The Utility of Electronic Health Records: A Study of Diabetes and Its Complications

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Bachelor of Information Technology

A thesis submitted in fulfilment of the requirement for the

Degree of Doctor of Philosophy

Faculty of Medicine and Health

University of Sydney

Year 2019

Statement of Authentication

A thesis submitted in fulfilment of the requirement for the Degree of Doctor of Philosophy.

The work undertaken in this thesis is to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, in either full or in part, for a degree at this or any other institution.

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Acknowledgements

This thesis does not represent just the work of the last six years; it is an acknowledgement of more than 30 years of work in diabetes. It has been a privilege to have been supported and inspired by many people in this extraordinary journey.

I wish to express my sincere appreciation and thank you to Professor Dennis Yue AM who offered me this opportunity, mentored and shaped my career. He supported and encouraged me to study information technology, which led to the development of the innovative RPAH Diabetes Centre electronic medical record. He had the foresight to develop a standardised diabetes data collection instrument, which provided the setting for the research questions explored in this thesis. Without his vision, life in diabetes, would have been quite different, I have no doubt!.

I have been blessed to have been surrounded by some extraordinary colleagues who have guided my research, questioned my thinking, enabled me to develop academic and research skills and above all they were there to support me on the dark days when nothing seemed to go right.

Foremost I would like to acknowledge Associate Professor Jencia Wong, my primary supervisor. She has astonishing research insight, knowledge and the ability to design or look at a research project and ask just the right question. Her eye for detail is next to none, and I cannot thank her enough for all the teaching, support, patience, time and coffee she provided me. I would like to especially thank her for believing in me and supporting me in the difficult times. I hope that I can always remember her lessons and try to emulate her as a teacher and researcher.

Associate Professor Margaret McGill AM with her friendship, mentoring, guidance, all-around support including reading my drafts and making them more “proper English”. Her passion for diabetes education is second to none, and she is a wonderful teacher to both patients and the diabetes workforce. I have been blessed to be taught by her, and I think it is amazing that as an outcome of this work we now have a clinic for young people with type 2 diabetes.

I am especially in debt to Ms Lynda Molyneaux who has been my right hand and absolute oracle in all things statistical. Lynda with her usual calm provided me with expert advice on statistics, guidance, help and unconditional support.

I would also like to acknowledge Dr Ted Wu and Professor Stephen Twigg for their support, facilitating my workload and helping with so many things including manuscript reviews.

I would also like to thank the staff at the RPAH Diabetes Centre, or as some say, my extended family, since we have been together in some cases for more than 25 years.

- Susan Tukuniu, Cheryl Hurley and Angela Patman. Thank you for all your support, humour and help with missing files and data, you keep me sane and grounded. I can never thank you enough for all you do for me.
- Colleague diabetes educators, past and present. You made possible to have such a high quality diabetes data resource and encouraged me along the way.

My co-authors not mentioned above for their guidance, expertise, provided time and reviewed work and papers willingly.

Finally, I need to acknowledge that without the unconditional support of my family and friends I would not have been able to accomplish this work. My husband Fernando, who only occasionally questioned “how much longer have you got?”, my daughters Nadia and Lucy for being so supportive, my mother and sister for always wanting the best for me and trying hard not to worry me with their health.

I am forever grateful.

Abstract

Type 2 diabetes is a heterogeneous condition, but evidence gaps exist with respect to risks and outcomes for sub-populations. The tenet of this thesis is that routinely collected clinical data captured within the eHR can be utilised for diabetes research; the eHR can provide new information with specific regard to further characterising diabetes sub-populations, which can meaningfully inform patient care.

Clinical data captured in the course of usual patient care for over 20,000 patients held within the longstanding RPAH Diabetes Centre eMR was studied. Data linkage was undertaken with the National Death Index to ascertain the survival status. Studies were undertaken to examine 1) the heterogeneity of survival outcomes for 7 different ethnic groups, 2) the survival of young onset type 2 diabetes compared with type 1 diabetes and usual onset type 2 diabetes, 3) how systematically collected retinopathy data could be used to inform public health decisions and 4) the comprehensiveness and degree of standardisation in the reporting of retinopathy sourced from optometrists and ophthalmologists.

Significant differences in diabetes complications and mortality were observed amongst ethnic groups; for Chinese, Indian, Arab and Mediterranean groups survival was better than the Anglo-Celtic reference group. In contrast, Indigenous Australians had the highest adjusted hazard for death.

We also found that young onset type 2 diabetes had a twofold greater mortality than type 1 diabetes, with deaths occurring at a significantly younger age. Furthermore, in comparison to older onset type 2 diabetes, we found the greatest mortality impact in

younger onset type 2 diabetes. Taken together these results newly highlighted the aggressive nature of early onset type 2 diabetes.

We demonstrated the potential utility of cross-sectional retinopathy data 1) in the prediction of the future retinopathy burden for different sub-groups and 2) to provide an index of past glycaemic exposure for subgroups to identify those most at risk. Finally, we identified a lack of standardisation in the reporting of retinopathy amongst providers.

Overall, this body of work demonstrated the wide-ranging utility of the routinely collected eHR, to further characterise heterogeneity in type 2 diabetes and to meaningfully inform future diabetes research and care.

Publications Arising From This Work

Article · Jul 2013 · Diabetes care

Long-Term Complications and Mortality in Young-Onset Diabetes: Type 2 diabetes is more hazardous and lethal than type 1 diabetes (1)

Maria I Constantino · Lynda Molyneaux · Franziska Limacher-Gisler · Abdulghani Al-Saeed· Connie Luo· Ted Wu· Stephen M. Twigg· Dennis K. Yue· Jencia Wong

ABSTRACT: To evaluate long-term clinical outcomes and survival in young-onset type 2 diabetes (T2DM) compared with type 1 diabetes (T1DM) with a similar age of onset. Records from the Royal Prince Alfred Hospital Diabetes Clinical Database, established in 1986, were matched with the Australian National Death Index to establish mortality outcomes for all subjects until June 2011. Clinical and mortality outcomes in 354 patients with T2DM, age of onset between 15 and 30 years (T2DM15-30), were compared with T1DM in several ways but primarily with 470 patients with T1DM with a similar age of onset (T1DM15-30) to minimise the confounding effect of age on outcome. For a median observation period of 21.4 (interquartile range 14-30.7) and 23.4 (15.7-32.4) years for the T2DM and T1DM cohorts, respectively, 71 of 824 patients (8.6%) died. A significant mortality excess was noted in T2DM15-30 (11 vs. 6.8%, P = 0.03), with an increased hazard for death (hazard ratio 2.0 [95% CI 1.2-3.2], P = 0.003). Death for T2DM15-30 occurred after a significantly shorter disease duration (26.9 [18.1-36.0] vs. 36.5 [24.4-45.4] years, P = 0.01) and at a relatively young age. There were more cardiovascular deaths in T2DM15-30 (50 vs. 30%, P < 0.05). Despite equivalent glycaemic control and shorter disease duration, the prevalence of albuminuria and less favourable cardiovascular risk factors were greater in the T2DM15-30 cohort, even

soon after diabetes onset. Neuropathy scores and macrovascular complications were also increased in T2DM15-30 ($P < 0.0001$). Young-onset T2DM is the more lethal phenotype of diabetes and associated with a greater mortality, more diabetes complications and unfavourable cardiovascular disease risk factors than T1DM.

