Multimorbidity in People with Type 2 Diabetes: Exploration of Associations with Mortality and Glycaemia.

PhD Thesis

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Submitted in total fulfilment of the requirements of the degree of Doctor of Philosophy

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Faculty of Medicine, Dentistry and Health Sciences

Produced on archival quality paper

Abstract

Background

Type 2 diabetes is a leading health priority of the 21st century. Type 2 diabetes management is complex for both practitioners and patients, made more so because diabetes rarely occurs on its own. Indeed, multimorbidity (the co-occurrence of two or more chronic conditions in an individual) is the norm in diabetes. Multimorbidity, brings about many challenges including difficulties in managing the competing demands of multiple conditions. This can result in reduced adherence to complicated therapeutic regimens. This in turn could lead to suboptimal glycaemia which has been shown to be associated with poorer health outcomes such as the development of downstream complications and increased mortality.

Currently, there is no universally accepted measure of multimorbidity. The literature has suggested that the type as well as number of conditions are both important when considering multimorbidity. It has been suggested that multiple conditions in those with type 2 diabetes should be categorised as concordant (diabetes-related) or discordant (unrelated).

While the associations between multimorbidity, glycaemia (HbA1c) and all-cause mortality in people with type 2 diabetes has been studied to some extent, significant gaps remain in the existing literature. In particular, the effects of different patterns of multimorbidity including concordant and discordant conditions have not been studied extensively. Similarly, little is known about the relationships between multimorbidity and emerging novel glycaemic measures, such as glycaemic variability and time-in-range. These new ways of understanding glycaemia may be important independent risk factors for developing complications in people with type 2 diabetes.

Aim

To explore associations between multimorbidity, all-cause mortality and glycaemic outcomes, including HbA1c and novel measures of glycaemic variability and time-in-range in people with type 2 diabetes.

Methods

My PhD includes a systematic review and three quantitative studies of more than 150,000 people with type 2 diabetes utilising UK, Taiwan and Australian datasets. This provides a clearer picture of the implications of multimorbidity for people with type 2 diabetes in different populations from different countries, health settings, healthcare systems and of different ethnicities.

Results

The findings of my studies identified that multimorbidity was highly prevalent among people with type 2 diabetes. More than 80% of the 150,000 people included in my studies were found to have at least one other chronic condition in addition to type 2 diabetes. I found the associations between multimorbidity, mortality and glycaemia were mostly consistent across my studies. Increasing multimorbidity was significantly associated with increased all-cause mortality. This was the case for total count of multimorbidity, as well as counts of concordant and discordant conditions. Increasing concordant counts had the greatest effect on mortality. However, when examining the effects of individual conditions and combinations of two conditions on mortality in the UK and Taiwan cohorts, the results differed between Caucasian and ethnic Chinese populations. I also found that across my studies, all measures of multimorbidity were not associated with higher HbA1c, glycaemic variability and time-in-range.

Conclusion

This PhD has contributed a novel and deeper understanding of the significance of multimorbidity in people with type 2 diabetes. It has provided an insight into the effects of different patterns of multimorbidity, including concordant and discordant conditions, on important health outcomes in different cohorts of people with type 2 diabetes. My findings highlight the need for clinical guidelines to support a holistic approach to the complex care needs of those with type 2 diabetes and multimorbidity, accounting for the various conditions they be may be living with. While managing glycaemia in people with diabetes is important, it should not overshadow efforts to address multimorbidity, both concordant and discordant. It is important to consider the overall multimorbidity disease burden as a way of recalibrating and personalising our clinical focus in supporting people with diabetes. By taking a holistic approach and caring for the whole person, this could potentially reduce their annual mortality risk by reducing the overall burden of multimorbidity.

Declaration

This is to certify that

- the thesis comprises only my original work towards the PhD, except where indicated in the preface
- due acknowledgment has been made in the text to all other material used,
- the thesis is fewer than 100 000 words in length, exclusive of tables, maps, bibliographies and appendices

Signed: Date: 13th May 2020

Preface

This thesis includes five multi-author papers. The citations and author contributions for each appear below.

Paper 1

Chiang JI, Furler J, Mair FS, Jani B, Nicholl BI, Jenkins A, et al. Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol. BMJ open. 2018;8(4):e021100.

Author contributions

Jason Chiang drafted the protocol and developed the search strategy, inclusion/exclusion criteria and the data extraction form with guidance from Jo-Anne Manski-Nankervis, John Furler, France Mair, Barbara Nicholl, Bhautesh Jani, Alicia Jenkins and David O'Neal. Patrick Condron contributed to the development of the search. Jason Chiang wrote the first draft of the manuscript. All co-authors read and provided feedback on the draft manuscript. All authors approved the final manuscript.

Paper 2

Chiang JI, Jani BD, Mair FS, Nicholl BI, Furler J, O'Neal D, et al. Associations between multimorbidity, all-cause mortality and glycaemia in people with type 2 diabetes: A systematic review. PLoS one. 2018;13(12):e0209585.

Author contributions

Jason Chiang, Bhautesh Dinesh Jani, Frances S. Mair, Barbara I. Nicholl, John Furler and Jo-Anne Manski-Nankervis conceptualised the study. Jason Chiang, Bhautesh Dinesh Jani, Frances S. Mair, Barbara I. Nicholl, John Furler, David O'Neal, Alicia Jenkins, and Jo-Anne Manski-Nankervis planned the analysis. Jason Chiang completed the analysis and wrote the first draft of the manuscript. All authors critically reviewed this and subsequent drafts. All authors approved the final draft for submission.

Paper 3

Chiang, J.I., Hanlon, P., Li, T.C., Jani, B.D., Manski-Nankervis, J., Furler, J., et al. Multimorbidity, mortality and HbA1c in type 2 diabetes: a cohort study with UK and Taiwanese cohorts. PLoS Med. 2020;17(5): e1003094.

Author contributions

Jason Chiang, Shing-Yu Yang, Bhautesh Jani, Jo-Anne Manski-Nankervis, Tsai-Chung Li, John Furler, Cheng-Chieh Lin, Barbara Nicholl, Sharmala Thuraisingam and Frances Mair planned the analysis. Jason Chiang did the literature search. Jason Chiang completed the analysis with support from Peter Hanlon, Bhautesh Jani, Shing-Yu Yang and Tsai-Chung Li. Jason Chiang, Peter Hanlon, Bhautesh Jani, Jo-Anne Manski-Nankervis, John Furler, Tsai-Chuang Li and Frances Mair interpreted the findings. Jason Chiang wrote the first draft of the manuscript. All authors critically reviewed this and subsequent drafts. All authors approved the final draft for submission.

Paper 4

Chiang, J.I., Furler, J., Mair, F., Jani, B.D., Nicholl, B.I., Thuraisingam, S., et al. Associations between multimorbidity and glycaemia (HbA1c) in people with type 2 diabetes in Australian general practice.

Submitted for publication in BMJ Open

Author contributions

Jason Chiang, John Furler, France Mair, Bhautesh Jani, Barbara Nicholl, Sharmala Thuraisingam and Jo-Anne Manski-Nankervis contributed to the study protocol. Jason Chiang, John Furler, France Mair, Bhautesh Jani, Barbara Nicholl, Sharmala Thuraisingam and Jo-Anne Manski-Nankervis contributed to the study design. Jason Chiang analysed the data and drafted the initial draft of the manuscript. Jason Chiang had full access to all study data, performed all the statistical analyses, and takes responsibility for the integrity of the data and the accuracy of data analyses. All authors assisted with iterative drafting of the manuscript and agree with the manuscript results and conclusions. All authors read and approved the final manuscript.

Paper 5

Chiang, J.I., Manski-Nankervis, J., Thuraisingam, S., Jenkins, A., O'Neal, D., Mair, F., et al. Multimorbidity, glycaemic variability and time in target range in people with type 2 diabetes: a baseline analysis of the GP-OSMOTIC trial.

Submitted for publication in Diabetes Research and Clinical Practice

Author contributions

Jason Chiang, Jo-Anne Manski-Nankervis, Alicia Jenkins, David O'Neal, France Mair, Bhautesh Jani, Barbara Nicholl, Sharmala Thuraisingam and John Furler contributed to the study protocol. Jason Chiang, John Furler, Sharmala Thuraisingam and Jo-Anne Manski-Nankervis contributed to the study design. Jason Chiang analysed the data and drafted the initial draft of the manuscript. Jason Chiang had full access to all study data, performed all the statistical analyses, and takes responsibility for the integrity of the data and the accuracy of data analyses. All authors assisted with iterative drafting of the manuscript and agree with the manuscript results and conclusions. All authors read and approved the final manuscript.

A complete list of all journal articles, conference presentations, grants, scholarships and prizes achieved during my PhD candidature are noted in the Appendix (see Section 12.7).

Acknowledgements

This PhD journey has been the most challenging experience of my life thus far. However, it has also been by far the most rewarding experience as well, giving me an incomparable sense of accomplishment.

I would like to express my sincere appreciation and gratitude to the many people that have made this undertaking possible for their ongoing help and guidance. Firstly, I would like to thank A/Prof John Furler and A/Prof Jo-Anne Manski-Nankervis for their invaluable wisdom and support since my Honours year, and for being my primary supervisors. John and Jo-Anne, together with Prof Frances Mair, have provided me with guidance throughout my PhD journey, given me support with my studies, read more drafts of my work than they would care to remember and have been an ongoing source of inspiration. With three vastly different personalities, they have provided the perfect balance, and have allowed me to see and understand research from different perspectives. I feel incredibly privileged to have access to their huge breadth of knowledge and tutelage.

I am also privileged to have an advisory panel of established researchers and academic clinicians. I thank Dr Bhautesh Jani and Dr Barbara Nicholl for providing their expertise and experiences in multimorbidity and utilising large datasets including the UK Biobank. I am also grateful for Prof Alicia Jenkins and Prof David O'Neal's guidance from clinical perspectives as endocrinologists. I would like to thank my PhD panel for their time and assistance, particularly with respect to the position of my PhD in the overall context of multimorbidity and diabetes research.

I consider myself extremely fortunate to have had the opportunity to travel considerably during my candidature. Spending time at the University of Glasgow in Scotland and the China Medical University in Taiwan to conduct two of my studies was a hugely enriching experience for me, and it was brilliant to experience academic life in different settings. I would like to thank Bhautesh, Frances, Barbara, Mr Alesso Albanese, Dr Kirsty Duncan, Dr Peter Hanlon, Dr Ross McQueenie and Dr Hamish Foster for making me feel at home in Glasgow and for letting me be part of the GPPC fantasy football league and the Tuesday football games at Garscube. I would also like to thank Prof Tsai-Chung Li and Ms Shing-Yu Yang for their statistical guidance and support during my time in Taichung to conduct the Taiwan study.

The OSMOTIC team have also been a fantastic support to me over my PhD journey. Ms Sharmala Thuraisingam has always provided advice on my STATA codes and data analysis plans for my studies with her experience as a biostatistician. Ms Katie de La Rue and Ms Rebecca Doyle have always been positive and helpful whenever I needed their assistance. In particular, I would also like to thank the OSMOTIC team for providing me the opportunity to co-supervise my very first students, Dr Erik Pålsson, Dr Joel Corin and Dr William Bergström from the University of Gothenburg.

I am very lucky to have undertaken my research career so far in the Department of General Practice at the University of Melbourne. In particular, I would like to thank Dr Phyllis Lau and Prof Meredith Temple-Smith for fostering such an encouraging environment for research training. I would also like to thank Ms Bernie Cooper, Ms Sam Parkin and Ms Weilun Nien for their help in administration. I have appreciated Dr Patty Chondros' statistical expertise since my Honours year, as well as the opportunity to tutor and mentor four cohorts of Honours students. The supportive network of the strong postgraduate student group in the department is also appreciated. Finally, Dr Malcolm Clark thank you for being an excellent mentor in life and your extensive knowledge in healthcare and unparalleled expertise in wine.

I would like to acknowledge funding support from the OSMOTIC PhD Scholarship, an NHMRC Postgraduate Scholarship, Research Training Program Scholarship (Australian Government), Family Medical Care Education and Research Grant (RACGP), Diabetes Australia Research Project Grant (Diabetes Australia) and Department of General Practice travel grants. This support has been crucial in allowing me to carry out my studies as well as providing the opportunity to travel and present at conferences and visit primary care researchers in London, Glasgow, San Francisco, Chicago, Taichung, Sydney and Adelaide.

Finally, I would like to acknowledge the support of friends and family during these extremely eventful and somewhat chaotic few years, especially Andrew, Nick, Isaac, Grantley, Nichol and Ellen for keeping me sane and always being there for me. I would also like to thank my parents, 老爸 江銘崇 and 老媽 孔佩文, and my brother, Mark, for encouraging me to believe that I could succeed at whatever I wanted as long as I worked hard. Finally, Amy, thank you for your unwavering patience, love and support.

With everyone's support, we have finished this PhD journey together. Thank you everyone for everything.

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Abbreviations

AF	Atrial fibrillation
CGM	Continuous glucose monitoring
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
GP	General practitioner
GV	Glycaemic variability
HbA1c	Glycated haemoglobin A1c
HF	Heart failure
MM	Multimorbidity
NDCMP	National Diabetes Care Management Program
NHMRC	National Health and Medical Research Council
OAD	Oral anti-diabetes medication
PVD	Peripheral vascular disease
RACGP	Royal Australian College of General Practitioners

RCT	Randomised controlled trial
SEIFA IRSD	Socioeconomic Index for Areas Index of Relative Socioeconomic
T2D	Type 2 diabetes
TIA	Transient ischemic attack
UK	United Kingdom
USA	United States of America

1: Introduction

I open this PhD thesis with my research and personal experiences that led to the conception of this PhD.

In 2015, during the summer break of my undergraduate biomedicine degree, I spent a considerable amount of time at a teaching university hospital in Taiwan. My father was undergoing renal transplant surgery and at that time, and by chance, I was introduced to a Professor in Biostatistics and Epidemiology, Professor Tsai-Chung Li. She introduced me to her research where most of her work focussed on people with type 2 diabetes[1]. This was my very first exposure to research and it really sparked my interest. What I found fascinating was the extent and depth of research into type 2 diabetes, yet there existed areas of this well-known condition that remain somewhat unexplored. Following this experience, in 2016, I decided to undertake a year of full-time research to complete my bachelor's degree with honours in biomedicine. During this time, I led a study that developed, piloted and evaluated an electronic clinical decision support tool in the evaluation of cardiovascular risk in general practice (1). Through that, I had the opportunity to work with and interview general practitioners. I was impressed by the work that general practitioners do, particularly in regards to the frequency of patient consultations that involve the complex management of multiple chronic conditions. It occurred to me that this phenomenon of having multiple conditions (multimorbidity) is more common than the general public realise. This realisation prompted me to wonder how multimorbidity can impact people's lives, and all the downstream problems that can come with multimorbidity. My experiences, academic curiosity to further understand this complex issue, and my interest in research led to the conception of my PhD where I aimed to further understand multimorbidity in people with type 2 diabetes.

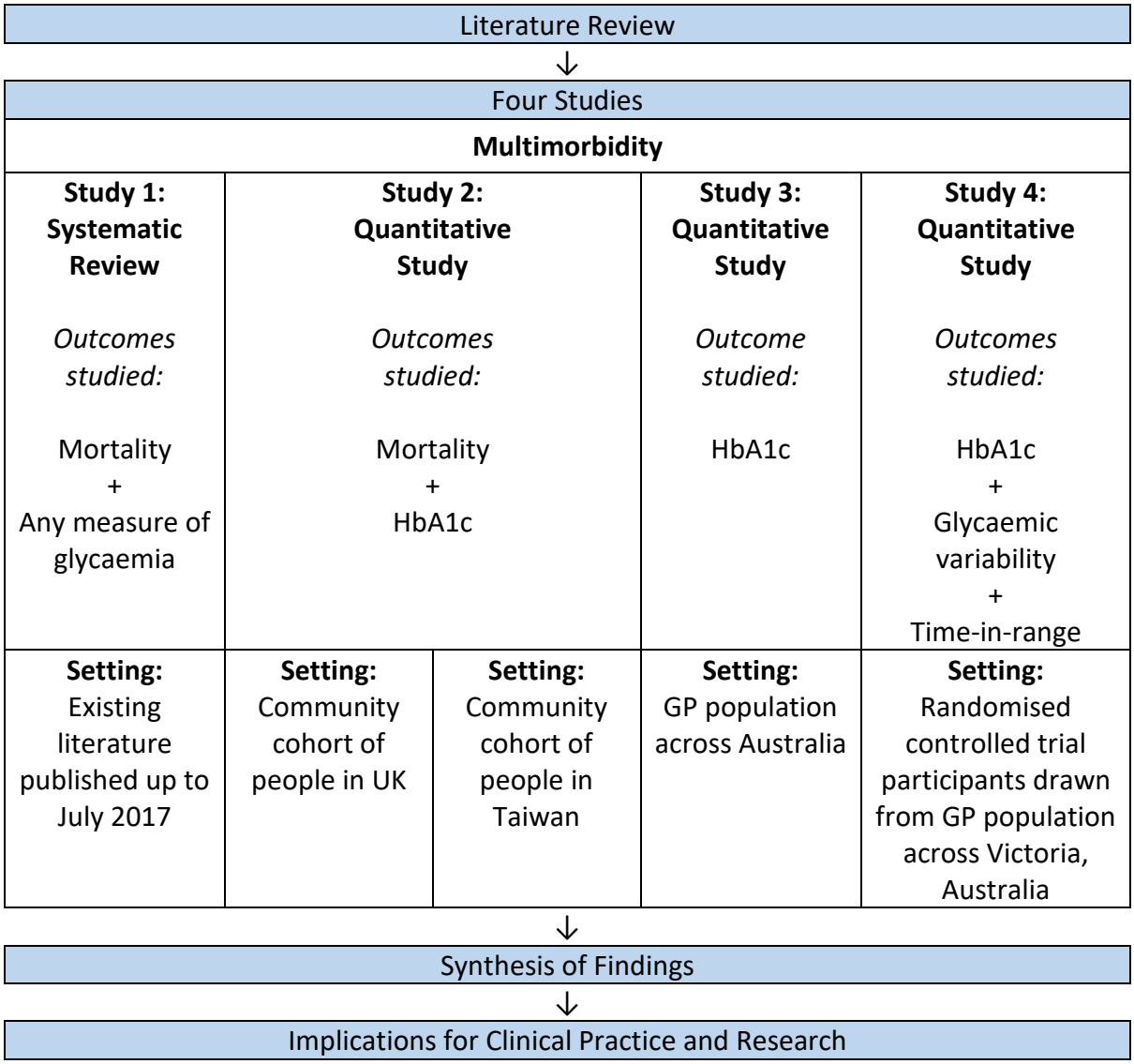
Type 2 diabetes is a health priority globally. It is a progressive chronic condition characterised by increased blood glucose as a result of reduced or ineffective insulin, which can lead to complications in multiple body systems (2). It imposes heavy health and

[1] I will be using the terms "type 2 diabetes" and "diabetes" interchangeably throughout the thesis and they will be referring to only type 2 diabetes.

economic burdens on people and communities. The management of type 2 diabetes is complex, requiring continuous efforts by both clinicians and patients to implement recommendations and pharmacotherapy to achieve evidence-based targets (see Section 2.1). This complexity is amplified because diabetes rarely occurs on its own (3). Multimorbidity, which is the norm in people with type 2 diabetes, refers to the co-occurrence of at least two chronic conditions in an individual (4). The coexistence of many chronic conditions causes complexity for people with diabetes, their families, communities and the health professionals that care for them. Multimorbidity further complicates diabetes management and may be associated with poorer health outcomes (see Section 2.2). However, the current evidence base shows unclear associations between multimorbidity and glycaemia. Glycaemia (commonly measured as glycated haemoglobin, HbA1c) is a key focus of clinical guidelines for the management of diabetes, and is an important factor in downstream complications and mortality. Advances in continuous glucose monitoring technology allows for further insight into blood glucose through novel glycaemic measures including glycaemic variability (GV) and time in range (TIR) (see Section 2.4). Currently, little is known about the relationship between multimorbidity and GV and TIR, which may be important risk factors for downstream complications in people with type 2 diabetes.

This brief background knowledge sets the scene for the work documented in this thesis. I explore the effects of multimorbidity on mortality and glycaemic outcomes, including novel measures of GV and TIR, through four studies that together provide a clearer picture of the implications of multimorbidity for people with type 2 diabetes. As I will show at the conclusion of my thesis, this PhD has contributed a novel and deeper understanding of the significance of multimorbidity in people with type 2 diabetes. Understanding the important relationships between multimorbidity and health outcomes can ultimately benefit both people with type 2 diabetes and health professionals, and the knowledge I have contributed will also guide future research. The structure of my thesis is outlined below (see Figure 1).

Figure 1: Structure of the thesis



The thesis begins with my literature review in Chapter 2 where I provide an overview of type 2 diabetes and the importance of multimorbidity. I discuss the methodological challenges facing researchers in the field of multimorbidity. For example, understanding the multiple methods that have been proposed to quantify multimorbidity. I then explore the clinical implications of multimorbidity and its associations with important health outcomes in people with type 2 diabetes including mortality and measures of glycaemia. The conclusion of my literature review is followed by Chapter 3 which starts with the generation of my over-arching research question for my PhD. Chapter 3 then outlines the overall methods for the four closely related studies that form this PhD.

I first conducted a systematic review (Study 1, Chapters 4 and 5) to identify what is currently known in the literature about the different measures of multimorbidity, and the effects of multimorbidity on mortality and glycaemic outcomes in people with diabetes. I then addressed the key evidence gaps identified in the systematic review through three epidemiological studies using four datasets from different settings, healthcare systems and countries. These studies together add rigour and generalisability, and provide insights into whether the effects of multimorbidity on key outcomes are consistent across different cohorts of people with type 2 diabetes. Study 2 (Chapter 6) explores the association between multimorbidity, all-cause mortality and HbA1c in two large community cohorts of people with T2D in the UK and Taiwan. Following this, Study 3 (Chapter 7) builds on the findings of Study 2 and examines the effects of multimorbidity on HbA1c in Australian general practice. Study 3 explored the findings of Study 2 in this different setting, investigating whether this would confirm or refute those findings from community studies. Finally, the association between multimorbidity and different measures of glycaemia including novel measures of GV and TIR was explored in Study 4 (Chapter 8).

In the penultimate chapter (Chapter 9), I present the synthesis of the findings from across my quantitative studies where I bring together and compare the results. The thesis concludes (Chapter 10) with implications of my findings for clinical practice and further research.

2: Literature Review

2.1 Type 2 Diabetes

Type 2 diabetes (T2D) is a chronic condition characterised by increased blood glucose levels as a result of reduced or ineffective insulin (2). It has significant health and economic impacts and is a major global health priority of the 21st century. Worldwide, 424 million people live with T2D accounting for $727 billion US dollars in annual healthcare expenditure (5). In Australia approximately 1.2 million (6%) people have been diagnosed with T2D (3), costing over $6 billion annually in direct and indirect healthcare costs (6).

People with T2D can develop serious long-term complications including retinopathy, nephropathy, neuropathy, coronary artery disease, stroke and peripheral vascular disease (7). As a result of this, approximately four million people die globally from diabetes related causes each year, equivalent to one death every eight seconds, with nearly half of these deaths in people under the age of 60 (5). There is no doubt that T2D imposes a heavy burden on communities and on individuals who live with T2D. This burden calls for effective responses to reduce the human and economic burden of T2D and the development of downstream complications. My PhD thesis brings an epidemiological perspective to understanding the health burden of T2D.

Whilst this is the main focus of my PhD, it is also important to acknowledge the clinical and lived experiences of people with T2D. The challenges of the complex management of T2D can be viewed from two perspectives – from the perspective of health professionals and from that of the person with T2D. The management of T2D requires continuous efforts by both parties to implement recommendations for evidence-based self-management and pharmacotherapy in a step wise manner to achieve evidence-based targets, which I will discuss later in Section 2.4. Multidisciplinary care has been recommended for the optimal management of T2D and has shown positive impacts on patient health (8-10). A multidisciplinary care team may involve a variety of health professionals including general practitioners (GPs), endocrinologists, nurses, dieticians, diabetes educators, podiatrists and optometrists (8). The complexity of management is compounded when the person with T2D also has other chronic conditions such as depression or cardiovascular disease. This is a

growing problem as the prevalence of multimorbidity increases (11). In Australia and the UK, the majority of those with T2D receive care in general practice, where GPs play important roles in managing and coordinating care for people with multiple conditions. In my PhD, I focus on people with T2D with multiple chronic conditions, otherwise known as multimorbidity.

2.2 Multimorbidity

Multimorbidity is an important issue in T2D. For many years, the terms multimorbidity and comorbidity have been used interchangeably (12). It has only been more recently that there has been a clearer distinction made between the two terms. Comorbidity is defined as the existence or occurrence of any additional condition(s) that co-occurs with an index disease (13). Multimorbidity however refers to the presence of two or more chronic conditions in an individual, with no reference to an index condition (4). These established definitions provide the basis of my PhD which exclusively focuses on multimorbidity in people with T2D. For the purposes of my PhD, I do not define T2D as the "index disease" but as a co-occurring condition in those who live with multimorbidity. I first define the population of people with T2D, then explore multimorbidity in this population. I want to approach this from the perspective of primary care clinical practice, where care of the whole person is the primary concern (14).

2.2.1 Multimorbidity and its Challenges

Multimorbidity is very common, particularly in primary care where more than 50% of patients over 50 years of age have two or more chronic conditions (15). Multimorbidity is even more prevalent in people with T2D where evidence suggests that 85% of those with T2D have at least one additional chronic condition (3).

Multimorbidity brings about many challenges, especially for people with T2D. This includes the difficulties of balancing the multiple competing self-management demands of different health conditions. Those self-managing chronic illness experience varying levels of treatment burden (16). Treatment burden can be defined as the workload of self-management experienced by the patient and their supporters and includes; the work required to make sense of a diagnosis, its management and implications, the effort required

to engage with a wide range of professionals, to learn and enact self-management practices, undergo investigations, and attend appointments and self-monitor. Those with multimorbidity are likely to experience a greater level of treatment burden due to the self-management requirements imposed by multiple different conditions (16). People will vary in their capacity or ability to manage any given level of treatment burden. If someone is overwhelmed by the weight of self-management then this may lead to poorer outcomes (17, 18). Evidence suggests that multimorbidity is associated with greater years of life lost with increased all-cause, vascular and cancer mortality (19). Multimorbidity is also associated with a reduced quality of life, increased healthcare costs, and complex therapeutic regimens which the patient may find challenging to manage (20).

For health professionals multimorbidity brings increased workload, and the clinical challenges of interactions between multiple conditions and medications (4). This is particularly significant in primary care as multimorbidity is linked to increased GP visits and polypharmacy, both of which have implications for a GP's workload (15, 21). There are guidelines available for clinicians to assist in making evidence-based decisions for people with T2D to optimise care, with the aim of improving quality of life and health outcomes. Current guidelines do acknowledge the complex nature of multimorbidity where the choice of glycaemic targets and treatment should be based on the patient's individual clinical needs, co-occurring conditions and the risks from polypharmacy (22). However, evidence suggest that clinicians may prioritise management of one condition at the expense of another (20). For people with diabetes, this could lead to clinicians focusing more on diabetes and less on the patient's other conditions and patient goals. Similarly, a focus on other conditions may lead to sub-optimal glycaemic management due to a lack of focus on diabetes-specific care goals (23, 24). This may be particularly problematic because achieving and maintaining glycaemic targets early is important in reducing downstream complications and all-cause mortality (25) (see Section 2.5). Furthermore, evidence suggests that there is a low level of agreement between the priorities of people with multimorbidity and clinicians (26). It is suggested that prioritisation by patients is mainly driven by their illness experiences where preserving functional ability is a key priority, while clinicians focus on longer-term risks.

2.3 Measures of Multimorbidity and their Associations with T2D

Multimorbidity can be measured and defined in a variety of ways. This is particularly important from a research perspective where key questions remain unanswered.

- Is multimorbidity best considered as simply a count of the co-occurring conditions? Or is it more than just a simple count, where we need to consider both the types and weighting of conditions?
- How do we measure multimorbidity to capture the complexity of the combination of conditions that a person needs to manage?

To address the first point, the difference between a count of the number of conditions and an index should be noted, where an index is a composite variable that involves weighting of certain conditions. A systematic review conducted by Diederichs *et al*.(27) had the primary objective of providing a comprehensive overview of existing instruments for the measurement of multiple chronic conditions and multimorbidity. It noted that there is no universally accepted measure of multimorbidity. The most frequently used measure is the Charlson Comorbidity Index (CCI), which was developed in 1987 to predict 1-year in-hospital all-cause mortality based on data from hospital charts that applied weighting to 17 conditions (28). Since its development, the CCI has been used widely in research (29-36) and researchers have independently developed coding algorithms using the International Classification of Diseases Ninth (37) and Tenth revisions (38, 39) (ICD-9 and ICD-10, respectively). However, a common limitation across the studies that have utilised the CCI is that the tool was developed in a hospital setting and has been validated largely for hospital settings (40). This creates potential concerns as the majority of people with multimorbidity and T2D are managed in general practice and primary care (41). Another limitation of the CCI is that with advancements in medicine and improvements in chronic disease management, treatment and intervention options and technology, the original weights of the 17 conditions developed by Charlson more than 30 years ago may not apply to the longer life expectancy of the population today. A prospective study demonstrated that using a count of conditions was not inferior to the more complex CCI in predicting mortality in people with T2D (42). Yet at present, there is no single set of conditions that qualify for a count that will suit all research questions and studies. As a result of this, existing measurements of multimorbidity are highly variable, ranging from considering four

conditions up to 102 different diseases (27). This is problematic as it leads to research which is extremely heterogeneous and difficult to compare and synthesise. In the section below, I further expand on condition counts and discuss the various approaches to measuring multimorbidity. I also show how the different measures are associated with different outcomes in people with T2D. Following that, I will then expand on important health outcomes in people with T2D.

2.3.1 Multimorbidity – Condition Count

At first glance what might seem straightforward for the measurement of multimorbidity is to assume that a simple count of the number of co-occurring conditions is the best measure. However, there is no criteria for the selection of chronic conditions that qualify for a multimorbidity count. This was reflected in Diederichs' systematic review findings where they emphasised the heterogeneity of existing measures of multimorbidity but noted that there is a focus on conditions with a high prevalence (27).

The measurement of multimorbidity in studies is usually dependent on the data available and researchers have to make subjective judgements on the inclusion and exclusion of specific chronic conditions. Studies using condition counts have shown associations between increasing multimorbidity condition count with increased health service use and reduced physical functioning in people with T2D (43-45). However, one study indicated that the quality of care increases as the number of chronic condition count increases (46). This is perhaps due to a higher utilisation of health services and increased GP (and other clinicians) visits leading to more opportunities to optimise care of these comorbid conditions. The seminal study by Barnett *et al.* (4) drew on the Diedrich review (27), health conditions included in the United Kingdom (UK) Quality Outcomes Framework (QOF) as well as long term disorders identified as important by policy documents of NHS Scotland to develop a list of 40 important conditions in the study of multimorbidity. This was pertinent and relevant to my work in T2D, a condition mostly managed in primary care (41), because it took into account health conditions that were deemed important in primary care settings, where it considered the UK QOF - the world's largest pay-for-performance scheme that rewards general practices financially for achieving patient outcomes and effectively delivering interventions (47). Furthermore, a morbidity score derived from conditions in the UK QOF has been shown to be more effective in predicting mortality compared to the Charlson

index in UK general practice (48). Barnett's list was then utilised in a study to explore the distribution of multimorbidity in a cohort of over 1.7 million people (4) and has subsequently been used in multimorbidity studies internationally (49-51). However, exploring the impact of multimorbidity measured as the total count of health conditions potentially ignores important considerations of whether conditions are concordant or discordant (52, 53), which I will discuss in detail in the next section.

2.3.2 Multimorbidity – Concordant and Discordant Conditions

Piette and Kerr have recommended that comorbid conditions should be "qualitatively assessed" as concordant or discordant (23). They argue that condition counts are insufficient in describing multimorbidity because they do not consider the types of conditions and their implications. Concordant conditions represent parts of the same overall pathophysiological risk profile and are more likely to be the focus of the same disease and self-management plan. Therefore, they are likely to be less burdensome in aggregate and less likely to produce conflicting guideline recommendations. Examples of conditions concordant with T2D include hypertension and chronic kidney disease. In contrast, discordant conditions are not directly related in their pathogenesis. The management of these conditions may interact and overlap in various ways with T2D management, which may in turn amplify burden and result in conflicting guidelines. Examples of discordant conditions include chronic obstructive pulmonary disease, asthma and back pain.

Evidence suggests those with more concordant conditions will have improved diabetes care due to synergistic care, and current diabetes guidelines often make specific recommendations for concordant conditions such as hypertension and cardiovascular diseases but do not address discordant conditions (23, 54).

As a result, some studies show that for people with discordant conditions, there may be a competition of focus of care due to multiple conditions and different priorities leading to sub-optimal diabetes management (23, 55). For people with T2D, this may mean distraction from optimising glycaemic management. However, it has also been suggested that people with T2D with discordant conditions may be as likely to receive the same care as those with T2D without discordant conditions (56). There is conflicting evidence when the effects on clinical outcomes are explored. There have been two studies that have explored the effects of both concordant and discordant conditions on glycaemia (HbA1c) and cholesterol levels

(57, 58). Both of which were conducted in people with T2D using two different US Veteran populations of predominantly males. The study by Woodard *et al.* of 35,872 people with T2D showed that having concordant conditions is associated with within target glycaemia (HbA1c) and cholesterol levels (58). Contrastingly, the Pentakota *et al.* study of 42,826 people with T2D showed only improved cholesterol control in those with concordant conditions (57). There were further contradictory findings when they examined the differences between the effects of concordant and discordant conditions on achieving glycaemic targets. Woodard *et al*. showed that those with discordant conditions only were more likely than those with no comorbidities and concordant conditions to achieve glycaemic targets (58). In contrast to this, Pentakota *et al*. suggested that there was no difference between people with concordant and discordant conditions in achieving glycaemic targets (57). Thus, the existing literature does not provide a clear picture of the effects of concordant and discordant conditions in people with T2D.

2.3.3 Multimorbidity – Condition Clusters

In addition to condition count and concordant and discordant conditions, particular clusters of conditions may be associated with a greater likelihood of adverse outcomes in people with T2D. This is also an issue with chronic diseases more broadly. For example, The Emerging Risk Factors Collaboration (ERFC) studied approximately one million people who had either, or in combination, diabetes, stroke and/or myocardial infarction. In this study they used the UK Biobank (n = 499,808) and pooled together individual participant data (n = 689,300) from 91 prospective population-based studies globally (mostly high-income countries). The ERFC explored the association between this cardiometabolic cluster of multimorbid conditions and mortality, and showed that combinations of these conditions were associated with multiplicative mortality risk (59). Another cross-sectional study explored clusters of conditions in 161,174 people with T2D in the US using electronic health record data supplied by health providers (60). It was suggested that the predicted odds of reaching HbA1c targets was highest for patients with co-existing hypertension, hyperlipidaemia and COPD/asthma, and lowest in people with no documented co-morbidities or with obesity only (60).

In summary, the conceptual complexity of multimorbidity is highlighted in the different measures of multimorbidity that have been explored. Currently, there is no one way to

measure multimorbidity. There are also mixed findings with health outcomes, particularly in people with T2D. As a result, there is no clear understanding of how best to measure multimorbidity associated with T2D. A clearer understanding of the relationship between multimorbidity and T2D can assist clinicians in personalising care to better meet the needs of the complex management of people with T2D. My PhD studies will therefore attempt to provide a clearer understanding of the associations between multimorbidity and T2D. A way to understand this relationship is through exploring important outcomes in people with diabetes, which I discuss in the following two sections (Sections 2.4 and 2.5).

2.4 Glycaemia in People with T2D

It has been well established that glycaemia is an important clinical outcome to consider in people with T2D. There are different ways to measure and monitor blood glucose. Glycated haemoglobin (HbA1c) is currently viewed as the "gold standard" in measuring glycaemia in people with T2D (61). It reflects the average blood glucose over the past three months. HbA1c is commonly used to monitor and guide treatment decisions and to measure the efficacy of T2D management. Substantial research has led to the development of T2D-specific HbA1c targets where the general target for HbA1c is ≤7% (53mmol/mol) (62). Early seminal longitudinal studies suggest that for every increase in 1% in HbA1c, there is a 21% increase in risk of serious and costly complications (63). The United Kingdom Prospective Diabetes Study (UKPDS) provided evidence that reducing HbA1c and avoiding hyperglycaemia (high blood glucose levels) resulted in clinical benefits including reduced microvascular and cardiovascular complications (64-67). This has become embedded in the approach to treating diabetes where a focus on glycaemia (HbA1c) was seen as the critical issue in reducing downstream cardiovascular disease and mortality (I expand on the issue of mortality in Section 2.5 below). There are, however, limitations to the use of HbA1c levels. The main limitation is that it provides only an average of blood glucose over the previous two to three months. It lacks information about acute glycaemic excursions, including acute hyper- and hypoglycaemic events, and it does not fully reflect changes occurring in response to exercise, diet and medication that can further assist in self-management. Another limitation is that it is tested using venous blood, which is invasive, requiring a blood sample from the patient. There are also interfering factors for the HbA1c test such as

haemoglobinopathies, haemolysis and renal failure. Despite limitations to HbA1c, substantial evidence still suggests its importance in clinical practice and, therefore, it should not be under-valued. Both the values and limitations of HbA1c were acknowledged by leaders from nine diabetes organisations around the globe during a meeting in 2017. They then went on to develop the "Beyond A1C Movement" presenting a unified case recommending the need for HbA1c to be supplemented by other measures of glycaemia in regulatory decisions and clinical care (68). This could be linked to the emergence of continuous glucose monitoring technology making it possible to capture adjunct glycaemic data to HbA1c. In the following sections, I will describe continuous glucose monitoring and its variants before then discussing important measures of glycaemia that can be obtained from continuous glucose monitoring data.

2.4.1 Continuous Glucose Monitoring

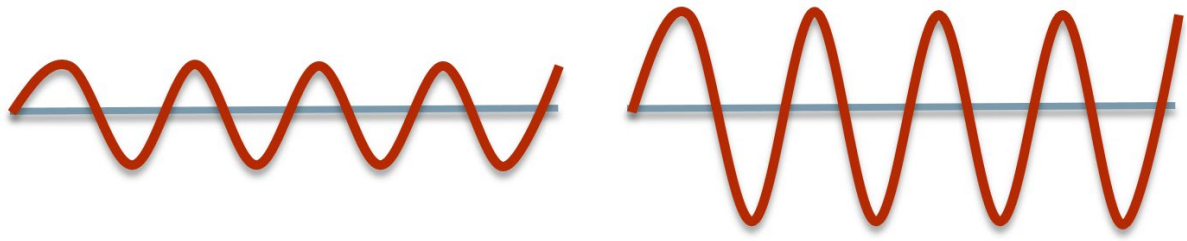
Continuous glucose monitoring (CGM) is another method to measure and monitor (interstitial fluid) glucose profiles. Broadly, interstitial fluid and blood glucose levels are correlated, but there can be a slight difference in both absolute values and a time lag between blood and interstitial fluid glucose levels (69). CGM can either be in real-time (personal mode) in which results are immediately available to the user, or retrospective (also known as professional mode) in which the results are not available in real-time to the user, but are downloaded after several days (usually 5-14 days) by a clinician and viewed/interpreted. This technology can identify within day and day-to-day glucose profiles to guide T2D management decisions. Flash glucose monitoring is a variant of CGM which also has real-time and retrospective modes that is factory calibrated without requiring finger pricks. For the retrospective professional mode version, an ambulatory glucose profile can be produced from data recorded through wearing the CGM device for two weeks. An ambulatory glucose profile is a standardised report with both graphical and quantitative characterisations of daily glucose patterns (70). This report can then be reviewed with clinicians to guide diabetes management decisions. An example of a CGM device that can do this is the FreeStyle Libre Pro® professional-mode flash glucose monitoring system (Abbott Diabetes Care, Witney, Oxon, UK). It utilises a sensor that measures interstitial glucose concentrations every 15 minutes using an enzyme coated filament inserted into the

subcutaneous tissue, usually inserted (by a clinician or the patient) into the user's upper arm. A separate reader device can be swiped close to the sensor and it will transmit both an instantaneous interstitial glucose level and a trend graph of the past readings. All the data from the sensor can be uploaded to a computer via the sensor providing information on day-to-day and within day glucose profiles and fluctuations to guide treatment decisions and management of T2D. This has the potential to overcome the limitations of HbA1c that I have described above. In the past few years, as a result of improvements in sensor accuracy and greater convenience and ease of use, the adoption of CGM has grown. With over 90% of all T2D care being provided within primary care, CGM solutions must address the unique environment and resource limitations within primary care (71). Currently, CGM is not subsidised for people with T2D in many countries, making it very expensive. In fact, the Australian National Diabetes Services Scheme (NDSS) and the UK National Health Service (NHS) have set strict criteria even for those with type 1 diabetes to be eligible to get funding for CGM devices (72, 73). This creates a barrier for people to access and use CGM. Despite this, the utility and benefits of CGM are now recognised by national and international organisations for people with T2D, which I will expand on in the following section. The success in utilising CGM data in routine clinical practice remains relatively low (74). Apart from the higher costs of CGM, this may in part relate to the lack of consensus in glycaemic measures using CGM data, and also the potential for confusion and information overload. There are two main methods of profiling blood glucose measures using CGM: 1) glycaemic variability and 2) time in (target glucose) range.

2.4.2 Glycaemic Variability

Glycaemic variability (GV) (which can be measured in the short or long-term – see below), is defined as the excursions of blood glucose, caused by factors such as medication (74), physical activity (75), stress and diet (76). An advantage of GV is that it represents fluctuations in glucose levels that could not otherwise be captured by HbA1c. As shown in Figure 2 below, individuals with the same average blood glucose (grey line) could have different GV (red line). This could potentially miss out on important variations in glucose that may contribute to the development of diabetes complications, which is discussed further below.

Figure 2: Visual representation of GV with the same mean glucose



GV has emerged as an important concept where it is a "physiological phenomenon that takes an even more important dimension in the presence of diabetes, as it favours the development of chronic diabetes complications"(77). An important consideration is the period of time in which GV is being calculated. GV can be evaluated according to different time frames including short-term and long-term periods, although currently there is no clear definition of each (78). However, studies on GV often report short-term GV as within day variability using data from CGM devices (79, 80), and long-term GV based on glucose measures from one month to several years, particularly referring to variations in HbA1c measured at clinical visits (visit-to-visit variability) (81-83). There have been no studies directly comparing short-term and long-term GV in people with T2D (78).

Past studies have linked micro- and macrovascular complications to both higher short-term and long-term GV (84-86). It is known that hyperglycaemia causes vascular damage through different metabolic pathways, which have been shown to be derived from an overproduction of mitochondrial reactive oxygen species, referred to as oxidative stress (87). Activation of oxidative stress has been shown to be associated with glucose fluctuations (88, 89) and studies have suggested that GV could induce higher levels of oxidative stress than chronic stable non-oscillating hyperglycaemia (90). A higher frequency of the glucose oscillations and a larger amplitude of the hyperglycaemic excursions seem to generate even more oxidative stress, which ultimately could lead to the development of long-term complications (88, 91). Previous studies in T2D have also shown that in people with diabetes, higher GV can predict adverse outcomes such as hip-fractures, stroke and chronic obstructive pulmonary disease (81-83). Even when individuals have HbA1c within target ranges, GV was associated with an increased risk of a cardiovascular event in the next ten years, suggesting it has an independent effect (85). It is evident that GV plays an

important role in the development of downstream complications. However, the concept of GV remains complex because there are multiple methods of calculating GV (77).

In 2017, an international expert panel consisting of clinicians, researchers and people with diabetes at the Advanced Technologies and Treatments for Diabetes (ATTD) congress identified that standardised metrics for measuring GV are lacking. The expert panel came to a consensus that "coefficient of variation (CV) should be considered the primary measure of glycaemic variability" (92). They have suggested that CV (which is the standard deviation divided by the mean) has the advantage of being a metric that considers and adjusts for the mean glucose value and is very easy to calculate. It can be utilised to calculate both short-term and long-term GV. Furthermore, there was also a consensus that stable glucose levels are defined as a CV of <36%, and unstable glucose levels are defined as CV of ≥36%, which was based on findings in the seminal study of GV by Monnier and colleagues (93). Their findings showed that as soon as this threshold is transgressed, there is a significantly increased frequency of hypoglycaemia in people with T2D, which is associated with increased mortality (94). As a result, in my PhD studies I will be utilising CV as the measure of GV in accordance with the international consensus.

2.4.3 Time-in-Range

Time-in-range (TIR) is another measure of glycaemia, made available through CGM, that assesses the amount of time that interstitial fluid glucose levels are within specified target ranges. Generalised recommended blood glucose ranges have been outlined by the RACGP diabetes guidelines as between 6-8mmol/L in the fasting state, and 6-10mmol/L following meals (41). The target time spent in target ranges should be individualised based on characteristics such as age, duration of diabetes and medication use (95). Hypoglycaemia is defined as blood glucose less than 4mmol/L (96). Hypoglycaemia has been shown to increase risk of mortality (94), and hyperglycaemia has also been shown to independently increase risk of cardiovascular disease (97), along with microvascular complications (98). With variations in target ranges defined differently by different studies, this leads to a body of research with results that are difficult to compare. In 2019 there was an international consensus (the American Diabetes Association 79th scientific sessions) that recommends a target range of 3.9-10.0 mmol/L that should be considered when exploring TIR derived from

CGM data in people with T2D (99). As a result, in my PhD I will explore TIR using this international consensus.

2.4.4 Conclusion on GV and Time-in-Range

CGM use provides the ability to obtain real time (or masked and delayed) feedback on glucose levels as well as direction and rate of change in glucose levels overcoming limitations of HbA1c. This insight into glucose levels using measures derived from CGM provides an opportunity for better management in people with T2D. Furthermore, the potential real time utility of CGM can aid in reacting to and appropriately mitigating or preventing acute hyper-and hypoglycaemic events. The metrics of assessing CGM data including GV (measured by CV) and TIR should complement HbA1c to optimise T2D management (68). I therefore explore glycaemic outcomes including HbA1c, GV and TIR in this PhD program.

2.5 Mortality in People with T2D

People with T2D often die earlier compared to people without diabetes. Globally, approximately 4 million people with T2D die from diabetes related causes each year (5). The important consideration of time must be noted when exploring mortality. Throughout this section and my thesis, when I refer to increased mortality or risk of death, I am capturing the increased number of deaths over the period of observation of a study.

Substantial evidence has shown that cardiovascular disease (CVD) is the most common cause of death in people with T2D (25, 100). Rates of all-cause mortality in people with T2D are two-times as high, and CVD mortality are two to four times higher, compared to those without diabetes (101). The United Kingdom Prospective Diabetes Study (UKPDS) showed that reducing HbA1c is associated with reduced microvascular and cardiovascular complications in people with T2D (64-67). The findings led to an accepted assumption amongst clinicians that achieving optimal glycaemic levels would aid in reducing CVD risk and, therefore, overall mortality in T2D given glycaemia is a pertinent aspect of T2D management. However later evidence raised questions about such an assumption. A number of large studies have since explored this using randomised controlled trial designs with a conventional therapy arm versus an intensive glycaemic control arm (64, 102-104).

These later trials created controversy because they failed to confirm that achieving target levels of HbA1c with intensive glycaemic therapy would provide clear benefits in reducing all-cause or CVD mortality and CVD events. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study even showed increased mortality in the intensive control arm (102). This suggests that there are multiple factors at play here for the risk of mortality independent of glycaemia as assessed by HbA1c (105), such as GV which can be difficult to detect without CGM. Given the complexity of this issue of increased mortality seen in people with T2D and the complication of T2D commonly co-occurring with other conditions, understanding the role of multimorbidity could provide further clarity. My work in this PhD will address this issue by clarifying associations between multimorbidity, presence of individual conditions and all-cause mortality in those with T2D.

2.6 Summary

In this review chapter I have described that T2D is a common condition with increasing prevalence, that rarely occurs on its own. The majority of people with T2D have additional chronic conditions making multimorbidity highly prevalent in this population. There are challenges that multimorbidity brings about, from both clinical and conceptual perspectives, making multimorbidity a highly complex concept. Important outcomes in people with T2D include mortality and different measures of glycaemia, particularly the emerging notion of GV.

Multimorbidity is common in people with T2D, yet there is a paucity of knowledge on the associations between multimorbidity and adverse outcomes in T2D particularly on mortality and glycaemia, and when available it is largely heterogenous and yields contrasting findings. It is clear from the current literature that more needs to be understood on these emerging concepts. The current RACGP guidelines for T2D management acknowledge the limitations of the existing evidence base and suggest clinical guidance regarding multimorbidity is currently lacking or sparse (41). Given the emerging and complex range of measures of glycaemia, an important area of research will be to identify the association each measure has with multimorbidity and the mechanisms through which these associations exist. It will be important to compare this to what is known about more traditional measures of glycaemia and the key outcome of mortality. My PhD will bring together these concepts and

attempt to fill these current research gaps and contribute to further understanding the relationship between the total burden of disease reflected in multimorbidity and mortality and measures of glycaemia in people with T2D.

In the next chapter I begin with the over-arching research question for my PhD. I then outline the overall methods for the four closely related studies that form this PhD.

3: Aim and Research Question, and Methods

The overall aim of my PhD is to explore associations between multimorbidity and key health outcomes (mortality and measures of glycaemia) in people with type 2 diabetes.

I will address my aim by answering the following overarching research question that underpins my PhD:

What is the relationship between multimorbidity, all-cause mortality and glycaemic outcomes in people with type 2 diabetes?

