignant neoplasm of the eye, brain and other parts of CNS+	1.28	0.03	1.02	1.60
Malignant neoplasms ill-defined, secondary and unspecified sites	1.37	0.00	1.18	1.60
Malignant neoplasms of lymphoid, haematopoietic and related tissues	2.29	0.00	1.88	2.78
Malignant neoplasms of skin, lip and oral cavity and in-situ and benign neoplasms	0.93	0.46	0.78	1.12
Malignant neoplasms of respiratory of intrathoracic organs	1.28	0.01	1.07	1.54
Malignant neoplasms of digestive organs	0.99	0.95	0.76	1.30
Malignant neoplasms of bone, articular cartilage, mesothelial or soft tissue	1.15	0.20	0.93	1.42
Malignant neoplasms of Genito-urinary tract	0.97	0.81	0.75	1.25
Metastatic cancer	1.18	0.03	1.01	1.36
Smoker	1.20	<0.001	1.10	1.31

Year	Hazard Ratio	P>|z|	95% CI	
BMI category•				
< 18.5 kg/m2	REFERENCE			
18.5 – 25 kg/m2	0.75	0.75	0.75	0.75
>25kg/m2	0.69	0.69	0.69	0.69
Charlson Comorbidity score				
1	1.20	0.10	0.96	1.50
2	1.12	0.20	0.94	1.34
3	1.36	0.16	0.89	2.07
4	1.49	0.05	1.00	2.23
5	3.84	0.02	1.26	11.72
6	1.06	0.87	0.53	2.15
7	2.06	0.16	0.75	5.68

*IHD – Ischaemic heart disease, #CKD – Chronic kidney disease, +CNS – Central nervous system, •BMI – Body mass index

Supplementary Table 4: Emergency Department visits (PWP-TT model)

	Hazard Ratio	P>|z|	95% CI	
Diabetes	1.12	<0.001	1.04	1.20
Age Group				
< 55	REFERENCE			
55 – 75	0.95	0.22	0.87	1.03
> 75	1.10	0.03	1.01	1.20
Sex (male)	1.04	0.21	0.98	1.11
IHD*	1.05	0.64	0.86	1.29
CKD# Stage				
No known CKD	REFERENCE			
CKD stage 2	0.91	0.73	0.55	1.52
CKD stage 3	1.22	0.36	0.80	1.87
CKD stage 4	0.95	0.86	0.56	1.62
CKD stage 5	1.05	0.81	0.70	1.59
Malignant neoplasm of				
Malignant neoplasm of the breast	0.68	0.01	0.51	0.91
Malignant neoplasm of the eye, brain and other parts of CNS+	0.75	0.04	0.57	0.98
Malignant neoplasms ill-defined, secondary and unspecified sites	1.69	<0.001	1.46	1.96
Malignant neoplasms of lymphoid, haematopoietic and related tissues	1.14	0.06	0.99	1.31
Malignant neoplasms of skin, lip and oral cavity and in-situ and benign neoplasms	0.75	<0.001	0.64	0.87
Malignant neoplasms of respiratory of intrathoracic organs	0.96	0.56	0.85	1.10
Malignant neoplasms of bone, articular cartilage, mesothelial or soft tissue	0.89	0.60	0.58	1.38
Malignant neoplasms of Genito-urinary tract	0.90	0.34	0.71	1.12
Metastatic cancer	1.05	0.21	0.97	1.14
Smoker	1.07	0.09	0.99	1.15
BMI category•				
< 18.5 kg/m2	REFERENCE			
18.5 – 25 kg/m2	0.95	0.22	0.87	1.03
>25kg/m2	1.10	0.03	1.01	1.20

	Hazard Ratio	P>|z|	95% CI	
Charlson Comorbidity score				
1	1.36	0.01	1.07	1.74
2	1.15	0.18	0.94	1.40
3	1.77	0.03	1.06	2.94
4	1.48	0.11	0.91	2.39
5	2.08	0.08	0.91	4.74
6	0.85	0.74	0.33	2.20
7	3.06	0.01	1.41	6.64

*IHD – Ischaemic heart disease, #CKD – Chronic kidney disease, +CNS – Central nervous system, •BMI – Body mass index

Supplementary Table 5: Length of stay (truncated negative binomial regression)