Article · Oct 2014 · Diabetes Research and Clinical Practice

Ethnic specific differences in survival of patients with type 2 diabetes: Analysis of data collected from an Australian multi-ethnic cohort over a 25 year period (2)

Turki J. Alharbi · Maria I. Constantino · Lynda Molyneaux · Ted Wu · Stephen M. Twigg · Dennis K. Yue · Jencia Wong

ABSTRACT: Aims To examine the survival of patients with type 2 diabetes from 7 ethnic groups, living in the shared environment of an Australian city. Methods Hazard Ratio of death (HR) after diagnosis of diabetes was compared between Anglo-Celtic (n = 5433), Indigenous Australian (n = 439), Pacific Islander (n = 354), Mediterranean (n = 3138), Arabic (n = 768), Indian (n = 702) and Chinese (n = 1632) patients who live in metropolitan Sydney. Mortality was ascertained by data linkage with the Australian National Death Index. The modulating effects of glycaemic control, diabetes/vascular complications and risk factors, year of diabetes diagnosis and duration of diabetes on ethnic differences were analysed by Cox regression. Socio-economic status and competence in English were also examined. Results There were significant differences in survival between the ethnic groups; the Indigenous Australians had the highest HR for death (2.3, 95% CI 1.7–3.0) and the Chinese the lowest (0.4, 95% CI 0.4–0.5). The survival of the Anglo-Celtics (HR 1) was surprisingly poorer than for Indian (0.6, 95% CI 0.5–0.8), Arab (0.7, 95% CI 0.6–0.8) and Mediterranean groups (0.8, 95% CI 0.7–0.9).

Prevalence of smoking and albuminuria were strongly associated with HR. The better survival of Chinese and Arab and the worse survival of Indigenous Australians remained after adjustment for risk factors. Need for an interpreter was a favourable risk factor for survival. Conclusions Ethnicity is a significant determinant of survival in type 2 diabetes, and this is substantially but not completely mediated by smoking and vascular risk factors. The favourable impact associated with less competence in English may represent a Healthy-migrant effect.

Article · Jan 2015 · Current Diabetes Reports

Morbidity and Mortality in Young-Onset Type 2 Diabetes in Comparison to Type 1 Diabetes: Where Are We Now? (3)

Jencia Wong · Maria Constantino · Dennis K Yue

ABSTRACT: Increasingly, we recognise that type 2 diabetes in youth is a disease with an aggressive time course and a significant complication risk. On the other hand, outcomes for youth with type 1 diabetes generally appear to be improving. With increasing numbers of both types of diabetes in youth, it is timely that a comparative perspective is offered to help clinicians prognosticate more appropriately. Contemporary comparative studies add a new perspective to a consistent story that for youth-onset type 2 diabetes, the development and progression of cardio-renal complications increased, and the survival prognosis is significantly worse than for type 1 diabetes. Here, we review this mounting evidence, highlight the importance of metabolic syndrome factors in the excess risk and underscore that there remains a significant mortality gap for youth with either type of diabetes, to be addressed as a matter of urgency

Article in the Journal of Diabetes and its Complications

DOI: http://dx.doi.org/10.1016/j.jdiacomp.2016.12.016

Data collection on retinopathy as a public health tool: The Hubble telescope equivalent of looking back in time (4)

M.I. Constantino · L. Molyneaux · T. Wu ·SM Twigg · J Wong · D.K. Yue

Abstract: To test whether the rate of diabetic retinopathy development in a population calculated from the prevalence of retinopathy and duration of diabetes can be used to assess their prior glycaemic control. **Research Design and Methods:** 9281 patients with type 2 diabetes (T2DM) were grouped by duration of diabetes and plotted against the % of retinopathy in each band. The slope was used to calculate retinopathy development/year (RD/y). We correlated the RD/y with updated HbA1c within groups of different ethnicity, age of diabetes onset, year of the eye examination, socio-economic status and fluency in English.

Results: Differences in ethnicity, age of diabetes onset and year of the eye examination affect RD/y to a degree predictable from their respective updated HbA1c. No such relationship with updated HbA1c was evident when a factor has no apparent effect on RD/y. **Conclusions:** This relationship between prevalence of retinopathy and duration of diabetes can be used to assess future retinopathy burden. Perhaps more intriguing, the camera can be reversed to allow an estimate of prior glycaemic control of a population from its retinopathy prevalence. Health care organisations can use this method to project future needs and to assess the adequacy of prior glycaemic control.

Article in Clinical and Experimental Ophthalmology · December 2016

DOI: 10.1111/ceo.12887

Communication in the multidisciplinary care of diabetic eye disease: Communication in diabetic eye disease (5)

Eddy J Tabet · Maria I Constantino · Jencia Wong · Dennis Yue

Article in Diabetes Care 39(5):dc150991 · March 2016

An Inverse Relationship between Age of Type 2 Diabetes Onset and Complication Risk and Mortality: The Impact of Youth-Onset Type 2 Diabetes (6)

Maria I. Constantino · Abdulghani H. Al-Saeed · Lynda Molyneaux · Mario D'Souza · Franziska Limacher-Gisler · Connie Luo · Ted Wu · Stephen M. Twigg · Dennis K. Yue · Jencia Wong

Abstract: This study compared the prevalence of complications in 354 patients with T2DM diagnosed between 15 and 30 years of age (T2DM15-30) with that in a duration-matched cohort of 1,062 patients diagnosed between 40 and 50 years (T2DM40-50). It also examined standardised mortality ratios (SMRs) according to diabetes age of onset in 15,238 patients covering a wider age-of-onset range. Complication status was assessed according to a standard protocol and extracted from our electronic database. Survival status was ascertained by data linkage with the Australian National Death Index. SMRs were calculated in comparison with the background Australian population and analysed according to age of onset. After matching for duration, despite their younger age, T2DM15-30 had more severe albuminuria (P = 0.004) and neuropathy scores (P = 0.003). T2DM15-30 were as commonly affected by metabolic syndrome factors as T2DM40-50 but less frequently treated for hypertension and dyslipidaemia (P

< 0.0001). An inverse relationship between age of diabetes onset and SMR was seen, which was the highest for T2DM15-30 (3.4 [95% CI 2.7-4.2]). SMR plots adjusting for duration show that for those with T2DM15-30, SMR is the highest at any chronological age, with a peak SMR of more than 6 in early midlife. In contrast, mortality for older-onset groups approximates that of the background population. The negative effect of diabetes on morbidity and mortality is greatest for those diagnosed at a young age compared with T2DM of usual onset. These results highlight the growing imperative to direct attention toward young-onset T2DM and for effective interventions to be applied before middle age.

