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Diabetes and Virtual Care: How COVID-19 impacted on a digital transformation

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Preface: Plain Language Summary/Abstract

Mobile phone applications and other virtual care interventions such as telehealth present both a big problem and a big opportunity for improving the health of people with chronic diseases, in particular type 2 diabetes. These diseases have become more common in recent years, and with this increasing prevalence despite prevention efforts one thing is clear: we must adapt our healthcare methods to meet this growing pressure. The advent of COVID-19 has only made this problem worse, as people's care has been fragmented and fractured during the outbreak of a global pandemic.

The downside to apps and other virtual care interventions is that people don't use them for very long. There's emerging research showing that people often stop using their mobile applications, even the health ones, very quickly. We aren't sure exactly how quickly this happens, and it seems to vary a lot between apps and health conditions, but it might be as many as 98% of people dropping out of app-based interventions within days of signing up. While other interventions such as telehealth may have better retention, even these have had challenges in getting people to use them long-term. Needless to say, a health intervention that lasts less than a week is not going to be as effective as one that people stick to for months or years.

On top of this, the COVID-19 pandemic has dramatically changed how we interact with virtual care. In February 2020 most people had smartphones, iPads, and laptops, but were not managing their diabetes or healthcare on them. The pandemic, lockdowns and distancing changed the way people lived, worked, and communicate, resulting in a forced digital acceleration. Some reached for apps and teleconsultations to help fill the gap. This thesis looks at the advantages and problems this brought. What makes a good diabetes app for consumers? Why do they stop using them?

This thesis presents evidence on the burden of diabetes before COVID-19, how people have behaved towards aspects of virtual care and theories as to why, and then evidence both that the pandemic has shifted behaviour and some assessment of why for people with diabetes. Finally, the thesis looks at what has changed and what we might change to enable better usage of virtual care into the future. Through a series of experiments, I show that the pandemic has changed behaviour in numerous ways for people with diabetes, but that these changes are complex and may not be long-lived. To keep improving care, we will have to take the lessons of the pandemic years to heart, rather than reverting to the way that things were before COVID-19.

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Finally, thanks to my wonderful wife Michelle and brilliant daughter Violet.

I couldn't have done it without you.

Gideon.

Certification

I certify that the work contained in this thesis is primarily my own original work. In some cases, I have included sections from studies published with colleagues, including two papers in which I was the senior (last) author. All writing aside from those elements which I have drawn from published papers are entirely my own work, including writing, figures, and analyses. This thesis has not been submitted for a degree at any other university or institution.

Gideon Meyerowitz-Katz

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Chapter One: Background

1.1 Introduction

Chronic disease has become the leading health issue of our time. Type 2 diabetes, heart disease, mental ill-health, and a host of other disease states are now the defining problems that health systems across the world are facing (2, 3). As the burden of disease due to chronic health issues increases, so too does the demand for health interventions for both prevention and management that are effective, cost-effective, and scalable to large populations.

Moreover, due to the emergence of COVID-19 as a global pandemic, it is urgent that we identify virtual care interventions with high efficacy, and improve the efficacy of those that do not work as well as they could. During the COVID-19 pandemic, it has been identified that people with chronic diseases are at an increased risk from this infection with SARS-CoV-2 (4, 5), which necessitated the quick evolution of virtual care methodologies – ways of managing patients that do not require face-to-face contact between care provider and patient.

Diabetes in particular has seen steep increases in prevalence over the last 2 decades. Worldwide prevalence rates have risen from less than 1% in the late 80s and early 90s to an estimated 6% today (3). Australia has seem similar increases, with estimates of diabetes prevalence increasing from 1.5% in the early 90s to above 6% in recent years (6). Given that up to 1/3 of all patients with diabetes are living undiagnosed, this figure may in fact be higher (3, 7). Type 2 diabetes is also a socially-influenced disease, with rates correlating with socio-economic and demographic factors such as wealth and ethnicity (8). Environmental influences also play a part, with factors such as green space, urban sprawl-ingrained car dependency, and air pollution likely driving rates of physical inactivity and therefore diabetes in major cities across the globe (9). With such a high and increasing prevalence of diabetes, it is important that strategies are developed to prevent the complications of diabetes that will undoubtedly occur as the epidemic grows into the future.

Prevention is a key element of diabetes management, with a variety of stages. At the primary end, there are programs focused on preventing diabetes itself, such as physical activity and diet initiatives (10). Once people have been diagnosed with diabetes, there are further, secondary prevention programs aimed at reducing the risk of future complications such as amputation (11). Secondary prevention efforts are very broad, ranging from programs that aim to prevent high-risk patients from progressing to end-stage disease to initiatives for medication adherence and more. More recently, efforts for type 2 diabetes secondary prevention have involved intensive lifestyle modification efforts that have been shown to potentially reverse the disease entirely (12).

There is a large body of research demonstrating that diabetes is amenable to intervention in a variety of ways. Pharmacotherapy is a common and effective method to reduce the impact of diabetes, but lifestyle changes such as diet improvement and increases to physical activity are a key part of diabetes interventions (13, 14). This is specifically for type 2 diabetes mellitus (T2DM), which may be prevented and even reversed through intensive lifestyle changes (12). Recent studies have also demonstrated that newer pharmacotherapies can reduce the risk of diabetic complications across a broad range of endpoints previously though immutable such as cardiovascular and renal disease (15, 16).

The problem with both pharmacotherapy and lifestyle change is that they are only effective when adhered to. For example, long-term adherence to sodium-glucose cotransporter 2 inhibitors (SGLT2i) such as empaglflozin is associated with up to 40% reduction in worsening nephropathy and albuminuria (16). However, with up to 50% of patients discontinuing their diabetes treatment yearly, the benefits of these therapies in the real world are often harder to find (17). Treatments only have a probability of working when a patient uses them. This presents a challenge – diabetic medication schedules can be very challenging, and have been demonstrated to be difficult for patients to follow (18). People are often tasked with taking multiple medications daily, storing their drugs in potentially challenging ways, and often even administration can be more difficult than many people expect. Lifestyle changes are extremely difficult as well, with the majority of people lapsing in both diet and exercise regimens after a relatively short period (19). Lifestyle modification requires changes to all elements of existence, which means that everything from psychosocial issues to demographic factors to socio-economics and neighbourhood design can influence a person's ability to adhere to a program (19).

This thesis considers the issues underlying app development and design, and charts a way forward to prevent dropout in app-based and other virtual care interventions and use them effectively in the management and control of diabetes.

1.2 Diabetes

Diabetes is the name given to several diseases that are characterized by elevated blood glucose. The term diabetes mellitus comes from the Greek word for going through and the Latin term mellitus meaning sweet. This is likely traced back to the original diagnosis of the disease, which was based on glycosuria or sweet urine. All types of diabetes share the commonality that they involve issues in glucose metabolism that result in excess glucose in the blood which results in a range of long-term outcomes and can cause severe acute disease and death.

There are a number of different causes of diabetes, which have been used to divide the disease into various types. Type 1 diabetes results from an autoimmune disorder that slowly destroys pancreatic beta cells, resulting in a lack of insulin production (20). This causes progressively higher blood glucose, resulting in damage to various organs around the body. Because this type of diabetes diminishes or entirely eliminates the body's ability to produce insulin, Type 1 diabetes has also been called insulin deficient diabetes. While the disease is potentially preventable due to advanced screening techniques and the development of novel immunotherapeutic medications (21), there is no cure for Type 1 diabetes. Once the disease has been diagnosed, in most cases it must be managed indefinitely through the administration of insulin.

Type 2 diabetes has a much more complex pathogenesis which involves a range of body systems. There are a number of proposed mechanisms for the pathogenesis of Type 2 diabetes (22). While the aetiology of Type 2 diabetes is still not fully elucidated, and involves a range of inflammatory and hormonal changes in the body, the results are a reduction in the production and action of insulin which causes a corresponding increase in blood glucose. Due to this reduction in the utility and abundance of insulin, Type 2 diabetes is sometimes referred to as insulin insufficient diabetes. Unlike Type 1 diabetes, Type 2 is rarely acutely fatal, and instead causes chronic harms as elevated blood glucose levels slowly damage organs including the heart, kidneys, and vascular system, which results in a wide range of negative health outcomes over the long term (22).

These two broad groupings of disease are the primary types of diabetes and represent the vast majority of cases of diabetes in the population. Additional causes of diabetes include uncommon cancers, some medications, and a range of other much rarer complications that also lead to higher blood glucose (23). In addition, hormonal changes during pregnancy can cause transitory elevated blood glucose, a condition which is known as gestational diabetes.

This thesis is largely concerned with chronic disease, and therefore the majority of the work relates to Type 2 and to some extent Type 1 diabetes. The term diabetes is used generally to refer to people with either Type 1 or Type 2 diabetes, and does not include either gestational diabetes or rare forms of diabetes which have very different aetiologies, pathogenesis, and treatment modalities.

1.3 Western Sydney Diabetes

Wester Sydney Diabetes (WSD) forms a large part of this thesis. It is the place I have worked at whilst doing the PhD research, and has been central to the development of large portions of the research work done within this document.

WSD is an integrated care initiative that is led by a joint team consisting of the state-based Western Sydney Local Health District (WSLHD), federally-funded Western Sydney Primary Health Network, PwC Australia, the NSW Department of Planning, Industry, and Environment, and Diabetes Australia, based in the geographic region of WSLHD (24). WSD has long been at the forefront of virtual care, and in early 2020 shifted services fully online in response to the pandemic, developing a comprehensive virtual care strategy for diabetes.

WSLHD is the location where much of the work involved in this thesis has been done, both where I sit as a researcher and the broader community of the district. It is a large, culturally diverse area of Sydney containing more than 1 million individuals, representing a wide range of nationalities and backgrounds. Previous estimates suggest that more than half of all people living in WSLHD were born overseas (25), while according to census records the district contains some of both the wealthiest and most deprived postcodes in the state of NSW.

As the pandemic has waxed and waned in Australia, WSD has adapted this strategy to cope with greater and lesser burdens of COVID-19, as well as the government restrictions that come with it. The WSD virtual care strategy has five major parts:

1. Digitally-enabled clinics using NSW Health's MyVirtualCare platform. This includes a detailed patient questionnaire that has been developed to guide treatment.
2. Concierge service to assist with patient and provider onboarding.
3. Diabetes case conferencing between GP, patient, and specialist team.
4. Distance continuous glucose monitoring, provided at four local pharmacies or even fully distanced.
5. A dedicated diabetes app to provide ideal patient self-management and monitoring.

This service was initially designed to be operated fully online, but now has also incorporated face-to-face interactions to become a true hybrid clinic. As of the end of 2022, approximately half of all occasions of care in this service are provided online or via telehealth, while half of services are face-to-face based on personal reporting from clinicians involved in the clinics and hospital reports. WSD has used the pandemic to initiate a huge leap forward in the provision of virtual care to patients, with very impressive results.

1.4 Mobile Apps

Mobile technologies are increasingly being used as a method of improving patient outcomes across a wide range of disease states (26-29). Advances in the technologies available, including the growing ubiquitousness of smartphones, have made mobile apps in particular a very attractive option in the management of health problems. While such interventions can have a high initial cost, the relatively

low running costs and ease of scalability make their use a promising area of investigation for research (30). A report from 2014 found at least 1,100 diabetes apps on the Apple store and Google Play (31), with hundreds more likely released in the years since then.   The use of apps as medical interventions is a new and growing field, with smartphones only being widely available in the last decade, but one that holds significant promise.

Smartphone applications also offer attractive means of tailoring services to specific sub-populations or even individuals – such as translating the text of an app, or re-working recipes in a food app for different ethnic groups - although in practice this has not yet been implemented in many areas. This is one of many areas that are currently being investigated as part of broader work towards personalized medicine or adaptive interventions. While initial costs are high, apps can be designed to cater to very specific disease states, such as groups of people suffering from post-traumatic stress disorder , which allows them to be used in a wide variety of settings and potentially reach groups that are otherwise resistant/face barriers to care (27).

Applications may also be able to be used to improve health equity. Health equity is the theory that there should be an absence of avoidable and/or unfair differences between groups of people, in particular remedying the disadvantages conferred upon individuals by the vagaries of geography and birth. Apps are low-cost – once developed – can be customized to specific populations, and may be able to remedy disparities in care that are caused by social and economic influences although motivation remains an issue regardless of these influences. For example, there is a gradient in diabetes detection and care by socio-economic status (SES), with greater disadvantage usually worsening outcomes across the board (2). It is likely that an app, targeted at or designed for high-risk populations, would be able to be accessed by a large proportion of these groups who are currently not able to get appropriate care for their disease. This is especially true given the growing ubiquitousness of smartphones, which are present even in very disadvantaged households.

Overall, the underlying rationale for application use is very strong for the reasons outlined above. They have also seen some success in clinical trials, with a recent systematic review finding that app-based interventions reduced glycated haemoglobin (HbA1c) in patients with diabetes by almost 1%, a highly clinically significant result (32). Apps have also been used with mixed success in the treatment of mental health disorders, lifestyle issues, and a range of other chronic health areas (27, 33-35). In some cases, there has been clinically significant improvement in trial settings, but less optimal uptake in real-world situations (33). In others, the specific benefits are harder to see: a systematic review of asthma applications found that, although there were some modest benefits attributable to these apps, it was impossible to recommend them currently for clinical use (34).

There are many barriers to the clinical success of apps, but they are one of the fastest-growing medical interventions in the world. There has been increasing academic interest in diabetes applications, with much of the research coming out very recently, exemplified in the increased production of systematic reviews on app-based interventions (33, 36), corresponding to an increase in consumer demand for applications that they can use to track health metrics and improve their health.

Apps present a potentially cost-effective method of targeting services for people with diabetes in the community. While there are important barriers to overcome, apps offer a growing resource for health services, particularly in bridging the equity gap for people who are currently disadvantaged by social, economic, or environmental reasons. They are also a form of virtual care made uniquely important by COVID-19, as both a method of improving the health of people with chronic diseases and a way to provide healthcare to vulnerable patients in a time of crisis.

There is also a very broad range of existing diabetes self-management application technology available to patients. One industry estimate from a company called Allis Health suggests that there were approximately 3,000 diabetes-focused apps published on the Google Play and Apple stores as of 2023, with a substantial growth rate year-on-year (37). These applications cover a broad range of use cases, including AI-enhanced diabetes education such as the Gro Health app (38), insulin and medication tracking applications such as Health2Sync (39), and general dietary or fitness applications such as the HealthyMoms app which is used for gestational diabetes and postnatal weight management (40).

There is mixed literature on the efficacy of these applications, which is discussed in greater detail in Chapter Four. A 2016 systematic review found that most randomized studies conducted on diabetes management and self-management applications reported a reduction in HbA_{1c} for these apps (41), however the pool of studies was fairly small, the applications highly heterogeneous, and thus the applicability of this finding remains questionable. In addition, by definition randomized clinical research on diabetes management applications must be open-label, which increases the likelihood that some measure of the benefit is caused by a placebo effect whereby people who are given the intervention improve their health despite the application potentially being ineffective. This is reinforced by the issue of dropout, which is discussed in detail throughout this thesis, as several studies have shown that only a small proportion of people enrolled in diabetes app RCTs actually use the application, suggesting that it is other aspects of these interventions providing the benefit (42).

The landscape of diabetes applications is also complicated by the question of what a diabetes app really is. While there are potentially thousands of apps targeted specifically at people with diabetes,

other fitness and health applications such as Strava and Google Health are used for purposes that cross over significantly with diabetes management and care. This thesis primarily reviews applications that specifically target people with diabetes, but it is important to remember that mobile health apps cover a huge range of uses and may impact diabetes in numerous interconnected ways.

There are, therefore, a wide range of diabetes applications available. These cover everything from primary prevention of diabetes and related metabolic disease, secondary prevention of progression to complications, and even tertiary prevention of further complications for people who have developed issues such as diabetic foot disease (43). These applications often include a wide range of components, and have a diverse array of theories that are referenced in construction. The range of applications and their design is more fully covered in Chapters Three and Four.

1.5 Telehealth

Telehealth, or telemedicine, is a branch of virtual care that deals with assisting people with their care using telephones, or similar applications such as Skype. While some consider the term telemedicine to only relate to services that are curative (44), the scientific and medical usage of the term is identical to telehealth and thus the two terms are used interchangeably in this thesis (45, 46). This has been around for decades, but in many areas patients and providers have been slow to take it up for a wide variety of reasons (47, 48). In general, the primary aim of telemedicine is to provide a similar service to face-to-face consultations, however there are numerous ways in which this has been applied.

There is also quite strong evidence for both the efficacy and cost-efficacy of telehealth generally (49). While clinical benefits have rarely been seen, this is usually not the primary aim of a telehealth service – the idea is to provide a clinical session at a distance without disadvantaging patient or clinician. In some cases, especially where the patient lives in a rural or remote area, this has very large economic benefits as well especially with the current climate change challenge and the importance of sustainable solutions.

Despite all of this, telehealth has traditionally faced large problems in uptake from both the patient and clinician ends. In some instances, this is due to existing hardware issues, such as poor phone lines or bad internet connections (50), which are real barriers to even starting a telehealth service. However, even with such issues addressed, and with internet speeds increasing rapidly over the last decades, provider and patient perspectives on telehealth (51), as well as institutional and government funding, have stymied the adoption of these initiatives in many places. In Australia there has long been a concerted effort by state and federal governments to implement wide-scale

telehealth services, but despite this they still represent a tiny fraction – well below 1% - of all potential services provided (47, 52).

This leads on to a similarity between most virtual care interventions – they are often potentially very good ways in which to improve health equity. Like applications, telehealth can reduce costs – in particular patient and clinician travel time to and from clinics (53) – and provide a similar service at a lower price (49). It can also be provided to people who would traditionally have difficulty accessing care, with those who experience disabilities, or patients from far-flung regions, potentially seeing the most benefit in this fashion (54, 55). It is likely that well-implemented virtual care methodologies, including a dedicated telehealth aspect, could make important reductions on the health inequities seen in our society.

This is all made that much more important by the advent of COVID-19. Where previously there may have been barriers to implementing telehealth services, with the onset of a global pandemic it became a necessity (4). The obvious problems caused by the pandemic aside, this presents an important opportunity to implement services that may help people who have previously struggled with access not just during a time of crisis but into the future as well.

Telehealth is also notable as the first form of virtual care. Unlike many other areas of virtual care, telehealth has been possible for decades, and therefore is much more well-established in the medical and scientific world than other more novel technologies such as mHealth and eHealth. In particular, this means that there are a great number of existing telehealth interventions for diabetes, although as noted above many of these have not had the originally anticipated impact on healthcare more broadly due to a range of factors that relate to patient and provider dissatisfaction with care provided exclusively through the telephone (48). In many ways, virtual care has been created as a multifaceted service which aims to improve upon telehealth by adding the missing elements that cause issues in telephone-only services.

1.6 Theory-Based Design

One major factor that is necessary to consider when looking at health interventions is the underlying theories that may be used in their design. This is particularly true for virtual care, which as noted faces important barriers in uptake and use. While many theories underlie different health interventions, apps are a new type of healthcare interaction that necessitates a new way of thinking (56). Robust theoretical frameworks allow interventions to be crafted in the most efficient way possible (57), as they may provide a consistent rationale for design decisions and ensure that there is an evidence-base in design that might otherwise be lacking, leading to arbitrary selection of design elements. Using theory in the design of apps is likely to be an important part of their development,

however it is currently an emerging field given the speed at which the app market has grown and is still changing. It is very challenging to create theories about interventions that themselves change rapidly every year, and were not existent only a decade ago.

This is in contrast, to some extent, to telehealth. While telemedicine is still a relatively new field, there is extensive research on the design and implementation of telehealth interventions that addresses the range of issues that can be experienced in their design (58, 59). However, examining the theory-based design of applications is useful in this context as a basis for reviewing the general backing for virtual care as a total method of practice, as opposed to various distance interventions in isolation.

Theory-based design is also important as it provides an underlying rationale which can be improved upon in later iterations of the intervention. Where many applications may currently be being developed in a haphazard way – based on what does and doesn't work in iterative assessments – a theoretical design allows for targeted evaluation and improvement on a schema (60). Theories may allow for a more scientific approach to the application development and improvement cycle that can otherwise be somewhat chaotic in progression.

There are numerous theories of both behaviour and society that may apply to apps, but unfortunately thus far there is little evidence of their uptake in the process of app creation. Recent systematic reviews have indicated that only a small proportion of published applications appear to be based on a specific theoretical construct (30, 56), and even those that are based on a theory – such as Social Cognitive Theory (SCT) – may only reference this in passing rather than incorporating it as a central point in the app's construction.

Despite the obvious need to create and utilize theories that underlie app usage and behaviours, there is currently a paucity of engagement with existing theories and little effort to create new ones. This may present a missed opportunity in the development of more effective app-based health interventions, which would almost certainly be improved were they to use theories that have already been demonstrated to explain key elements of human behaviour.

1.7 Virtual care For Health Equity

Virtual care also presents the opportunity to address serious issues with health equity in diabetes. Diabetes has known interactions with socio-demographic factors, in particular a very strong relationship with socio-economic status (SES) (61, 62). Previous research has demonstrated a consistent link between type 2 diabetes and environmental factors such as green space and walkability (61), as well as a strong interrelationship between disadvantage and both type 2 and gestational diabetes (which is a known risk factor for type 2 diabetes itself) (9, 63).

There is strong reason to believe that disadvantage is causally linked with type 2 diabetes, most likely through limiting access to a lifestyle that is conducive to good health. One study found that a higher ratio of fast food outlets to fresh food stores is associated with a higher risk of obesity in the nearby inhabitants (64) . There is also evidence that walkability and green space are associated with both fitness more broadly and type 2 diabetes specifically (65). Given the well-known association between physical inactivity, obesity, and diabetes, it is almost certain that disadvantage causes diabetes by preventing people from taking part in a lifestyle that would otherwise lead to better health. This is particularly true of remote areas, where both healthcare services and healthy environments are lacking, and where telehealth potentially has the greatest impact on reducing health inequity (66).

Applications and other methodologies present a way not just to treat people who are suffering from diabetes, but to help bridge this health equity gap. We know that diabetes is socially influenced, and that our most vulnerable populations are the most at risk of developing and suffering from the disease. The biggest problem here is that delivering health interventions to people individually across large areas to treat a socially caused problem is ineffective and unsustainable. While traditional models of care for diabetes call for individual sessions with specialists and other medical professionals, it is unlikely that we will ever be able to provide such a service for every person who is suffering from the disease, especially as the numbers grow (67).

These interventions provide a way to potentially ease this significant burden. While there is no way that an app can ever fully address societal causes of ill health, properly designed applications may be able help put people on the path to better health. High-grade evidence has demonstrated that apps are effective at treating diabetes and obesity (32), which provides ample rationale for their use at scale in various populations. This is also the key to the social argument for applications – while most interventions require significant funding and ongoing commitments, applications are fairly cheap and can be provided at scale to large groups of people much more cheaply. This will never replace traditional medical care, but in a disadvantaged population who are currently unable to access effective treatments, apps may be an important element of future interventions to improve health.

1.8 The Quadruple Aim

Another framework from which to view virtual care is the quadruple aim, which reviews healthcare interventions in light of the key indicators that such interventions can be scored against (68). The quadruple aim is a schema that incorporates the three main elements of the previous triple aim, patient satisfaction, reducing costs, and clinical benefit, and adds the final element of provider/clinician satisfaction to the equation (68). The quadruple aim is an important concept as

part of the growing virtual care environment, because virtual care has such a strong possibility of providing improvements across these four regions (69).

Virtual care has a unique ability to bridge the gaps that currently impact care across different aspects of the patient and provider experience, which may in turn allow for the effective addressing of the quadruple aim in ways that have previously not been possible. However there are also barriers that are unique to care provided at a distance that may reduce the chance of virtual care impacting the quadruple aim (45, 70). Despite these barriers, the quadruple aim remains a useful framework on which to examine the impact of virtual care interventions.

This is particularly important in Australia, where there is a well-known divide between primary care and specialist teams mostly based in hospitals (71). In large part, this is due to the design of the healthcare system, whereby the state government funds and pays for most hospital care, while the federal government funds primary care and community services. While there is a great deal of crossover between funders, particularly in the area of population health, this issue pervades the healthcare system across a number of issues.

1.9 Applications and Attrition

Despite this, there remains a very important barrier to the use of applications in the real world: attrition. Dropout in most clinical interventions, despite being important and sometimes extremely problematic for the intervention, is usually low enough that the intervention can be considered effective so long as a reasonable cohort of people continue to use it. Applications, on the other hand, often have very high rates of attrition that may make them entirely unsuitable as treatments for any disease or disorder.

One recent systematic review of mental health applications found that the 'real-world' uptake of these interventions was very low, with up to 80% of all users engaging in "minimal use", which was usually defined as only logging in once to the application (33). In many of these trials, only a very small proportion of individuals continued with the consistent, long-term use of the application that had been demonstrated as necessary to achieve positive health outcomes (33).

Another study looked at the rate of use in an application used for capturing dietary choices on mobile phones and monitoring healthy lifestyle choices that was downloaded nearly 200,000 times over the course of 6 months (72). With numbers that would make any interventional clinician jealous, it might be expected that this app was remarkably effective, however the usage statistics paint a different picture. Of the people who downloaded the application, only 2.5% used the app 'actively' (72). Considering that 'active' use was defined as one week of continuous engagement with

the application, and that the application was entirely free to use, it is even more noteworthy that such a small proportion of people were 'active' users.

These stories seem to mirror the commercial experience of mobile applications. One such app, Pokemon Go, was launched to great fanfare. Within a month it had more than 5 million daily users, but only three months later had lost at least a third of these (73). While the app now maintains an impressive user-base, it is notable that a large proportion of the total users engaged in what could be described as 'minimal use', despite the enormous investment in design and gamifying that the app underwent before release. It appears that even well-funded and highly anticipated apps may experience very high rates of dropout, and the phenomenon is a very important one across the boundaries of disease states and game playing alike.

Mobile app use in diabetes is likely to be an effective and important method of management moving forward, but attrition presents a very significant barrier. While diabetes applications may be effective at improving surrogate outcomes in a clinical trial setting, it remains to be seen whether they can be used effectively in the real world for real people who may not want or be able to use the app actively in a way that would impact their long-term health outcomes.

Attrition is also likely to be closely related to social disadvantage, which makes this issue even more important. While apps may provide a tool to lessen social inequity, if they are used more often and for longer by the most advantaged people in society, and largely not used by the people who need assistance the most. Thus, equity is a vital part of the attrition question, and it is imperative that we understand the rate of dropout in disadvantaged groups and how it can be minimized.

1.10 Diabetes And COVID-19

A major aspect of this thesis is related to diabetes and how the disease interacted with COVID-19. As I will show in later chapters, the behaviour of people with diabetes was substantially impacted by the pandemic, likely due to advice given by public health agencies throughout the world on the dangers of coronavirus infections for people with complex underlying comorbidity (46).

From the early stages of the pandemic, there was strong evidence that older people, and in particular those with a number of comorbidities, were at higher risk of severe disease and death from COVID-19 (74, 75). This led to governments advising people with diabetes to avoid infections, often noting that people with diabetes are not at an increased risk of catching COVID-19, but are at substantially increased risks if they are unfortunate enough to be infected (76).

This advice was then substantiated almost immediately. The large OpenSAFELY cohort study of 17 million adults in the UK demonstrated that having a diagnosis of diabetes (either Type 1 or 2)

increased risk of hospitalization and death by a factor of between 50-150% depending on whether the individual was well controlled (77). In this study, diabetes control was categorized as having a recent HbA$_{1c}$ result consistent with low risk of future complications. Smaller studies on the same question have also demonstrated a similar risk increase for people with diabetes who have caught COVID-19 (78).

The issue of increased risk, and precisely how much the risk is increased particularly for older people with multiple comorbidities, has taken up a large portion of this thesis. Chapter 5 in particular looks at robustly ascertaining the risk of death for people who caught COVID-19, and the impacts that this risk might have on policy.

In addition, the question of COVID-19 and diabetes has impacted this PhD program as it had a great impact my own work. At the start of the pandemic, many traditional functions that I was initially researching as part of my program changed dramatically, as did my own job. During the pandemic, I went from an exclusively chronic disease epidemiologist to everything from a contact tracer, an outbreak tracker, and became an internationally cited expert on the usefulness of serology tests as a method for determining the true prevalence of past infections in a novel pandemic. My thesis therefore reflects not just the dramatic changes that happened at a societal level, but also the diverse range of topics that I was lucky (or unlucky) enough to be thrust into over the past three years.