	Incidence Risk Ratio	P>|z|	95% CI	
Diabetes	1.14	0.01		1.25
Age Group				
< 55	REFERENCE			
55 – 75	0.98	0.66	0.89	1.08
> 75	1.00	0.96	0.89	1.11
Sex (male)	1.01	0.81	0.93	1.10
IHD*	1.17	0.13	0.95	1.44
CKD# Stage				
No known CKD	REFERENCE			
CKD stage 2	1.08	0.83	0.54	2.14
CKD stage 3	1.20	0.19	0.91	1.58
CKD stage 4	0.87	0.41	0.64	1.20
CKD stage 5	0.91	0.52	0.68	1.22
Malignant neoplasm of				
Malignant neoplasm of the breast	1.24	0.03	1.02	1.51
Malignant neoplasm of the eye, brain and other parts of CNS+	1.47	<0.001	1.22	1.77
Malignant neoplasms ill-defined, secondary and unspecified sites	1.43	<0.001	1.19	1.72
Malignant neoplasms of lymphoid, haematopoietic and related tissues	3.41	<0.001	2.88	4.04
Malignant neoplasms of skin, lip and oral cavity and in-situ and benign neoplasms	1.40	<0.001	1.21	1.62
Malignant neoplasms of respiratory of intrathoracic organs	1.50	<0.001	1.29	1.74
Malignant neoplasms of bone, articular cartilage, mesothelial or soft tissue	3.22	<0.001	2.64	3.93
Malignant neoplasms of Genito-urinary tract	1.13	0.19	0.94	1.36
Metastatic cancer	1.09	0.37	0.91	1.31
Death during admission	1.18	0.07	0.98	1.43
Smoker	1.05	0.22	0.97	1.14

	Incidence Risk Ratio	P>|z|	95% CI	
BMI category•				
< 18.5 kg/m2	RREFERENCE			
18.5 – 25 kg/m2	0.93	0.46	0.77	1.13
>25kg/m2	0.75	0.00	0.63	0.90
Charlson Comorbidity score				
1	1.92	<0.001	1.61	2.30
2	1.84	<0.001	1.61	2.10
3	2.28	<0.001	1.61	3.23
4	1.69	<0.001	1.25	2.29
5	1.18	0.63	0.60	2.29
6	2.34	0.01	1.20	4.59
7	3.52	<0.001	1.61	7.66

*IHD – Ischaemic heart disease, #CKD – Chronic kidney disease, +CNS – Central nervous system, •BMI – Body mass index

Supplementary Table 6: Survival (multivariate Cox-regression model)

	Hazard Ratio	P>|z|	95% CI	
Diabetes	1.48	<0.001	1.23	1.77
Age Group				
< 55	REFERENCE			
55 – 75	1.33	0.03	1.02	1.73
> 75	2.81	<0.001	2.15	3.66
Sex (male)	1.00	0.96	0.84	1.19
IHD*	0.74	0.25	0.44	1.24
CKD# Stage				
No known CKD	REFERENCE			
CKD stage 2	1.08	0.83	0.54	2.14
CKD stage 3	1.20	0.19	0.91	1.58
CKD stage 4	0.87	0.41	0.64	1.20
CKD stage 5	0.91	0.52	0.68	1.22
Malignant neoplasm of				
Malignant neoplasm of the breast	1.05	0.84	0.67	1.64
Malignant neoplasm of the eye, brain and other parts of CNS+	1.76	0.01	1.17	2.66
Malignant neoplasms ill-defined, secondary and unspecified sites	1.06	0.72	0.76	1.50
Malignant neoplasms of lymphoid, haematopoietic and related tissues	5.98	<0.001	4.42	8.10
Malignant neoplasms of skin, lip and oral cavity and in-situ and benign neoplasms	0.71	0.02	0.53	0.95
Malignant neoplasms of respiratory of intrathoracic organs	1.87	<0.001	1.45	2.42
Malignant neoplasms of bone, articular cartilage, mesothelial or soft tissue	1.02	0.94	0.58	1.79
Malignant neoplasms of Genito-urinary tract	1.24	0.21	0.89	1.74
Metastatic cancer	5.49	<0.001	3.91	7.72
Smoker	1.11	0.23	0.93	1.33
BMI category•				
< 18.5 kg/m2	1.45	0.05	0.99	2.12
18.5 – 25 kg/m2	REFERENCE			
>25kg/m2	0.76	<0.001	0.63	0.92

	Hazard Ratio	P>|z|	95% CI	
Charlson Comorbidity score				
1	2.01	<0.001	1.43	2.83
2	3.03	<0.001	2.28	4.03
3	5.67	<0.001	3.38	9.52
4	5.74	<0.001	3.72	8.86
5	9.27	<0.001	3.71	23.14
6	5.92	<0.001	1.88	18.58
7	26.80	<0.001	3.66	196.18