There are also sub-questions that fall under my overarching question to understand multimorbidity in people with type 2 diabetes:

- ***What is the prevalence of multimorbidity and individual long-term conditions in people with type 2 diabetes?***
- ***What are the associations between multimorbidity (total, concordant and discordant) counts and 1) all-cause mortality; 2) HbA1c; 3) glycaemic variability and 4) time-in-range in people with type 2 diabetes?***

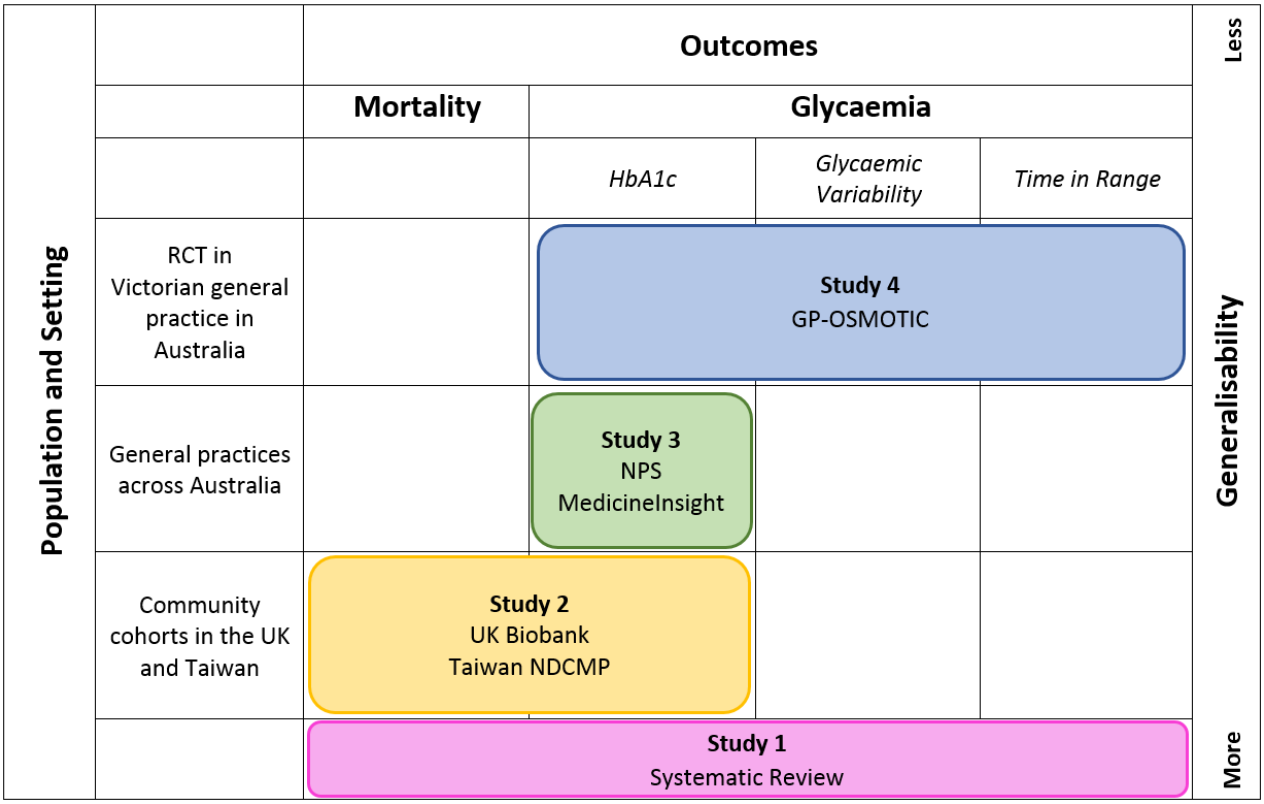
3.1 Methods

In this section I first briefly summarise the methodology I used to conduct a series of linked studies to address my research questions. This was achieved in a systematic review and closely related studies, drawing on my links[2] with existing datasets in the UK, Taiwan, and Australia (See Figure 3). Each of the studies are presented as published or submitted papers in peer-reviewed journals in their respective chapters, each containing detailed presentations of the methods used. In this section I also outline the measure of multimorbidity used throughout my quantitative studies.

[2] My co-supervisor Prof. Frances Mair, Head of General Practice and Primary Care at the University of Glasgow, and her department has access to the UK Biobank data. Prof. Tsai-Chung Li, who I mentioned in the introduction of this thesis, and her department at the China Medical University has access to the Taiwan National Diabetes Care Management Program (NDCMP) dataset. During my PhD, I had the opportunity to travel to, and spend time at, the University of Glasgow in Scotland, UK, and China Medical University in Taichung, Taiwan to conduct my study using the UK Biobank and Taiwan NDCMP datasets respectively. I will describe the datasets in detail in Section 3.1.2 below.

In Figure 3 below, I describe the flow of my PhD thesis and studies. It presents a summary of the three quantitative studies and their study populations/settings and the outcomes[3] examined. Moving from bottom to top, the study populations become increasingly specialised from people with type 2 diabetes (T2D) across two countries [Study 2 (see Chapter 6)], to those attending general practice across Australia [Study 3 (see Chapter 7)], and finally to those recruited for a randomised controlled trial in in general practice in Victoria, Australia [Study 4 (see Chapter 8)]. The findings for the studies therefore have varying levels of generalisability to the wider T2D population.

Figure 3: Studies that form this PhD



The systematic review, Study 1, provides an important foundation of current knowledge and identified the evidence gaps in the academic literature and methodological issues (details of which can be found in Paper 2, see Chapter 5) when exploring associations between

[3] In this PhD I consider glycaemia as an outcome; this aligns with the work of John Yudkin (Yudkin et al. BMJ. 2011) where HbA1c is used as a surrogate marker and proxy for outcomes of importance in people with diabetes. I made the decision not to explore hypoglycaemia and acute hypoglycaemic events in this PhD. This was mainly because data on hypoglycaemia were not available in the datasets used in Studies 2 and 3. This was also to ensure consistency and comparability of my quantitative studies. I further discuss this in the limitations and areas of future research sections of this thesis (see Sections 10.3.2 and 10.4).

multimorbidity and outcomes in T2D. Study 1 resulted in two published papers, the first outlined the protocol of the systematic review (Paper 1, see Chapter 4), the second presented the findings of the review (Paper 2, see Chapter 5). The subsequent three studies aimed to address the gaps and methodological issues identified in the systematic review and to further explore effects of multimorbidity using four separate datasets, each dataset offering varying outcomes to explore.

3.1.1 Multimorbidity Measure Used

In the previous literature review chapter, I identified the conceptual complexity of multimorbidity highlighting the different measures of multimorbidity that have been explored. I have made the decision to use a condition count based on important long-term conditions identified by the seminal Barnett multimorbidity (4). This decision was made because it took into account health conditions that were deemed important in primary care settings. This is significant because the majority of people with multimorbidity and T2D are managed in general practice and primary care (41). As mentioned previously in the literature review, evidence has suggested that conditions in the UK QOF, which the Barnett list drew on, are more effective in predicting mortality in a general practice setting compared to the commonly used Charlson Comorbidity Index (48). The straightforward approach of using a count of conditions was not inferior to the more complex Charlson Index in predicting mortality in people with T2D (42). To address the important considerations of types of conditions in people with T2D (52, 53), I drew on Piette and Kerr's concept, as described above, where I qualitatively assessed conditions to be either concordant or discordant based on their definitions (23).

In this PhD, I therefore explored multimorbidity with a condition count based on the Barnett list of long-term conditions. I also categorised the counts into total, concordant and discordant condition counts. The list of conditions used to measure multimorbidity in each of my quantitative studies differed slightly. This is because information on long-term conditions for the participants were collected differently in each of the studies. Detailed presentations of the methods used to collect and identify long-term conditions are described in the methods sections of their respective papers. The lists for Studies 2, 3 and 4 can be found in the appendix, Sections 12.3, 12.5 and 12.6, respectively.

3.1.2 Quantitative Studies

Study 2

The first of my three qualitative studies, Study 2, explores the associations between multimorbidity, glycaemia (HbA1c) and mortality in two large community cohorts of people with T2D in the UK and Taiwan. I utilised the UK Biobank which is a large prospective cohort of more than 500,000 participants (aged 37-73 years) recruited between 2006 and 2010, with linkage to routine healthcare data until 2018 (106). The participants attended assessment centres across the UK to complete a touch screen and nurse-led questionnaire with information on demographics, health-related behaviour, and self-reported chronic conditions at the time of recruitment. The participants gave consent for prospective data linkage to national mortality data. The chronic conditions were also identified using hospital admissions data. In this UK cohort, I identified 20,569 people with T2D using a published algorithm[4] developed by Eastwood *et al.* (107). For the Taiwan subset of the study, I utilised the Taiwan National Diabetes Care Management Program (NDCMP) which includes approximately 60,000 ethnic Chinese participants with T2D across Taiwan recruited between 2001 and 2004, followed until 2011 (108). The NDCMP was a program established by the Taiwan Ministry of Health and Welfare in 2001 aiming to enhance the quality of diabetes care by augmenting the frequency of monitoring, improving continuity of care, and preventing diabetes-related complications. The NDCMP data was from inpatient hospital care and outpatient visits including primary care, where chronic conditions were identified using the International Classification of Disease ICD-9-CM codes.

Exploring the two datasets in one study provides the opportunity to compare effects of multimorbidity in people with T2D across populations of two different countries, ethnicities, base rates of T2D, and healthcare systems. This study and its findings are presented in Chapter 6 (Paper 3).

Study 3

Study 3 explored the association between multimorbidity and glycaemia (HbA1c) in people with T2D in Australian general practice. This cross-sectional study was conducted using data

[4] The Eastwood algorithm has been used widely in the literature to identify people with type 2 diabetes in the UK Biobank considering and cross-tabulating self-report baseline data (including information on diagnosis, age at diagnosis, diabetes type, diabetes medications and diabetes complications). The algorithm has also been externally validated using primary care data.

from MedicineInsight, which is a national database managed by NPS MedicineWise established to support quality improvement in Australian general practice (109). This differs to the community cohorts of T2D in Study 2 described previously, as this NPS study includes data from 557 Australian general practices, located in every Australian state and territory, representing more than 3.8 million patient records (109). MedicineInsight extracts and collates longitudinal, de-identified patient health records, including demographics, encounters, diagnoses, prescriptions and pathology tests from general practice clinical information systems. The data from the NPS dataset for my study was extracted on the 1st of September 2015. The data extraction algorithm I used only included those aged ≥18 years who had a recorded diagnosis of T2D. The resultant dataset consisted of 105,135 people. This study adds to my PhD by allowing me to explore and compare multimorbidity in people with T2D from community cohorts and routinely collected general practice data. The findings from this study can be used to either confirm or refute the findings from community studies. Study 3 and its findings are presented in Chapter 7 (Paper 4). Additionally, this study also allowed some insights into the use of routinely collected primary care data for research and evaluation purposes in Australia, which I discuss in more detail in Section 10.2.2.

Study 4

Study 4 contributes new knowledge by providing an insight into the effect of multimorbidity on three measures of glycaemia: 1) HbA1c, 2) glycaemic variability and 3) time-in-range, in people with T2D. This study is unique in that it provides the opportunity to explore novel glycaemic measures of glycaemic variability and time-in-range using CGM data. As I have discussed above, they may be important in the context of multimorbidity and T2D (see Sections 2.4.2 and 2.4.3). This study included 279 people with T2D using baseline data (October 2016 – November 2017) from the General Practice Optimising Structured MOnitoring To Improve Clinical outcomes (GP-OSMOTIC) randomised controlled trial (110, 111). To summarise, the GP-OSMOTIC trial aimed to explore the effectiveness of a CGM device (FreeStyle Libre Pro® Flash Glucose Monitoring System, Abbott Diabetes Care, Witney, Oxon, UK) used in the clinical care of people with T2D in 25 general practices in Victoria, Australia (110-112). At the time of recruitment, the participants completed nurse-led survey interviews which included demographic questions and questions on whether they have specific chronic conditions. This was then cross-checked with the participants'

medical history retrieved from their clinical electronic medical records. This study and its findings are presented in Chapter 8 (Paper 5).

3.1.3 Summary

To summarise, my PhD thesis consists of four studies including a systematic review and three quantitative studies using four different datasets allowing for comparative work to further understand multimorbidity in people with T2D. In the following chapters (Chapters 4 to 8), I present the five papers resulting from my studies. As my studies are presented as individual papers, I acknowledge that there may be some overlap in the introduction and discussion of important issues. I then present a synthesis of the results across the studies (Chapter 9) before I discuss the implications of my findings (Chapter 10).

4: Paper 1 – Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol

In this section of my thesis I present a systematic review protocol that I developed to conduct a systematic review. My aim was to develop a comprehensive and robust protocol with a search strategy that would fully capture existing literature exploring associations between any numerical counts/measures of multimorbidity, all-cause mortality and any measures of glycaemia in people with type 2 diabetes. I also developed procedures within the protocol to extract all relevant information and data from the included studies. I also specified relevant processes for evaluating the quality of the content that was being extracted and also assessing the risk of bias across the studies.

This systematic review protocol appears overleaf and has been published with the following citation: Chiang JI, Furler J, Mair FS, Jani B, Nicholl BI, Jenkins A, et al. Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol. BMJ open. 2018;8(4):e021100.

Copies of the full search strategy and data extraction form referred to as additional files in the paper are available in the Appendix (see Section 12.1).

BMJ Open

Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol

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*BMJ Open*2018 8:
doi: 10.1136/bmjopen-2017-021100

BMJ Open

Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol

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To cite: Chiang JI, Furler J, Mair FS, *et al*. Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol. *BMJ Open* 2018;**8**:e021100. doi:10.1136/bmjopen-2017-021100

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-021100).

Received 11 December 2017
Revised 15 March 2018
Accepted 20 March 2018

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ABSTRACT

Introduction Type 2 diabetes (T2D) is a leading health priority worldwide. Multimorbidity (MM) is a term describing the co-occurrence of two or more chronic diseases or conditions. The majority of people living with T2D have MM. The relationship between MM and mortality and glycaemia in people with T2D is not clear.

Methods and analysis Medline, Embase, Cumulative Index of Nursing and Allied Health Complete, The Cochrane Library, and SCOPUS will be searched with a prespecified search strategy. The searches will be limited to quantitative empirical studies in English with no restriction on publication date. One reviewer will perform title screening and two review authors will independently screen the abstract and full texts using Covidence software, with disagreements adjudicated by a third reviewer. Data will be extracted using a using a Population, Exposure, Comparator and Outcomes framework. Two reviewers will independently extract data and undertake the risk of bias (quality) assessment. Disagreements will be resolved by consensus. A narrative synthesis of the results will be conducted and meta-analysis considered if appropriate. Quality appraisal will be undertaken using the Newcastle-Ottawa quality assessment scale and the quality of the cumulative evidence of the included studies will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation approach. This protocol was prepared in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines to ensure the quality of our review.

Ethics and dissemination This review will synthesise the existing evidence about the impact of MM on mortality and glycaemic outcomes in people living with T2D and increase our understanding of this subject and will inform future practice and policy. Findings will be disseminated via conference presentations, social media and peer-reviewed publication.

PROSPERO registration number CRD42017079500.

Strengths and limitations of this study

- This will be the first systematic review to explore the impact of multimorbidity (MM) on all-cause mortality and glycaemia in people with type 2 diabetes (T2D) and has the potential to make a valuable contribution to the literature in this area.
- Our review benefits from a comprehensive search strategy including key terms, synonyms and medical subject headings that describe the research questions with a deliberate inclusion of the 'comorbidity' term to address the identified issue of the terms 'comorbidity' and 'multimorbidity' being used interchangeably.
- We expect the literature to be quite heterogeneous in terms of how MM is defined and the way outcomes are reported so that a narrative synthesis may be likely.

INTRODUCTION

Rationale

Type 2 diabetes (T2D) is a major health priority of the 21st century. Worldwide, it is estimated that more than 424 million people live with diabetes, resulting in US$727 billion in healthcare expenditures.[1] Approximately 4 million people die from diabetes-related causes each year, equivalent to 1 death every 8 s, with nearly half of these deaths in people under the age of 60.[1] There is no doubt that T2D imposes a heavy burden on communities.

The management of T2D is complex, requiring continuous efforts to implement recommendations for self-management and pharmacotherapy in a stepwise manner to achieve evidence-based targets. This complexity is increased when the patient has other chronic conditions in addition to T2D because T2D rarely occurs on its own. Data suggest that as many as 85% of those with T2D have at least one other chronic condition,[2] which is higher than the 52% in the general population that is multimorbid.[3]

For many years, the terms comorbidity and multimorbidity (MM) were used interchangeably.[4] It has only been more recently that there has been a clearer distinction and understanding between the two terms.

Comorbidity is defined as the existence or occurrence of any additional condition(s) that co-occurs with an index disease.[5] MM however refers to the presence of two or more chronic conditions in an individual, with no reference to an index condition.[6] These established definitions provide the basis of our systematic review which exclusively focuses on MM in T2D.

MM presents multiple challenges. It is associated with a reduced quality of life, increased costs, a reduced ability to make lifestyle changes and may be associated with complex therapeutic regimens which the patient may be challenged to manage.[7] For health professionals, MM brings increased workload and the clinical challenges of interactions between multiple conditions and medications.[4] Most condition-specific management guidelines do not account for MM and prioritise management of one condition at the expense of another.[7] For people with diabetes, this can lead to clinicians focusing on diabetes only without consideration of the patient's other conditions and patient goals. Similarly, a focus on other conditions may lead to suboptimal glycaemic management due to a lack of focus on diabetes-specific care goals.[8 9] This is particularly problematic because achieving and maintaining glycaemic targets early is important in reducing downstream complications and all-cause mortality.[10]

Currently, little is known about the associations between MM and T2D. In particular, there is little information regarding the relationship of the total burden of disease reflected in MM's multiple dimensions to the association between all-cause mortality and glycaemia.

Our systematic review will focus on current knowledge regarding the impact of MM on mortality and glycaemia in people with T2D and provide insights regarding the implications of MM in the context of this chronic disease. It may provide an important foundation of knowledge for improving care for patients with T2D and multiple chronic conditions.

Objectives

The primary objective of our systematic review is to determine the impact of MM reflected in condition count on all-cause mortality and glycaemia in people with T2D. We will have two primary outcomes of equal interest: (1) all-cause mortality; and (2) glycaemia (measured by glycated haemoglobin (HbA1c)).

Secondary outcomes of interest include: (1) hypoglycaemia, (2) hyperglycaemia and (3) glycaemic variability.

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines has been used to prepare this protocol.[11]

Eligibility criteria

Study characteristics/design

All quantitative empirical studies published in the English language will be included. Our target studies will be observational studies that use either longitudinal cohort (retrospective and prospective) or cross-sectional designs. While we recognise the limitation of cross-sectional studies in terms of assessment of temporality, cross-sectional studies provide a snapshot of the association between MM count and our glycaemia-related outcomes of interest. We will have no restrictions on publication date. The search end date will be 28 July 2017.

Randomised controlled trials, non-diabetes drug intervention studies, all qualitative studies, case reports, review articles and conference abstracts will be excluded as they will not give us information on our primary outcomes of interest. Randomised controlled trials and non-diabetes drug intervention studies have primary objectives of testing particular interventions so the effect of MM will not be captured, thus inappropriate for our review which is focused on the effects on MM. All non-English studies will also be excluded.

Population

Our target study population is adults (18 years of age or older) with T2D.

Studies including populations of children and adolescents (under 18 years of age) or people without T2D (eg, people with prediabetes, type 1 diabetes/gestational diabetes/monogenic diabetes) will be excluded. Animal studies will also be excluded.

Exposure

The primary exposure of interest is MM count. We will accept any type of MM count, which may include a list of chronic conditions from a variety of datasets including electronic medical records, administrative and prescription datasets. Only studies that assess the relationship

Table 1 Search terms

Key terms	Multimorbidity	Diabetes	Outcomes of interest: mortality glycaemia
Other related terms or synonyms	multimorbid* multi morbid* condition count* multiple condition* multiple disease* multiple disorder* multicondition* multidisease* multidisorder* multi condition* multi disease* multi disorder* comorbid* co morbid*	diabet* diabetes adj2 (type 2 or type ii)	mortality death surviv* surviv* analys* glycaemia* glycemia* hypoglycaem* hypoglycem* hyperglycaem* hyperglycem* glycem* varia* glycaem* varia*

between a numerical count of MM and our outcomes of interest will be included.

Studies with single nominated specific conditions (ie, only one comorbid condition) linked with T2D without MM count will be excluded.

Comparators (control)

A comparator/control group is defined by people with T2D with no other chronic conditions. Studies that do not include such a control group will not be excluded.

Outcome

A study will be included in our review if data is provided regarding either all-cause mortality or glycaemic outcomes. It is expected that glycaemia will be reported in the form of HbA1c, however, we will include any measure of glycaemia, for example, hypoglycaemia, hyperglycaemia or glycaemic variability.

Information sources

We will search five electronic databases including Medline (Ovid interface), Embase (Ovid interface), Cumulative Index of Nursing and Allied Health Complete (EBSCO interface), The Cochrane Library (Ovid interface) and SCOPUS with no restrictions on publication date.

We will check the International Prospective Register of Systematic Reviews regularly for ongoing and completed systematic reviews for MM and T2D.

Search strategy

The search strategy will include medical subject headings, terms and synonyms relating to or describing our primary objectives. These terms will be combined using appropriate Boolean logic operators to create our search strategy. The truncation symbol (*) will also be included at the end of the stem of a word to retrieve all words that start with that stem. Our strategy has been reviewed by a librarian from a biomedical library and members of our review panel with expertise in MM and T2D. A number of test runs will first be conducted with Medline, and any necessary adjustments will be made prior to running the search. Once the search strategy is finalised, the searches will be adapted for each of the five electronic databases prior to conducting the searches. The search terms are listed in table 1. The full search strategy is available in online supplementary file 1.

Study records

Data management

Literature search results will be downloaded to EndNote (V.7; Clarivate Analytics) and duplicates will be removed. The non-duplicate studies will then be uploaded to Covidence,[12] a systematic review management software, for the selection process.

Selection process

The selection process of the studies for inclusion in our review will be conducted in three stages. First, titles of the studies identified in the five database searches will be screened by the primary researcher (JC) against the predefined eligibility criteria outlined above. A deliberately inclusive approach will be adopted for this title screening stage to reduce the risk of missing potentially relevant studies.

Second, all abstracts will be screened by two reviewers independently. The primary researcher (JC) will screen all abstracts against the predefined eligibility criteria outlined above to identify a subset of potentially relevant studies. An independent second screening of the abstracts will be completed between the following reviewers (JMN, JF, BN, BJ, AJ, FM). Any inter-reviewer disagreements will be discussed and resolved by a third reviewer (JMN, JF).

Finally, we will obtain full-text articles for all studies that appear to meet our eligibility criteria after the title and abstract screening stages. Full-text screening will be conducted by two reviewers independently. The primary researcher (JC) will screen all full texts against our predefined eligibility criteria. This will then be repeated independently by a second reviewer (JMN, JF, BJ). Online supplementary material will be consulted when necessary. Again, any inter-reviewer disagreements will be discussed and resolved by a third reviewer (JMN, JF). Reasons for exclusion at the full-text screening process will be recorded.

Data extraction

Data will be extracted in a structured manner from all included studies and recorded in a predefined data extraction form designed by the primary researcher (JC) following a prespecified Population, Exposure, Comparator, Outcomes framework in the data extraction stage. This is an adapted framework based on the Cochrane PICO statement where 'I' for intervention is replaced with an 'E' for exposure. We will also be including an extra 'study characteristics' parameter to record characteristics of the study including study design, setting, period of study and aims and objectives (see online supplementary file 2). The form will be reviewed, refined and adjusted where necessary by the review team. Again, online supplementary material will be consulted when necessary for data extraction.

Data items

We will be extracting relevant data in each of the following five parameters:

Populations

We will extract data on characteristics of study populations (sample size, sex, age, ethnicity, socioeconomic status, occupation, education, diabetes duration, HbA1c, insulin treatment and oral antidiabetes drugs), as well as definition/measure of T2D, method of recruitment and sampling and inclusion and exclusion criteria.

Exposure

We will describe the definition/measure of MM count and number of subjects reported.

Comparator

We will provide details provided in the publication of any comparator groups including the definition/measure of people with T2D with no other chronic/long-term conditions and numbers in group.

Outcomes

We will provide details as to how all-cause mortality and/or glycaemia is defined/measured, as well as length of follow-up, number of subjects and the statistical analyses employed by the authors to evaluate the relationship between MM count and the measured outcomes.

Study characteristics

We will extract details of study design, setting, period of study and aims and objectives.

Outcomes and prioritisation

One of the primary clinical outcomes of interest is all-cause mortality. We expect that studies will calculate the effect estimate as either HRs, ORs, incidence rates or survival percentages.

For our other primary outcome, glycaemia, we will prioritise those studies that measure glycaemia in terms of HbA1c. We will further divide studies into one of two groups: those that measure HbA1c as a continuous variable and those that measure HbA1c as a categorical variable.

We will accept all other measures of glycaemia as secondary outcomes.

Risk of bias assessment (quality assessment in individual studies)

Two reviewers will independently assess the risk of bias (quality) in each of the included studies.

All studies will be assessed using the Newcastle-Ottawa quality assessment scale.[13] The choice of this tool was informed by recommendations from the Cochrane Handbook on assessing the quality of non-randomised studies.[14] Any inter-reviewer disagreements will be discussed and resolved by a third reviewer.

The Newcastle-Ottawa quality assessment scale has a star system to judge three broad perspectives of the included studies: the selection of the study groups; the comparability of the groups and the ascertainment of the outcome of interest.

Data synthesis

For data synthesis, we will group the included studies according to the two outcomes of all-cause mortality and glycaemia. Within the glycaemia outcome group, we will further subgroup the studies into the different measures of glycaemia. For our primary analysis, we will consider either all-cause mortality or glycaemia each as a composite outcome. However, dependent on the number of studies retrieved, an analysis of glycaemia subtype will be conducted. Furthermore, dependent on the characteristics of the study populations, we will consider stratifying our results according to either exposure ascertainment (MM count) or population characteristics (ie, age group, gender and socioeconomic status).

A narrative synthesis of findings will be conducted which will describe the findings from each of the included studies. For each study we will present details relating to the following:

- The number and characteristics of participants in the study.
- Setting.
- Study design.
- The outcome-level risk of bias of the study.
- Findings for quantitative outcomes.
- Inconsistent findings within individual studies will be indicated.

If further information relevant to our review is required, we will attempt to contact the authors of the included studies.

A meta-analysis will be conducted if appropriate. Tests for publication bias and heterogeneity will be conducted. If the included studies are sufficiently homogenous in terms of study design, study population, outcomes and data analysis, a meta-analysis will be considered. I^2 statistic will be used to assess statistical heterogeneity and to guide the choice of either fixed or random effects model. Given sufficient numbers of included studies, a funnel plot will be used to assess publication bias and other reporting bias, and a Begg's test will be used to test for asymmetry. A sensitivity analysis will also be used to determine the consistency of the results. However, if a meta-analysis and the above tests are not possible, possible sources of bias across studies will be discussed in the narrative synthesis, and this limitation will be considered when drawing conclusions.

Confidence in cumulative evidence

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guideline is recommended by the Cochrane Handbook for grading the quality and strength of evidence.[15] We will use the GRADE guidelines to assess the quality of evidence for our research questions.

Patient and public involvement

Patients were not involved in the development of this protocol.

ETHICS AND DISSEMINATION

Ethics

Ethics was not required for this study as this is a systematic review and it does not contain individual patient data. We will disseminate the results of our review via conference presentations, social media and peer-reviewed publication. This review also forms part of the lead investigator's (JC) PhD.

DISCUSSION

This systematic review will aim to synthesise the existing evidence on the effects of MM in T2D on mortality and

glycaemic control and will be the first on this subject. Clinical management in patients with T2D and MM is a growing international healthcare challenge, and our review will make important contributions to understanding of the impact of MM, if any, in the context of T2D on key clinical outcomes which should enhance the understanding in this field. We hypothesise that increasing MM will be associated with increased all-cause mortality; however, the effects on glycaemic outcomes may vary. Our review will be the first to bring together existing literature exploring associations between MM and T2D, and therefore clarifying the effects of increasing MM on mortality and glycaemia in people with T2D.

Key strengths of our review will be our adherence to the PRISMA-P guidelines, our comprehensive search strategy and the fact that all screening and data extraction will be performed by two reviewers independently. We expect the literature to be quite heterogeneous in terms of how MM is defined and the way outcomes are reported so a narrative synthesis may be likely which may be a limitation. In addition, we have restricted our review to English language publications which is a potential limitation.

As the first review on this subject, it will help identify what is known on this subject and whether any gaps in knowledge exist. It will therefore help highlight whether there are areas requiring further investigation as well as clarify the key messages from the evidence, to date, including implications for future guidelines for those with T2D.

Contributors JC drafted the protocol and developed the search strategy, inclusion/exclusion criteria and the data extraction form with guidance from JMN, JF, FM, BN, BJ, AJ and DO. PC contributed to the development of the search. All coauthors read and provided feedback on the draft manuscript. All authors approved the manuscript for submission.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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5: Paper 2 – Associations between multimorbidity, all-cause mortality and glycaemia in people with type 2 diabetes: A systematic review

In the previous section I outlined the protocol that I developed to conduct my systematic review. In this chapter I present the results and discuss the implications of the findings of the systematic review. The aim of this review was to get a comprehensive overview of current knowledge about associations between multimorbidity and health outcomes in people with type 2 diabetes, and the degree to which they had been explored.

This systematic review appears overleaf and has been published with the following citation: Chiang JI, Jani BD, Mair FS, Nicholl BI, Furler J, O'Neal D, et al. Associations between multimorbidity, all-cause mortality and glycaemia in people with type 2 diabetes: A systematic review. PLoS one. 2018;13(12):e0209585.

All supplementary files (S1 Table. Inclusion and exclusion criteria for papers; S2 Table. Participant detail; S3 Table. Summary of methods and results; S1 Text. Search strategy; S2 Text. Adapted Newcastle-Ottawa quality assessment scale) referred to in the paper are available in the Appendix (see Section 12.2).

Following the paper, I provide a summary of the findings and how they set a foundation of knowledge for the subsequent studies of my PhD.

PLOS ONE

RESEARCH ARTICLE

Associations between multimorbidity, all-cause mortality and glycaemia in people with type 2 diabetes: A systematic review

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OPEN ACCESS

Citation: Chiang JI, Jani BD, Mair FS, Nicholl BI, Furler J, O'Neal D, et al. (2018) Associations between multimorbidity, all-cause mortality and glycaemia in people with type 2 diabetes: A systematic review. PLoS ONE 13(12): e0209585. https://doi.org/10.1371/journal.pone.0209585

Editor: Wen-Jun Tu, Chinese Academy of Medical Sciences and Peking Union Medical College, CHINA

Received: July 2, 2018

Accepted: December 8, 2018

Published: December 26, 2018

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: T2D, Type 2 diabetes; MM, Multimorbidity; HbA1c, glycated haemoglobin; GV,

Abstract

Introduction

Type 2 diabetes (T2D) is a major health priority worldwide and the majority of people with diabetes live with multimorbidity (MM) (the co-occurrence of ≥2 chronic conditions). The aim of this systematic review was to explore the association between MM and all-cause mortality and glycaemic outcomes in people with T2D.

Methods

The search strategy centred on: T2D, MM, comorbidity, mortality and glycaemia. Databases searched: MEDLINE, EMBASE, CINAHL Complete, The Cochrane Library, and SCOPUS. Restrictions included: English language, quantitative empirical studies. Two reviewers independently carried out: abstract and full text screening, data extraction, and quality appraisal. Disagreements adjudicated by a third reviewer.

Results

Of the 4882 papers identified; 41 met inclusion criteria. The outcome was all-cause mortality in 16 studies, glycaemia in 24 studies and both outcomes in one study. There were 28 longitudinal cohort studies and 13 cross-sectional studies, with the number of participants ranging from 96–892,223. Included studies were conducted in high or upper-middle-income countries. Fifteen of 17 studies showed a statistically significant association between increasing MM and higher mortality. Ten of 14 studies showed no significant associations between MM and HbA1c. Four of 14 studies found higher levels of MM associated with higher HbA1c. Increasing MM was significantly associated with hypoglycaemia in 9/10 studies. There was no significant association between MM and fasting glucose (one study). No studies explored effects on glycaemic variability.

Glycaemic variability; CCI, Charlson Comorbidity Index.

Conclusions

This review demonstrates that MM in T2D is associated with higher mortality and hypoglycaemia, whilst evidence regarding the association with other measures of glycaemic control is mixed. The current single disease focused approach to management of T2D seems inappropriate. Our findings highlight the need for clinical guidelines to support a holistic approach to the complex care needs of those with T2D and MM, accounting for the various conditions that people with T2D may be living with.

Systematic review registration

International Prospective Register of Systematic Reviews CRD42017079500

Introduction

Type 2 diabetes (T2D) is a leading health priority. Over 424 million people live with diabetes worldwide, leading to $727 billion US dollars in healthcare expenditure [1]. It is estimated that four million people die from diabetes related causes every year, equivalent to one death every eight seconds [1].

T2D management is complex and requires continuous efforts from both clinicians and patients to implement recommendations for self-management and pharmacotherapy to achieve evidence-based targets. For patients who have other chronic conditions in addition to T2D, this complexity is amplified. This is important as T2D rarely occurs on its own–multimorbidity (MM) (presence of $\geq$ 2 conditions) is the norm, with approximately 85% of those living with T2D having at least one other chronic condition [2].

MM produces many challenges. It is associated with lower quality of life, increased costs, a reduced ability to make lifestyle changes and may be associated with complex therapeutic regimens [3], increasing the treatment burden experienced by the patient [4]. This in turn may challenge and overwhelm individuals, resulting in reduced adherence and poorer outcomes [4]. MM presents health professionals with increased workloads, and the clinical challenge of interactions between multiple conditions and medications (4).

While MM brings about multiple challenges in a clinical sense, it also presents multiple considerations from a conceptual perspective. The terms comorbidity and MM are often used interchangeably [5]. Only more recently has there been a clearer understanding and distinction between the two terms. Comorbidity is defined as the occurrence or existence of an additional condition that co-occurs with an index disease [6]. MM however refers to the presence of two or more chronic conditions in an individual, with no reference to an index condition [7]. The former term illustrates the traditional approach to understanding T2D along with its well-known micro- and macro-vascular complications. The latter term covers a different view where a person's overall illness burden is the focus and provides the basis for our systematic review, which focuses on MM in people with T2D.

Despite MM presenting many challenges, there is no "gold standard" for the measurement of MM [8]. We still lack clear and comprehensive criteria for the measurement of MM and selection of chronic conditions that qualify for MM. As a result, a numerical count is an acceptable form of measurement of MM, including particular scales (e.g. Charlson Comorbidity Index) [9] that count particular conditions.

MM is common in T2D and brings many challenges, yet currently little is understood about the association between MM and outcomes in T2D. This systematic review seeks to explore literature on the association between MM condition count in people with T2D and the following two primary outcomes: 1) all-cause mortality; and 2) glycaemia (measured by HbA1c). Secondary outcomes of interest include other measures of glycaemia: 1) hypoglycaemia, 2) hyperglycaemia; and 3) glycaemic variability.

Methods

Our detailed review protocol has been published elsewhere [10] and is summarised below.

We have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [11] and our review is registered on the International Prospective Register of Systematic Reviews (CRD42017079500).

Search strategy

A comprehensive search strategy was used to identify empirical quantitative studies with data on associations between MM condition count and our outcomes of interest in people with T2D. Target studies were observational studies that used either a cross-sectional or longitudinal cohort design. The search was limited to papers published in English but there was no restriction on publication date. A formal database search strategy was developed in consultation with a librarian (PC) from a biomedical library and members of our author group with expertise in MM and T2D, using a combination of free text search and medical subject headings; this is shown in S1 Text. Databases searched were MEDLINE (OVID interface), EMBASE (OVID interface), CINAHL Complete (EBSCO interface), The Cochrane Library (OVID interface), and SCOPUS. The search centred around five key concepts: T2D, MM, comorbidity, glycaemia and mortality. The search was carried out to include literature published up to 28th July 2017.

Inclusion/exclusion criteria

We included empirical quantitative studies that included data on associations between MM condition count and adults with T2D and all-cause mortality or glycaemic outcomes. Full details of inclusion and exclusion criteria for studies are shown in S1 Table and discussed in detail elsewhere [10].

Data screening, extraction and analysis

The data screening process was conducted in three stages. Titles of identified studies in the searches were screened by the primary researcher (JC) with a deliberately inclusive approach to reduce the risk of missing potentially relevant studies. Abstract, full paper screening, data extraction and quality appraisal were undertaken by two individual reviewers with any inter-reviewer disagreements resolved by a third reviewer. Covidence [12], a systematic review management software, was used to store, share and assess papers, and undertake selection for inclusion (beyond the title screen). Data were extracted in a structured manner using a predefined data extraction form. Details of the data extraction instrument developed and used are published elsewhere [10]. Data were analysed using a prespecified Population, Exposure, Comparator, Outcomes (PECO) framework which was an adapted framework based on the Cochrane PICO statement where "I" for intervention is replaced with an "E" for exposure. "Study Characteristics" were also included in the framework to take characteristics including study design, setting, period of study, and aims and objectives into account. This PECO

approach is acceptable as informed by the Cochrane Handbook [13] and has been utilised previously in a range of published systematic reviews [14, 15]. During data analysis and synthesis, we grouped the included studies according to the two outcomes of interest (all-cause mortality and glycaemia), further subgrouping the latter into different measures of glycaemia. We then considered the implications of the overall findings for each of the outcomes, in order to identify knowledge gaps and clarify the key messages from the evidence, including implications for future research and clinical guidelines for the management of people with T2D.

Quality appraisal

Quality appraisal was conducted by two reviewers independently. All studies were assessed using the Newcastle-Ottawa quality assessment scale [16] which was informed by recommendations from the Cochrane Handbook on assessing the quality of non-randomised studies [13]. The Newcastle-Ottawa quality assessment scale utilises a star system to judge three broad domains of the included studies: *the selection of the study groups; the comparability of the groups;* and *the ascertainment of the outcome of interest*. We adapted the quality assessment scale to suit our systematic review; shown in S2 Text. The Newcastle-Ottawa quality assessment scale was designed so that it could be modified for specific systematic reviews for non-randomised studies. For example, in the comparability domain, the scale asks the review authors to select the two most important factors that the included studies should control for. The scale's face/content validity and inter-rater reliability have been established [16] and our approach with the modified scale has been previously used in a published systematic review [14]. Studies were not excluded based on the quality appraisal because our aim was to develop a comprehensive understanding of the existing literature that explored associations between MM and T2D.

Results

Retrieved studies

In total, 4,882 papers were identified with our search strategy, and 41 subsequently met our inclusion criteria. Fig 1 demonstrates the inclusion and exclusion of papers at each stage of the screening stages utilising the PRISMA flow diagram [11].

Included studies and their characteristics

We included 41 studies in our review. Twenty-four studies [17–40] had glycaemia as an outcome, 16 studies [41–56] had all-cause mortality as an outcome and one study [57] included both outcomes.

Key descriptive information of the included studies is summarised in Table 1 below. Participant numbers ranged from 96 to 892,223. There were 28 longitudinal cohort studies [18, 21, 28, 29, 32–37, 40–57] and 13 cross-sectional studies [17, 19, 20, 22–27, 30, 31, 38, 39]. All included studies were conducted in high or upper-middle-income countries.

Measure of MM

The measure of MM condition count used in the included studies varied considerably. The majority of studies (24/41 (59%)) [19, 21, 27, 28, 30–37, 39–41, 43, 46, 49–53, 55, 57] measured MM in terms of the Charlson Comorbidity Index (CCI) [9]. MM was represented as a simple count of conditions that were available in the study datasets in 15 studies (32%) [17, 18, 22–25, 29, 38, 44, 47, 48, 50, 52, 54, 56]. The remaining studies measured MM with other indices including the chronic diseases score [20], cumulative illness rating scales [26], total illness

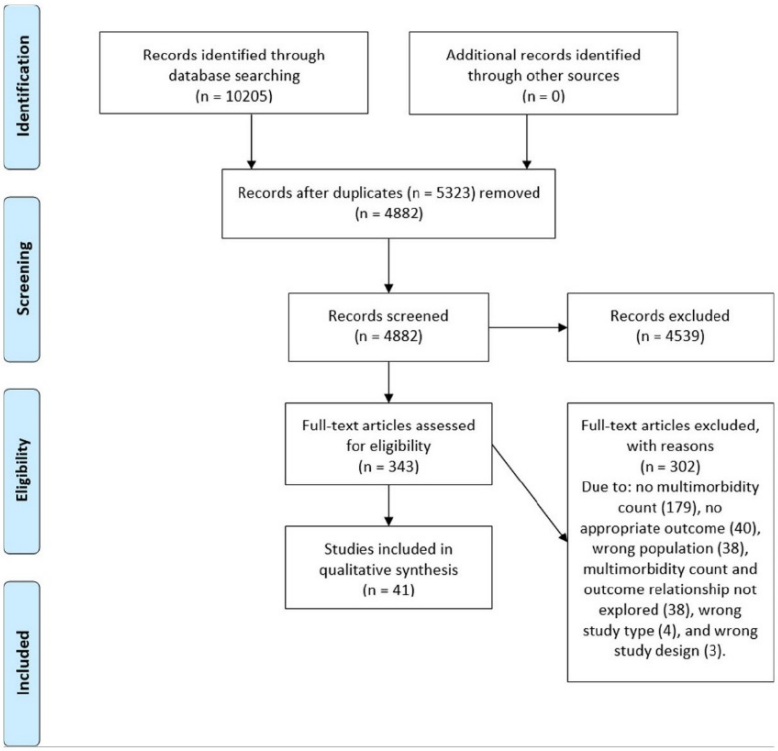

Fig 1. PRISMA flow diagram.

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burden index [42], severity of illness index [45] and the Elixhauser index [52], or a combination of multiple MM measures [50, 52]. The measure of MM for each of the studies is summarised in S2 Table. This further highlights the heterogeneity of included studies. Meta-analysis was not possible due to variation in measurement of MM.

Only 11/41 (27%) [20, 26, 29, 38, 42, 43, 47, 50, 52, 54, 57] studies had the primary objectives of exploring the relationship between MM and our outcomes of interest, however, all included studies provided data about the association between MM and mortality or glycaemia. 9/41 (22%) studies [24, 27, 28, 33, 37, 39, 46, 49, 56] had broad scoping aims of determining factors that were associated with mortality or glycaemia outcomes. More than half, 21/41 (51%) studies [17–19, 21–23, 25, 30–32, 34–36, 40, 41, 44, 45, 48, 51, 53, 55] did not state the investigation of MM as a research objective, but contained MM count as a covariate when exploring the impact of other factors on mortality or glycaemia, including data allowing us to identify the association between MM count and our outcomes of interest. The research aims included describing the effects of a range of factors (e.g. medication adherence, treatment complexity, anti-diabetic oral treatment, treatment interactions, social support, economic burden, obesity) on glycaemic control and mortality. This wide range of research objectives demonstrates the heterogeneity of the included studies.

Description of the demographics of patients included in the studies is summarised in Table 2 below. The mean age of participants ranged from 38 to 83 years; this was unclear or could not be calculated from the data provided in seven studies [23, 25, 27, 35, 38, 45, 48, 49]. Gender of participants were not described in two studies [23, 49] and in those that did (n = 39) [17–22, 24–48, 50–57], the percentage of female ranged from 2% to 70%. Ethnicity was reported in 11 studies [19, 20, 24, 29, 31, 32, 39, 44, 45, 49, 53] and socioeconomic status was seldom reported (n = 7) [29, 32, 38–40, 52, 54]. Full details of participants are shown in S2 Table.

Table 1. Summary of included studies.

Reference	Outcome measure	Country	Study setting and design	Number of participants	MM measure
	Both				
Escalada J et al., 2016	All-cause mortality Hypoglycaemic event	US	Community; cohort study	N = 31,035	Charlson comorbidity index
	All-cause mortality				
Castro-Rodriguez M et al., 2016	All-cause mortality	Spain	Community; cohort study	N = 363	Charlson comorbidity index
Greenfield S et al., 2009	All-cause mortality	Italy	Diabetes outpatient clinic and primary care; cohort study	N = 2,613	Total illness burden index
Huang YQ et al., 2014	All-cause mortality	China	Hospital; cohort study	N = 533	Charlson comorbidity index
Hunt KJ et al., 2013	All-cause mortality	US	Veterans administrations; cohort study	N = 892,223	Condition count
Kheirbek RE et al., 2013	All-cause mortality	US	Veterans administrations; cohort study	N = 17,773	Severity of illness index
Lin WH et al., 2015	All-cause mortality	Taiwan	Community; cohort study	N = 65,559	Charlson comorbidity index
Lynch CP et al., 2014	All-cause mortality	US	Veterans administrations; cohort study	N = 625,903	Condition count
Martin WG et al., 2014	All-cause mortality	Australia	Hospital; cohort study	N = 210	Condition count
McEwen LN et al., 2012	All-cause mortality	US	Community; cohort study	N = 8,334	Charlson comorbidity index
Monami M et al., 2007	All-cause mortality	Italy	Hospital; cohort study	N = 1,667	Charlson Comorbidity Index and Condition Count
Monami M et al., 2006	All-cause mortality	Italy	Hospital; cohort study	N = 2,002	Charlson comorbidity index
Walker J et al., 2016	All-cause mortality	Scotland	Community; cohort study	N = 126,648	Charlson Comorbidity Index, Elixhauser Comorbidity Index and Condition Count
Wang CP et al., 2014	All-cause mortality	US	Veterans administrations; cohort study	N = 2,415	Charlson comorbidity index
Weir DL et al., 2016	All-cause mortality	US	Community; cohort study	N = 285,231	Condition count
Wilke T et al., 2015	All-cause mortality	Germany	Hospital; cohort study	N = 35,661	Charlson comorbidity index
Zelada H et al., 2016	All-cause mortality	Peru	Hospital; cohort study	N = 499	Condition count
	Glycaemic outcomes				
Gallegos-Carrillo K et al., 2009	Fasting plasma glucose	Mexico	Community; cross-sectional	N = 666	Condition count
Abbatecola AM et al., 2015	HbA1c	Italy	Nursing homes; cross-sectional	N = 1,845	Condition count
Bae JP et al., 2016	HbA1c	US	Primary care; cross-sectional	N = 248,567	Charlson comorbidity index
El-Kebbi IM et al., 2001	HbA1c	US	Diabetes clinic; cross-sectional	N = 823	Chronic disease score
Foran E et al., 2015	HbA1c	Ireland	Primary care; cross-sectional	N = 283	Condition count
Fox KM et al., 2006	HbA1c	UK	Primary care; cross-sectional	N = 11,866	Condition count
Frei A et al., 2012	HbA1c	Switzerland	Primary care; cross-sectional	N = 326	Condition count
Hudon C et al., 2008	HbA1c	Canada	Primary care; cross-sectional	N = 96	Cumulative illness rating scale
Luijks H et al., 2015	HbA1c	Netherlands	Primary care; cohort study	N = 610	Condition count
Mosen DM et al., 2017	HbA1c	US	Hospitals and outpatient; cross-sectional	N = 19,600	Charlson comorbidity index
Pollack M et al., 2010	HbA1c	US	Community; cohort study	N = 16,168	Charlson comorbidity index
Romero SP et al., 2013	HbA1c	Spain	Hospital; cohort study	N = 1,519	Charlson comorbidity index

(*Continued*)

Table 1. (Continued)

Reference	Outcome measure	Country	Study setting and design	Number of participants	MM measure
Svensson E et al., 2016	HbA1c	Denmark	Community; cohort study	N = 38,418	Charlson comorbidity index
Teljeur C et al., 2013	HbA1c	Ireland	Primary care; cross-sectional	N = 424	Condition count
Walker RJ et al., 2015	HbA1c	US	Primary care; cross-sectional	N = 615	Charlson comorbidity index
Abbatecola AM et al., 2015	Hypoglycaemic event	Italy	Nursing homes; cohort study	N = 2,258	Condition count
Fonseca V et al., 2017	Hypoglycaemic event	US	Community; cohort study	N = 18,918	Charlson comorbidity index
Kim HM et al., 2016	Hypoglycaemic event	Korea	Community; cross-sectional	N = 307,170	Charlson comorbidity index
Kostev K et al., 2014	Hypoglycaemic event	Germany	Primary care; cohort study	N = 32,545	Charlson comorbidity index
McCoy RG et al., 2013	Hypoglycaemic event	US	Primary care and specialty practices; cross-sectional	N = 326	Charlson comorbidity index
Quilliam BJ et al., 2011	Hypoglycaemic event	US	Hospital; nested case control study	N = 14,729	Charlson comorbidity index
Rathmann W et al., 2013	Hypoglycaemic event	Germany	Primary care; cohort study	N = 50,294	Charlson comorbidity index
Signorovitch JE et al., 2013	Hypoglycaemic event	US	Community; cohort study	N = 33,492	Charlson comorbidity index
Yu HC et al., 2014	Hypoglycaemic event	Taiwan	Hospital; cohort study	N = 399,252	Charlson comorbidity index

https://doi.org/10.1371/journal.pone.0209585.t001

Quality appraisal

The quality appraisal of the included studies is summarised in S2 Text. Generally, the papers were of moderate to high quality based on the Newcastle-Ottawa quality assessment scale. There were 12 (29%) papers assessed as representative of the general T2D population as they were based on large national datasets. Furthermore, under the *comparability* domain, only 10 (24%) of the 41 included studies considered both age and known duration of diabetes in their data analyses.

All-cause mortality

We identified 17/41 studies [41–57] that included sufficient data to explore the association between MM condition count and all-cause mortality. All but two studies [41, 52] demonstrated that increasing MM count is associated with statistically significant increased odds ratios (ORs) or hazard ratios (HRs) of death. Studies differed in the analytic methods used to determine the relationship between MM and mortality. These included: two-sample t-test to compare MM between surviving and non-surviving participants; multivariable logistic regression models; and multivariable Cox proportional hazard models. Furthermore, MM was treated in analysis either as a continuous or categorical variable in different studies. For studies that showed a significant increase in mortality whilst treating increasing MM as a continuous variable, the HRs from Cox proportional hazard models that explored MM represented by CCI ranged from 1.22 to 1.95 [50, 51, 53, 55]. Whilst the study that represented MM as total illness burden index, the HR was 1.02 [42]. Studies that reported MM in categories presented more difficulties in comparing the results because they differed in the MM categories that were treated as reference groups [43–49, 54, 56]. This varied from treating 0 conditions, 1 condition, 0–2 CCI and 1–2 CCI as reference in the analyses. The OR results therefore also varied greatly. The OR for mortality was 1.26 for having 1+ conditions in addition to T2D when 0

Table 2. Participant demographics.