1.11 Answering The Questions

This leads to the problem statement and ultimate question for this PhD. The problem statement is as follows:

Retention has been a serious problem in app interventions. Most apps experience between 70 and 99% dropout before completion in real-world conditions, and up to 50% dropout even in short-term clinical trials with well-motivated participants. Other distance methodologies, such as telehealth, suffer similar issues. This is particularly concerning for diabetes, an area where there are numerous apps aimed at improving management and self-management, but with little research on how to promote effective use of these applications. There is also reason to believe that behaviours and the need for such interventions have changed due to COVID-19. Identifying the reasons for people dropping out of diabetes app interventions and finding ways to prevent this in the future is a necessary condition for the burgeoning field of self-management applications and other virtual care methodologies to proceed effectively and keep people healthy.

The questions that this thesis seeks to answer are complex: what potential causes are there for people dropping out of virtual care interventions for diabetes? how has COVID-19 changed this

equation? These are broad and difficult to answer, but this thesis will attempt to at least begin the process of disentangling the literature and providing a path to solutions. In particular, the thesis aims to at least understand how people do and do not drop out of virtual care interventions, and what impact the pandemic has had on this. This is key to treatment of diabetes, which is often a lifelong condition with no certain cure, only long-term treatment. Overcoming this fast drop is key to keeping virtual care modalities relevant to people with lifelong disease. It will also allow us to look at the impact of COVID-19 on virtual care methodologies and use this to drive the development of new methods of helping people manage their care without face-to-face contact that could drive infection numbers up.

This question will be addressed in a series of chapters, many of which are made up of now-published papers. Chapter two presents the initial thesis work, reviewing the disease burden of diabetes and why this thesis is so important. Chapter three is a review of the underlying issues that we face when trying to improve patient care in the virtual space. Chapter four then looks at specific evidence on how people drop out of mobile phone applications, and what impact this has on virtual care more broadly. Chapter five examines the burden that COVID-19 had on people, and the risks that those at older ages faced from the pandemic. Chapter six and seven then look at how this specifically impacted people with diabetes, both those using the hospital, general practice, and mobile phone applications. Chapter eight looks to the future, and what we might expect from virtual care now that the pandemic is moving into a different phase, while chapter nine summarizes and concludes the thesis. Overall, the aim is to review the underlying information about why the question of this thesis is so important, and then assess not just the question of whether COVID-19 has changed things, but look at why the changes have come about and how we might be able to leverage this information to improve virtual care into the future. We do not know what the future will bring, but we do know that digital solutions will be part of that landscape. How these solutions interface with the 'real world' is unknown, but what we can say is that everything from ChatGPT to the Metaverse will be important to healthcare as we move into a new, more virtually enabled, world.

The aims of this research thesis are to define the burden that we are facing with diabetes, review issues that existed before the pandemic, and look into the pandemic's impact on how people interact with virtual care. This will then allow a broader examination of the reasons for participating in virtual care both before COVID-19, during the pandemic, and longitudinally afterwards, which will drive both better implementation and potentially point a way forward for the use of these interventions long term after the pandemic has passed.

Chapter Two: The Disease Burden

This chapter refers to a paper published in 2019 as part of this PhD project looking at the burden of diabetes in Western Sydney. This demonstrates the extremely important issue of diabetes, above and beyond that which is often formally recognized, and presents the scope of intervention that is necessary for virtual care. It also provides context on the importance of these virtual care interventions during COVID-19, as if the diabetes burden is far higher than we were expecting, then the need for virtual care interventions is concomitantly higher as well. We found in this study that there were many more people with diabetes than we were expecting, and along with previous research this demonstrates an increased burden in this geographically disadvantaged area as well as a very large problem that could be made worse if people with diabetes were unable to access face-to-face care.

This paper was published in April 2019 in the journal of Diabetes Research and Clinical Practice (79), and is reproduced in this chapter.

In short, the paper looked at the results of two testing groups in GP clinics and hospital emergency departments for diabetes. While the initial estimates of diabetes in these areas were quite low, the results from this sampling indicated a rate of tests consistent with diabetes of 17% in those people who were tested. While this represented a biased sample, it was also substantially higher than the expected results in these patient groups and demonstrated a significant burden of undiagnosed/unrecognized diabetes in the population of Western Sydney. These estimates have since been incorporated into NSW Health policy (80), along with diabetes prevalence estimates from a range of other sources.

The key information that this question answered was to provide better estimates the true prevalence of diabetes in a large population. Diabetes is an often-underdiagnosed condition (81) with some estimates showing that up to half of all people suffering from the disease have been correctly recognized as such by healthcare professionals (81). This paper has confidently shown that diabetes was substantially under-diagnosed in Western Sydney, that the problem was far larger than traditional estimates showed, and that the need for novel healthcare interventions such as virtual care was far greater than previously acknowledged. This evidence was used to drive policy, including a distance insulin titration project which resulted in a published cohort study which also forms part of the thesis work (82).

2.1 Detecting the hidden burden of pre-diabetes and diabetes in Western Sydney

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2.2 Introduction

Diabetes has become a leading cause of morbidity across the world, with rates increasing dramatically over the last two decades (3). Australia has had similar rises, going from a diabetes prevalence rate of 2.4% in the late 90s (83) to more than 6% today (2). This is likely to be an underestimate of the true prevalence as the proportion of people living with undiagnosed diabetes is thought to lie between one-fifth to one-third of the people with diabetes (3, 7).

Geographic variability can influence the rates of diabetes. At the small-area level, indices of social disadvantage have been found to be strongly predictive of increased diabetes rates, with various social factors such as green space, income, and access to fresh food implicated in the inequity (9, 61, 62). Western Sydney is such an area, and has been identified as a diabetes hotspot with rates of diabetes double that of the more socio-economically advantaged suburbs to the city's east (62).

Informed estimates of the diabetes burden on the health system are very important (84). Firstly, the provision of services relies on understanding the burden: we cannot treat what we do not see. Diabetes in particular involves very high costs to the health system (85, 86), with the true cost increasing due to the undiagnosed population. Targeting services effectively also relies on

understanding the population at hand. It is also important to identify people with pre-diabetes, who are at an elevated risk of developing diabetes within the next 10 years (87).

A pilot study undertaken in the ED of Blacktown hospital in Western Sydney noted that 33% of individuals with glycated haemoglobin A1c (HbA1c) results consistent with diabetes were unaware that they were affected(7). As a result, glycated haemoglobin (HbA$_{1c}$) has been routinely measured since mid-2016 in all blood samples obtained through the EDs of Blacktown and Mt Druitt Hospitals. GPs and individuals with abnormal tests are sent letters notifying them of the results along with recommendations for lifestyle intervention. To further understand the burden in our health district, we approached Bridgeview Medical Practice (BVMP) due to its size and proximity to Blacktown hospital to replicate the previously described HbA1c testing process in order to obtain comparative data. After 1 year of testing at BVMP, the scope for testing was widened in the month of June 2018 to include a number of other general practices within the Western Sydney Local Health District to provide a better estimate across the health district.

This paper presents the results from the two HbA1c testing initiatives: 24 months of data from the EDs of Blacktown and Mt Druitt hospitals, and 12 months of data from general practices within the health district. We describe the rates of diabetes in these settings, as well as the trend over time in the hospital.

2.3 Methods

Assessment of HbA1c was routinely undertaken on all blood samples sent to the laboratory from individuals that presented to the ED at Blacktown or Mt Druitt Hospital, irrespective of their reason for attending hospital. This test is added on in the laboratory unless (1) the individual is <18 years of age; (2) HbA1c had previously been measured within the last 3 months; (3) the appropriate blood sample was not available or adequate; (4) haemoglobin values were outside of the laboratory reference value (90-200 g/L) and (5) the blood sample was required for another test that took priority. Steps 1-3 were mirrored in the general practices. HbA1c was measured using a turbidimetric inhibition immunoassay (TINIA) on a Siemens Dimension Vista 1500 platform. Coefficient of Variation was 2.9% and 2.4% at HbA1c levels of 5.7% and 10.1% respectively. The data presented is for a 2-year period beginning the 1st of June 2016. This protocol was mirrored in 11 GP practices during the month of June 2018, as well as the prior 11 months in one practice (BVMP). In ED this represented approximately 35% of individuals presenting each day, with a similar proportion tested in general practice. This study was approved by the Human Research Ethics Committee of the Western Sydney Local Health District.

Test results were obtained from the CERNER system in hospital and by the PEN Clinical Audit Tool in general practice. Results were analysed using SPSS for proportion and trend calculations. The least-squares method was used to obtain an estimate of the goodness of fit for the trend data comparing the proportion of positive tests in ED across weekly averages in the time period. A multivariate Poisson regression model was developed comparing the correlation between diabetes rates and time with adjustments for age, gender, and season. Comparison of the costs of hospital stay was calculated using an ANOVA with Bonferroni correction using NWAU (Nationally-Weighted Activity Unit (88)).

Hospital coding data included all individuals admitted to either Blacktown or Mt Druitt hospital with a code of non-gestational diabetes (ICD-10, E08-E14) between the financial years of 2015 and 2017, consisting of 25,778 records.

The American Diabetes Association criteria was used to define the categories of prediabetes (HbA1c 5.7-6.4% or 39-46 mmol/mol) and diabetes (HbA1c ≥ 6.5% or 48 mmol/mol)(89). As the definition of prediabetes based on HbA1c is yet to be defined, the data for pre-diabetes based on International Expert Committee (IEC) criteria (90) (HbA1c 6.0-6.4% or 42-46 mmol/mol) is also presented for comparative analysis.

2.4 Results

The samples included 55,568 presentations from the emergency departments and 5,911 individuals from the general practices. Data for the ED was collected over a 2-year period beginning the 1st of June 2016. Limited demographic details were available for all individuals; in the ED, the average age was 51.3 years with a 45:55 ratio of male to female individuals. In primary care, the average age was 47.7 years with a male to female ratio of 49:51.

The proportion of individuals with results consistent with diabetes, pre-diabetes, and a normal range is given for both settings in figure 1. In ED 17% of tests were consistent with diabetes, and 30% consistent with pre-diabetes. High rates were also recorded in GP with 17% consistent with diabetes, and 27% consistent with pre-diabetes. The data by testing location is given in table 1.

Chapter 2 Table 1: Rates of pre-diabetes and diabetes by sampling location

Location of Detection	Number of people tested	Time Period	Normal % HbA$_{1c}$ ≤ 5.6% (38 mmol/mol)	Pre-Diabetes % HbA$_{1c}$ 5.7-6.4% (39-46 mmol/mol)	Pre-Diabetes % HbA$_{1c}$ 6.0 -6.4% (42-46 mmol/mol)	Diabetes % HbA$_{1c}$ ≥6.5% (48 mmol/mol)
Blacktown & Mt Druitt Hospital	55,568	24 months	52%	30%	13%	18%
General Practice	5,911	Variable (see below)	56%	27%	11%	17%
Toongabbie (BVMP)	2,855	12 months	59%	23%	10%	18%
Blacktown	2,630	1 month	54%	31%	12%	15%
Mt Druitt	211	1 month	38%	33%	12%	29%
Hills District	118	1 month	50%	28%	14%	21%
Westmead	97	1 month	66%	17%	9%	16%

Chapter 2 Figure 1: Distribution of Pre-diabetes and Diabetes in the ED cohort (Figure 1a) and in General Practice (Figure 1b)

Figure 1a: ED

Diabetes(HbA$_{1c}$ ≥6.5)
n=9,704
17%

Normal (HbA$_{1c}$ < 5.7)
n=29,010

Pre-Diabetes (HbA$_{1c}$ 5.7-6.4)
n=16,854
30%

Figure 1b: GP

Diabetes (HbA$_{1c}$ ≥6.5)
n= 1,027
17%

Normal (HbA$_{1c}$ <5.7)
n=3,308
56%

Pre-Diabetes (HbA$_{1c}$ 5.7-6.4)
n=1,576
27%

■ Normal   ■ Pre-Diabetes (5.7-6.4)   ■ Diabetes
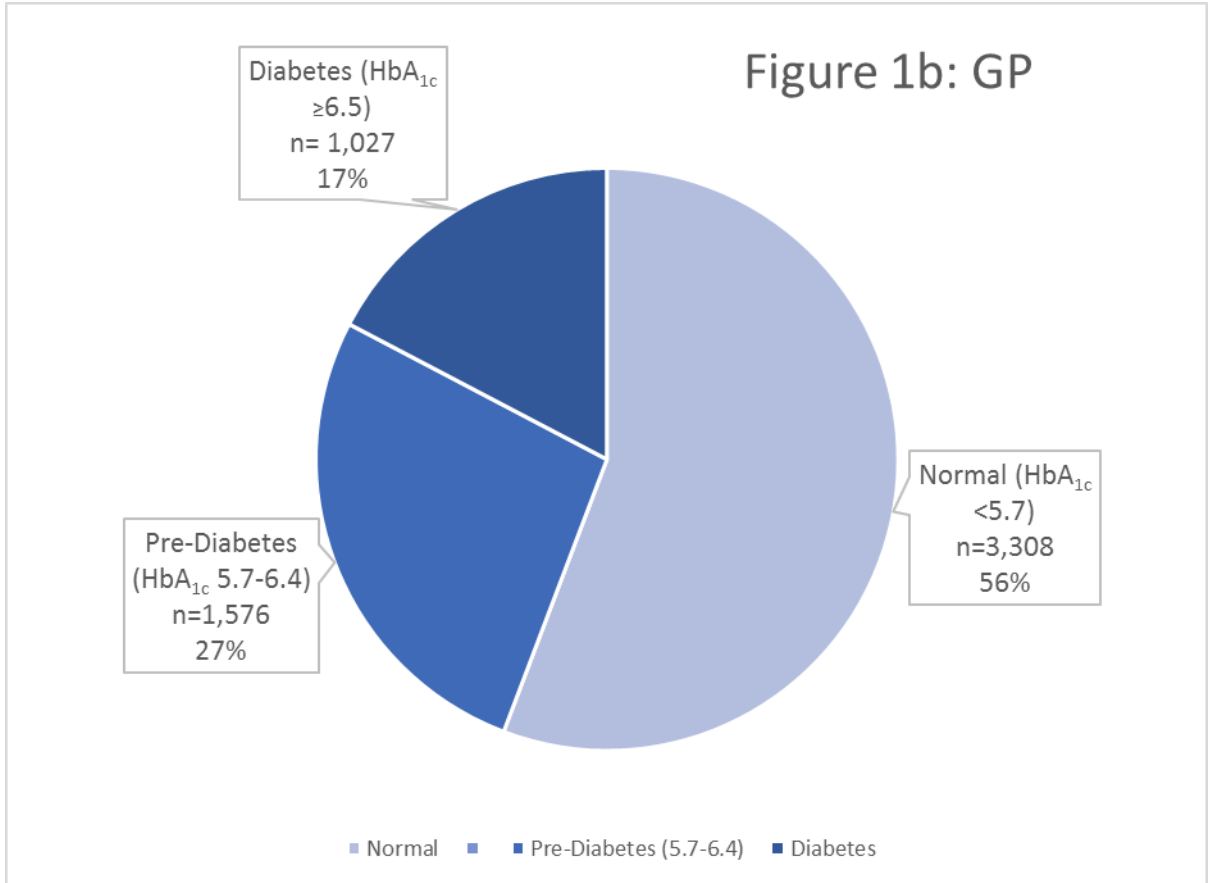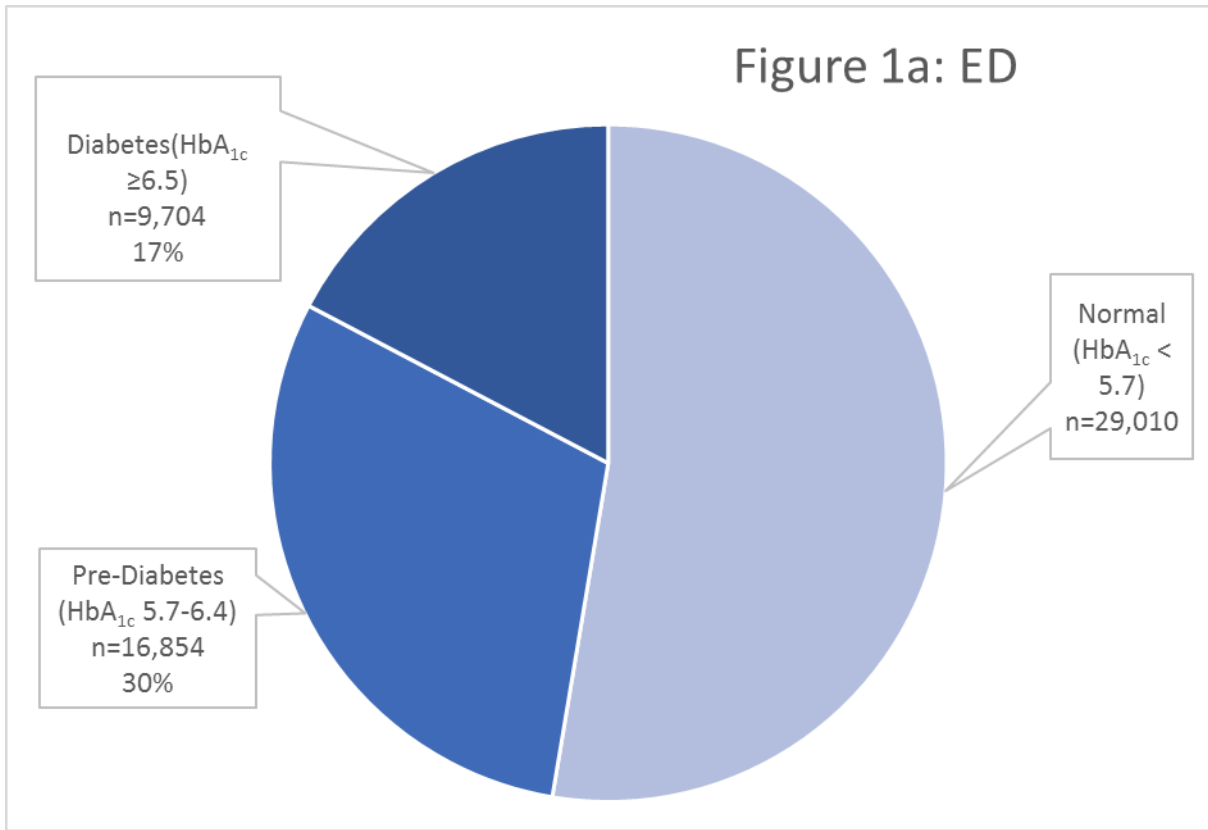
Figure 2 illustrates the proportion of individuals with diabetes presenting each week over the 2 year period of testing in the ED. There was a 1% year-on-year increase in the rate of diabetes (R^2=0.1) represented by the red trend line in the figure.

Chapter 2 Figure 2: Increase in the rate of diabetes, by week of the year
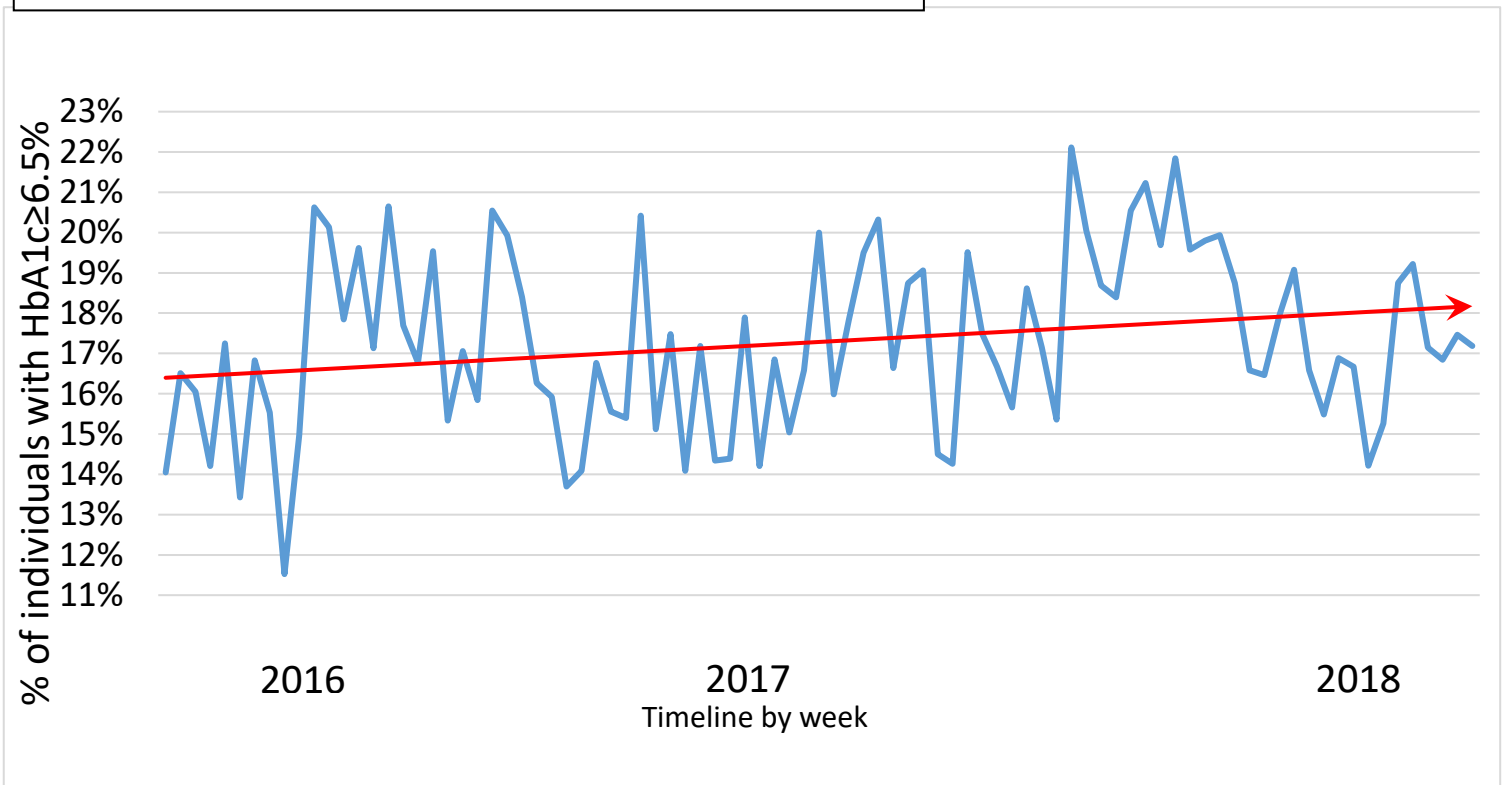
Multivariate regression, adjusted for age, season, and gender, demonstrated an odds ratio of 1.015 (CI 1.012-1.027, p<0.000001) and 1.011 (95% CI 1.008-1.014, p<0.000001) by week for pre-diabetes and diabetes respectively. Over the course of the year, this appears to be generating a 1% absolute increase in the rate of diabetes in ED.

Analysis of the records of admitted individuals revealed a similarly high rate of diabetes amongst all admissions. 20% of all individuals admitted during the 2015 financial year had a code for diabetes, which increased by 1% each year to 22% in the 2017 financial year.

As data for GP clinics only allowed for a cross-sectional view of diabetes rates, similar analyses to the ED cohort were not possible. However, analysis of the GP data from BMVP, which undertook testing on active patients for 12 months, indicated that there were more individuals testing positive for diabetes at the end of the testing period (10.8% or 710 of 6604 individuals) when compared to the start (8.9% or 601 of 6,799 individuals). Active patients were defined as individuals who visited the practice at least 3 times in 24 months. This represents a 22% increase in the rate of diagnosed diabetes from prior to the testing regimen.

Figure 3 provides an overview of the glycaemic categories by age bracket. There is worsening glucose tolerance with increasing age in both the ED and general practice cohorts. There is a notable decline in the diabetes category of the hospital cohort by the age of 80. By the age of 55, the number of individuals with pre-diabetes and diabetes outnumber those with normal glucose tolerance.

Chapter 2 Figure 3: Distribution of glycaemic tolerance by age group

Figure 3a: Diabetes by age in ED patients tested
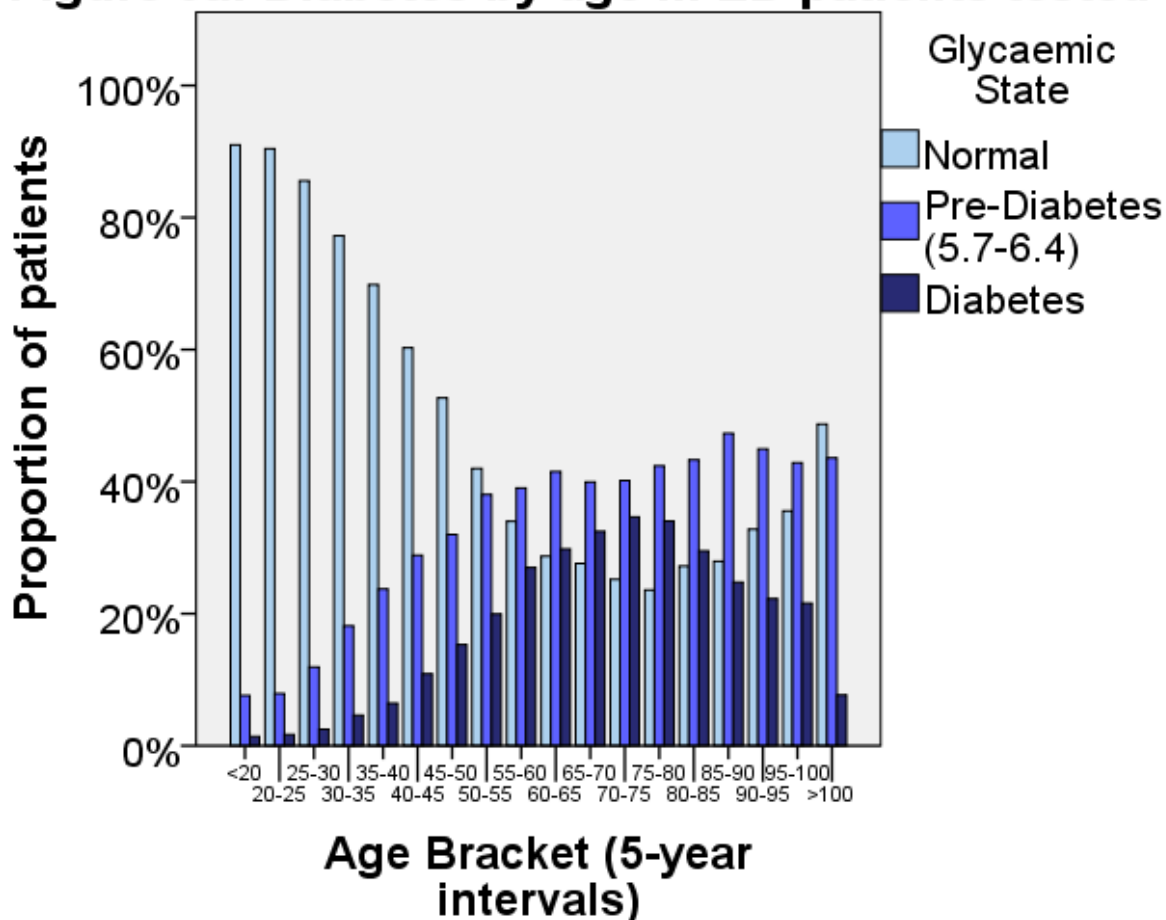
Figure 3b: Diabetes by age in GP patients tested
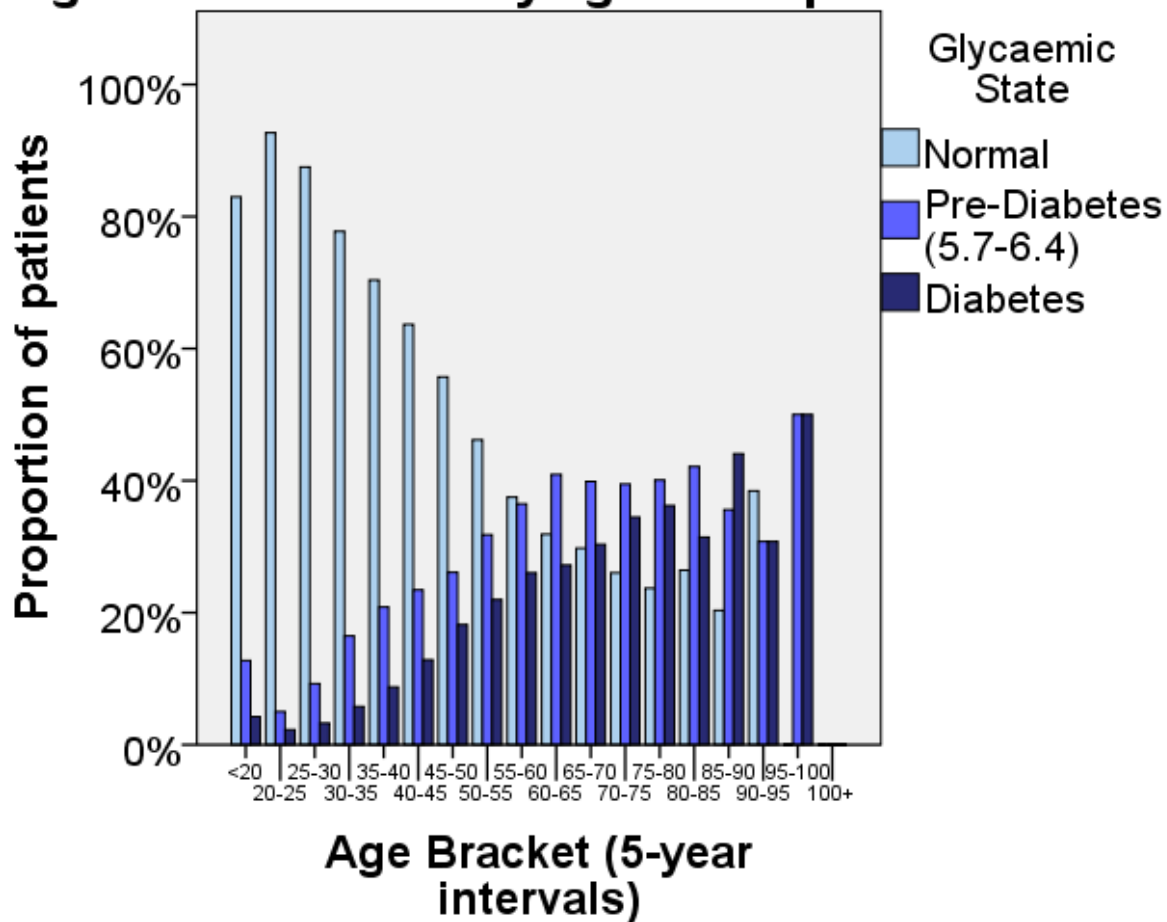
The mean cost of hospital admission (NWAU calculation) for a patient with diabetes was higher than a patient with a normal HbA1c, and that increasing categories of glucose intolerance– from normal range ($5,498), to pre-diabetes ($6,307) and then diabetes ($7,849) - was associated with higher costs. (Figure 4, F=61.55, p<0.00001).