Conference Presentations

Information Technology in Diabetes Care: An Evolving Scene 9th IDF-WPR Congress & 4th AASD Scientific Meeting **Invited speaker** symposium "Information Technology in Management of Diabetes." 2012

Data and Technology Management in Diabetes **Invited speaker** Sanofi Educators day 2013 Sydney

Diabetes, Age and Social Media Awareness as Predictors for Technology Utilization in Diabetes Care, **Oral Poster** 781. Presentation at the American Diabetes Association's 73rd Scientific Sessions, June 21-25, 2013 in Chicago, Illinois.

A Multi-Ethnic Study of Diabetic Retinopathy: Poorer Outcomes Continue for Australian Aborigines and Pacific Islanders. **Oral Presentation**. International Diabetes Epidemiology Group (IDEG) and International Diabetes Federation (IDF) Congress Melbourne 2013

Secular Trends in Diabetes Related Mortality: Increasing Longevity but Also Complexity ADS-ADEA Scientific Meeting 2013 ADS **Oral Presentation** 2013

Reduced Secular trends in diabetes mortality but not complications: The burden of diabetes treatment success 2729 – **Published poster**, 73rd Scientific Sessions, June 21-25, 2013 in Chicago, Illinois.

A Cross-Sectional Multiethnic Study of Diabetic Retinopathy: A Useful Method of Assessing Quality of Diabetes Care; **Poster**; American Diabetes Association's 74th Scientific Sessions Moscone Center, San Francisco, CA June 13 - 17, 2014

Data Collection in The Diabetic Foot International Diabetes Federation (IDF) –Western Pacific Region (IDF-WPR) Foot Care Project Meeting 2014" held on 21-22 February 2014 in Osaka, Japan. **Invited Speaker**

Complications And Comorbidities In Type 2 Diabetes In Youth - World Diabetes Congress 2015 Vancouver: Date: 3 December 2015. **Invited Speaker**

The use of systematic data collection on retinopathy to assess prior glycaemic control: The Hubble telescope equivalent of looking back in time", ADS ADEA 2015 Annual Scientific Meeting program, **Oral presentation**, **Finalist** ADS Clinical Young Investigator Awards

Thesis Overview

The prevalence of Diabetes Mellitus (diabetes) is increasing worldwide with the International Diabetes Federation (IDF) estimating that in 2017, 455 million people were affected by diabetes. This number is expected to rise to 629 million in 2045 with the majority having type 2 diabetes (7).In addition to diabetes, the IDF estimates that globally more than 352 million adults have pre-diabetes/ impaired glucose tolerance and that 16.2% of live births in 2017 were affected by hyperglycaemia in pregnancy, the majority having gestational diabetes. The latter observation is particularly concerning given the increased risk of later diabetes in the mother and the transgenerational impact on obesity in the offspring. Diabetes (and pre-diabetes) is a major public health concern impacting on both developed and developing countries, affecting every age group and placing great demands on healthcare budgets globally. The IDF reports that on average the proportional expenditure on treating diabetes and related complications ranged from 6% of the total health care budget in Africa to 17% in Middle East and North African regions in 2017 (7). Future expenditure will be further increased, with the added pressures of increased urbanisation, lifestyle changes and population growth in low and middle-income countries all negatively impacting diabetes prevalence(7). It is clear the greatest impact will be from the numbers with type 2 diabetes and although we have greater clarity over the projected burden, there remain large gaps in our knowledge, and there is much research to be done to overcome this epidemic. There are many challenges in diabetes research and this is made especially so by the realisation that type 2 diabetes is a heterogeneous disorder (8) and that the “diabetes” landscape is evolving not least due to rapid changes in lifestyle, migration and quality of medical care in recent decades. It is clear that a one- size fits all approach to diabetes

care is not ideal given this heterogeneity and the challenge now is to know how to personalise and provide a precision medicine approach to diabetes care. Thus, further research into diseases subtypes is thought to provide the answer.

In terms of diabetes research, it is the randomised controlled trials (RCTs) that have long been promulgated as the gold standard and the ideal source of evidence and the data on which clinical decisions should be made. However, for many reasons RCTs cannot provide all the answers; the trials are usually of short duration with a restricted population characteristic not always generalisable to the wider population. Furthermore, research involving complications, given the long timeframe over which these develop may not be served adequately by the RCT design, which is expensive and time limited. On the other hand, widespread observational data such as population based epidemiological studies may not contain specific patient level data to illuminate this issue of heterogeneity nor provide information regarding specific subgroups. New ways of obtaining valuable health information need to be utilised.

Patient level data are often captured now in electronic format of various forms, and one of the largest repositories is the electronic health record (eHR) which contains information captured in the course of usual patient care. Such datasets, given their longevity, can provide many years of follow up, especially important as diabetes complications require a long time over which to develop. Such “real world data” can potentially augment the shorter term RCT approach. Furthermore, the ability to link disparate datasets can potentially provide new knowledge despite a non-randomised approach and could potentially be a powerful research tool. In this situation, the data contained in various forms of routinely collected electronic health records, which are collected, systematically and longitudinally, provide a possible alternative source of valuable information, complementary to approaches that are more traditional.

The overarching tenet of this thesis is that routinely collected clinical data captured within the eHR can be utilised for diabetes research; the eHR can provide new information with specific regard to further characterising sub-populations within the diagnosis of diabetes, which can meaningfully inform patient care. The success or failure of such an approach could inform future new approaches to utilising such data sources for diabetes research and care. To examine the value of this type of dataset, this thesis presents studies, which interrogated a long established eHR, the Royal Prince Alfred Hospital clinical diabetes database, to investigate some areas of type 2 diabetes which have changed, emerged or gained prominence in recent decades.