Reference	Outcome measure	No of participants and gender % F = female M = male	Mean (SD) age in years	Ethnicity	Socioeconomic status
	Both				
Escalada J et al., 2016	All-cause mortality Hypoglycaemic event	31035 (53%F 37%M)	72 (9.2)	Not reported	Not reported
	All-cause mortality				
Castro-Rodriguez M et al., 2016	All-cause mortality	363 (54.8%F 45.2%M)	76	Not reported	Not reported
Greenfield S et al., 2009	All-cause mortality	2613 (54.8%F 45.2%M)	62.8	Not reported	Not reported
Huang YQ et al., 2014	All-cause mortality	533 (43.4%F 56.6%M)	65.2 (10.8)	Not reported	Not reported
Hunt KJ et al., 2013	All-cause mortality	892223 (2.4%F 97.6% M)	66.2 (11.15)	Non-Hispanic White 61.5%, Non-Hispanic Black 12.1%, Hispanic 13.9%, Other 12.5%	Not reported
Kheirbek RE et al., 2013	All-cause mortality	17773 (4.8%F 95.2%M)	Unclear	White 26.1%, Hispanic 29.9%, Unclear 44%	Not reported
Lin WH et al., 2015	All-cause mortality	65559 (47.9%F 52.1% M)	60.5 (12.9)	Not reported	Not reported
Lynch CP et al., 2014	All-cause mortality	625903 (2.2%F 97.8% M)	65 (11.1)	Non-Hispanic Black 72.1%, Non-Hispanic White 13.2%, Hispanic 5.3%, Other/Unknown race 9.4%	Not reported
Martin WG et al., 2014	All-cause mortality	210 (42.9%F 57.1%M)	Unclear	Not reported	Not reported
McEwen LN et al., 2012	All-cause mortality	8334 (Gender unclear)	Unclear	Non-Hispanic White 50%, Hispanic 15%, African American 18%, Asian/Pacific Islander 9%, Other 8%	Unclear–was included in analysis but not described
Monami M et al., 2007	All-cause mortality	1667 (49.3%F 50.7%M)	65.7 (11.0)	Not reported	Not reported
Monami M et al., 2006	All-cause mortality	2002 (50.1%F 49.9%M)	65.8 (10.8)	Not reported	Not reported
Walker J et al., 2016	All-cause mortality	126648 (44.6%F 55.4% M)	61.9	Not reported	Q1 (most deprived) 23.2%, Q2 22.7%, Q3 20.4, Q4 18.6%, Q5 15.1%
Wang CP et al., 2014	All-cause mortality	2415 (2%F 98%M)	73.7	White/others 83%, Hispanic 7%, Black 10%	Not reported
Weir DL et al., 2016	All-cause mortality	285231 (49.1%F 50.9% M)	53 (10.5)	Not reported	Mean (SD) income in USD $48842 (6567)
Wilke T et al., 2015	All-cause mortality	35661 (54.2%F 45.8% M)	65.91	Not reported	Not reported
Zelada H et al., 2016	All-cause mortality	499 (63.6%F 36.4%M)	61.6 (13.8)	Not reported	Not reported
	Glycaemic outcomes				
Gallegos-Carrillo K et al., 2009	Fasting plasma glucose	666 (64.7%F 35.3%M)	Unclear	Not reported	Not reported
Abbatecola AM et al., 2015	HbA1c	1845 (70%F 30%M)	82 (8)	Not reported	Not reported
Bae JP et al., 2016	HbA1c	248567 (50.9%F 49.1% M)	64 (med)	Caucasian 66.5%, African American 14.3%, Asian 2.8%, Other 16.4%	Not reported

(*Continued*)

Table 2. (Continued)

Reference	Outcome measure	No of participants and gender % F = female M = male	Mean (SD) age in years	Ethnicity	Socioeconomic status
El-Kebbi IM et al., 2001	HbA1c	823 (65%F 35%M)	53 (1)	African American 90%, Unclear 10%	Not reported
Foran E et al., 2015	HbA1c	283 (42%F 58%M)	68 (9.5)	Not reported	Not reported
Fox KM et al., 2006	HbA1c	11866 (Gender unclear)	Unclear	Not reported	Not reported
Frei A et al., 2012	HbA1c	326 (42.6%F 57.4%M)	67.1 (10.6)	Swiss 91.8%, Unclear 8.2%	Not reported
Hudon C et al., 2008	HbA1c	96 (51%F 49%M)	66.99	Not reported	Not reported
Luijks H et al., 2015	HbA1c	610 (52%F 48%M)	63 (12.5)	Not reported	Low 52.1%, Middle 40%, High 7.9%
Mosen DM et al., 2017	HbA1c	19600 (48%F 52%M)	63.1	White 78.9%, Hispanic 7.4%, Asian American/Pacific Islander 6.5%, African American 3.9%, Other 3.3%	Not reported
Pollack M et al., 2010	HbA1c	16198 (44.1%F 55.9% M)	52.8	Caucasian 77%, African American 6%, Hispanic 4.3%, Unclear 12.7%	At least 50% had a yearly income >US$65,000 and a net worth of at least US$100,000
Romero SP et al., 2013	HbA1c	1519 (54.2%F 45.8%M)	71.4 (7.6)	Not reported	Not reported
Svensson E et al., 2016	HbA1c	38418 (44%F 56%M)	63	Not reported	Not reported
Teljeur C et al., 2013	HbA1c	424 (46.5%F 53.5%M)	Unclear	Not reported	Low 40.1%, Unclear 59.9%
Walker RJ et al., 2015	HbA1c	615 (38.4%F 61.6%M)	61.3 (10.9)	Non-Hispanic Black 64.9%, Non-Hispanic White 33%, Other/ Hispanic 2.1%	Annual income (USD) <$10k 20.2%, $10k-14.9k 11.3%, $15k-19.9k 10.1%, $20k-24.9k 10.4%, $25k-34.9k 14.7%, $35k-49.9k 13.8%, $50k-74.9k 10.1%, $75k+ 9.4%
Abbatecola AM et al., 2015	Hypoglycaemic event	2258 (69%F 31%M)	83 (7)	Not reported	Not reported
Fonseca V et al., 2017	Hypoglycaemic event	18918 (48%F 52%M)	64 (13)	Not reported	Not reported
Kim HM et al., 2016	Hypoglycaemic event	307170 (58.3%F 41.7% M)	Unclear	Not reported	Not reported
Kostev K et al., 2014	Hypoglycaemic event	32545 (49.7%F 50.3% M)	70.2 (11.2)	Not reported	Not reported
McCoy RG et al., 2013	Hypoglycaemic event	326 (44.5F% 55.5%M)	69.3 (12.0)	Not reported	Not reported
Quilliam BJ et al., 2011	Hypoglycaemic event	14729 (46.5%F 53.5% M)	54.8	Not reported	Not reported
Rathmann W et al., 2013	Hypoglycaemic event	50294 (47.1%F 52.9% M)	67.3	Not reported	Not reported
Signorovitch JE et al., 2013	Hypoglycaemic event	33492 (45.3%F 54.7% M)	59.7	Not reported	Not reported
Yu HC et al., 2014	Hypoglycaemic event	399252 (47.4%F 52.6% M)	54.96 (12.51)	Not reported	Monthly salary (NTD), dependants 24.6%, ≤$17280 4.9%, $17281–22800 37.1%, $22801–28800 15.7%, $28801–36300 5.1%, $36301–45800 6.3%, $45801–57800 2.5%, $57801 3.8%

https://doi.org/10.1371/journal.pone.0209585.t002

conditions was the reference group [54], whilst the OR for mortality was 5.46 for CCI of 5 + when CCI of 1–2 was the reference group [43]. The HR results also varied extensively. When CCI of 0–2 was the reference group, the HR for CCI of 3–4 was 1.4 [46]. When having 1

condition in addition to T2D was the reference group, the HR for having 3+ conditions was 21.12 [56]. Despite the heterogeneity of the studies, it is evident that increasing MM count, irrespective of the measure used, is associated with increased all-cause mortality. A summary of the results can be found in S3 Table.

Glycaemia

We identified 25 studies [17–40, 57] that explored associations between MM condition count and glycaemic outcomes. Fourteen studies [17, 19, 20, 22–24, 26, 29, 31, 32, 35, 37–39] reported HbA1c, 10 studies [18, 21, 27, 28, 30, 33, 34, 36, 40, 57] hypoglycaemia, and one study [25] measured glycaemia in terms of fasting plasma glucose. All results of the included studies are summarised in S3 Table.

HbA1c. The majority of studies (10/14)[17, 20, 22–24, 26, 29, 31, 35, 38] showed no association with MM count while four studies [19, 32, 37, 39] found that increased MM count was associated with higher HbA1c. These four studies used different methods of data analysis (S3 Table). Heterogeneity was also seen in the analysis of the effect on HbA1c (continuous for the linear regression model but categorical for the remaining statistical methods).

Hypoglycaemia. An increase in MM count was significantly associated with hypoglycaemia in nine of the 10 included studies that presented hypoglycaemia as a glycaemic outcome [18, 21, 27, 28, 33, 34, 36, 40, 57]. Nine of these studies presented MM in terms of the CCI. However, the analysis of data differed greatly (S3 Table). For those that treated MM as a continuous variable using the CCI, the ORs for hypoglycaemia ranged from 1.06 to 1.37 per 1 unit increase in CCI [28, 33]. Similar to the mortality studies, the hypoglycaemia studies that reported MM in categories also presented difficulties in comparing the results due the various reference categories used. One study that used logistic regression models categorised CCI into 1 (reference group), 2, 3, 4 and 5+ with ORs for hypoglycaemia of 1.00, 1.31, 1.81, 2.49 and 4.80, respectively [27]. Another study that used Cox proportional hazard models categorised CCI into 0 (reference group), 1, 2, 3, 4 and 5+; the results showed HRs of 1.00, 1.04, 1.22, 1.16, 1.34 and 1.38, respectively [40]. Despite this heterogeneity, it is evident in the included studies that an increase in MM count is associated with a significantly increased risk of hypoglycaemia.

Fasting plasma glucose. One study explored the relationship between MM count and glycaemia as a continuous measure of fasting plasma glucose [25]. The study used a multivariable linear regression model to investigate the association between increasing number of conditions and fasting plasma glucose, and found no statistically significant association.

Glycaemic variability. No study reported glycaemic variability as an outcome measure when exploring the relationship between MM count and glycaemia.

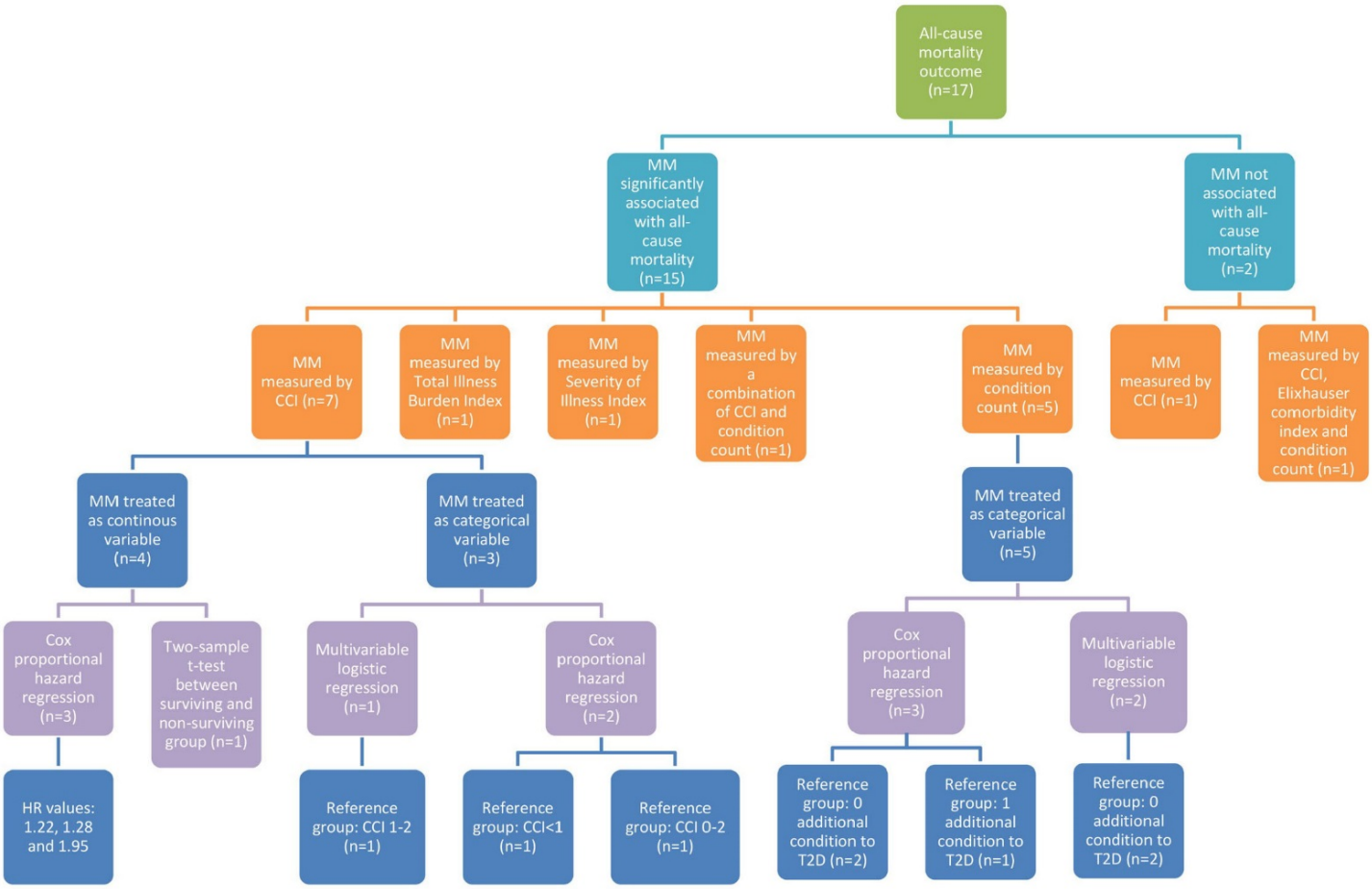
Study heterogeneity

Heterogeneity of the included studies can be seen in multiple aspects. It arises from the multiple MM measures used in the included studies, the treatment of MM in data analysis either as continuous or categorical variables and the different statistical analyses used. This is summarised in Figs 2 and 3. As a result, meta-analysis and sub-group analysis are not possible.

Discussion

Summary of results

To the best of our knowledge, this is the first systematic review to synthesise the existing evidence on associations between MM, all-cause mortality and glycaemia in people with T2D.



n: number of papers, MM: multimorbidity, CCI: Charlson Comorbidity Index, HR: hazard ratio

Fig 2. Summary of all-cause mortality outcome papers.

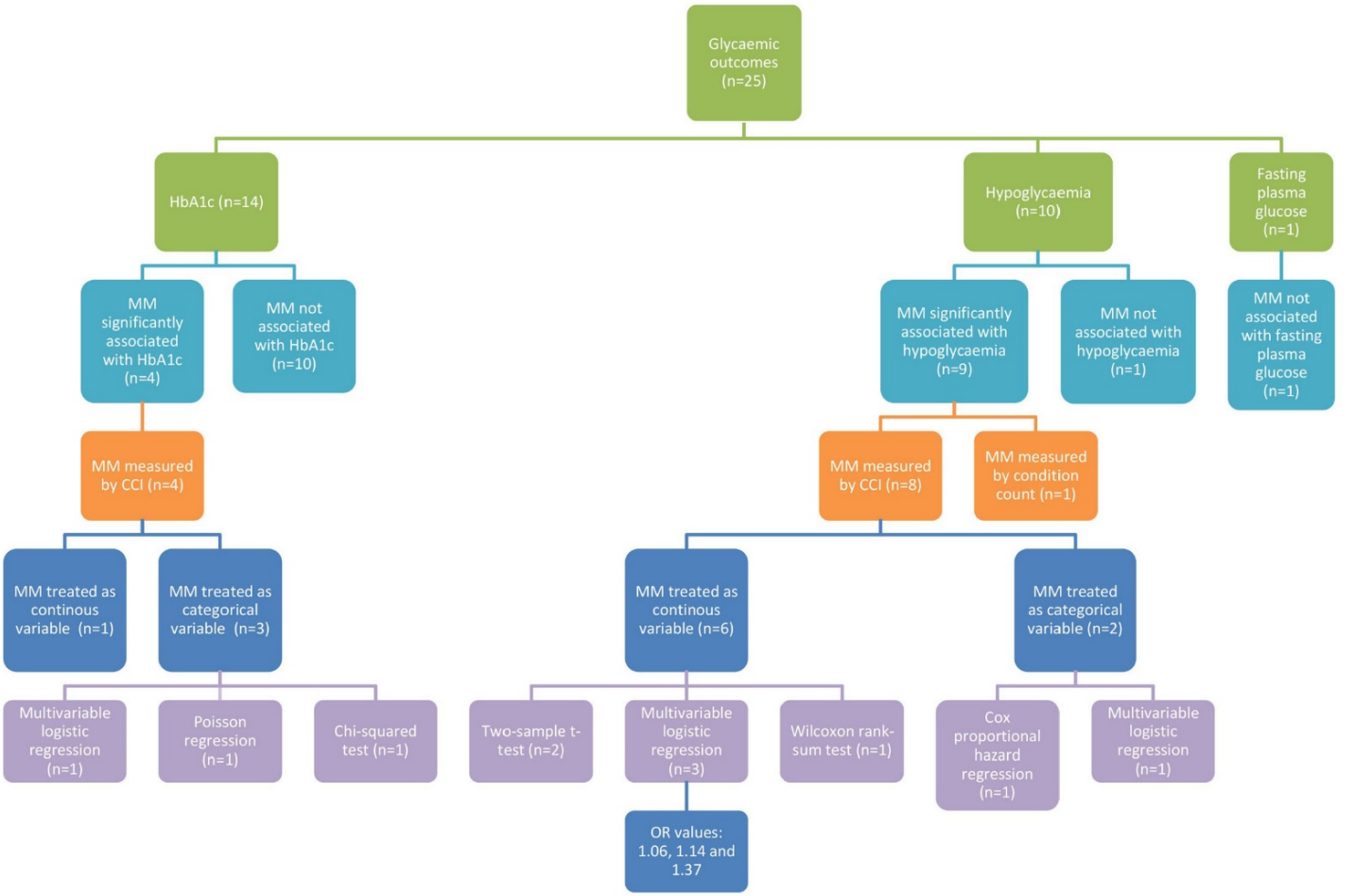
https://doi.org/10.1371/journal.pone.0209585.g002

The key findings from our review were that increased MM condition count in those with T2D is significantly associated with all-cause mortality and hypoglycaemia. However, the evidence of effects on other measures of glycaemia including HbA1c and fasting plasma glucose is mixed. No studies explored the associations of MM with glycaemic variability.

How this fits in with current knowledge

Our findings are consistent with previous literature where increasing MM has been shown to be associated with increased mortality in people with T2D [58–60]. Our findings demonstrated this in a range of settings, countries and study sample sizes. Furthermore, despite variations in the methodologies, measures of MM and statistical analyses, the evidence still suggests an increase in risk of death with increasing MM.

We found no convincing evidence of an association between MM count and HbA1c. This was unexpected as it has been well-established that HbA1c is an important clinical outcome to consider in people with T2D and glycaemic management is a key component of clinical guidelines for T2D. This suggests that the association of MM with mortality that we identified is not necessarily strongly mediated by glycaemia. Studies that have explored the relationship



n: number of papers, MM: multimorbidity, CCI: Charlson Comorbidity Index, OR: odds ratio

Fig 3. Summary of glycaemic outcomes papers.

https://doi.org/10.1371/journal.pone.0209585.g003

between HbA1c and mortality showed conflicting results where some studies suggested that increased HbA1c was significantly associated with increased mortality [61, 62] however, another demonstrated that the use of intensive therapy to target HbA1c levels below 6.0% increased the rate of death [63]. This mixed picture regarding the relationship between MM count and HbA1c highlights the need for future research to examine how people with T2D and their health professionals approach glycaemic management and targets in the context of MM. It is recognised in many clinical guidelines that HbA1c targets should be individualised based on factors such as age, diabetes duration and MM conditions [64, 65].

We found a significant association between MM and hypoglycaemia with 9/10 studies demonstrating this. Previous studies have suggested that the presence of coexisting conditions may increase a person's vulnerability to both adverse clinical outcomes, including death, and severe hypoglycaemia [66, 67]. This hypoglycaemia could be as a result of over-treatment or intensive treatment for those that are less healthy (i.e. with greater MM), but a key paper from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed that mortality among those that reported hypoglycaemia was higher for those receiving standard treatment than those receiving intensive treatment [68]. Hypoglycaemia could be a mediating factor for

those with increased MM who ultimately have an increased risk of death. It is interesting to note that the one study [30] in our review that reported no association between MM and hypoglycaemia, used self-report hypoglycaemia as an outcome, which was highlighted as a study limitation, as hypoglycaemia awareness may be impaired and / or patient recall may be inaccurate [69, 70].

Another key finding is that despite our comprehensive search of the literature, there was no study that explored the effects of MM count on glycaemic variability. Glycaemic variability, which refers to fluctuations in blood (or interstitial fluid) glucose levels, is a relatively new measure of glycaemia in people with T2D. There is growing interest in targeting reduced glycaemic variability as an independent clinical goal because higher glucose variability is thought to be associated with the development of chronic diabetes complications [71]. It is clear that there is a need for new knowledge to be generated to further understand the association between glycaemic variability and MM, and whether it will be clinically important or just another surrogate marker with little clinical importance to people with T2D.

Methodological findings and implications

The studies included in our review were highly heterogenous, particularly in the way that MM was measured. There is no consensus as to what is the best method to measure MM, and which is most appropriate to use to predict mortality and other clinical outcomes. Monami *et al*, however, demonstrated that using a condition count was not inferior to the more complex CCI (which applies weightings to the count) when predicting mortality in people with T2D [50]. The attribution of different weights to comorbidities, based on the severity, in the CCI does not seem to add prognostic value in predicting mortality relative to a simple condition count. Moreover, as evident in our findings, increasing counts of conditions and other indices other than the CCI can also be significant predictors of all-cause mortality in people with T2D. Although our findings suggest that various measures of MM showed significant associations with increased mortality, we cannot identify the best measure of MM in predicting mortality. Nor can we identify the type of multimorbid conditions that could have stronger associations with mortality and glycaemia. Piette and Kerr have recommended that multimorbid conditions should be qualitatively assessed as concordant (related to T2D) or discordant (unrelated to T2D) [72] and argue that condition counts are insufficient in describing MM. Therefore, the implications for future research are that well-designed comparative studies of separate measures including concordant and discordant conditions are warranted using large international datasets. Finally, while it will be essential to understand what patterns of MM are associated with the worst outcomes it will also be important to investigate the mechanisms underpinning the increased mortality experienced by those with T2D and MM. Importantly, it will be essential to explore to what extent poor outcomes are explained by biology and how much is a result of health-care systems that may be fragmented and failing to provide coordinated, supportive and holistic care, tailored to the needs of people with complex health care problems [73].

Strengths and limitations

Key strengths of our review are our adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines, our comprehensive search strategy, and that all screening and data extraction were performed by two reviewers independently.

We restricted our search to studies in the English language, which might be viewed as a limitation, although there is increasing evidence that this is unlikely to be a particular problem [74]. We did not apply any geographical limitations, and our review included studies from a

variety of countries, all of which were high-income countries or upper-middle-income countries according to the United Nations country classifications. However, there were no studies conducted in low-income countries. We also recognise the limitation of cross-sectional studies in terms of assessment of temporality however, cross-sectional studies provide a snapshot of the relationship between MM count and glycaemia related outcomes of interest.

Important strengths of our review are that we conducted an exhaustive search of five electronic databases and our tight inclusion and exclusion criteria allowed us to gather any data that explored associations between MM and our outcomes of interest, even if the study did not specifically aim to explore this relationship.

A major advantage of our review is that it brings together information about the effects of MM in people with T2D from various sources to create a comprehensive picture of its effects on a number of outcomes. However, one limitation is that the included studies and therefore study participants were highly heterogenous, making comparisons between studies difficult, which prevented meta-analyses and limited us to a narrative synthesis. The large variation arose from the many ways MM is defined, the way outcomes are reported and the varying methods of statistical analyses. Another limitation of our review is that we did not explore the effects of specific multimorbid conditions on our outcomes of interest. While specific comorbidities such as diabetic nephropathy may potentially have contributed to hypoglycaemia as an endpoint in the included studies we were not able to explore this. Our focus is on the overall burden of illness experienced by people with T2D in the form of a MM count. The impact of specific conditions on outcomes in people with MM could be explored in future studies.

Conclusions

We have reviewed the existing literature to provide a comprehensive summary of the effects of MM count in people with T2D on all-cause mortality and glycaemic outcomes. Our findings show that MM is significantly associated with increased mortality and hypoglycaemia. However, the effects of MM on other measures of glycaemic control, particularly HbA1c, is mixed.

Our review findings emphasise the need for clinical guidelines and clinicians to support a holistic approach to the complex care needs of those with T2D living MM, where care of the whole person should be the primary concern, an approach that accounts for the full range of conditions that people with T2D may be living with.

Supporting information

S1 Table. Inclusion and exclusion criteria for papers.
(DOCX)

S2 Table. Participant detail.
(XLSX)

S3 Table. Summary of methods and results.
(XLSX)

S1 Text. Search strategy.
(DOCX)

S2 Text. Adapted Newcastle-Ottawa quality assessment scale.
(DOCX)

S3 Text. PRISMA-P Checklist statement.
(DOC)

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5.1 Summary of Findings

The key findings of the systematic review were:

1. Increasing numerical counts of multimorbidity are significantly associated with increased all-cause mortality, irrespective of multimorbidity measures, study settings, designs and methodologies used.
2. Associations between multimorbidity and HbA1c are unclear and studies provide contradictory findings.
3. No publications exploring the relationship between multimorbidity, glycaemic variability and time-in-range were identified
4. Well-designed comparative studies of separate measures of multimorbidity (including concordant and discordant conditions) and studies of glycaemic variability and time-in-range are warranted for future research.

My systematic review has set a valuable foundation of knowledge of the current understanding of multimorbidity in people with type 2 diabetes. However, more work needs to be done to explore in more detail the relationship between multimorbidity and outcomes in diabetes, particularly exploring separate measures of multimorbidity and to further clarify their associations with glycaemic outcomes.

In the following three chapters of my thesis I present findings from my three quantitative studies where I addressed important issues and research gaps identified in my literature review and systematic review findings.

6: Paper 3 – Multimorbidity, mortality and HbA1c in type 2 diabetes: a cohort study with UK and Taiwanese cohorts

In this chapter I present a study that aimed to explore associations between multimorbidity, mortality and HbA1c in population cohorts of people with type 2 diabetes in the UK Biobank and Taiwan NDCMP.

This paper appears overleaf and has been published with the following citation: Chiang, J.I., Hanlon, P., Li, T.C., Jani, B.D., Manski-Nankervis, J., Furler, J., et al. Multimorbidity, mortality and HbA1c in type 2 diabetes: a cohort study with UK and Taiwanese cohorts. PLoS Med. 2020;17(5): e1003094.

All supplementary files referred to in the paper are available in the Appendix (see Section 12.3).

After the paper I show the results of additional analyses I conducted with the Taiwan NDCMP. In this cohort I was able to explore the associations between multimorbidity and long-term glycaemic variability which was measured by CV of HbA1c measurements from clinical visits within the first year of the index date. Exploration of long-term glycaemic variability was only possible in the Taiwan NDCMP. I decided to present the long-term glycaemic variability results separately instead of including them in the paper in an effort to maintain consistency and comparability of the outcomes explored in both the UK Biobank and the Taiwan NDCMP, and also across my PhD studies.

PLOS MEDICINE

RESEARCH ARTICLE

Multimorbidity, mortality, and HbA1c in type 2 diabetes: A cohort study with UK and Taiwanese cohorts

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OPEN ACCESS

Citation: Chiang JI, Hanlon P, Li T-C, Jani BD, Manski-Nankervis J-A, Furler J, et al. (2020) Multimorbidity, mortality, and HbA1c in type 2 diabetes: A cohort study with UK and Taiwanese cohorts. PLoS Med 17(5): e1003094. https://doi.org/10.1371/journal.pmed.1003094

Academic Editor: Ronald Ching Wan Ma, Chinese University of Hong Kong, CHINA

Received: September 11, 2019

Accepted: April 10, 2020

Published: May 7, 2020

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pmed.1003094

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Abstract

Background

There is emerging interest in multimorbidity in type 2 diabetes (T2D), which can be either concordant (T2D related) or discordant (unrelated), as a way of understanding the burden of disease in T2D. Current diabetes guidelines acknowledge the complex nature of multimorbidity, the management of which should be based on the patient's individual clinical needs and comorbidities. However, although associations between multimorbidity, glycated haemoglobin (HbA1c), and mortality in people with T2D have been studied to some extent, significant gaps remain, particularly regarding different patterns of multimorbidity, including concordant and discordant conditions. This study explores associations between multimorbidity (total condition counts/concordant/discordant/different combinations of conditions), baseline HbA1c, and all-cause mortality in T2D.

Methods and findings

We studied two longitudinal cohorts of people with T2D using the UK Biobank ($n = 20,569$) and the Taiwan National Diabetes Care Management Program (NDCMP) ($n = 59,657$). The number of conditions in addition to T2D was used to quantify total multimorbidity, concordant, and discordant counts, and the effects of different combinations of conditions were also studied. Outcomes of interest were baseline HbA1c and all-cause mortality. For the UK Biobank and Taiwan NDCMP, mean (SD) ages were 60.2 (6.8) years and 60.8 (11.3) years; 7,579 (36.8%) and 31,339 (52.5%) were female; body mass index (BMI) medians (IQR) were 30.8 (27.7, 34.8) kg/m^2 and 25.6 (23.5, 28.7) kg/m^2; and 2,197 (10.8%) and 9,423 (15.8) were current smokers, respectively. Increasing total and discordant multimorbidity counts were associated with lower HbA1c and increased mortality in both datasets. In Taiwan NDCMP, for those with four or more additional conditions compared with T2D only, the mean difference (95% CI) in HbA1c was −0.82% (−0.88, −0.76) $p < 0.001$. In UK Biobank, hazard ratios (HRs) (95% CI) for all-cause mortality in people with T2D and one, two, three,

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HbA1c, glycated haemoglobin; HES, Hospital Episode Statistics; HF, heart failure; HR, hazard ratio; ICD, International Classification of Disease; NDCMP, National Diabetes Care Management Program; NTD, New Taiwan dollar; OAD, oral antidiabetes drug; PVD, peripheral vascular disease; T2D, type 2 diabetes; TIA, transient ischaemic attack..

and four or more additional conditions compared with those without comorbidity were 1.20 (0.91–1.56) $p < 0.001$, 1.75 (1.35–2.27) $p < 0.001$, 2.17 (1.67–2.81) $p < 0.001$, and 3.14 (2.43–4.03) $p < 0.001$, respectively. Both concordant/discordant conditions were significantly associated with mortality; however, HRs were largest for concordant conditions. Those with four or more concordant conditions had >5 times the mortality (5.83 [4.28–7.93] $p < 0.001$). HRs for NDCMP were similar to those from UK Biobank for all multimorbidity counts. For those with two conditions in addition to T2D, cardiovascular diseases featured in 18 of the top 20 combinations most highly associated with mortality in UK Biobank and 12 of the top combinations in the Taiwan NDCMP. In UK Biobank, a combination of coronary heart disease and heart failure in addition to T2D had the largest effect size on mortality, with a HR (95% CI) of 4.37 (3.59–5.32) $p < 0.001$, whereas in the Taiwan NDCMP, a combination of painful conditions and alcohol problems had the largest effect size on mortality, with an HR (95% CI) of 4.02 (3.08–5.23) $p < 0.001$. One limitation to note is that we were unable to model for changes in multimorbidity during our study period.

Conclusions

Multimorbidity patterns associated with the highest mortality differed between UK Biobank (a population predominantly comprising people of European descent) and the Taiwan NDCMP, a predominantly ethnic Chinese population. Future research should explore the mechanisms underpinning the observed relationship between increasing multimorbidity count and reduced HbA1c alongside increased mortality in people with T2D and further examine the implications of different patterns of multimorbidity across different ethnic groups. Better understanding of these issues, especially effects of condition type, will enable more effective personalisation of care.

Author summary

Why was this study done?

- People with type 2 diabetes (T2D) commonly have other coexisting chronic medical conditions ('multimorbidity'). These conditions can be either concordant (T2D related) or discordant (T2D unrelated).
- Multimorbidity is associated with higher mortality and hypoglycaemia; however, the effect of multimorbidity on glycaemia (measured by glycated haemoglobin [HbA1c]) is mixed.
- Significant knowledge gaps remain, particularly regarding the prevalence and impacts of different patterns of multimorbidity, including concordant and discordant conditions, and their associations with HbA1c and mortality.

What did the researchers do and find?

- We assessed the associations between different counts of multimorbidity, including concordant and discordant conditions, and HbA1c and the effects of different combinations of conditions on all-cause mortality in people with T2D.

- In two large community cohorts of people with T2D (UK Biobank and Taiwan National Diabetes Care Management Program [NDCMP]), we found that increasing multimorbidity is significantly associated with increased mortality and with lower HbA1c.
- The combinations of conditions with the greatest association with mortality differed between UK Biobank, a population predominantly comprising people of European descent, and the Taiwan NDCMP, a predominantly ethnic Chinese population.

What do these findings mean?

- To our knowledge, this is the first study to assess and compare the relationship between total, concordant, and discordant multimorbidity counts; HbA1c; and all-cause mortality in people with T2D or to look at the effects of such a range of combinations of comorbid conditions.
- Our findings suggest the need for further research to explore the effects of different combinations of conditions on outcomes in those with T2D across different ethnic groups.
- Our findings suggest that poor glycaemic control is unlikely to explain the increased mortality seen in those with increasing multimorbidity count.

Introduction

Multimorbidity, the presence of two or more chronic conditions [1], is the norm in people with type 2 diabetes (T2D). Approximately 85% of people with T2D have at least one other chronic condition [2], making multimorbidity in this population an important clinical and public health priority. Multimorbidity brings many challenges, including difficulties in managing the competing demands of multiple conditions. Self-management of any chronic condition can be burdensome, and those with multimorbidity are likely to experience greater levels of treatment burden because of the complex self-management requirements imposed by different conditions [3]. This can result in reduced adherence to complicated therapeutic regimens and poorer outcomes [4]. For people with T2D, this could lead to suboptimal glycaemic management, which has been shown to result in the development of complications and increased mortality [5,6].

Currently, there is no universally accepted measure of multimorbidity. Despite this, studies using a range of different methodologies in varying study settings consistently show that multimorbidity in people with T2D is associated with higher risk of death [7]. However, only one study attempted to assess the influence of type of condition included in their multimorbidity count by differentiating between physical and mental health condition counts [8]. This resonates with the wider multimorbidity literature, which suggests that type as well as number of conditions is important [1]. Piette and Kerr have suggested that multiple conditions in those with T2D should be qualitatively assessed as concordant or discordant [5]. Concordant conditions are closely related to T2D and represent parts of the same overall pathophysiologic risk profile and are more likely to be the focus of the same disease and management plan (e.g., hypertension), whereas discordant conditions are not directly related in either their pathogenesis or management (e.g., depression, osteoarthritis, and cancer) [5].

Although the associations between multimorbidity, glycated haemoglobin (HbA1c) [7,9], and all-cause mortality [7,8,10] in people with T2D have been studied to some extent,

significant gaps remain in the existing literature, particularly regarding different patterns of multimorbidity, including concordant and discordant conditions, and their associations with HbA1c and mortality. This study addresses this evidence gap and aims to assess the associations between different counts of multimorbidity, including concordant and discordant conditions, on HbA1c and all-cause mortality in people with T2D. We also aim to understand whether associations between multimorbidity and our outcomes are universally consistent across separate cohorts from two countries with different healthcare systems and differing ethnicities, using data from the UK Biobank (a large community cohort of more than half a million people across the United Kingdom) [11] and the Taiwan National Diabetes Care Management Program (NDCMP) (a large cohort of people with T2D across Taiwan) [12].

Methods

Study design and participants

Two large community cohorts were used in this study. The UK Biobank (described elsewhere) [11] includes 502,640 participants recruited between 2006 and 2010, with linkage to routine healthcare data until 2018. We identified 20,569 people with T2D using a published algorithm developed by Eastwood and colleagues [13], which has been validated externally using primary and secondary care hospital data linked to the UK Biobank [13]. All 20,569 people with T2D in the UK Biobank were included in the statistical analysis.

The Taiwan NDCMP (described elsewhere) [12] includes 63,084 ethnic Chinese participants with any type of diabetes recruited between 2001 and 2004 and followed until 2011. We excluded those with type 1 diabetes and gestational diabetes. In the final analysis, 59,657 people with T2D from the Taiwan NDCMP were included.

Ethics approvals were granted by the NHS National Research Ethics Service (generic ethics approval for UK Biobank studies, approval letter dated 17 June 2011, Ref 11/NW/0382), the China Medical University Hospital Ethical Review Board (CMUH106-REC1-148), and the University of Melbourne Human Research Ethics Committee (Ethic ID: 1851038.1). Our detailed study protocol is shown in S1 Text, and we have adhered to the STROBE statement (see S2 Text).

Procedures

We classified multimorbidity on the basis of a count of 42 chronic conditions in addition to T2D based on previously published literature (see S1 Table) [1]. In the UK Biobank, conditions were identified using self-reported conditions from the nurse-led interview as well as using linkage to Hospital Episode Statistics (HES). Participants were considered to have a condition if it was either self-reported or if they had relevant International Classification of Disease (ICD)-10-CM codes from a hospital episode occurring prior to the assessment centre date. In the Taiwan NDCMP, conditions were identified using ICD-9-CM codes to search hospital data from inpatient care and outpatient visits including primary care. We qualitatively assessed each of the comorbid conditions and categorised these as either concordant or discordant based on Piette and Kerr's [5] definitions mentioned previously. We presented multimorbidity in three ways: total, concordant, and discordant condition counts. Each of the counts were categorised into zero, one, two, three, or four or more conditions (in addition to T2D).

In both datasets, age, body mass index (BMI), duration of diabetes, and baseline HbA1c were used as continuous variables. Sex and use of corticosteroids were used as categorical variables. Use of glucose-lowering drugs was classified into no medication, one noninsulin antidiabetic drug (oral antidiabetes drug [OAD]), two OADs, three OADs, more than three OADs, insulin only, or insulin and OAD.

In the UK Biobank, socioeconomic status was classified into quintiles based on Townsend score (an area-based measure of deprivation in the UK) on the whole UK Biobank [14]: category 1 was the least deprived, and category 5 was the most deprived category. Smoking status was classified into two categories: yes (current) or no. Alcohol intake was based on self-reported frequency of alcohol intake: never or special occasions only, one to three times per month, one to four times per week, or daily. Physical activity was self-reported based on responses from the UK Biobank physical activity questionnaire. We categorised the responses into none (no physical activity in the last 4 weeks), low (light activity [e.g., pruning, watering the lawn] only in the last 4 weeks), medium (heavy activity [e.g., weeding, lawn mowing, carpentry, and digging] and/or walking for pleasure and/or other exercises in the last 4 weeks), or high (strenuous sports in the last 4 weeks). Data on physical activity were only available in the UK Biobank dataset.

In the Taiwan NDCMP, socioeconomic status was measured by amount of health insurance premium, insured unit, and residential area. Smoking status and alcohol consumption were classified into two categories: yes (current) or no. Number of outpatient visits was used as a continuous variable and was only available in the Taiwan NDCMP dataset.

Outcome

There were two outcomes of interest: baseline HbA1c and all-cause mortality. We explored the cross-sectional association between multimorbidity counts and the most recent HbA1c measure collected at time of recruitment. In contrast, the association between multimorbidity counts and all-cause mortality explored was longitudinal. In the UK Biobank, all-cause mortality data were from the national mortality records linked by the UK Biobank up to 2018. The median (IQR) follow-up duration was 8.8 years (97–104 months). In the Taiwan NDCMP, all participants were followed from time of entry into the study to 31 December 2011 or until death or withdrawal from the NDCMP. The median (IQR) follow-up duration was 8.8 years (98–110 months).

Statistical analysis

Statistical analyses for the UK Biobank and the Taiwan NDCMP cohorts were conducted separately. Descriptive statistics summarised the overall characteristics of the participants and the prevalence of individual health conditions.

Multivariable linear regression models were used to compare baseline HbA1c between different categorical combinations of multimorbidity counts (total condition count, concordant condition count, discordant condition count). Adjustments were made for age, gender, BMI, smoking status, alcohol consumption, socioeconomic status, duration of diabetes, use of OADs, and use of corticosteroids.

Cumulative survival plots were used to compare cumulative survival between participants with T2D with different multimorbidity counts. This was done for total condition count, concordant condition count, and discordant condition count.

Multivariable Cox proportional hazards models were used to compare all-cause mortality between different categorical combinations of multimorbidity counts (total condition count, concordant condition count, discordant condition count). Adjustments made were the same as those described above plus baseline HbA1c.

Multivariable Cox proportional hazards models were fitted to each of the individual chronic conditions that had a prevalence of >1% in our study population to examine their association with all-cause mortality.

Multivariable Cox proportional hazards models were fitted to all possible combinations of two conditions in addition to T2D to examine their association with all-cause mortality. We present the top 20 combinations in terms of hazard ratios (HRs).

For the UK Biobank, all analyses were performed using R software (version 3.4.1). Syntax for the generation of derived variables and for the analysis used for this study were submitted to UK Biobank for record. For the Taiwan NDCMP, all analyses were performed with the SAS statistical package for Windows (version 9.3, SAS; Cary, NC, United States).

Sensitivity analysis

For the multivariable linear regression models on HbA1c and multivariable Cox proportional hazards models on mortality, we further adjusted for variables that were only available in each of the datasets. In the UK Biobank analyses, we additionally adjusted for physical activity, and for the Taiwan NDCMP, we additionally adjusted for number of outpatient visits.

For the multivariable linear regression models on HbA1c and multivariable Cox proportional hazards models on mortality in the UK Biobank, we reran the models using only HES data to identify multimorbidity.

Results

In total, 20,569 and 59,657 people with T2D in the UK Biobank and the Taiwan NDCMP, respectively, were included in the study for analysis. In the UK Biobank, more than 90% of participants were multimorbid (having at least one chronic condition in addition to T2D), whereas approximately 80% of those in the Taiwan NDCMP were multimorbid. Table 1 describes the overall characteristics of participants included in our study.

Table 2 shows the prevalence of individual conditions included in our multimorbidity total, concordant, and discordant counts. In the UK Biobank, 15,654 (76.1%) participants had at least one concordant condition, and 13,753 (66.9%) had at least one discordant condition in addition to T2D. In the Taiwan NDCMP, a slightly lower proportion of participants had at least one concordant condition (57.2%), and a similar proportion had at least one discordant condition compared (58.0%) with the UK Biobank. The most prevalent condition was hypertension, with a prevalence of 69.0% and 48.2%, respectively.

Table 3 shows the mean difference in HbA1c between participants with different multimorbidity counts. Participants with T2D only were the reference group. In both the UK Biobank and the Taiwan NDCMP, increasing total multimorbidity and discordant counts were associated with lower HbA1c. Notably, the mean difference in HbA1c was greater in the Taiwan NDCMP compared with the UK Biobank. For concordant conditions, associations between increasing concordant counts and lower HbA1c were only observed in the Taiwan NDCMP, whereas there was no association in the UK Biobank. In the sensitivity analysis, when physical activity was additionally adjusted for in the UK Biobank, the results were similar. However, when the number of outpatient visits was additionally adjusted for in the Taiwan NDCMP, the associations between all multimorbidity counts and HbA1c attenuated slightly (S2 Table). When we used only the HES data to identify multimorbidity in the UK Biobank, the results for associations between multimorbidity and HbA1c were similar to our main analysis (S4 Table).

Fig 1 compares the unadjusted survival among the study participants on the basis of total multimorbidity, concordant, and discordant condition counts, respectively. For a given count of concordant conditions, mortality was higher (or survival lower) than for an equivalent count of discordant conditions or any conditions. Notably, in all three counts of multimorbidity (total, concordant, and discordant) the survival rate in the Taiwan NDCMP compared with the UK Biobank was much lower, with a steeper increase in proportion of death.

Table 1. Characteristics of participants with T2D.

UK Biobank (*N* = 20,569)	
Age (years), mean (SD)	60.2 (6.8)
Female, *n* (%)	7,579 (36.8)
BMI (kg/m^2), median (IQR)	30.8 (27.7, 34.8)
Missing	179
Smoking status, yes (current), *n* (%)	2,197 (10.8)
Missing	223
Alcohol frequency, *n* (%)	
Never	7,154 (34.9)
1–3 times per month	2,521 (12.3)
1–4 times per week	7,851 (38.3)
Daily	2,946 (14.4)
Missing	97
Physical activity, *n* (%)	
None	2,830 (14.1)
Low	1,209 (6.0)
Medium	15,322 (76.4)
High	684 (3.4)
Missing	524
Baseline HbA1c (%), mean (SD)	6.8 (1.2)
Missing	1,597
Duration of diabetes (years), median (IQR)	4 (2, 8)
Type of glucose-lowering drug use, *n* (%)	
No medication	6,778 (33.0)
1 OAD	8,036 (39.1)
2 OADs	4,412 (21.4)
3 OADs	715 (3.5)
>3 OADs	9 (0.0)
Insulin + OAD	619 (3.0)
Use of corticosteroids, *n* (%)	203 (0.0)
Townsend score, *n* (%)	
Category 1—least deprived	2,993 (14.6)
Category 2	3,315 (16.1)
Category 3	3,687 (18.0)
Category 4	4,334 (21.1)
Category 5—most deprived	6,209 (30.2)
Missing	31
Number of chronic conditions, *n* (%)	
None	1,918 (9.3)
1	5,114 (24.9)
2	5,109 (24.8)
3	3,643 (17.7)
≥4	4,785 (23.3)
Taiwan NDCMP (*N* = 59,657)	
Age (years), mean (SD)	60.8 (11.3)
Female, *n* (%)	31,339 (52.5)
BMI (kg/m^2), median (IQR)	25.6 (23.5, 28.7)
Missing	1,376

(*Continued*)

Table 1. (Continued)

UK Biobank (N = 20,569)	
Smoking status, yes (current), *n* (%)	9,423 (15.8)
Missing	45
Alcohol consumption, yes, *n* (%)	5,140 (8.6)
Missing	55
Baseline HbA1c (%), mean (SD)	8.2 (2.0)
Missing	276
Duration of diabetes (years), median (IQR)	5 (1, 9)
Type of glucose-lowering drug use, *n* (%)	
No medication	1,880 (3.2)
1 OAD	10,714 (18.0)
2 OADs	24,401 (40.9)
3 OADs	10,361 (17.4)
>3 OADs	3,000 (5.0)
Insulin use	1,719 (2.9)
Insulin + OAD	7,582 (12.7)
Use of corticosteroids, *n* (%)	2,964 (5.0)
Urbanisation level, *n* (%)	
1—most deprived	12,495 (21.0)
2	18,962 (31.9)
3	10,504 (17.7)
4	11,735 (19.7)
>4—least deprived	5,808 (9.8)
Missing	153
Amount of insured premium (NTD$ per month), median (IQR)	21,900 (1,317, 31,800)
Insured unit, *n* (%)	
Government, school, or private enterprise employees	20,491 (34.5)
Member of occupational, farmers, fishermen groups	24,625 (41.5)
Low-income households and veterans	14,206 (24.0)
Missing	335
Number of outpatient visits, mean (SD)	23.75 (15.4)
Number of chronic conditions, *n* (%)	
None	12,950 (21.7)
1	15,485 (26.0)
2	15,139 (25.4)
3	8,330 (14.0)
≥4	7,753 (13.0)

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; NDCMP, National Diabetes Care Management Program; NTD, New Taiwan dollar; OAD, oral antidiabetes drug; T2D, type 2 diabetes

https://doi.org/10.1371/journal.pmed.1003094.t001

Table 4 shows the unadjusted and adjusted HRs comparing categories of total, concordant, and discordant multimorbidity counts with T2D and all-cause mortality (with a reference group of those with T2D only). In both the UK Biobank and the Taiwan NDCMP, increasing total, concordant, and discordant multimorbidity counts were all significantly associated with increased all-cause mortality. In the UK Biobank, the HRs (95% CI) for having one, two, three, and four or more total multimorbidity conditions compared with those with T2D only were 1.20 (0.91–1.56) $p < 0.001$, 1.75 (1.35–2.27) $p < 0.001$, 2.17 (1.67–2.81) $p < 0.001$, and 3.14

Table 2. Prevalence of individual multimorbid conditions in participants with T2D.

Presence of chronic conditions concordant with T2D, *n* (%)	**UK Biobank (*N* = 20,569)**	**Taiwan NDCMP (*N* = 59,657)**
At least one chronic condition concordant with diabetes	15,654 (76.1)	34,111 (57.2)
Hypertension	14,187 (69.0)	28,771 (48.2)
Coronary heart disease	3,773 (18.3)	8,639 (14.5)
Peripheral vascular disease	488 (2.4)	1,711 (2.9)
Chronic kidney disease	323 (1.6)	1,919 (3.2)
Stroke/TIA	1,024 (5.0)	4,350 (7.3)
Diabetic retinopathy	2,174 (10.6)	1,494 (2.5)
Diabetic neuropathy	74 (0.4)	642 (1.1)
Atrial fibrillation	641 (3.1)	472 (0.8)
Heart failure	426 (2.1)	1,394 (2.3)
Presence of chronic conditions discordant with T2D, *n* (%)	**UK Biobank (*N* = 20,569)**	**Taiwan NDCMP (*N* = 59,657)**
At least one chronic condition discordant with diabetes	13,753 (66.9)	34,592 (58.0)
Depression	1,643 (8.0)	628 (1.1)
Painful conditions (excluding diabetic neuropathy)	6,250 (30.4)	13,754 (23.1)
Asthma	2,959 (14.4)	1,404 (2.4)
Dyspepsia	3,815 (18.5)	12,297 (20.6)
Thyroid disorders	1,688 (8.2)	1,618 (2.7)
Rheumatoid arthritis and other connective tissue disorders	618 (3.0)	309 (0.5)
COPD	841 (4.1)	4,000 (6.7)
Anxiety	509 (2.5)	3,398 (5.7)
Irritable bowel syndrome	500 (2.4)	636 (1.1)
Cancer	2,110 (10.3)	1,107 (1.9)
Alcohol problems	427 (2.1)	370 (0.6)
Other psychoactive substance misuse	13 (0.1)	23 (0.0)
Constipation	288 (1.4)	2,670 (4.5)
Diverticular disease	1,056 (5.1)	86 (0.1)
Prostate disorders	890 (4.3)	2,513 (4.2)
Glaucoma	458 (2.2)	305 (0.5)
Epilepsy	211 (1.0)	135 (0.2)
Dementia	10 (0.0)	330 (0.6)
Schizophrenia/bipolar disorder	187 (0.9)	380 (0.6)
Psoriasis/eczema	792 (3.9)	1,704 (2.9)
Inflammatory bowel disease	924 (4.5)	24 (0.0)
Migraine	306 (1.5)	162 (0.3)
Chronic sinusitis	176 (0.9)	152 (0.3)
Anorexia/bulimia	2 (0.0)	148 (0.3)
Bronchiectasis	56 (0.3)	162 (0.3)
Parkinson disease	42 (0.2)	309 (0.5)
Multiple sclerosis	71 (0.3)	4 (0.0)
Viral hepatitis	56 (0.3)	1,263 (2.1)
Chronic liver disease	326 (1.6)	7,047 (11.8)
Osteoporosis	340 (1.7)	1,322 (2.2)
Chronic fatigue syndrome	71 (0.3)	0 (0.0)
Endometriosis	162 (0.8)	100 (0.2)

(*Continued*)

Table 2. (Continued)

Meniere disease	52 (0.3)	493 (0.8)
Pernicious anaemia	134 (0.7)	31 (0.1)
Polycystic ovary	31 (0.2)	17 (0.0)

Abbreviations: COPD, chronic obstructive pulmonary disease; NDCMP, National Diabetes Care Management Program; T2D, type 2 diabetes; TIA, transient ischaemic attack

https://doi.org/10.1371/journal.pmed.1003094.t002

Table 3. Multivariable linear regression model: Relationship between HbA1c and multimorbidity in participants with type 2 diabetes.