Chapter 2 Figure 4: Costs of hospital stay (calculated by NWAU) by glycaemic category
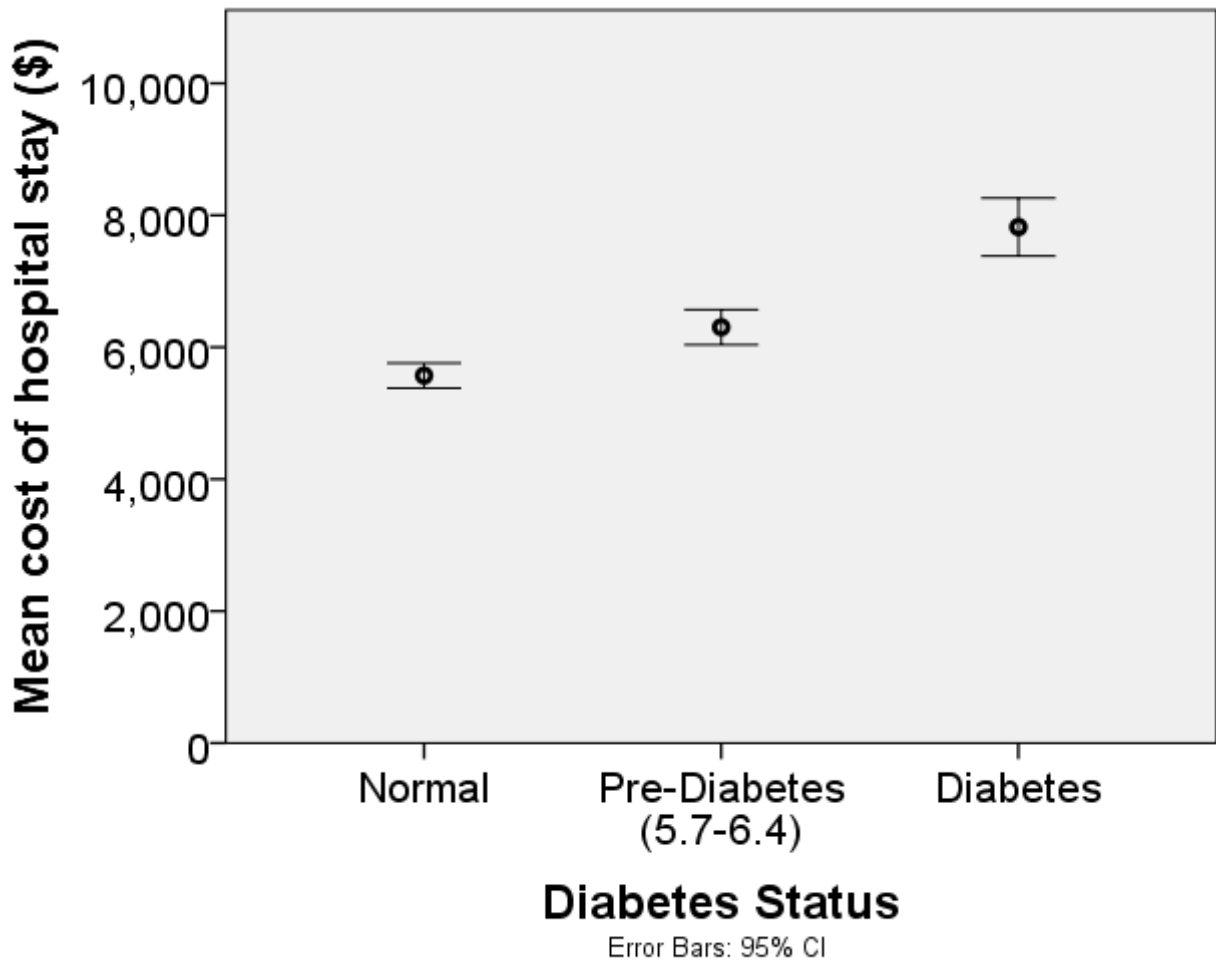
2.5 Discussion

Based on registration data sourced by the National Diabetes Services Scheme, the prevalence of diabetes in Western Sydney is 6.3%, which compares to the national prevalence of 5.2% (6). NSW Health estimates that diabetes prevalence has risen in the general population from 7.9% in 2014 to 11.5% at the most recent estimate in 2017(91). This study reports rates of diabetes that are much higher and there also appears to be a year-on-year increase in the proportion of individuals presenting to ED with diabetes. The data from primary care (BVMP) also suggests increased rates of diabetes over 12 months.

At an individual level, HbA1c measurements are used to monitor treatment and diagnose diabetes in individuals at risk. In our centre, HbA1c testing is part of routine care in individuals presenting to the ED. To the best of our knowledge, there are no other centres in Australia undertaking HbA1c testing at this scale. It is important to emphasize that the HbA1c data needs to be viewed from an

epidemiological perspective as the allocation of individuals to the categories (normal, pre-diabetes and diabetes) is undertaken based on the absolute HbA1c result and ADA criteria. No clinical information has been taken into account in this process and it is possible that imprecise allocation may occur in some individuals (e.g., HbA1c < 6.5% may indicate pre-diabetes or alternatively well controlled diabetes).

The GP testing would not have been possible without the close relationship fostered in this and other work with the Primary Health Network. A surprising finding was the similar rates of pre-diabetes and diabetes detected between the ED and general practice cohorts, which conflicts with the literature that has previously indicated that diabetes severity is higher in hospital (92). This suggests that diabetes may be more pervasive in the community than previously thought. This has implications for healthcare policy and resource allocation for both State and Federal governments. Given the cost-benefit of diagnosing and treating diabetes early (93), these results suggest that routine testing in GP and ED settings may be a reasonable approach.

Whilst the data presented captures information about the rates of diabetes, it also provides important information about those at-risk of developing diabetes. Regardless of how pre-diabetes is defined (ADA vs IEC criteria), it is clear that there are at least equal or double the number of individuals at risk. Figure 3a suggest approximately 13% of women in the childbearing age (20-40 years) who were tested have prediabetes. It is likely that most will also have diabetes in pregnancy and a subsequent high rate of conversion to diabetes post-partum (94).

This study has also demonstrated the utility of routine HbA$_{1c}$ testing in both ED and GP settings in Western Sydney. While population screening is considered unfeasible and not useful clinically, opportunistic testing as conducted in this study is comparatively cheap, easy to implement, and fits within existing hospital and GP frameworks. Widespread testing is likely to reduce the cost per test and better prevention and management strategies could reduce health care costs in Australia. Such testing should be accompanied by adequate resources to manage the increased detection rate, particularly in the hospital setting. In addition, it is clear that the costs of inpatient care increase with worsening glycaemic tolerance which has implications for the hospital budget.

There are a number of limitations to our study design. This population tested was opportunistic with high acuity, which implies that our observed figures are likely to be higher than the true rate of diabetes. However, the fact that the proportions have remained similar across several suburbs

within the district and across large numbers of individuals indicate that data is robust. These findings are specific in our high-risk area and may might not be generalizable to more affluent or less culturally diverse regions elsewhere in the state or country. Our analysis was limited to the data available through the hospital and GP systems which leaves residual confounding as an issue. While we did control for age, further research is needed to identify whether the increased rates of diabetes are due to obesity, socio-economic factors, or other unidentified reasons. The small sample size at several collection locations also means that the geographically specific estimates have wide margins of error. Individuals presenting to the ED on multiple occasions (n=8,968) may have influenced the results; the data collection process in GP did not allow for duplicate patient testing due to the limitations of the PEN clinical software used. Moreover, a sensitivity analysis excluding representations from the ED did not significantly affect any results. The use of HbA_{1c} alone to delineate diabetes can be flawed due to allocation bias as discussed above and a range of clinical scenarios returning an incorrect result (95). Apart from extreme haemoglobin levels, the other factors were not controlled in this analysis.

2.6 Conclusion

This study demonstrated that HbA1c testing in ED and GP reveal a similarly high burden of diabetes and pre-diabetes across different areas of the healthcare system. The rates themselves are alarming, as well as the similarity between what are traditionally considered very different areas of the healthcare system. This has important policy implications, as early intervention for diabetes and pre-diabetes through lifestyle modification programs can have large benefits both to individual individuals and the health system.

Chapter Three – Theoretical Design and Applications for Apps

3.1 The State Of The Literature

The first step to exploring any problem is to identify how big the issues are. While diabetes applications for management and self-management are a relatively new field, there is still a remarkable body of evidence that has been built up examining them in various clinical settings. However, this does not extend far enough to make conclusions about attrition or dropout specifically, so this review includes a number of studies that look at other chronic disease management apps. While these may not relate directly to diabetes applications – at this point, it is hard to make a conclusive statement either way – they do provide some insight into the issue of dropout in similar interventions, and how this relates to the use of diabetes apps in practice.

This chapter examines the literature to date on dropout in diabetes and other chronic disease mobile applications, and what important considerations have already been identified in this nascent field.

Diabetes is a complex disease requiring intensive medical management as well as self-management by patients. Previous research has demonstrated that effective self-management in diabetes is associated with significantly reduced risks of health complications, making it one of the key elements of any diabetes management protocol (13, 96, 97). One method to encourage both management and self-management of diabetes is using mobile applications and telehealth interventions. Systematic review evidence indicates that this is can be a successful way to encourage improved glycemic control for people with diabetes (98). Applications are also a very tempting method of intervention as they are relatively cheap to produce, and can be disseminated widely once introduced.

While the reach of an app may be large, outside of clinical trials they are beset with issues. In particular, retention and dropout rates are high in app-based interventions. One study found that, of the 190,000 people who downloaded a dietary self-monitoring app, only 2.6% used it at least once a week in a 6 month period (72). While this finding has not been replicated in clinical trials – most trials of applications in a clinical setting report rates of 10-30% dropout (96) – it is in line with a more general use of applications in a real-world setting (72). A 2017 systematic review similarly reported that digital self-help interventions for depression, low mood, or anxiety had widely varying uptake and use, with between 0.5% and 28.6% of participants reaching completion depending on the intervention (33). This review also indicated that between 33 and 88% of all users in all interventions engaged in only minimal use, which was defined as using the application/intervention at least once (33). This indicates that a large proportion of the users were not using the app enough to lead to

positive changes in behaviour. While apps may have many advantages, it appears that there are serious barriers to their uptake as a clinical intervention more broadly.

Logically, intervention type, app content, and delivery method will affect retention rate, however there have been few studies explicitly examining this. The aforementioned systematic review found that retention for app-based interventions was higher for PTSD than depression and general self-care, however given the significant heterogeneity between these interventions it is difficult to assess the reasons for this (33). One study found in interviews that a web-based intervention was an acceptable method of delivering a weight-loss intervention for postnatal women, but that an app would have enhanced the retention rate (99). In general, there appears to be a lack of evidence comparing dropout across different app-based interventions, with most studies focusing on efficacy for those who complete the intervention. This is compounded by the fact that research in the area of app-based self-management interventions is relatively sparse – two Cochrane reviews from 2013 and 2016 found a total of 14 studies on apps for asthma and smoking cessation respectively (34, 100). While the field appears to be emerging, with the majority of studies published in the last 3 years, there is still a lack of literature on how to best manage app-based interventions.

Dropout rates appear to be compounded by societal inequalities. Several studies have found that dropout for app-based interventions is highest in disadvantaged groups, in particular more elderly and culturally and linguistically diverse (CALD) groups (28, 98). There is evidence that non-white US patients are more likely to drop out of app-based interventions (28). However, there is some evidence that implementing these interventions in a culturally appropriate way can have an improved effect – in terms of clinical endpoints for the selected intervention - although this is currently not well demonstrated in the literature (101).

While there have been few studies that quantitatively evaluated app retention and dropout, there has been some effort to examine this qualitatively. In one study, low retention rates caused a clinical trial to become unviable, and so the researchers used an iterative survey methodology to examine the reasons for low retention and change their approach (102). In this study a number of issues were identified, including the perceived usefulness of the app, the incentive structure, and health communication components (102). Participants reported that they were less likely to use an app that they did not think was working: in particular, they wanted to have visible impacts on things like weight and health as opposed to changes in obscure clinical markers.

Overall, while there are many studies examining retention of participants in clinical trials, the range of literature examining the question of mobile applications appears to be much smaller. Some

studies examine the question tangentially, but those that directly address retention, particularly in real-world settings, are rare.

There is also limited research on strategies aimed at preventing dropout from interventions. There are currently few studies that specifically address how apps might be improved to get higher usage rates, and of the few studies that have looked at this question – in this literature review, only two were able to be identified – none include quantitative evaluations of retention for their apps.

There is also wide variability in the theoretical backing of app-based interventions. Diabetes guidelines generally recommend interventions that align with behaviour change theory, although some also include elements of social-cognitive theories as well (103). The crux of this difference in conceptual thinking seems to be that those developing these applications believe that they should focus on the most effective strategies to change behaviour, rather than a more integrated approach to change cognition as well. One content-based review found that applications varied widely on behaviour-change theoretical design, and that better quality apps tended to score more highly on theoretical ratings (26). With the iterative, fast-paced structure of most applications, theory is often not an important part of the design process. However, many apps focus on a behaviour change model that incorporates elements of the theory even if this is not always intentional (26).

There is a broad weakness to this theoretical design, in that behaviourally focused interventions often ignore the social and cultural issues within which they operate. Given the importance of social influences in the use of health services and the efficacy of health interventions, it is unlikely that a pure behavioural model will adequately address inequities in healthcare (104). This will also impact the way in which the app works – the basic model is that application usage will lead to improved clinical markers (such as HbA_{1c}), which will lead to improved health, in a linear fashion. However, it is more likely that app usage is influenced by numerous external factors, which then also impact the continued adherence to the intervention, as well as modify the efficacy in terms of clinical benefit.

3.2 Diabetes Apps In Practice

What research has been done appears to indicate that, while people drop out of apps for a range of reasons, these can be boiled down into a few key areas. Firstly, if the perceived efficacy of the app is small – whether it is not working as expected, or not seen as being useful (perhaps due to the low cost of the service) – it will have difficulty retaining people beyond a very short period of time. While this period differs from intervention to intervention, it appears that most people drop out within the first few weeks (72). Secondly, standalone apps are often less effective at retaining individual participation than those linked with secondary interventions. For example, one app that was linked to a podcast maintained very high rates of retention at the 6 month mark(28). Thirdly, app design is extremely important. Apps that are targeted and informed by health literacy and cultural factors are more likely to engage and retain participation and may experience less dropouts as a result. Finally, the efficacy of the app is, unsurprisingly, extremely important. While the perceived efficacy has a large impact, whether the app actually works for the condition that it is being used for, and whether this can be backed up with some sort of incentive, can be a large factor in adherence to the intervention.

It is also worth noting that there is very little research into apps for diabetes specifically. Much of the app work at the moment appears to be centred on apps for mental health issues, with diabetes apps appearing to be a somewhat new area for research purposes.

While the research is somewhat limited, it is still emerging, with most of the referenced literature being conducted in the last 3 years. It is likely that there will be further developments in the near future.

Ultimately, the literature seems to indicate that there are a range of factors that are important to application design and implementation, not least the social context in which apps are created. Some or all of these are likely to impact on the efficacy of an application at reducing rates of attrition which would otherwise scupper its usefulness.

3.3 Theoretical Applications

One major barrier facing app development currently is the relative paucity of theoretical constructs that apply to app-based interventions. While many theories underlie different health interventions, apps are a new type of healthcare interaction that necessitates a new way of thinking [8]. Robust theoretical frameworks allow interventions to be crafted in the most efficient way possible [9], as they provide a consistent rationale for design decisions and ensure that there is an evidence basis to design elements that otherwise might be selected arbitrarily.

This also links to an important issue for app development, that of retention. While recent research has shown promising results for app-based interventions in terms of effects on biomarkers such as blood sugar in patients with diabetes [10], there is emerging evidence that the dropout from such interventions in real-world scenarios is very high [11]. Addressing this gap is vital to improving app-based interventions, and it is likely that a theoretical design will assist in this important element of mobile applications.

This chapter presents an overview of the traditional theories that have been used to design healthcare interventions and how might be applied to application-based interventions that use smartphone or similar devices to deliver self-management services.

3.4 Behaviour Change

There are, broadly speaking, two theoretical approaches to self-management interventions. The first are the behaviour change theories, which look at the impact of a variety of constructs on the individual decision-making process.

Perhaps the most well-known of these behavioural theories is the Theory of Planned Behaviour (TPB). The TPB grew out of the Theory of Reasoned Action (TRA), and is centred on the idea that the key driver of action is intention to perform the action [12]. Thus, ideations and internalities that influence intention – for example, beliefs about the behaviour and perceived control – are the main drivers of behaviour, through the mediating influence of intention. This theory has been used to design some successful interventions, for example to aid couples in their fertility decisions [13].

There are quite a few limitations to the TPB, however, in particular the criticism that it inadequately describes external influences on behaviour and does not account for situations in which a certain behaviour is either extremely difficult or impossible [14]. For example, intention to wear a seatbelt is unimportant for someone driving a car that is not equipped with seatbelts. This has led to the Integrated Behavioural Model (IBM), which is a new theoretical construct that combines intention with external influences to create a more intricate and complete model of behaviour than simple intention allows [15, 16]. IBM theory includes aspects of TPB such as the influence of attitudes and

perception, but also involves modelling external factors such as capacity and autonomy of the individual actor [15], however this theory is still emerging and does not yet have the evidential backing of TPB.

Another commonly used behavioural theory is the Social-Cognitive Theory (SCT). Under this paradigm, behaviours are part of a complex web of interaction between the actor and environment. The central idea of SCT is that human behaviour is derived from learning cues from the social environment [17]. SCT has implications for agency as well as action, with behaviour being the product not just of the desires and beliefs of the actor themselves, but also the social context around them [17]. SCT is commonly used to design interventions that are part of a broader social paradigm, but has been criticized for its generality and lack of specific applicability to individual situations [14].

A final common transtheoretical behaviour change model is the Stages of Change (SoC) model. This has been widely used in smoking cessation and similar programs [18], and is based on the idea that behavioural change can be predicted based on the "stage" that a person has reached: a) precontemplative, b) contemplative c) preparation and d) action [18]. The central premise of this theory is that the most effective behaviour change interventions will be implemented based on the population readiness to change. For example, if a group is in the contemplative stage – considering making a change – then programs aimed at facilitating their preparation will be the most effective, as opposed to programs that would require positive action on their part.

There are innumerable other theories that have been used to design programs, including applied behavioural analysis [18], the health belief model [19], patient/provider trust [20], self-regulation theory [21], cognitive behavioural models [21], and many more. These theories all have a common thread: they position the behaviour as the result of an individual's choices and/or actions, sometimes influenced by society, but always controlled at the individual level. One major criticism of such approaches is that they do not take into account the impact of society on how behaviour is moulded, which gives rise to another form of self-management theory focused at the societal level.

These theories are already being used in the design of apps. For example, the MyBehaviour app was designed with an explicit focus on SCT, Learning Theory, and the Fogg Behaviour model, which were incorporated in the intervention through design of the suggestions that the app offers to users for their health [22]. Other apps have been designed using behavioural change theories but without explicit reference to such, for example the Diabeo application which incorporates a range of TPB modalities without explicitly relying on these for its design [23]. It is however worth noting that these theories are usually only applied as part of the active intervention, rather than informing

design elements of the app itself (i.e. interactivity, interface etc). This may limit how these theories are affecting the design of mobile applications.

3.5 Societal Theories

The second approach to self-management theory takes a more societal approach, and looks at changing behaviour by changing the environment that the behaviour exists in. These theories are often based on the idea of health equity, and focus on closing the gap between the most and least disadvantaged members of society, rather than the individual interventions which look primarily at what can be done to increase an individual or small population's likelihood of managing their disease.

One important example of a societal theory is the equity-effectiveness gap [24], sometimes called the "Staircase Effect", which looks at societal influences on the process of adherence to a public health intervention. This theory posits that individuals will drop out at every stage – or "stair" – of an intervention for a variety of reasons, and that we must address this before an intervention can be successfully implemented [24]. This paradigm proposes the equity-effectiveness loop to create interventions, which is an iterative process that involves evaluation and re-evaluation to ensure that participants are not lost to the intervention due to societal reasons. As with many societal theories, the major criticism of this approach is that it is very general and can be challenging to apply to individual interventions or populations.

Another approach in this area is to focus on ecology, using the Health Promotion Framework(105). This theory combines behaviour change at the individual level with an environmental approach that includes modifying problem areas to affect the desired outcome. An example here is smoking prevention, which has relied on large-scale interventions such as taxation as well as grassroots programs aimed at reducing smoking rates in individual communities.

Other societal methods include community-based approaches, purely regulatory designs, and various combination theories [18] that can be applied in many diverse situations. The common thread in all of these is the idea that individual behaviour change is a function of society, and that to be effective an intervention must put the influence of society first and foremost.

3.6 Moving Forward

Applying these theories to apps can be challenging. Many theoretical designs were developed long before smartphones, and so do not capture the intricacies of the new technology. The field of application development is fast-moving and so even more recently developed theory may not easily apply, with techniques and technologies changing in months or even weeks.

Nevertheless, there have been attempts to incorporate theory into the design of internet and app-based interventions [8]. Both the TPB and SCT have been used in online interventions, with varied results [8]. There is some evidence that using such theories results in a more effective intervention, but this is still an emerging field and so the effect is not well established. For example, one application designed using a behaviour-change model has been demonstrated to be effective at reducing blood sugar and improving control for people with type 1 diabetes [26]. Unfortunately, as noted in a 2016 systematic review, the size and duration of trials looking at theory-designed applications currently makes it very difficult to draw any consistent conclusions about the efficacy of this approach [27].

Applying theories in many cases will likely require some modification of the design – for example, the effect of social cues is much harder to control for when an intervention is designed without any direct human contact – but is also an important step forward in such self-management designs. Another important element is to include broader societal theories in these interventions, particularly given that a number of studies have demonstrated that similar interventions are more effective when designed with a theoretical framework [8].

It is also worth noting that few theory-based approaches engage significantly with both behaviour-change and societal theories. This may be detrimental in two ways: firstly, it will reduce the efficacy of an app if the design does not incorporate both the behaviours and environment of users. Secondly, it is likely that any app designed without a specific focus on health equity – for example, improving health literacy for disadvantaged populations – will result in perverse outcomes with regards to health equity. Our diabetes problem is not limited to one segment of society, and it would be a tragic mistake to design solutions that only work for those who experience significant socioeconomic or similar advantages in life.

While the rationale for using theory in the development of apps specifically – as opposed to not using theory - has not been investigated, there is evidence both that theory can lead to more effective internet-based interventions [8], and improve the impact of chronic disease self-management programs [7]. However, there still remain questions about what proportion of behaviour is explained by these theories [14, 15], with research indicating that between 5 and 30% may be attributable to a specific theoretical design [7, 15]. This presents an opportunity to develop more integrated theories that address both social and individual factors that can have a positive impact on the implementation on app-based interventions.

3.7 Conclusion

Many current app-based interventions do not use a specific theory in their design, despite research indicating that theory-based interventions are often more robust [8, 27]. Fewer still look beyond individual behaviour change to attempt incorporation with a broader theory of society. This gap in app development is likely inhibiting the efficacy of such interventions, with potentially haphazard development and intervention due to a lack of coherent, consistent theoretical backing.

Retention is another issue mentioned in many studies that may be improved using a more solid theoretical approach. While the dropout rate for many apps is very high even in clinical studies, it seems likely that a design centred on theories of behaviour and society could reduce the impact of this issue for future applications.

In other areas of patient self-management, interventions are often based on theory. It is likely that the app development environment, and the relative youth of the field, are contributing to the paucity in theoretical backing for app-based interventions. Whatever the reason, it is clear that the incorporation of theory in the development of self-management applications for chronic disease is an important step forward in the maturation of the field.

This chapter presents an overview of some self-management theories that have been developed and applied in a self-management setting, and how they might be used to improve application-based interventions in chronic disease. This area presents a promising way to improve interventions that are attractive in many ways, and will likely form a large part of our healthcare system into the future.

Chapter Four: Dropout in App-based interventions

This chapter represents a systematic review and meta-analysis of app-based interventions for chronic disease that forms the second study submitted for this PhD. It is vital for any effort examining apps and virtual care that we actually get a good handle on how many people do drop out of these interventions, something that is currently not researched at all. It is also vital to better understand the current proposed reasons for dropout, and what has been studied in practice, to better inform our knowledge of the issues that there may be with these applications and attrition in the real world.

This study has been published in the Journal of Medical Internet Research, and is reproduced in this chapter.

4.i A systematic review and meta-analysis of rates of attrition and dropout in app-based interventions for chronic disease

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4.1 Introduction

Chronic diseases are a large and growing issue worldwide, with rates increasing dramatically in recent years, including infectious diseases that are now managed chronically such as HIV. One example is diabetes, with global prevalence nearly doubling from less than 5% in the 90s to more than 8% today (3). As with other chronic diseases, the economic and social cost of diabetes is enormous, with large direct healthcare costs often eclipsed by the societal impacts of the disease (3, 79). This has led to a large body of research focusing on how to prevent and manage these diseases, with many recommendations now advising moving from a model of care that is medically-focused to patient-centric and community focused (84). However, there are many difficulties in implementing programs for chronic disease prevention and care, in particular the challenges posed by catering to a large, diverse, and growing population of people requiring these services (3, 106). One such difficulty is the dropout rate, or attrition, whereby patients discontinue use of interventions either entirely or

enough that the benefit from the intervention is negligible. This is an area of particular concern for new technological innovations such as mobile phone applications.

Management of chronic disease is often complex. Patients may be on numerous medications, follow strict dietary regimens, and have lifestyle goals to fulfil to optimally manage their disease (13). Professional assistance from health workers – doctors, educators, dieticians and others – is an important component of this management, but increasingly international evidence has shown that self-management – empowering patients to manage their own care – is another effective way to improve outcomes (30, 107, 108).