IHD – Ischaemic heart disease, #CKD – Chronic kidney disease, +CNS – Central nervous system, •BMI – Body mass index

Supplementary Table 7: Outcomes using average treatment effect on the treated (95% CIs) sensitivity to large weights

	Full sample	Trimmed sample*
ATT		
All-cause mortality	HR: 1.16 (0.96, 1.39)	HR: 1.25 (1.02, 1.53)
Emergency department presentation	HR: 1.10 (1.01, 1.20)	HR: 1.15 (1.05, 1.27)
Inpatient admission	HR: 1.14 (1.02, 1.28)	HR: 1.17 (1.04, 1.33)
Hospital length of stay	IRR: 1.06 (0.91, 1.23)	IRR: 1.16 (1.01, 1.35)

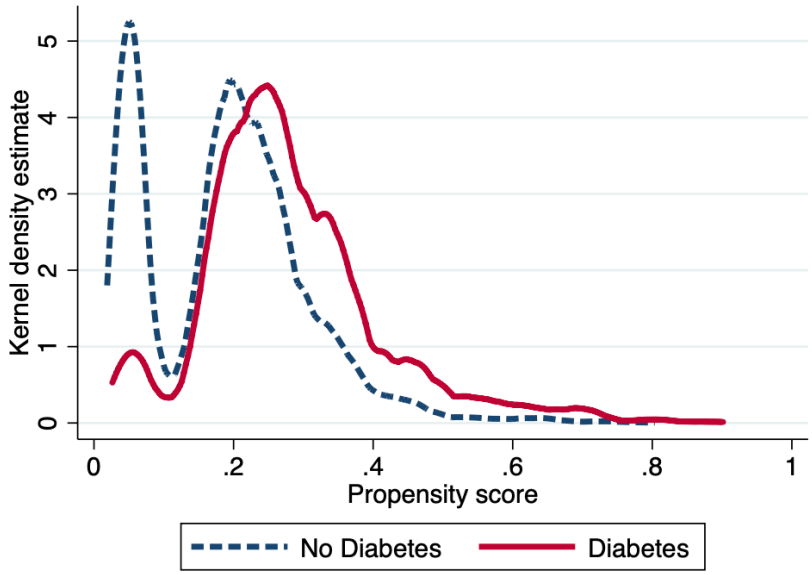
* Includes all observations, except those trimmed at the fifth centile

Supplementary Table 8: Multivariate Cox-regression model for lymphoid and heamatological cancers

	Hazard Ratio	P>|z|	95% CI	
Diabetes	2.27	<0.001	1.41	3.65
Age Group				
< 55	REFERENCE			
55 – 75	1.88	1.88	1.88	1.88
> 75	3.32	3.32	3.32	3.32
Sex (male)	1.01	0.96	0.61	1.68
IHD*	2.05	0.14	0.78	5.38
CKD# Stage				
No known CKD	REFERENCE			
CKD stage 2	0.97	0.97	0.97	0.97
CKD stage 3	0.86	0.86	0.86	0.86
CKD stage 4	1.96	1.96	1.96	1.96
CKD stage 5	1.15	1.15	1.15	1.15
Metastatic cancer	7.46	<0.001	2.47	22.52
Smoker	1.11	0.23	0.93	1.33
BMI category•				
< 18.5 kg/m2	1.15	0.81	0.37	3.56
18.5 – 25 kg/m2	REFERENCE			
>25kg/m2	0.60	0.04	0.36	0.98
Charlson Comorbidity score				
1	2.02	0.08	0.92	4.45
2	4.18	<0.001	2.11	8.26
3	5.67	<0.001	1.84	17.50
4	7.58	<0.001	2.98	19.29
5	51.63	<0.001	10.65	250.24

*IHD – Ischaemic heart disease, #CKD – Chronic kidney disease, +CNS – Central nervous system, •BMI – Body mass index

Supplementary Figure 1: Distribution of propensity scores by diabetes status



Chapter 8: Thesis Conclusions and Future Directions

Key Findings

The overall aim of this thesis was to assess trends in diabetes related complications over time, with particular focus on cardiovascular and renal disease. A summary of the key findings of each chapter are outlined below.