	UK Biobank					Taiwan NDCMP				
Predictor variables		**Unadjusted**		**Adjusted***			**Unadjusted**		**Adjusted***	
Categories of diabetes and multimorbidity	**Deaths/ *N***	**Mean difference in HbA1c (95% CI)**	***P* value**	**Mean difference in HbA1c (95% CI)**	***P* value**	**Deaths/*N***	**Mean difference in HbA1c (95% CI)**	***P* value**	**Mean difference in HbA1c (95% CI)**	***P* value**
Diabetes only (reference)	79/1,918	Ref		Ref		1,493/ 12,950	Ref		Ref	
Diabetes plus 1 chronic condition	280/ 5,114	−0.07 (−0.14, −0.01)	0.024	−0.07 (−0.13, −0.01)	0.031	2,430/ 15,480	−0.49 (−0.54, −0.45)	<0.001	−0.62 (−0.67, −0.58)	<0.001
Diabetes plus 2 chronic conditions	421/ 5,109	−0.13 (−0.19, −0.06)	<0.001	−0.12 (−0.18, −0.06)	<0.001	3,318/ 15,139	−0.57 (−0.61, −0.52)	<0.001	−0.72 (−0.76, −0.67)	<0.001
Diabetes plus 3 chronic conditions	395/ 3,643	−0.11 (−0.17, −0.04)	0.002	−0.13 (−0.19, −0.06)	<0.001	2,505/ 8,330	−0.55 (−0.61, −0.49)	<0.001	−0.75 (−0.80, −0.69)	<0.001
Diabetes plus ≥4 chronic conditions	759/ 4,785	−0.16 (−0.23, −0.10)	<0.001	−0.20 (−0.26, −0.14)	<0.001	3,477/ 7,753	−0.55 (−0.60, −0.49)	<0.001	−0.82 (−0.88, −0.76)	<0.001
Categories of diabetes and concordant conditions										
Diabetes only (reference)	79/1,918	Ref		Ref		1,493/ 12,950	Ref		Ref	
Diabetes plus 1 concordant condition	768/ 10,251	−0.14 (−0.20, −0.08)	<0.001	−0.11 (−0.18, −0.06)	<0.001	5,043/ 22,407	−0.59 (−0.63, −0.54)	<0.001	−0.70 (−0.74, −0.65)	<0.001
Diabetes plus 2 concordant conditions	507/ 3,867	−0.06 (−0.12, 0.01)	0.098	−0.10 (−0.16, −0.03)	0.003	2,950/ 8,865	−0.59 (−0.65, −0.54)	<0.001	−0.74 (−0.80, −0.69)	<0.001
Diabetes plus 3 concordant conditions	247/ 1,131	−0.07 (−0.15, 0.02)	0.153	−0.13 (−0.22, −0.04)	0.003	1,140/ 2,221	−0.58 (−0.67, −0.48)	<0.001	−0.78 (−0.87, −0.69)	<0.001
Diabetes plus ≥4 concordant conditions	129/402	0.05 (−0.07, 0.19)	0.417	−0.03 (−0.16, 0.09)	0.608	427/618	−0.38 (−0.55, −0.22)	0.029	−0.66 (−0.83, −0.50)	<0.001
Categories of diabetes and discordant conditions										
Diabetes only (reference)	79/1,918	Ref		Ref		1,493/ 12,950	Ref		Ref	
Diabetes plus 1 discordant condition	574/ 6,387	−0.11 (−0.18, −0.06)	<0.001	−0.11 (−0.17, −0.04)	<0.001	4,187/ 19,177	−0.52 (−0.57, −0.48)	<0.001	−0.68 (−0.73, −0.63)	<0.001
Diabetes plus 2 discordant conditions	393/ 3,793	−0.14 (−0.20, −0.07)	<0.001	−0.14 (−0.20, −0.08)	<0.001	2,678/ 9,615	−0.52 (−0.58, −0.47)	<0.001	−0.73 (−0.78, −0.67)	<0.001
Diabetes plus 3 discordant conditions	246/ 1,951	−0.22 (−0.30, −0.14)	<0.001	−0.20 (−0.28, −0.13)	<0.001	1,335/ 3,770	−0.54 (−0.62, −0.47)	<0.001	−0.81 (−0.89, −0.74)	<0.001
Diabetes plus ≥4 discordant conditions	271/ 1,621	−0.19 (−0.27, −0.11)	<0.001	−0.23 (−0.31, −0.15)	<0.001	945/ 2,030	−0.48 (−0.57, −0.38)	<0.001	−0.79 (−0.89, −0.70)	<0.001

*Adjusting for age, gender, BMI, smoking status, alcohol consumption, socioeconomic status, duration of diabetes, use of oral antidiabetes drugs, and use of corticosteroids.

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; NDCMP, National Diabetes Care Management Program; Ref, reference

https://doi.org/10.1371/journal.pmed.1003094.t003

(2.43–4.03) $p < 0.001$, respectively. The HRs for the Taiwan NDCMP were slightly lower yet still statistically significant. For the Taiwan NDCMP, the HRs (95% CI) for having one, two, three, and four or more total multimorbidity conditions compared with those with T2D only were 1.17 (1.09–1.25) $p < 0.001$, 1.39 (1.30–1.48) $p < 0.001$, 1.79 (1.67–1.92) $p < 0.001$, and 2.50 (2.34–2.67) $p < 0.001$, respectively.

For concordant conditions, the HRs were larger compared with the HRs observed for total multimorbidity counts. In the UK Biobank, the HRs (95% CI) for having one, two, three, and four or more concordant conditions compared with those with T2D were 1.58 (1.23–2.03) $p < 0.001$, 2.41 (1.87–3.13) $p < 0.001$, 4.00 (3.03–5.27) $p < 0.001$, and 5.83 (4.28–7.93) $p < 0.001$, respectively. Again, the HRs for the Taiwan NDCMP were slightly lower yet still statistically significant. For the Taiwan NDCMP, the HRs (95% CI) for having one, two, three, and four or more concordant conditions compared with those with T2D were 1.42 (1.33–1.51) $p < 0.001$, 1.87 (1.75–2.00) $p < 0.001$, 2.80 (2.58–3.05) $p < 0.001$, and 3.79 (3.38–4.25) $p < 0.001$, respectively.

For discordant conditions, the HRs were smaller compared with the HRs observed for both total multimorbidity and concordant counts. In the UK Biobank, the HRs (95% CI) for having one, two, three, and four or more discordant conditions were 1.89 (1.46–2.43) $p < 0.001$, 2.09 (1.61–2.71) $p < 0.001$, 2.58 (1.95–3.40) $p < 0.001$, and 3.50 (2.65–4.62) $p < 0.001$, respectively. The HRs for the Taiwan NDCMP were slightly lower yet still statistically significant. For the Taiwan NDCMP, the HRs (95% CI) for having one, two, three, and four or more discordant conditions were 1.42 (1.33–1.51) $p < 0.001$, 1.64 (1.54–1.76) $p < 0.001$, 2.05 (1.89–2.22) $p < 0.001$, and 2.62 (2.40–2.86) $p < 0.001$, respectively.

For all the mortality analyses for the UK Biobank, the sensitivity analysis further adjusted for physical activity, whereas in the Taiwan NDCMP, further adjustment was made for number of outpatient visits. The sensitivity analyses made little difference to the associations between all counts of multimorbidity and mortality (S3 Table). When we used only the HES data to identify multimorbidity in the UK Biobank, the results for associations between multimorbidity and all-cause mortality were similar to our main analysis (S4 Table).

Figs 2, 3, 4 and 5 compare the adjusted HRs of the presence of individual concordant (Figs 2 and 3) and discordant conditions (Figs 4 and 5) (>1% prevalence) on mortality. All concordant conditions with the exception of diabetic retinopathy (in the UK Biobank) and diabetic neuropathy (in the Taiwan NDCMP) showed significant associations with increased mortality. Presence of heart failure (HF) had the largest HR in both datasets, with HR (95% CI) of 3.24 (2.69–3.91) $p < 0.001$ in the UK Biobank. Following HF, the presence of peripheral vascular disease (PVD), chronic kidney disease (CKD), and atrial fibrillation (AF) is associated with greater than 2-fold the risk of mortality in the UK Biobank. Similarly, both HF and CKD are also associated with greater than 2-fold the risk of mortality in the Taiwan NDCMP.

Among discordant conditions, presence of alcohol problems (alcohol dependency, alcoholic liver disease/alcoholic cirrhosis) (HR 2.58, 95% CI 2.07–3.21, $p < 0.001$), chronic liver disease (HR 2.29, 95% CI 1.75–3.01, $p < 0.001$), chronic obstructive pulmonary disease (COPD) (HR 2.00, 95% CI 1.69–2.36, $p < 0.001$), and cancer (HR 1.79, 95% CI 1.58–2.04, $p < 0.001$) had the largest HRs in the UK Biobank, all of which were associated with greater than 1.5-fold the risk of mortality, whereas presence of cancer (HR 2.25, 95% CI 2.06–2.45, $p < 0.001$) and viral hepatitis (HR 2.00, 95% CI 1.81–2.20, $p < 0.001$) had the largest HRs in the Taiwan NDCMP.

Figs 6 and 7 compare the adjusted HRs of the presence of the top 20 combinations (by effect size) of two conditions and all-cause mortality in the UK Biobank (Fig 6) and the Taiwan NDCMP (Fig 7). Cardiovascular diseases are present in 18 of the top 20 combinations on mortality in the UK Biobank, whereas in the Taiwan NDCMP, cardiovascular diseases are present

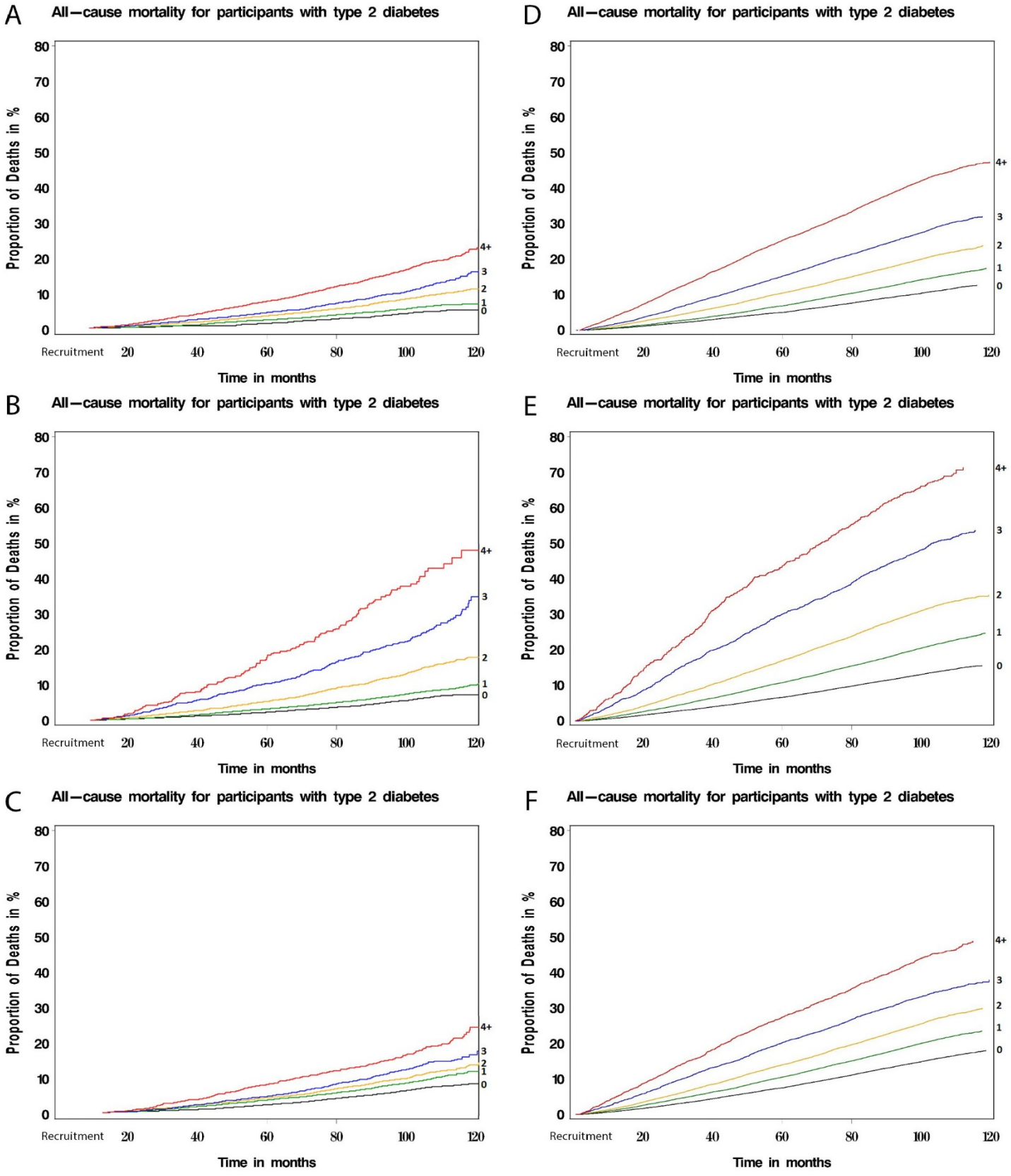
A
All—cause mortality for participants with type 2 diabetes
Proportion of Deaths in %
Recruitment
Time in months
4+
3
2
1
0
B
All—cause mortality for participants with type 2 diabetes
Proportion of Deaths in %
Recruitment
Time in months
4+
3
2
1
0
C
All—cause mortality for participants with type 2 diabetes
Proportion of Deaths in %
Recruitment
Time in months
4+
3
2
1
0
D
All—cause mortality for participants with type 2 diabetes
Proportion of Deaths in %
Recruitment
Time in months
4+
3
2
1
0
E
All—cause mortality for participants with type 2 diabetes
Proportion of Deaths in %
Recruitment
Time in months
4+
3
2
1
0
F
All—cause mortality for participants with type 2 diabetes
Proportion of Deaths in %
Recruitment
Time in months
4+
3
2
1
0

Fig 1. Cumulative survival plot showing probability of all-cause mortality among type 2 diabetes participants with different levels of multimorbidity. (A) Total multimorbid conditions in UK Biobank; (B) concordant conditions in UK Biobank; (C) discordant conditions in UK Biobank; (D) total multimorbid conditions in Taiwan NDCMP; (E) concordant conditions in Taiwan NDCMP; (F) discordant conditions in Taiwan NDCMP. NDCMP, National Diabetes Care Management Program.

https://doi.org/10.1371/journal.pmed.1003094.g001

in 12 of the top 20 combinations on mortality. In the UK Biobank, a combination of coronary heart disease (CHD) and HF had the largest effect size on mortality, with HR (95% CI) of 4.37 (3.59–5.32) $p < 0.001$. Following the combination of CHD and HF, the CHD–CKD and HF–dyspepsia combinations are each associated with greater than 4-fold the risk of mortality in the UK Biobank. The remaining top 20 combinations of conditions in the UK Biobank had greater

Table 4. Cox's proportional hazards model: Relationship between all-cause mortality and multimorbidity in participants with type 2 diabetes.

	UK Biobank					Taiwan NDCMP				
Predictor variables		**Unadjusted**		**Adjusted***			**Unadjusted**		**Adjusted***	
Categories of diabetes and multimorbidity	**Deaths/*N***	**HRs (95% CI)**	***P* value**	**HRs (95% CI)**	***P* value**	**Deaths/*N***	**HRs (95% CI)**	***P* value**	**HRs (95% CI)**	***P* value**
Diabetes only (reference)	79/1,918	1		1		1,493/12,950	1		1	
Diabetes plus 1 chronic condition	280/5,114	1.33 (1.04–1.71)	0.024	1.20 (0.91–1.56)	<0.001	2,430/15,480	1.38 (1.29–1.47)	<0.001	1.17 (1.09–1.25)	<0.001
Diabetes plus 2 chronic conditions	421/5,109	2.04 (1.61–2.60)	<0.001	1.75 (1.35–2.27)	<0.001	3,318/15,139	2.00 (1.88–2.13)	<0.001	1.39 (1.30–1.48)	<0.001
Diabetes plus 3 chronic conditions	395/3,643	2.73 (2.14–3.48)	<0.001	2.17 (1.67–2.81)	<0.001	2,505/8,330	2.90 (2.72–3.01)	<0.001	1.79 (1.67–1.92)	<0.001
Diabetes plus ≥4 chronic conditions	759/4,785	4.14 (3.28–5.22)	<0.001	3.14 (2.43–4.03)	<0.001	3,477/7,753	4.89 (4.60–5.20)	<0.001	2.50 (2.34–2.67)	<0.001
Categories of diabetes and concordant conditions										
Diabetes only (reference)	79/1,918	1		1		1,493/12,950	1		1	
Diabetes plus 1 concordant condition	768/10,251	1.84 (1.46–2.32)	<0.001	1.58 (1.23–2.03)	<0.001	5,043/22,407	2.06 (1.95–2.18)	<0.001	1.42 (1.33–1.51)	<0.001
Diabetes plus 2 concordant conditions	507/3,867	3.35 (2.64–4.24)	<0.001	2.41 (1.87–3.13)	<0.001	2,950/8,865	3.29 (3.09–3.50)	<0.001	1.87 (1.75–2.00)	<0.001
Diabetes plus 3 concordant conditions	247/1,131	5.90 (4.58–7.61)	<0.001	4.00 (3.03–5.27)	<0.001	1,140/2,221	5.94 (5.50–6.42)	<0.001	2.80 (2.58–3.05)	<0.001
Diabetes plus ≥4 concordant conditions	129/402	9.51 (7.18–12.58)	<0.001	5.83 (4.28–7.93)	<0.001	427/618	9.83 (8.83–10.95)	<0.001	3.79 (3.38–4.25)	<0.001
Categories of diabetes and discordant conditions										
Diabetes only (reference)	79/1,918	1		1		1,493/12,950	1		1	
Diabetes plus 1 discordant condition	574/6,387	2.23 (1.77–2.83)	<0.001	1.89 (1.46–2.43)	<0.001	4,187/19,177	1.99 (1.88–2.11)	<0.001	1.42 (1.33–1.51)	<0.001
Diabetes plus 2 discordant conditions	393/3,793	2.62 (2.06–3.33)	<0.001	2.09 (1.61–2.71)	<0.001	2,678/9,615	2.64 (2.48–2.81)	<0.001	1.64 (1.54–1.76)	<0.001
Diabetes plus 3 discordant conditions	246/1,951	3.22 (2.50–4.14)	<0.001	2.58 (1.95–3.40)	<0.001	1,335/3,770	3.59 (3.34–3.87)	<0.001	2.05 (1.89–2.22)	<0.001
Diabetes plus ≥4 discordant conditions	271/1,621	4.39 (3.42–5.64)	<0.001	3.50 (2.65–4.62)	<0.001	945/2,030	5.17 (4.76–5.61)	<0.001	2.62 (2.40–2.86)	<0.001

*Adjusting for age, gender, BMI, smoking status, alcohol consumption, socioeconomic status, baseline HbA1c, duration of diabetes, use of oral antidiabetes drugs, and use of corticosteroids.

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; HR, hazard ratio; NDCMP, National Diabetes Care Management Program

https://doi.org/10.1371/journal.pmed.1003094.t004

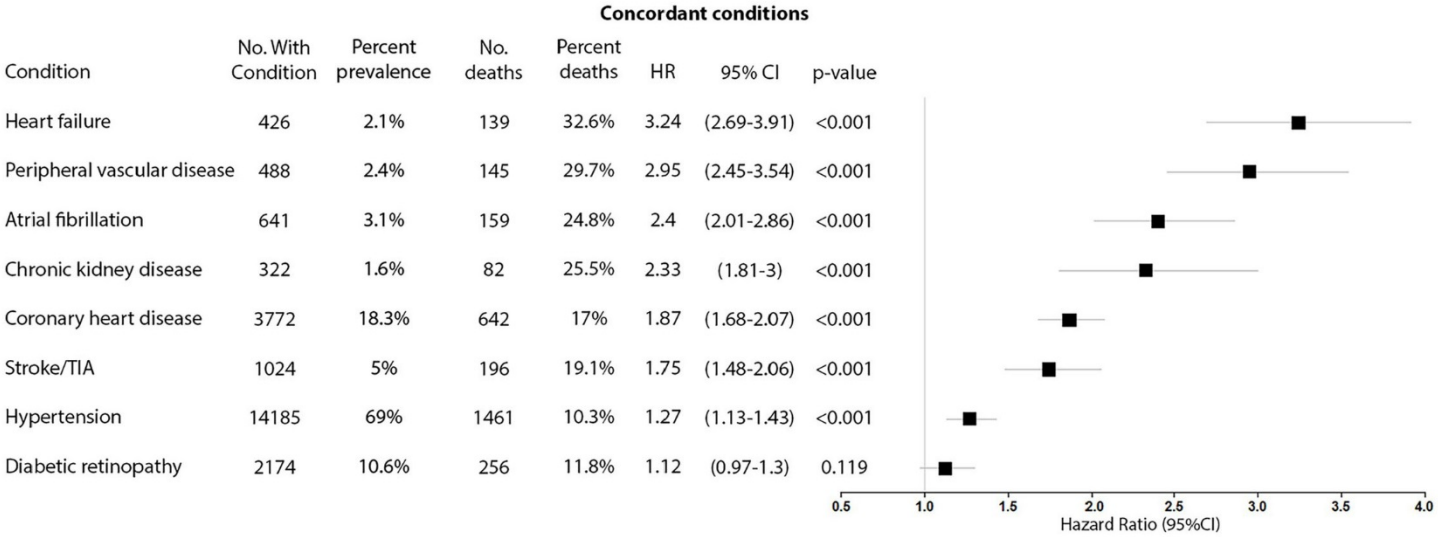

Fig 2. Forest plot of HR for the presence of different concordant conditions (prevalence >1%) and all-cause mortality in participants with type 2 diabetes in UK Biobank. HR, hazard ratio; No., number; TIA, transient ischaemic attack.

https://doi.org/10.1371/journal.pmed.1003094.g002

than 2.5-fold risk of mortality. In the Taiwan NDCMP, a combination of painful conditions and alcohol problems had the largest effect size on mortality, with HR (95% CI) of 4.02 (3.08–5.23) $p < 0.001$. Following that, combinations of dyspepsia and alcohol problems, cancer and chronic liver disease, alcohol problems and chronic liver disease, and HF and asthma are associated with greater than 3-fold the risk of mortality. The remaining top 20 combinations of conditions in the Taiwan NDCMP had greater than 2-fold risk of mortality.

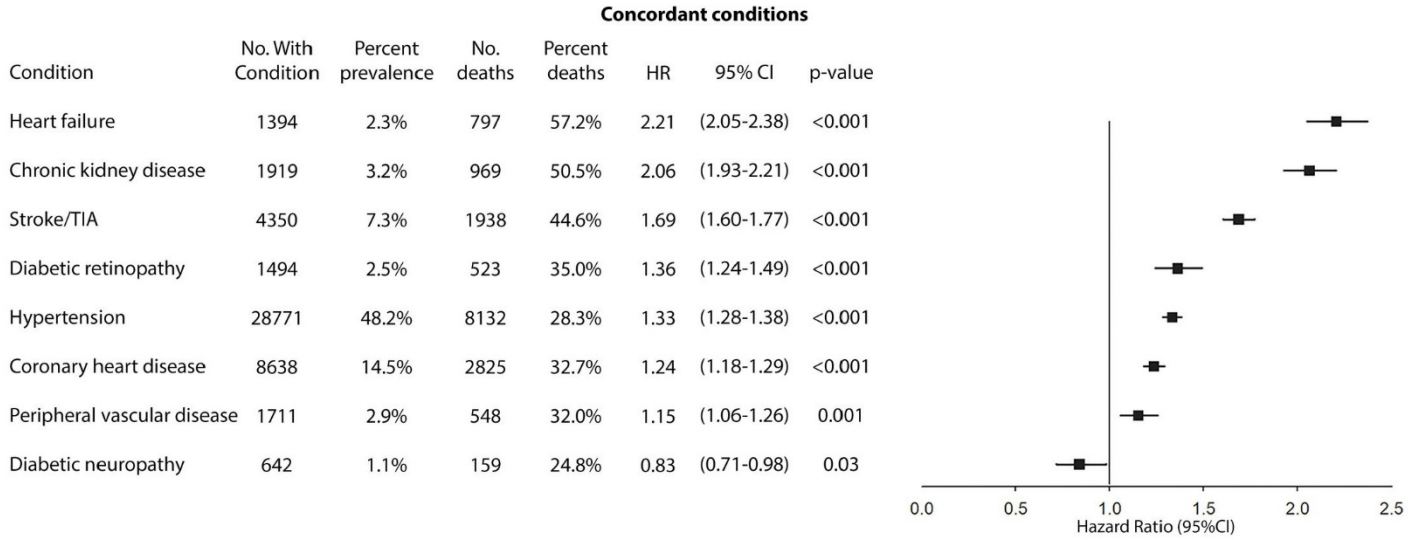

Fig 3. Forest plot of HR for the presence of different concordant conditions (prevalence >1%) and all-cause mortality in participants with type 2 diabetes in Taiwan NDCMP. HR, hazard ratio; NDCMP, National Diabetes Care Management Program; No., number; TIA, transient ischaemic attack.

https://doi.org/10.1371/journal.pmed.1003094.g003

Concordant conditions

Condition	No. With Condition	Percent prevalence	No. deaths	Percent deaths	HR	95% CI	p-value
Alcohol problems	427	2.1%	110	25.8%	2.58	(2.07-3.21)	<0.001
Chronic Liver disease	326	1.6%	76	23.3%	2.29	(1.75-3.01)	<0.001
COPD	841	4.1%	190	22.6%	2	(1.69-2.36)	<0.001
Cancer	2110	10.3%	345	16.4%	1.79	(1.58-2.04)	<0.001
Inflammatory bowel disease	924	4.5%	128	13.9%	1.56	(1.28-1.89)	<0.001
Depression	1643	8%	198	12.1%	1.41	(1.2-1.66)	<0.001
Anxiety	509	2.5%	60	11.8%	1.39	(1.05-1.84)	0.002
Psoriasis/eczema	792	3.9%	92	11.6%	1.32	(1.06-1.65)	0.012
Dyspepsia	3815	18.5%	455	11.9%	1.3	(1.16-1.46)	<0.001
Constipation	288	1.4%	37	12.8%	1.25	(0.86-1.82)	0.241
Thyroid disorders	1687	8.2%	160	9.5%	1.24	(1.04-1.49)	0.015
Asthma	2959	14.4%	315	10.6%	1.22	(1.07-1.39)	0.003
Rheumatoid arthritis and other connective tissue disorders	618	3%	79	12.8%	1.15	(0.89-1.5)	0.286
Glaucoma	458	2.2%	55	12%	1.14	(0.85-1.52)	0.389
Diverticular disease	1056	5.1%	124	11.7%	1.09	(0.89-1.32)	0.414
Painful conditions	6250	30.4%	642	10.3%	1.04	(0.93-1.15)	0.511
Prostate disorders	890	4.3%	116	13%	1	(0.82-1.23)	0.975
Irritable bowel syndrome	500	2.4%	32	6.4%	0.62	(0.4-0.96)	0.032
Migraine	306	1.5%	15	4.9%	0.55	(0.31-0.97)	0.040

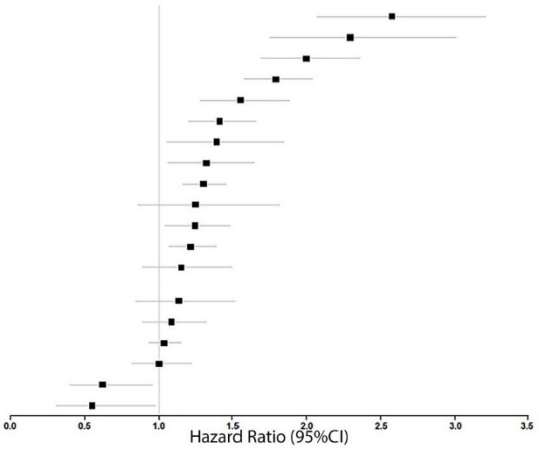

Fig 4. Forest plot of HR for the presence of different discordant conditions (prevalence >1%) and all-cause mortality in participants with type 2 diabetes in UK Biobank. COPD, chronic obstructive pulmonary disease; HR, hazard ratio; No., number.

https://doi.org/10.1371/journal.pmed.1003094.g004

Discussion

In this study, comprising more than 80,000 middle-aged and older-aged people from two national datasets, we identified that multimorbidity was highly prevalent among people with T2D. More than 80% were found to have at least one other chronic condition in addition to T2D. We found that the associations between multimorbidity, HbA1c, and mortality are similar across two separate cohorts from two countries with different healthcare systems and differing ethnicities. Increasing total multimorbidity and discordant condition counts were associated with slightly lower HbA1c. We found significant associations between increasing multimorbidity and risk of mortality. This finding was consistent for total count of

Concordant conditions

Condition	No. With Condition	Percent prevalence	No. deaths	Percent deaths	HR	95% CI	p-value
Cancer	1107	1.9%	563	50.9%	2.25	(2.06-2.45)	<0.001
Viral hepatitis	1263	2.1%	431	34.1%	2.00	(1.81-2.20)	<0.001
COPD	4000	6.7%	1632	40.8%	1.49	(1.41-1.57)	<0.001
Asthma	1404	2.4%	544	38.8%	1.48	(1.35-1.62)	<0.001
Chronic liver disease	7047	11.8%	1785	25.3%	1.42	(1.35-1.49)	<0.001
Constipation	2670	4.5%	1058	39.6%	1.31	(1.23-1.40)	<0.001
Depression	628	1.1%	191	30.4%	1.23	(1.06-1.42)	0.006
Psoriasis/eczema	1704	2.9%	515	30.2%	1.20	(1.10-1.31)	<0.001
Painful conditions	13754	23.1%	3798	27.6%	1.15	(1.10-1.19)	<0.001
Dyspepsia	12297	20.6%	3425	27.9%	1.14	(1.09-1.18)	<0.001
Prostate disorders	2513	4.2%	1001	39.8%	1.06	(0.99-1.14)	0.10
Anxiety	3398	5.7%	847	24.9%	1.02	(0.95-1.10)	0.51
Osteoporosis	1322	2.2%	349	26.4%	0.99	(0.89-1.11)	0.89
Thyroid disorders	1618	2.7%	291	18.0%	0.96	(0.85-1.08)	0.46
Irritable bowel syndrome	636	1.1%	149	23.4%	0.85	(0.72-100)	0.06

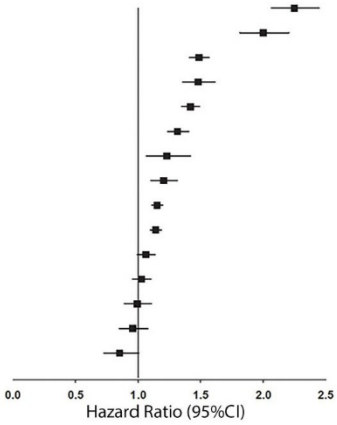

Fig 5. Forest plot of HR for the presence of different discordant conditions (prevalence >1%) and all-cause mortality in participants with type 2 diabetes in Taiwan NDCMP. COPD, chronic obstructive pulmonary disease; HR, hazard ratio; NDCMP, National Diabetes Care Management Program.

https://doi.org/10.1371/journal.pmed.1003094.g005

Combinations of conditions: Top 20 effect sizes

Condition	HR	95% CI	Total	p-value
Coronary heart disease and Heart Failure	4.37	(3.59-5.32)	310	<0.001
Coronary heart disease and Chronic Kidney Disease	4.29	(3.15-5.84)	128	<0.001
Heart Failure and Dyspepsia	4.23	(3.1-5.78)	109	<0.001
Hypertension and Heart Failure	3.88	(3.15-4.79)	354	<0.001
Peripheral Vascular Disease and Dyspepsia	3.77	(2.92-4.87)	168	<0.001
Atrial Fibrillation and Heart Failure	3.75	(2.81-5)	138	<0.001
Coronary heart disease and Peripheral Vascular Disease	3.7	(2.98-4.59)	299	<0.001
Hypertension and Peripheral Vascular Disease	3.39	(2.77-4.16)	413	<0.001
Coronary heart disease and Atrial Fibrillation	3.35	(2.73-4.11)	340	<0.001
Coronary heart disease and COPD	3.31	(2.67-4.09)	327	<0.001
Atrial Fibrillation and Dyspepsia	3.29	(2.48-4.37)	159	<0.001
Hypertension and Chronic Kidney Disease	3.27	(2.55-4.19)	287	<0.001
Heart Failure and Painful condition	3.25	(2.51-4.2)	196	<0.001
Atrial Fibrillation and Asthma	3.07	(2.17-4.33)	117	<0.001
Coronary heart disease and Stroke or TIA	2.94	(2.37-3.64)	364	<0.001
Peripheral Vascular Disease and Painful condition	2.84	(2.17-3.73)	195	<0.001
Chronic Kidney Disease and Painful condition	2.73	(1.95-3.83)	147	<0.001
Depression and COPD	2.65	(1.81-3.89)	129	<0.001
Hypertension and COPD	2.62	(2.16-3.17)	647	<0.001
Hypertension and Atrial Fibrillation	2.53	(2.07-3.11)	528	<0.001

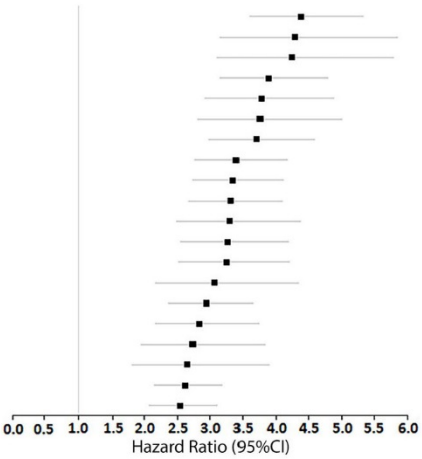

Fig 6. Forest plot of HR for the presence of the top 20 combinations (by effect size) of two conditions and all-cause mortality in participants with type 2 diabetes in UK Biobank. COPD, chronic obstructive pulmonary disease; HR, hazard ratio; TIA, transient ischaemic attack.

https://doi.org/10.1371/journal.pmed.1003094.g006

multimorbidity as well as counts of concordant and discordant conditions. This association was strongest for increasing concordant conditions. Each concordant condition, except diabetic retinopathy and neuropathy, was associated with significantly higher risk of mortality, and the presence of HF, PVD, CKD, and AF had the largest effect sizes. Presence of certain discordant conditions (alcohol problems, chronic liver disease, COPD, cancer, and viral hepatitis) had similar risk of mortality compared with concordant conditions. Our findings also show that cardiovascular diseases play a significant role in the increased mortality seen in those with multimorbidity because such conditions were in 18 of the top 20 combinations (by effect size) of two conditions in UK Biobank, whereas they were present in 12 of the top 20 combinations

Combinations of conditions: Top 20 effect sizes

Condition	HR	95% CI	Total	p-value
Painful conditions and Alcohol problems	4.02	(3.08-5.23)	111	<0.001
Dyspepsia and Alcohol problems	3.90	(3.18-4.80)	188	<0.001
Cancer and Chronic liver disease	3.65	(3.08-4.32)	230	<0.001
Alcohol problems and Chronic liver disease	3.52	(2.97-4.18)	314	<0.001
Heart failure and Asthma	3.32	(2.70-4.08)	132	<0.001
Chronic kidney disease and Heart failure	2.97	(2.51-3.51)	190	<0.001
Heart failure and COPD	2.90	(2.54-3.30)	340	<0.001
COPD and Cancer	2.73	(2.25-3.31)	155	<0.001
Coronary heart disease and Viral hepatitis	2.57	(2.06-3.20)	170	<0.001
Dyspepsia and Viral hepatitis	2.56	(2.19-2.99)	379	<0.001
Chronis kidney disease and Stroke/TIA	2.53	(2.22-2.89)	352	<0.001
Stroke/TIA and Heart failure	2.51	(2.16-2.92)	262	<0.001
Hypertension and Alcohol problems	2.50	(1.93-3.25)	153	<0.001
COPD and Viral hepatitis	2.50	(1.91-3.27)	114	<0.001
Atrial fabrillation and Heart failure	2.46	(2.02-2.99)	152	<0.001
Stroke/TIA and Dementia	2.45	(2.01-2.98)	155	<0.001
Chronic kidney disease and Diabetic retinopathy	2.40	(1.93-2.98)	137	<0.001
Heart failure and Chronic liver disease	2.38	(1.91-2.97)	153	<0.001
Coronary heart disease and Heart failure	2.36	(2.14-2.61)	704	<0.001
Viral hepatitis and Chronic liver disease	2.36	(2.07-2.68)	627	<0.001

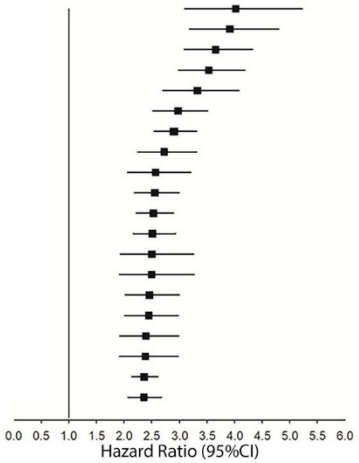

Fig 7. Forest plot of HR for the presence of the top 20 combinations (by effect size) of two conditions and all-cause mortality in participants with type 2 diabetes in Taiwan NDCMP. COPD, chronic obstructive pulmonary disease; HR, hazard ratio; NDCMP, National Diabetes Care Management Program; TIA, transient ischaemic attack.

https://doi.org/10.1371/journal.pmed.1003094.g007

in the Taiwan NDCMP. We have also shown that there are key differences in the top combinations (by effect size) of two conditions in addition to T2D associated with increased risk of death between the two cohorts.

Our results indicate that increasing total multimorbidity and discordant counts were associated with lower HbA1c. This adds to the existing literature and a recent systematic review, findings from which showed mixed results in terms of the associations between multimorbidity and HbA1c [7]. This is particularly interesting because it has been established that achievement of HbA1c targets is a key component of T2D management and is important in reducing all-cause mortality [15]. Although studies have also noted associations between low HbA1c and increased mortality, the causal link between the two remains unclear [16,17]. The slightly lower HbA1c observed in our study aligns with a previous study that showed that those who live with more chronic conditions receive better quality of care and higher health service use, leading to more opportunities for care of multimorbidity conditions [18]. This could also mean earlier diagnosis of the range of conditions they are living with. For example, those that have heart disease could be diagnosed earlier, meaning they are more likely to have HbA1c tests that are only mildly elevated, and subsequently receive treatment earlier. In light of this, our sensitivity analyses in the Taiwan NDCMP, in which the inclusion of the number of outpatient visits attenuated the association between multimorbidity and HbA1c, suggests that higher health service utilisation may play a role in glycaemic management in those with T2D living with multimorbidity. Furthermore, another possible explanation of the lower HbA1c seen in our results is that of survival bias. In the UK Biobank, those who live with more chronic conditions (higher degree of multimorbidity) and a higher HbA1c may not be well enough or alive to attend the baseline assessment and, hence, unable to participate in the UK Biobank; however, this would not explain the similar findings in the Taiwan dataset.

Although our results indicate associations between increasing multimorbidity and slightly lower HbA1c, a major caveat is that the degree of difference observed in HbA1c (ranging from −0.07% to −0.82%) seen in our results is not likely to be clinically significant despite being statistically significant. There have been discussions around what degree of reduction in HbA1c could be seen as clinically significant; however, it would be patient dependent [19]. Not all HbA1c improvements are equal in regard to clinical benefit; for example, a reduction of 1% in HbA1c offers different benefits if the improvement was from 12% to 11% compared with 7% to 6%. Furthermore, it is generally regarded that it is easier for patients with poorer glycaemic control to reduce their HbA1c (for example, from 10% to 9%) than for patients with relatively good glycaemic control. Although the UK Biobank cohort represents a relatively healthy population with good glycaemic control in which the mean (SD) HbA1c was 6.8 (1.2)%, it is important to note that the results were similar in the Taiwan NDCMP cohort, which is a population cohort in which the mean (SD) HbA1c was 8.2 (2.0)%.

Our study findings are consistent with previous literature in which increasing multimorbidity counts are significantly associated with higher mortality in people with T2D [7]. However, it is the first to assess the implications of concordant versus discordant multimorbidity counts and the associations between individual conditions and mortality. Only one study has assessed the type of condition in multimorbidity by differentiating between physical and mental health conditions [8]. Evidence suggests that those with more concordant conditions have improved diabetes care because of synergistic care, in which diabetes guidelines often make specific recommendations for concordant conditions but do not address discordant conditions [5,20]. As a result, to date it has been suggested that those with discordant conditions may have suboptimal care because of competition for limited resources and distraction from diabetes care, which could ultimately lead to worse outcomes and increased mortality [5,21]. Our study contributes to understanding of which patterns of multimorbidity are associated with poorer

outcomes [5,7] and demonstrates that both concordant and discordant conditions are associated with mortality but that discordant conditions generally have lower risks of death. However, we show that particular discordant conditions, such as alcohol problems, chronic liver disease, COPD, and cancer, have equal risk of mortality to concordant conditions. We also contribute to the understanding of patterns of multimorbidity that are associated with poorer outcomes in different ethnic groups through exploring associations between the top combinations of conditions and mortality in a predominantly white population (UK Biobank) and predominantly ethnic Chinese one (Taiwan NDCMP cohort). Our findings show that cardiovascular diseases are present in the majority of the top combinations that are associated with the highest risk of death in both cohorts, consistent with previous literature [22,23]. Importantly, although we have noted the significant contributions of cardiovascular diseases to increased mortality, particularly in the UK Biobank population, our findings also suggest that certain combinations of discordant conditions are also strongly associated with increased mortality. This was particularly marked in the Taiwan NDCMP cohort, in which alcohol problems, chronic liver disease, cancer, painful conditions, and dyspepsia were in the top four combinations (by effect size) of two conditions associated with increased risk of death, whereas only dyspepsia featured as part of a combination in the top five combinations in UK Biobank. This highlights the need for further research to consider the importance of ethnic differences when considering the implications of multimorbidity in people with T2D. It also underscores the importance of personalised care that takes account of individual characteristics, including ethnicity, along with number and type of conditions when managing those with T2D living with multimorbidity. Current guidelines do acknowledge the complex nature of multimorbidity, for which the choice of glycaemic targets and treatment should be based on the patient's individual clinical needs, comorbidities, and the risks from polypharmacy [24]. Therefore, it is important to consider the overall multimorbidity disease burden as a way of recalibrating and personalising our clinical focus in managing people with T2D [25]. However, future studies should aim to explore the mechanisms underpinning the increased mortality and lower HbA1c associated with multimorbidity observed in our findings. This could contribute to better understanding of how to manage specific patterns of multimorbidity and how this should be balanced across the treatment of all multimorbidity conditions. Better understanding of these issues, including effects of condition type, will enable more effective personalisation of care for those with T2D and multimorbidity.

To our knowledge, this is the first study to assess and compare the relationship between total, concordant, and discordant multimorbidity counts; HbA1c; and all-cause mortality in people with T2D. We also show the associations of a wide range of individual conditions included in our multimorbidity counts and mortality. Our study is also novel in that we explored combinations of conditions that were associated with the highest risk of death. Key strengths include use of two national datasets, large sample sizes, recruitment from the UK and Taiwan, and adjustment of our analyses for a wide range of sociodemographic and lifestyle factors. We utilised a robust method to capture multimorbidity conditions using both self-report data and coded hospital data. However, these data were only available at baseline, and we were unable to model for changes in multimorbidity over our study period. Therefore, a limitation of our study is that we were unable to consider the temporality and duration of the conditions in addition to diabetes, which is important for serious conditions such as stroke, TIA, and cancer. UK Biobank is not a random population sample: the participants are more likely to be people of European descent and comparatively less deprived socioeconomically compared with the general UK population [26], suggesting that our findings are likely to be conservative regarding the prevalence of multimorbidity and its associations with mortality. A limitation to note is that despite depression being increasingly common in those with T2D,

there was a comparatively low prevalence of depression in our Taiwan NDCMP cohort. However, this is consistent with evidence suggesting the prevalence of depression is significantly lower in Asia Pacific countries compared with western European countries[27], perhaps because of underdiagnosis of depression due to cultural and social stigma associated with mental health conditions in Asian countries [28]. Although we have classified mental health conditions including depression and anxiety as discordant conditions, there are still debates regarding whether this is appropriate. Studies have shown that depression and anxiety may share biological and behavioural mechanisms [29], which could mean that our classification of these conditions could lead to underestimating the associations between concordant conditions and our outcomes. There was a large overlap between the concordant and discordant condition groups, so a limitation of our study was that for cases in which a person lives with both concordant and discordant conditions, we did not explore this overlap and the individual effects of the two condition groups on HbA1c and mortality. Furthermore, we also did not explore the overlap of the effects of individual conditions within the same condition group; for example, the overlap between chronic liver diseases and alcohol problems. Finally, the fact that the 35 conditions considered in our discordant conditions count included many that are not strong predictors of death may have diluted the overall relationship between discordant condition count and mortality.

In conclusion, increasing multimorbidity is significantly associated with increased mortality in those with T2D and with lower HbA1c. This was observed in two large community cohorts of people from different healthcare systems. The highest risk of mortality is seen in those with concordant conditions, but discordant conditions such as alcohol problems, chronic liver disease, and COPD in UK Biobank and cancer and viral hepatitis in the Taiwan NDCMP cohort were still associated with more than 2-fold the risk of mortality. A key finding is that the combinations of conditions with the greatest association with mortality differed between UK Biobank, a population predominantly comprising people of European descent, and the Taiwan NDCMP, a predominantly ethnic Chinese population. These findings suggest that we need to know more about the influence of different patterns of multimorbidity on outcomes across different ethnic groups in T2D populations. Furthermore, a more cautious approach to tight glycaemic control in some patterns of multimorbidity and T2D may merit consideration. However, further research is needed to explore the mechanisms underpinning these findings. It will be important for clinicians to better understand the biology or healthcare delivery approaches that are contributing to these associations in order to tailor advice to better meet the needs of these diverse and complex populations of people with T2D from different ethnic backgrounds.

Supporting information

S1 Text. Study protocol.
(DOCX)

S2 Text. STROBE checklist. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.
(DOC)

S1 Table. List of long-term conditions considered for multimorbidity count.
(DOCX)

S2 Table. Sensitivity analysis. Relationship of multimorbidity total count with HbA1c.
(DOCX)

S3 Table. Sensitivity analysis. Relationship of multimorbidity total count with all-cause mortality.
(DOCX)

S4 Table. Sensitivity analysis. Hospital-verified data.
(DOCX)

S5 Table. Spline plots of multimorbidity condition count and mortality.
(DOCX)

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6.1 Additional Results

In the Taiwan subset of the study presented in the paper above, I had the opportunity to explore long-term glycaemic variability (GV). The Taiwan NDCMP dataset included multiple HbA1c measures for the participants. I was therefore able to calculate variations in HbA1c measures using the coefficient of variation (CV) of HbA1c measurements from clinical visits within the first year of the index date. I explored the associations between total multimorbidity condition count and HbA1c-CV using the same multivariable linear regression model described in the methods section of the paper above.

In this cohort the mean (SD) of HbA1c-CV was 10.65 (8.69)%. In Table 1 below, the results indicate that those with one, two and three additional chronic conditions were associated with slightly lower GV, whereas those with four or more conditions were associated with slightly higher GV, compared to the those with type 2 diabetes only. However, the observed small degree of difference in HbA1c-CV, although statistically significant, it is not likely to be clinically significant, particularly in this cohort with a mean HbA1c-CV of 10.65% (the consensus stable glucose levels are defined as CV of <36%, as described in my literature review (Section 2.4.2)). The implications of these results will be discussed later in the thesis in the Clinical Implications of Findings Section (Section 10.1.3).

Table 1: Associations between multimorbidity and long-term glycaemic variability (HbA1c-CV) in Taiwan NDCMP

Predictor variables	**Unadjusted**		**Adjusted***	
Categories of T2D and multimorbidity	Mean difference in HbA1c-CV (95% CI)	P-value	Mean difference in HbA1c-CV (95% CI)	P-value
T2D only (reference)	Ref		Ref	
1 chronic condition + T2D	-2.94 (-3.22, -2.67)	<0.001	-1.20 (-1.46, -0.93)	<0.001
2 chronic conditions + T2D	-3.16 (-3.43, -2.88)	<0.001	-0.98 (-1.26, -0.70)	<0.001
3 chronic conditions + T2D	-2.79 (-3.11, -2.47)	<0.001	-0.39 (-0.71, -0.07)	0.018
≥4 chronic conditions + T2D	-2.19 (-2.52, -1.86)	<0.001	0.54 (0.19, 0.89)	0.002

*Adjusting for age, gender, BMI, smoking status, alcohol consumption, duration of diabetes, socioeconomic status, use of oral anti-diabetes drugs, use of corticosteroids and number of outpatient visits.

7: Paper 4 – Associations between multimorbidity and glycaemia (HbA1c) in people with type 2 diabetes in Australian general practice.