An initial study was performed to examine the heterogeneity of survival outcomes in type 2 diabetes in different ethnic groups (**Chapter 3**), important given the changing demographics of this disease, particularly in Australia with its rapidly evolving multicultural background. Previously, many such studies on diabetes and ethnicity have focussed on assessing a single ethnic population, either in the minority (e.g., Pima Indians) or the majority (e.g., Chinese) often residing in their own country. The multicultural society in Australia brought on by increasing migration, affords an opportunity to compare seven different ethnic groups in their diabetes phenotype, complications and mortality whilst living in a similar environment. Significant differences in diabetes complications and mortality were observed amongst these 7 ethnic groups, allowing the roles of medical and sociological factors such as language fluency and socioeconomic status to be assessed. A surprising finding was that for some ethnic groups with type 2 diabetes, despite, perhaps being more socially disadvantaged, survival was better than the majority Anglo-Celtic Australian group. For example, the Chinese had the lowest hazard ratio for death (HR 0.4, CI 0.4 – 0.5) and the survival of the Anglo-Celtics (HR 1) was also poorer than for Indian (HR 0.6, CI 0.5 – 0.8), Arab

(0.7, CI 0.6 – 0.8) and Mediterranean (HR 0.8, CI 0.7 – 0.9) groups. These findings may be due to the pre-selection of the migrant groups according to health status before migration. By contrast, the Indigenous Australians had the highest HR for death (HR 2.3, CI 1.7 – 3.0).

We noted that some of the ethnic groups (Indigenous Australian, Pacific Islander, Indian and Arabic) are characterised by the younger onset of type 2 diabetes (9) than what has been traditionally described for this condition and this raised the question as to whether there were differential survival patterns by the age of diagnosis.

Therefore, the second area examined in this thesis compared the survival and clinical characteristics of young onset type 2 diabetes (YT2DM) against the reference group of young onset type 1 diabetes (YT1DM) with a similar age of onset (**Chapter 4**). Here the two types of diabetes were compared, and cohorts of similar age of onset were examined allowing us to equate for duration of diabetes. This minimised the possibility of a lead-time bias affecting survival due to the longer duration of T1DM at any given age compared to usual type 2 diabetes. Interestingly, when the age of onset and duration of diabetes were accounted for, our study revealed a greater adverse impact of YT2DM than YT1DM on survival. We were able to demonstrate that YT2DM is associated with a 2 fold greater hazard for mortality than YT1DM (HR for death 2.0, CI 1.2- 3.2, p=0.003) and deaths occurred after a significantly shorter diabetes duration (26.9 vs. 36.5 years). There were more cardiovascular deaths in YT2DM (50% vs 30%, $p < 0.05$) and the HR for CVD deaths were 3.5 (1.4-8.5, p=0.004). Furthermore, despite equivalent glycaemic control and shorter disease duration, the prevalence of albuminuria and less favourable cardiovascular risk factors were greater in the YT2DM cohort, even soon after diabetes onset. Neuropathy scores and macrovascular complications were also increased in YT2DM. Additionally, this study illustrated the

utility of research by data linkage, in this case between an eHR and the Australian National Death Index (NDI), a repository of all mortality statistics in Australia. The survival data are concerning, and the published results were editorialised as until recently, a previously unreported finding (10).

The above study then led to the question, "what is the survival impact of diabetes at a young age, i.e. YT2DM relative to those with the more usual age of diabetes onset?". The next study outlined in **Chapter 5** examined the mortality of YT2DM versus those with onset in the middle and older age groups. By the nature of the question being examined, those with an older age of onset at any given duration would inevitably be older. As age alone is a significant confounding factor in mortality, a Standard Mortality Ratio (SMR) method was employed to understand risk by age of onset against the age and gender matched background Australian population. A Poisson modelling approach was utilised to compare age of onset groups by current age and duration of diabetes. Once analysed in this way, the results showed an unequivocally higher impact of a younger age of type 2 diabetes onset on relative mortality. An inverse relationship between age of diabetes onset and SMR was seen, which was the highest for YT2DM (3.4, CI 2.7 – 4.2). SMR plots at any duration of diabetes or at any current age show that for those with YT2DM, SMR is the highest; the peak SMR of more than 6 is seen in early midlife.

In contrast, SMR for older onset groups at any current age approximate that of the background population. These findings have significant implications for health care planning. It suggests that future strategies for screening and intensive treatment of diabetes should focus on those with YT2DM.

One of the pressing public health concerns is the targeting of finite and limited health resources to different patient groups. A clear understanding of sub-population risk and the ability to predict future burden of disease would greatly assist in public health planning. The latter half of this thesis is therefore concerned with the utility of routinely and systematically collected retinopathy data in informing patient care and service delivery.

The relationship between retinopathy and duration of diabetes is well established. Furthermore, the direct impact of glycaemic control on retinopathy development is equally well understood. In **Chapter 6**, we explore the utility of using these relationships to predict the future burden of disease for different groups and to explore the heterogeneity of risk that exists within diabetes. We used cross-sectional retinopathy data and plotted group retinopathy prevalence against diabetes duration for various sub-populations with diabetes. By using simple linear regression, the slope of this relationship provides a population estimate of the cross-sectional "rate" of retinopathy development over time. Such an analysis provides an estimate of population retinopathy burden and an index of relative susceptibility to retinopathy. We demonstrated the consistency of this method across diverse populations defined by ethnicity, age of diabetes onset, year of eye examination, socio-economic strata and language fluency. Furthermore, by plotting the cross-sectional 'rate' of retinopathy for a particular group against updated HbA1c, a linear relationship is confirmed for all subgroups, which suggests that the rate of retinopathy development can be further used as a relative index of population glycaemic control. These findings and methodology can be extrapolated to administration databases for any arbitrary sub-group of interest and thus, may have widespread potential application as a public health tool to estimate future retinopathy burden and past glycaemic control.

The studies, which underpin this thesis, were made possible by the systematic and ongoing collection of clinical data captured within the Royal Prince Alfred Hospital diabetes database. One of the core issues in the use of such databases in a clinical setting is data quality. Some of the steps taken to maintain this are outlined in **Chapter 2**, describing the procedures for ongoing data collection. Nevertheless, despite implementing quality measures, many changes in the knowledge and mode of clinical care over the decades can also have a major impact on data collection. One example of this is the availability of retinal photography in the primary care setting brought on by changes in technology, medical manpower and government regulation. In the course of processing data for the prior studies, it became apparent that the comprehensiveness of the retinopathy data in the RPAH diabetes database had declined, primarily due to the outsourcing of eye examinations. This led to the systematic examination of the difficulties involved in the retrieval and interpretation of eye data from non-hospital based ophthalmologists and optometrists; this study and its publication is presented in **Chapter 7**. In reviewing 355 letters from ophthalmologists and optometrists, we showed that when retinopathy is present,16.2% of communications to the Diabetes Centre did not clearly differentiate vision-threatening retinopathy from milder forms of retinopathy and 38.3% of correspondence did not comment on the presence of macular pathology. Given the presence or absence of significant complications can impact on management decisions such as glycaemic targets and the use of fibrates, these data illustrate the need for standardised and accurate reporting of retinopathy grading to facilitate patient care.