In Chapter 3, trends for the cardiovascular outcomes of incident AMI, stroke and heart failure between 2004 and 2016, were examined for patients without diabetes, with type 1 diabetes and with 2 diabetes, using hospital admission data for the state of Victoria, Australia. All rates of cardiovascular outcomes for the above three groups of patients decreased over this time period. The greatest declines were observed in patients with type 2 diabetes for the outcomes of AMI and stroke. The greatest decline in heart failure rates over time were seen in patients with type 1 diabetes. The inclusion of an appropriate comparator group of patients without diabetes was a crucial strength of my study as this has been an element missing in a large number of recent publications. Although patients without diabetes also experienced declines in the cardiovascular event rates, the magnitude was not as great as that seen by patients with diabetes. The results of this chapter suggest that multifactorial, target driven interventions that have been shown to reduce cardiovascular disease in clinical trials may have translated into clinical practice, especially in patients with diabetes.

Chapter 4 examined one of the leading causes of worldwide morbidity and mortality, chronic kidney disease, at which people with diabetes are at a particular risk. Admission rates for end stage renal disease (separate to that of dialysis and transplantation), and dialysis or transplantation in patients with type 1 or type 2 diabetes and without diabetes were assessed for Victoria, Australia between 2009-2016. Rates of admission with diabetic nephropathy were also assessed for patients with type 1 or type 2 diabetes. There was a significant decrease in the rate of end stage renal disease in all groups, with the greatest declines being observed in patients with either form of diabetes. Rates of diabetic nephropathy and dialysis or transplantation appear to have remained stable over this time period. It is possible that although there are fewer patients with end stage renal disease, a greater number of patients are being accepted onto renal replacement programs over this time period, which has negated an expected corresponding decline. A particular strength of this chapter was that it was able to look at patients that presented with end stage renal disease but that did not progress to dialysis or transplantation. Of concern, my results also highlight the large number of patients admitted with diabetic nephropathy, of which no change was observed over time, who may progress to end stage renal disease and require

dialysis or transplantation in the future. These findings may represent an opportunity for the better implementation of best practice guidelines which may see reductions in rates of diabetic nephropathy in the future and corresponding declines in end stage renal disease and dialysis and transplantation.

The results presented in Chapter 5 enhanced the understanding of the impact that type 1 diabetes or type 2 diabetes has on any lower extremity amputation (LEA), minor lower extremity amputation, major amputation and mortality 12-months following a lower amputation and how these trends have changed over time in Victoria, Australia between 2004 and 2016. Different trends in LEAs were observed by diabetes type, sex and age group. Overall rates of lower extremity amputations significantly declined for patients with type 2 diabetes, compared to patients with type 1 diabetes who did not display a decline. An analysis of the types of amputations performed showed that, in fact, minor amputations rates were actually increasing in patients with type 1 diabetes. Of concern, rates of all types of lower extremity amputations rose for younger patients with type 1 diabetes, compared to older patients with type 2 diabetes who experienced declines. I was also able to show that there has been a significant decline in mortality rates post LEA for patients with type 2 diabetes. However, patients with type 1 diabetes did not experience the same significant decline.

Given that different subgroups experienced significantly different rates of lower extremity amputations there are most likely different plausible explanations for the above findings. Rates of minor lower amputations may be increasing due to a change in practice in order to avoid further and major lower extremity amputations. More basic risk factor modification may be lacking, especially in patients with type 1 diabetes as well as screening for diabetic foot disease in younger patients. Given the high burden of disease that lower extremity amputations pose, and their apparent resurgence in younger patients this chapter provides key information on current trends and burden of diseases in subgroups and allows for the better targeting of future healthcare interventions.

Chapter 6 expanded on the knowledge of the outcomes of cardiovascular disease in Chapter 3 and examined the extent of coronary artery disease as assessed by coronary angiography over time in patients with and without type 2 diabetes. The potential impact of preventative therapies on coronary artery disease severity was assessed. A significant increase in severity of disease detected was observed in patients with type 2 diabetes over time, compared to patients without diabetes, in whom no significant changes were observed. This is in contrast to our findings in Chapter 3, where we demonstrated a decrease in rates of AMI. However, these findings were based on a coronary angiogram not a clinical event and may represent improvements in screening and lower thresholds for performing

angiograms in patients with diabetes. A key finding of this chapter was that in the analysis of cardiovascular protective medications (statins, renin-angiotensin system inhibitors and anti-platelet drugs), there was no significant difference in the extent of coronary artery disease between patients with and without type 2 diabetes following adjustment for the use of these medications.