The aim of this study presented in this chapter was to explore associations between multimorbidity and HbA1c in people with type 2 diabetes attending general practice in Australia.

The submitted manuscript for this paper appears below.

This is the final author-produced PDF-proof of an article submitted for publication in BMJ Open: Chiang, J.I., Furler, J., Mair, F., Jani, B.D., Nicholl, B.I., Thuraisingam, S., et al. Associations between multimorbidity and glycaemia (HbA1c) in people with type 2 diabetes in Australian general practice.

All supplementary files referred to in the paper are available in the Appendix (see Section 12.5).

The methods section of the paper below does not fully capture the efforts required to identify each of the 43 long-term conditions (LTCs) included in my measure of multimorbidity. As mentioned in the methods of the paper below, I coded for conditions based on data entered into three fields of the electronic medical records: the reason for visit, reason for prescription or medical history fields. I also undertook an additional search of specific terms to capture diagnoses recorded in free text. However, to achieve that I needed to identify the search terms for each of the LTCs. I needed to take into account the variations (such as abbreviations, commonly used lay terms, and typographical errors) in which each condition can be entered into the free-text fields, and this is solely based on the clinician's recording practices. The first step in identifying appropriate search terms included utilising the Clinical Audit Tool (CAT) mapping guide for Medical Director and Best Practice[5] (113-115). The mapping guide included all terms used to record conditions in the medical history fields. Through searching the free text using the root of terms from the CAT mapping guide I identified variations in conditions recorded. For example, to identify osteoporosis, I first searched "osteop" which captured terms like "osteoporosis", "osteoprosis", and

[5] Medical Director and Best Practice are the most commonly used clinical information systems in Australian general practice.

"osteoporsis" to capture typographical errors. I then manually reviewed the retrieved terms from my search with a panel of academic general practitioners (my supervisors A/Prof John Furler, A/Prof Jo-Anne Manski-Nankervis and Dr Bhautesh Jani from my advisory panel). This ensured all terms were reviewed and accepted by at least two people and a third in cases of discrepancy to reach consensus. I also took into account other terms that correctly reflect the condition I was trying to identify. For example, for chronic kidney disease, terms like "CKD", "haemodialysis" and "end stage kidney" all reflect chronic kidney disease. Again, these terms were reviewed by the panel of academic clinicians. I also had procedures in place to ensure that I didn't misidentify conditions. For example, I conducted a separate search for exclusion terms. I would exclude entries of conditions when terms like "family history" and "possible" preceded the conditions. The steps I have outlined above were taken for each of the 43 LTCs included in my multimorbidity counts. All of the terms that were included in my STATA (statistical software package used for this study) codes for identifying the LTCs were reviewed by the panel of clinicians and my codes were also reviewed by a biostatistician in our department. In summary, this was a general outline of the six months of work required to identify LTCs prior to any analysis exploring multimorbidity in this NPS MedicineInsight cohort of people with type 2 diabetes. As a result of my work, this in turn created a coding dictionary for multimorbidity and a comprehensive list of LTCs for use in future studies. In the appendix (see Section 12.4), I have provided an example of coding for a condition where I show all of the terms that I used to capture the condition.

BMJ Open

Associations between multimorbidity and glycaemia (HbA1c) in people with type 2 diabetes in Australian general practice.

Journal:	*BMJ Open*
Manuscript ID	Draft
Article Type:	Original research
Date Submitted by the Author:	n/a
Complete List of Authors:	Chiang, Jason; University of Melbourne Department of General Practice and Primary Health Care, Furler, John; University of Melbourne Mair, Frances; University of Glasgow, General Practice and Primary Care Jani, Bhautesh; University of Glasgow Nicholl, Barbara; University of Glasgow, General Practice and Primary Care Thuraisingam, Sharmala; University of Melbourne Manski-Nankervis, Jo-Anne; University of Melbourne, Department of General Practice
Keywords:	DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, PRIMARY CARE

Associations between multimorbidity and glycaemia (HbA1c) in people with type 2 diabetes in Australian general practice.

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ABSTRACT

Objectives:

To explore the prevalence of multimorbidity as well as individual and combinations of long-term conditions (LTCs) in people with type 2 diabetes (T2D) attending Australian general practice, using electronic health record (EHR) data. We also examine the association between multimorbidity condition count (total/concordant(T2D-related)/discordant(unrelated)) and glycaemia (HbA1c).

Design:

Cross-sectional study.

Setting:

Australian general practice.

Participants:

69,718 people with T2D with a general practice encounter between 2013-15 captured in the MedicineInsight database (EHR Data from 557 general practices and >3.8 million Australian patients).

Primary and secondary outcome measures:

Prevalence of multimorbidity, individual and combinations of LTCs. Multivariable linear regression models used to examine associations between multimorbidity counts and HbA1c (%).

Results:

Mean (SD) age 66.42 (12.70) years, 46.1% female and mean (SD) HbA1c 7.1 (1.4)%. More than 90% of participants with T2D were living with multimorbidity. Discordant conditions were more prevalent (83.4%) than concordant conditions (69.9 %). The 3 most prevalent discordant conditions were: painful conditions (55.4%), dyspepsia (31.6%), and depression (22.8%). The 3 most prevalent concordant conditions were hypertension (61.4%), coronary heart disease (17.1%), and chronic kidney disease (8.5%). The 3 most common combinations of conditions were: painful conditions and hypertension (38.8%), painful conditions and dyspepsia (23.1%) and hypertension and dyspepsia (22.7%). We found no associations between any multimorbidity counts (total, concordant and discordant) or combinations and HbA1c.

Conclusions:

Multimorbidity was common in our cohort of people with T2D attending Australian general practice, but was not associated with glycaemia. Our results suggest that the increased mortality in those with multimorbidity and T2D observed in other studies may not be linked to glycaemia. Interestingly, discordant conditions were more prevalent than concordant conditions with painful conditions being the second most common comorbidity. Better understanding of the implications of different patterns of multimorbidity in people with T2D will allow more effective tailored care.

Strengths and limitations of this study

- This is the first study to assess the effects of total, concordant and discordant multimorbidity counts and multimorbidity combinations on HbA1c in people with type 2 diabetes (T2D) in Australian general practice.
- The study utilised a large, national, routinely collected real world general practice dataset from 557 Australian general practices.
- We recognise the limitation of a cross-sectional study design where we did not consider the changes in LTCs and HbA1c over time, and the duration of LTCs in addition to T2D.
- The study relies on data entered into the electronic health records and therefore there is a possibility in under-reporting of conditions as a result of non-recording of diagnoses and the way each long-term condition is recorded which is dependent on the clinicians' recording practices.

BACKGROUND

Type 2 diabetes (T2D) is recognised as a leading health priority associated with increased risk for premature mortality and is a global economic burden (1). Multimorbidity is the co-occurrence of two or more long term health conditions (LTCs) in an individual (2, 3), which is the norm in T2D. It has been estimated that approximately 85% of those living with T2D have at least one other LTC (4). Multimorbidity amplifies the complex management of T2D including the challenges in managing higher treatment burden due to complicated self-management requirements as a result of having multiple LTCs (5) and has been associated with increased mortality (6). Multimorbidity in those with T2D could result in reduced adherence to complex therapeutic regimens and poorer outcomes including suboptimal glycaemic management (7-9) which may underpin poor outcomes. Glycated haemoglobin (HbA1c) is an important clinical measure to consider in T2D and glycaemic management is a key component of clinical guidelines for people with T2D.

HbA1c has been used to established glycaemic targets and measure efficacy of T2D management and treatment. It is evident that reducing HbA1c and avoiding hyperglycaemia results in clinical benefits including reduced microvascular and cardiovascular complications (9-12). Indeed, for every 1% increase in HbA1c, there is a 21% increase in risk of serious and costly complications (13).

A recent systematic review examined all existing studies that explored associations between multimorbidity and any glycaemic outcomes, including HbA1c, in people with T2D (14, 15). It identified 14 cross-sectional studies that showed mixed associations between multimorbidity and HbA1c, however none of the studies were conducted in an Australian setting or population. Despite the importance of examining the impact of multimorbidity in people with T2D, particularly its effect on glycaemia, currently there is no universally accepted measure of multimorbidity. However it has been suggested that multiple LTCs in people with T2D should be qualitatively assessed as concordant or discordant (8). Concordant conditions are those closely related to T2D that are more likely to be the focus of the same disease and management plan (e.g. hypertension), whereas discordant conditions are not directly related in their pathophysiology or management (e.g. depression and cancer).

While the association between multimorbidity and HbA1c in people with T2D has been studied to some extent (14), we do not have a good understanding of the different patterns of multimorbidity, including concordant and discordant conditions, and how they are associated with HbA1c in T2D in Australian general practice. The Academy of Medical Sciences has highlighted the importance of

increasing understanding of different patterns of multimorbidity internationally, including identifying common clusters of LTCs (16). A study has examined the prevalence of combinations of two and three LTCs in Australian general practice though not in people with T2D (17). One of the guiding principles for multimorbidity in the Royal Australian College of General Practitioner (RACGP) guidelines for T2D management was to be aware of common comorbidities with T2D (18). We therefore explored the prevalence of multimorbidity including the prevalence of individual, concordant and discordant LTCs and condition combinations, in a cohort of people with T2D attending Australian general practice using MedicineInsight which routinely collects electronic health record (EHR) data (19). We also examined the associations between multimorbidity count (total, concordant and discordant) and HbA1.

METHODS

Study design and participants

This cross-sectional study was conducted using data from MedicineInsight. This national database is managed by NPS MedicineWise and was established to support quality improvement in Australian general practice and post-market surveillance of medicines (19). MedicineInsight extracts and collates longitudinal, de-identified patient health records, including demographics, encounters (excluding progress notes), diagnoses, prescriptions and pathology tests from general practice clinical information systems (CIS) Medical Director and Best Practice. Data extraction for our study was 1 September 2015, and included data from 557 Australian general practices, located in every Australian state and territory, and represented more than 3.8 million patient records (19).

Patients aged ≥18 years that had ever had a recorded diagnosis of T2D, marked as an active patient (20) (defined as having at least three encounters recorded over a two year period(between 1 September of 2013 and 2015)) at 1st September 2015 were included in this study. This MedicineInsight dataset consisted of 105,135 people with T2D during this time period. Of these, 35,417 did not have HbA1c data recorded and were excluded from the study. We therefore analysed data from 69,718 people.

Procedures

The included LTCs were based on previous published literature on multimorbidity (21). These consist of 43 individual LTCs where nine conditions were concordant with diabetes and the remainder discordant with diabetes (Table S1). We coded the conditions based on data entered in the reason for visit, reason for prescription or medical history fields and undertook an additional search to

capture diagnoses recorded in free text. All codes were carefully reviewed by at least two expert academic general practitioners. In cases of uncertainty, a consensus was reached after discussion with a third expert. We included LTCs ever recorded in the MedicineInsight database. We created three new variables: the total number of LTCs, the number of concordant only conditions and number of discordant only conditions.

Clinical outcome

The outcome measure of interest was HbA1c (%) and we used the most recently recorded HbA1c, treated as a continuous variable. Results of HbA1c tests were identified using text searches on pathology test names (as, for example, HbA1c test may be recorded as HbA1c or glycated HbA1c or Haemoglobin A1c) and Logical Observation Identifiers Names and Codes (LOINC), a code for a pathology test that is provided by pathology laboratories for our previous studies undertaken using this dataset (22-24).

Statistical analysis

Descriptive statistics were used to summarise overall characteristics of the participants including age, sex, smoking status, HbA1c, use of diabetes medication (number of non-insulin anti-diabetic medications, insulin use only or both), and socioeconomic status measured by Socio-Economic Indexes for Areas (SEIFA) scores presented in deciles (25). The SEIFA scores for each participant postcode are calculated by summarising attributes of the population collected through Australia's national census, such as income, educational attainment, employment and occupation. These scores are grouped into deciles where decile 1 represents the most disadvantaged and decile 10 represents the least disadvantaged. The counts and proportions of LTCs concordant and discordant with diabetes were also summarised. Summaries include frequencies and percentages for categorical data, means and standard deviations for normally distributed continuous data and medians and interquartile range for skewed continuous data. Chi-squared and t-tests were used to compare differences between people with T2D who had multiple LTCs and people with T2D only.

Multivariable mixed-effects linear regression models were used to examine the association between HbA1c and each of the multimorbidity counts (total; total of concordant conditions; total of discordant conditions) controlling for age, sex, SEIFA decile, smoking status and number of diabetes medications. Duration of diabetes was originally included in the adjusted model but was removed due to multicollinearity with age. The model without the inclusion of diabetes duration resulted in a

better fit of the data with variance inflation factors reduced to within acceptable limits and improved stability.

In a secondary analysis, we selected the LTCs in our multimorbidity count that occur with a prevalence of more than 1% in this cohort. For each of the LTCs identified, multivariable mixed-effects linear regression models were used to examine the association with HbA1c, adjusting for age, sex, SEIFA decile, smoking status, and number of diabetes medication. Consistent with the RACGP guidelines for multimorbidity in people with T2D, we also selected the top 10 most prevalent LTCs and examined all possible combinations of two conditions and their association with HbA1c using multivariable mixed-effects linear regression models.

In all the regression models, we treated the confounding factors as fixed effects and the general practice as a random effect to allow for the correlation of HbA1c within each practice. All analyses were carried out using STATA version 15.1 (StataCorp, College Station, Texas). Ethics approval for this study was obtained from the Human Research Ethics Committee at the University of Melbourne (Ethics ID 1759587). Data access was approved by the independent Data Governance Committee for MedicineInsight (Ref: 002-2015).

Sensitivity analysis

In the sensitivity analysis, we categorised our study participants by the general treatment target of HbA1c (those with HbA1c >7% and ≤7%) (26). We explored the association between HbA1c and each of the multimorbidity counts using multivariable mixed-effects linear regression models in each of the HbA1c groups. We adjusted for the same co-variates as the main analysis described above.

RESULTS

In this cohort of 69,718 people with T2D attending Australian general practice the mean (SD) age was 66.42 (12.70) and 46.1% were female. In our study, multimorbidity was present in 63,326 (90.8%). Table 1 describes the overall characteristics of our study participants and compares the characteristics between those with T2D and multimorbidity and those with T2D only. The characteristics of those with T2D and multimorbidity and those with T2D only were similar.

Table 1. Characteristics of participants with type 2 diabetes

Demographics	Total N=69,718	T2D only N=6,392	T2D + ≥1 chronic condition N=63,326	p
Age, years, mean (SD)	66.42 (12.70)	65.08 (12.72)	67.55 (12.58)	0.948
Female, n(%)	32,137 (46.1)	13,822 (43.2)	18,315 (48.6)	0.172
Missing	29 (0.0)	16 (0.1)	13 (0.0)	
SEIFA deciles, n(%)				0.082
Decile 1- most deprived	6,223 (8.9)	2,525 (7.9)	3,698 (9.8)	
Decile 2	7,924 (11.4)	3,454 (10.8)	4,470 (11.9)	
Decile 3	5,367 (7.7)	2,280 (7.1)	3,087 (8.2)	
Decile 4	7,508 (10.8)	3,142 (9.8)	4,366 (11.6)	
Decile 5	7,343 (10.5)	3,299 (10.3)	4,044 (10.7)	
Decile 6	8,169 (11.7)	3,823 (11.9)	4,346 (11.5)	
Decile 7	6,344 (9.1)	2,935 (9.2)	3,409 (9.0)	
Decile 8	6,192 (8.9)	2,958 (9.2)	3,234 (8.6)	
Decile 9	7,630 (10.9)	3,986 (12.5)	3,644 (9.7)	
Decile10 – least deprived	6,402 (9.2)	3,285 (10.3)	3,117 (8.3)	
Missing	616 (0.9)	329 (1.03)	287 (0.8)	
Smoking status, n(%)				0.912
Current/previous	31,608 (45.4)	13,758 (43.0)	17,850 (47.3)	
Never smoked	32,792 (47.0)	15,566 (48.6)	17,226 (45.7)	
Missing	5,318 (7.6)	2,692 (8.4)	2,626 (7.0)	
HbA1c, mmol/mol, mean (SD)	54 (16)	55 (16)	54 (15)	0.672
HbA1c, %, mean (SD)	7.1 (1.4)	7.2 (1.5)	7.1 (1.4)	0.672
HbA1c, %, n(%)				0.449
≤7	41,265 (59.2)	18,404 (57.5)	22,861 (60.6)	
>7	28,453 (40.8)	13,612 (42.5)	14,841 (39.4)	
Diabetes medication, n(%)				0.278
No medication	19,556 (28.1)	9,026 (28.2)	10,530 (27.9)	
1 Anti-diabetic medication	23,762 (34.1)	10,845 (33.9)	12,917 (34.3)	
2 Anti-diabetic medications	12,879 (18.5)	6,191 (19.3)	6,688 (17.7)	
3 Anti-diabetic medications	3,037 (4.4)	1,429 (4.5)	1,608 (4.3)	
≥4 Anti-diabetic medications	244 (0.4)	119 (0.4)	125 (0.3)	
Insulin use only	2,930 (4.2)	1,206 (3.8)	1,724 (4.6)	
Insulin + anti-diabetic medication(s)	7,310 (10.5)	3,200 (10.0)	4,110 (10.9)	
Number of chronic conditions, n(%)				n/a
T2D only	6,392 (9.2)	6,392 (100)	n/a	
T2D + 1 chronic condition	8,497 (12.2)	n/a	8,497 (13.4)	

T2D + 2 chronic condition	10,614 (15.2)	n/a	10,614 (16.8)	
T2D + 3 chronic condition	10,516 (15.1)	n/a	10,516 (16.6)	
T2D + ≥4 chronic conditions	33,699 (48.3)	n/a	33,699 (53.2)	
Concordant conditions only, n(%)	5,175 (7.4)	n/a	5,175 (8.2)	
Discordant conditions only, n(%)	14,593 (20.9)	n/a	14,593 (23.0)	

T2D, type 2 diabetes; SD, standard deviation; SEIFA, Socio-Economic Indexes for Areas; IQR, inter-quartile range;

The prevalence of individual LTCs included in our multimorbidity total, concordant and discordant counts are shown in Table 2. In our study cohort, 48,733 (69.9%) people had at least one concordant condition and 58,151 (83.4%) had at least one discordant condition in addition to T2D. The most prevalent concordant condition was hypertension (61.4%) while painful conditions (55.4%) was the most prevalent discordant condition.

Table 2. Prevalence of individual multimorbid conditions in participants with type 2 diabetes

Presence of chronic conditions concordant with type 2 diabetes, n(%)	**N=69,718**
At least 1 chronic condition concordant with diabetes	48,733 (69.9)
Hypertension	42,812 (61.4)
Coronary heart disease	11,953 (17.1)
Chronic kidney disease	5,919 (8.5)
Atrial fibrillation	5,318 (7.3)
Stroke/TIA	4,730 (6.8)
Heart failure	4,410 (6.3)
Diabetic retinopathy	2,266 (3.3)
Peripheral vascular disease	1,945 (2.8)
Diabetic neuropathy	1,117 (1.6)
Presence of chronic conditions discordant with type 2 diabetes, n(%)	**N=69,718**
At least 1 chronic condition discordant with diabetes	58,151 (83.4)
Painful conditions	38,645 (55.4)
Dyspepsia	22,022 (31.6)
Depression	15,926 (22.8)
Anxiety	14,262 (20.5)
Psoriasis/eczema	14,037 (20.1)
Cancer	12,733 (18.3)
Asthma	10,276 (14.7)
Thyroid disorders	7,613 (10.9)
Diverticular disease	6,039 (8.7)
COPD	5,521 (7.9)
Constipation	5,162 (7.4)
Chronic liver disease	4,864 (7.0)
Osteoporosis	4,567 (6.6)
Glaucoma	3,102 (4.5)
Migraine	2,643 (3.8)
Rheumatoid arthritis and other connective tissue disorders	2,622 (3.8)
Dementia	2,247 (3.2)
Schizophrenia/bipolar disorder	2,198 (3.2)

Irritable bowel syndrome	1,540 (2.2)
Alcohol problems	1,447 (2.1)
Viral hepatitis	815 (1.2)
Epilepsy	754 (1.1)
Parkinson's disease	628 (0.9)
Chronic sinusitis	597 (0.9)
Meniere's disease	520 (0.8)
Inflammatory bowel disease	515 (0.7)
Polycystic ovary	488 (0.7)
Other psychoactive substance misuse	463 (0.7)
Bronchiectasis	448 (0.6)
Pernicious anaemia	330 (0.5)
Endometriosis	280 (0.4)
Chronic fatigue syndrome	168 (0.2)
Prostate disorders	154 (0.2)
Anorexia/bulimia	148 (0.2)
Multiple sclerosis	114 (0.2)

T2D, type 2 diabetes; TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease

Table 3 shows the mean difference in HbA1c between participants with different multimorbidity counts where participants with T2D only were the reference group. For all increasing counts of multimorbidity (total, concordant and discordant) there were no association with HbA1c.

In the sensitivity analysis, when we categorised the study participants into HbA1c of >7% and ≤7% the results for the effect of all multimorbidity counts on HbA1c were similar to the main analysis, where there was no evidence to support any associations between multimorbidity counts and HbA1c (Table S2).

Table 3. Multivariable linear regression model: Relationship between HbA1c(%) and multimorbidity in participants with type 2 diabetes.

	Non-adjusted			Adjusted*		
Predictor variables	**Mean difference in HbA1c (SE)**	**95% CI**	**p**	**Mean difference in HbA1c (SE)**	**95% CI**	**p**
Categories of diabetes and multimorbidities						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 chronic condition	-0.01 (0.02)	-0.05, 0.04	0.757	-0.01 (0.02)	-0.05, 0.04	0.685
Diabetes present and 2 chronic conditions	-0.02 (0.02)	-0.07, 0.02	0.348	-0.02 (0.02)	-0.06, 0.02	0.341
Diabetes present and 3 chronic conditions	-0.01 (0.02)	-0.06, 0.03	0.549	0.00 (0.02)	-0.04, 0.04	0.968
Diabetes present and 4 or more chronic conditions	0.00 (0.02)	-0.04, 0.04	0.912	-0.01 (0.02)	-0.04, 0.03	0.731
Categories of diabetes and concordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 concordant condition	0.01 (0.01)	-0.02, 0.03	0.701	0.00 (0.01)	-0.02, 0.03	0.799
Diabetes present and 2 concordant conditions	0.02 (0.02)	-0.01, 0.05	0.250	0.02 (0.02)	-0.01, 0.05	0.150
Diabetes present and 3 concordant conditions	0.00 (0.02)	-0.04, 0.05	0.947	-0.01 (0.02)	-0.05, 0.03	0.556
Diabetes present and 4 or more concordant conditions	0.05 (0.03)	-0.01, 0.10	0.100	0.04 (0.03)	-0.02, 0.09	0.175
Categories of diabetes and discordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 discordant condition	-0.03 (0.02)	-0.06, 0.01	0.159	-0.03 (0.02)	-0.06, 0.01	0.099
Diabetes present and 2 discordant conditions	-0.03 (0.02)	-0.07, 0.00	0.077	-0.02 (0.02)	-0.06, 0.01	0.223
Diabetes present and 3 discordant conditions	-0.01 (0.02)	-0.05, 0.03	0.622	-0.01 (0.02)	-0.05, 0.02	0.508
Diabetes present and 4 or more discordant conditions	0.00 (0.02)	-0.03, 0.04	0.838	0.00 (0.02)	-0.03, 0.03	0.886

SE: Standard error

*Adjusting for age, sex, SEIFA, smoking status, and number of diabetes medication. All co-variates were treated as fixed effects and the general practice as a random effect to allow for the correlation of HbA1c within each practice.

Table 4 shows the association between individual LTCs that had a prevalence of greater than 1% in our study population and HbA1c. All concordant conditions and 23 discordant conditions met this criterion. We did not find any associations between each of the individual LTCs (prevalence 1%) and HbA1c.

Table 4. Multivariable linear regression model: Relationship between HbA1c(%) and the presence of individual conditions (prevalence > 1%) in participants with type 2 diabetes.

		Non-adjusted			Adjusted		
Predictor variables	**Prevalence N(%)**	**Mean difference in HbA1c (SE)**	**95% CI**	**p-value**	**Mean difference in HbA1c (SE)**	**95% CI**	**p-value**
Concordant conditions							
T2D only (reference)							
Hypertension	42,812 (61.4)	0.01 (0.01)	-0.01, 0.03	0.364	0.01 (0.01)	-0.01, 0.03	0.336
Coronary heart disease	11,953 (17.1)	0.03 (0.02)	0.00, 0.06	0.022	0.03 (0.01)	0.00, 0.05	0.040
Chronic kidney disease	5,919 (8.5)	0.01 (0.02)	-0.03, 0.05	0.745	-0.01 (0.02)	-0.05, 0.02	0.456
Atrial fibrillation	5,318 (7.3)	0.01 (0.02)	-0.03, 0.05	0.567	0.00 (0.02)	-0.04, 0.04	0.907
Stroke/TIA	4,730 (6.8)	-0.01 (0.02)	-0.05, 0.03	0.692	0.00 (0.02)	-0.42, 0.04	0.919
Heart failure	4,410 (6.3)	0.02 (0.02)	-0.02, 0.07	0.333	0.01 (0.02)	-0.03, 0.05	0.622
Diabetic retinopathy	2,266 (3.3)	-0.02 (0.03)	-0.08, 0.04	0.547	0.00 (0.03)	-0.06, 0.06	0.996
Peripheral vascular disease	1,945 (2.8)	0.05 (0.03)	-0.02, 0.11	0.151	0.02 (0.03)	-0.05, 0.08	0.509
Diabetic neuropathy	1,117 (1.6)	-0.01 (0.04)	-0.10, 0.07	0.763	0.01 (0.04)	-0.07, 0.09	0.892
Discordant conditions							
T2D only (reference)							
Painful conditions	38,645 (55.4)	0.01 (0.01)	-0.04, 0.01	0.211	-0.02 (0.01)	-0.04, 0.00	0.122
Dyspepsia	22,022 (31.6)	0.00 (0.01)	-0.02, 0.02	0.954	0.00 (0.01)	-0.02, 0.03	0.746
Depression	15,926 (22.8)	0.00 (0.01)	-0.03, 0.80	0.801	-0.01 (0.01)	-0.03, 0.02	0.600
Anxiety	14,262 (20.5)	0.00 (0.01)	-0.02, 0.03	0.772	-0.01 (0.01)	-0.03, 0.02	0.621
Psoriasis/eczema	14,037 (20.1)	0.02 (0.01)	-0.01, 0.04	0.193	0.02 (0.01)	-0.01, 0.04	0.13
Cancer	12,733 (18.3)	0.01 (0.01)	-0.01, 0.04	0.319	0.00 (0.01)	-0.02, 0.03	0.704
Asthma	10,276 (14.7)	-0.01 (0.02)	-0.04, 0.02	0.412	-0.02 (0.01)	-0.05, 0.01	0.219
Thyroid disorders	7,613 (10.9)	0.02 (0.02)	-0.02, 0.05	0.309	0.00 (0.02)	-0.03, 0.03	0.961
Diverticular disease	6,039 (8.7)	0.02 (0.19)	-0.02, 0.06	0.279	0.02 (0.02)	-0.02, 0.05	0.366
COPD	5,521 (7.9)	0.02 (0.02)	-0.02, 0.06	0.315	0.02 (0.02)	-0.02, 0.06	0.273
Constipation	5,162 (7.4)	0.02 (0.02)	-0.02, 0.06	0.339	0.01 (0.02)	-0.03, 0.05	0.524

Chronic liver disease	4,864 (7.0)	0.03 (0.02)	-0.01, 0.08	0.129	0.02 (0.02)	-0.02, 0.06	0.222
Osteoporosis	4,567 (6.6)	0.00 (0.02)	-0.04, 0.05	0.882	0.01 (0.02)	-0.03, 0.05	0.761
Glaucoma	3,102 (4.5)	0.05 (0.03)	0.00, 0.11	0.038	0.03 (0.02)	-0.02, 0.08	0.235
Rheumatoid arthritis and other connective tissue disorders	2,643 (3.8)	-0.01 (0.03)	-0.06, 0.05	0.8	0.01 (0.03)	-0.04, 0.07	0.597
Migraine	2,622 (3.8)	-0.03 (0.03)	-0.09, 0.03	0.305	-0.01 (0.03)	-0.07, 0.04	0.575
Dementia	2,247 (3.2)	0.05 (0.03)	-0.01, 0.11	0.09	0.03 (0.03)	-0.02, 0.09	0.255
Schizophrenia/ bipolar disorder	2,198 (3.2)	-0.01 (0.03)	-0.08, 0.05	0.655	-0.01 (0.03)	-0.07, 0.05	0.694
Irritable bowel syndrome	1,540 (2.2)	-0.01 (0.04)	-0.08, 0.06	0.756	-0.01 (0.03)	-0.08, 0.05	0.676
Alcohol problem	1,447 (2.1)	0.00 (0.04)	-0.07, 0.08	0.96	0.00 (0.04)	-0.07, 0.07	0.974
Viral hepatitis	815 (1.2)	0.02 (0.05)	-0.08, 0.12	0.689	0.04 (0.05)	-0.05, 0.13	0.393
Epilepsy	754 (1.1)	0.09 (0.05)	-0.02, 0.19	0.108	0.08 (0.05)	-0.01, 0.18	0.082

SE: Standard error

*Adjusting for age, sex, SEIFA, smoking status, and number of diabetes medication. All co-variates were treated as fixed effects and the general practice as a random effect to allow for the correlation of HbA1c within each practice.

Figure 1 below shows the prevalence of all possible combinations of two conditions of the top 10 most prevalent conditions in our cohort. The most prevalent combinations were painful conditions and hypertension (38.8%), painful conditions and dyspepsia (23.1%), hypertension and dyspepsia (22.7%), painful conditions and depression (15.8%), and hypertension and depression (14.9%).

Figure 1. the presence of combinations of top 10 most prevalent conditions in participants with type 2 diabetes.

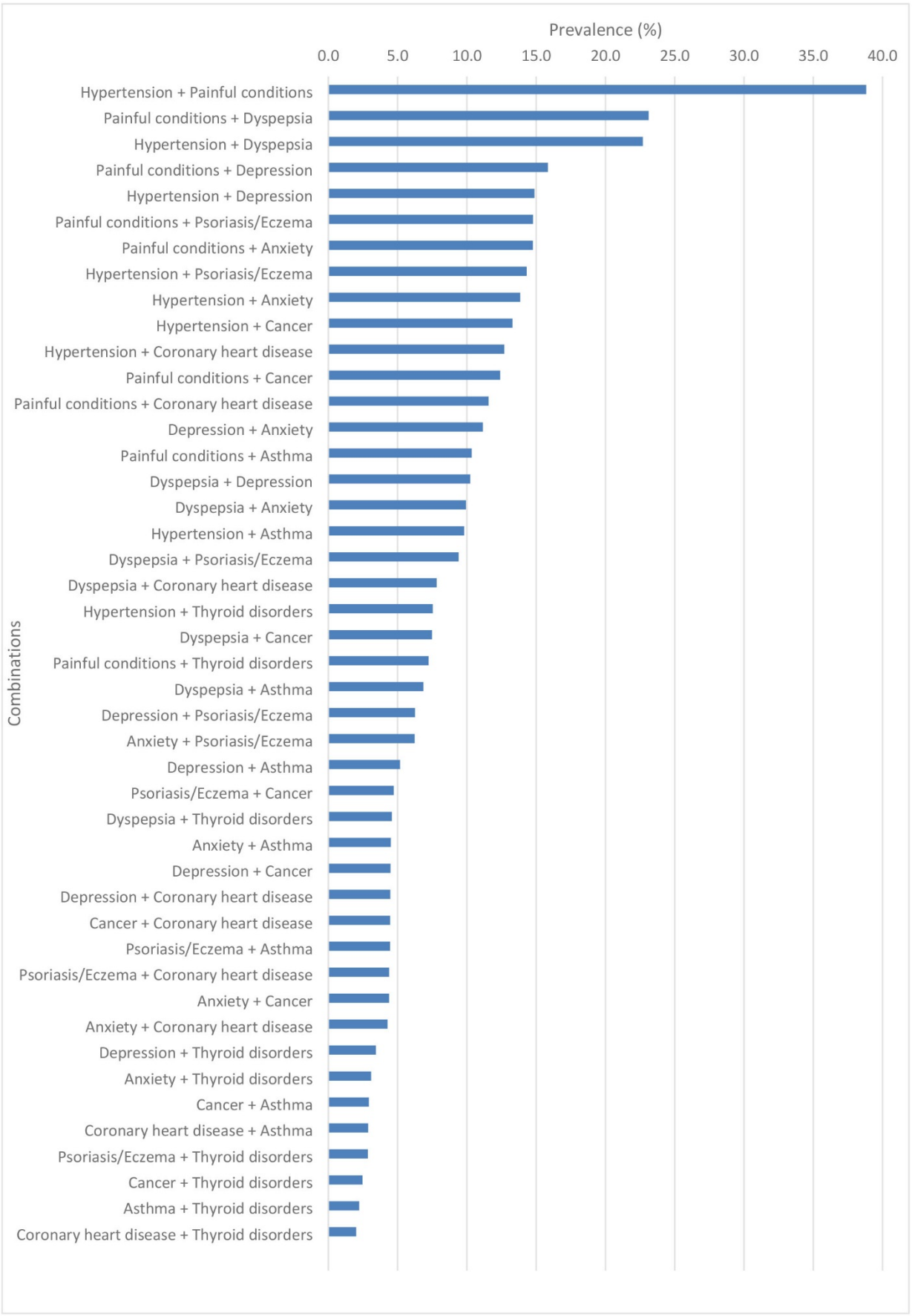

Table 5 shows the association between combinations of two LTCs from the top 10 most prevalent conditions in our cohort and HbA1c. We did not find any associations between any combinations and HbA1c.

Table 5. Multivariable linear regression model: Relationship between HbA1c(%) and the presence of combinations of top 10 most prevalent conditions in participants with type 2 diabetes.

		Non-adjusted			Adjusted		
Predictor variables	**Prevalence N (%)**	**Mean difference in HbA1c (SE)**	**95% CI**	**p-value**	**Mean difference in HbA1c (SE)**	**95% CI**	**p-value**
Concordant conditions							
T2D only (reference)							
Hypertension + Painful conditions	27,063 (38.8)	-0.01 (0.01)	-0.03, 0.02	0.615	-0.01 (0.01)	-0.03, 0.01	0.399
Painful conditions + Dyspepsia	16,117 (23.1)	-0.01 (0.01)	-0.04, 0.01	0.325	-0.01 (0.01)	-0.03, 0.02	0.674
Hypertension + Dyspepsia	15,827 (22.7)	0.01 (0.01)	-0.02, 0.03	0.502	0.01 (0.01)	-0.01, 0.03	0.413
Painful conditions + Depression	11,046 (15.8)	0.00 (0.01)	-0.03, 0.03	0.907	-0.01 (0.01)	-0.03, 0.02	0.675
Hypertension + Depression	10,369 (14.9)	0.00 (0.02)	-0.03, 0.03	0.791	0.01 (0.01)	-0.03, 0.02	0.693
Painful conditions + Psoriasis/Eczema	10,297 (14.8)	0.01 (0.02)	-0.02, 0.04	0.494	0.01 (0.01)	-0.02, 0.04	0.630
Painful conditions + Anxiety	10,291 (14.8)	-0.01 (0.02)	-0.04, 0.02	0.558	-0.02 (0.01)	-0.04, 0.01	0.260
Hypertension + Psoriasis/Eczema	9,977 (14.3)	0.02 (0.02)	-0.01, 0.05	0.220	0.02 (0.01)	0.00, 0.05	0.087
Hypertension + Anxiety	9,655 (13.9)	0.01 (0.02)	-0.02, 0.04	0.557	0.01 (0.01)	-0.02, 0.04	0.559
Hypertension + Cancer	9,268 (13.3)	0.02 (0.02)	-0.01, 0.05	0.154	0.01 (0.02)	-0.01, 0.04	0.443
Hypertension + Coronary heart disease	8,853 (12.7)	0.03 (0.02)	0.00, 0.06	0.050	0.03 (0.02)	0.00, 0.06	0.025
Painful conditions + Cancer	8,645 (12.4)	0.02 (0.02)	-0.02, 0.05	0.299	0.01 (0.02)	-0.02, 0.04	0.702
Painful conditions + Coronary heart disease	8,066 (11.6)	0.02 (0.02)	-0.01, 0.06	0.191	0.02 (0.02)	-0.01, 0.05	0.260
Depression + Anxiety	7,778 (11.2)	-0.01 (0.02)	-0.04, 0.03	0.692	-0.02 (0.02)	-0.05, 0.01	0.184
Painful conditions + Asthma	7,213 (10.4)	-0.02 (0.02)	-0.06, 0.01	0.256	-0.03 (0.02)	-0.07, 0.00	0.048
Dyspepsia + Depression	7,139 (10.2)	0.01 (0.02)	-0.02, 0.05	0.450	0.01 (0.02)	-0.02, 0.05	0.386
Dyspepsia + Anxiety	6,927 (9.9)	0.02 (0.02)	-0.01, 0.06	0.282	0.01 (0.02)	-0.02, 0.05	0.446
Hypertension + Asthma	6,835 (9.8)	0.00 (0.02)	-0.04, 0.03	0.862	-0.01 (0.02)	-0.05, 0.02	0.452
Dyspepsia + Psoriasis/Eczema	6,558 (9.4)	0.02 (0.02)	-0.01, 0.06	0.242	0.02 (0.02)	-0.01, 0.06	0.169
Dyspepsia + Coronary heart disease	5,447 (7.8)	0.04 (0.02)	0.00, 0.08	0.051	0.04 (0.02)	0.00, 0.07	0.051
Hypertension + Thyroid disorders	5,258 (7.5)	0.03 (0.02)	-0.01, 0.07	0.172	0.01 (0.02)	-0.03, 0.04	0.723
Dyspepsia + Cancer	5,214 (7.5)	0.02 (0.02)	-0.02, 0.06	0.364	0.02 (0.02)	-0.02, 0.06	0.366

Painful conditions + Thyroid disorders	5,046 (7.2)	0.00 (0.02)	-0.04, 0.04	0.953	-0.02 (0.02)	-0.06, 0.02	0.403
Dyspepsia + Asthma	4,780 (6.9)	-0.01 (0.02)	-0.06, 0.03	0.533	-0.02 (0.02)	-0.06, 0.02	0.318
Depression + Psoriasis/Eczema	4,363 (6.3)	-0.01 (0.02)	-0.05, 0.04	0.800	-0.01 (0.02)	-0.06, 0.03	0.498
Anxiety + Psoriasis/Eczema	4,343 (6.2)	0.00 (0.02)	-0.04, 0.04	0.889	0.00 (0.02)	-0.05, 0.04	0.839
Depression + Asthma	3,610 (5.2)	-0.02 (0.02)	-0.07, 0.03	0.477	-0.03 (0.02)	-0.08, 0.01	0.173
Psoriasis/Eczema + Cancer	3,293 (4.7)	0.04 (0.03)	-0.01, 0.09	0.117	0.03 (0.02)	-0.02, 0.07	0.275
Dyspepsia + Thyroid disorders	3,193 (4.6)	0.05 (0.03)	0.00, 0.10	0.068	0.03 (0.02)	-0.02, 0.07	0.268
Anxiety + Asthma	3,144 (4.5)	-0.04 (0.03)	-0.09, 0.15	0.169	-0.05 (0.02)	-0.10, 0.00	0.044
Depression + Cancer	3,126 (4.5)	0.03 (0.03)	-0.02, 0.09	0.206	0.01 (0.02)	-0.04, 0.06	0.721
Depression + Coronary heart disease	3,115 (4.5)	0.08 (0.03)	0.03, 0.14	0.001	0.08 (0.02)	0.03, 0.12	0.003
Cancer + Coronary heart disease	3,106 (4.5)	0.06 (0.03)	0.01, 0.11	0.027	0.05 (0.02)	0.00, 0.10	0.059
Psoriasis/Eczema + Asthma	3,103 (4.5)	-0.03 (0.03)	-0.09, 0.02	0.203	-0.04 (0.02)	-0.08, 0.01	0.147
Psoriasis/Eczema + Coronary heart disease	3,059 (4.4)	0.06 (0.03)	0.01, 0.11	0.031	0.05 (0.00)	0.00, 0.10	0.037
Anxiety + Cancer	3,057 (4.4)	0.06 (0.03)	0.01, 0.11	0.026	0.04 (0.02)	-0.01, 0.09	0.130
Anxiety + Coronary heart disease	2,977 (4.3)	0.08 (0.03)	0.02, 0.13	0.005	0.06 (0.03)	0.01, 0.11	0.014
Depression + Thyroid disorders	2,396 (3.4)	0.01 (0.03)	-0.05, 0.07	0.681	-0.01 (0.03)	-0.06, 0.05	0.815
Anxiety + Thyroid disorders	2,152 (3.1)	0.02 (0.03)	-0.04, 0.08	0.533	-0.01 (0.03)	-0.06, 0.05	0.847
Cancer + Asthma	2,040 (2.9)	-0.02 (0.03)	-0.08, 0.04	0.516	-0.03 (0.03)	-0.08, 0.04	0.496
Coronary heart disease + Asthma	2,002 (2.9)	0.01 (0.03)	-0.06, 0.07	0.818	0.01 (0.03)	-0.05, 0.07	0.771
Psoriasis/Eczema + Thyroid disorders	1,986 (2.9)	0.04 (0.03)	-0.02, 0.11	0.215	0.04 (0.03)	-0.02, 0.10	0.25
Cancer + Thyroid disorders	1,720 (2.5)	0.04 (0.04)	-0.03, 0.11	0.241	0.01 (0.03)	-0.05, 0.08	0.712
Asthma + Thyroid disorders	1,551 (2.2)	0.00 (0.04)	-0.07, 0.07	0.963	0.00 (0.03)	-0.07, 0.07	0.972
Coronary heart disease + Thyroid disorders	1,400 (2.0)	0.06 (0.04)	-0.01, 0.14	0.109	0.07 (0.04)	0.00, 0.14	0.065

SE: Standard error

*Adjusting for age, sex, SEIFA, smoking status, and number of diabetes medication. All co-variates were treated as fixed effects and the general practice as a random effect to allow for the correlation of HbA1c within each practice.

DISCUSSION

In this study, comprising of nearly 70,000 people with T2D regularly attending Australian general practice, 90.8% of people were living with at least one other LTC in addition to T2D. Discordant conditions (such as painful conditions, dyspepsia, depression or psoriasis) were more prevalent (83.4%) than concordant conditions (69.9%). Our findings showed no evidence of an association between any counts of multimorbidity (total, concordant and discordant) and HbA1c. The presence of individual and combinations of LTCs in addition to T2D were not associated with HbA1c.

Our prevalence findings of multimorbidity add to existing literature where it has been estimated that approximately 85% of those living with T2D have at least one other LTC (4). The prevalence of individual LTCs identified in our study align with a recent study that explored multimorbidity in people with T2D across the UK and Taiwan (6). This is in spite of the study examining community cohorts of people with T2D rather than people attending general practice. This confirms how commonly people are burdened by multimorbidity and that that this is likely to impact on the already complex nature of T2D management. Currently, the Royal Australia College of General Practitioners (RACGP) guidelines for T2D acknowledge that clinical guidance regarding the management of comorbid conditions is currently lacking or sparse (18). However, one guiding principle was to be aware of common comorbidities with diabetes. Our findings regarding the commonest LTCs associated, either singly or in combination, with T2D have direct implications for this. We showed that for concordant conditions, hypertension was the most common condition, and following that was coronary artery disease. It should be noted that the treatment and prevention of these conditions with the exception of atrial fibrillation and partially heart failure have been incorporated into the diabetes guidelines (18). However, importantly, discordant conditions were more prevalent than concordant conditions in our study, where painful conditions was the most common comorbidity. Although the RACGP guideline recommends that clinicians should be aware of commonly occurring conditions, another guiding principle is to set treatment priorities with the patient (18). It is important to focus on outcomes and co-occurring conditions that matter most to the individual because shared decision making is vital to ensure care is tailored to the individual (8, 27-29). Given how common painful conditions are, patients may prioritise therapeutic interventions differently, for example pain relief being considered above diabetes management.

We also contribute to the understanding of patterns of patterns of multimorbidity in people with T2D through exploring the most common combinations of two LTCs. Our LTC combinations findings further confirms the significance of discordant conditions in T2D. We showed that painful conditions,

dyspepsia, depression, psoriasis/eczema, anxiety, cancer and one concordant condition, hypertension, were present in the majority of the most common combinations. While managing concordant conditions, namely cardiovascular diseases, are important, it should not overshadow efforts to address discordant conditions in people with T2D.

Our results add to the findings of a recent systematic review which highlighted mixed associations between multimorbidity and HbA1c in T2D (14). It has been well established that achieving HbA1c targets is a key component of T2D management and clinical guidelines and is important in reducing downstream complications and risk of mortality (30). Our findings contrast with a recent study of diabetes and multimorbidity using data from UK Biobank and the Taiwan National Diabetes Care Management Program which suggested that increasing total and discordant multimorbidity counts were associated with lower HbA1c and increased mortality in both datasets (6). Although the degree of observed difference in HbA1c noted in that study is very small and not likely to be clinically significant despite being statistically significant. Our findings could possibly be linked to the higher health care utilisation (31) and better quality of care (32) seen in people with LTCs, hence leading to more opportunities for clinical interventions leading to achieving HbA1c targets. This is further highlighted by our study cohort being relatively healthy with good glycaemic control (mean (SD) HbA1c 7.1 (1.4)%), similar to the Australian general treatment target of 7% (26). Moreover, 28% of our study cohort was not on any diabetes medication further highlighting our generally healthy cohort of participants with T2D.

To the best of our knowledge, this is the first study to assess the effects of total, concordant and discordant multimorbidity counts on HbA1c in people with T2D in Australian general practice. The strength of the study includes using a large, national, routinely collected real world general practice dataset from 557 Australian general practices. We recognise the limitation of a cross-sectional study design where we did not consider the temporality of LTCs and HbA1c, and the duration of LTCs in addition to diabetes. Another limitation of the study is that the quality of MedicineInsight data is dependent on the accuracy and completeness of data recorded in general practice clinical information systems, in fields that can be extracted or in a useable format. To improve the quality of the data, selection criteria for both patients and practices, and extensive data cleaning procedures are applied (19). For privacy reasons, MedicineInsight does not include data from progress notes, which may contain further clinical information. As such, this may result in underestimating the number of conditions experienced by people with T2D. In 2018, MedicineInsight published a report (33) comparing their dataset in terms of the prevalence of LTCs captured to the Australian Bureau of

Statistics (ABS) data, which is based on self-report (4), and data from the BEACH study, which is prospectively collected by general practitioners recording patient encounters on structured paper-based recording sheets (34). It is reported that the prevalence of chronic conditions in the MedicineInsight data align with ABS data or are slightly higher. When compared to data from the BEACH study, the MedicineInsight conditions, rates per 100 encounters were slightly lower. This may be the case because conditions that have been previously entered into EHR might not be re-entered by the clinicians into the relevant CIS fields used for analysis (reason for visit, reason for prescription or medical history fields), or data may be entered into the progress notes (which are not accessible to MedicineInsight). Furthermore, in the BEACH study, general practitioners were asked to provide complete information on structured paper-based recording sheets for a given encounter. Despite our efforts to compensate for the challenges of the MedicineInsight dataset by using a panel of expert academic general practitioners coding for conditions in multiple fields with additional searches in free text fields there is still a possibility in under-reporting of conditions as a result of non-recording of diagnoses and the way each LTC is recorded which is dependent on the clinicians' recording practices. Furthermore, it is possible that some patients captured in the dataset may have performed chronic disease screening elsewhere because in Australia, people are free to attend other and multiple general practice clinics although the majority tend to stay with one practice. Despite this, the prevalence of multimorbidity and LTCs identified in our study align with a recent study that explored multimorbidity in T2D using community cohorts in the UK and Taiwan (6). This supports the validity of the NPS MedicineInsight dataset in capturing LTC prevalence in the community.
Limitations also exist in regards to the current infrastructure and standards of EHRs. Currently, there are still no nationally agreed and implemented standards for the EHR, particularly for data structure, universally accepted systems of classification and terminology, and consistent data items with clear definitions (35). Furthermore, there is no minimum requirement for the types of patient data that should be collected at every patient consultation that could form a standardised minimum dataset. Although these limitations are highlighted, they also pose as important findings. With the increasing interest and use of routinely collected data in research, quality improvement and data evaluation, our study highlights important issues of data quality that must be addressed in the future. Datasets using routinely collected data will need further validation and perhaps data linkage through combination with other data sources, could enhance their value in research studies.

Whilst our current study did not specifically explore mortality, our results suggest that there is a need for future research to examine other factors independent of HbA1c that contribute to the increased mortality seen in people with multimorbidity and T2D (14) and investigate how people

with T2D and their health professionals approach glycaemic management and targets in the context of multimorbidity. Patient-reported outcome measures such as quality of life, patient reported health and function may also be important to consider, however these are not incorporated in the EHR. Linkage of MedicineInsight data to hospital and mortality datasets to explore health outcomes for people with multimorbidity and T2D is warranted. Improving our understanding of the biology or health care delivery approaches that are contributing to the effects of multimorbidity may benefit clinicians in tailoring care for the needs of this complex population of people with T2D. Gaining a greater understanding of the implications of different patterns of multimorbidity will also be important.

CONCLUSION

In approximately 70,000 people with T2D in Australian general practice, we have demonstrated that most people (>90%) with T2D live with multimorbidity and that for over 80% the comorbidity was discordant in nature. Importantly while hypertension was the most common LTC, painful conditions was the second most common LTC. We have found no evidence to support any associations between EHR different patterns or counts of multimorbidity and HbA1c. While it is important for clinicians to consider the impact of multimorbidity in people with T2D, the reasons for the increased mortality observed elsewhere remain unclear and at present are not clearly linked to HbA1c. Our study demonstrates the use of routinely collected real world clinical data in research, and highlights opportunities to enhance its value in the study of multimorbidity. Better understanding of the implications of multimorbidity in people with T2D, for example, focusing on the importance of common comorbid conditions such as painful conditions will allow more effective tailored care for people with T2D.

DECLARATIONS

Ethics approval

Ethics approval for this study was obtained from the Human Research Ethics Committee at the University of Melbourne (Ethics ID 1759587) and data access was approved by MedicineInsight Data Governance Committee (APP 002-2015).

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Royal Australian College of General Practitioners Family Medical Care Education and Research (FMCER) Grant 2017 (FMC17a 565484).