The study also revealed that the prevalence of retinopathy varied according to whether the eye examination was performed in-house or by an ophthalmologist or optometrist in a non-hospital setting. For any duration of diabetes, more patients from

ophthalmologists had retinopathy compared to the RPAH cohort. However, the difference in prevalence between these two groups diminished over time with the longer duration of diabetes. Patients screened by optometrists had a very low prevalence of retinopathy in the first 15 years of diabetes compared to the other two groups. These observations may reflect the issue of referral bias to optometrists and ophthalmologists and highlights the importance of understanding patient selection criteria in the interpretation of any data extracted from any given system.

In summary, this thesis describes a series of studies in the area of diabetes and its complications based on the use of healthcare information captured and stored within the routinely collected eHR used for usual care by a single ambulatory diabetes service. The results highlight the ongoing utility of clinical information systems to facilitate meaningful clinical research and the caveats within. The published studies in this thesis support the use of such routinely collected datasets to provide information of value, and allow this to be done quickly in a cost-effective way; a process so keenly sought by health administrators. The harnessing, mining and data linkage of routinely collected datasets in this manner can provide valuable insights into how to individualise therapy within a heterogeneous disease such as diabetes.

The results presented herein, some with translational impact, support the noble sentiment expressed by Atul Butte that “Hiding within those mounds of data is knowledge that could change the life of a patient, or change the world” (11). The hope is with the now widespread use of the electronic health record (or electronic medical record) that systematic collection can be championed by health professionals and data managers alike with the specific understanding of the value of such data to the broader population with diabetes.

Central Aim and Hypotheses of the Thesis

The overriding postulate is that routinely collected clinical data within an electronic health record (eHR) over time can provide new information with respect to diabetes and has utility in terms of health decision making in the context of personalised and precision medicine.

To examine this issue, this thesis specifically addresses the following questions

1. Can the electronic health record be used to examine the clinical outcomes and mortality in subgroups of patients with type 2 diabetes, specifically by
    a. Ethnicity
    b. Age of onset
2. Can the electronic health record be used to inform public health measures and identify gaps in patient care specifically looking at diabetic retinopathy data?

Chapter 1

Literature Review

Introduction

Diabetes Mellitus (diabetes) refers to a disorder characterised by hyperglycaemia which is thought to arise from impairment of both insulin secretion and action to varying degrees. The name '"diabetes mellitus' is an ancient one; a term first ascribed to the Greek physician Aretaeus who in 100 C.E. observed that the urine of patients so afflicted was sweet to the taste. Since that time, diabetes has risen to now be one of the most prevalent chronic diseases of this century with a now well documented and seemingly inexorable rising global burden (7).

Rather than describing a single disorder, diabetes refers to a heterogeneous group of disorders. In common, the various forms of diabetes can lead to acute and life threatening presentations with ketoacidosis or hyperosmolar coma. More chronically, persistent hyperglycaemia is associated with long term microvascular complications (including retinopathy, nephropathy and neuropathy) and macrovascular complications (including cerebrovascular accidents, cardiovascular disease and peripheral vascular disease). The most common form of diabetes is type 2 diabetes, which is the subject of this thesis.

Despite recent advances, type 2 diabetes remains a challenging disease with still many knowledge gaps. Traditional research avenues have known limitations such that novel approaches are now needed as a pathway to new knowledge to inform clinical care. As outlined before, the overriding postulate for this thesis is that routinely collected clinical data within an electronic health record (eHR) over time can provide new knowledge with respect to diabetes and as such has the added utility of being a valuable research resource. This is particularly relevant as the eHR is increasingly being utilised by

healthcare services. In this context, the present chapter provides a background for the research presented in this thesis. **Part I** is concerned with modalities used in clinical research and the current use of electronic data (eData). **Part II** provides a general overview of diabetes with specific areas highlighted relevant to this thesis. With reference to the specific aims and hypothesis outlined, the areas highlighted and discussed in Part II are (i) the relationship between ethnicity on diabetes outcomes and (ii) retinopathy management. **Part III** provides an overview of the emerging phenomenon of young onset type 2 diabetes. This provides context for the specific aim outlined to examine the impact of age of onset on diabetes outcomes.

Part I: Health decision making and the current role of eData:

What do we use to make health decisions? The current approach to gathering data to inform health decision making is discussed herein.

1.1 Evidence based medicine

Prior to the advent of what has now been termed evidence based medicine (EBM), much clinical decision making was made on experiential grounds*;* expert opinion with a degree of intuition thrown in. However, from the early 1990's a paradigm shift in medical science occurred which advocated scientific evidence as the basis for clinical decision making and the only rational basis from which to make clinical decisions. The foundation of this new paradigm was the success of the randomised clinical trial (RCT) and the utility of this methodology to analyse the efficacy of new pharmacotherapy*,* to test surgical interventions and diagnostic tests. The assumptions made in this new paradigm are firstly "that in the absence of systematic observation, one must be careful in the interpretation of information derived from clinical experience and intuition, for it may at times be misleading" and secondly that "the rationales for diagnosis and treatment, which follow from basic pathophysiologic principles, may, in fact, be incorrect, leading to inaccurate predictions about the performance of diagnostic tests and the efficacy of treatments" and that thirdly "understanding certain rules of evidence is necessary to correctly interpret literature on causation, prognosis, diagnostic tests, and treatment strategy" (12). Overall the EBM paradigm emphasises a shift away from (although not a rejection of) authority and opinion towards the primacy of data. Thus, the practice of evidence-based medicine de-emphasised the importance of unsystematic clinical experience and tools such as the pyramid of evidence in Figure 1

which shows how to access the quality and quantity of evidence available. More recently, grading systems have been developed to assess the quality of evidence. Examples of these grading systems used in medicine are*:*

- Centre for Evidence Based Medicine (CEBM) Levels of Evidence Developed by Oxford Centre for Evidence-Based Medicine (13)
- National Health & Medical Research Council (NHMRC) Evidence Hierarchy Levels of evidence for intervention, diagnostic accuracy, prognosis, aetiology and screening intervention questions (14).
- JBI Levels of Evidence Developed by the Joanna Briggs Institute Levels of Evidence and Grades of Recommendation Working Party, 2013 (15).

Figure 1: Pyramid of Evidence for RCTs
(from https://www.ellismedlibrary.org/uploads/9/1/9/0/91901496/evidencepyramid_orig.jpg ; viewed on line 08/01/2019)

1.1.1 Randomised Controlled Trials And Their Limitations.

Evolving from the above paradigm and the general principle that best medical practice should be based on the highest quality of scientific data, modern research in medicine has had its basis strongly rooted in the use of evidence arising from RCTs to inform patients and clinicians on the effects of treatments. The RCT is considered to be the highest form of evidence in clinical grading systems with randomisation accounting for both known and unknown confounders. However, these grading systems are biased towards the RCTs and potentially discourage consideration of non-RCT data to answer important questions in health.