In conclusion, Chapter 7 covered the increasingly recognised impact of type 2 diabetes on hospitalisation and mortality in people with malignancy. Chapters 3-6 covered the traditionally associated complications of diabetes, given the increasing evidence that people are now avoiding and surviving these complications there has been a corresponding growth in other conditions including malignancies. We reported a that patients with type 2 diabetes were at a significantly increased risk of emergency department presentations and inpatient admissions and following this, all-cause mortality. This risk was especially increased in certain types of malignancies and patients who were underweight.

Implications and Future Directions

The decline of traditional diabetes-related complications observed in this thesis, including AMI, stroke and heart failure, may lead to a corresponding rise in non-traditional complications including cancer, pulmonary hypertension, osteoporosis and chronic obstructive pulmonary disease. This shift will require a change in the way that health services screen and manage people with diabetes and these co-morbid conditions.

However, given the recognition of more aggressive phenotypes described in Chapter 1 such as young-onset type 2 diabetes and double diabetes, there are concerns that the recent decline in rates of traditional diabetes related complications may potentially be attenuated in coming years. This may especially be reflected by increasing rates of cardiovascular disease and lower extremity amputations in younger age groups.

The results of my studies need to be confirmed in a larger nationwide study. These studies should also expand on my work by linking hospital admission data to databases of with medication use and if possible, those that also contain information on clinical and biochemical parameters. This approach would allow for a more direct link to be drawn between the achievement of certain risk factor modifications, the achievement of metabolic targets and the use of medications that have been shown to have vascular and renal protective effects with hopefully, improved clinical outcomes for patients.

In addition to the above, the use of medications with known cardio- and renal protective effects, the SGLT-2 inhibitors and GLP-1 receptors agonists, have been well studied in clinical trials, and there are now studies emerging on real-world groups. However, population

level studies are yet to be conducted, and given the expansion of these medications to be used for populations without diabetes, further work remains to be conducted on evaluating their true efficacy in the real-world setting. Another aspect of the application of the above medications may relate to emerging complications such as pulmonary hypertension. On this note, I would be of interested to expand my studies to include a more contemporary observation period to gauge the impact of the increased update of SGLT-2 inhibitors and GLP-1 receptor agonists on hospital admission rates for various diabetes related complications.

My results show that whilst there have been significant improvements in many of the complications of diabetes, a large and significant gap still exists between the disease burden of people with and without diabetes. Given projections that the prevalence of diabetes prevalence will continue to rise, both in Australia and worldwide, an expected corresponding absolute rise in complications associated with a diagnosis of diabetes can be expected. This requires health professionals, policy makers and governments to have a comprehensive understanding of diabetes and its associated complications in order to ensure that health systems are capable of providing optimal care to patients with diabetes, and to provide lifestyle modification programs in order to prevent the development of type 2 diabetes and its associated complications.

Updated methods for the early detection of the development of diabetes related complications may result in further improvements in the rate of decline of diabetes related complications. As yet there is no universally accepted method for testing asymptomatic patient's subclinical coronary artery disease for the presence of clinically meaningful disease that may require interventions such as angioplasty, stenting or coronary bypass surgery. Possibly, the more routine use of transthoracic echocardiograms may help to detect sub-clinical heart failure in patients with diabetes and aid in prompting the use of medications that have been shown to prevent hospitalisation for heart failure. Unfortunately, it appears that one of the routine tests that is commonly used to detect peripheral vascular disease in patients with diabetes, the ankle-brachial index lacks specificity to detect this condition. Furthermore, although I was able to show a decline in ESRD (separate to dialysis and transplantation), I was not able to detect on significant change in hospital presentations for patients coded for "diabetic nephropathy". Increased screening at the primary care levels, with estimates of glomerular filtration rate and urinary albumin to creatinine ratios may help to identify high risk patients and allow for the more widespread application of preventive therapies that hopefully will translate into a reduction in hospital admissions.

Conclusions

In conclusion, this thesis adds to the current literature available on diabetes related complications and highlights those complications growing in prevalence. It is clear that although rates of a number of traditional diabetes related complications have declined, there is still an excess risk observed which requires further attention. This thesis adds to the established base of literature that recommends good traditional multifactorial interventions. It highlights the importance and efficacy of primary prevention in all patients, but especially those high-risk patients with diabetes. Recent years have seen the introduction of newer glucose control agents which have both cardio and renal protective agents which will see a further corresponding drop in rates of traditional diabetes related complications. It is likely there that there will be a rise in complications that have not been previously associated with diabetes, such as malignancies, cognitive impairment/dementia and respiratory complications. In the future, it is possible that there may be a change in the recommended screening, evaluation and assessment of comorbidities for patients with diabetes.