Authors' contributions

JC, JF, FSM, BDJ, BIN, ST and JMN contributed to the study protocol. JC, JF, FSM, BDJ, BIN, ST and JMN contributed to the study design. JC analysed the data and drafted the initial draft of the manuscript. JC had full access to all study data, performed all the statistical analyses, and takes responsibility for the integrity of the data and the accuracy of data analyses. All authors assisted with iterative drafting of the manuscript and agree with the manuscript results and conclusions. All authors read and approved the final manuscript.

Patient and Public Involvement

No patients or public were involved in this study during design, conduct or analysis.

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8: Paper 5 – Multimorbidity, glycaemic variability and time in target range in people with type 2 diabetes: a baseline analysis of the GP-OSMOTIC study

In this chapter I describe a sub-analysis of data from the GP-OSMOTIC Study. The aim of this study was to explore associations between multimorbidity count (total, concordant and discordant) and blood glucose (reflected by HbA1c, short-term glycaemic variability and time in range) using baseline data from a randomised controlled trial in people with T2D in general practice in Victoria, Australia (110-112).

The submitted manuscript for this paper appears overleaf.

This is the final author-produced PDF-proof of an article submitted for publication in Diabetes Research and Clinical Practice: Chiang, J.I., Manski-Nankervis, J., Thuraisingam, S., Jenkins, A., O'Neal, D., Mair, F., et al. Multimorbidity, glycaemic variability and time in target range in people with type 2 diabetes: a baseline analysis of the GP-OSMOTIC study.

All supplementary files referred to in the paper are available in the Appendix (see Section 12.6).

Multimorbidity, glycaemic variability and time in target range in people with type 2 diabetes: a baseline analysis of the GP-OSMOTIC trial

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ABSTRACT

Aims:

To explore associations between multimorbidity counts (total/ concordant/discordant) and glycaemia (HbA1c/glycaemic variability (GV)/time in range(TIR)) using data from a randomised controlled trial examining effectiveness of continuous glucose monitoring (CGM) in people with type 2 diabetes (T2D).

Methods:

Cross-sectional study: 279 people with T2D using baseline data from the General Practice Optimising Structured MOnitoring To Improve Clinical outcomes (GP-OSMOTIC) trial from 25 general practices in Australia. Number of long-term conditions (LTCs) in addition to T2D used to quantify total/concordant/discordant multimorbidity counts. GV (measured by coefficient of variation (CV)) and TIR derived from CGM data. Multivariable linear regression models used to examine associations between multimorbidity counts, HbA1c (%), GV and TIR.

Results:

Mean (SD) age of participants 60.4 (9.9) years; 40.9% female. Multimorbidity present in 89.2% of participants. Most prevalent comorbid LTCs: hypertension (57.4%), painful conditions (29.8%), coronary heart disease (22.6%) and depression (19.0%). No evidence of associations between multimorbidity counts, HbA1c, GV and TIR.

Conclusions:

While multimorbidity was common in this T2D cohort, it was not associated with HbA1c, CV or TIR. Future studies should explore factors other than glycaemia that contribute to the increased mortality observed in other studies of multimorbidity in T2D.

Keywords:

multimorbidity; glycaemia; HbA1c; glycaemic variability; time in range; continuous glucose monitoring (CGM); general practice; primary care

1. INTRODUCTION

Multimorbidity is defined as the co-occurrence of two or more long term health conditions (LTCs) in an individual (1, 2). This is common in people with type 2 diabetes (T2D) where approximately 85% have at least one other LTC (3, 4). The often complicated clinical management of T2D can be more challenging in the presence of multimorbidity and associated higher treatment burden related to having multiple LTCs (5). This can result in poorer outcomes including suboptimal glycaemic management which is a key component of clinical guidelines for T2D (6-8).

Although HbA1c is traditionally recognised as the gold standard for monitoring glycaemia, it does not characterise daily fluctuations in blood glucose (9). In 2017 the Beyond A1c Movement, initiated by nine diabetes organisations around the globe, presented a unified case for the need to incorporate outcomes beyond HbA1c into regulatory decisions and clinical care (10). Two outcomes of importance identified were glycaemic variability (GV) and time in range (TIR) derived from data from continuous glucose monitoring (CGM) systems. CGM technology measures interstitial fluid glucose levels on a regular basis (every five to 15 minutes, depending on the device), providing insights into short-term fluctuations in glucose levels. Several measures of GV exist. The Beyond HbA1c Movement recommended that the coefficient of variation (CV) should be considered the primary measure of glycaemic variability (11) and that a CV ≥36% is considered high variability. In 2019 another international consensus recommended that a range of 3.9-10.0 mmol/L be used to calculate TIR in people with T2D (12). Both GV and TIR, which are dependent on medication, physical activity and diet, and are known to be associated with the development of micro- and macrovascular complications (13-15).

We recently conducted a systematic review of the effect of multimorbidity on outcomes in people with T2D (16, 17). We identified 14 cross-sectional studies that demonstrated associations between multimorbidity and HbA1c were variable. Importantly, the review also identified that no studies had explored the relationship between multimorbidity, GV and TIR. An important limitation of our review was that we were not able to explore the effect of different types of multimorbid conditions. This is an important consideration in studies of multimorbidity in T2D (18). LTCs can be considered as either concordant or discordant with T2D (7). LTCs that are closely related to T2D, such as hypertension and cardiovascular

disease, are considered concordant whereas unrelated conditions like asthma and cancer are considered as discordant.

It was therefore our aim to explore the associations between multimorbidity count (total, concordant and discordant) and blood glucose (reflected by HbA1c, GV and TIR) using baseline data from a randomised controlled trial examining the effectiveness of CGM in people with T2D in general practice in Australia (19, 20).

2. SUBJECTS, MATERIALS AND METHODS

2.1 Study design and participants

This is a cross-sectional study consisting of 279 people with T2D using baseline data (October 2016 – November 2017) from the General Practice Optimising Structured MOnitoring To Improve Clinical outcomes (GP-OSMOTIC) randomised controlled trial (RCT) (19, 20). To summarise, the GP-OSMOTIC trial aimed to explore the effectiveness of a CGM device (FreeStyle Libre Pro® Flash Glucose Monitoring System, Abbott Diabetes Care, Witney, Oxon, UK) used in the clinical care of people with T2D in 25 general practices in Victoria, Australia (21). The inclusion criteria were adults (≥18 years) with a diagnosis of T2D, whose most recent HbA1c level (within 30 days prior to recruitment) was 0.5% (6mmol/mol) above the general Australian target of 7% (53mmol/mol) (22). A detailed description of the GP-OSMOTIC trial is provided elsewhere (19, 20).

2.2 Procedures

Multimorbidity is measured as a condition count of LTCs based on previous published literature (18). This condition count was adapted for use in our cohort and consists of 35 individual LTCs where eight conditions were concordant with T2D and the remainder discordant with T2D (Table S1). We identified the LTCs based on the participant's medical history retrieved from their clinical electronic medical records, and baseline nurse-led survey interviews which included demographic questions and questions on whether they have specific LTCs. Three variables were created for multimorbidity: total number of LTCs, number of concordant conditions and number of discordant conditions.

Masked CGM data were collected at baseline of the GP-OSMOTIC trial, prior to any therapeutic intervention. The CGM device was applied by clinically trained research

assistants to the underside of the participant's upper arm to measure individual interstitial fluid glucose levels in 15 minute intervals for two weeks. After two weeks, the sensor was removed, and data were uploaded to Microsoft Office Excel 365 (Microsoft Corp., Seattle, WA, USA) on a secure computer. Survey and clinical data were entered into REDCap© (REsearch Data CAPture software), a secure, web-based application designed to support research data capture (23).

2.3 Clinical outcome

We had three glycaemic outcome measures of interest, all treated as continuous variables: HbA1c, GV, and TIR. We used the most recently collected HbA1c at baseline. Both GV and TIR were calculated using baseline CGM data. CV was used as the measure of GV based on the international consensus (11) and was calculated using EasyGV© (24). TIR is defined as the percentage of time spent in the consensus suggested target range of 3.9-10.0 mmol/L (12). The duration of CGM for inclusion in the study was five to 14 days which is consistent with recommendations from the CGM manufacturer (25).

2.4 Statistical analysis

Descriptive statistics were used to summarise overall characteristics of the participants. The multimorbidity counts and prevalence of individual LTCs were also summarised. Summaries include means and standard deviations for normally distributed continuous data and medians and interquartile range for skewed continuous data, frequencies and percentages for categorical data.

Multivariable mixed-effects linear regression models were used to examine the association between each of the multimorbidity counts (total; total of concordant conditions; total of discordant conditions) and each of our outcomes of interest adjusting for age, gender, socioeconomic status (measured by Index of Relative Socioeconomic Disadvantage (IRSD) deciles) (26), body mass index (BMI), smoking status, insulin use, and number of non-insulin hypoglycaemic medications. Duration of diabetes was excluded from the adjusted model due to multicollinearity with age. In our regression models, all co-variates were treated as fixed effects and the general practice as a random effect to allow for the correlation of our outcomes of interest within each practice. All analyses were carried out using STATA version 15.1 (StataCorp, College Station, Texas). Ethics approval for this study was obtained from

the Human Research Ethics Committee at the University of Melbourne (Ethics ID 1647151·1).

3. RESULTS

In our cohort of 279 people with T2D attending Victorian general practice the mean (SD) age was 60.4 (9.9) years and 40.9% were female. Mean (SD) HbA1c was 8.9 (1.2)% (74 (13)mmol/mol), CV 30.0 (8.3)% and TIR 41.1 (25.6)% and number of days that CGM was worn was 12.3 (2.4) days. Multimorbidity was present in the majority (249 (89.2%)) of participants. Table 1 describes the overall characteristics of our study participants.

Table 1. Characteristics of participants with type 2 diabetes

Demographics	**Total (n = 279)**
Age, years, mean (SD)	60.4 (9.9)
Female, n(%)	114 (40.9)
IRSD Decile, n(%)	
Decile 1- most deprived	24 (8.7)
Decile 2	59 (21.5)
Decile 3	13 (4.7)
Decile 4	34 (12.4)
Decile 5	9 (3.3)
Decile 6	41 (14.9)
Decile 7	45 (16.4)
Decile 8	23 (8.4)
Decile 9	22 (8.0)
Decile10 – least deprived	5 (1.8)
Missing	4 (1.4)
Current smoker, n(%)	39 (14.0)
BMI, kgm^{-2}, median (IQR)	33.9 (7.8)
Know diabetes duration, years, median (IQR)	12 (9, 20)
Duration of r-CGM use, days, mean (SD)	12.3 (2.4)
HbA1c, %, mean (SD)	8.9 (1.2)
HbA1c, mmol/mol, mean (SD)	74 (13)
Glycaemic variability, CV, %, mean (SD)	30.0 (8.3)
High glycaemic variability (CV≥36%), n (%)	57 (20.4)
Time-in-range, %, mean (SD)	41.1 (25.6)
Prescribed insulin, n (%)	143 (51.3)
Number of non-insulin hypoglycaemic agents, n(%)	
0 agents	11 (3.9)
1 agent	35 (12.5)
2 agents	142 (50.9)
3 agents	81 (29.0)

≥4 agents	10 (3.6)
Number of chronic conditions, n(%)	
T2D only	30 (10.8)
T2D + 1 chronic condition	70 (25.1)
T2D + 2 chronic condition	68 (24.4)
T2D + 3 chronic condition	42 (15.1)
T2D + ≥4 chronic conditions	69 (24.7)

T2D, type 2 diabetes; SD, standard deviation; IRSD, Index of Relative Socioeconomic Disadvantage; IQR, inter-quartile range

The prevalence of individual LTCs included in our multimorbidity counts are shown in Table 2. Of the 279 study participants, 192 (68.8%) people had at least one concordant condition and 183 (65.6%) had at least one discordant condition in addition to T2D. Hypertension (57.4%) was the most prevalent concordant condition followed by coronary heart disease (22.6%). Painful conditions (29.8%) was the most prevalent discordant condition followed by depression (19.0%).

Table 2. Prevalence of individual multimorbid conditions in participants with type 2 diabetes

Presence of chronic conditions concordant with type 2 diabetes, n (%)	**N=279**
At least 1 chronic condition concordant with diabetes	192 (68.8)
Hypertension	160 (57.4)
Coronary heart disease	63 (22.6)
Peripheral vascular disease	8 (2.9)
Chronic kidney disease	17 (6.1)
Stroke/TIA	9 (3.2)
Diabetic retinopathy	28 (10.0)
Diabetic neuropathy	28 (10.0)
Atrial fibrillation	12 (4.3)
Presence of chronic conditions discordant with type 2 diabetes, n (%)	**N=279**
At least 1 chronic condition discordant with diabetes	183 (65.6)
Depression	53 (19.0)
Painful conditions	83 (29.8)
Asthma	39 (14.0)
GORD	39 (14.0)
Thyroid disorders	14 (5.0)
Rheumatoid arthritis and other connective tissue disorders	6 (2.2)
COPD	12 (4.3)
Anxiety	13 (4.7)
Irritable bowel syndrome	1 (0.4)

Cancer	7 (2.5)
Alcohol problems	0 (0)
Other psychoactive substance misuse	0 (0)
Treated constipation	0 (0)
Diverticular disease	16 (5.7)
Prostate disorders	6 (2.2)
Glaucoma	5 (1.8)
Epilepsy	0 (0)
Dementia	0 (0)
Schizophrenia/bipolar disorder	4 (1.4)
Psoriasis/eczema	21 (7.5)
Inflammatory bowel disease	1 (0.4)
Migraine	4 (1.4)
Chronic sinusitis	1 (0.4)
Anorexia/bulimia	0 (0)
Bronchiectasis	0 (0)
Parkinson's disease	1 (0.4)
Multiple sclerosis	0 (0)
Viral hepatitis	1 (0.4)
Chronic liver disease	4 (1.4)

T2D, type 2 diabetes; TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease; GORD, gastroesophageal reflux disease

The mean difference in HbA1c, CV and TIR between participants with different multimorbidity counts are presented in Tables 3, 4 and 5, respectively. The reference group was people with T2D and no other LTCs. For all increasing counts of multimorbidity (total, concordant and discordant) there were no statistically significant associations with HbA1c, GV nor TIR.

Table 3. Multivariable linear regression model: Relationship between HbA1c (%) and multimorbidity in participants with type 2 diabetes.

	Non-adjusted			Adjusted		
Predictor variables	**β (SE)**	**95% CI**	**P**	**β (SE)**	**95% CI**	**p**
Categories of diabetes and multimorbidities						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 chronic condition	-0.31 (0.26)	-0.84, 0.21	0.240	-0.27 (0.29)	-0.83, 0.29	0.345
Diabetes present and 2 chronic conditions	-0.15 (0.27)	-0.68, 0.38	0.575	-0.22 (0.29)	-0.79, 0.35	0.450
Diabetes present and 3 chronic conditions	-0.00 (0.29)	-0.58, 0.57	0.996	0.06 (0.32)	-0.56, 0.68	0.844
Diabetes present and 4 or more chronic conditions	-0.20 (0.27)	-0.73, 0.32	0.460	-0.20 (0.30)	-0.78, 0.38	0.504
Categories of diabetes and concordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 concordant condition	-0.18 (0.18)	-0.52, 0.17	0.317	-0.10 (0.19)	-0.47, 0.26	0.578
Diabetes present and 2 concordant conditions	-0.04 (0.22)	-0.46, 0.39	0.865	-0.04 (0.24)	-0.50, 0.43	0.880
Diabetes present and 3 concordant conditions	0.04 (0.29)	-0.54, 0.60	0.915	0.21(0.31)	-0.39, 0.83	0.488
Diabetes present and 4 or more concordant conditions	-0.06 (0.39)	-0.83, 0.71	0.884	-0.01 (0.42)	-0.83, 0.80	0.979
Categories of diabetes and discordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 discordant condition	0.14 (0.18)	-0.21, 0.50	0.433	0.13 (0.19)	-0.26, 0.51	0.517
Diabetes present and 2 discordant conditions	0.26 (0.20)	-0.13, 0.66	0.183	0.21 (0.21)	-0.20, 0.61	0.320
Diabetes present and 3 discordant conditions	-0.14 (0.27)	-0.68, 0.40	0.611	-0.20 (0.29)	-0.78, 0.37	0.488
Diabetes present and 4 or more discordant conditions	0.03 (0.35)	-0.65, 0.72	0.927	0.11 (0.38)	-0.63, 0.87	0.761

SE: Standard error

Adjusting for age, gender, socioeconomic status, BMI, smoking status, insulin use, and number of non-insulin hypoglycaemic medication. All co-variates were treated as fixed effects and the general practice as a random effect to allow for the correlation of HbA1c within each practice.

Table 4. Multivariable linear regression model: Relationship between glycaemic variability (CV) and multimorbidity in participants with type 2 diabetes.

	Non-adjusted			Adjusted		
Predictor variables	**β (SE)**	**95% CI**	**P**	**β (SE)**	**95% CI**	**p**
Categories of diabetes and multimorbidities						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 chronic condition	2.52 (1.76)	-0.94, 5.97	0.154	0.09 (1.75)	-3.34, 3.52	0.959
Diabetes present and 2 chronic conditions	4.44 (1.78)	0.96, 7.93	0.012	1.70 (1.78)	-1.78, 5.18	0.338
Diabetes present and 3 chronic conditions	1.97 (1.94)	-0.83, 5.78	0.309	-1.20 (1.93)	-4.99, 2.58	0.533
Diabetes present and 4 or more chronic conditions	3.93 (1.81)	0.39, 7.48	0.029	-0.45 (1.87)	-4.11, 3.21	0.808
Categories of diabetes and concordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 concordant condition	2.92 (1.14)	0.70, 5.15	0.010	1.34 (1.11)	-0.85, 5.53	0.230
Diabetes present and 2 concordant conditions	4.84 (1.39)	2.11, 7.56	0.001	2.57 (1.42)	-0.20, 5.36	0.070
Diabetes present and 3 concordant conditions	0.49 (1.88)	-3.19, 4.17	0.794	-1.43 (1.86)	-5.08, 2.22	0.442
Diabetes present and 4 or more concordant conditions	5.53 (2.57)	0.50, 10.55	0.031	-0.98 (2.65)	-6.18, 4.21	0.711
Categories of diabetes and discordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 discordant condition	-0.34 (1.23)	-2.75, 2.07	0.782	-1.33 (1.17)	-3.63, 0.97	0.258
Diabetes present and 2 discordant conditions	-0.61 (1.38)	-3.31, 2.09	0.657	-1.84 (1.29)	-4.37, 0.68	0.153
Diabetes present and 3 discordant conditions	0.39 (1.83)	-3.20, 3.98	0.832	-1.10 (1.77)	-4.57, 2.37	0.536
Diabetes present and 4 or more discordant conditions	-1.45 (2.35)	-6.06, 3.15	0.536	-2.31 (2.33)	-6.86, 2.25	0.322

SE: Standard error

Adjusting for age, gender, socioeconomic status, BMI, smoking status, insulin use, and number of non-insulin hypoglycaemic medication. All co-variates were treated as fixed effects and the general practice as a random effect to allow for the correlation of GV within each practice.

Table 5. Multivariable linear regression model: Relationship between percentage time-in-range and multimorbidity in participants with type 2 diabetes.

	Non-adjusted			Adjusted		
Predictor variables	**β (SE)**	**95% CI**	**P**	**β (SE)**	**95% CI**	**p**
Categories of diabetes and multimorbidities						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 chronic condition	3.09 (5.58)	-7.84, 14.04	0.579	0.92 (5.96)	-10.77, 12.61	0.877
Diabetes present and 2 chronic conditions	-5.84 (5.63)	-16.85, 5.17	0.299	-6.75 (6.04)	-18.58, 5.09	0.264
Diabetes present and 3 chronic conditions	-2.46 (6.13)	-14.47, 9.55	0.688	-6.51 (6.56)	-19.37, 6.36	0.322
Diabetes present and 4 or more chronic conditions	-2.93 (5.66)	-14.01, 8.16	0.605	-4.96 (6.28)	-17.26, 7.34	0.430
Categories of diabetes and concordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 concordant condition	1.71 (3.69)	-5.51, 8.94	0.642	0.77 (3.84)	-6.76,8.30	0.841
Diabetes present and 2 concordant conditions	-6.02 (4.49)	-14.82, 2.78	0.180	-7.95 (4.85)	-17.47,1.56	0.101
Diabetes present and 3 concordant conditions	-0.66 (6.09)	-12.60, 11.28	0.914	-3.73 (6.43)	-16.34, 8.86	0.561
Diabetes present and 4 or more concordant conditions	4.89 (8.24)	-11.27, 21.04	0.553	2.64 (8.71)	-14.43, 19.72	0.762
Categories of diabetes and discordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 discordant condition	-1.92 (3.81)	-9.39, 5.54	0.615	-2.30 (3.98)	-10.11, 5.50	0.563
Diabetes present and 2 discordant conditions	-8.59 (4.19)	-16.81, -0.37	0.040	-7.87 (4.24)	-16.18, 0.43	0.063
Diabetes present and 3 discordant conditions	5.85 (5.70)	-5.33, 17.03	0.305	8.40 (5.98)	-3.32, 20.11	0.160
Diabetes present and 4 or more discordant conditions	-8.65 (7.28)	-22.92, 5.61	0.234	-9.52 (7.82)	-24.86, 5.82	0.224

SE: Standard error

Adjusting for age, gender, socioeconomic status, BMI, smoking status, insulin use, and number of non-insulin hypoglycaemic medication. All co-variates were treated as fixed effects and the general practice as a random effect to allow for the correlation of TIR within each practice.

4. DISCUSSION

In this study, we examined associations between multimorbidity and measures of glycaemia in 279 people with T2D in Australian general practice using baseline data from the GP-OSMOTIC trial. The majority of people with T2D in this cohort (89.2%) were living with multimorbidity. We used CGM data to derive GV and TIR in this cohort. Our findings suggest that there was no significant relationship between multimorbidity (total, concordant and discordant) and various measures of glycaemia, including HbA1c, GV (using CV), and TIR, reflecting glucose control over 3-months to several weeks respectively.

Uncertainty exists about the association between multimorbidity and HbA1c in people with T2D (16). We did not find significant relationships between multimorbidity and a single concurrent measure of HbA1c, nor CGM related measures of glycaemia in this cohort. Our findings may be linked to the higher health care utilisation (27) and better quality of care (28) seen in people with other LTCs. Higher health care utilisation may result in more opportunities for clinical interventions leading to better glycaemic management. We did not explore health utilisation, nor did we evaluate HbA1c measures over the longer term.

Evidence suggests associations between higher GV and micro- and macrovascular complications (13, 14) including the development of diabetes peripheral neuropathy (29), and the development of cardiovascular diseases (30). Lower TIR has been linked to the development of diabetic retinopathy and diabetic nephropathy (15). There is good evidence of a relationship between higher GV, lower TIR and complications of T2D, yet we did not find any significant associations between concordant LTCs (which include some important complications of T2D), GV and TIR.

To the best of our knowledge, this is the first study to explore the effect of the total burden of disease reflected in multimorbidity on GV and TIR in people with T2D. The prevalence of multimorbidity and individual LTCs in this study align with the prevalence numbers found in studies of community cohorts of people with T2D in the UK and Taiwan (4). This suggests that a strength of this study is that we could capture multimorbidity and LTCs similar to the general population of people with T2D despite using a specialised RCT T2D cohort in general practice. There are some limitations to note for our study. This was a cross-sectional analysis of baseline data of the GP-OSMOTIC trial, which was powered to detect differences in HbA1c between the intervention and control groups. Therefore, there may be insufficient

statistical power to observe differences in GV and TIR across different multimorbidity categories. We therefore did not explore the effects of individual LTCs on glycaemic measures. Information on LTCs for this cohort was only collected at baseline and we were unable to model for changes in multimorbidity. Therefore, a limitation of our study is that we were unable to consider the temporality and duration of the conditions in addition to diabetes. Another limitation is that the study only included people attending general practice. It is possible that people attending general practice, as opposed to those receiving care from specialists, may have a lower GV as we observed the mean (SD) CV was 30.0 (8.3)% which was below the consensus cut-off of 36% defining high GV (11). As a result, we do not know if our results apply to the population that experience higher levels of GV. Therefore, those with worse GV and TIR, who may be seeing specialists and attending hospital clinics with possibly worse GV and TIR may not be represented. However, this cohort of people with T2D had HbA1c levels significantly above the recommended target.

There is an association between multimorbidity and increased mortality in people with T2D (4, 16). We explored multimorbidity's effects on measures of blood glucose as a way to understand the underlying mechanisms to the increased mortality seen in those with LTCs. Our findings suggest that future studies should explore factors other than glycaemic measures, that could contribute to the increased mortality that has been observed elsewhere. Future research involving larger patient populations to examine how clinicians and people with T2D utilise CGM and interpret CGM outputs to approach glycaemic targets and make treatment decisions in the context of multimorbidity are warranted.

CONCLUSION

In 279 well characterised people with T2D in Australian general practice, we found no significant associations between multimorbidity counts, HbA1c, GV and TIR. This study, together with recent publications on this topic (4, 16), suggest that suboptimal glycaemic levels do not explain the increased mortality seen in those with T2D and multimorbidity. Future studies should try to identify which factors, other than glycaemic measures, contribute to the increased mortality in those with T2D and multimorbidity.

ACKNOWLEDGEMENTS

Source of funding

The GP-OSMOTIC trial was supported by a Project Grant from the National Health and Medical Research Council (NHMRC) of Australia (ID APP1104241). Additional funding was provided by Sanofi Australia. In-kind support (Flash Libre Pro reader devices, sensors, and software) was provided by Abbott Diabetes Care. JC was supported by a NHMRC postgraduate scholarship (ID APP1168372). AJ was supported by a NHMRC Practitioner Fellowship and was a Sydney Medical School Foundation Fellow. JMN was supported by a Next Generation Clinical Researchers Program – TRIP Fellowship Funded from the Medical Research Future Fund.

Declaration of competing interest

No competing financial interests exist.

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9: Synthesis of Findings

In the preceding chapters (Chapters 4 to 8) I presented the five papers resulting from my systematic review and three quantitative studies. In this penultimate chapter of my thesis, I first briefly summarise how my systematic review led to my three quantitative studies. I then compare the study settings and methodologies of my studies. Finally, I present the synthesis of the findings from my quantitative studies where I bring together and compare the results to address my study aim and overarching research question:

> ***What is the relationship between multimorbidity, all-cause mortality and glycaemic outcomes in people with type 2 diabetes?***

The wider implications of my collective findings will be discussed in the following chapter (Chapter 10).

I first conducted a systematic review. In short, I explored the existing literature, all numerical counts and indices of multimorbidity and their effects on mortality and any measures of glycaemia including HbA1c, fasting plasma glucose, hypoglycaemia, glycaemic variability and time-in-range, in people with type 2 diabetes. This review identified key issues that my subsequent quantitative studies addressed. The review findings suggested that increasing multimorbidity count is significantly associated with increased mortality and risk of hypoglycaemia, though its effects on glycaemia as represented by HbA1c are mixed. My review identified that no studies have explored glycaemic variability nor time-in-range in the context of multimorbidity, and that it will be important for future studies to investigate specific patterns of multimorbidity, including concordant and discordant conditions and how they can have effects on people with type 2 diabetes. I identified a need for comparable future studies of multimorbidity in type 2 diabetes using large national and international datasets that are statistically powerful, taking into consideration specific patterns of multimorbidity including concordant and discordant conditions. I also highlighted that more work is needed to tease apart the uncertain relationship between multimorbidity and glycaemia and to understand multimorbidity's effects on emerging measures of glycaemia including glycaemic variability and time-in-range.

Therefore, my systematic review provided a foundation of knowledge in associations between multimorbidity and type 2 diabetes and identified research gaps and methodological issues that need to be addressed. My quantitative studies aimed to address the gaps identified and to explore the effects of multimorbidity with methodological rigour using four separate datasets, including different study populations, settings and countries, with each dataset offering varying outcomes to explore.

9.1 Study Settings and Methodologies

In the table below (Table 2), I summarise the settings, designs and methods of my quantitative studies. It is important to first understand the contextual settings of the study populations across my studies, because in my literature review and systematic review I found that all existing studies of multimorbidity in people with type 2 diabetes demonstrated significant heterogeneity. This was the case in all aspects of study design, multimorbidity measures used, and outcomes explored, making the findings difficult to compare. In contrast to this body of literature, my studies were similar in study designs and methodologies, and the measure of multimorbidity used. The only differences were the study settings, data collection methods and different outcomes explored. This enables comparison of results across different populations and health settings, adding methodological rigour to my PhD.

Table 2: Summary of study and participant characteristics

Database	**Study 2** **UK Biobank**	**Study 2** **Taiwan NDCMP**	**Study 3** **NPS MedicineInsight**	**Study 4** **GP-OSMOTIC**
Study characteristics				
Sample size	20,569	59,677	69,718	279
Setting	Community	Community	General practice	General practice (RCT participants – specifically selected as out-of-target HbA1c)
Country/Region	United Kingdom	Taiwan	Australia	Victoria, Australia
Study design	Longitudinal	Longitudinal	Cross-sectional	Cross-sectional
Study period	Recruited 2006 – 2010 Followed until 2018	Recruited 2001 – 2004 Followed until 2011	Extraction date: 30 Sept 2015	Recruited 2016 – 2017
Data collection	Self-report Hospital data National mortality data	Hospital data National mortality data	Extracted electronic medical records	Interview with clinically trained research assistant/nurse Electronic medical records
Outcomes explored	All-cause mortality HbA1c	All-cause mortality HbA1c	- HbA1c	- HbA1c Glycaemic variability Time-in-range
Statistical analyses	Cox proportional hazards model Multivariable linear regression	Cox proportional hazards model Multivariable linear regression	- Multivariable linear regression	- Multivariable linear regression
Participant characteristics				
Age (years), mean (SD)	60.2 (6.8)	60.8 (11.3)	66.4 (12.7)	60.4 (9.9)
Female, n (%)	7,579 (36.8)	31,339 (52.5)	32,137 (46.1)	114 (40.9)
Duration of diabetes (years), median (IQR)	4 (6)	5 (8)	Excluded variable*	12 (11)
Baseline HbA1c (%), mean (SD)	6.8 (1.2)	8.2 (2.0)	7.1 (1.4)	8.9 (1.2)

*Excluded duration of diabetes in the NPS MedicineInsight dataset: I decided to exclude this variable as there was a large proportion of participant who did not have a recorded diabetes duration in the electronic medical records. Of the 69,718 participants only 14,745 (21%) have a recorded diabetes duration which had a median (IQR) duration of 0.6 (0.5) years. After review with an academic GP (my supervisor, Jo-Anne Manski-Nankervis), we questioned the accuracy and validity of the recorded data and made the decision to exclude this variable from the study.

In summary, my three studies can be broken down into two types of settings: cohorts of people with type 2 diabetes in the community (Study 2), and cohorts of people with type 2 diabetes attending general practice (Studies 3 and 4), although study 4 was a selected subsample. Below I will briefly outline the similarities and differences in the settings and methodologies of the studies, and outcomes explored.

Community cohorts across the UK and Taiwan – Study 2: The UK Biobank and Taiwan NDCMP studies are both longitudinal studies, include large population cohorts of people with type 2 diabetes across the UK (n=20,569) and Taiwan (n=59,677) respectively, and provided the opportunity to explore all-cause mortality and HbA1c as outcomes. The two differ in the way data was collected. For the UK Biobank, data was collected through self-reporting, supplemented by hospital admissions data and linkage with national mortality data whereas the Taiwan NDCMP only used hospital data linked with national mortality data.

General practice cohort across Australia – Study 3: The NPS MedicineInsight study explored a large cohort of people with type 2 diabetes attending general practice across Australia (n=69,718). The study was cross-sectional in design using data extracted directly from the electronic medical records of the general practice clinics. The dataset provided the opportunity to explore HbA1c as the study outcome.

General practice cohort across Victoria, Australia – Study 4: The GP-OSMOTIC study explored a cohort of people with type 2 diabetes recruited for a randomised controlled trial in Victoria, Australia (n=279) that had relatively tight inclusion criteria. The data collection involved clinically trained research assistants and nurses that asked study participants specific and structured questions regarding demographics and medical histories. This was then cross-checked with the participants' electronic health records. Although this study included a relatively small sample size, it is unique in that it provided CGM data which allowed for the exploration of glycaemic variability and time-in-range as outcomes. I therefore explored HbA1c, glycaemic variability and time-in-range in this study.

9.2 Study Participants

In the previous section above, I compared the study settings and methodologies. In this section I describe the similarities and differences of the study participants across my studies.

Across the four populations of people with type 2 diabetes, the baseline characteristics were generally similar (see Table 2 above). The NPS MedicineInsight cohort had the highest mean age of 66 years whereas the other studies had mean ages of around 60 years. The Taiwan NDCMP cohort had the highest proportion of females (52.5%) and the UK Biobank had the lowest proportion of females (36.8%). Compared to the UK Biobank and Taiwan NDCMP cohort, the GP-OSMOTIC cohort had a significantly longer median diabetes duration of 12 years. This is pertinent as diabetes duration plays an important role in those with type 2 diabetes with evidence suggesting longer diabetes duration is independently associated with development of macro- and microvascular complications, cardiovascular deaths and all-cause mortality (116-118). It is important to note that both the UK Biobank and NPS MedicineInsight cohorts demonstrated more optimal glycaemic levels with mean (SD) HbA1c of 6.8 (1.2)% and 7.1 (1.4)%, respectively, compared to the Taiwan NDCMP and GP-OSMOTIC cohorts. This can be explained by the Taiwan NDCMP dataset being based on hospital data which includes those admitted into the hospital who are usually less healthy, and hence the comparatively higher mean HbA1c. The Taiwan NDCMP cohort contrasts with the UK Biobank which is a volunteer cohort known to include individuals that are less socioeconomically deprived and healthier (119). Randomised controlled trials like the GP-OSMOTIC trial have specific inclusion criteria for recruiting study participants to aid in answering the research aim. In this case the GP-OSMOTIC trial only recruited those with a HbA1c 0.5% above the general treatment target of 7%, i.e. those with HbA1c levels of greater than 7.5% (62). This cohort is therefore not representative of the broader community/general practice population of people with type 2 diabetes. However, the GP-OSMOTIC cohort represents those with high need in general practice with out-of-target HbA1c, meaning I was able to study multimorbidity in a more vulnerable group of people with diabetes.

9.3 Multimorbidity in Type 2 Diabetes

In this section, I describe the prevalence of multimorbidity and presence of individual conditions across my quantitative studies. In Table 3 below I summarise the prevalence of multimorbidity in my studies.

Table 3: Prevalence of multimorbidity in each of the study cohorts

Characteristics	**UK Biobank n = 20,569**	**Taiwan NDCMP n = 59,677**	**NPS MedicineInsight n = 69,718**	**GP-OSMOTIC n = 279**
Multimorbidity, n (%)	18,651 (90.7)	47,182 (79.0)	63,326 (90.8)	249 (89.2)
Number of chronic conditions in addition to T2D, n (%)				
None	1,918 (9.3)	12,495 (21.0)	6,392 (9.2)	30 (10.8)
1	5,114 (24.9)	18,962 (31.9)	8,497 (12.2)	70 (25.1)
2	5,109 (24.8)	10,504 (17.7)	10,614 (15.2)	68 (24.4)
3	3,643 (17.7)	11,735 (19.7)	10,516 (15.1)	42 (15.1)
≥4	4,785 (23.3)	5,808 (9.8)	33,699 (48.3)	69 (24.7)

The results were generally consistent across my studies. I showed that multimorbidity is extremely prevalent across my type 2 diabetes study populations with prevalence of 90.7%, 79.0%, 90.8% and 89.2% in the UK Biobank, Taiwan NDCMP, NPS MedicineInsight and GP-OSMOTIC datasets respectively. However, there are some slight differences. The prevalence of multimorbidity in the Taiwan cohort was slightly lower compared to the other three cohorts. For the frequency of the number of comorbid conditions, the UK Biobank and GP-OSMOTIC cohorts were similar. In the Taiwan NDCMP it seemed to be skewed to the right (greater proportion had lower condition counts) whereas it seemed to be skewed to the left for the NPS MedicineInsight (greater proportion had higher condition counts).

Tables 4 and 5 below present the prevalence of individual concordant and discordant conditions respectively. In Table 4, I show the prevalence of individual concordant conditions in each of the study cohorts. In Table 5, I present the top 10 most prevalent discordant conditions. The discordant conditions were presented differently because I wanted to highlight the most prevalent conditions from the long list of conditions included in my multimorbidity count.

As shown in Table 4, it was consistent across my studies that hypertension was the most prevalent condition followed by coronary heart disease.

*Table 4: Prevalence of concordant conditions in each of the study cohorts**

Condition	**UK Biobank n = 20,569**	**Taiwan NDCMP n = 59,677**	**NPS MedicineInsight n = 69,718**	**GP-OSMOTIC n = 279**
Hypertension	14,187 (69.0)	28,771 (48.2)	42,812 (61.4)	160 (57.4)
Coronary heart disease	3,773 (18.3)	8,639 (14.5)	11,953 (17.1)	63 (22.6)
Peripheral vascular disease	488 (2.4)	1,711 (2.9)	1,945 (2.8)	8 (2.9)
Chronic kidney disease	323 (1.6)	1,919 (3.2)	5,919 (8.5)	17 (6.1)
Stroke/TIA	1,024 (5.0)	4,350 (7.3)	4,730 (6.8)	9 (3.2)
Diabetic retinopathy	2,174 (10.6)	1,494 (2.5)	2,266 (3.3)	28 (10.0)
Diabetic neuropathy	74 (0.4)	642 (1.1)	1,117 (1.6)	28 (10.0)
Atrial fibrillation	641 (3.1)	472 (0.8)	5,318 (7.3)	12 (4.3)
Heart failure	426 (2.1)	1,394 (2.3)	4,410 (6.3)	Not available

*The numbers within the cells represent n (%).

The prevalence of the discordant conditions across my studies varied. In Table 5 below, I present the top 10 most prevalent discordant conditions in each of the studies. Painful conditions were the most prevalent discordant condition across all of the studies. Following that, dyspepsia is the second most prevalent condition in three of the four cohorts (not in the top 10 of the GP-OSMOTIC study). Conditions that were across all studies in the top 10 discordant conditions were asthma, COPD and thyroid disorders. Conditions that were across three of the four cohorts in the top 10 included dyspepsia (not in GP-OSMOTIC study), depression (not in Taiwan NDCMP), cancer (not in Taiwan NDCMP), diverticular disease (not in Taiwan NDCMP), psoriasis/eczema (not in UK Biobank) and anxiety (not in UK Biobank).

Table 5: Prevalence of top 10 discordant conditions in each of the study cohorts

	UK Biobank n = 20,569		**Taiwan NDCMP n = 59,677**		**NPS MedicineInsight n = 69,718**		**GP-OSMOTIC n = 279**	
	Condition	**n (%)**	**Condition**	**n (%)**	**Condition**	**n (%)**	**Condition**	**n (%)**
1	Painful conditions	6,250 (30.4)	Painful conditions	13,754 (23.1)	Painful conditions	38,645 (55.4)	Painful conditions	83 (29.8)
2	Dyspepsia	3,815 (18.5)	Dyspepsia	12,297 (20.6)	Dyspepsia	22,022 (31.6)	Depression	53 (19.0)
3	Asthma	2,959 (14.4)	Chronic liver disease	7,047 (11.8)	Depression	15,926 (22.8)	Asthma	39 (14.0)
4	Cancer	2,110 (10.3)	COPD	4,000 (6.7)	Anxiety	14,262 (20.5)	Dyspepsia	39 (14.0)
5	Thyroid disorders	1,688 (8.2)	Anxiety	3,398 (5.7)	Psoriasis /eczema	14,037 (20.1)	Psoriasis /eczema	21 (7.5)
6	Depression	1,643 (8.0)	Constipation	2,670 (4.5)	Cancer	12,733 (18.3)	Diverticular disease	16 (5.7)
7	Diverticular disease	1,056 (5.1)	Prostate disorders	2,513 (4.2)	Asthma	10,276 (14.7)	Thyroid disorders	14 (5.0)
8	Inflammatory bowel disease	924 (4.5)	Psoriasis /eczema	1,704 (2.9)	Thyroid disorders	7,613 (10.9)	COPD	12 (4.3)
9	Prostate disorders	890 (4.3)	Thyroid disorders	1,618 (2.7)	Diverticular disease	6,039 (8.7)	Anxiety	13 (4.7)
10	COPD	841 (4.1)	Asthma	1,404 (2.4)	COPD	5,521 (7.9)	Cancer	7 (2.5)

9.4 Multimorbidity and All-Cause Mortality in Type 2 Diabetes

I was able to explore the effect of multimorbidity on all-cause mortality in two cohorts of people with type 2 diabetes in the UK and Taiwan. This provides the opportunity to compare the findings across cohorts of people with different ethnicities in two different countries and healthcare systems.

9.4.1 Summary of Mortality Findings

The synthesis of the mortality findings has already been presented in Chapter 6 (Paper 3). The mortality findings were generally consistent across the UK and Taiwan cohorts except when I explored combinations of conditions. To summarise briefly:

- Across the two cohorts, increasing counts of multimorbidity (total, concordant and discordant) were significantly associated with increased mortality.
- Increasing counts of concordant conditions had the greatest effect on mortality.

- Individual concordant conditions, with the exception of microvascular conditions (diabetic retinopathy and neuropathy), were also significantly associated with increased mortality.
- Particular discordant conditions including alcohol problems, liver diseases, cancer and COPD had equal risk of mortality to concordant conditions.
- The mortality findings differed in the two studies when combinations of two conditions in addition to diabetes were explored.
- Whilst I have highlighted the significant contributions of cardiovascular diseases to increased mortality in the UK Biobank, my results suggest combinations of certain discordant conditions were also strongly associated with increased mortality in the Taiwan study. For example, these discordant conditions include painful conditions, alcohol problems, dyspepsia, cancer and chronic liver disease.

The implications of these findings will be discussed in detail in the following chapter (Section 10.1.2).

9.5 Multimorbidity and Glycaemic Outcomes in Type 2 Diabetes

9.5.1 Multimorbidity Counts and HbA1c

I explored associations between multimorbidity and HbA1c in people with type 2 diabetes in all of my quantitative studies. This provides the opportunity to compare the findings across different cohorts of people in different countries, healthcare systems and settings. In Table 6 below, I bring together the HbA1c results from all my studies.

Table 6: Summary of findings: associations between multimorbidity and HbA1c

	Study 2 UK Biobank		**Study 3 Taiwan NDCMP**		**Study 4 NPS MedicineInsight**		**Study 5 GP-OSMOTIC**	
Predictor variables	Adjusted [1]		Adjusted [1]		Adjusted [2]		Adjusted [3]	
Categories of T2D and multimorbidity	Mean difference in HbA1c (95% CI)	P-value	Mean difference in HbA1c (95% CI)	P-value	Mean difference in HbA1c (95% CI)	P-value	Mean difference in HbA1c (95% CI)	P-value
T2D only (reference)	ref		ref		ref		ref	
1 chronic condition + T2D	-0.07 (-0.13, -0.01)	0.031	-0.62 (-0.67, -0.58)	<0.001	-0.01 (-0.05, 0.04)	0.685	-0.27 (-0.83, 0.29)	0.345
2 chronic conditions + T2D	-0.12 (-0.18, -0.06)	<0.001	-0.72 (-0.76, -0.67)	<0.001	-0.02 (-0.06, 0.02)	0.341	-0.22 (-0.79, 0.35)	0.450
3 chronic conditions + T2D	-0.13 (-0.19, -0.06)	<0.001	-0.75 (-0.80, -0.69)	<0.001	0.00 (-0.04, 0.04)	0.968	0.06 (-0.56, 0.68)	0.844
≥4 chronic conditions + T2D	-0.20 (-0.26, -0.14)	<0.001	-0.82 (-0.88, -0.76)	<0.001	-0.01 (-0.04, 0.03)	0.731	-0.20 (-0.78, 0.38)	0.504
Categories of T2D and concordant conditions								
T2D only (reference)	ref		ref		ref		ref	
1 concordant condition + T2D	-0.11 (-0.18, -0.06)	<0.001	-0.70 (-0.74, -0.65)	<0.001	0.00 (-0.02, 0.03)	0.799	-0.10 (-0.47, 0.26)	0.578
2 concordant conditions + T2D	-0.10 (-0.16, -0.03)	0.003	-0.74 (-0.80, -0.69)	<0.001	0.02 (-0.01, 0.05)	0.150	-0.04 (-0.50, 0.43)	0.880
3 concordant conditions + T2D	-0.13 (-0.22, -0.04)	0.003	-0.78 (-0.87, -0.69)	<0.001	-0.01 (-0.05, 0.03)	0.556	0.21(-0.39, 0.83)	0.488
≥4 concordant conditions + T2D	-0.03 (-0.16, 0.09)	0.608	-0.66 (-0.83, -0.50)	<0.001	0.04 (-0.02, 0.09)	0.175	-0.01 (-0.83, 0.80)	0.979
Categories of T2D and discordant conditions								
T2D only (reference)	ref		ref		ref		ref	
1 discordant condition + T2D	-0.11 (-0.17, -0.04)	<0.001	-0.68 (-0.73, -0.63)	<0.001	-0.03 (-0.06, 0.01)	0.099	0.13 (-0.26, 0.51)	0.517
2 discordant conditions + T2D	-0.14 (-0.20, -0.08)	<0.001	-0.73 (-0.78, -0.67)	<0.001	-0.02 (-0.06, 0.01)	0.223	0.21 (-0.20, 0.61)	0.320
3 discordant conditions + T2D	-0.20 (-0.28, -0.13)	<0.001	-0.81 (-0.89, -0.74)	<0.001	-0.01 (-0.05, 0.02)	0.508	-0.20 (-0.78, 0.37)	0.488
≥4 discordant conditions + T2D	-0.23 (-0.31, -0.15)	<0.001	-0.79 (-0.89, -0.70)	<0.001	0.00 (-0.03, 0.03)	0.886	0.11 (-0.63, 0.87)	0.761

1. Adjusting for age, gender, smoking status, socioeconomic status, BMI, alcohol consumption, duration of diabetes, use of oral anti-diabetes drugs and use of corticosteroids.
2. Adjusting for age, gender, smoking status, socioeconomic status, and diabetes medication
3. Adjusting for age, gender, smoking status, socioeconomic status, BMI, insulin use, and number of non-insulin hypoglycaemic medication.

My findings showed that in community cohorts of people with type 2 diabetes (in the UK Biobank and the Taiwan NDCMP), there were statistically significant associations between increasing multimorbidity counts and lower HbA1c. This was the case for increasing total and discordant counts in the UK Biobank whereas in the Taiwan NDCMP all counts (total, concordant and discordant) of multimorbidity were associated with lower HbA1c. However, the degree of difference observed in HbA1c (ranging from -0.07% to -0.23%) seen in the UK Biobank results is not likely to be clinically significant. The relationship between increasing multimorbidity and lower HbA1c observed in the Taiwan NDCMP seemed to be non-linear. In contrast, I found no association between multimorbidity and HbA1c in the NPS MedicineInsight and GP-OSMOTIC studies. To summarise, in two community cohorts, increasing multimorbidity was associated with statistically significant lower HbA1c although in the UK Biobank it was not likely to be clinically significant, while two studies in general practice participants identified no differences in HbA1c. Across my studies, findings consistently showed that there was no relationship between all counts of multimorbidity and higher, or worse, HbA1c. The implications of the HbA1c findings will be discussed in detail in the following chapter (Section 10.1.3).

9.5.2 Multimorbidity Counts, Glycaemic Variability and Time-in-Range

In one of my studies, the GP-OSMOTIC study, I was able to explore other glycaemic outcomes, including short-term glycaemic variability and time-in-range, in addition to HbA1c because the study included CGM data. In this cohort of 279 people with type 2 diabetes attending general practice in Victoria, Australia, I found no evidence to support any associations between multimorbidity, glycaemic variability (measured by coefficient of variation) and time-in-range (Tables 3-5 of Paper 5, Chapter 8).

I also conducted an additional analysis in the Taiwan subset of Study 3 to explore the effect of total multimorbidity condition count on long-term GV measured by the coefficient of variation (CV) of HbA1c measurements from clinical visits. In short, I found statistically significant associations between one, two and three additional conditions and slightly lower HbA1c-CV; and a statistically significant association between four or more additional conditions and slightly higher HbA1c-CV. However, the small difference in HbA1c-CV is not likely to be clinically significant (see Section 6.1 Table 1).

The implications of the glycaemic variability and time-in-range findings will be discussed in the following chapter (Section 10.1.3.2).

9.5.3 Summary of Glycaemic Outcomes Findings

To summarise:

- In community cohorts of people with type 2 diabetes (UK Biobank and Taiwan NDCMP), there were statistically significant associations between increasing multimorbidity counts and lower HbA1c. However, the slightly lower HbA1c in the UK Biobank is unlikely to be clinically significant. The associations between increasing multimorbidity and lower HbA1c observed in the Taiwan NDCMP seemed to be non-linear.
- In people with type 2 diabetes attending Australian general practice (NPS MedicineInsight and GP-OSMOTIC), there was no association between multimorbidity and HbA1c.
- There were no associations between multimorbidity and emerging glycaemic outcomes including glycaemic variability (both short and long-term) and time-in-range.

The implications of my glycaemic outcomes findings will be discussed in detail in the following discussion chapter (Section 10.1.3).

9.6 Summary of Synthesis of Findings

In this penultimate chapter of my thesis, I presented the synthesis of the findings from my quantitative studies where I brought together and compared the results. In my final chapter I will discuss the wider implications of my collective findings.

10: Discussion and Conclusion

In the introduction to this thesis I described the significance of type 2 diabetes and its burden on people worldwide. This burden, and the complexity that comes with diabetes, is amplified when people live with additional chronic conditions. Living with multimorbidity is the norm for people with type 2 diabetes. In my literature review I identified that there are challenges with multimorbidity from both clinical and conceptual perspectives. I also described and highlighted clinical outcomes of importance to people with diabetes and their clinicians who care for them. These important outcomes include mortality and measures of glycaemia such as HbA1c, glycaemic variability and time-in-range. Although multimorbidity is common in type 2 diabetes, there is a paucity of knowledge about, and an unclear understanding of, the associations between multimorbidity and these outcomes. I explained how there was a clear need to better understand these important issues to move towards better and more effective care for those with diabetes who live with additional conditions. Understanding the relationship between multimorbidity and each measure of glycaemia may be a means to explore in finer detail the pathways through which multimorbidity may impact on people with type 2 diabetes.