Despite all the benefits, there remain several limitations to RCTs. Firstly, these are notoriously difficult and expensive to carry out; they may take many years to plan and execute and by the time they report, newer strategies may have already arrived, limiting the ability of the RCT to keep pace with new developments. The RCT by design may study a restricted population defined by various characteristics which limit generalisability. Also this strategy may mask potential adverse reactions seen in the wider population, not seen in the study population (16). Further, the resource-intensive nature of the RCT has led to the use of surrogate markers which may or may not correlate with important endpoints. This is evidenced, for example, by studies using reduction in albuminuria as an endpoint for reno-protection in diabetes (17). In truth, much of current clinical medicine is not supported by RCT data, and this would be particularly true in the situation of rare disease or phenotypic variations. Thus, researchers need to consider other methodologies to fill remaining evidence gaps.

1.1.2 Meta-Analysis

In this context other study designs can offer alternatives to RCTs. One of these is the use of meta-analysis as in theory it can use all the data available from all the studies that address a particular question. Gene V. Glass (18) coined the term meta-analysis by saying "...Meta-analysis refers to the analysis of analyses"; this type of study design is particularly good in providing information on rare conditions by pooling results where RCTs may be difficult to perform as the number of subjects may be limited. Using this technique the statistical power to test a hypothesis can be reached and it allows for patterns and effects to be identified without new data collection undertaken. The process of aggregating all the data available from single trials in a meta-analysis can provide more power and precision allowing for more definite information than one reported by each trial individually. Although in theory meta-analysis should be considered an excellent tool to provide evidence based medicine it has weaknesses (and has suffered from some bad press as a consequence) when studies of diverse quality are included. Scoring systems are now available when undertaking such a project that can help with evaluating study quality for inclusion and meta-analysis (19; 20). Furthermore, there is a well-known bias in the scientific literature towards publication of only positive results; hence a publication bias may be present with potential impact on meta-analysis results. Careful consideration should be given to the total number of studies included as if there are not sufficient published literature, it can be a meaningless exercise. This is quite important for very rare diseases where there is not a great breadth of publications. Another issue is to ensure that the data are comparable given that different methods may be used to measure the same outcome. In fact, for a meta-analysis to be considered of a high standard, it should include individual patient data obtained from the original studies. This increases the complexity

of requirements as the original authors need to be contacted and agree to provide the data. Nevertheless, this action will improve the quality of the analysis as it can reveal differences between the different studies that had not been previously highlighted. Without these requirements, meta-analyses, in general, can provide a false sense of precision. With the caveats mentioned above other largely observational study designs have been employed. These are further discussed.

1.1.3 Prospective Cohort Studies

Prospective studies are designed to follow a group of study participants over a period of time who are observed to determine how long it takes for a pre-set condition or disease to manifest. The data collected are bespoke to the study and the outcome of interest. They allow authors to identify risk or protection factors involved in the disease manifestation. Some issues with prospective studies include the need for significant resourcing over long periods of time. Furthermore, as subjects have to be followed-up for long periods of time, there is potential for the inclusion of less representative study populations due to losses to follow up of certain patient groups, for example, exclusion of less mobile patients who may not be able to attend visits. This will introduce bias, which must be considered in the interpretation of such studies.

1.1.4 Retrospective Cohort Studies

In a retrospective study, an outcome of interest is identified and by looking back at a group of subjects these studies can help to establish temporal relationships, a range of outcomes per exposure or protective or risk factors. The major problem encountered is that such studies can be subject to bias such as recall bias and misclassification. Some strategies that can be used to reduce this confounding are the use of

randomisation to avoid selection bias and subject matching to control for variables that are known to impact; for example, matching for age if the outcome of interest is vascular disease.

1.1.5 Case-control Studies

Case-control studies provide a comparison between a group of individuals with a disease (case) and a group of individuals without the disease that is observed (controls) (21). The same data are collected in both groups regarding the exposure to the study subject. In this type of study, the outcome data are used in a comparison of the proportion of the exposed individuals in the case group versus the control group. Case-control studies can provide significant scientific findings with comparatively little time, funding and effort compared with other study designs. Schulz and Grimes (22) in their paper “Case-control studies: research in reverse” describe important caveats required to make sure that the study is valid and reliable. Some of these include a rigorous description of criteria used for diagnosis of a case; the control population must be from the same population as the cases studied and they should be selected because they are at risk of developing a similar disease. The research team collecting the data should be blinded to the main hypothesis of the study. Careful consideration needs to be given to study procedures. For example, it would be important to train the research team when interviewing both cases and controls that the same words and memory aids be used in order to obtain the exposure information in the same manner.

1.2 Electronic data (eData) and Research

Recognition of the limitations of the RCT and the acceptance of other observational studies to provide valid evidence as described above comes with an understanding that

there is no single best approach to the study of health interventions. Decisions are often made with imperfect data. However, new ways of obtaining valuable information need to be sought, and potential opportunities are provided by the modern digital era. The use of electronic health records has the promise of overcoming some of the limitations of the RCT and cohort studies. Obviously, many pre-planned research programs would design a purpose-built system to capture the necessary data to facilitate analysis. However, many computer information systems in use are designed to capture data, which can be subsequently "mined" to show patterns and trends for the purpose of informing diabetes care. In this regard post marketing and surveillance studies have been utilised to support evidence from RCTs and facilitate access to new pharmaceutical agents. Expert bodies have recently endorsed the evidence from such observational studies, where the data are high quality, to aid therapeutic decisions (23).

The term **"electronic health record ' (eHR**), sometimes also known as the electronic medical record (eMR) has been defined as the systematised collection of patient and population health information stored in a digital format (24). These can encompass a wide variety of electronic data sources including but not limited to data from medical care records, disease specific registries and health insurance claims databases. There are several potential advantages to the use of the eHR for research. Firstly, studies are cost-effective given that data are already collected for other purposes (25). Recall bias that plague retrospective studies are not an issue given that data collection is prospective and often collected in real-time, with near real-time availability for analysis. The large sample sizes and patient level clinical data often allow for greater granularity to ascertain specific risk or protective factors for example. Depending on the source, data may include prescribing and dispensing information and allow for detailed health economic analyses. The potential for linkage across many datasets exists, and often

the data can be widely generalisable given the source population are less selective than for RCT. Several eHRs internationally and within Australasia have been used or may be available for use in diabetes research. These are discussed further.