Self-management interventions range from providing educational materials to highly supportive, multi-faceted programs including a variety of measures (108). One method of self-management assistance that is increasingly popular is providing web-based eHealth or mobile applications (mHealth) to people in order to assist in their management of their disease (60). These interventions have demonstrated efficacy in terms of markers for management, with a recent systematic review finding that, although the evidence is preliminary, mHealth interventions are effective in reducing weight and glycated haemoglobin in people with diabetes (32). Another recent review looking only at the efficacy of mobile applications for diabetes care found that there was limited evidence supporting the effectiveness of diabetes apps to improve blood glucose markers for people with diabetes(109). Overall, there is a growing body of evidence that mHealth interventions, and apps in particular, may be an effective method of promoting self-management in patients.

However, a major barrier to patient care in the use of mHealth interventions is attrition. Previous research has identified that up to 80% of all participants in mHealth interventions may engage in only "minimal use", defined as logging into the service less than twice, and only a small fraction of users consistently use the intervention long-term (33, 102). While clinical trials often report 70%+ retention, these are often short in duration – some fewer than two months - and may not represent the situation in real-world use (32). One observational trial of app usage in a large real-world cohort found that only 2% had sustained continuous use of the kind that would be expected to improve clinical outcomes (72). If only 2% of people who download an app actually use it, there is clearly minimal benefit for the majority. Demonstrating that mHealth interventions are effective in clinical trials is not enough: retention in real-world settings is a necessary precondition for these interventions to be considered effective.

This paper presents a systematic review and meta-analysis into the rate and causes of dropout in mHealth interventions for diabetes and other chronic health issues. This is divided into clinical trials and observational research, to estimate the rates in both controlled and uncontrolled settings, to

estimate the effect both in studies with a large support network to prevent attrition, and the more 'real-world' experience that might be expected when these apps are actually rolled out into clinical practice. These are also qualitatively synthesized.

4.2 Methods

A reproducible strategy was used to identify studies examining mHealth interventions for self-management of chronic disease, either mobile application or internet based. Studies were identified by electronically searching Medline, Pubmed, Cochrane CENTRAL, and Embase from 2003 to the present day. Search terms are fully outlined below, and are loosely based on previous systematic reviews looking at similar topics (110). Searches were performed in June 2019 by GMK, and duplicates excluded using Microsoft Excel and Endnote.

Electronic downloads of searched titles were then performed using the data collection process for each individual database, with titles being screened by a GMK and SM against inclusion criteria to determine eligibility. Abstracts were then be reviewed by these two reviewers independently. Any disagreements were adjudicated between the two authors. References from included studies were also assessed to identify further trials for inclusion. Both experimental and quasi-experimental study designs were included in this review. As the analysis is based on a secondary endpoint (i.e., attrition), no formal risk of bias tool was used to assess the quality of included studies.

For the meta-analysis, total rate of dropout was extracted from each study, as well as number of participants in control and intervention group. The primary summary measure was the rate of dropout in these trials.

Eligibility criteria for inclusion will include studies:

1) Published in English
2) Addressed at an adult population (18+ years)
3) Either randomized-controlled trials (RCT) or observational interventions (case-control/cohort)
4) Looking at app usage in chronic disease AND
5) With a measure of dropout/attrition

A systematic narrative synthesis was produced to describe the included studies and their findings relating to dropout. This narrative synthesis reviewed the findings from all included studies and provide an overall summation of the subject matter.

STATA version 15.1 was used to meta-analyze the included studies, using the metaprop command, with results pooled from RCTs looking at the rate of dropout in clinical trials. There was also a second meta-analysis, by trial type (observational vs. RCT). The primary outcome is the rate of dropout. Heterogeneity was assessed using the i^2 statistic and visual inspection of funnel plots and Egger's weighted meta-regression was used to determine the influence of publication bias. If studies are identified that attempted to prevent dropout, these will form the basis of a subgroup analysis. A sensitivity analysis was conducted looking at attrition comparing short (<2 months) studies with long (>2 months) studies.

4.3 Results

Use of mhealth solutions in managing chronic conditions is increasing, however the effective and long-term engagement (attrition rate) have been attributed to various factors.

After database searches were performed, a total of 1420 articles were identified. After excluding duplicates, 831 unique records remained. Of these, 797 were excluded prior to review. A further 2 records were identified through reference screening from included studies, leaving a total of 36 studies to be included in the review (figure 1). Of the 36 studies included in the final review, 19 were excluded based on the exclusion criteria of studies including children, only looked at acute or infectious diseases. Studies that were purely online, telephone and texting interventions and those that didn't have any measurement of rates of dropout/attrition were also excluded.

This left 17 studies to be included in the final qualitative and quantitative synthesis.

4.3.1 Characteristics of included studies

Included studies ranged were published between 2011 and 2019 (111-128). Of these, most (n=14) examined a range of chronic diseases, including single studies targeting lower back pain, chronic kidney disease, pain, dysmenorrhea, HIV medications, and the remainder(n=9) looking at more general lifestyle improvement such as eating behaviour and physical activity. Three studies included in the review looked specifically at diabetes. There were 9 RCTs included in the final synthesis, and 8 observational trials. This is summarized in Table 1.

Studies ranged significantly in duration, size, attrition rate, methodology, and other areas. The shortest trial included in this review lasted two weeks, and a total of 5 lasted one month or less. Two RCTs looked at a year of data, and a number of observational trials were conducted over a period of 6-10 months. The lowest attrition rate in any study was 9% in an RCT lasting a year (126), and the highest was 82% in an observational trial lasting 6 weeks (122). The largest trial was an observational

study lasting 24 weeks with nearly 200,000 participants, the smallest was a small cohort study including just 20 people.

4.3.2 Meta-Analysis

Results from the meta-analysis are presented in Figure 2. The average attrition rate overall was 43% (95% CI 29-57%), with very high between-study heterogeneity indicated by an I^2 statistic of >99%. The very high heterogeneity is not unexpected in this case, as studies were extremely varied in terms of time, implementation, and the disease state that they were examining.

Looking at the breakdown of results by the type of study, there was a much higher degree of attrition in the observational 'real-world' studies at 57% (95% CI 40-75%) than RCTs in more controlled scenarios with only 32% (95% CI 17-47%) dropping out. Sensitivity analyses looking at differences in length of study (short vs long), diabetes vs other chronic diseases, or whether the studies were numerically large did not find any similar differences in attrition rate between trials.

4.3.3 Attrition Rates

One reason associated with lower attrition rates was the behavioural characteristics of the included participants. Low attrition rates were characterised by reasons such as the perception of own health as poor – thus incentivizing the need to change - (113) and those who wanted to be involved in their healthcare (115). Other factors that were associated with attrition in included studies were health literacy, age (with younger participants dropping out less), and post-graduate education (113, 117). Very low attrition was also reported in those who were on strict diets or who had been healthy eaters prior to the initiation of the study (119). Another association with low attrition was those engaged in multiple interventions. Those engaged in internet or phone programs as well as applications were more likely to remain in the research (118). Conversely, there did not appear to be much influence on attrition rates in terms of length of study, the disease studied, or the size of the app trial.

Findings from these studies suggest ways to improve attrition rate and long-term engagement by using varying message contents or format to maintain users' interests. For example, tailored messages may have the potential to improve adherence to a clinically significant degree (111). Other studies suggest less of a benefit - despite low attrition rate 22% at 4 months and 1 year, in two studies the app and health counselling didn't reduce HbA1c between the intervention group and usual care groups (112, 128). In addition, self-management skills and ability to contact health professional was found to increase whilst users feedback input improved usability and enhance user experience for daily self-reports (112, 114). Classifying different types of users may be important to

improve long-term engagement. Low retention rate might also be because of unguided self-help approach and further engaging those who needs self-monitoring remains challenging.

Another issue with attrition was that definitions varied significantly. While some studies reported users who only logged in a single time as "dropouts" others expanded the definition to include those who only used an app once or twice. For example, the RCT with the lowest dropout rate overall included patients who only sent a single report through the app during the entire follow-up time, which did not indicate sustained, long-term use (126). While these users may have been non-dropouts by the definitions used in this study, they had significantly lower benefits from the intervention, and would likely be considered dropouts had the analysis been less broad.
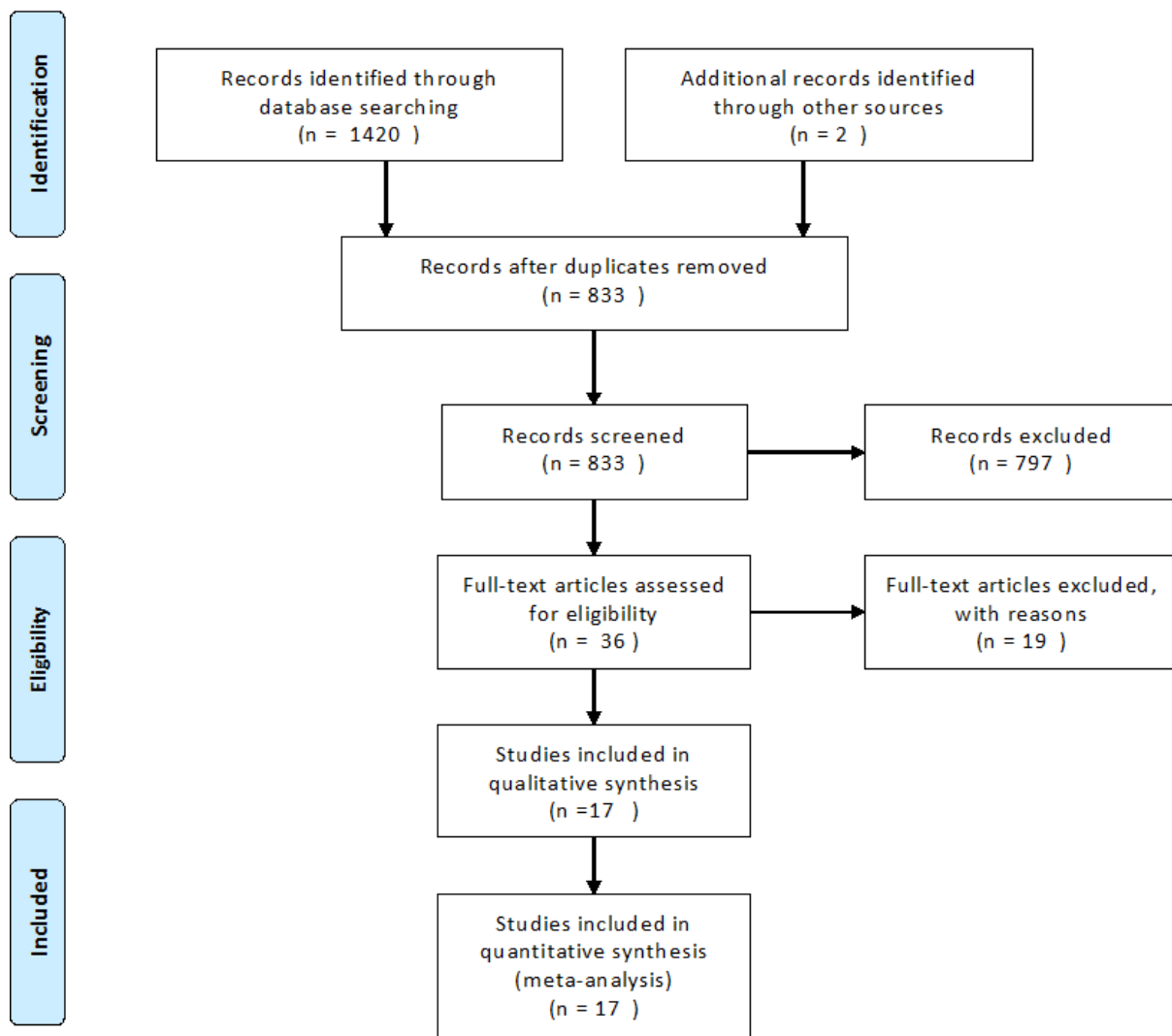
Chapter 4 Figure 1 – PRISMA flow diagram

Chapter 4 Figure 2 – meta-analysis of attrition rates

4.4 Discussion

Attrition in app-based interventions is an important and yet under-researched element. For these interventions to work, it is a necessary component that people use and continue to use the app, however, there appears to be evidence that this is not always the case. In this systematic review and meta-analysis, the pooled estimate of dropout rates was 43%, with higher rates seen in real-world research, and lower rates in highly supported RCTs. This may indicate a very serious underlying issue, as high dropout in these interventions will limit their use and uptake in healthcare across a range of chronic diseases.

While dropout rates in RCTs was notably lower than observational trials, it is worth noting that attrition was often defined differently in this research. RCTs tended to describe all participants as users of the app unless they had ceased using it entirely – while this is in line with best-practice intention-to-treat analyses, it also presents an important limitation with the pooled results above.

Including people in analyses as randomized is laudable, but also obscures the fact that large proportions of people even in these randomized trials with detailed patient support and follow-up barely used the app, if at all. This is worrying, because it implies that even with very high levels of support, apps are not an intervention with substantial staying power for people with various chronic diseases.

It was also concerning that there does not appear to have been much examination of the reasons behind this attrition in many studies. Some few attempted to explain why people dropped out, with this being attributed to health literacy, age, and education, but it is unlikely that these are the only factors that would be related to attrition in the use of apps. For example, as mentioned in the results, people whose health saw greater improvements were more likely in some studies to stay using the app. It is likely that there are a range of unidentified issues that could potentially be targeted to ameliorate this problem, but thus far there has been little recognition of the issue formally, which may have limited the research that has been done to remedy the situation. Many studies do not even address the possibility that people dropping out of an app-based intervention at alarming rates could be an issue for the intervention's adoption at scale, nor the issue that this could cause in terms of aggravating health inequities depending on the reasons for dropout. This is especially concerning when considering that age and social status are likely to be barriers to app access – as some included studies hinted – which may further compound the issues caused by selection bias of those who use apps in the first place. If younger, healthier people are more likely to use apps overall, which is often the case (129), and are then more likely to use them long term, the apps may be less useful for the very populations that we most want them to help.

This is a common theme among trials, in which attrition or non-usage is barely addressed, or only given very surface-level appraisal. If there is a significant difference between the group assigned to the intervention, there is a general attitude that the attrition is unimportant – this appears fairly common in randomized controlled trials, and may be because the aim of this research is specifically to evaluate the app in an intention-to-treat framework (126, 128). However, there are clear drawbacks to this, not least that we may be seeing a large underestimate in the literature of the efficacy of app-based interventions, caused by their generally low use in the populations who have been studied.

There are a number of very important limitations to this research. Firstly, the estimates produced are certainly not comprehensive. Many studies (N>30) that fit all of the inclusion criteria failed to report dropout or attrition in a way that could be extracted. Given the number of trials on app-based interventions, it was not considered feasible to follow-up with every author group that had these

figures, but it is worth noting that this best guess represents a relatively small number of the total pool of potential evidence.

There is also the issue with heterogeneity. Given the nature of the included studies, it is not surprising to find very significant levels of heterogeneity statistically, but it is concerning for the meta-analysis as a reasonable estimate of attrition. These studies were conducted across different disease-states, with very variable interventions – the fact that they all included an app is a thin bond that did not overcome the vast differences that they had between them.

It is also worth noting that the research in this space is quickly evolving. We found no published research to be included before 2010, very little in the years leading up to 2015, and then an explosion of studies in the years after. It is likely that redoing this meta-analysis in 2025 will yield a much more reliable estimate of the figures. This may also allow for analysing by disease-state, which could prove to be a more accurate estimation of the rate of attrition.

There are a number of theories that might pertain to attrition in app-based interventions, with several different focuses. One area that could help inform attrition research in the future is behavioural theory, perhaps by examining the socio-cognitive aspects of people who do and do not drop out of applications. Integrated behavioural theories might also be useful in examining the relationship between social factors and the behaviours they cause, to come to an understanding of the process by which people decide to use or discontinue use of apps.

This would ideally tie into an examination of the broader social and demographic drivers of attrition. While some few of these have been identified in research so far – in particular age – there remains a large evidential gap pertaining to how society influences behaviour to prevent people from using app-based interventions. Future research should combine these two theoretical approaches to define the background reasons for attrition, so that interventions can be designed to minimize it.

Aside from the estimates of application attrition, there are some important implications of this research. Future studies looking at app-based interventions should include attrition as a secondary endpoint, and develop methods to prevent it if possible. One important aspect would be to develop a standard measure of minimum use in app-based interventions – a reasonable example is that used in some of the included trials of one or fewer logins to the app in any given period of time (i.e., one login per month). Lower use than this basic threshold could then be considered 'attrition' for the purposes of research studies. There should be trials looking at ways to reduce the rate of dropouts, as well as the potential inequity in the rate of attrition, in app-based interventions as well. Without such research, we have no way of knowing if applications can be effective in the general population.

4.5 Conclusion

This systematic review and meta-analysis found that the pooled estimate for dropout in trials of app-based interventions for chronic disease was 43% over a variety of timelines, with the length of time having little impact on the rate of dropout. Attrition was higher in observational "real-world" studies, with randomized clinical research seeing less than a third of patients drop out before the trial was completed. However, findings were limited by high heterogeneity and the lack of reporting in many trials on attrition rates. Future research should focus on how often patient's dropout, and examine reasons why so this important issue can be addressed in app-based interventions for chronic disease.

Chapter Five: The impacts of COVID-19

5.1 Background

Setting the scene up until this point, we have reviewed the burden of diabetes, how virtual care can, in theory, assist us with this problem, and the issue of dropout and nonusage attrition, particularly how it relates to mobile applications. It is quite apt that this is where our journey diverges, because it is precisely at this point in my PhD, having published one paper and had another accepted for publication, that the pandemic hit and changed the trajectory of my work moving forward.

It is obvious that the emergence of COVID-19 has changed the way in which we work in the medical sphere. Further chapters will go into more detail proving precisely what changes have occurred, but sitting in my study as a public health worker trying to help with contact-tracing and policy decisions in April and May 2020 it was obvious that things were never going to be quite the same again. From a work environment where digital and virtual interventions were a nice add-on that were gaining traction, we were suddenly plunged into a world where every single service had to be moved online overnight.

This drastically changed the focus of my work, and thus had an impact on my thesis. It would be folly to pretend that the pandemic didn't impact virtual care, and so I have incorporated COVID-19 into the work that this thesis represents. The first part of this work was a series of studies conducted with national and international colleagues looking at the severe impacts of COVID-19, and more importantly how divergent these impacts were across age groups and local settings. Along with the experimental work shown in this chapter, this body of work has led to a number of scoping and narrative reviews on which I am first author, including one in particular, published in BMJ Global Health, that is attached as an appendix (130).

Specifically, this chapter looks at how COVID-19 has impacted people, and the risks of the disease since it emerged. At the outset of the pandemic, SARS-CoV-2 was recognised as a novel and dangerous virus, causing global concern and fast-paced government action across the world to contain the spread of infection (131). Early reports cobbled together from a variety of sources indicated that the disease was particularly damaging for people at high risk of infection for a variety of reasons, including age, co-morbidities, and other potential risk factors (77).

During this period, as part of the global investigation into the risks of COVID-19, it became very important to identify the specific risks to individuals from the virus. Traditionally, the case-fatality rate of an infectious disease is used to derive estimates of lethality, by dividing the number of deaths by the number of pathologically-confirmed infections to identify a proportional risk of death per case (132).

However, this strategy has important drawbacks. COVID-19 is a disease that causes severe issues in a large group of those infected, however in some subset of individuals the infection can present with few or even no symptoms (133, 134). This asymptomatic cohort may represent a large proportion of those infected, particularly in younger age groups who are likely to experience less severe disease. This means that to correctly identify the lethality of COVID-19, there was a need to review the infection fatality rate (IFR), or the proportion of people dying per infection that occurred.

There are three studies that have been undertaken as part of this thesis to review the IFR of COVID-19. All are appended to the document, and form the bulk of this chapter. The first paper is a systematic review and meta-analysis that looks at the overall IFR of COVID-19 in a range of populations, either using seroprevalence or modelling to derive the rate of death per infection (135). The second study looked at the primary risk-factor for COVID-19 death, modelling the IFR of COVID-19 using seroprevalence estimates across age. This pivotal study, which has been cited by public health authorities across the globe, including the WHO, CDC, UN, and others, demonstrated that the risk of COVID-19 tracks very closely with the risk of diabetes, increasing exponentially by age from very low rates of under 1 in 100,000 at age 10 to nearly 1 in 100 at age 60 and above (136). The final study of this triplet of research proved that not only does COVID-19 risk increase exponentially with age, but it also is roughly double as high in developing nations as in high-income countries (137). I lead all three investigations, and lead the writing of all three papers, with the first listing me as first author and the final two listing me as senior and corresponding author, with Professor Andrew Levin as first. This was in agreement with Prof Levin, who said that as the one behind much of the work, I should take the most senior position on the paper.

These papers are important, as they prove that not only is COVID-19 a very dangerous disease, but it also increases in risk for those people who were already more vulnerable at the start of the pandemic. This was recognized early on (74), and taken on board in public advice for people with diabetes and other chronic diseases across the world. Authorities told people that they should stay home and avoid infection if they were at higher risk, and as the next chapters show, in general people followed this advice very well.

This has led to a huge change in the use of virtual care, which is still occurring today. Where once people with chronic diseases had few options for attending services online or virtually, they now are able to access most regular healthcare appointments without any face-to-face contact as a direct consequence of the pandemic and how it has changed the way that healthcare systems function. Moreover, the barriers that previously existed preventing virtual care from being adopted, particularly institutional and systemic barriers such as funding paradigms and the sign-off of

executives, have largely disappeared during the course of the global change that has occurred due to COVID-19.

These papers have also been some of the more impactful work published during the pandemic. The first IFR paper was quickly picked up and cited by both the CDC and WHO, while the initial age-stratified IFR paper is still cited internationally to this day (138). The developing nations paper, which was published in 2022 in BMJ Global Health, has been cited by international organizations including Oxfam (139). In total, these three papers have been cited academically over 1,000 times since publication, according to Google Scholar, and have had an objectively large impact on the global response to COVID-19.

The rest of this chapter is a compilation of the three papers, including the background and results, with an overall discussion at the end to describe how they fit into the COVID-19 pandemic and this thesis.

5.2 A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates

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2020 saw the emergence of a global pandemic, COVID-19, caused by the SARS-CoV-2 virus, which began in China and then spread across the world. One of the most challenging questions to answer during the COVID-19 pandemic has been regarding the true infection-fatality rate (IFR) of the disease. While case-fatality rates (CFR) are eminently calculable from various published data sources (140) – CFR being the number of deaths divided by the number of confirmed cases - it is far more difficult to extrapolate to the proportion of all infected individuals who have died due to the infection because those who have very mild, atypical or asymptomatic disease are frequently left undetected and therefore omitted from fatality-rate calculations (141). Given the issues with obtaining accurate estimates, it is not unexpected that there are wide disparities in the published estimates of case numbers. This is an issue for several reasons, most importantly in that policy is dependent on modelling, and modelling is dependent on assumptions. If we do not have a robust estimate of IFR, it is challenging to make predictions about the true impact of COVID-19 in any given susceptible population, which may stymie policy development

and may have serious consequences for decision-making into the future. While CFR is a more commonly used statistic, and is very widely understood among experts, IFR provides important context for policy makers that is hard to convey, particularly given the wide variation in CFR estimates. While CFR is naturally a function of the denominator – i.e., how many people have been tested for the disease – policy-makers are often most interested in the total burden in the population rather than the biased estimates given from testing only the acutely unwell patients.

There are a number of methods for investigating the IFR in a population. Retrospective modelling studies of influenza, as a common cause of global pandemics, have successfully predicted the true number of cases and deaths from influenza-like-illness records and excess mortality estimates (132, 142). However, these may not be accurate, in part due to the general difficulty in attributing influenza cases to subsequent mortality, meaning that CFRs may both overestimate and equally underestimate the true number of deaths due to the disease in a population (143). The standard test for COVID-19 involves polymerase chain reaction testing (PCR) of nasopharyngeal swabs from patients suspected of having contracted the virus. This can produce some false negatives (144), with one study demonstrating almost a quarter of patients experiencing a positive result following up to two previous false negatives (145). PCR is also limited in that it cannot test for previous infection. Serology testing is more invasive, requiring a blood sample, however it can determine if there has been previous infection and can be performed rapidly at the point of care (PoC). Serology PoC testing cannot determine if a person is infectious, or if infection is recent and there is risk of misinterpretation of results (146). Serology testing is more sensitive and specific than PCR, but will still likely overestimate prevalence when few people have been infected with COVID-19 and underestimate in populations with more infections (147).

This first paper, published in the International Journal of Infectious Diseases presented a systematic effort to collate and aggregate these disparate estimates of IFR using an easily replicable method. While any meta-analysis is only as reliable as the quality of included studies, this provided a realistic estimate to the IFR given the evidence published at the time.

5.2.1 A Note About Convenience Samples

One key metric used for exclusion of studies in this first systematic review was the use of convenience samples to estimate the seroprevalence of COVID-19 antibodies. During the COVID-19 pandemic, one major question has been how many people have been infected in any one place (148). This has proven to be a remarkably difficult question to answer, with earlier studies focusing on official, confirmed cases , and later research proving that this under-estimates the prevalence of COVID-19 in

a region to a great degree (149, 150). It is likely that, due to mild and asymptomatic cases of the disease, much spread of COVID-19 is not captured through official reports and thus the confirmed cases represent a substantial under-estimate which is not useful for future planning and assessing the characteristics of the disease itself.

This presents a challenge, as policymakers and physicians require robust estimates of the disease spread to make decisions regarding population health, but they are unable to trust that the reported case numbers truly reflect the number of people who have had COVID-19 in a population. While this issue may be negligible in some areas with remarkable testing regimens, in the majority of locations in the world it presents a very large issue to be addressed.

One method of overcoming this problem is to conduct a large, randomly selected serosurvey including entire populations, using a probabilistic method to select participants. This is the methodology employed in a number of places including Spain (151), Italy (152), Hungary (153), the Czech Republic (154), and other areas across the globe. These serosurveys represent impressive, often nationwide efforts to understand the spread of the disease, and produce reliable estimates that can usually be easily interpreted for the population.

However, studies of this kind have important drawbacks. They take lengthy periods of time, with careful protocols required, training of staff to collect samples, and the simple issue of coordinating large numbers of samples from a diverse array of locations. Thus, scientists have turned to other avenues in pursuit of estimates of the spread of COVID-19 in a population, in particular blood donor and other convenience samples from hospitals and urgent care clinics. These represent a very useful convenience sample, as they are already giving blood and so do not require additional prompting to be recruited, and they are often a large group that may represent a reasonable fraction of the population of interest (155, 156).

Unfortunately, there are also drawbacks to using convenience samples, which are usually non-probabilistic, from which to estimate population statistics. They are by nature a biased group, who may be more or less likely to have acquired infections than the general population for a number of reasons. The sampling of blood donors, for example, usually excludes the very elderly and young, making it hard to use these studies to draw inferences in populations outside of young, healthy adults. While the samples are undoubtedly useful for sentinel surveillance, it is an open question whether they are applicable for population inferences such as assessing the infection-fatality rate of COVID-19 (150).

There are now published estimates of the importance of sampling on estimates of COVID-19, and why taking into account convenience samples is so important when calculating estimates such as IFR (157, 158). Below is a table showing how convenience samples can both under and over-estimate the sample of individuals who have previously had a COVID-19 infection:

Area	Type of Convenience Sample	Convenience	Representative	Ratio
England 2	Blood Donors	6.8%	6.0%	1.13
England 1	Blood Donors	8.2%	6.2%	1.32
Lombardy	Blood Donors	24.2%	7.5%	3.23
Denmark	Blood Donors	1.7%	1.2%	1.42
Netherlands	Blood Donors	2.7%	2.8%	0.98
New York State	Healthcare Patients	33.6%	14.0%	2.40
Ohio	Healthcare Patients	3.0%	1.5%	2.00
Tokyo	Healthcare Patients	4.6%	0.1%	46
Barcelona	Healthcare Patients	14.3%	6.7%	2.13
New York City	Healthcare Patients	44.1%	22.7%	1.94
Wuhan	Healthcare Patients	8.5%	2.4%	3.55
Scotland	Healthcare Patients	3.7%	3.5%	1.07
Ile-De-France	Other	50.6%	10.0%	5.06
Utah	Residual Sera	2.2%	1.0%	2.29
Connecticut	Residual Sera	4.9%	4.0%	1.23
France	Residual Sera	6.7%	4.6%	1.48
Lisbon	Blood Donors	2.6%	3.5%	0.76
Auvergne-Rhone-Alpes	Residual Sera	2.8%	4.4%	0.63
Bretagne	Residual Sera	1.4%	2.7%	0.52
Bourgogne Franche-Comte	Residual Sera	3.0%	1.0%	2.92
Central-Val de Loire	Residual Sera	1.3%	1.6%	0.79
Grand-Est	Residual Sera	7.0%	6.4%	1.10
Hauts-de-France	Residual Sera	2.4%	2.5%	0.97
Ile-de-France	Residual Sera	7.3%	8.9%	0.82
Normandie	Residual Sera	1.9%	1.4%	1.32
Nouvelle-Aquitaine	Residual Sera	1.4%	1.5%	0.91
Occitainie	Residual Sera	1.2%	1.4%	0.83
Pays de la Loire	Residual Sera	2.2%	3.0%	0.74
Provence-Alpes-Cote d'Azur	Residual Sera	1.5%	4.8%	0.31
Scotland 2	Blood Donors	2.6%	3.5%	0.75

5.2.1 Results

This first IFR paper found a total of 25 studies, after applying various exclusions, with 24 included in the quantitative synthesis and meta-analysis which is reproduced below. The overall IFR of COVID-19 was estimated at 0.68% (0.53-0.82%) using studies aggregated in this review, with very high heterogeneity indicating that the overall rate of death from the disease varied widely by population. Indeed, this

study, originally preprinted in early May 2020, was among the earlier analyses confirming the high-risk that many people with diabetes and older populations faced, and showing that virtual care was a highly important modality for the pandemic as a whole.