My PhD, therefore, aimed to further understand the relationship between the total burden of disease reflected in multimorbidity and mortality and measures of glycaemia in people with type 2 diabetes.

In the first part of my discussion I reflect on my findings particularly through a clinical lens. I want to bring to life the findings as they relate to the daily burden of living with type 2 diabetes and the complex work that clinicians and patients do together. In the second part of my discussion I turn to the methodological challenges that have been highlighted in my work. I reflect on the methodological implications of my studies in two main areas. I first discuss the measurement of multimorbidity. A critical issue facing the research community is generating useful and robust evidence through comparison of studies and consolidation of findings from multiple studies being conducted globally. Secondly, I reflect on the use of different data sources in the study of multimorbidity. My studies incorporated different data sources and allowed important insights into the benefits, and constraints of these in a

world of mass data availability. Finally, I expand on the overall strengths and limitations of my thesis before exploring the implications of my findings to inform further work and future research.

10.1 Clinical Implications of Findings

10.1.1 Implications of Prevalence Findings

In the results synthesis chapter (Section 9.3) I highlighted the high prevalence of multimorbidity across all of my studies which ranged from 79.0% to 90.7%. This confirms the growing evidence base and provides a foundation from which to explore the way multimorbidity further amplifies and impacts on the already complex nature of type 2 diabetes management. This is the case for both the people who live with diabetes and the clinicians that care for them. As mentioned previously in my literature review, treatment burden is the workload of all aspects of self-management experienced by the patient and their support network. This includes the effort of engaging with a wide range of health professionals, to understand and enact self-management practices, undergo investigations, attend appointments and self-monitor (16). It is therefore likely that those with multimorbidity may experience greater levels of treatment burden due to the self-management requirements imposed by multiple different conditions, including the challenges of the competing self-management demands. With greater levels of treatment burden and the challenges of competing demands of multiple conditions, multimorbidity could lead to poorer outcomes (16-18), including reduced quality of life and increased healthcare costs (20). With these challenges, multimorbidity has been shown to be associated with increased cancer, vascular and all-cause mortalities (19). Given the complex management of multimorbidity faced by both people with type 2 diabetes and the clinicians that care for them, there exists the opportunity to develop guidelines or tools for tailored and personalised care.

The current RACGP guidelines for type 2 diabetes management acknowledge that the existing evidence base is limited and the clinical guidance regarding the management of multimorbid conditions is currently lacking (41). To address this, the guideline has set a number of principles to guide approaches for caring for those with type 2 diabetes living with multimorbidity. One of the guiding principles was “Be aware of common comorbidities

with diabetes" (41) and the findings from my studies have direct implications for this, where I identify the most commonly co-occurring conditions with diabetes across different cohorts of people. Indeed, my findings represent the most up to date and comprehensive description of the prevalence of multimorbidity in people with type 2 diabetes. The prevalence of individual conditions varied slightly across my studies. For concordant conditions, hypertension was, perhaps unsurprisingly, the most common condition, and following that were cardiovascular diseases including coronary heart disease, stroke, atrial fibrillation, peripheral vascular disease, and heart failure. It should be noted that the treatment and prevention of these conditions with the exception of atrial fibrillation and heart failure have been incorporated in the diabetes guidelines (41).

The most prevalent discordant condition across my studies was painful conditions (Section 9.3, Table 5). The guidelines recommend that clinicians should be aware of commonly occurring conditions and a guiding principle is to set treatment priorities with the patient (41). It is important to focus on the outcomes and co-occurring conditions that matter most to the individual. This is where shared decision making can be vital to ensure care is tailored to the individual (23, 35, 36, 120). Patients with multimorbidity may prioritise therapeutic interventions differently to their clinician, which could include pain relief being considered above diabetes management. As a result, we need to understand how concordant and discordant conditions, and combinations of conditions are associated with important outcomes including mortality and glycaemic outcomes in people with diabetes. An area of potential interest is how these diverse priorities could lead to different clinical trajectories that then shape the way multimorbidity impacts on mortality and glycaemic outcomes. Understanding these relationships can help both the clinician and patient in setting priorities, and implementing shared decision making in an informed way could help optimise outcomes that matter to the person with T2D and multimorbidity.

In this section, I have emphasised the high prevalence of multimorbidity in people with type 2 diabetes. With my results suggesting as many as 9 in 10 of those with diabetes live with multimorbidity, it highlights how common the challenge of living with multiple conditions is (16). Accompanying this challenge is the increased risk of mortality which I expand on in the following section, where I also discuss how my findings may potentially shape clinical care.

10.1.2 Implication of All-Cause Mortality Findings

The International Diabetes Federation states that there is one death every eight seconds as a result of type 2 diabetes and its complications (121). With these high rates of mortality, it is important to understand the causes of this excess risk of death in people with type 2 diabetes. Multimorbidity offers one particular insight into this.

In my studies I showed how multimorbidity is significantly associated with mortality in people with type 2 diabetes, including identifying the types of conditions and individual conditions that have the greatest effects on their risk of death. Increasing counts of any chronic condition are associated with increased risk of mortality, as outlined in Section 9.4, and this is consistent with previous literature (122, 123). However, my studies are the first to assess the implications of concordant versus discordant multimorbidity counts and the effects of individual conditions on mortality. My findings highlight that those with concordant conditions have the highest risk of death, with those having four or more concordant conditions having a mortality rate of approximately six times that of those without multimorbidity in the observed study period. Each concordant condition, with the exception of microvascular conditions (diabetic retinopathy and neuropathy), was associated with significantly higher risk of mortality. The presence of heart failure, peripheral vascular disease, chronic kidney disease, atrial fibrillation and coronary heart diseases had the largest effect sizes on mortality. This is consistent with existing evidence where most deaths in people with type 2 diabetes are due to concordant conditions and that myocardial infarction is the most common cause of death in type 2 diabetes (25, 100, 124-126). This prompts the question of whether it is appropriate to prioritise managing and treating the concordant conditions that have the greatest effect on mortality? It is evident that type 2 diabetes is a strong risk factor for cardiovascular disease independent of multimorbidity however my findings also show the presence of discordant conditions are also associated with increased mortality. Certain discordant conditions including alcohol problems, chronic liver disease, COPD, cancer and viral hepatitis each had similar effect sizes compared to concordant conditions on mortality. Thus, a holistic approach is important, as both concordant and discordant conditions contribute to increased mortality. My findings support the need to give important considerations to discordant conditions and their effects

on people with type 2 diabetes. As a result, generalist care may be most useful compared to a more disease specific lens for this patient group.

The effects of concordant and discordant conditions in people with type 2 diabetes have been studied previously to some extent (23, 58). However, their effects on mortality have never been explored. My findings have contributed novel knowledge to the literature with regards to the different effects of concordant and discordant conditions on mortality. My findings also highlighted the combinations of conditions that are associated with the highest mortality rate. I showed that cardiovascular diseases are present in the majority of the top combinations related to the highest risk of death, and noted the significant contributions of cardiovascular disease on mortality in the UK Biobank cohort, which is consistent with previous literature (125, 126). Certain combinations of discordant conditions are also strongly linked to increased mortality. This was noted in the Taiwan cohort (a population of primarily Chinese ethnicity) where alcohol problems, chronic liver disease, cancer and painful conditions were present in the top combinations associated with the highest risk of death. All of my findings highlight the importance of holistic and personalised care, taking into account the individual characteristics including ethnicity as well as the number and type of comorbid conditions when managing those with type 2 diabetes and multimorbidity.

A key recommendation from the recent National Institute for Health and Care Excellence (NICE) guidelines on multimorbidity is to develop prediction tools and algorithms for patients to predict mortality based on multimorbidity (127). I have identified individual conditions that are associated with the highest risk of death, namely the concordant conditions and certain discordant conditions, as discussed previously. My findings could contribute to addressing the recommendation from the NICE guidelines by providing more detailed evidence of the effects of conditions. However, there is still a need to understand the mechanisms underpinning my mortality findings, which should be an area of focus for future research (see Section 10.4). Through unpacking the details of the patterns and clusters of conditions that have effects on mortality, there could be enough information to aid clinicians and patients in making personalised priority decisions with the goal of health optimisation.

My findings could also be incorporated into clinical practice and potentially translated into risk stratification for people who live with diabetes and multimorbidity. This has the

potential to contribute to the development of clinical decision support guides to assist in interventions and treatment for people who live with multimorbidity.

To summarise, the findings from my studies highlight significant associations between increasing multimorbidity counts and increased mortality and that the effect on mortality was greatest in those with increasing concordant multimorbidity counts. Importantly, I found that having discordant conditions are also associated with increased mortality. It will be important to explore the underlying mechanisms behind the increased mortality observed in my findings (see Section 10.4). An approach I undertook to examine the mechanism underpinning this relationship was to further understand the role of glycaemia in people with type 2 diabetes in the context of multimorbidity, given evidence suggests HbA1c is a reliable risk factor for all-cause mortality in people with diabetes (128). In the following section, I expand on the findings from my studies where I explored the effects of multimorbidity on glycaemic outcomes to answer my research question and to better understand multimorbidity in people with type 2 diabetes.

10.1.3 Implications of Glycaemic Outcomes Findings

In my PhD I explored the effects of multimorbidity on a number of glycaemic outcomes in people with type 2 diabetes. This was important because it has been well established that achieving HbA1c targets is a key component of type 2 diabetes management and clinical guidelines, and is important in reducing downstream complications and risk of mortality (25). I first discuss the findings from my studies exploring the impact of multimorbidity on HbA1c and the implications of my results. I then discuss the findings and the implications when I explored the effects of multimorbidity on emerging measures of glycaemia including glycaemic variability and time-in-target range.

10.1.3.1 Multimorbidity and HbA1c in Type 2 Diabetes

In my systematic review (Chapter 5), I found that there is an unclear relationship between multimorbidity and HbA1c. This warranted further investigation to better understand how multimorbidity could impact HbA1c in people with type 2 diabetes.

The overall finding of my quantitative studies was that there was no association between increasing multimorbidity and higher HbA1c. In my community studies, the findings showed

that there were statistically significant associations between increasing multimorbidity and lower HbA1c, though the degree of difference was not likely to be clinically significant in the UK Biobank. In the Taiwan NDCMP, there was a non-linear relationship between increasing multimorbidity and lower HbA1c. My findings in general practice participants showed multimorbidity was not associated with HbA1c. This was consistent with the Teljeur et al. study (129) which was a secondary analysis exploring multimorbidity and HbA1c in a randomised controlled trial in general practice (Ireland, UK). They also showed no associations between multimorbidity and HbA1c levels and that the presence of additional chronic conditions does not appear to have a detrimental impact on an individual's HbA1c (129). My results could possibly be linked to findings from previous studies that suggested increasing number of chronic conditions is associated with better quality care (46) and higher health service utilisation (130), therefore, leading to more opportunities of care for co-existing conditions. When I considered the number of outpatient visits in the sensitivity analysis of my Taiwan NDCMP study (see Chapter 6, Paper 3), the effects of multimorbidity on HbA1c was attenuated. This is in keeping with the notion that higher health service use may play a role in glycaemic control in those with multimorbidity (an area that could inform future research as I discuss in Section 10.4 below). In people with multimorbidity and diabetes, there may be an increased focus on process measures such as HbA1c control compared to other clinical outcomes, which may be why people with multimorbidity may have worse outcomes. This was evident in a study where it suggested that older people with diabetes with additional comorbidities were more commonly overtreated with oral anti-diabetes medication and insulin, which suggest a greater focus in targeting HbA1c levels (131). Furthermore in a recent study it was evident that the proportion of patients achieving low HbA1c levels was highest among older people with diabetes and multimorbidity (132). The same study showed that older patients and those with higher comorbidity burden were more likely to be treated with insulin to achieve HbA1c levels despite potential for hypoglycaemia and uncertain long-term benefits. Across my studies I have consistently shown that multimorbidity is not associated with higher HbA1c. My findings challenge the notion of distraction from optimising glycaemia in people with multimorbidity, which I discussed as a potential issue in my literature review (see Section 2.3.2). On the contrary, my studies have highlighted that the reverse may be occurring. My findings suggest that the

increased mortality associated with increasing multimorbidity in diabetes does not seem to be related to poor HbA1c levels, which I further discuss below.

In the previous section (Sections 9.4 and 10.1.2), I highlighted associations between increasing multimorbidity and increased all-cause mortality, and that it will be important to understand the underlying mechanisms of the increased mortality observed in those with multimorbidity and type 2 diabetes. Previous literature has suggested that HbA1c is a known risk factor of mortality in people with diabetes (128). I did not explicitly explore whether the association between multimorbidity and mortality is mediated by HbA1c, however, it could be concluded from my findings that in the context of multimorbidity the increased mortality observed may not be clearly linked with higher HbA1c levels. Therefore, it is important to examine other factors in addition to HbA1c that could contribute to the increased mortality, including clinically important emerging measures of glycaemia such as glycaemic variability and time-in-target range. Furthermore, it would be pertinent to consider other factors such as patient-reported outcome measures and the way people with type 2 diabetes', and their health professionals', approach glycaemic management and targets in the context of multimorbidity. I do address these in both the discussion of limitations (Section 10.3.2) and in the section on future research (Section 10.4).

To summarise, my findings contribute novel knowledge in that they showed increasing multimorbidity counts of any type including both concordant and discordant were not associated with higher HbA1c levels. This is a robust finding across my study populations. Furthermore, the reason for the observed increased mortality in people with multimorbidity and type 2 diabetes remains unclear and merits exploration. These findings present no evidence of a clear connection to glycaemia, measured by HbA1c, and mortality in those with T2D and multimorbidity. Therefore, my findings support the generalist approach to care with a focus on the person and all the conditions they are living with, rather than focusing on a single disease.

10.1.3.2 Multimorbidity, Glycaemic Variability and Time-in-Range in Type 2 Diabetes

In the previous section, I expanded on my results with HbA1c and showed that there was no evidence that multimorbidity was associated with poor glycaemic control, as represented by

this established gold standard measure. My findings suggested it would be valuable to explore glycaemic outcomes, in addition to HbA1c, in those with diabetes and multimorbidity. As mentioned in my literature review (Section 2.4.2), in 2017 a meeting held with leaders from nine diabetes organisations around the globe led to the development of the "Beyond A1C Movement", which presented a unified case for the need to incorporate outcomes beyond HbA1c into regulatory decisions and clinical care (68). Two outcomes of importance included the consideration of glycaemic variability and time-in-range in people with type 2 diabetes using data derived from continuous glucose monitoring (CGM) systems (68). My systematic review also identified a potential evidence gap in that no studies have explored these measures in the context of multimorbidity and diabetes. I therefore now turn to my findings on these important measures of glycaemia beyond HbA1c including glycaemic variability and time-in-range.

Only one of my three quantitative studies provided the opportunity to explore short-term glycaemic variability and time-in-range in the context of multimorbidity. In my study utilising CGM data from the GP-OSMOTIC dataset, I found no evidence to support any associations between multimorbidity, glycaemic variability (measured by coefficient of variation(CV)) and time-in-range in people with type 2 diabetes (Chapter 8). I also had the opportunity to conduct additional analysis in the Taiwan subset of Study 3 (see Section 6.1) to explore the effect of multimorbidity on long-term glycaemic variability (represented by HbA1c-CV). I found no clinically significant associations between total multimorbidity condition count and HbA1c-CV. My findings were contrary to what I expected. I hypothesised that those who live with multimorbidity would have greater glycaemic variability (both short and long-term) and have lower time-in-range. This may occur because of the difficulties in maintaining regular lifestyles, diet, exercise patterns and adhering to medication regimens as a result of living with multimorbidity, all of which can contribute to fluctuations in blood glucose levels, as mentioned in my literature review (Section 2.4.2).

Glycaemic variability refers to fluctuations in blood glucose levels (133). The amplitude of fluctuations have been linked to risk of both hypoglycaemia and hyperglycaemia (134), which could be important in people who live with multimorbidity and diabetes. This is because these people may have complex therapeutic regimens, being on multiple diabetes medications, and therefore have an even greater risk of hypoglycaemia and hence greater

glycaemic variability. In previous studies there were associations between both greater short-term and long-term glycaemic variability, and micro- and macrovascular complications (88, 91) including the development of diabetes peripheral neuropathy (86), and the development of cardiovascular diseases (135). Previous studies conducted with the Taiwan NDCMP have shown that an increased level of long-term glycaemic variability is associated with stroke, mental health conditions, neurodegenerative conditions and chronic obstructive pulmonary disease (81-83, 136, 137). In contrast, my findings suggest that there is no association between complications as reflected in multimorbidity counts and glycaemic variability (both short and long-term). Perhaps this is also linked to the notion I discussed above (Section 10.1.3.1), where those living with multiple conditions are more likely to be exposed to and receive opportunities for clinical care leading to more optimal glycaemic management. This could also relate to the effect of some diabetes medications such as sodium-glucose co-transporter 2 (SGLT2) inhibitors which has been shown to be associated with lower glycaemic variability (138). In turn, better glycaemic management could result in less fluctuations in blood glucose and lower glycaemic variability, leading to more stable HbA1c levels (which aligns with my HbA1c findings described above).

Time-in-range is another important outcome to consider using data from CGM for people with type 2 diabetes (99). It has been linked to the development of complications including diabetic retinopathy and diabetic nephropathy which could progress to end-stage chronic kidney disease (139). Evidence also suggests that time-in-range is particularly important in older and/or high-risk individuals, which includes those with comorbid conditions who have more complicated treatment regimens (140). Despite this, my results did not find any associations between multimorbidity and time-in-range.

The potential to develop diabetes complications may be negated by the higher health care utilisation (130) and better quality of care (46) seen in people with additional conditions, thus resulting in more opportunities for clinical interventions leading to better glycaemic management. However, my findings have implications for further research in multimorbidity which should explore other glycaemic measures including those that can be derived from CGM data. These could include hypoglycaemia, time-below-range and time-above-range. I expand on these implications later in the future research section (Section 10.4).

10.1.4 Summary of Clinical Implications

To summarise, my findings suggest that increasing multimorbidity is significantly associated with increased mortality in people with type 2 diabetes but is not associated with higher HbA1c levels and novel measures of glycaemia. My findings support a generalist approach when caring for those with multimorbidity and type 2 diabetes where both the number and types of conditions, including discordant conditions, are important. While optimal glycaemic levels are known to be important for preventing complications, managing glycaemia should not overshadow efforts to address multimorbidity – both concordant and discordant. Holistic, patient-centred and shared decision-making approaches are likely to be effective and important when dealing with multimorbidity, equally so as the development of multimorbidity algorithms and clinical guidelines. Ultimately, it is important to consider the overall multimorbidity disease burden as a way of recalibrating and personalising our clinical focus in managing people with diabetes. By taking a holistic approach and caring for the whole person, this could potentially reduce their risk of mortality, aiding in reducing their overall burden of multimorbidity.

10.2 Methodological Implications of Findings

In the section above, I discussed the clinical implications of my findings (Section 10.1). In this section I shift to the methodological findings from my PhD. Firstly, I expand on the measurement of multimorbidity, which is a critical issue facing the research community in terms of generating comparable evidence across studies of multimorbidity. I then reflect on the use of different data sources in the study of multimorbidity in people with type 2 diabetes.

10.2.1 Measurement of Multimorbidity

There is no universally accepted measure of multimorbidity. In my PhD I measured multimorbidity using a count of conditions derived from a list of 40 important conditions developed by the foundational multimorbidity study by Barnett *et al.* (4). I chose this because in contrast to the commonly used Charlson Comorbidity Index, this multimorbidity count incorporates conditions that are commonly managed in the primary care setting. The findings from a systematic review that provided a comprehensive overview of existing measures of multiple chronic conditions and multimorbidity showed that existing measures

usually focused on diseases with high prevalence and severe impact on individuals (27). This finding also contributed to the identification of important conditions in the Barnett study. Despite Barnett's list of conditions being used internationally to study multimorbidity, there are still debates around whether all of the conditions identified are appropriate to be included in measuring multimorbidity (19, 49-51, 141). I explored the associations between this list of conditions, categorised by total, concordant and discordant counts, and important outcomes including mortality and glycaemic outcomes in diabetes. This can contribute to the discussions around whether the conditions are appropriate in the consideration of multimorbidity by identifying highly prevalent conditions and those with the greatest effects on mortality. My findings suggest that along with concordant counts of multimorbidity, certain discordant conditions have the greatest effects on mortality. My work could help in refining Barnett's list of conditions and stratifying impactful conditions, particularly in people with diabetes. I mentioned previously (Section 10.1.2) that the UK NICE guidelines for multimorbidity have recommended the development of algorithms and prediction tools to predict mortality based on multimorbidity (127). My findings have direct implications for this. Currently my work provides an up to date and comprehensive description of the multimorbidity burden in people with type 2 diabetes. I have identified the prevalence of multimorbidity, both concordant and discordant, and the most prevalent comorbid conditions and clusters of conditions to diabetes. I have also identified their effects on mortality. My findings can contribute to the development of an up-to-date prediction tool/algorithm for mortality based on multimorbidity count, weighting the most prevalent conditions that have the greatest effect on mortality.

10.2.2 Use of Data in the Study of Multimorbidity

Across my studies I used different datasets to identify conditions and quantify multimorbidity. The data collection methods for each of my studies are summarised in Table 2 (Section 9.1). This included using self-reported data from a community cohort, community and hospital data, routinely collected primary care data and data from a research cohort of a randomised controlled trial in general practice.

My findings indicate that even with different methods of identifying chronic conditions, the prevalence of multimorbidity and individual conditions were similar across my studies (see

Section 9.3). This contrasts with concerns that have suggested that different methods of identifying chronic conditions might produce different results. A study in Italian primary care showed that participants tended to self-report fewer conditions than were reported in their medical records suggesting they may underestimate their burden of disease (142). This questions the accuracy of self-reported data, however, it has been suggested that self-reporting is related to self-awareness of an individual's own health. A study in people with type 2 diabetes in primary care showed that participants who correctly reported a higher proportion of their chronic conditions had significantly lower HbA1c levels (129). This suggests that patients who have higher health literacy and are knowledgeable about their conditions may manage their health status better. This may also suggest that investing time in educating patients about their illnesses could have benefits in terms of their engagement in treatment and illness management (129), both of which are important in people living with multimorbidity.

My PhD still highlights important issues of using data in the study of multimorbidity, particularly in Australia. In my NPS Study (Study 4, Chapter 7), I utilised routinely collected general practice data from across Australia to identify multimorbidity. The prevalence of multimorbidity and LTCs identified in the NPS study align with my UK Biobank and Taiwan NDCMP study (Study 3, Chapter 6) that explored multimorbidity in community cohorts. However, this was only achieved through a comprehensive and time-consuming process of manually coding for conditions, as outlined in the introduction to Chapter 7. Under-reporting of conditions is still possible because there could be non-recording of diagnoses in the electronic medical records, as the data documented is dependent on the clinicians' recording practices. This may be due to limitations in current infrastructure and standards of electronic medical records in Australia. Currently, there are still no nationally agreed and implemented standards for electronic medical records, particularly for data structure, universally accepted systems of classification and terminology, and consistent data items with clear definitions (143). Although there are diagnostic codes for conditions, there is also a free text field within the electronic medical records that clinicians can use which often includes important clinical information. There is also no minimum requirement for the amount and types of patient data that should be collected at every patient consultation, which could help form a standardised minimum dataset. In spite of these limitations, it

should be noted that that electronic medical records were primarily developed and are being used primarily for providing clinical care, and thus will need further validation to add value to research. This is in contrast to the UK where there are systems in places to support better quality electronic medical records data which make them more useful in research. The UK Quality Outcomes Framework (QOF) is an ongoing pay-for-performance system in primary care (see Section 2.3.1) that incentivises correct coding of conditions within a certain timeframe (47). In the QOF, conditions are given diagnostic Read codes, a clinical terminology system widely used by the UK National Health Service, to systematise patient and record management, and ensure appropriate prescribing.

There is increasing interest in the use of routinely collected data in research, especially with respect to multimorbidity, where the identification of conditions is important for quality improvement and data evaluation. My PhD highlights important issues of data quality that must be addressed in the future, particularly in routinely collected general practice data in Australia. To enhance the value of routinely collected data in research, evaluation and meaningful quality improvement initiatives, these datasets will need further validation. Perhaps data linkage could be a way forward to assist in data validation through combining routinely collected general practice datasets with other data sources, such as hospital data and national mortality data. However, it must be acknowledged that there are currently barriers to data linkage. This is particularly marked in Australia where unique identifiers for each individual across datasets do not exist or use of unique identifiers is restricted (144). Therefore, individuals are matched using partially identifying non-unique variables (e.g. name, address and date of birth), and probabilities are calculated for a true match. This is in contrast to the UK where there is a unique identifier (National Health Service number) for each individual. Other barriers and challenges to data linkage include concerns about privacy, security and ethical issues surrounding consent related to the use of patient data (144). Perhaps development of methodologies that can systematically overcome the issues I have identified in this section is warranted for routinely collected data to contribute value to research.

10.3 Strengths and Limitations

I have acknowledged the strengths and limitations of each of the five studies in detail in each of their respective chapters in this thesis. However, it is important to acknowledge some of the strengths and limitations of my thesis as a whole.

10.3.1 Strengths

A major strength of my PhD is that it is a novel program including a comprehensive systematic review and three quantitative studies utilising large international and national datasets. My PhD studied a large sample size of more than 150,000 people with type 2 diabetes across four datasets in three different countries with different healthcare systems and settings. This allowed for comparability of findings across well-designed studies of separate measures of multimorbidity including total, concordant and discordant conditions, as well as range of outcomes including mortality and multiple measures of glycaemia. This provides statistically powerful information on the effects of multimorbidity in type 2 diabetes, adding to the rigour of my overall program of work. Another major strength of my PhD is that all of my studies are novel. To the best of my knowledge, my systematic review was the first of its kind, and I was the first to assess and compare the relationship between total, concordant and discordant multimorbidity counts, all-cause mortality and glycaemic outcomes in people with type 2 diabetes. Furthermore, I was the first to explore novel measures of glycaemia including glycaemic variability and time in range in the context of multimorbidity.

10.3.2 Limitations

There are some limitations to note for my PhD. A common limitation across my studies is that I identified multimorbidity conditions at baseline, and when exploring glycaemic outcomes in my PhD they were cross-sectional analyses. I was unable to explore the changes in multimorbidity during my study periods; hence I was not able to explore important considerations of the temporality and duration of conditions included in my measure of multimorbidity. I was also unable to explore the severity of the different conditions included in my multimorbidity counts. Throughout my PhD I focused on the epidemiological perspective to exploring the burden of multimorbidity, however I do acknowledge that this is a complex problem with potential social (including the role of carers), public health and political dimensions, which I did not explore and should be

explored in future studies. Another limitation is that in my mortality analyses, I did not consider the effect of interventions and medications for the conditions included in my multimorbidity count. This could attenuate the effect on mortality seen in those with multimorbidity and diabetes. Another limitation is that I did not explore hypoglycaemia in my quantitative studies. This was in part because I aimed to ensure consistency and comparability across my studies and the outcomes explored, and data on hypoglycaemia was unavailable in two of my three datasets. Hypoglycaemia could be an important area to explore because previous studies have highlighted that hypoglycaemia is associated with the development of cardiovascular complications, and increased cardiovascular events and mortality which further amplifies the multimorbidity burden in those with diabetes (145). Furthermore, a study suggests that more than 20% of people with type 2 diabetes receive intensive treatment that may be unnecessary where those with high clinical complexity, intensive treatment nearly doubles the risk of severe hypoglycaemia (146). Hypoglycaemia will be an important area to explore for future studies, which I further discuss in the future research section below.

A limitation is that although I have classified mental health conditions including depression and anxiety as discordant conditions to type 2 diabetes, there are still debates on whether this is appropriate. Studies have shown that depression and anxiety may share biological and behavioural mechanisms (147), which could mean that our classification of these conditions could lead to underestimating the associations between concordant conditions and our outcomes. In my studies there was a large overlap between the concordant and discordant condition groups. In cases where a person lives with both concordant and discordant conditions, I did not explore this overlap and the individual effects of the two condition groups on HbA1c and mortality. I did not examine the combinations of concordant and discordant conditions because it was outside the scope of my PhD which was more focused on the overall burden of multimorbidity, and this may have obscured important findings from my work. Moreover, I also did not explore the overlap of the effects of individual conditions within the same condition cluster, for example, the overlap between chronic liver diseases and alcohol problems. Another limitation across my studies is the fact that a long list of discordant conditions was considered in my multimorbidity count, including many with lower prevalence, which may have diluted the overall effects on the

outcomes I explored. Finally, I identified important findings in the study of multimorbidity in people with type 2 diabetes, however, they may not always be appropriate to extrapolate to the wider population of people with multimorbidity.

10.4 Implications for Future Research

There are a number of implications for future research related to better understanding multimorbidity in type 2 diabetes.

I have shown that multimorbidity is associated with increased mortality in type 2 diabetes but not with measures of glycaemia. This has implications for future research where it will be important to understand the mechanisms underpinning thes observed higher mortality rates. It will also be pertinent for future studies to conduct mediation analyses of HbA1c to understand the extent to which the relationship between multimorbidity and mortality is mediated by HbA1c. It will also be important to see whether this is feasible using routinely collected data, given the challenges of data linkage between routinely collected data and information on mortality, as I have described above.

Another important consideration for future research is the role which health service utilisation plays in the relationship between multimorbidity and glycaemia. In the sensitivity analysis of the Taiwan subset of Study 3, I found that when I considered health utilisation using the number of outpatient visits as a proxy measure, it attenuated the effect on HbA1c. Future studies should further explore health service use in people with multimorbidity and diabetes to confirm whether having multimorbidity is associated with more opportunities for care (due to higher health utilisation) and thus leading to more optimal glycaemic management.

Conducting qualitative investigations is another important method to further understand multimorbidity in people with type 2 diabetes which could add to my quantitative findings. There is substantial amount of qualitative work in people with multimorbidity more generally exploring the experiences of patients and clinicians (148), however not specifically related to type 2 diabetes in the context of multimorbidity. Future qualitative studies in people with diabetes could focus on the clinician and patient's perspectives on the treatment burden experienced by those with multimorbidity, and in particular their

approach to concordant and discordant conditions. Qualitative work could also be conducted to understand the role of glycaemia in the context of multimorbidity, for example exploring how patients and their clinicians approach glycaemic targets and management whilst balancing the management of additional conditions to diabetes.

Although I have explored novel measures of glycaemia including glycaemic variability and time in range using continuous glucose monitoring data, it will be important for future research to explore other measures of glycaemia. An important area to explore is hypoglycaemia, particularly in the context of multimorbidity and diabetes. It could be a potential contributing factor to the increased mortality seen in those with multimorbidity and diabetes (94, 149). Future studies could also explore other novel glycaemic measures such as time-below-range and time-above-range at different time periods throughout the day to gain a better insight into how multimorbidity could be associated with acute hyper- and hypoglycaemic excursions. However, we must consider whether increasing complex and nuanced measures of glycaemia using continuous monitoring data are truly going to provide insight into how multimorbidity impacts on people's lives. It may be too premature to assume this, therefore, it may be worthy of further research.

Exploring factors independent of HbA1c could help to better understand the mechanisms behind the increased mortality. An area of importance for future studies is to consider exploring polypharmacy in the context of multimorbidity in those with type 2 diabetes. There is evidence that polypharmacy, regardless of type of medication and/or conditions is associated with disease progression and mortality (49, 150, 151). Future studies could also examine patient-reported outcome measures that I was unable to explore in my studies where I used large datasets. These patient-reported outcome measures could include quality of life measures which can be difficult to be captured by quantitative studies. In particular, they are not always available in large epidemiological datasets or in routinely collected primary care data. A previous study had explored quality of life in those with type 2 diabetes using data from a patient experience survey among the attendees at specialist outpatient clinics in Hong Kong (152). It will be important for future studies, perhaps using mixed approaches, to explore the lived experiences of those with multimorbidity and type 2 diabetes through understanding their quality of life. It may a method to further understand the underlying causes of the increased mortality we see in this complex group of patients.

10.5 Summary and Conclusion

At the beginning of my PhD, I aimed to understand the complex issue of multimorbidity in people with type 2 diabetes. At the conclusion of my thesis I can reflect that this PhD has contributed a novel and deeper understanding of the significance of multimorbidity in those with diabetes. I have identified that multimorbidity is extremely common and imposes a significant burden on people living with type 2 diabetes. I have provided an insight into the effects of different patterns of multimorbidity on important health outcomes in different cohorts of people with type 2 diabetes. I have highlighted the increased mortality in those with multimorbidity, both concordant and discordant, and that there is no relationship between multimorbidity and glycaemic outcomes. While managing glycaemia in people with type 2 diabetes is important, it should not overshadow efforts to address multimorbidity, both concordant and discordant. It is important to consider the overall multimorbidity disease burden as a way of recalibrating and personalising our clinical focus in caring for people with diabetes. Approaching the care of these complex patients through a holistic lens has the potential to reduce their risk of mortality, and ultimately lower the overall burden of multimorbidity.

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12: Appendices

12.1 Additional files for Paper 1

Supplementary Document 1

Full Search Strategy – MEDLINE (OVID)

#	Searches
1	multimorbid* or multi morbid*
2	condition count*
3	multiple condition* or multiple disease* or multiple disorder*
4	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
5	or/1-4
6	diabet*
7	5 and 6
8	limit 7 to english
9	animal not human
10	8 not 9
11	multimorbid* or multi morbid*
12	condition count*
13	multiple condition* or multiple disease* or multiple disorder*
14	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
15	comorbid* or co morbid*
16	or/11-15
17	glycaem* or glycem* or hyperglycaem* or hyperglycem* or hypoglycaem* or hypoglycem* or glycem* varia* or glycaem* varia*
18	(mortality or death or surviv* or surviv* analys*) or mortality
19	(diabetes adj2 ("type 2" or "type ii"))
20	19 and 16
21	20 and (17 or 18)
22	limit 21 to english
23	10 or 22

Supplementary Document 2

Data extraction form

Reviewer Name	
Review Date	
STUDY	
First author	
Year	

STUDY CHARACTERISTICS

	Response	Notes
Setting		
Country		
Study Design		
Period of Study		
Aims and Objectives		

POPULATION and COMPARATOR

POPULATION	Response	Notes
Total number of participants		
Total number of participants with T2D		
How was T2D defined or measured in this population?		
How was the study population recruited?		
What were the sampling methods? Explain		
Inclusion criteria for study population		
Exclusion criteria for study population		
COMPARATOR		
Was there data on people with T2D with no other chronic condition (only T2D)?	☐Yes ☐No	If yes, please fill in both columns of table 1. If no only fill in the left column.
Total number of participants with T2D		

with <u>no</u> other chronic condition		

Table 1: Characteristics of those with and without type 2 diabetes

Characteristics	**T2D population n =**	**T2D Only (T2D with no other conditions – control group) n =**
Age, mean (SD)		
Female sex, N (%)		
Ethnicity, N (%) - Caucasian - Etc.		
Social economic status -		
Occupation -		
Education -		
Diabetes duration, mean (SD)		
HbA1c, mean (SD)		
Body mass index, kg/m^2, mean (SD)		
Insulin treated, N (%)		
Oral anti-diabetes drugs, N(%) - None - One - Two or more - Etc.		

EXPOSURE

	Response	Notes
How was multimorbidity count defined in this population?		
List the conditions included for multimorbidity count		

Table 2: Multimorbidity characteristics of those with type 2 diabetes
Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

Multimorbidity Characteristics	**Number of people with MM characteristic recorded n =**
Multimorbidity count	
0 comorbidity, N (%)	
1 comorbidity, N (%)	
2 comorbidities, N (%)	
3 comorbidities, N (%)	
4 comorbidities, N (%)	
5 comorbidities, N (%)	
6+ comorbidities, N (%)	
Comorbid conditions	
e.g. Hypertension, N(%)	
e.g. Cardiovascular disease, N(%)	
Add additional columns and rows if needed	

OUTCOMES

MORTALITY OUTCOME:

	Response	Notes
Is all-cause mortality an outcome?	☐Yes ☐No	
How was all-cause mortality measured?		
Statistical analysis; How was the relationship between multimorbidity count and all-cause mortality explored?		
Length of follow up		

Table 3: Hazard ratios and 95% Confidence Interval (reword if MM count and mortality relationship explored differently) for effect of MM count on Mortality in people with T2D
Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

Multimorbidity Characteristics	**HR (95% CI)**
Multimorbidity count	
0 comorbidity	
1 comorbidity	
2 comorbidities	
3 comorbidities	
4 comorbidities	
5 comorbidities	
6+ comorbidities	
Comorbid conditions	
e.g. Hypertension	
e.g. Cardiovascular disease	

What variables were adjusted in the statistical analysis?: ___

GLYCAEMIC OUTCOME:

	Response	Notes
Are any measures of glycaemia an outcome?	☐Yes ☐No	
How was glycaemia measured?	☐HbA1c ☐Fasting plasma glucose ☐Hypoglycaemic event ☐Hyperglycaemic event ☐Any measure of glycaemic variability Explain:	
Statistical analysis; How was the relationship between multimorbidity count and glycaemia explored?		
What was glycaemic outcome treated as	☐Continuous outcome ☐Categorical outcome ☐Both Explain:	
Length of follow up		this may not be applicable as we are only looking at cross sectional data

If glycaemic outcome is measured as a continuous variable use this: ☐Yes ☐No

Table 4: Estimated mean change, β1 and 95% Confidence Interval, in HbA1c (reword if MM count and glycaemia relationship measured differently) for effect of MM count on glycaemia (measured in HbA1c) in people with T2D

Or

If glycaemic outcome is measured as a categorical variable use this: ☐Yes ☐No

Table 4: Odds ratios and 95% Confidence Interval (reword if MM count and glycaemia relationship measured differently) for effect of MM count on glycaemia (if measured in OR, glycaemia most likely measured in hypoglycaemic/hyperglycaemic events) in people with T2D

Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

	Reviewer uses 1 of the columns below depending on whether glycaemic outcome is measured as continuous or categorical			
Multimorbidity Characteristics	**Continuous: Estimated mean change, β1 (95% CI)**	**p-value**	**Categorical: OR (95% CI)**	**p-value**
Multimorbidity count				
0 comorbidity, N (%)				
1 comorbidity, N (%)				
2 comorbidities, N (%)				
3 comorbidities, N (%)				
4 comorbidities, N (%)				
5 comorbidities, N (%)				

6+ comorbidities, N (%)				
Comorbid conditions				
e.g. Hypertension, N(%)				
e.g. Cardiovascular disease, N(%)				

What variables were adjusted in the statistical analysis?: ___

OTHER

	Response	Notes
Was there missing data? **Explanation**	☐Yes, explain: ☐No	
Attrition? **Explanation:**	☐Yes, explain: ☐No	
Authors' conclusion		
Miscellaneous comments		
Funding source		
Other		
Additional notes		

12.2 Additional files for Paper 2

Table S1 - Inclusion and exclusion criteria for papers.

The inclusion and exclusion criteria used during the screening process.

Inclusion Criteria	
Types of studies	No restrictions on publication date. The search end date will be 28 July 2017.
	Studies from any geographical location.
	English language.
	Target studies were studies that use either longitudinal cohort (retrospective and prospective) or cross-sectional designs.
Types of participants	Adults (18 years of age or older) with type 2 diabetes (T2D).
Types of exposure measures	Multimorbidity (MM) condition count. Any type of MM count, including numerical counts and particular scales. This may include a list of chronic conditions from a variety of datasets including electronic medical records, administrative and prescription datasets. Only studies that assess the relationship between a numerical count of MM and our outcomes of interest were included.
Types of outcome measures	All-cause mortality or any glycaemic outcomes.

Exclusion Criteria	
Types of studies	Non English language.
	Grey literature / not published in a peer reviewed journal.
	Dissertations /theses.
	Proceedings.
	Published abstracts.
	Studies using the following methodologies: randomised controlled trials, non-diabetes drug intervention studies, all qualitative studies, case reports and review articles.
Types of participants	Children (<18 yrs).
	People without T2D (eg, people with prediabetes, type 1 diabetes/gestational diabetes/monogenic diabetes)
	Animals.
Types of exposure measures	Studies with single nominated specific conditions (ie, only one comorbid condition) linked with T2D without MM count.

Tables S2 and S3

Table S2 can be accessed via this link:

https://doi.org/10.1371/journal.pone.0209585.s002

Table S3 can be accessed via this link:

https://doi.org/10.1371/journal.pone.0209585.s003

Text S1 – Full Search Strategy

Full Search Strategy – MEDLINE(OVID) Search Date: 28/07/17

#	Searches
1	multimorbid* or multi morbid*
2	condition count*
3	multiple condition* or multiple disease* or multiple disorder*
4	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
5	or/1-4
6	diabet*
7	5 and 6
8	limit 7 to English
9	animal not human
10	8 not 9
11	multimorbid* or multi morbid*
12	condition count*
13	multiple condition* or multiple disease* or multiple disorder*
14	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
15	comorbid* or co morbid*
16	or/11-15
17	glycaem* or glycem* or hyperglycaem* or hyperglycem* or hypoglycaem* or hypoglycem* or glycem* varia* or glycaem* varia*
18	mortality or death or surviv* or surviv* analys*
19	(diabetes adj2 ("type 2" or "type ii"))
20	19 and 16
21	20 and (17 or 18)
22	limit 21 to English
23	10 or 22

Full Search Strategy – EMBASE(OVID) Search Date: 28/07/17

#	Searches
1	multimorbid* or multi morbid*
2	condition count*
3	multiple condition* or multiple disease* or multiple disorder*
4	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*

5	or/1-4
6	diabet*
7	5 and 6
8	limit 7 to English
9	animal not human
10	8 not 9
11	conference*.pt.
12	10 not 11
13	multimorbid* or multi morbid*
14	condition count*
15	multiple condition* or multiple disease* or multiple disorder*
16	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
17	comorbid* or co morbid*
18	or/13-17
19	glycaem* or glycem* or hyperglycaem* or hyperglycem* or hypoglycaem* or hypoglycem* or glycem* varia* or glycaem* varia*
20	mortality or death or surviv* or surviv* analys*
21	(diabetes adj2 ("type 2" or "type ii"))
22	21 and 18
23	22 and (19 or 20)
24	limit 23 to English
25	conference*.pt.
26	24 not 25
27	21 or 26

Full Search Strategy – The Cochrane Library (OVID) Search Date: 28/07/17

#	Searches
1	multimorbid* or multi morbid*
2	condition count*
3	multiple condition* or multiple disease* or multiple disorder*
4	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
5	or/1-4
6	diabet*
7	5 and 6
8	limit 7 to English
9	multimorbid* or multi morbid*
10	condition count*
11	multiple condition* or multiple disease* or multiple disorder*
12	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
13	comorbid* or co morbid*
14	or/9-13
15	glycaem* or glycem* or hyperglycaem* or hyperglycem* or hypoglycaem* or hypoglycem* or glycem* varia* or glycaem* varia*
16	mortality or death or surviv* or surviv* analys*
17	(diabetes adj2 ("type 2" or "type ii"))

18	17 and 14
19	18 and (15 or 16)
20	limit 19 to English
21	8 or 20

Full Search Strategy – CINAHL Complete (Ebsco) Search Date: 28/07/17

#	Searches
1	multimorbid* or multi morbid*
2	condition count*
3	multiple condition* or multiple disease* or multiple disorder*
4	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
5	1 or 2 or 3 or 4
6	diabet*
7	5 and 6
8	limit 7 to English
9	multimorbid* or multi morbid*
10	condition count*
11	multiple condition* or multiple disease* or multiple disorder*
12	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
13	comorbid* or co morbid*
14	9 or 10 or 11 or 12 or 13
15	glycaem* or glycem* or hyperglycaem* or hyperglycem* or hypoglycaem* or hypoglycem* or glycem* varia* or glycaem* varia*
16	mortality or death or surviv* or surviv* analys*
17	diabetes N2 "type 2"
18	diabetes N2 "type ii"
19	17 or 18
20	14 and 19
21	15 or 16
22	21 and 20
23	limit 22 to English
24	23 or 8

Full Search Strategy – SCOPUS Search Date: 28/07/17

((TITLE-ABS-KEY (diabet*)) AND (TITLE-ABS-KEY (multimorbid* OR "multi morbid*" OR "condition count*" OR "multiple condition*" OR "multiple disease*" OR "multiple disorder*" OR multicondition* OR multidisease* OR multidisorder* OR "multi condition*" OR "multi disease*" OR "multi disorder*")) OR ((TITLE-ABS-KEY (multimorbid* OR "multi morbid*" OR "condition count*" OR "multiple condition*" OR "multiple disease*" OR "multiple disorder*" OR multicondition* OR multidisease* OR multidisorder* OR "multi condition*" OR "multi disease*" OR "multi disorder*" OR comorbid* OR "co morbid*"))) AND ((TITLE-ABS-KEY (glycaemia* OR glycemia* OR hypoglycaem* OR hypoglycem* OR hyperglycaem* OR hyperglycem* OR "glycem* varia*" OR "glycaem* varia*" OR mortality OR death OR surviv* OR "surviv* analys*"))) AND ((TITLE-ABS-KEY (diabetes W/2 "type 2")) OR (TITLE-ABS-KEY (diabetes W/2 "type ii")))) AND (LIMIT-TO (DOCTYPE , "ar ")) AND (LIMIT-TO (LANGUAGE , "English "))

Text S2 – Quality Appraisal

ID	First Author	Year	Outcome	Selection: 1) Representativeness of the exposed cohort Max 1	2) Selection of the non-exposed cohort Max 1	3) Ascertainment of exposure Max 1	Comparability: 1) Comparability of cohorts on the basis of the design or analysis Max 2	Outcome: 1) Assessment of outcome Max 1	2) Was follow-up long enough for outcomes to occur (3 years for mortality outcome, 1 year for cohort studies with glycaemic outcomes, n/a for cross sectional studies) Max 1	3) Adequacy of follow up of cohorts Max 1
12	Escalada	2016	Both	*	*	*	*	*		*
19	Gallegos-Carrillo	2009	FPG	*	*		**	*	n/a	n/a
1	Abbatecola	2015	HbA1c			*		*	n/a	n/a
5	Bae	2016	HbA1c	*	*	*	**	*	n/a	n/a
11	El-Kebbi	2001	HbA1c			*	**	*	n/a	n/a
15	Foran	2015	HbA1c		*		*	*	n/a	n/a
16	Fox	2006	HbA1c	*	*	*		*	n/a	n/a
17	Frei	2012	HbA1c		*			*	n/a	n/a
24	Hudon	2008	HbA1c		*	*	*	*	n/a	n/a
35	Luijks.	2015	HbA1c	*	*	*	**	*	*	
46	Mosen	2017	HbA1c	*	*	*	*	*	n/a	n/a
49	Pollack	2010	HbA1c	*	*	*	*	*	*	*
52	Romero	2013	HbA1c		*	*		*	*	*
54	Svensson	2016	HbA1c	*	*	*	**	*		*
55	Teljeur	2013	HbA1c	*	*	*	*	*	n/a	n/a
57	Walker	2015	HbA1c	*	*	*	**	*	n/a	n/a
2	Abbatecola	2015	Hypo	*	*	*	**	*	*	*
14	Fonseca	2017	Hypo	*	*	*		*	*	*
28	Kim	2016	Hypo	*	*	*		*	n/a	n/a
29	Kostev	2014	Hypo	*	*	*	*	*	*	*
39	McCoy	2013	Hypo	*	*	*			n/a	n/a
50	Quilliam	2011	Hypo	*	*	*	*	*		*
51	Rathmann	2013	Hypo	*	*	*	**	*	*	*

53	Signorovitch	2013	Hypo	*	*	*		*	*	*
61	Yu	2014	Hypo	*	*	*	*	*	*	*
7	Castro-Rodriguez	2016	Mortality	*	*	*	*	*	*	*
20	Greenfield	2009	Mortality	*	*		*	*	*	*
23	Huang	2014	Mortality		*	*			*	
25	Hunt	2013	Mortality		*	*	*	*	*	*
27	Kheirbek	2013	Mortality		*	*	*	*		*
30	Lin	2015	Mortality	*	*	*	*	*	*	*
36	Lynch	2014	Mortality		*	*	*	*	*	*
37	Martin	2015	Mortality	*	*	*	*	*		*
40	McEwen	2012	Mortality	*	*	*	*	*	*	*
43	Monami	2007	Mortality	*	*	*	*	*	*	
44	Monami	2006	Mortality	*	*	*	**	*	*	*
56	Walker	2016	Mortality	*	*	*	*	*		*
58	Wang	2014	Mortality		*	*	**	*	*	*
59	Weir	2016	Mortality	*	*	*	*	*	*	
60	Wilke	2015	Mortality	*	*	*		*		*
62	Zelada	2016	Mortality		*	*	*	*		*

All studies were assessed using the Newcastle-Ottawa quality assessment scale (1). We adapted the quality assessment scale to suit our systematic review. We omitted the final item in the selection domain which seeks to determine whether the outcome of interest was or was not present at the start of study. This item was deemed inappropriate for our review where mortality as an outcome would not be present at the start of the study being assessed and the majority of the studies would have glycaemic measures present at the start of the study.

A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability; one star (*) given if the study controls for age in analysis and two stars (*) given if study controls for both age and duration of diabetes.

1. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [cited 2017 28 July]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

12.3 Additional files for Paper 3:

Table S1 – List of long-term conditions considered for multimorbidity count

Long term conditions grouping	Conditions included
Concordant conditions	
1. Hypertension	Hypertension Essential hypertension
2. Coronary heart Disease	Heart attack/Myocardial infarction Angina
3. Peripheral vascular disease	Peripheral vascular disease Leg claudication/intermittent claudication
4. Chronic kidney disease	Polycystic kidney Diabetic nephropathy Renal/kidney failure Renal failure requiring dialysis Renal failure not requiring dialysis Kidney nephropathy Immunoglobulin A (IgA) nephropathy
5. Stroke/Transient Ischaemic Attack (TIA)	Stroke TIA Subarachnoid haemorrhage Brain haemorrhage Ischaemic stroke
6. Diabetic retinopathy	Diabetic eye disease
7. Diabetic neuropathy	Diabetic neuropathy/ulcers
8. Atrial fibrillation	Atrial fibrillation
9. Heart failure	Cardiomyopathy Hypertrophic cardiomyopathy Heart failure/pulmonary oedema
Discordant conditions	
10. Depression	Depression Postnatal depression
11. Painful conditions	Back pain Joint pain Headaches (not migraine) Sciatica Plantar fasciitis Carpal tunnel syndrome Fibromyalgia Arthritis Shingles Disc problem Prolapsed disc/slipped disc

	Spine arthritis/spondylitis Ankylosing spondylitis Back problem Osteoarthritis Gout Cervical spondylosis Trigeminal neuralgia Disc degeneration Trapped nerve/compressed nerve
12. Asthma	Asthma
13. Dyspepsia	Gastro-oesophageal reflux (GORD)/gastric reflux Oesophagitis /Barrett's oesophagus Gastric stomach ulcers Gastric erosions/gastritis Duodenal ulcer Dyspepsia/indigestion Hiatus hernia Helicobacter pylori
14. Thyroid disorders	Thyroid problem (not cancer) Hyperthyroidism/thyrotoxicosis Hypothyroidism/myxoedema Grave's disease Thyroid goitre Thyroiditis
15. Rheumatoid arthritis and other connective tissue disorders	Myositis/myopathy Systemic Lupus Erythematosus Connective tissue disorder Sjogrens syndrome/sicca syndrome Dermatopolymyositis Scleroderma/systemic sclerosis Rheumatoid arthritis Psoriatic arthropathy Dermatomyositis Polymyositis Polymyalgia Rheumatica Malabsorption/coeliac disease
16. Irritable bowel syndrome	Irritable bowel syndrome
17. Cancer	Lifetime diagnosis
18. Alcohol problems	Alcohol dependency Alcoholic liver disease/alcoholic cirrhosis
19. Other psychoactive substance misuse	Opioid dependency Other substance abuse/dependency
20. Constipation	Constipation
21. Diverticular disease	Diverticular disease Diverticulitis
22. Prostate disorders	Prostate problem (not cancer)

	Enlarged prostate Benign prostatic hypertrophy
23. Glaucoma	Glaucoma
24. Epilepsy	Epilepsy
25. Dementia	Dementia Alzheimer's disease Cognitive impairment
26. Schizophrenia/bipolar disorder	Schizophrenia Mania/ Bipolar disorder Manic depression
27. Psoriasis/eczema	Eczema Dermatitis Psoriasis
28. Inflammatory bowel disease	Inflammatory Bowel Disease Crohn's disease Ulcerative colitis
29. Migraine	Migraine
30. Chronic sinusitis	Chronic sinusitis
31. Anorexia/bulimia	Anorexia Bulimia Other eating disorders
32. Bronchiectasis	Bronchiectasis
33. Parkinson's disease	Parkinson's disease
34. Multiple sclerosis	Multiple sclerosis
35. Viral hepatitis	Infective/viral hepatitis Hepatitis B Hepatitis C Hepatitis D Hepatitis E
36. Chronic liver disease	Oesophageal varices Non infective hepatitis Liver failure/cirrhosis Primary biliary cirrhosis
37. Osteoporosis	Osteoporosis
38. Chronic fatigue syndrome	Chronic fatigue syndrome
39. Endometriosis	Endometriosis
40. Meniere's disease	Meniere's disease
41. Pernicious anaemia	Pernicious anaemia
42. Polycystic ovary	Polycystic ovary

Table S2 – Sensitivity analysis: Relationship of multimorbidity total count with HbA1c in participants with type 2 diabetes using multivariable linear regression model in UK Biobank and Taiwan NDCMP

	UK Biobank		**Taiwan NDCMP**	
Predictor variables	**Adjusted***		**Adjusted****	
Categories of diabetes and multimorbidity	**Mean difference in HbA1c (95% CI)**	**P-value**	**Mean difference in HbA1c (95% CI)**	**P-value**
Diabetes present and no chronic conditions (reference)	ref		ref	
Diabetes present and 1 chronic condition	-0.07 (-0.13, -0.01)	0.027	-0.44 (-0.49, -0.40)	<0.001
Diabetes present and 2 chronic conditions	-0.13 (-0.18, -0.06)	<0.001	-0.47 (-0.52, -0.42)	<0.001
Diabetes present and 3 chronic conditions	-0.14 (-0.20, -0.07)	<0.001	-0.44 (-0.50, -0.38)	<0.001
Diabetes present and ≥4 chronic conditions	-0.21 (-0.28, -0.15)	<0.001	-0.41 (-0.48, -0.35)	<0.001
Categories of diabetes and concordant conditions				
Diabetes present and no chronic conditions (reference)	Ref		ref	
Diabetes present and 1 concordant chronic condition	-0.13 (-0.18, -0.07)	<0.001	-0.22 (-0.26, -0.18)	<0.001
Diabetes present and 2 concordant chronic conditions	-0.11 (-0.17, -0.04)	0.001	-0.20 (-0.25, -0.15)	<0.001
Diabetes present and 3 concordant chronic conditions	-0.13 (-0.21, -0.04)	0.003	-0.14 (-0.23, -0.05)	0.002
Diabetes present and ≥4 concordant chronic conditions	-0.06 (-0.19, 0.07)	0.366	-0.05 (-0.10, -0.21)	0.509
Categories of diabetes and discordant conditions				
Diabetes present and no chronic conditions (reference)	ref		ref	
Diabetes present and 1 discordant chronic condition	-0.12 (-0.17, -0.06)	<0.001	-0.20 (-0.24, -0.16)	<0.001
Diabetes present and 2 discordant chronic conditions	-0.15 (-0.21, -0.08)	<0.001	-0.17 (-0.22, -0.12)	<0.001
Diabetes present and 3 discordant chronic conditions	-0.22 (-0.29, -0.14)	<0.001	-0.19 (-0.26, -0.12)	<0.001
Diabetes present and ≥4 discordant chronic conditions	-0.25 (-0.33, -0.17)	<0.001	-0.04 (-0.13, -0.06)	0.411

* Adjusting for age, gender, BMI, smoking status, alcohol consumption, socioeconomic status, baseline HbA1c, duration of diabetes, use of oral anti-diabetes drugs and use of corticosteroids, and physical activity

****** Adjusting for age, gender, BMI, smoking status, alcohol consumption, socioeconomic status, baseline HbA1c, duration of diabetes, use of oral anti-diabetes drugs, use of corticosteroids, and number of outpatient visits

Table S3 – Sensitivity analysis: Relationship between multimorbidity total count and all-cause mortality in participants with type 2 diabetes using multivariable Cox's Proportional Hazards model in UK Biobank and Taiwan NDCMP

	UK Biobank		Taiwan NDCMP	
Predictor variables	**Adjusted***		**Adjusted****	
Categories of diabetes and multimorbidity	**HRs (95% CI)**	**P-value**	**HRs (95% CI)**	**P-value**
Diabetes present and no chronic conditions (reference)	1		1	
Diabetes present and 1 chronic condition	1.14 (0.89, 1.48)	<0.001	1.19 (1.11, 1.27)	<0.001
Diabetes present and 2 chronic conditions	1.69 (1.32, 2.16)	<0.001	1.43 (1.33, 1.52)	<0.001
Diabetes present and 3 chronic conditions	2.03 (1.58, 2.61)	<0.001	1.84 (1.72, 1.98)	<0.001
Diabetes present and ≥4 chronic conditions	2.91 (2.28, 3.71)	<0.001	2.60 (2.42, 2.80)	<0.001
Categories of diabetes and concordant conditions				
Diabetes present and no chronic conditions (reference)	1		1	
Diabetes present and 1 concordant chronic condition	1.52 (1.19, 1.96)	<0.001	1.22 (1.16, 1.27)	<0.001
Diabetes present and 2 concordant chronic conditions	2.28 (1.76, 2.96)	<0.001	1.60 (1.51, 1.69)	<0.001
Diabetes present and 3 concordant chronic conditions	3.79 (2.87, 5.01)	<0.001	2.38 (2.21, 2.56)	<0.001
Diabetes present and ≥4 concordant chronic conditions	5.26 (3.83, 7.21)	<0.001	3.19 (2.86, 3.55)	<0.001
Categories of diabetes and discordant conditions				
Diabetes present and no chronic conditions (reference)	1		1	
Diabetes present and 1 discordant chronic condition	1.83 (1.42, 2.36)	<0.001	1.15 (1.10, 1.20)	<0.001
Diabetes present and 2 discordant chronic conditions	1.99 (1.53, 2.60)	<0.001	1.32 (1.25, 1.39)	<0.001
Diabetes present and 3 discordant chronic conditions	2.44 (1.85, 3.23)	<0.001	1.63 (1.53, 1.74)	<0.001
Diabetes present and ≥4 discordant chronic conditions	3.22 (2.43, 4.26)	<0.001	2.06 (1.91, 2.23)	<0.001

* Adjusting for age, gender, BMI, smoking status, alcohol consumption, socioeconomic status, baseline HbA1c, duration of diabetes, use of oral anti-diabetes drugs and use of corticosteroids, and physical activity

**** Adjusting for age, gender, BMI, smoking status, alcohol consumption, socioeconomic status, baseline HbA1c, duration of diabetes, use of oral anti-diabetes drugs, use of corticosteroids, and number of outpatient visits

Table S4 – Sensitivity analysis using only hospital verified data for identifying chronic conditions

Prevalence of individual multimorbid conditions in participants with type 2 diabetes in the UK Biobank using hospital data only, and combined self-report and hospital data

	Using only hospital data	**Using both self-report and hospital data (Table 2 from manuscript)**
Presence of chronic conditions concordant with type 2 diabetes, n (%)	**UK Biobank (N = 20,569)**	**UK Biobank (N = 20,569)**
Hypertension	5632 (27.4)	14,187 (69.0)
Coronary heart disease	2918 (14.2)	3,773 (18.3)
Peripheral vascular disease	429 (2.1)	488 (2.4)
Chronic kidney disease	244 (1.2)	323 (1.6)
Stroke/TIA	434 (2.1)	1,024 (5.0)
Diabetic retinopathy	2,174 (10.6)	2,174 (10.6)
Diabetic neuropathy	74 (0.4)	74 (0.4)
Atrial fibrillation	641 (3.1)	641 (3.1)
Heart failure	389 (1.9)	426 (2.1)
Presence of chronic conditions discordant with type 2 diabetes, n (%)	**UK Biobank (N = 20,569)**	**UK Biobank (N = 20,569)**
Depression	419 (2.0)	1,643 (8.0)
Painful conditions (excluding diabetic neuropathy)	3140 (15.3)	6,250 (30.4)
Asthma	1162 (5.6)	2,959 (14.4)
Dyspepsia	2528 (12.3)	3,815 (18.5)
Thyroid disorders	627 (3.0)	1,688 (8.2)
Rheumatoid arthritis and other connective tissue disorders	275 (1.3)	618 (3.0)
COPD	397 (1.9)	841 (4.1)
Anxiety	181 (0.9)	509 (2.5)
Irritable bowel syndrome	185 (0.9)	500 (2.4)
Cancer	1477 (7.2)	2,110 (10.3)
Alcohol problems	402 (2.0)	427 (2.1)
Other psychoactive substance misuse	10 (0.0)	13 (0.1)
Constipation	275 (1.3)	288 (1.4)
Diverticular disease	895 (4.4)	1,056 (5.1)
Prostate disorders	516 (2.5)	890 (4.3)
Glaucoma	152 (0.7)	458 (2.2)
Epilepsy	132 (0.6)	211 (1.0)
Dementia	8 (0.0)	10 (0.0)
Schizophrenia/bipolar disorder	76 (0.4)	187 (0.9)

Psoriasis/eczema	170 (0.8)	792 (3.9)
Inflammatory bowel disease	871 (4.2)	924 (4.5)
Migraine	57 (0.3)	306 (1.5)
Chronic sinusitis	87 (0.4)	176 (0.9)
Anorexia/bulimia	0 (0.0)	2 (0.0)
Bronchiectasis	37 (0.2)	56 (0.3)
Parkinson's disease	23 (0.2)	42 (0.2)
Multiple sclerosis	49 (0.2)	71 (0.3)
Viral hepatitis	28 (0.1)	56 (0.3)
Chronic liver disease	302 (1.5)	326 (1.6)
Osteoporosis	141 (0.7)	340 (1.7)
Chronic fatigue syndrome	10 (0.0)	71 (0.3)
Endometriosis	84 (0.4)	162 (0.8)
Meniere's disease	13 (0.1)	52 (0.3)
Pernicious anaemia	20 (0.1)	134 (0.7)
Polycystic ovary	10 (0.0)	31 (0.2)

Abbreviations: T2D, type 2 diabetes; TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease

Relationship between multimorbidity total count and HbA1c in participants with type 2 diabetes using multivariable linear regression model in UK Biobank

	Using only hospital data				Using both self-report and hospital data (Table 3 from manuscript)			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
Categories of diabetes and multimorbidity	**Mean difference in HbA1c (95% CI)**	**P-value**	**Mean difference in HbA1c (95% CI)**	**P-value**	**Mean difference in HbA1c (95% CI)**	**P-value**	**Mean difference in HbA1c (95% CI)**	**P-value**
Diabetes only (reference)	ref		ref		ref		ref	
Diabetes plus 1 chronic condition	-0.01 (-0.05, 0.03)	0.687	-0.02 (-0.13, -0.01)	0.448	-0.07 (-0.14, -0.01)	0.024	-0.07 (-0.13, -0.01)	0.031
Diabetes plus 2 chronic conditions	-0.03 (-0.08, 0.02)	0.208	-0.03 (-0.18, -0.06)	0.270	-0.13 (-0.19, -0.06)	<0.001	-0.12 (-0.18, -0.06)	<0.001
Diabetes plus 3 chronic conditions	-0.07 (-0.13, -0.01)	0.025	-0.08 (-0.19, -0.06)	0.006	-0.11 (-0.17, -0.04)	0.002	-0.13 (-0.19, -0.06)	<0.001
Diabetes plus ≥4 chronic conditions	-0.09 (-0.15, -0.03)	0.002	-0.13 (-0.26, -0.14)	<0.001	-0.16 (-0.23, -0.10)	<0.001	-0.20 (-0.26, -0.14)	<0.001

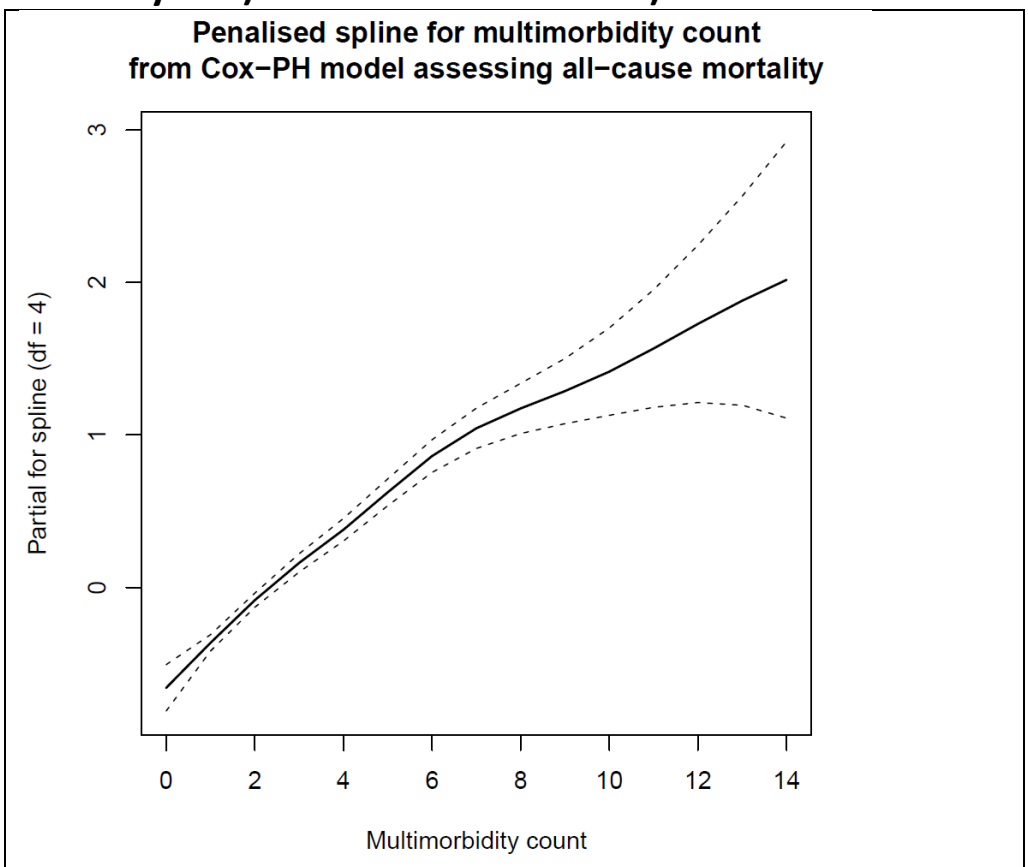
* Adjusting for age, gender, BMI, smoking status, alcohol consumption, socioeconomic status, baseline HbA1c, duration of diabetes, use of oral anti-diabetes drugs and use of corticosteroids

Relationship between multimorbidity total count and all-cause mortality in participants with type 2 diabetes using multivariable Cox's Proportional Hazards model in UK Biobank

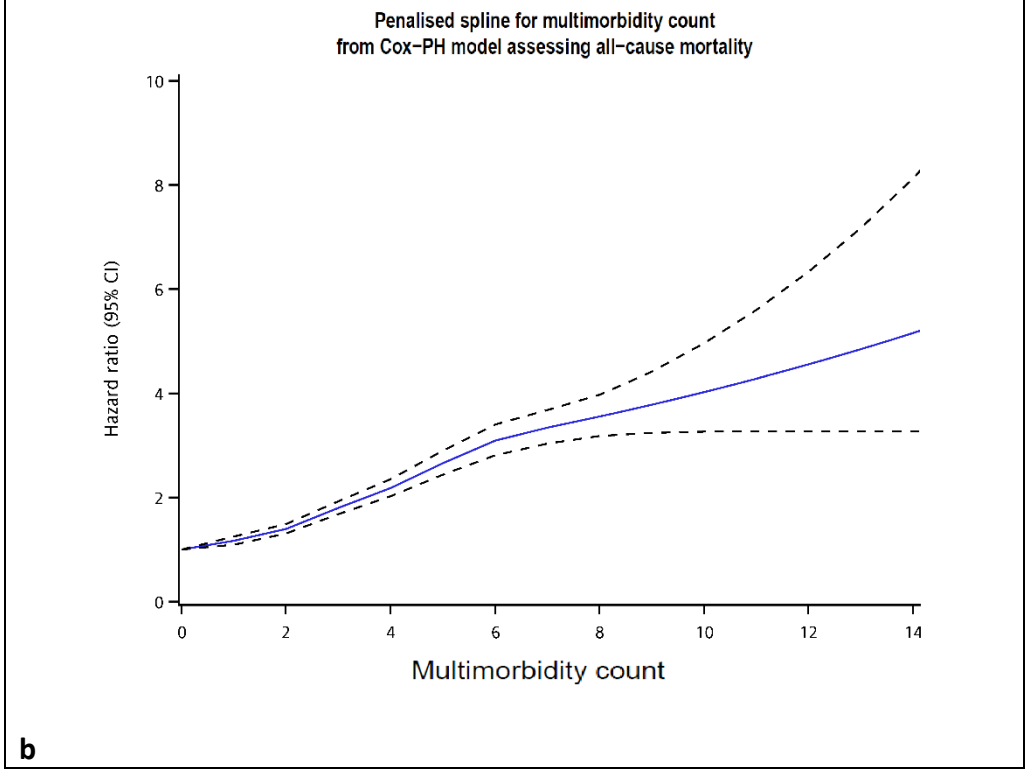
	Using only hospital data				Using both self-report and hospital data (Table 4 from manuscript)			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
Categories of diabetes and multimorbidity	**HRs (95% CI)**	**P-value**	**HRs (95% CI)**	**P-value**	**HRs (95% CI)**	**P-value**	**HRs (95% CI)**	**P-value**
Diabetes only (reference)	1		1		1		1	
Diabetes plus 1 chronic condition	1.48 (1.30, 1.69)	<0.001	1.33 (1.15, 1.52)	<0.001	1.33 (1.04, 1.71)	0.024	1.20 (0.91, 1.56)	<0.001
Diabetes plus 2 chronic conditions	1.89 (1.64, 2.16)	<0.001	1.58 (1.36, 1.83)	<0.001	2.04 (1.61, 2.60)	<0.001	1.75 (1.35, 2.27)	<0.001
Diabetes plus 3 chronic conditions	2.71 (2.35, 3.14)	<0.001	2.10 (1.79, 2.46)	<0.001	2.73 (2.14, 3.48)	<0.001	2.17 (1.67, 2.81)	<0.001
Diabetes plus ≥4 chronic conditions	4.20 (3.70, 4.77)	<0.001	3.26 (2.83, 3.75)	<0.001	4.14 (3.28, 5.22)	<0.001	3.14 (2.43, 4.03)	<0.001

* Adjusting for age, gender, BMI, smoking status, alcohol consumption, socioeconomic status, baseline HbA1c, duration of diabetes, use of oral anti-diabetes drugs and use of corticosteroids

Table S5 – Spline plots of multimorbidity condition count and mortality in a) the UK Biobank and b) the Taiwan NDCMP



a



b

12.4 Example coding terms for NPS MedicineInsight Study (Study 4, Paper 4)

Below I show an example of the steps and all the terms I used to code one condition (chronic kidney disease). This was done for all 43 conditions included in my multimorbidity count for the NPS MedicineInsight study.

1. I utilised the list of terms from Pen Clinical Systems (PenCS) mapping, 2. I reviewed the list of conditions and terms from Best Practice downloaded 3/2/16 (search "renal" "kidney" "dialysis"; exclude anatomical, structural, infections), 3. I reviewed the list of conditions and terms from Medical Director downloaded 3/2/16 (search "renal" "kidney" "dialysis"; exclude anatomical, structural, infections).

The terms in the three columns on the left of the table below were then coded as "Diagnosis of CKD coded in record". An additional search was conducted using the terms in the "NPS Downloaded Terms" column and the retrieved results were reviewed by myself and an academic GP.

PenCS Mapping	**Best Practice**	**Medical Director**	**NPS Downloaded Terms**
Chronic kidney disease	Chronic kidney disease		Searched "CHRONIC KID"
Chronic kidney disease, stage 1	Chronic kidney disease, stage 1		CHRONIC KID
Chronic kidney disease, stage 2	Chronic kidney disease, stage 2		
Chronic kidney disease, stage 3	Chronic kidney disease, stage 3		Searched "CKD"
Chronic kidney disease, stage 4	Chronic kidney disease, stage 4		CKD
Chronic kidney disease, stage 5	Chronic kidney disease, stage 5		
	Chronic kidney disease, stage 3a		Searched "CHRONIC REN"
	Chronic kidney disease, stage 3b		CHRONIC REN
Chronic Kidney Disease - Stage 1			
Chronic Kidney Disease - Stage 2			Searched "RENAL IMPA"
Chronic Kidney Disease - Stage 3			RENAL IMPA

Chronic Kidney Disease - Stage 4			IMPAIRMENT - RENAL
Chronic Kidney Disease - Stage 5			IMPAIRMENTRENAL
Chronic Renal Failure	Chronic Renal Failure	Chronic Renal Failure	RENEAL IMPAIRMENT SEC TO HTN, T2DM AND PREVIOUS NEPHRITIS
Chronic Renal Failure - Hyperparathyroidism	Chronic Renal Failure - Hyperparathyroidism	Chronic Renal Failure - Hyperparathyroidism	
Chronic renal impairment			Searched “DIALY”
CKD (Chronic Kidney Disease) Stage 1		CKD (Chronic Kidney Disease) Stage 1	DIALY
CKD (Chronic Kidney Disease) Stage 2		CKD (Chronic Kidney Disease) Stage 2	
CKD (Chronic Kidney Disease) Stage 3		CKD (Chronic Kidney Disease) Stage 3	Searched “KIDNEY DIS”
CKD (Chronic Kidney Disease) Stage 4		CKD (Chronic Kidney Disease) Stage 4	KIDNEY DIS
CKD (Chronic Kidney Disease) Stage 5		CKD (Chronic Kidney Disease) Stage 5	
	Continuous ambulatory peritoneal dialysis	Continuous ambulatory peritoneal dialysis	Searched “KIDNEY IMP”
Dialysis	Dialysis		KIDNEY IMP
	Dialysis, peritoneal		
		Dialysis - peritoneal	KIDNEY FAILURE
Dialysis - haemodialysis		Dialysis - haemodialysis	
Haemodialysis	Haemodialysis	Haemodialysis	RENAL DAMAGE
Hemodialysis		Hemodialysis	
Impairment - renal		Impairment - renal	Searched “RENAL DIS”
Kidney Disease - Chronic - Stage 1		Kidney Disease - Chronic - Stage 1	RENAL DIS
Kidney Disease - Chronic - Stage 2		Kidney Disease - Chronic - Stage 2	
Kidney Disease - Chronic - Stage 3		Kidney Disease - Chronic - Stage 3	Search “RENAL INS”
Kidney Disease - Chronic - Stage 4		Kidney Disease - Chronic - Stage 4	ADVANCED RENAL INSUFFICIENCY,

			ANALGESIC NEPHROPATHY
Kidney Disease - Chronic - Stage 5		Kidney Disease - Chronic - Stage 5	CHRONIC RENAL INSUFFICIENCY
		Kidney excretion - reduced	EGFR 21: CHRONIC RENAL INSUFFICIENCY
Kidney impairment	Kidney impairment	Kidney impairment	RENAL INSUFFICIENCY - CHRONIC
Kidney failure	Kidney failure	Kidney failure	RENAL INSUFFICIENCY NEPHROSCLEROSIS
Kidney failure - chronic		Kidney failure - chronic	RENAL INSUFFICIENCY, CHRONIC
Kidney failure, chronic	Kidney failure, chronic		
	Peritoneal catheterisation for dialysis	Peritoneal catheterisation for dialysis	
	Peritoneal dialysis	Peritoneal dialysis	
Renal damage	Renal damage	Renal damage	Searched "RENAL FAIL"
Renal dialysis	Renal dialysis	Renal dialysis	RENAL FAILURE
Renal Disease - Chronic - Stage 1		Renal Disease - Chronic - Stage 1	
Renal Disease - Chronic - Stage 2		Renal Disease - Chronic - Stage 2	URAEMIA
Renal Disease - Chronic - Stage 3		Renal Disease - Chronic - Stage 3	
Renal Disease - Chronic - Stage 4		Renal Disease - Chronic - Stage 4	END STAGE KIDNEY
Renal Disease - Chronic - Stage 5		Renal Disease - Chronic - Stage 5	ENDSTAGE KIDNEY
Renal impairment	Renal impairment	Renal impairment	END-STAGE KIDNEY
Renal insufficiency – chronic			END STAGE RENAL
Renal failure		Renal failure	ENDSTAGE RENAL
Renal failure, chronic	Renal failure, chronic		END-STAGE RENAL
		Renal failure due to cirrhosis	
		Surgery – Abdomen – Dialysis - Catheterisation	
Uraemia			

An additional search was conducted to capture any additional diagnoses recorded in free text incorporating the following terms:

"CHRONIC KIDNEY DISEASE", "RENAL IMPAIRMENT", "CKD", "ACUTE ON CHRONIC RENAL FAILURE", "CHRONIC RENAL DISEASE", "CHRONIC RENAL FAILURE", "END STAGE KIDNEY FAILURE", "RENAL IMPAIR", "RENAL FAILURE", "RENAL DISEASE - CHRONIC", "RENAL FAILURE - CHRONIC", “DIALYSIS”

An additional search was conducted to capture any terms that do not reflect the conditions. I searched the terms below to rule those out.

Drop if terms
?
NO
LIKELY
POSS
PROB
POLYCYSTIC KIDNEY DISEASE
POLYCYSTIC
SCREEN
TEST

All of the results that was retrieved from the search was reviewed by me and also an academic GP. In cases of discrepancy, another GP would help to reach consensus after discussion.

12.5 Additional files for Paper 4:

SUPPLEMENTARY DATA

Table S1. List of chronic conditions considered for multimorbidity count

Chronic conditions grouping	Conditions included
Concordant conditions	
1. Hypertension	Hypertension Essential hypertension
2. Coronary heart Disease	Heart attack/Myocardial infarction Angina
3. Peripheral vascular disease	Peripheral vascular disease Leg claudication/intermittent claudication
4. Chronic kidney disease	Polycystic kidney Diabetic nephropathy Renal/kidney failure Renal failure requiring dialysis Renal failure not requiring dialysis Kidney nephropathy Immunoglobulin A (IgA) nephropathy
5. Stroke/Transient Ischaemic Attack (TIA)	Stroke TIA Subarachnoid haemorrhage Brain haemorrhage Ischaemic stroke
6. Diabetic retinopathy	Diabetic eye disease
7. Diabetic neuropathy	Diabetic neuropathy/ulcers
8. Atrial fibrillation	Atrial fibrillation
9. Heart failure	Cardiomyopathy Hypertrophic cardiomyopathy Heart failure/pulmonary oedema
Discordant conditions	
10. Depression	Depression Postnatal depression
11. Painful conditions	Back pain Joint pain Headaches (not migraine) Sciatica Plantar fasciitis Carpal tunnel syndrome Fibromyalgia Arthritis Shingles Disc problem Prolapsed disc/slipped disc Spine arthritis/spondylitis Ankylosing spondylitis Back problem Osteoarthritis Gout Cervical spondylosis Trigeminal neuralgia Disc degeneration

	Trapped nerve/compressed nerve
12. Asthma	Asthma
13. Dyspepsia	Gastro-oesophageal reflux (GORD)/gastric reflux Oesophagitis /Barrett's oesophagus Gastric stomach ulcers Gastric erosions/gastritis Duodenal ulcer Dyspepsia/indigestion Hiatus hernia Helicobacter pylori
14. Thyroid disorders	Thyroid problem (not cancer) Hyperthyroidism/thyrotoxicosis Hypothyroidism/myxoedema Grave's disease Thyroid goitre Thyroiditis
15. Rheumatoid arthritis and other connective tissue disorders	Myositis/myopathy Systemic Lupus Erythematosus Connective tissue disorder Sjogrens syndrome/sicca syndrome Dermatopolymyositis Scleroderma/systemic sclerosis Rheumatoid arthritis Psoriatic arthropathy Dermatomyositis Polymyositis Polymyalgia Rheumatica Malabsorption/coeliac disease
16. Chronic Obstructive Pulmonary Disease (COPD)	COPD/chronic obstructive airways disease Emphysema/chronic bronchitis Emphysema
17. Irritable bowel syndrome	Irritable bowel syndrome
18. Cancer	Lifetime diagnosis
19. Alcohol problems	Alcohol dependency Alcoholic liver disease/alcoholic cirrhosis
20. Other psychoactive substance misuse	Opioid dependency Other substance abuse/dependency
21. Constipation	Constipation
22. Diverticular disease	Diverticular disease Diverticulitis
23. Prostate disorders	Prostate problem (not cancer) Enlarged prostate Benign prostatic hypertrophy
24. Glaucoma	Glaucoma
25. Epilepsy	Epilepsy
26. Dementia	Dementia Alzheimer's disease Cognitive impairment
27. Schizophrenia/bipolar disorder	Schizophrenia Mania/

	Bipolar disorder Manic depression
28. Psoriasis/eczema	Eczema Dermatitis Psoriasis
29. Inflammatory bowel disease	Inflammatory Bowel Disease Crohn's disease Ulcerative colitis
30. Migraine	Migraine
31. Chronic sinusitis	Chronic sinusitis
32. Anorexia/bulimia	Anorexia Bulimia Other eating disorders
33. Bronchiectasis	Bronchiectasis
34. Parkinson's disease	Parkinson's disease
35. Multiple sclerosis	Multiple sclerosis
36. Viral hepatitis	Infective/viral hepatitis Hepatitis B Hepatitis C Hepatitis D Hepatitis E
37. Chronic liver disease	Oesophageal varices Non infective hepatitis Liver failure/cirrhosis Primary biliary cirrhosis
38. Osteoporosis	Osteoporosis
39. Chronic fatigue syndrome	Chronic fatigue syndrome
40. Endometriosis	Endometriosis
41. Meniere's disease	Meniere's disease
42. Pernicious anaemia	Pernicious anaemia
43. Polycystic ovary	Polycystic ovary

Table S2. Sensitivity analysis - multivariable linear regression model: Relationship between HbA1c(%) and multimorbidity in participants with type 2 diabetes.

	Non-adjusted			Adjusted*		
Predictor variables	**Mean difference in HbA1c (SE)**	**95% CI**	**p**	**Mean difference in HbA1c (SE)**	**95% CI**	**p**
Participants with HbA1c > 7%						
Categories of diabetes and multimorbidities						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 chronic condition	0.00 (0.03)	-0.07, 0.07	0.995	0.00 (0.04)	-0.07, 0.07	0.915
Diabetes present and 2 chronic conditions	-0.03 (0.03)	-0.10, 0.03	0.322	-0.03 (0.03)	-0.10, 0.04	0.359
Diabetes present and 3 chronic conditions	0.02 (0.03)	-0.05, 0.08	0.624	0.02 (0.03)	-0.05, 0.09	0.553
Diabetes present and 4 or more chronic conditions	0.01 (0.03)	-0.05, 0.07	0.726	0.02 (0.03)	-0.04, 0.07	0.592
Categories of diabetes and concordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 concordant condition	0.02 (0.02)	-0.02, 0.05	0.422	0.02 (0.02)	-0.02, 0.06	0.315
Diabetes present and 2 concordant conditions	0.02 (0.03)	-0.03, 0.07	0.338	0.04 (0.02)	-0.01, 0.09	0.122
Diabetes present and 3 concordant conditions	-0.02 (0.03)	-0.08, 0.05	0.609	-0.02 (0.03)	-0.08, 0.05	0.650
Diabetes present and 4 or more concordant conditions	0.03 (0.04)	-0.056, 0.11	0.513	0.03 (0.04)	-0.05, 0.11	0.472
Categories of diabetes and discordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 discordant condition	-0.05 (0.03)	-0.10, 0.00	0.063	-0.07 (0.03)	-0.12, 0.02	0.012
Diabetes present and 2 discordant conditions	-0.02 (0.03)	-0.07, 0.04	0.540	-0.03 (0.03)	-0.08, 0.03	0.293
Diabetes present and 3 discordant conditions	0.02 (0.03)	-0.04, 0.07	0.572	0.00 (0.03)	-0.06, 0.06	0.993
Diabetes present and 4 or more discordant conditions	0.00 (0.03)	-0.05, 0.05	0.879	-0.00 (0.03)	-0.05, 0.05	0.970
Participants with HbA1c ≤ 7%						
Categories of diabetes and multimorbidities						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 chronic condition	0.01 (0.01)	-0.02, 0.03	0.586	0.00 (0.01)	-0.02, 0.02	0.929
Diabetes present and 2 chronic conditions	0.01 (0.01)	-0.01, 0.03	0.317	0.01 (0.01)	-0.01, 0.03	0.562

Diabetes present and 3 chronic conditions	-0.01 (0.01)	-0.03, 0.01	0.548	-0.01 (0.01)	-0.03, 0.01	0.277
Diabetes present and 4 or more chronic conditions	0.00 (0.01)	-0.02, 0.02	0.771	0.00 (0.01)	-0.02, 0.02	0.978
Categories of diabetes and concordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 concordant condition	0.01 (0.01)	0.00, 0.02	0.233	0.01 (0.01)	0.00, 0.02	0.232
Diabetes present and 2 concordant conditions	0.01 (0.01)	0.00, 0.03	0.076	0.01 (0.01)	0.00, 0.03	0.136
Diabetes present and 3 concordant conditions	0.01 (0.01)	-0.01, 0.03	0.480	0.00 (0.01)	-0.02, 0.02	0.855
Diabetes present and 4 or more concordant conditions	0.00 (0.01)	-0.03, 0.02	0.939	0.00 (0.01)	-0.03, 0.02	0.919
Categories of diabetes and discordant conditions						
Diabetes present and no chronic conditions (reference)						
Diabetes present and 1 discordant condition	0.01 (0.01)	-0.01, 0.02	0.448	0.00 (0.01)	-0.02, 0.02	0.921
Diabetes present and 2 discordant conditions	-0.02 (0.01)	-0.03, 0.00	0.027	-0.02 (0.01)	-0.04, 0.00	0.020
Diabetes present and 3 discordant conditions	-0.01 (0.01)	-0.02, 0.01	0.495	-0.01 (0.01)	-0.02, 0.01	0.462
Diabetes present and 4 or more discordant conditions	0.00 (0.01)	-0.02, 0.01	0.825	0.00 (0.01)	-0.02, 0.01	0.628

SE: Standard error

*Adjusting for age, sex, SEIFA, smoking status, and number of diabetes medication. All co-variates were treated as fixed effects and the general practice as a random effect to allow for the correlation of HbA1c within each practice.

12.6 Additional files for Paper 5:

Table S1. List of chronic conditions considered for multimorbidity count

Chronic conditions grouping	Conditions included
Concordant conditions	
1. Hypertension	Hypertension Essential hypertension
2. Coronary heart Disease	Heart attack/Myocardial infarction Angina
3. Peripheral vascular disease	Peripheral vascular disease Leg claudication/intermittent claudication
4. Chronic kidney disease	Polycystic kidney Diabetic nephropathy Renal/kidney failure Renal failure requiring dialysis Renal failure not requiring dialysis Kidney nephropathy Immunoglobulin A (IgA) nephropathy
5. Stroke/Transient Ischaemic Attack (TIA)	Stroke TIA Subarachnoid haemorrhage Brain haemorrhage Ischaemic stroke
6. Diabetic retinopathy	Diabetic eye disease
7. Diabetic neuropathy	Diabetic neuropathy/ulcers
8. Atrial fibrillation	Atrial fibrillation
Discordant conditions	
9. Depression	Depression Postnatal depression
10. Painful conditions	Back pain Joint pain Headaches (not migraine) Sciatica Plantar fasciitis Carpal tunnel syndrome Fibromyalgia Arthritis Shingles Disc problem Prolapsed disc/slipped disc Spine arthritis/spondylitis Ankylosing spondylitis Back problem Osteoarthritis Gout Cervical spondylosis

	Trigeminal neuralgia Disc degeneration Trapped nerve/compressed nerve
11. Asthma	Asthma
12. Gastro-oesophageal reflux (GORD)	Gastro-oesophageal reflux (GORD)/gastric reflux
13. Thyroid disorders	Thyroid problem (not cancer) Hyperthyroidism/thyrotoxicosis Hypothyroidism/myxoedema Grave's disease Thyroid goitre Thyroiditis
14. Rheumatoid arthritis and other connective tissue disorders	Myositis/myopathy Systemic Lupus Erythematosus Connective tissue disorder Sjogrens syndrome/sicca syndrome Dermatopolymyositis Scleroderma/systemic sclerosis Rheumatoid arthritis Psoriatic arthropathy Dermatomyositis Polymyositis Polymyalgia Rheumatica Malabsorption/coeliac disease
15. Irritable bowel syndrome	Irritable bowel syndrome
16. Cancer	Lifetime diagnosis
17. Alcohol problems	Alcohol dependency Alcoholic liver disease/alcoholic cirrhosis
18. Other psychoactive substance misuse	Opioid dependency Other substance abuse/dependency
19. Constipation	Constipation
20. Diverticular disease	Diverticular disease Diverticulitis
21. Prostate disorders	Prostate problem (not cancer) Enlarged prostate Benign prostatic hypertrophy
22. Glaucoma	Glaucoma
23. Epilepsy	Epilepsy
24. Dementia	Dementia Alzheimer's disease Cognitive impairment
25. Schizophrenia/bipolar disorder	Schizophrenia Mania/ Bipolar disorder Manic depression
26. Psoriasis/eczema	Eczema Dermatitis

	Psoriasis
27. Inflammatory bowel disease	Inflammatory Bowel Disease Crohn's disease Ulcerative colitis
28. Migraine	Migraine
29. Chronic sinusitis	Chronic sinusitis
30. Anorexia/bulimia	Anorexia Bulimia Other eating disorders
31. Bronchiectasis	Bronchiectasis
32. Parkinson's disease	Parkinson's disease
33. Multiple sclerosis	Multiple sclerosis
34. Viral hepatitis	Infective/viral hepatitis Hepatitis B Hepatitis C Hepatitis D Hepatitis E
35. Chronic liver disease	Oesophageal varices Non infective hepatitis Liver failure/cirrhosis Primary biliary cirrhosis

12.7 List of publications, conference presentations, award and grants achieved during PhD candidature

During this PhD candidature I have achieved 1 international award, 3 national scholarships, 5 competitive grants, 3 PhD study publications (and a further 2 submitted), 7 other publications, 8 international conference presentations and 5 national conference presentations.

12.7.1 Award

- Dr Barbara Starfield Distinguished Trainee Research Award 2018 (North American Primary Care Research Group Chicago, US)

12.7.2 Scholarships

- National Health and Medical Research Council Postgraduate Scholarship 2019-20 ($32,278.50)
- GP OSMOTIC PhD Scholarship, 2017-18 ($56,576)
- Australian Government Research Training Program Scholarship, 2017-20 ($84,750)

12.7.3 Grants

- Department of General Practice Travel Grant 2019 ($800)
- Department of General Practice Travel Grant 2018 ($1,500)
- Department of General Practice Travel Grant 2017 ($1,050)
- Diabetes Australia Research Project Grant 2017 ($60,000)
- Royal Australian College of General Practitioners (RACGP) Family Medical Care Education and Research (FMCER) Grant 2017 ($20,000)

12.7.4 Publications

Chiang JI, Hanlon P, Li T-C, Jani BD, Manski-Nankervis J-A, Furler J, et al. Multimorbidity, mortality, and HbA1c in type 2 diabetes: A cohort study with UK and Taiwanese cohorts. PLoS Med. 2020;17(5): e1003094.

Chiang JI, Jani BD, Mair FS, Nicholl BI, Furler J, O'Neal D, et al. Associations between multimorbidity, all-cause mortality and glycaemia in people with type 2 diabetes: A systematic review. PLoS One. 2018;13(12):e0209585.

Chiang, JI., Furler, J., Mair, F., Jani, B., Nicholl, BI., Jenkins, A., O'Neal, D., Condron, P., & Manski-Nankervis, J. Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol. BMJ Open. 2018;8(4).

12.7.4.1 Publications unrelated to PhD

Furler J, O'Neal D, Speight J, Blackberry I, Manski-Nankervis JA, Thuraisingam S, Holmes-Truscott, E., Khunti, K., Dalziel, K., **Chiang, JI.**, et al. Use of professional-mode flash glucose monitoring, at 3-month intervals, in adults with type 2 diabetes in general practice (GP-OSMOTIC): a pragmatic, open-label, 12-month, randomised controlled trial. Lancet Diabetes Endocrinol. 2020;8(1):17-26.

Wong MC, Huang J, Huang JL, Pang TW, Choi P, Wang J, **Chiang JI**, et al. Global Prevalence of Colorectal Neoplasia: a Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2020;18(3):553-61 e10.

Thuraisingam S, Chondros P, Catchpool M, Dalziel K, Manski-Nankervis JA, Speight J, Holmes-Truscott, E., Audehm, R., **Chiang, JI**., et al. Update on the General Practice Optimising Structured Monitoring to Improve Clinical Outcomes in Type 2 Diabetes (GP-OSMOTIC) trial: statistical analysis plan for a multi-centre randomised controlled trial. Trials. 2019;20(1):93.

Lin CC, Li CI, Liu CS, Lin WY, Lin CH, **Chiang JI**, et al. Obesity paradox in associations between body mass index and diabetes-related hospitalization and mortality in patients with type 2 diabetes: Retrospective cohort studies. Diabetes & Metabolism. 2019;45(6):564-72.

Furler, J., O'Neal, D., Speight, J., Blackberry, I., Manski-Nankervis, J., Browne, J., Holmes-Truscott, E., Khunti, K., Dalziel, K., **Chiang, J.**, et al. The GP-OSMOTIC trial protocol: an individually randomised controlled trial to determine the effect of retrospective continuous glucose monitoring (r-CGM) on HbA1c in adults with type 2 diabetes in general practice. BMJ Open. 2018;8(7):e021435.

Chiang J, Furler J, Boyle D, Clark M, Manski-Nankervis JA. Electronic clinical decision support tool for the evaluation of cardiovascular risk in general practice: A pilot study. Australia Family Physician. 2017;46(10):764-8.

Chiang JI, Li TC, Li CI, Liu CS, Meng NH, Lin WY, et al. Visit-to-visit variation of fasting plasma glucose is a predictor of hip fracture in older persons with type 2 diabetes: the Taiwan Diabetes Study. Osteoporosis International. 2016;27(12):3587-97.

12.7.5 Conferences

Chiang, J.I., Furler, J., Mair, F., Jani, B.D., Nicholl, B.I., Thuraisingam, S., et al. (2019) Associations between multimorbidity and HbA1c in people with type 2 diabetes in Australian general practice. Oral Presentation, RACGP GP19 Conference, **Adelaide, Australia, 24-26 October 2019**

Chiang, J.I., Furler, J., Mair, F., Jani, B.D., Nicholl, B.I., Thuraisingam, S., et al. (2019) Associations between multimorbidity and HbA1c in people with type 2 diabetes in Australian family practice. Poster Presentation, American Diabetes Association 79th Scientific Sessions, **San Francisco, US 7-11 June 2019**

Chiang, J.I., Hanlon, P., Jani, B.D., Manski-Nankervis, J., Furler, J., Nicholl, B.I., et al. (2019) Multimorbidity and Its Associations with All-Cause Mortality in People with Type 2 Diabetes: A Prospective Analysis of the UK Biobank. Poster Presentation, American Diabetes Association 79th Scientific Sessions, **San Francisco, US 7-11 June 2019**

Chiang, JI., Yang, SY., Manski-Nankervis, J., Thuraisingam, S., Furler, J., Mair, F., Jani, B., Nicholl, BI., Li, TC., & Lin, CC. (2018) Examining the Relationship Between Multimorbidity and Glycaemia, Glycaemic Variability and All-Cause Mortality in People With Type 2 Diabetes in Taiwan: Findings From a Longitudinal Cohort. Oral Presentation, North American Primary Care Research Group (NAPCRG) Annual Scientific Meeting, **Chicago, US 9-13 November 2018**

Chiang, JI., Furler, J., Mair, F., Jani, B., Nicholl, BI., Jenkins, A., O'Neal, D., Condron, P., & Manski-Nankervis, J. (2018) Associations Between Multimorbidity, All-Cause Mortality and Glycaemic Outcomes in People With Type 2 Diabetes: A Systematic Review. Oral Presentation, North American Primary Care Research Group (NAPCRG) Annual Scientific Meeting, **Chicago, US 9-13 November 2018**

Chiang, JI., Yang, SY., Manski-Nankervis, J., Thuraisingam, S., Furler, J., Mair, F., Jani, B., Nicholl, BI., Li, TC., & Lin, CC. (2018) Examining the relationship between multimorbidity and glycaemia, glycaemic variability and all-cause mortality in people with type 2 diabetes in Taiwan: Findings from a Longitudinal Cohort Study. Poster Presentation, Society for Academic Primary Care (SAPC) Annual Scientific Meeting, **London, UK 10-12 July 2018**

Chiang, JI., Furler, J., Mair, F., Jani, B., Nicholl, BI., Jenkins, A., O'Neal, D., Condron, P., & Manski-Nankervis, J. (2018) What is the relationship between multimorbidity, all-cause mortality and glycaemic outcomes in people with type 2 diabetes? A systematic review. Oral Presentation, Society for Academic Primary Care (SAPC) Annual Scientific Meeting, **London, UK 10-12 July 2018**

Chiang, JI., Manski-Nankervis, J., Furler, J., Nicholl, BI., Jani, B., Jenkins, A., O'Neal, D., Condron, P., & Mair, F. (2017) Impact of Multimorbidity on All-Cause Mortality and Glycaemic Outcomes in People with Type 2 Diabetes: A Systematic Review Protocol. Oral Presentation, RACGP GP17 Conference, **Sydney, Australia, 26-28 October 2017**

Januszewski, A., Jenkins, A., Joglekar, M., **Chiang, JI.**, Carroll, L., Scott, E., O'Neal, D., Hardikar, A., Furler, J. & Manski-Nankervis, J. (2019) Preliminary Results of microRNA Signatures of Glucose Variability and of Cardiovascular Disease in adults with Type 2 Diabetes: A GP-OSMOTIC Sub-study. Oral Presentation, Australasian Diabetes Congress, **Sydney, Australia 21-23 August 2019**

Furler, J., O'Neal, D., Speight, J., Blackberry I., Manski-Nankervis, J., Thuraisingam, S., de La Rue, K., Ginnivan, L., Doyle, R., Holmes-Truscott, E., Khunti, K., Dalziel, K., Catchpool, M., **Chiang, JI.,** et al. (2019) GP-OSMOTIC: An RCT to Determine the Effect of 3-Monthly Retrospective Continuous Glucose Monitoring (rCGM) On 12-Month Hba1c In Adults with Type 2 Diabetes (T2D) In Primary Care. Poster Presentation, Society for Academic Primary Care (SAPC) Annual Scientific Meeting, **Exeter, UK 3-5 July 2019**

Furler, J., O'Neal, D., Speight, J., Blackberry I., Manski-Nankervis, J., Thuraisingam, S., de La Rue, K., Ginnivan, L., Doyle, R., Holmes-Truscott, E., Khunti, K., Dalziel, K., Catchpool, M., **Chiang, JI.**, et al. (2019) GP-OSMOTIC: An RCT to Determine the Effect of 3-Monthly Retrospective Continuous Glucose Monitoring (rCGM) On 12-Month Hba1c In Adults with Type 2 Diabetes (T2D) In Primary Care. Poster Presentation American Diabetes Association 79th Scientific Sessions, **San Francisco, US 7-11 June 2019**

Furler, J., O'Neal, D., Speight, J., Blackberry, I., Manski-Nankervis, J., Browne, J., Holmes-Truscott, E., Khunti, K., Dalziel, K., **Chiang, JI.**, et al. (2017) General Practice Optimising Structured Monitoring to Improve Clinical Outcomes in Type 2 Diabetes: The GP-OSMOTIC Study Protocol. Poster Presentation, 2017 Primary Health Care Research Conference, **Brisbane, Australia, 7-9 August 2017**

Furler, J., O'Neal, D., Speight, J., Blackberry, I., Manski-Nankervis, J., Browne, J., Holmes-Truscott, E., Khunti, K., Dalziel, K., **Chiang, J.**, Tan, M., Audehm, R., Kennedy, M., Clarke, M., Liew, D., Clarke, P., Jenkins, A., & Best, J. (2017). General Practice Optimising Structured Monitoring to Improve Clinical Outcomes in Type 2 Diabetes: The GP-OSMOTIC Study Protocol. Poster Presentation, 2017 Primary Health Care Research Conference, **Brisbane, 7-9 August 2017**