1.2.1 Disease Registries:

These are a clearly defined set of data kept in computerised systems primarily for recording the presence of diabetes in affected individuals. Originally such registries were more commonly designed to capture those with childhood onset type 1 diabetes due to the smaller numbers of individuals affected, the relative ease of capturing the targets in hospital-based facilities and the better defined features of this condition. However, with the emerging higher prevalence of young onset type 2 diabetes, the exclusivity of registries for type 1 diabetes is becoming less. Examples of the use of such registries for research include the Diamond Study (26) and the EURODIAB study based in Europe (27). Particularly relevant to the studies described in this thesis involving young onset diabetes is the SEARCH for Diabetes in Youth study based in the United States (28). This observational registry study over many States in the USA was designed to record individuals with type 1 or type 2 diabetes diagnosed when less than 20 years of age. This study now provides information on the prevalence, the incidence of diabetes in young people as well as their demography and treatment. As an example of how registries can facilitate research, the SEARCH Study, in its wisdom, has an embedded longitudinal cohort to study the natural development and of the risk factors for acute and chronic diabetes-related complications, the quality of care and life of persons with diabetes from diagnosis to adulthood (28).

Locally, the Australasian Paediatric Endocrine Group (APEG) (29) collects information on young people aged less than 15 years who require insulin to treat their diabetes and

therefore the great majority of these people are likely to have Type 1 diabetes. This registry exists in every state of Australia and data are ascertained by contacting diabetes services, diabetes educators, general practitioners and specialists. The National Insulin-Treated Diabetes Register (30) is another registry maintained by the Australian Institute of Health and Welfare (AIHW) and captures information on people with T2DM, gestational diabetes and other forms of diabetes as long as they take insulin as part of their treatment. For this registry, the data are sourced from APEG as well as the National Diabetes Services Scheme (NDSS). NDSS is discussed later under administration databases.

It is evident that registries differ in their targets and their approach to case ascertainment; thus there will be variations in the capture rate of the total cohort in the community (31). They also differ in the additional data they may collect to assist research. In general, information gathered is relatively restricted to ensure the registration process is not cumbersome. This fact imposes several limitations on the utility of such registries as they lack the granularity regarding patient indices that add the necessary detail to add context to any observations. Further limitations may be imposed, as formal diagnostic criteria for diabetes type may not be available. Another limitation highlighted in a review of using registries to identify type 2 diabetes patients are the limited data linkage possibilities as personal records are often de-identified. Often and unlike the SEARCH study, the lack of systematic follow-up of registry patients limits the analyses to cross-sectional data only (32).

1.2.2 Audits and Surveys

Computerised information systems can be used to monitor various aspects of a population with diabetes. For example, in Australia for the last two decades, the

Australian National Diabetes Audit (ANDA) and its forerunner Australian National Diabetes Information Audit & Benchmarking (ANDIAB) have collected biennially, clinical diabetes data ascertained as a one month cross-sectional snapshot of selected patient populations. The participating centres are given instructions as to which de-identified data fields are required and in what format they are to be collected. Results are then forwarded to a central site for analysis. In so doing, the ANDA data provides a picture of the current status and time trends, which can be used by the Department of Health and other agencies. This is one of the few long-standing national data collections in Australia. The ANDA definitions are the first clinical diabetes definitions to be included in the National Health Data Dictionary. The dataset has since been enhanced and is now online as part of the AIHW – Metadata Online Registry ('METeOR') as the clinical Diabetes Data Set Specification (33). Collective data are reported to the Department of Health annually. For example in 2015, 48 diabetes centres and one private specialist provided de-identified data on 5183 patients (34). The ANDA data set is also utilised for benchmarking of diabetes performance measures for participant sites, and most recently these ANDA data has been utilised for diabetes research (35).

Internationally, other surveys include data on diabetes but are not specific for this condition. Examples of these are the National Health Interview Survey (NHIS) (36) and the National Health and Nutrition Examination Surveys (NHANES) (37). The NHIS is an ongoing nationwide cross-sectional survey of the health status and behaviours of Americans and conducted by the National Centre for Health Statistics and by the US Bureau of Census (38). The NHANES survey measures the health and nutritional status of both adults and children in the United States of America (39).

The accuracy, comprehensiveness and utility of information that can be extracted from such systems depend on the cooperation and in-house data collection system of the

feeder sites. Major limitations for research are similar to those for registry data; difficulty with data linkage given the de-identified nature of the collections and that only limited types of clinical data are collected to facilitate ease of collection.

1.2.3 Administrative Databases

Some computerised information systems are established by governmental agencies to facilitate and supervise the distribution of resources to assist in the treatment of diabetes. In Australia, the National Diabetes Services Scheme (NDSS) includes such an administrative database. The NDSS collects information on people with diabetes who join the scheme voluntarily so they can access subsidised consumables such as blood glucose testing strips, insulin needles and insulin infusion pump equipment. The database generated from this organisation can also be used to provide information on diabetes such as the number of individuals on insulin or the types of diabetes and many other items. Being a voluntary system encouraged by incentives, the completeness of enrolment would be higher in those favourably affected by the subsidies. This in itself may introduce an ascertainment bias, for example, only those who are willing to self-test blood glucose would be interested in registering for the NDSS strip subsidy, potentially excluding those who might not be testing, for example those treated with diet alone or arguably those with more limited adherence to self-care practices. Healthcare insurance companies have often established their digitised information systems to service their clientele and collect information on their health status and requirements including those pertaining to diabetes. A good example of this is Kaiser Permanente, a large health care organisation based in the USA, which has used its database to publish information on diabetes (40; 41). By definition, it would only include data on those who have health insurance, and thus, information such as treatment modalities

would be biased by in-house regulations of the company. It is noteworthy that the Australian universal health care provider (Medicare) collects information on the usage of individual patients on healthcare but not their disease status. Thus, the computerised information in Medicare systems cannot by itself provide useful information on diabetes. Further limitations may be introduced by the criteria for inclusion such as patients on diet alone who are underrepresented in a prescription database, and inaccuracy over the type of diabetes recorded; for example type 1 diabetes being recorded on the basis that treatment is with insulin and therefore may include insulin treated type 2 diabetes.