Meta-analysis of infection fatality rates of COVID-19 as of research published by 16/06/2020

Study	Month	ES (95% CI)	% Weight
Tian et al	Feb	1.15 (0.00, 2.43)	1.09
Jung et al	Feb	0.70 (0.18, 1.22)	3.10
Verity et al	March	0.66 (0.20, 1.30)	2.94
Russell et al	March	0.60 (0.20, 1.30)	2.94
Nishiura et al	Feb	0.45 (0.36, 0.54)	5.13
Rinaldi et al	April	1.29 (0.89, 2.01)	2.90
Roques et al	April	0.80 (0.45, 1.25)	3.71
Villa et al	April	1.60 (1.10, 2.10)	3.18
Modi et al	April	0.95 (0.47, 1.70)	2.65
Salje et al	May	0.70 (0.40, 1.00)	4.25
New York City	April	0.92 (0.77, 0.94)	5.14
Bendavid et al	April	0.18 (0.12, 0.20)	5.22
Streeck et al	May	0.36 (0.29, 0.45)	5.15
Spain	May	1.15 (1.00, 1.30)	4.95
Indiana	May	0.58 (0.57, 0.59)	5.24
Shakiba et al	May	0.09 (0.08, 0.12)	5.23
Sweden (Stockholm)	May	0.60 (0.40, 1.10)	3.98
Stringhini et al	May	0.64 (0.38, 0.98)	4.25
Snoeck et al	May	0.84 (0.67, 1.00)	4.90
Slovenia	May	0.16 (0.13, 0.25)	5.18
Czech Republic	May	0.68 (0.43, 3.48)	0.75
Denmark	May	0.79 (0.48, 1.70)	2.67
Hallal Et al	May	1.01 (0.01, 2.40)	1.12
ONS England	May	0.83 (0.65, 1.08)	4.68
Herzog et al	June	1.10 (1.02, 1.35)	4.89
Finland	June	0.21 (0.09, 0.49)	4.76
Overall (I-squared = 99.2%, p = 0.000)		0.68 (0.53, 0.82)	100.00

NOTE: Weights are from random effects analysis

Chapter 5 Figure 1 – Meta-analytic results *Taken from (1)*

Indeed, arguably the most important finding from this paper was that people were at significantly higher risk from COVID-19 than common respiratory diseases such as influenza. While the analysis did not discriminate between high and low risk groups per se, the qualitative review of papers did show the key finding that certain groups of patients would experience very dramatically increased risks from the virus.

As the results and discussion sections of this paper notes, there was wide variability in the reported estimates of COVID-19 IFR, and the immediately obvious reason for this was the age of people in various regions of the world. Thus, the following paper was conducted to provide more accurate estimates of the risk of COVID-19 for people at different stages of life.

5.3 Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications

Andrew T Levin, William P Hanage, Nana Owusu-Boaitey, Kensington B Cochran, Seamus P Walsh, Gideon Meyerowitz-Katz

This second paper, published in the European Journal of Epidemiology, is perhaps the most impactful work that I conducted during the pandemic. The following is a brief overview of the introduction and results, edited to remove some elements that were already addressed in the previous paper in this chapter.

Divergences in study design and reporting have hampered comparisons of seroprevalence and IFRs across locations and demographic groups. For example, a number of studies have analyzed a representative sample of the general population, while other studies have made use of "convenience samples" of residual sera collected for other purposes (such as laboratory tests or blood donations).(159-161) Some studies have simply reported results for raw prevalence (the fraction of seropositive results), whereas other studies have reported results adjusted for antibody test characteristics (sensitivity and specificity).

While the NYC data indicate a population IFR of about 1%, seroprevalence estimates from other locations have yielded a wide array of population IFR estimates, ranging from about 0·6% in Geneva to levels exceeding 2% in northern Italy. Such estimates have fueled intense controversy about the severity of COVID-19 and the appropriate design of public health measures to contain it, which in turn hinges on whether the hazards of this disease are mostly limited to the elderly and infirm. Indeed, a recent meta-analysis noted the high degree of heterogeneity across aggregate estimates of IFR and concluded that research on age-stratified IFR is "urgently needed to inform policymaking."(1)

This paper reports on a systematic review and meta-analysis of age-specific IFRs for COVID-19. We specifically consider the hypothesis that the observed variation in IFR across locations may primarily reflect the age specificity of COVID-19 infections and fatalities. Based on these findings, we are able to assess and contextualize the severity of COVID-19 and examine how age-specific prevalence affects the population IFR and the total incidence of fatalities.

5.3.1 Results

After an initial screening of 1146 studies, we reviewed the full texts of 113 studies, of which 54 studies were excluded due to lack of age-specific data on COVID-19 prevalence or fatalities (162-215). Seroprevalence estimates for two locations were excluded because the outbreak was still accelerating during the period when the specimens were being collected and from two other locations for which age-specific seroprevalence was not distinguishable from zero (216-219). Studies

of non-representative samples were excluded as follows: 13 studies of blood donors; 5 studies of patients of hospitals, outpatient clinics, and dialysis centers; 4 studies with active recruitment of participants, and 6 narrow sample groups such as elementary schools (156, 193, 217, 220-244).

Consequently, our meta-analysis encompasses 27 studies of 34 geographical locations, of which 28 are included in our metaregression and 6 are used for out-of-sample analysis. The metaregression observations can be categorized into three distinct groups:

- Representative samples from studies of England, France, Ireland, Italy, Netherlands, Portugal, Spain, Geneva (Switzerland), and four U.S. locations (Atlanta, Indiana, New York, and Salt Lake City) (245-257).

- Convenience samples from studies of Belgium, Sweden, Ontario (Canada), and eight U.S. locations (Connecticut, Louisiana, Miami, Minneapolis, Missouri, Philadelphia, San Francisco, and Seattle) (216, 258-260).

- Comprehensive tracing programs for Australia, Iceland, Korea, Lithuania, and New Zealand (261-265).

The metaregression includes results from the very large REACT-2 seroprevalence study of the English population (251). Thus, to avoid pitfalls of nested or overlapping samples, two other somewhat smaller studies conducted by U.K. Biobank and the U.K. Office of National Statistics are not included in the metaregression but are instead used in out-of-sample analysis of the metaregression results (187, 266). Similarly, the metaregression includes two large-scale studies involving representative samples from three French provinces and from Salt Lake City, and hence two other studies using convenience samples from laboratories in France and in Utah are used in the out-of-sample analysis along with two other small-scale studies (216, 250, 267-269).

We obtain the following metaregression results:

$$log_{10}(IFR) \quad = \quad -3.27 \quad + \quad 0.0524 * age$$
$$\phantom{log_{10}(IFR) = } (0.07) (0.0013)$$

where the standard error for each estimated coefficient is given in parentheses. These estimates are highly significant with t-statistics of -44·5 and 40·4, respectively, and p-values below 0·0001. The residual heterogeneity $\tau^2 = 0\cdot071$ (p-value < 0.0001) and $I^2 = 97\cdot0$, confirming that the random effects are essential for capturing unexplained variations across studies and age groups. The adjusted R^2 is 94·7%.

As noted above, the validity of this metaregression rests on the condition that the data are consistent with a Gaussian distribution. The validity of that assumption is evident in the figure on the following page. Nearly all of the observations fall within the 95% prediction interval of the metaregression, and the remainder are moderate outliers.

This specification of the metaregression also assumes that the intercept and slope parameters are stable across the entire age distribution. We have confirmed the validity of that assumption by estimating alternative specifications in which the parameters are allowed to differ between three distinct age categories (ages 0–34, 35–59, and 60+ years). The estimated parameters are similar across all three age categories, and the null hypothesis of parameter constancy is consistent with the metaregression data. We have also confirmed that the metaregression results are not sensitive to exclusion of open-ended top age groups.

Evidently, the SARS-CoV-2 virus poses a substantial mortality risk for middle-aged adults and even higher risks for elderly people: The IFR is very low for children and young adults (e.g., 0.002% at age 10 and 0.01% at age 25) but rises to 0·4% at age 55, 1·4% at age 65, 4·6% at age 75, 15% at age 85, and exceeds 25% for ages 90 and above. These metaregression predictions are well aligned with the out-of-sample IFRs.

The log-linear relationship between IFR and age
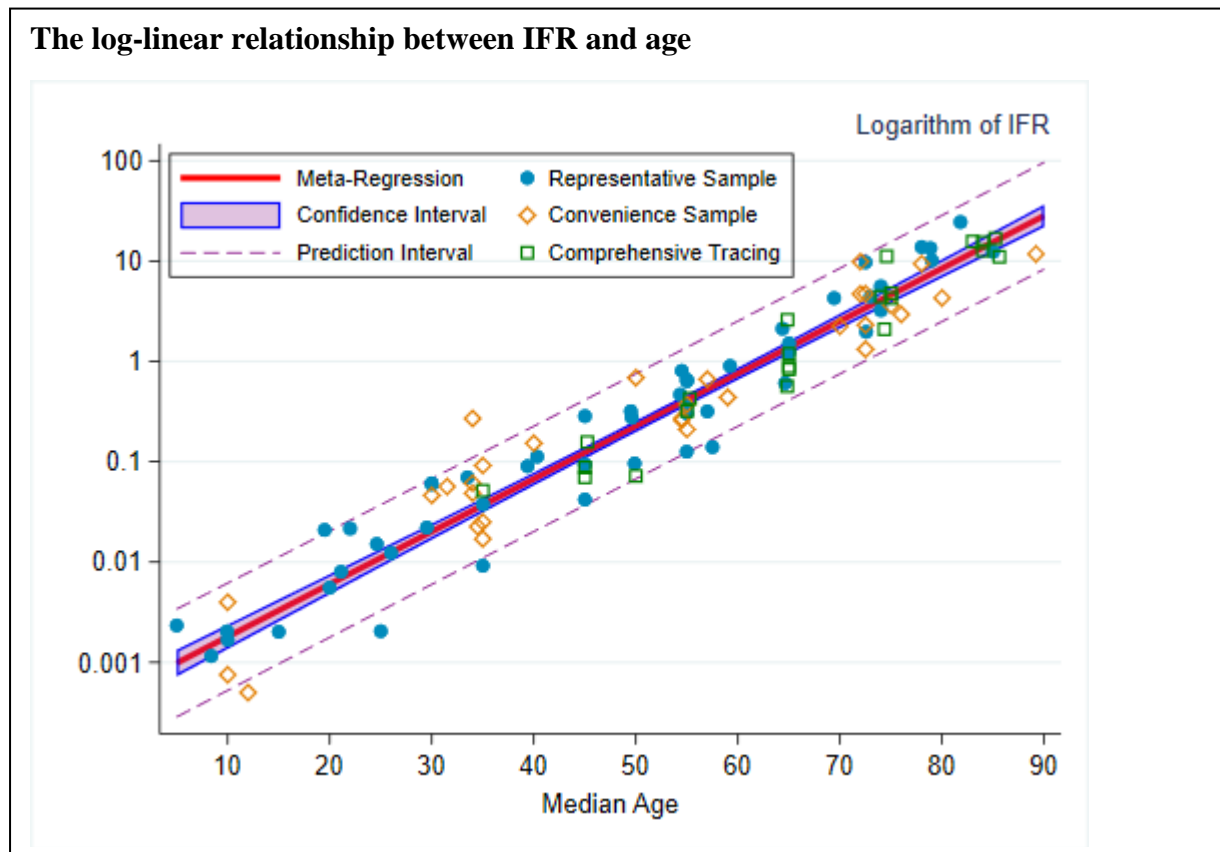
This study proved again the importance of considering different populations in the COVID-19 response, and presented a rationale for the continued calls during the pandemic for people with diabetes and older individuals to avoid healthcare services and access care predominantly through virtual care. The success of these calls is shown later in the thesis, as the behaviour of people with diabetes shifted dramatically due to evidence such as this.

5.4 Assessing the Burden of COVID-19 in Developing Countries: Systematic Review, Meta-Analysis, and Public Policy Implications

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This paper added an important piece of context to the discussion of COVID-19 IFRs – that those in lower-income settings had substantially increased risks from the disease. Again, parts of the introduction and results are reproduced below that add useful information for the purposes of the thesis. This paper was published in 2022 in the British Medical Journal Global Health.

An important unknown during the COVID-19 pandemic has been the relative severity of the disease in developing countries compared to higher-income nations. The incidence of fatalities in many developing countries appeared to be low in the early stages of the pandemic, suggesting that the relatively younger age structure of these countries might have protected them against the harms of the disease. More recently, however, it has become clear that the perceived differences in mortality may have been illusory, reflecting poor vital statistics systems leading to underreporting of COVID-19 deaths (270, 271). Moreover, relatively low mortality outcomes in developing countries would be starkly different from the typical pattern observed for many other communicable diseases, reflecting the generally lower access to good-quality healthcare in these locations (272, 273).

As shown in the below table, mortality attributable to COVID-19 in many developing locations exceeds 2,000 deaths per million. Of the twelve nations with the highest number of deaths attributed to COVID-19, eight are developing countries. Furthermore, these statistics may understate the true death toll in a number of lower- and middle-income countries. Numerous studies of excess mortality have underscored the limitations of vital registration and death reporting, particularly in developing countries (270, 271, 274-278). For example, recent studies of India have found that actual deaths from COVID-19 were about ten times higher than those in official reports

(271, 274). Similarly, a study in Zambia found that only 1 in 10 of those who died with COVID-19 symptoms and whose post-mortem COVID-19 test was positive were recorded as COVID-19 deaths in the national registry (279). Strikingly, the continuation of that study has demonstrated the catastrophic impact of COVID-19 in Zambia, raising the overall mortality by as much as five to ten times relative to a normal year (280).

There was, however, a relative dearth of systematic research concerning the early experience of COVID-19 and the associated infection fatality rate (IFR) in developing countries. Previous evaluations have largely focused on assessing these patterns in high-income countries, where high quality data on seroprevalence and fatalities has been readily available throughout the pandemic (281, 282). In particular, seroprevalence studies conducted in high-income countries in 2020 found low overall prevalence of antibodies to COVID-19 (generally less than 10%) (283), with much lower prevalence among older adults compared to younger cohorts. Analysis of these data has clearly underscored the extent to which the IFR of COVID-19 increases exponentially with age; that is, the disease is far more dangerous for middle-aged and older adults compared to children and young people (136, 281, 282). Two prior meta-analytic studies have considered variations in IFR by age but did not consider the possibility that IFR in developing locations might differ systematically from high-income countries due to healthcare quality, access, and other socioeconomic factors (135, 281).

Confirmed COVID-19 Deaths as of 20 March 2022

Country	Cumulative Deaths	Mortality Rate per Million
United States	971 162	2 917·1
Brazil	657 495	3 072·5
India	516 510	370·7
Russia	357 234	2 448·3
Mexico	322 072	2 472·5
Peru	211 865	6 351·0
United Kingdom	163 658	2 399·4
Italy	157 785	2 613·7
Indonesia	153 738	556·3
France	141 002	2 091·3
Iran	139 610	1 641·9
Colombia	139 452	2 720·2

Chapter 5 Table 2 – confirmed COVID-19 deaths by country

In order to remedy this issue, we performed a systematic review of all available literature to identify what the ratio of IFR in developing nations was to high-income nations. This involved an extensive

systematic review of serological studies, as well as a cutting-edge Bayesian statistical model that is also published as a separate paper. The full methodology can be read in the published research in BMJ Global Health.

5.4.1 Results

We identified a total of 2,384 study records, with 2,281 records identified from online databases and a further 124 from Twitter, Google Scholar, and a prior publication (284). After excluding 2,062 records, we assessed 343 records and determined that 97 studies satisfied the criteria for inclusion in the final analyses, of which 62 studies (representing a total of 25 developing countries) could be used to produce IFR estimates.

Infection Fatality Rates

Our statistical analysis produced age-specific IFRs and confidence intervals for 28 locations, and population IFRs for those locations as well as an additional 27 places. We obtain the following metaregression results:

$$log_{10}(IFR) \quad = \quad -2.75 \quad + \quad 0.0478 * age$$
$$\qquad\qquad\qquad (0.10) \qquad\quad (0.0023)$$

where IFR is expressed in percentage points, and the standard error for each estimated coefficient is given in parentheses. These estimates are highly significant with t-statistics of -28.7 and 21.0, respectively, and p-values below 0·0001. The residual heterogeneity τ^2 = 0.039 (p-value < 0.0001) and I^2 = 92.5, confirming that the random effects are essential for capturing unexplained variations across studies and age groups. The adjusted R^2 is 91.1%. Location-specific fixed effects are only distinguishable from zero for three locations: Maranhão, Brazil (-0.50); Chennai, India (-0.68); and Karnataka, India (-1.29).

The metaregression results can be seen below. Nearly all of the observations fall within the 95% prediction interval. The importance of the location-specific effects is readily apparent. Indeed, these effects imply that the age-specific IFRs for Maranhão are about 1/3 of the metaregression prediction, while those for Chennai and Karnataka are 1/5 and 1/20, respectively.

Chapter 5 Figure 3 – metaregression results for developing countries' IFR
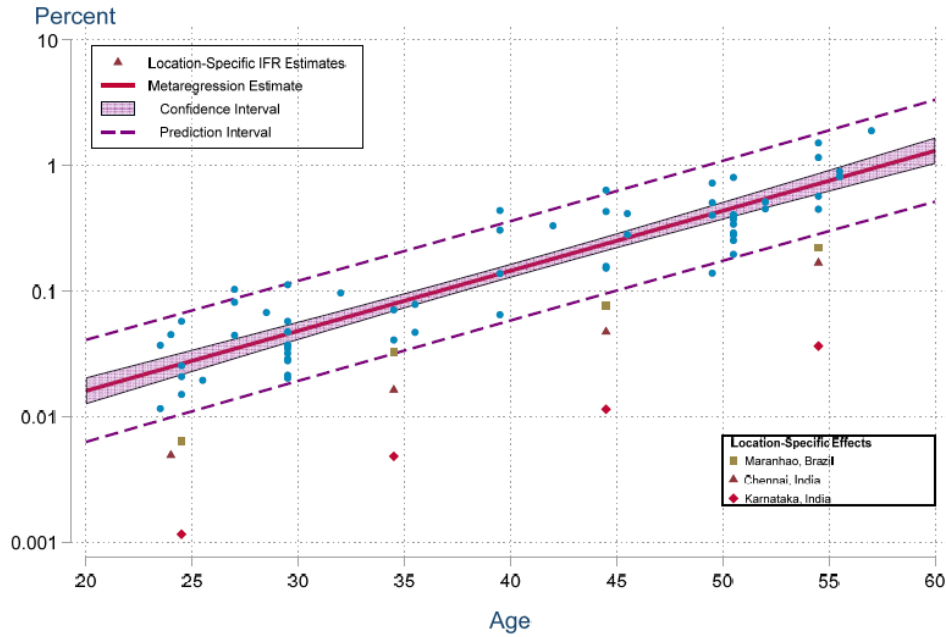
Figure 5 – This figure shows the metaregression estimated using the location-specific IFR estimates shown here. Location-specific effects are included for three locations: Maranhao, Brazil; Chennai, India; and Karnataka, India.

This metaregression analysis uses age-specific IFRs based on reported COVID-19 deaths in each location. The precision of IFR estimates varied by age. At lower age groups, the number of deaths becomes very small, and thus the uncertainty is large regarding the IFR. Conversely, at older ages the number of infections and deaths can be very small in countries with extremely small populations of those aged over 65, and thus these estimates are also uncertain.

The figure below shows that these age-specific IFRs are systematically higher than those of a prior metaregression estimated using studies of high-income countries(136). That benchmark metaregression has a slope of 0.0524 (CI: 0.0499-0.0549), and a Welch test strongly rejects the hypothesis of equality in the slope parameters for developing countries vs. high-income countries with a p-value<0.0001. This figure also shows a variant of our metaregression, estimated using studies of developing country locations conducted over the same timeframe as in the benchmark metaregression (April to September 2020) and excluding the three outlier locations (Maranhão, Chennai, and Karnataka); the estimated intercept and slope coefficient of this variant (-2.68 and 0.0480, respectively) are statistically indistinguishable from the baseline values shown above.

Chapter 5 Figure 4 – IFR in developing countries compared to high-income countries
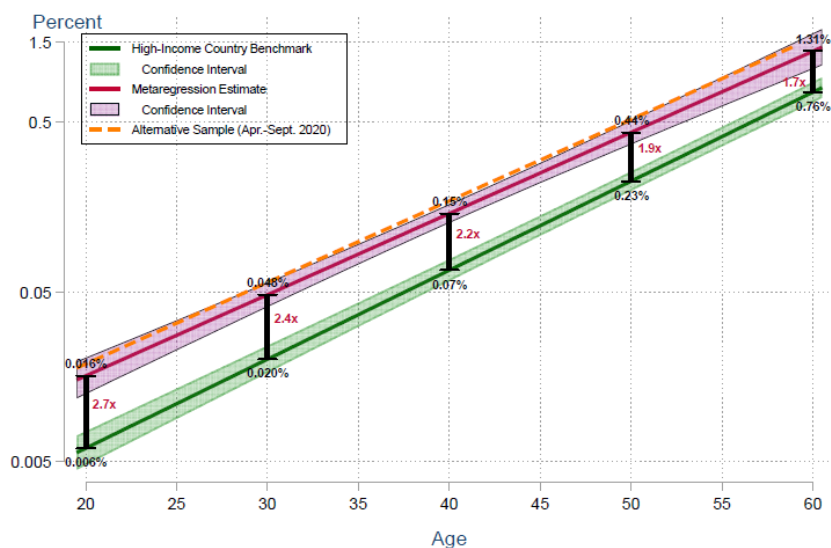
Figure 6 – Comparison of IFRs at different ages for high-income vs developing countries. The estimated metaregression is given in equation (1). The variant metaregression uses age-specific IFRs from serology studies conducted between April and September 2020. The high-income country benchmark is taken from a prior metaregression study (15).

5.5 Conclusion

Overall, these three studies paint a stark picture of the risks of COVID-19, and provide a strong insight into the impact of the pandemic on those considered high-risk. As diabetes is strongly correlated with age, any impact on age is likely to impact the behaviour of people with diabetes as well. Indeed, the following chapter of this thesis shows precisely that – people with diabetes were informed early on in the course of the worldwide pandemic that they were at higher risk from COVID-19, and they acted on that risk in a rational way.

These three papers form some of the most important work that I have ever done, and have been cited by the WHO, UN, CDC, and others during the course of the pandemic. Combined, they have been cited over 1,500 times.

Chapter Six: COVID-19 and Hospital Admissions

This chapter is made up of a study published by the journal BMC Health Services Research, which looks at the changing behaviour of people with diabetes during COVID-19. We empirically prove that people avoided hospital and tertiary care, and show that this is likely due to a replacement in care by telehealth and other virtual services during the pandemic by primary care institutions and General Practitioners.

6.i Diabetes during the COVID-19 pandemic: are people getting access to the right level of care?

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6.1 Introduction

The emergence of COVID-19 as a global pandemic has dramatically changed the way healthcare has been delivered. In preparation for large upsurges in patient numbers requiring care, people were originally discouraged from attending healthcare services at the beginning of 2020. Moreover, people with diabetes were quickly identified as having a very significantly increased risk from COVID-19, with higher risks of hospitalization and death if they catch the disease (1). The ongoing fear of COVID-19, particularly for high-risk people, has also been demonstrated to have impacted their movement (2, 3) and likelihood of seeking care for medical issues. Moreover, there is evidence that lockdowns have been associated with reduced access of care in many situations, despite the lockdown itself not necessarily impeding the ability to attend a medical institution (4).

Western Sydney is a moderately large area in the west of Sydney, Australia, encompassing roughly 1 million inhabitants (5). It is one of the most culturally diverse places in Australia, with nearly 60% of inhabitants having been born overseas (5), and it also has the numerically largest population of Aboriginal people of any local health area in Australia. The region is also home to very disadvantaged neighbourhoods, including the most disadvantaged postcode in the city of Sydney. Given these characteristics, Western Sydney is a diabetes 'hotspot' with rates of diabetes double that of the less disadvantaged areas in the city (6, 7).

To improve care in this locality, routine testing to detect diabetes in patients attending the Emergency Department (ED) has been established in some of the local hospitals (8). Using this protocol, HbA1c testing is undertaken in all patients over the age of 18 who had blood sampled in ED. This protocol confirmed the findings of high rates of diabetes undertaken in a previous study (9). A recent study looking at a similar protocol in nearby community general practice clinics identified a similar burden of diabetes in this setting, with the rate of HbA1c consistent with diabetes estimated at 17% in both of these studies (8). HbA1c levels consistent with pre-diabetes based on American Diabetes Association criteria (10) was found to be 30% using this testing protocol. Since the start of the hospital testing methodology, over 170,000 tests have been performed on more than 100,000 patients, providing a large dataset for analyses in this study.

Another extremely valuable source of information in this local area is the accumulation of general practice data in aggregate form by the primary health network, Wentwest. This represents the de-identified data of all patients attending 188 general practices (GP) across the region. While not as granular as the testing information from EDs, this dataset is extremely large, with close to 2 million patients – including historical data - included overall.

Another useful facet of the healthcare relationship to consider is the potential switch from face-to-face (FTF) services during the pandemic to virtual care (VC) modalities. During times where social distancing was of key importance and health services often could not offer FTF services, VC became the primary modality through which patients with diabetes accessed ongoing services for their chronic condition (11). Where previously VC was one option of many, it became the method of access for most outpatient and ongoing healthcare services during both lockdowns and periods of high transmission.

This study presents an analysis of the rate of HbA1c tests consistent with diabetes in patients presenting to Blacktown/Mount Druitt emergency departments before and since the COVID-19 pandemic has begun, with a similar examination of diagnosed COVID-19 cases in GP clinics, as well as some interrogation of the reasons that this rate may have changed with a particular focus on a switch to VC. We hypothesize that the rates have varied substantially due to the pandemic, and that this has had an impact on the reasons for using VC.

6.2 Methods
This analysis used an existing dataset of those who have had HbA1c tests through the ED in Blacktown and Mount Druitt Hospitals in western Sydney. The detailed methodology for this testing has previously been published (8). Briefly, all patients who attend the ED and have a blood test irrespective of reason for presentation will undergo HbA1c testing on the proviso that there is

sufficient sample to undertake this measurement. Patients are not re-tested if they represent within 3 months of a previous test. This dataset represents 173,805 tests performed between 1st June 2016 and 12th November 2021. 75 HbA1c tests were missing in this population, leaving 173,730 to be analysed in this study.

We also analysed a sample of all patients attending selected General Practice clinics in western Sydney. This represented the de-identified aggregate information of 188 individual clinics, and a total of 1.8 million patients. Within this dataset, we looked at the proportion of patients with diabetes attending GP clinics before and during the implementation of lockdown measures. This also included an examination of HbA1c testing rates in GP clinics, as a measure of the care that was being offered during this time. Diabetes in this dataset is defined as a GP flag of diabetes, excluding gestational diabetes. The dataset included data from the start of collection for these 188 clinics, September 2019, until the most recent extract date at the end of October 2021. Prior to September 2019, a smaller number of GP clinics were included in this dataset, with about 130 as of the start of 2019.

Finally, we retrospectively reviewed routinely collected hospital data from Blacktown/Mt Druitt hospitals, two hospitals in western Sydney with a total of 600 beds. We also reviewed the VC provision using routinely collected data from the Western Sydney Diabetes (WSD) clinics, which service both of these hospitals.

WSD is an integrated care program spanning primary and secondary prevention, with an aim to both prevent people from getting diabetes, targeting high-risk individuals to improve their health, and preventing further complications for those who already have diabetes. WSD has a series of clinics including a joint case-conferencing service (12), complex diabetes clinics, post-discharge clinics, insulin stabilisation services, app-based healthcare provision, and various other VC services. These provide around 5,500 occasions of service to over 1,000 patients per year. Services were classified into either those provided by VC (including telehealth, audiovisual consultations, email, and mHealth) or those provided FTF.

All analysis was performed using Stata 15.1. In the hospital dataset, we computed the average weekly proportion of people with an HbA1c meeting the American Diabetes Association criteria for a test consistent with diabetes (10) of 6.5% (48 mmol/mol), as well as the 95% confidence interval for this figure. We then compared this to the observed proportion of people presenting since the state of New South Wales (NSW) began its lockdown on the week beginning 16th March. We also stratified this by age and sex to examine whether these factors were influencing the rate of diabetes in this population. We compared the average rate of diabetes in the population both using the 95%

confidence intervals and performing a simple t-test comparing the rates before and during the pandemic to gauge statistical significance.

6.3 Results

Demographics for the ED population are presented in Table 1. The mean age of the entire sample was 51 years, with the average age increasing with HbA1c. There was a slightly higher proportion of females to males in the sample, with 55% of the overall sample being female. Men made up a larger proportion of those with elevated HbA1c.

Chapter 6 Table 1 – demographics by HbA$_{1c}$ status			
	No Diabetes	Pre-diabetes	Diabetes
All (n)	62,473 (52%)	36,751 (31%)	20,859 (17%)
Age*	42.3 (19.3)	59.1 (19.0)	64.2 (16.0)
HbA$_{1c}$*			
HbA$_{1c}$ (%)	5.3 (0.3)	6.0 (0.2)	8.0 (1.6)
HbA$_{1c}$ (mmol/mol)	34	42	64
Sex^			
Female	36,321 (58.1%)	19,256 (52.4%)	10,151 (48.7%)
Male	26,152 (41.9%)	17,495 (47.6%)	10,708 (51.3%)
BMI (Kg/m^2) *	27.5 (7.2)	29.1 (8.0)	31.2 (8.8)
Aboriginality^			
Aboriginal or Torres Strait Islander	3559 (5.7%)	1275 (3.5%)	863 (4.1%)
Neither Aboriginal nor Torres Strait Islander	58,914 (94.3%)	35,475 (96.5%)	19,996 (95.9%)

*Mean with standard deviation in brackets ^ proportion of total. Diabetes/pre-diabetes defined using ADA criteria of >6.5% and 5.7-6.4% as above.

In the time period since the week beginning March 16th, the number of tests performed in these EDs has declined, from an average just below 3,000 per month to just above 2,600 per month. This appears to correspond to a decline in the rate of ED attendances, with roughly half the expected attendances per week in late March and April of 2020 compared to 2019. There have also been differences in the people attending ED, with fewer people over the age of 65, and a decline in the proportion who are female. This is shown in Table 2.

	Pre-COVID	During COVID-19
Tests per week	642	556
Median age	50	47
% male	44.95	46.39
% over 65 years old	29.46	26.86
% under 40 years old	36.97	40.86

Chapter 6 Table 2 – tests characteristics before and during COVID-19 pandemic

The primary findings are presented in Figure 1. During the time period from when NSW began legally enforcing isolation measures due to the epidemic of COVID-19, there has been a significant decrease in the proportion of people attending ED with elevated HbA1c consistent with diabetes. The proportion has decreased from a mean varying between 15-20% to an average of just over 11% consistent with diabetes during this period.

Chapter 6 Figure 1 – Percentage of patients with tests consistent with diabetes tested in ED by week since 2016.
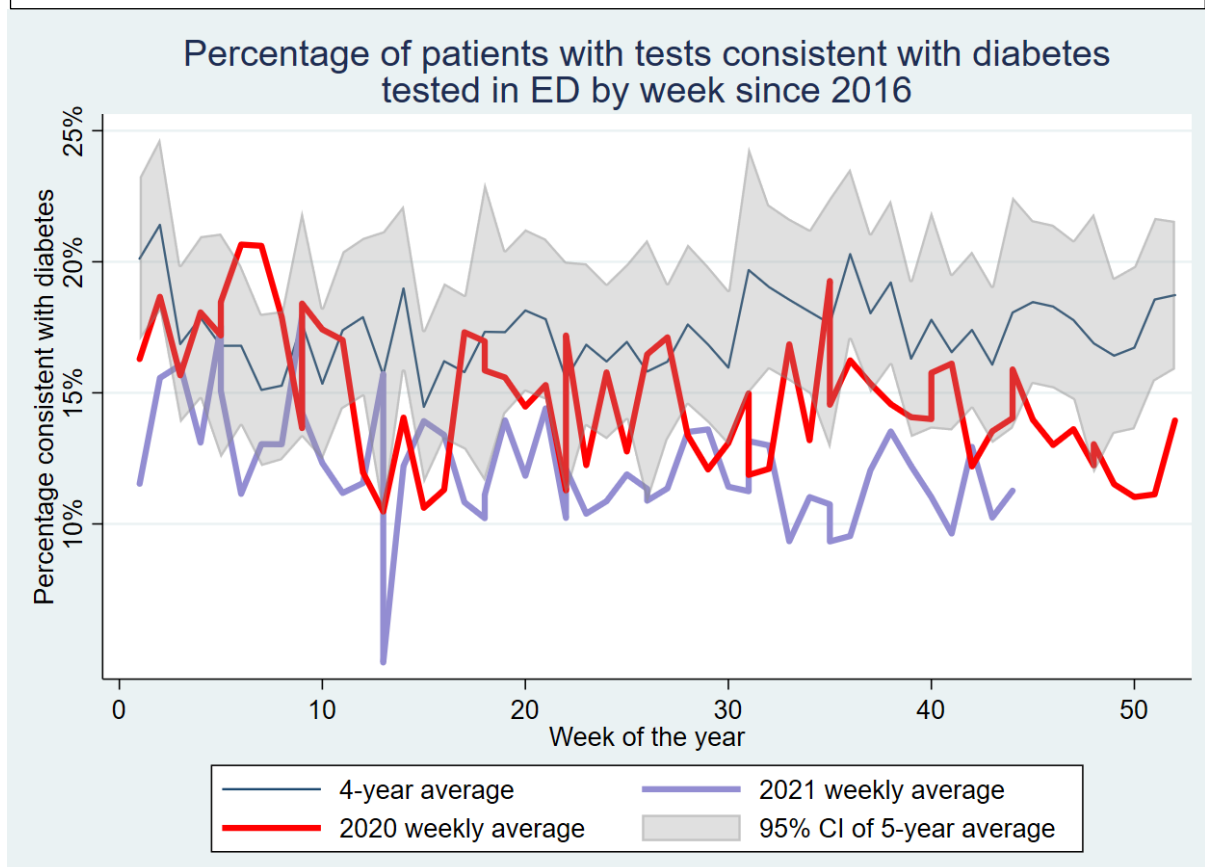
Examining this rate by gender and age, there are some important findings. The reduction in the rate of tests consistent with diabetes appears to be largely driven by a decrease in the median age of

people presenting. Once age-stratified, there appears to be some difference in diabetes percentages by age group,. This is shown in Figure 2. There is also indication of a significant interaction with gender, with females in this sample showing a downward trend in high Hba1c results, however this trend was not apparent in the male population until the second wave in NSW. This is shown in Figure 3.

Chapter 6 Figure 2 – Percentage of patients with tests consistent with diabetes tested in ED by week since 2016 by sex

Percentage of patients with tests consistent with diabetes tested in ED by week since 2016
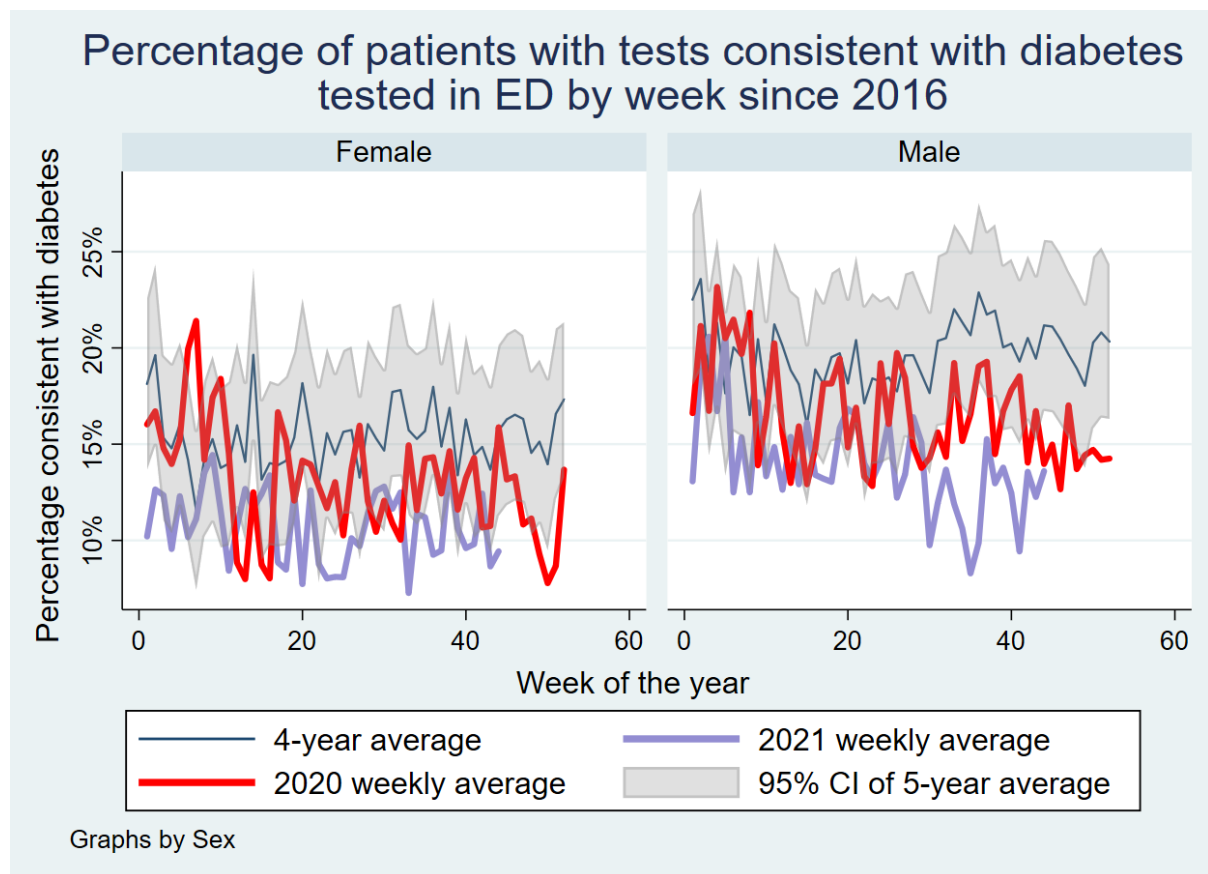
Chapter 6 Figure 3 - Percentage of patients with tests consistent with diabetes tested in ED by week since 2016 by age tested in ED by week since 2016
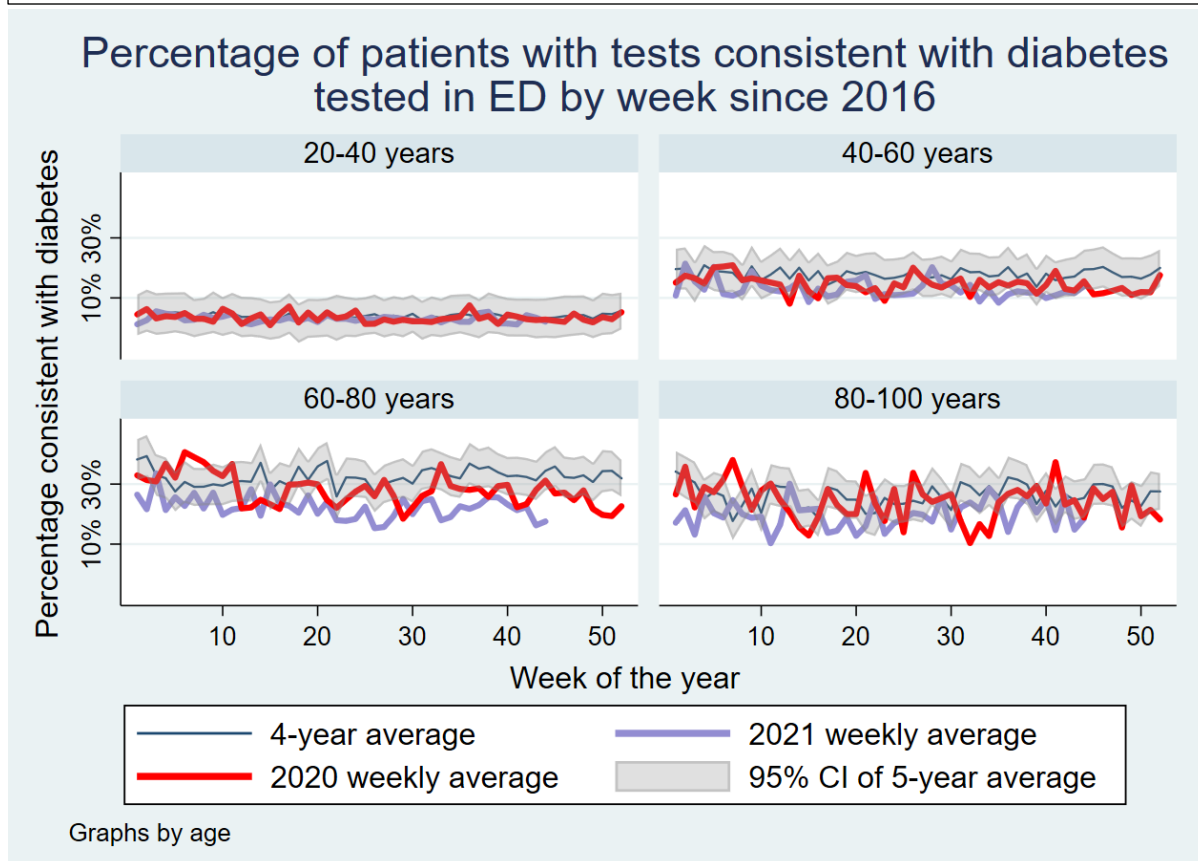
Comparing the pre-COVID-19 rates of diabetes with the current proportion using t-test gives a p-value <0.001, with the average rate of diabetes-consistent tests at 17.3% prior to COVID-19 and only 13.1% now.

These findings were not matched in the GP data. The mean rate of diabetes patient attendance in adults in the GP dataset prior to March in 2020 was 11.3%, which rose slightly to 11.8% during the pandemic period as seen in Figure 4. This then continued to rise throughout the pandemic, with the rate stabilizing at 12% towards the end of 2021. However, the average number of adults active in the system fell slightly from 633,228 to 609,936, a drop of 3.7%.

Moreover, there did not appear to be a greater proportion of diabetes in hospitalized adults, with similar trends both before and during the pandemic.

Figure 4: Proportion of adults attending GP clinics with diagnosed diabetes (n=615k per month)
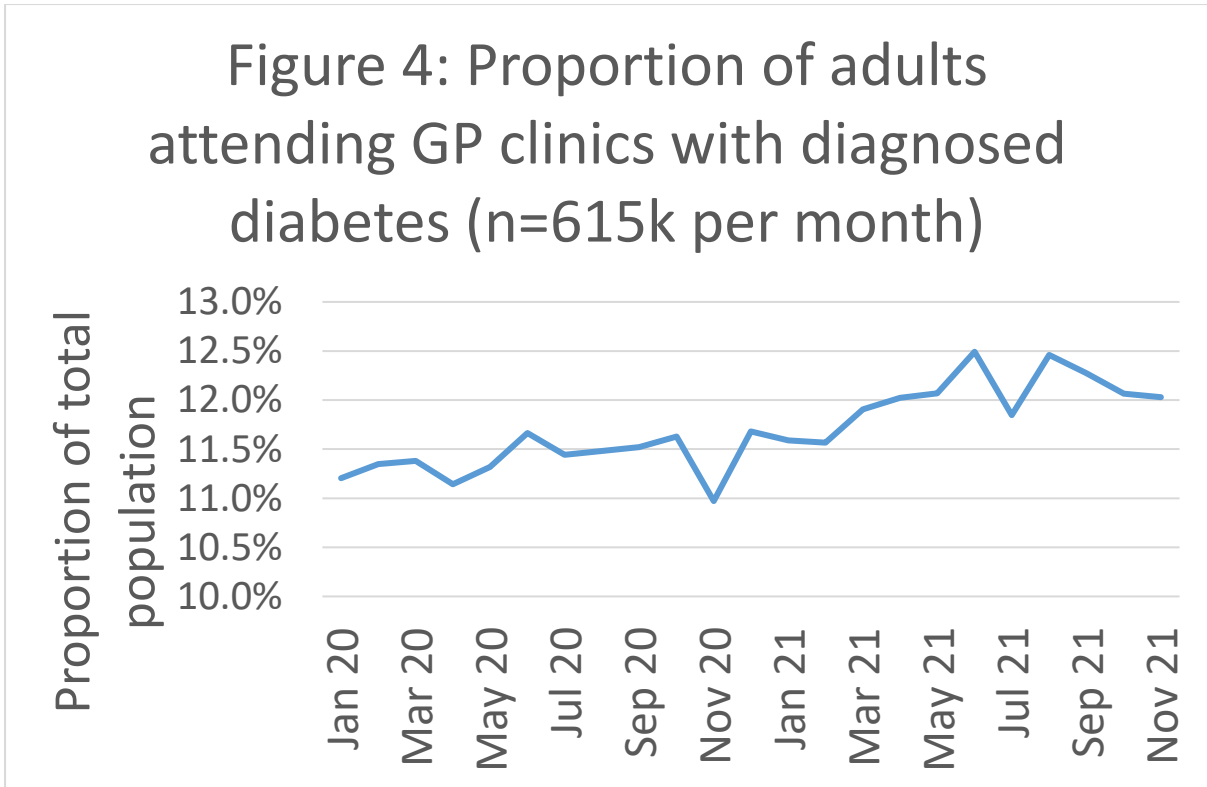
During the pandemic, the proportion of services offered through VC rose sharply from an average of 9.1% prior to March 2020 to 76.8% after that time (p<0.0001), despite the average monthly number of consultations remaining steady during this time-period. This can be seen quite clearly in figure 5, which shows the stark divide between the proportion of services used before and during the pandemic. There was something of an initial lag during March/April 2020 as VC was being set up. Virtual Care had been temporarily halted at these clinics before March 2020 due to the setting up of a new service that was due to begin mid-2020 – the pandemic brought forward this new service substantially.

Chapter 6 Figure 5 - Proportion of services provided through Virtual Care before and during COVID-19 pandemic
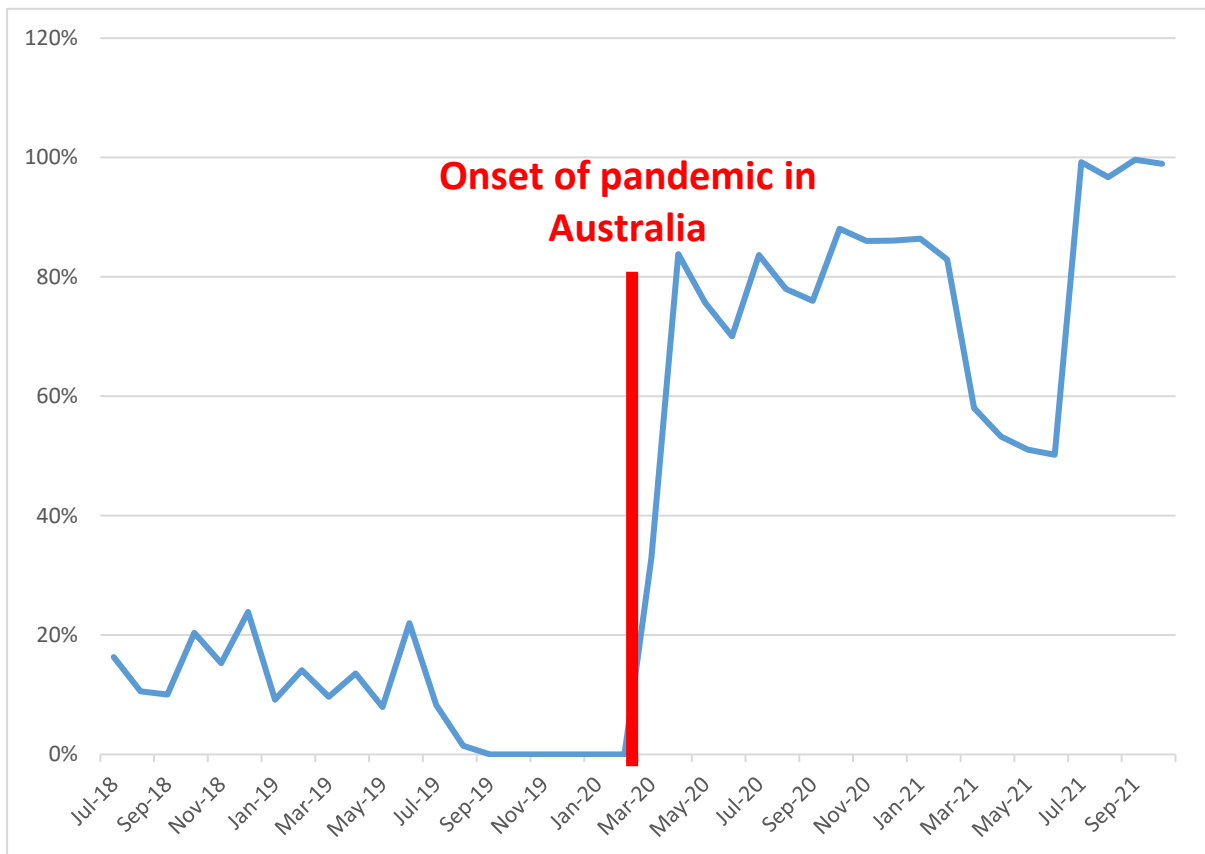
There was also a noticeable change in the proportion of services used when there were outbreaks compared to none. The first lockdown in NSW occurred at the point of the red line, with a second wave of restrictions coming through due to an outbreak in October 2020. These were relaxed in January 2021, at which point VC fell dramatically, and then reinstated during the 2021 lockdown in July 2021. Looking at the proportion of services provided through VC, where there were interventions in place to control outbreaks (April, May, June, November, December in 2020 and January, July, August, September, October in 2021) the average use of virtual care was 90.3% compared to 65.8% in non-outbreak months (p=0.0014). All services continued to be provided during the pandemic period, although the denominator increased modestly as a new clinic was started in May 2020.

Hospital services appeared to be unaffected, with similar numbers pre and during pandemic for admissions due to hypoglycaemia, retinopathy, and diabetic chronic kidney disease (p>0.05) in these hospitals.

6.4 Discussion

In this study, we demonstrate that there is a significant trend in established datasets towards reduced proportion of people having tests consistent with diabetes in ED but not in GP. Indeed, in

contrast to the effect seen in ED, there appear to be more people attending GP with diabetes in 2021 than the prior rate in adults during 2019/20. While this may be related to increased testing, it is also likely to be some evidence of replacement of services as people have avoided hospitals and instead attended GP clinics for their chronic disease during COVID-19.

Moreover, at the onset of the COVID-19 pandemic, there was a steep increase in use of VC services in two hospitals in western Sydney. From a very low baseline of less than 10% of services provided through VC, clinics pivoted to provide many or even most appointments through VC modalities. This has allowed these outpatient chronic care services to continue despite ongoing restrictions during the pandemic, and has no noticeable acutely negative impact on patient care.

This is similar to trends seen elsewhere during the pandemic. Numerous studies have demonstrated reduced use of hospital and GP services during lockdowns and other high-transmission periods internationally (13, 14). Moreover, there has been a hypothesized impact on diabetes-specific services during COVID-19 from patients wary of infection or unable to attend services due to lockdowns (15, 16). We have now proven that these worries may be well-founded, as people with diabetes have substantially reduced their interaction with hospital services during the pandemic, especially during high-transmission periods.

These findings have important implications to current and future practice. While it may be difficult to manage diabetes during a pandemic, the fact that people with diabetes began avoiding the hospital and community services well before cases peaked in various waves has some potential negative connotations. While NSW began locking down on the 16th of March, there were at this point few deaths in the state. However, there was a marked decline in both the number and proportion of people with HbA1c consistent with diabetes attending ED, and fewer people attending their GP, perhaps indicating an undercurrent of fear in the general population of being infected with the virus, in terms of accessing health services. The concern here is that individuals with diabetes may become unwell independent of factors directly related to the pandemic; any delay in them presenting to hospital may result in a more severe and complicated illness.

However, there is also a positive reading of these data. If this represents a replacement of services, it may actually be a good outcome, by reducing the usage of high-cost tertiary services and pushing people towards more care in the community. This is also noticeable in the massively increased use of VC in hospital clinics that has continued even after restrictions were lifted.

This may also be seen in a positive light. During this time of increased activity within the health facilities preparing to combat COVID-19, a reduction in presentations of individuals with chronic

disease to higher risk facilities is possibly ideal to reduce the risk of viral infection. The fact that GP attendance for the management of diabetes has not dropped, and appear to have increased slightly, may represent a shift towards telemedicine during this time, although the data is not yet in to demonstrate this.

However, this reluctance to attend ED and GP has led to the rapid development and maturation of services to support community-based management with the availability of new funding through the Medicare Benefits Scheme (MBS) facilitating the process. In Blacktown Hospital, the majority of ambulatory care services, including clinics for complex type 2 diabetes have been converted from face-to-face encounters to telephone and telehealth services, which persisted in some form throughout the pandemic period. This includes the provision of video consultations for joint GP-specialist case conferencing and diabetes education, the establishment of pathways for flash glucose monitoring utilizing local pharmacies and a package of app-based interventions, to ensure that people with diabetes are still able to access care during this period.

Indeed, the potential replacement of ED with other service echoes international evidence demonstrating that patients have often switched from existing services to virtual care modalities to avoid in-person consultations during the pandemic (17). This change in the use of healthcare services has the potential to improve diabetes care, insofar as it reduces reliance on high-cost emergency services and provides more sustainable chronic care for patients who have long-term chronic disease (18). However, this approach may also have drawbacks – these primary care services do not always have sufficient resources to treat severe or complex cases (19), and the reduction in presentations to ED does not perfectly mirror the increases seen in GP. It is likely that some individuals have missed out on needed care even if some replacement took place, which may represent a burden in terms of untreated chronic disease as time goes on (4).

Overall, we demonstrated that during a during the COVID-19 pandemic, the rate of presentations consistent with diabetes in a busy ED declined significantly from 17.4% to 13.1% per week. The rate of attendances to GP clinics for diabetes in the same area was not similarly impacted, with the proportion of patients diagnosed with diabetes actually increasing, however the total number of presentations was reduced. This was primarily driven by a smaller proportion of older patients presenting, with a younger median age in the group attending the ED than in previous periods and a significant age interaction with the trend, and may indicate a less acute patient population overall in the hospital outside of COVID-19 presentations. This complex interaction requires further exploration, and may have both costs and benefits for the healthcare system. A key future goal will

be to identify whether people have replaced their missed ED care through GP services, or if this represents a worrying increase in diabetes service use in the healthcare system more broadly.

Chapter Seven: Modelling App Usage

7.1 Background

During the pandemic, there has been a substantial change in mobile application usage that has broadly tracked the impacts of lockdown and other social restrictions that have modified behaviour – as people stayed at home more, they used mobiles and other handheld technological devices more. Examples of this abound, with surveys identifying reported increases in usage among individuals in Canada (285) and South Korea, while large retrospective analyses of mobile phone data have similarly shown enormous spikes in the early pandemic period which have continued to some extent as time has gone on (286).

Part of this PhD thesis has focused on the changes that were likely occur to virtual care usage and implementation during the pandemic, and thus part of the investigation is to look at how people have changed their use of healthcare applications. There is some published evidence indicating that healthcare apps have also had a great upsurge in use due to the pandemic, including the rapid development and adoption of mobile applications specifically for COVID-19 (287) as well as the increased use by individuals already using healthcare apps for existing services (288). However, there has been some question over the precise impact of the pandemic to the use of apps by people with chronic health conditions such as diabetes, and how these changes may have been different across different areas of the world.

This question is important as, to gauge the impact of the pandemic on virtual care, we must have context-specific estimates of the changes in behaviour. Moreover, while there are a range of published estimates asking people to recall retrospectively how their behaviour has changed over the pandemic, there are few analyses of how behaviour actually changed that look directly at application usage data for the time period. This is likely due to the commercial nature of this data, and also the fragmentation of healthcare services and app products across the wide domain of virtual care.

Based on the evidence thus far in the thesis, there was a theorized increase in app usage, but there also remain questions about how long-lasting this usage increase would be. There is abundant evidence that people may revert their changes in behaviour that occurred in March/April 2020 when restrictions and local pandemic influences were lifted. However, there is also a plausible argument that people would instead continue to use apps in an increased fashion, and which could have long-lasting benefits for population health if true.

To investigate both the usage of apps during the pandemic period, how this has changed during the initial stages of COVID-19, and what demographic factors might be associated with this usage, I

conducted a retrospective analysis of data collected by the application company Health2Sync. Health2Sync is a Taiwanese company that provides diabetes self-management and management services through an online portal and mobile application, with large client bases in Japan, Taiwan, the United States of America, and some other regions of the world.

The main aims of this investigative project were to answer two central questions:

1. How has app usage changed during the pandemic?
2. Has this been impacted by the region of the world that the app was used in?

The hypothesis to be tested was that there had been a change in app usage, but that these changes would be location specific.

7.2 Methods

3,000 individual records were downloaded from the Health2Sync database of patient records. Patients were randomly selected from the full database of over 100,000 patients, with the following criteria applied:

1. At least 6 months of data before/after March 2020
2. At least 12 months of total usage of the application
3. Registered user with at least one data input after registration

Data was extracted on user's demographic and clinical information, including gender, length of diabetes diagnosis, diabetes type, country of registration, and age. Data was also gathered on the number of times users logged weight, blood pressure, or blood glucose readings on a monthly basis. The onset of the pandemic was defined as March 2020 for the purposes of the analysis.

This data was cleaned and then imported into Stata 15 where all analyses were conducted. There were several analyses performed to review the impact of the pandemic on user's behaviour. Firstly, continuous variables were summarized over time, by graphing the usage patterns, and then before/after pandemic onset usage was summarized using means and compared using t-tests. This was then input into a longitudinal model using an ARIMA design to assess the potential seasonal patterns, with either a 1-month, 2-month, or 6-month pattern used for the ARIMA regression. These analyses were conducted by aggregating all countries together and separately, to review the local impact of COVID-19.

Finally, a series of linear regressions controlling for demographic and country-specific factors were run to examine the impact of other covariates on the usage of the mobile application before and after the onset of the pandemic.

7.3 Results

There were a total of 3,000 individuals included in the Health2Sync dataset, with demographics and other information summarized in Table 1.

Chapter 7 Table 1 – demographics for Health2Sync data by country

	Japan	Taiwan	United States
All	(n=1,000)	(n=1,000)	(n=1,000)
Age	55.3 (11.8)	51.9 (13.3)	55.4 (14.1)
Gender			
Female	232 (23.2%)	371 (37.1%)	400 (40.0%)
Male	732 (73.2%)	454 (45.4%)	566 (56.6%)
BMI (Kg/m^2)	25.7 (4.8)	26.0 (5.2)	31.4 (8.2)
Count of Measurements (Average)			
Blood Glucose	13.7 (31.5)	14.4 (27.5)	17.8 (33.3)
Blood Pressure	9.0 (22.9)	3.5 (11.1)	5.0 (21.6)
Weight	8.2 (17.2)	1.9 (7.1)	3.3 (11.0)

Graphing differences in mobile app usage over time displayed a very pronounced spike in March 2020. This can be seen in Figures 1a, 1b, and 1c, which display the usage patterns and changes overall for the three variables of blood glucose, blood pressure, and weight over time by country.

Mean blood pressure entries over time

Mean blood glucose entries over time
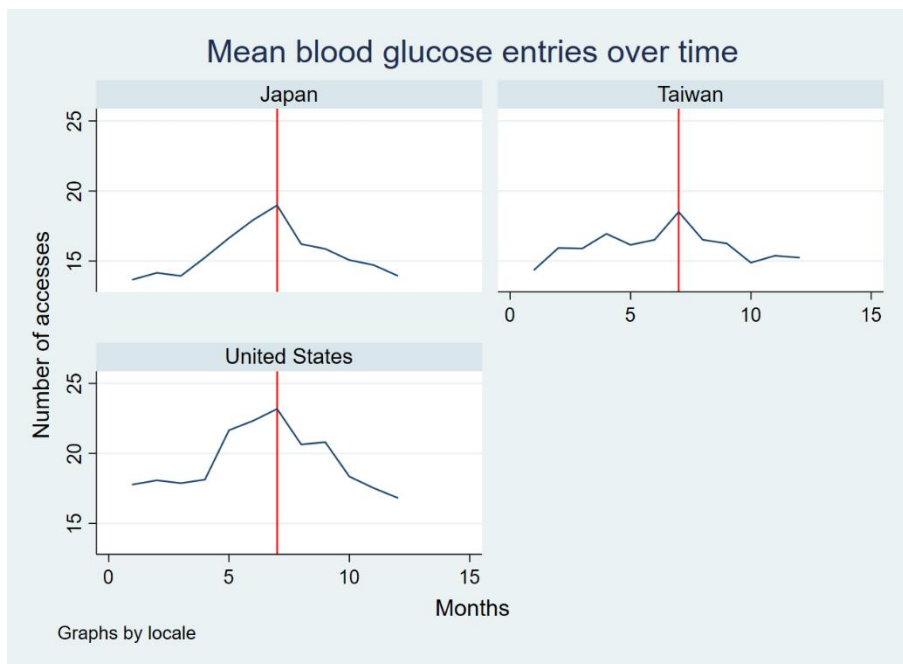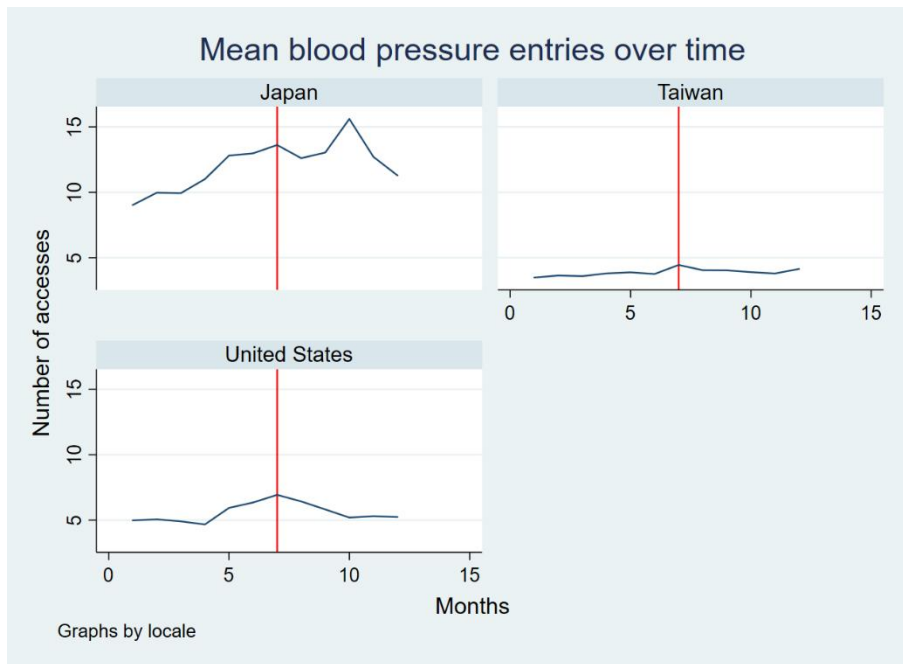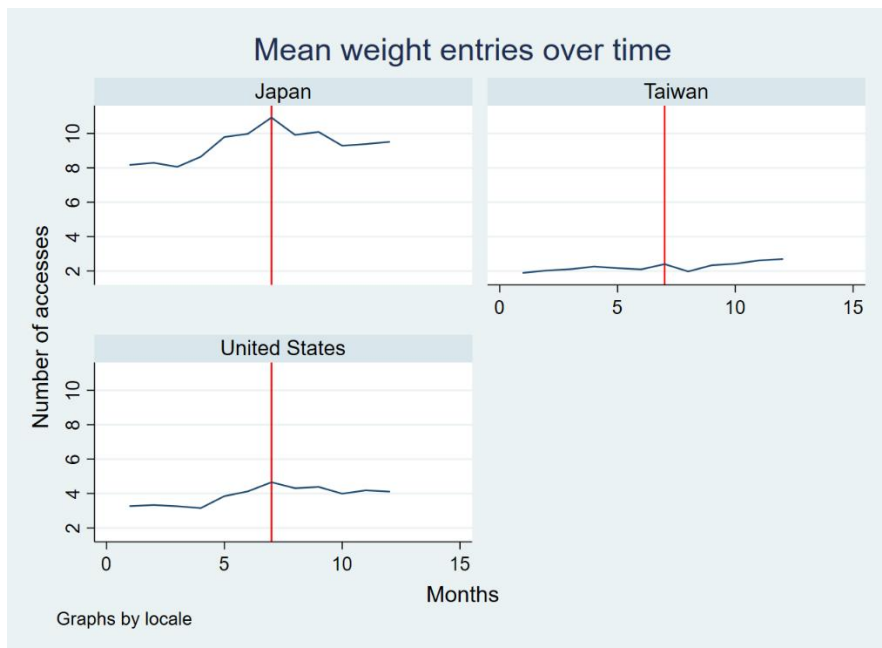
Figures 1a, 1b, and 1c show the rate of people entering in blood pressure, glucose, and weight into the Health2Sync applications over time. Lines are graphed by month, with a red line indicating the onset of the pandemic period.

As seen in Figures 1a, b, and c, while there were substantial changes at the onset of the pandemic, these changes differed greatly between both regions and types of app engagement. Assessing this change using simple paired t-tests demonstrates that while people were more likely to increase their logging of weight data (mean increase 0.61 entries per month, p=0.0001) and had some increase in logging of their blood pressure data (mean increase 0.53 entries per month, p=0.0089), there was no such increase in the logging of blood glucose data (mean decrease of .45 entries per month, p=0.25). While there did appear to be a spike in blood glucose logging at the onset of the pandemic, this drastically declined almost immediately afterwards.

This effect was also highly sensitive to region. While there were no changes in blood glucose logging in any region analyzed, there were region-specific effects for both of the other measures examined. For blood pressure logging, the increase was only observed in Japan, with an average of 1.02 extra entries per month in this region (p=0.028) while in Taiwan and the USA there were no such increases seen (P>0.1). In contrast, weight logging was significantly increased both in Japan (mean increase of 0.81 entries per month, p=0.015) and the USA (mean increase of 0.70 entries per month, p=0.006) but not Taiwan (mean increase of 0.32 entries per month, p=0.09).

As shown in Figure 2, controlling for potentially confounding factors did not substantially change this analysis. Weight logging increased significantly in all regions except for Taiwan before/after the pandemic after controlling for age, sex, and the duration of diabetes.

Chapter 7 Figure 2 – average change before/after pandemic in weight logging by region
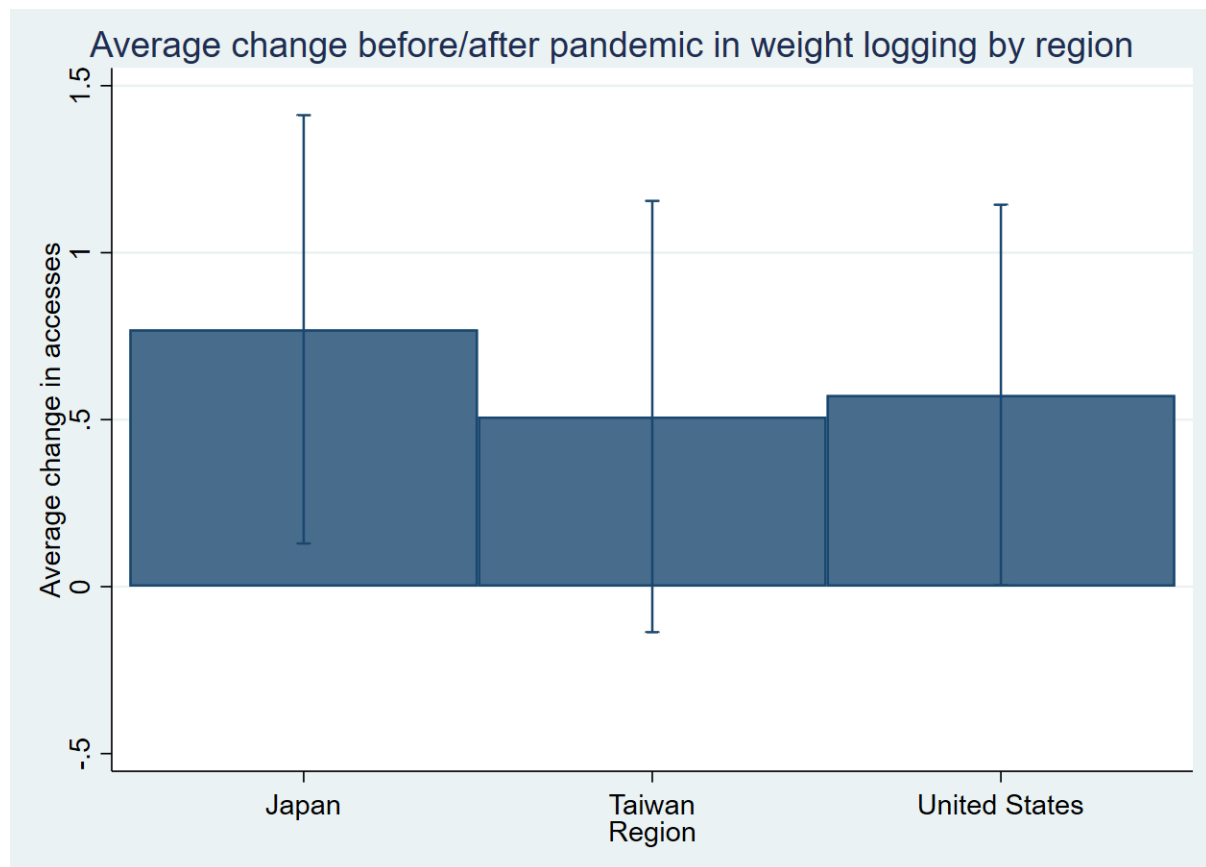
The final ARIMA regressions on each variable looking at 1-, 2-, and 6-month seasonal patterns showed highly significant interactions for blood glucose, pressure, and weight. However, there were complex seasonal interactions that were likely due to the changing patterns of mHealth usage.

7.4 Discussion

There were substantial changes to the usage of the Health2Sync mobile application in terms of weight, blood pressure, and blood glucose logging by patients during the COVID-19 pandemic. These differed by location, and were somewhat impacted by patient-reported characteristics such as age, sex, and duration of diabetes.

In general, the changes were moderate, and often reverted back to baseline levels shortly after the onset of the pandemic. The biggest increases were seen in blood glucose logs; however these were also the quickest to revert to levels seen before the pandemic. There were some small, sustained

increases, mostly in people living in Japan, with a modest long-term boost in the average number of entries for weight and blood pressure in Japan in this time.

Overall, the impact of the pandemic does not appear to be large on people already using the app during this early lockdown period. This is contrary to expectations, and somewhat contradicts the earlier evidence indicating that people were much more likely to use apps during the pandemic. This raises the question of whether survey studies that have indicated an increase in mHealth during the early stages of COVID-19 may have suffered from recall bias, or potentially indicates that the increases to mHealth usage were mostly centred on apps that dealt with infectious disease rather than chronic diseases such as diabetes.

This raises an interesting question about the changing perceptions of virtual care during COVID-19 – while there is clearly an increased interest in participating in virtual care modalities since the pandemic has begun, there is also the possibility that this is mostly focused on infectious disease and will not work to address long-lasting chronic issues such as diabetes. Indeed, the current analysis supports this hypothesis, as it shows a very minimal impact of the pandemic on the use of the Health2Sync app by people with diabetes, despite the overall increase in app usage noted across the world in March 2020.

This study also raises questions about the longevity of pandemic-caused behaviour change in terms of mHealth usage. As shown in Chapter 6, some pandemic behaviour changes are relatively short-lived, even if they are significant in that time period. Indeed, reviewing the graphs from the analysis presented in Chapter 7, it is likely that while there may have been a large increase in people logging their blood glucose immediately as pandemic restrictions were enacted, this did not commonly result in long-term changes to behaviour that might be expected to result in positive health outcomes.

This study also shows interesting facets of the country-specific interactions that COVID-19 has had on populations. Japan, with relatively mild restrictions as per the Our World In Data dashboard (289), which uses the Oxford Clinical Response Group Tracker (290) to grade countries' responses, and with a very highly technologically-enabled population prior to the pandemic, had the largest changes in all three parameters of control used within Health2Sync. Taiwan, with much more stringent restrictions, and which might be expected to have even larger changes, did not see such a difference and indeed had few if any significant differences pre/post pandemic in terms of logging metrics through the app. The United States saw some differences, but it is hard to parse how these may have been influenced by the pandemic, and how long-lasting they may be.

This study has had important implications for the thesis. Firstly, it proves that while some COVID-19 changes are long-lasting, not all of them will be. There are likely country- and location-specific factors that will impact individuals and how they access care well into the future. There are innumerable differences between the healthcare systems of all three nations examined in this study, as well as political systems and even interpersonal/social factors. Japan has had a famously minimalist pandemic response which relied heavily on social control and community cooperation (291, 292), with a focus on social rather than government enforcement of key pandemic mitigation measures. In contrast, Taiwan has had a far more government-focused response, particularly in the 2020 period, which relied on restrictive measures to control the virus in the population (292), while the United States has had a fractured response which differed from region to region (293). Unfortunately, the database used in this study did not allow for more granular assessment (i.e., state-by-state), but it does indicate at least that the pandemic response and how this impacted individual healthcare is not a simple thing to parse.

In addition, the virtual care of each region is drastically different, and this is likely to impact the long-term uptake of such interventions. While the United States has a famously private health system, where the majority of services are provided by private providers, both Taiwan and Japan are drastically different, with a heavy emphasis on government control and subsidy for health insurance and care (294, 295). This is likely to have some influence on the way in which people access all healthcare, but particularly virtual care which has until the pandemic often not been covered through traditional healthcare payment systems. Indeed, one plausible explanation for the differences between Japan and the other locations studied is that telehealth and virtual care were more embedded within the healthcare system before the pandemic occurred (296), providing better grounding for both patients and providers when the pandemic caused large shutdowns in the healthcare system in 2020.

Of note, the analysis did not identify a difference in the duration of diabetes, indicating that people who had been recently diagnosed were not more likely to start logging more interactions, and neither were people who had been diagnosed for a long time. This may indicate that virtual care longevity is not always predicted by the duration of disease, and could be due to other factors such as whether patients are in regular contact with healthcare providers or the situation regarding reimbursement.

Of course, this analysis suffers from many limitations. Health2Sync is a single application, and while this analysis did use a representative random sample from their users, the application only has around 100,000 registered users. There are many thousands of diabetes applications online, many of

which will likely have had different use patterns during the pandemic, and so this single analysis does not allow us to draw conclusions about the use of virtual care more broadly during the pandemic.

We were also unable to review all use-cases for applications, focusing instead on self-management as this was likely to be the most impacted by the pandemic. However, it could certainly be true that other forms of healthcare such as direct insulin titration did not have the same use patterns associated with pandemic disruptions to healthcare.

In addition, the ARIMA regression models show that there is some uncertainty to the before/after impacts, and that some elements of the change may be due to seasonal or time-based changes instead. This is complex to unpack without a very long-term dataset, which is a future avenue for research that will be pursued after this PhD has been completed. This is discussed later in the thesis in Chapter Ten.

Overall, this study shows that there were complex and difficult to parse changes in behaviour at the start of the COVID-19 pandemic, which indicates that there is likely to be complexity in addressing the problems of virtual care. It is likely that there is no single "silver bullet", even after the pandemic, that will fix virtual care, and instead we need to focus on whole-of-system designs which look both at virtual care itself as well as the healthcare and social situations surrounding the provision of that care in order to better understand the various factors that may assist people with their healthcare long term. This is particularly true for lifelong diseases such as diabetes, where people's situations may change and thus long-term use of virtual care interventions post-pandemic will rely on support from many areas, not just their healthcare providers.

Chapter Eight: The Future

8.1 Changes Over Time

There have been substantial impacts on the literature regarding use of virtual care services since the start of this PhD work, and indeed partly because of the work conducted in this PhD. The systematic review on app dropout and nonusage attrition that has been incorporated as Chapter 4 in this document has so far been cited 91 times since publication in the academic literature (297), which is indicative of the general move towards addressing some of the issues that were originally the thrust of this PhD research program in 2018.

While there was minimal evidence surrounding the impact of attrition in virtual care and app-based research prior to the systematic review published as part of this thesis, there are now a range of studies that examine the question in detail.

A recent study of Flemish adolescents shows the changing nature of the field (298). This study conducted a secondary analysis on data from a pilot study of mHealth, reviewing data on why individuals stopped using the application. The study showed that there was very high nonusage attrition, with 95.7% of adolescents ceasing to use the app, and nearly 1/3rd of participants only opening the app when they were signed up on the first day. A similar study conducted as part of a randomized trial in Iceland found that 6-week attrition rates in their adolescent population were 35%, and that while the application had some efficacy, many participants ceased using the app before the follow-up period finished (299).

Qualitative evaluations have also begun reviewing the proportion of individuals who are not using virtual care interventions over time due to a variety of constraints. One evaluation of a mental health application found that participants were often left feeling unsupported and underacknowledged and thus became uninterested in the service (300).

In addition, there are increasingly published systematic reviews and other scientific reviews that acknowledge the importance of attrition and non-usage in virtual care.

These papers demonstrate the increasing acknowledgement in scientific research of the importance of ensuring that people stick to virtual care interventions. As I showed at the very start of this thesis, and as has only been reinforced by the research throughout, it is not simply enough to develop an intervention and give it to people. Even if that intervention is ineffective, there is a strong likelihood that, in the virtual care space, you will be required to update and improve your offerings over time, as otherwise people will fall out of interest with their services and end up not using them long-term.

The issues with virtual care and how people engage with the subject, particularly in light of the COVId-19 pandemic, are interesting, but the key question is: what can we do about these issues?

One example from my own research during the pandemic offers at least some insight into what not to do. One project attempted as part of this PhD was to run a survey of virtual care, usage both before and during the COVID-19 period, which would then provide insight into how people were using services as the pandemic progressed. The protocol is below:

8.2 Survey Protocol

This study will be a quantitative survey looking at the experiences of people who are or could be using virtual care for diabetes in Australia. To this end, inclusion criteria will be:

1.   Diagnosed diabetes

2.   Living in Australia

3.   Able to complete the survey (i.e read and write English)

4.   >18 years of age

The survey has been designed to take between 10 and 15 minutes, with 10 demographic questions, 5 questions on diabetes status, and a further 10 on virtual care perceptions and utilization. This will give a range of ideas about virtual care barriers, and how the use has changed during the COVID-19 pandemic.

This survey will use a convenience sample of patients who have diabetes. These patients will be recruited in a number of ways, to ensure a reasonably diverse sample in the patient cohort:

1.   Online/telehealth diabetes management clinics at Blacktown/Mt Druitt hospitals

2.   Patients who have received a test positive for diabetes from the ED screening programs within WSLHD

3.   Patients with diabetes who attend participating General Practices in the area

4.   Social media recruitment

A number of GPs in the area will be approached to offer the survey to their patients so that the sample can be improved. The ED screening programs involve sending letters out to a large number of patients who have had tests positive for diabetes while in the EDs of WSLHD hospitals. This is a routine screening program that affects all patients who have a blood test for any reason. These

people will be invited to participate in the survey. Twitter and Facebook will also be used to amplify the recruitment pool.

The survey will be conducted online, using the Redcap platform. Participants will be assigned a study number when recruited, which will be stored in a secure database alongside their email address. The secure database will be maintained by the study lead, allowing for re-identification of participants if necessary. This will allow the survey to be filled out anonymously, but also allow for longitudinal linkage of results. Participants will be asked to enter their previously given study number when re-doing the survey at later dates, and if they are unable to remember it, they can request their number from the chief investigator.

Potential participants will be sent a link generated by the study coordinator that is linked to their email address in a secure Excel file. The Excel file will be locked in a secure folder on WSLHD servers, and only accessible to the coordinating principal investigator and study coordinator. This will be sent with a brief description of the study i.e. "Have you used an app or telehealth to manage your diabetes during the pandemic? We are conducting a survey into virtual care attitudes, click this link to learn more". This will direct them to the PICF (attached), which will be hosted on Redcap.

As this is a very low-risk, anonymous survey, consent will be through an implied consent process. Participants will be presented with a full PICF (attached) when clicking on the survey link, which will explain the details of the study. They will then have to click a button which says, "By clicking this link you consent to take part in the study". A phone number, email address, and Skype account associated with the study will be provided on this form so that participants can ask questions face to face with the study team (via videolink) if they have any. This procedure is common for anonymous online surveys used for research purposes, and has been used previously in surveys by several members of the research team.

To ensure an appropriately large sample, the study will continue until 200 people have responded to the survey. This is anticipated to take 6-8 months overall.

Statistical anlaysis will be conducted in Stata 15.

Once ethics is approved, the step-by-step plan will be to quickly send this survey out to the target group. This will mean including the survey in materials sent out by the WSD team during regular clinic appointments, and including it in the regular communication as part of the DDMS (in letters/texts sent out). It will also be disseminated on Twitter and Facebook at this time, using the study link.

We expect the 200-person recruitment to be reached within 6 months, with the diverse recruitment methodologies. If this is not successful, it may be possible to move to paid Facebook and Twitter ads using a modest sum to encourage more people to take the survey. For reference, last time GMK tweeted out a survey link, more than 300 people took the survey within 24 hours.

8.3 Complications

However, after obtaining ethics approval to conduct this survey, the pandemic situation changed dramatically in Australia. This survey was proposed and then approved while cases were low, but shortly after approval we saw the Delta outbreak, dramatically shifting the healthcare service perspective and also changing the requirements to conduct research within most institutions in Australia. Nationally, health services faced extreme difficulties in managing patients, and locally in WSLHD almost all research was immediately halted.

Indeed, I was personally seconded during this time to the COVID-19 team, working on large venues with outbreaks at the time. This meant that work on the survey was largely halted during this period, particularly with the more restrictive requirements that were enacted for conducting scientific research even online.

This led to the survey being cancelled with only 79 completed responses after more than a year's collecting data. What was originally planned as a quick exercise to garner some meaningful responses instead became an extremely difficult task that had no good end once the pandemic changed the situations. There are currently no further responses to the survey, and no further work planned on completing it. Of the 79 people who completed the survey, 47% were female and the average age was 57 years. 71% of these people had used a virtual care service, most of whom had used either mobile phone applications or telehealth services. Of those who used virtual care services, most were planning on using such services again in the near future.

This period of the PhD demonstrates the challenges that have come with implementing virtual care services during the pandemic. While it is certainly true that there was an incentive to shift services online, and that this became the primary method of contact for many patients and clinicians regardless of how useful the virtual care services was, it was still not necessarily an optimized experience. The survey's failure also ties into the ongoing departure from virtual care that is being seen across the healthcare industry, as people move back to familiar modalities of healthcare rather than the online services that they were required to use during periods of high transmission. This precise phenomenon was shown to some extent in chapters six and seven of this thesis.

Which brings us to the final challenge of this PhD – where do we go from here? It is certainly true that there are some elements of the pandemic that will remain with virtual care services for some

time, perhaps forever. However, it is also important to note that attrition and non-usage remain a huge issue, and that diabetes services cannot simply expect to run things as they did during COVID-19 OR before as neither of these options quite fit the new landscape we find ourselves in.

As this PhD has shown, it is important to consider a multitude of aspects when designing a virtual care service. It is not usually enough to simply implement an app or videoconferencing, as patients are unfamiliar with such services and even if they are at high risk will often prefer face-to-face rather than poorly run or inappropriate healthcare options virtually. Moreover, as the world moves on from the extreme rigors of the COVID-19 pandemic, there is an urgent need to develop methods to retain the virtual care services we have implemented, lest the forward progress that we achieved during this troubled time is lost. This could take the form of qualitative evaluations of perspectives on virtual care, but will also require some measure of quantitative evaluation looking at hybrid models into the future. WSD is currently planning a stepped-wedge randomized trial with a mixed-methods qualitative analysis looking at a broad array of virtual care implementation activities that will hopefully provide exactly this sort of information for the future.

Chapter Nine: Discussion

9.1 Background

My work on this PhD started in 2018 with a fairly simple goal – review the use and nonuse of mobile health applications, and how attrition might be both tied to existing inequity in healthcare services and potentially remedied by methods that we could develop to counter those issues.

Chapter Two showed that diabetes was a much bigger problem than previously recognized. Most estimates of diabetes, particularly in Australia, rely on official reporting which misses many cases of the disease as large numbers of people, particularly low-income and disadvantaged people, are never diagnosed. We showed this using both hospital and general practice data, in a paper published in the International Diabetes Federation's flagship journal, and proved that the rates of diabetes in these settings were far higher than previously imagined. This meant that the issue – improving diabetes care in the community – was similarly far bigger than we previously thought.

The initial scoping review presented in Chapter Three demonstrated quite convincingly that, while applications and other virtual care interventions held a great deal of promise in the medical world, we were a far cry from a truly theory-based design of virtual care services. This review showed that there was little engagement with theories of the human mind when people developed virtual care services – that we were more likely to implement gamification than to truly connect with the way patients accessed their healthcare services in a digital world.

Moving on, I demonstrated that this was, in fact, a big issue. The systematic review in Chapter Four, conducted mostly in 2019, provided the first evidence in the world that attrition and nonusage were a key problem for mobile applications and by extension virtual care. We aggregated evidence in a novel way to prove that, while apps in general had a great deal of success in helping people with chronic diseases, a large portion of people who started using these applications either stopped immediately or barely logged in once creating an account.

As I've shown, this also has major implications for the literature. At the time of writing this thesis, the paper from Chapter Four has been cited nearly 100 times, as it is becoming common practice to consider, when developing a medical application for a mobile device, the issue of nonusage attrition. This ties back to the third chapter, showing that there is indeed an issue and that we need more focused design in order to solve the problems that we have found.

And then, in 2020, about one third of the way through my PhD program (I have been working full time and pursuing my studies part time for the entirety of the course), the global COVID-19 pandemic hit. It was clear that this event would forever change the way in which people interacted with their digital devices. The flow-on effects for digital health were huge.

In order to capture this complexity, I shifted the topic of my PhD from a focus entirely on mobile applications, to the broader scheme of virtual care. Rather than focusing exclusively on diabetes and nonusage attrition, I moved to look at the wider schema defining our switch to digital health in the wake of a pandemic where human interaction was potentially harmful and often banned outright.

Shortly after the onset of the pandemic, studies were published showing that COVID-19 was more dangerous for older people (74), and those with chronic comorbidities such as diabetes (77). However, putting a specific figure on these questions became of vital importance globally. This was also extremely important for the work contained in this PhD, as the behaviour of people with diabetes and other chronic diseases would have been driven by their perceived and actual risk from the pandemic. This was extensively theorized at the start of the pandemic in a number of ways, with great concern that detrimental behaviour changes driven by pandemic concerns would damage the health of people with diabetes and other chronic diseases (301, 302).

Thus, I rapidly conducted several studies that are summarized in Chapter Five, looking not just at the traditional estimates of the lethality of novel infectious diseases, but generating a specific series of figures that are based on the number of infections overall. These studies have since been cited by global authorities such as the OECD (303), WHO (304), CDC (138, 304), and a range of other organizations such as the World Intellectual Property Organization. These studies established that COVID-19 was a leading threat to older people and those with chronic diseases, and showed that the pandemic-related fears of these people were justified. This was expected to cause a large change in behaviour for those with such chronic diseases in relation to their virtual care habits.

This then led to chapters Six and Seven, where I demonstrated that the pandemic had impacts on how people used mobile applications, as well as how they interacted with traditional healthcare services. Chapter Seven in particular showed that app usage was substantially changed over the course of the initial outbreaks. However, both of these studies appear to also show that pandemic-related behaviour change is not always long-lived, and that external pressures caused by COVID-19 may not have revolutionized the virtual care space as much as was initially hoped.

9.2 Longevity

This brings us to what is in many ways the key message of this PhD: longevity. Virtual care interventions are based on the simple premise that the world is changing and that we must change with it. People spend more time on their devices, and that time could in theory be better used to help their health than the impact which more common social media or gaming apps currently provide.

Unfortunately, while simple in theory, this idea is complex in practice. There are many competing stratagems that we could be implementing when it comes to the theory behind virtual care interventions, however in general we are instead throwing things out and trying what works. Indeed, over the course of this PhD it has become quite widely accepted that the design of virtual care interventions should be more focused to take into account theories of human behaviour (305) rather than simply attempting to muddle our way through design.

Indeed, the COVID-19 pandemic has shown precisely how problematic it can be to design virtual care interventions without closely considering how humans behave when crafting such interventions. Locally, in Western Sydney, we have seen rapid changes as the pandemic progressed in how people have used and engaged with virtual care, and this is something that has been echoed across the world. While pandemic services were successfully implemented at the very beginning of the global crisis, many of these fractured by the end of 2020 and did not have the longevity that we look for in successful virtual care services. It is hard to know precisely why this might be, although the work done in this thesis and my own personal experience points towards a combination of external pressures – such as a desire to 'return to normal' – along with a lack of continuing support for virtual care in times when social distancing was not as important. Despite over a decade of work on virtual care, and a global event forcing many people to become much more familiar with the concept overnight, the figures seem to indicate that we may be back to where we were before the pandemic in terms of usage quite soon.

One possible solution to this is better integration into existing healthcare services. This is, in essence, the same result as discussed in Chapter Three of combining societal and behaviour-change theories for virtual care interventions. Much of the reduction in longevity for virtual care appears to be related through a complex network of interrelated issues to a lack of capability in the system to assist patients with accessing needed services through virtual means *even if those services are offered virtually (66, 306)*. This would mean that, to be successful, we may have to incorporate society-level interventions into virtual care in order to improve the way in which these services engage with individuals.

For example, many people are not able to access virtual care due to a variety of socio-economic factors which prevent ready access to the internet, mobile phones, etc. Enhancing longevity would thus not simply be a matter of addressing the design of the service, because if someone has no internet connection, we cannot reach them regardless of how well-constructed the mobile application or virtual clinic might be. First, there must be the basic structure allowing for the patient

to connect to the virtual care services – which may require society-wide social support – which will then allow these individuals long-lasting access to the highest quality virtual care.

This is very similar to the idea of Upstream and Downstream intervention effects, as discussed in a number of papers by Prof H Rutter (307). While we can certainly make virtual care interventions more attractive in and of themselves – we can, say, use the most up to date behavioural theories to design a diabetes app that people find much more attractive to use than the existing offerings – if we do not also address societal barriers to healthcare we will likely lose people along the way. The Downstream intervention of improving the service has a smaller impact, but is far easier to implement, than the Upstream intervention of ensuring that everyone who might need it has access to a mobile phone and internet connection, and is educated enough to use both of those things in a healthcare setting.

This is, again, shown quite well by the COVID-19 pandemic. Despite years of protest that virtual care interventions were simply too challenging to implement wholesale, most advanced economies did precisely that overnight as restrictions were put into place preventing people from accessing healthcare through traditional face-to-face services. Prior to COVID-19, fewer than 1 in 1,000 Medicare Benefits Scheme billings by GPs were telehealth. In March 2020, this switched overnight, with more than half of all services being provided on the telephone nationally (308). The barriers that existed before this did not simply disappear overnight, but the key drivers of people's behaviour were almost entirely shifted due to the risks from COVID-19.

And thus, the answer to the question "how can we get people to use virtual care services for longer?" is answered quite simply – all you need is a global pandemic. While disastrous and damaging to health across the globe, one thing the pandemic did make abundantly clear is that it is entirely *possible* to overcome the many barriers to virtual care if there is sufficient incentive. The challenge for us is to incentivize people to use these effective options without the need for a global catastrophe to provide a reason to do so.

We are, of course, unlikely to see pandemic restrictions re-enacted in the near future. While it is perhaps not beyond the realm of imagination that we might see future lockdowns in Australia and other places in the world, it is extremely unlikely. Similarly, the unprecedented social support offered by many governments during this time was most likely a once in a lifetime occurrence. In Australia, for example, the government more than halved the population living in poverty during 2020 and part of 2021 due to the significantly higher social support payments enacted to assist in mitigating the pandemic impact (309) . It is entirely possible, given the evidence on the importance of social interventions to improve virtual care usage, that the enhanced social support during the

pandemic years was as important as the lockdowns and other restrictions that forced people to stay at home. Suddenly, people who previously had no way of even trying to contact their providers by telephone could afford a monthly plan, and it is entirely possible that this impacted the use of virtual care in a major way.

9.3 Conclusion

This brings us to arguably the most difficult question of the thesis – how to conclude 5 years of work, conducted during a pandemic, in a readable fashion?

I think that the message of this thesis could be summarized fairly simply: virtual care faces similar issues to existing healthcare services, and if we want to improve how people use it, we must go back to the fundamentals of care integration that have already assisted us with face-to-face services. The COVID-19 pandemic drastically changed how people use virtual care services, but without a systems approach that includes interfacing with existing healthcare services as well as a theory-based design and integration with societal levers than can control behaviour, we are likely to lose much of this progress as the world shifts back to the way it was prior to COVID-19.

Of course, even this simple summarization is complex. There are likely places where the virtual care services enacted during COVID-19 have remained and are being used effectively, as well as some areas where such changes were never made. It is not hard to think of low-income regions of developing countries where it is unlikely that large portions of the population even have access to regular healthcare services never mind complex integrated virtual care. One Lebanese doctor with whom I corresponded during the pandemic talked about the difficulty of providing services during regular blackouts – with such hurdles in place, it is hard to imagine that virtual diabetes clinics are a top priority for their healthcare service.

The message of this thesis is also, to a great extent, a hopeful one. While the pandemic has been a great tragedy in many ways, as my own research has proven, there are some things that have changed for the better during this troubled time. We have shown, across the world, that virtual care can and should be offered as a standard provision, and much of the community dislike of such services has dissipated. Indeed, a survey which I assisted on found that most people thought that their virtual care services during the pandemic were as good as if not better than the services that they were receiving before COVID-19 (310). While some people have leapt straight back to face-to-face services, there are certainly indications that the general attitude towards receiving healthcare at a distance is dramatically changed since the start of COVID-19.

What of the future? Well, this thesis provides a useful guide for future research. One vital question to answer is how we can better interface virtual care services with existing face-to-face

interventions. At WSD, we are currently actively looking into this question, and it will form future work for both myself and our other researchers.

Another more general question is how we can manoeuvre society to better allow individuals to use virtual care. There appears to be some evidence that improving welfare and other social services may have knock-on effects not just for healthcare generally but specifically for virtual care. This leads to questions such as "does improving unemployment benefits reduce the cost of providing care by allowing low-income people to utilise applications for their chronic disease?", which are important but challenging to answer.

There is also a great deal of work to do looking at the long-term impacts of the pandemic, and seeing how the epidemiological questions pan out. Most of the predictions of this thesis are extremely uncertain, because it is being done during the pandemic and not a decade after. It is entirely possible that the changes made during COVID-19 will disappear by 2024, just as it is possible that they will continue forever. As they say, the hardest thing to predict is the future.

There are also a number of interesting places where this research intersects with existing virtual care services design. There does not seem to be strong support for gamification, despite the very eager uptake of these measures by many application developers, while standard integrated care appears to be a better route. If you want to have an effective healthcare app/telephone service/etc, the key seems to be to talk to doctors and patients who use existing services rather than spending time on making your buttons look flashy.

This is perhaps a useful place to conclude this work. Virtual care is similar to face-to-face services in many ways, and the key differences may be more social than programmatic. This means that solutions to problems in the virtual care space are likely to be just as complex as solutions in the non-virtual arena. Virtual care certainly has promise, and the benefits discussed in the first chapters of this thesis are real – you can design an app for a fraction of the cost of existing clinics, and online healthcare tends to be far cheaper than brick-and-mortar work – but we cannot simply expect to design healthcare around a virtual setting and immediately reap the benefits without putting in the careful construction that we have in face-to-face settings.

At the beginning of this PhD, I posed a complex question, and to this it seems we are left with a complex answer. There is no single, easily identifiable reason why people stop using virtual care services, perhaps because there is no single reason that they start using these in the first place. Improving virtual care modalities therefore requires multifaceted approaches that take into account

not just individually focused interventions that play to personal motivations, but also society-wide changes that allow people to access these services better.

In addition, COVID-19 changed the entire landscape of healthcare services, likely forever. The ways in which people with diabetes interact with their providers has shifted dramatically, and virtual care services must change too to accommodate these differences.

Society is complex, and therefore so is virtual care. The pandemic has impacted how we use online services in many ways – as one tiny example, I am writing this PhD mostly in my home office, which I set up in the last week of February 2020 as I could not work from home before then – and these changes are unpredictable and difficult to navigate. Nevertheless, I am hopeful that we have overcome many of the biggest barriers to using virtual care due to COVID-19. Despite the horrors of the pandemic, there has been at least some good to come of it.

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Is the cure really worse than the disease? A narrative review of the health impacts of lockdowns during COVID-19

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Key Points:

- Restrictive non-pharmaceutical interventions against COVID-19 (known as "lockdowns") are associated with health harms.
- However, it is challenging to determine whether lockdowns have caused the harms or whether these harms are a direct consequence of the underlying health disaster of the pandemic.
- Careful analysis of excess mortality suggests that lockdowns are not associated with large numbers of deaths in places that avoided large COVID-19 epidemics (e.g., Australia, New Zealand)
- This evidence must be weighed against the very severe harms caused by COVID-19 itself, as seen for example in Brazil and India
- It is unlikely that government interventions have been worse than the pandemic itself in most situations using data collected to date.

Introduction

During the pandemic, there has been ongoing and contentious debate around the impact of restrictive government measures to contain SARS-CoV-2 outbreaks, often termed "lockdowns". We define a "lockdown" as a highly restrictive set of non-pharmaceutical interventions (NPIs) against COVID-19, including either stay-at-home orders or interventions with an equivalent effect on movement in the population through restriction of movement. While necessarily broad, this definition encompasses the strict interventions embraced by many nations during the pandemic, particularly those that have prevented individuals from venturing outside of their homes for most reasons.

The claims often include the idea that the benefits of lockdowns on infection control may be outweighed by the negative impacts on the economy, social structure, education, and mental health. A much stronger claim that has still persistently appeared in the media as well as peer-reviewed research concerns only health effects: that there has been a large toll of death and disease attributable directly to government action against COVID-19, a toll larger than that of COVID-19 itself (311, 312). The tagline for this claim is that "the cure is worse than the disease." (313).

Here, we consider the claim that lockdowns cause more health harms than COVID-19 by examining their impacts on mortality, routine health services, global health programs, and suicide and mental health. We examine the evidence regarding whether government interventions are to blame for negative health consequences, or whether the lethality and infectiousness of SARS-CoV-2 is as much or more of a driver behind adverse health impacts. The grave harms from ineffectively mitigated epidemics have been clearly seen in places such as India and Brazil (314). Given the benefits from government intervention against COVID-19—slowing spread and preventing COVID-19 deaths—we explore whether the harms of lockdowns are likely to exceed the harms of COVID-19, or if the health harms sometimes attributed to lockdowns may instead be explained directly by the pandemic itself.

Short-Term Mortality

The World Mortality Dataset (315) is the largest international dataset of all-cause mortality, including many countries that have imposed and not imposed restrictive measures against COVID-19. This project has accumulated excess mortality data on 94 nations from the onset of the pandemic, with the most recent data being reported up until mid-2021. The project defines excess mortality as mortality greater than the anticipated modelled number of deaths given existing trends. Using this dataset, we can examine a range of locations that both have and have not imposed lockdowns in terms of their potential damage to population health.

Using these data, we can see that New Zealand and Australia, two countries that imposed several lockdowns and heavy restrictions, experienced no excess mortality during 2020. Similarly, South Korea, Taiwan, and Thailand had either no excess mortality or only very modest increases in mortality during lockdown periods when there were few or no COVID-19 cases. Indeed, there are no locations in the dataset that experienced both excess mortality *and* lockdowns concurrently with low numbers of COVID-19 cases, which is what we would expect if lockdowns were independently causing large numbers of short-term deaths. Conversely, places with few COVID-19 restrictions, such as Brazil, Sweden, Russia, or at times certain parts of the United States have had large numbers of excess deaths throughout the pandemic.

This pattern indicates that, while there may be multifaceted impacts of intensive government restrictions, including social and economic costs, these are not apparent in short term increases in mortality. In fact, the World Mortality Dataset appears to show that countries with concerted COVID-19 restrictions have had fewer deaths than in previous years, with the authors estimating that lockdowns may reduce annual mortality by 3-6% from eliminating influenza transmission alone (315). This finding is supported by data from Peru showing that lockdowns are likely to reduce death risks from common sources such as automobile accidents in the short term, resulting in a reduction in the immediate mortality burden when implemented (316).

The high excess mortality in countries with few restrictions, or less voluntary behaviour change, may not be surprising given the high infectiousness and fatality rate of COVID-19 (136, 281, 282). For example, in Manaus, Brazil, COVID-19 spread was largely un-mitigated and as of March 15 2021 more than 10% of the entire population aged over 85 years had died of COVID-19 (317). Similarly, the United States did not impose highly restrictive sets of NPIs to contain the spread of SARS-CoV-2 in fall and winter 2020, and COVID-19 became the leading cause of death in the United States for several months in late 2020 and early 2021. While different places require different measures to stop exponential spread, data from Brazil, the US and other countries (318, 319) show that moderate containment measures can be insufficient to stop exponential growth of COVID-19 epidemics, in turn leading to unparalleled mortality burden in the populations affected.

However, the excess mortality data does not refute the position that lockdowns have caused harm in some instances. Comparing the United Kingdom and Sweden, for example, does not show a clear benefit of lockdowns in terms of excess mortality (the United Kingdom imposed three national lockdowns, yet both countries had very severe impacts). It is impossible to determine from this

evidence whether lockdowns have a net benefit, especially given the very high excess mortality in many nations that did pursue such strategies. What is clear is that locations that locked down without experiencing large epidemics of COVID-19 (e.g., Australia, New Zealand) did not have large numbers of excess deaths, which provides strong evidence that lockdowns themselves are not sufficient to cause such surges in deaths.

Disruptions to Health Services

Another common claim is that government interventions themselves are responsible for reduced access to and use of healthcare services, which in turn causes harms to health in the long term. However, the available evidence to date does not reliably nor consistently support this assertion. There is clearly an association between large outbreaks of COVID-19, government interventions, and reductions in attendance for vital non-COVID health services, and thus the connection between lockdowns and missed contact with health systems is very well-established. However, this association may be related to lack of capacity of healthcare services or impacts of the pandemic itself rather than measures taken by governments to reduce cases. It may also simply be caused by the public perception of risk due to fear of the pandemic (i.e. people may fear becoming infected by SARS-CoV-2 in healthcare settings and thus they stay home rather than attend health services).

This avoidance of health services can clearly be seen in accident and emergency (A&E) attendance data from England, and emergency department (ED) use in Australia (320-322). In both countries, emergency activity was suppressed weeks before stay-at-home orders were implemented, and remained suppressed well after they were lifted. While this activity was at its lowest level during lockdowns, patients avoided emergency rooms even when they were free to access them. There is also evidence that patients who attend A&E departments that are overwhelmed by COVID-19 cases have poorer health outcomes (323).

Moreover, where there are data indicating an association between government interventions and disruptions to healthcare utilization, it is yet again challenging to disentangle whether the association relates to restrictions intended to prevent COVID-19 cases or the epidemic itself. For example, one study found that there was an increase in out-of-hospital cardiac arrests in England associated with the first wave of COVID-19, but it could not identify whether this was a result of government action or a consequence of SARS-CoV-2 infections (324). Another study found that missed cancer screenings in the United Kingdom could be associated with a very large increase in cancer deaths, but argued that these missed screenings could be attributed to healthcare staff being reallocated to care for COVID-19 patients during epidemic peaks *or* due to government action causing patients to avoid care (325). It may be that lockdowns tend to disincentivize people from going to routine screenings, but so will overwhelmed health services or a high perceived risk of infection at health facilities – equally, there is a plausible impact on health and wellbeing directly caused by lockdowns. With current evidence, it is simply not possible to support either causal assertion adequately. This is not to say that the evidence is weak, or insufficient in and of itself, but that untangling the causal implications of government interventions from the pandemic is extremely challenging.

Suicide and Mental Health

In many parts of the world, there are substantial lags in reporting of deaths from suicide due to the time it takes for coroners to determine the cause of death. However, despite these lags, there is consistent and robust evidence from many countries that government interventions to control COVID-19 have not been associated with increased deaths from suicide (316, 326-332). Indeed, some evidence suggests that the number of deaths from suicide may have dropped in some age groups, particularly children, during the pandemic (332-334).

While government intervention has not been associated with an increase in deaths from suicide, changes in other mental health conditions are a far more complex issue. There is abundant evidence that mental health has declined in the population since the onset of the pandemic (335-338), which may provide evidence that lockdowns cause mental health problems. However, research into this area is fraught with known limitations and confounders, meaning that it is extremely challenging to ascertain whether government intervention causes or is simply associated with mental health declines, perhaps both driven by the underlying confounder of the pandemic itself.

Furthermore, while the relationship between mental health and lockdowns is commonly discussed, the equally important link between large-scale COVID-19 outbreaks and depression and anxiety is often overlooked. The high mortality of COVID-19, resulting burden of bereavement, and the accompanying anxiety of individuals regarding the personal risk of infection, means that again a false dichotomy exists. There are likely mental health problems, particularly in children, attributable to lockdowns; however, there is an equally plausible burden due to SARS-CoV-2. Missing school clearly affects children's mental health, but so does losing a loved one to COVID-19 (339). Recent estimates suggest that the number of children who have lost a parent to COVID-19 is extremely high, with a recent paper estimating that 43,000 children have lost a parent in the United States (340). The same study estimated that 2 million children have lost at least one grandparent to COVID-19 (33).

Generally, the evidence indicates that government interventions against COVID-19 are not associated with increases in suicide figures. Where suicide rates have increased, as in Japan, this was not associated with government action but with large-scale unemployment that occurred well after the government had lifted restrictions and encouraged individuals to return to life largely as normal (341). While it certainly appears likely that extended periods of social isolation are problematic for mental health, this can be caused by large outbreaks as well as government action, and is therefore more complex than a simple model of causality. Governments also can and have made attempts to improve mental health, particularly for pediatric populations where schools have been closed, which may have been part of the reason that mental health declines have not generally led to increased rates of suicide.

Global Health Programs

Surveys conducted by multilateral health agencies found that services for a variety of conditions—including HIV, tuberculosis (TB), and malaria—were disrupted by the pandemic. For example, a survey by the Global Fund to Fight AIDS, Tuberculosis and Malaria found that 80% of HIV programs and 75% of TB programs reported disruption to service delivery (342). By May 2020, childhood vaccination campaigns had been disrupted in 68 countries (343). However, these disruptions have been caused by multiple complex direct and indirect consequences of COVID-19, not just stay-at-home orders.

Many low- and middle-income countries, such as Brazil, India, and South Africa, have seen huge waves of COVID-19 that have put enormous strain on their health systems and thus disrupted non-COVID-services. In many countries, health workers and health financing that were supposed to be directed at HIV and TB prevention and treatment were redirected to COVID-19 testing and treatment (344). For example, a survey by the Stop TB Partnership of 20 countries with a high burden of TB found that at least 40% of national TB programs were using TB facilities (hospitals and dispensaries) for the COVID-19 response (345). Lockdowns could of course have contributed to disruptions. For example, a study by South Africa's National Institute for Communicable Diseases found that during South Africa's first lockdown, TB testing volumes and positive diagnoses of TB fell even though testing capacity was maintained (346). The authors suggest that restrictions on public transport could explain this finding. If South Africa had not locked down at this point, would TB testing volumes have been maintained? Evidence from elsewhere in the globe suggests not – for example, a recent UN report indicated that the country with the greatest reduction in TB testing in

2020 was Indonesia, which also had one of the least restrictive responses to COVID-19 of any country in the world (347).

So, while there is no doubt that global health programs have been disrupted, it remains difficult to tease out the relative contributions of the pandemic itself versus the public health measures put in place to curb SARS-CoV-2.

Lockdowns: Costs and Benefits

Public health ethicists and practitioners have long known that stringent control measures aimed at reducing disease mortality and morbidity would be accompanied by negative consequences in many sectors of the economy (348). These harms are real, multifaceted and potentially long term, and are therefore an important factor for policy makers to consider when choosing which intervention packages to implement. However, this cost-benefit view must also recognize harms caused by large and ongoing epidemics of COVID-19, and it is often extremely difficult to separate the potential impacts of "lockdowns" from those of the pandemic itself. Most crucially, many harms are not mutually independent; negative consequences arising from interventions are also present during generalised COVID-19 epidemics. Table 1 summarizes the key arguments for the proposition that the "cure is worse than the disease" and the counter-arguments that we presented in this paper.

We do not mean for the conclusion of this paper to be that lockdowns cannot cause any harm. The reality is that whether lockdowns, and other government interventions, have a net benefit is a challenging question which requires evaluating social, economic, and health aspects.. Furthermore, the question poses a false dichotomy. Governments were not faced with the choice between the harms of lockdown and the harms of COVID-19, but rather sought to find the means to minimise the impact of both. When looking at secondary health impacts, in particular, often the most that it is possible to say is that there are harms associated with both large COVID-19 outbreaks and government interventions to prevent the disease. It is also important to consider voluntary behaviour change, with evidence that some economic and social harms of the pandemic can plausibly be explained by individual responses to rising infection numbers (349). The causal relationships are, unfortunately, extremely difficult to untangle.

It is also important to emphasize the health equity perspective in this discussion. There is a strong interrelationship between disadvantage and the risk of death from COVID-19 (350), and this is also likely to be true of government interventions against the disease. Where possible, governments should provide support for individuals impacted by *both* COVID-19 *and* lockdowns, because regardless of whether the disease runs rampant the human cost will not be insignificant.

While it is difficult to know what harms have been directly caused by lockdowns, what is clear is that government interventions have a strong impact on COVID-19 cases and deaths (293, 318, 351), which has become even more pertinent as new, more dangerous variants of the disease have emerged. Moreover, countries such as New Zealand and Australia, which largely avoided large-scale epidemics of COVID-19, have not seen many of the most severe negative impacts that have occurred in other places, including short-term excess deaths. There is even some evidence that greater restrictions against COVID-19 have reduced death rates below the expected range overall. While it is likely that lockdowns do have negative effects, the fact that there are no locations anywhere in the world where a lockdown without large numbers of COVID-19 cases was associated with large numbers of excess deaths shows quite convincingly that the interventions themselves cannot be worse than large COVID-19 outbreaks, at least in the short term.

While there are certainly costs to be expected from intervening against COVID-19 – every decision has a cost, after all – the counterfactual of an unmitigated epidemic makes these restrictions far less damaging than some have suggested. These counterfactuals are not hypothetical and have been observed tragically globally. It appears clear from evidence to date that government interventions,

even more restrictive ones such as stay-at-home orders, are beneficial in some circumstances and unlikely to be causing harms more extreme than the pandemic itself.

Table 1. Arguments for the proposition that the "cure is worse than the disease" and the key counter-arguments

Health domain	Argument	Key counter-arguments
Short-term mortality	Lockdowns themselves caused an increase in short-term excess mortality (defined as mortality greater than the anticipated modelled number of deaths given existing trends).	Countries that imposed several strict lockdowns without experiencing large COVID-19 epidemics (e.g., Australia, New Zealand) did not have large numbers of excess deaths. This provides strong evidence that lockdowns themselves are not sufficient to cause surges in deaths.
Disruption to health services	Lockdowns are directly responsible for reduced access to and use of healthcare services, which in turn causes harms to health in the long term.	The association between large outbreaks of COVID-19, government interventions, and reduced use of non-COVID health services is well-established. However, this association may be due to healthcare services being redirected to handle COVID-19 cases or other impacts of the pandemic itself rather than by lockdowns. In addition, there is evidence that people fear becoming infected by SARS-CoV-2 in healthcare settings and thus stay home rather than attend health services.
Suicide and mental health	Lockdowns have driven increases in the suicide rate	There is consistent and robust evidence from many countries that government interventions to control COVID-19 have not been associated with increased deaths from suicide.
Global health programs	Lockdowns have disrupted services for HIV, TB, malaria, and vaccination programs.	Such service disruptions are well documented, but the evidence shows that these have been caused by multiple complex direct and indirect consequences of COVID-19, not just stay-at-home orders.