1.2.4 Clinical Databases and Electronic Medical Records:

Due to the large number of patients, increasingly healthcare facilities from primary, secondary care and some hospitals have developed in-house computer information systems to house eHRs, often termed electronic medical records (eMR) in this context. In general, the increased digitisation of information for use in health care settings over the last few years has become more prevalent particularly in hospitals where administrative and financial databases form the backbone of the day to day workload. These systems can identify and track the progress of individual patients with diabetes (42; 43). This was the primary original purpose and structure of the diabetes database at RPAH Diabetes Centre which provides the data used in this thesis. These in-house systems have the advantage that the format of data and its capture can be more easily standardised and more detail can be captured, overcoming some of the deficiencies encountered by the other data systems mentioned above. The granularity in terms of clinical detail captured by these datasets is often superior to the aforementioned forms of electronic health record. Diagnosis of acute and chronic conditions, prescription data, clinical monitoring metrics (blood tests, BP, health check data), as well as

demographic, family and lifestyle information (e.g. alcohol and smoking), may all be captured within. Other data on admissions, procedural codes and administrative data allow for more detailed cost analysis.

These data sets have the additional and important advantage, as they are often longstanding and therefore allow the progress of individual patients or types of patients to be tracked longitudinally. Furthermore, such detailed and sequential clinical data can be linked to external datasets to produce important and novel information. For example data linkage with databases such as ANZDATA (Australian and New Zealand Dialysis and transplant registry) and the Australian National Death Index potentially will allow for renal and mortality outcomes to be ascertained respectively. The use of data linkage with a clinical eHR form the basis of the studies presented in **Chapter 4 and** 5 of this thesis.

Independent and standalone systems such as the Diabetes Centre database at RPAH are challenged to keep up with the advances in database design; often their original creators have faded from the market leaving most of these products without support. Thus in parallel, web-based systems that are set up for collaboration with other institutions have been developed. As an example, the JADE program in Hong Kong has broadened this approach of “in house” database by making available a web-based interface allowing participation of other hospitals and centres in various countries to document patient profiles and care delivered at primary and specialist levels using the same standardised data (44-46). The BIOGRID system in Australia is also attempting to standardise data collection so that again many hospitals can jointly pool their data to give more numbers and more generalised representations using a data sharing platform. Currently, there are only 6 institutions that are using this system (47).

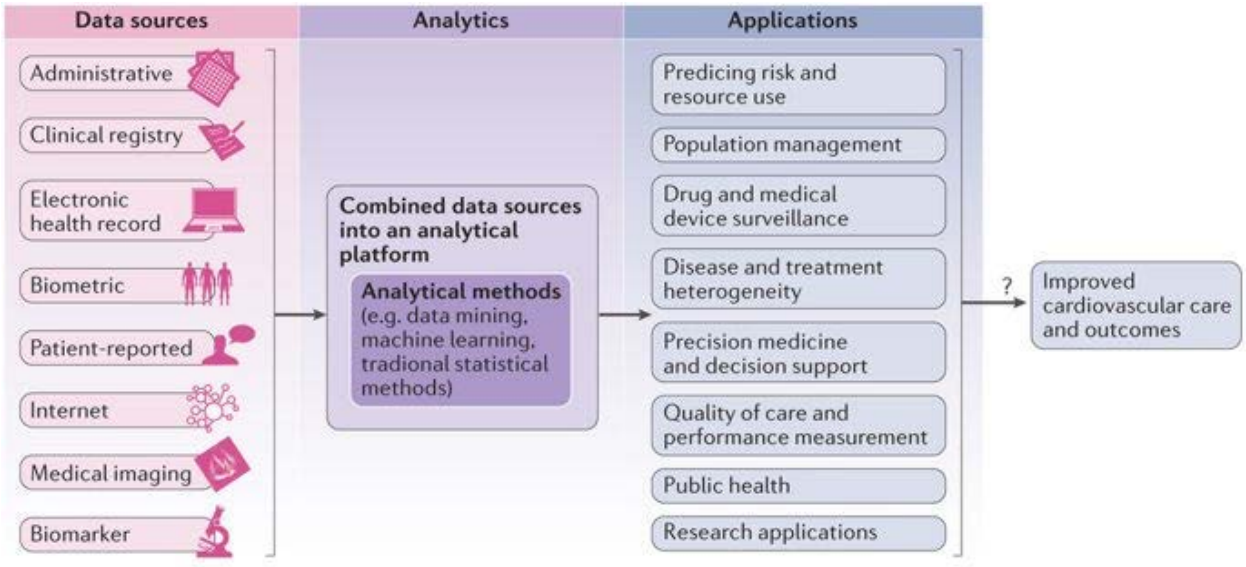
In practice, there are often difficulties in designing systems that cater to both clinical care as well as research. One of the main issues is that clinicians continue to prefer to document in free text in the eMR. Clinicians perceive that structured data would not allow them to express the problems and nuances of each case in an adequate manner. Nevertheless, the ability to data mine free text has increased with improvements in analytical tools. Largely to date, the eMR has been relatively underutilised as a research tool in diabetes, and its utility as a research tool is not widely recognised. Thus, the overriding focus of this thesis is to explore the utility of such an eHR to provide new knowledge in the diabetes arena.

1.2.5 Big Data

Health care organisations such as insurers and hospitals have used information systems for decades to collect data but these data usually only provided knowledge related to their subscribers or patients and mostly the data remains in silos. Following on from the increasing prevalence of eHRs, in recent years there has been a change in the data landscape with greater ascertainment and availability facilitated by a revolution in hardware technology allowing more efficient data storage at low cost. Furthermore international and national initiatives such as Obama Care (Health Information Technology for Economic and Clinical Health Act Of 2009 (48)) and the Australian National Digital Health Strategy 2016, have facilitated greater access. Thus, the amount of digital health data being collected that could inform patient outcomes and clinical decisions is potentially vast and has increased remarkably in recent times. Notably the amount of health care data availability in the USA has been cited to be approaching the zettabyte level (10^{21} bytes of data) (49). The utility of large data repositories termed "Big Data" have been used in business to improved efficiency and productivity.

Businesses such as Google have been using their expertise in cloud technology and data science to create partnerships with research teams to get better and more precise outcomes in research (50). The converging of this increasing data availability and the development of large data analytical systems have resulted in what has been termed the 'big data analytics' (BDA) era in healthcare. To date, there is no formally accepted definition of what constitutes big data however, it is often defined by the presence of the three v's ; volume, variety and velocity of data (49; 51). Volume is often in the order of at least 1 petabyte (10^{15} bytes) of data. Variety in big data comes from the combination of data from multiple sources including diverse data types (see Fig 2). The velocity of the analytical systems is essential for the data to provide meaningful results in a timely manner.

Figure 2: Overview of big data analytics and applications. From (49)



Data sources and analytical methods can be diverse and in theory, are unconstrained. In healthcare, these include eHR datasets such as administrative databases, clinical prescribing databases and pharmaceutical claims, clinical records and registries (52). Datasets can also include biometric data, imaging data from wearable technologies and even social media use. Modern analytical platforms and computational capacity are

available as open source frameworks with a view to true democratisation of the technology of BDA.

In terms of analytical frameworks, in general, analysis is correlative and focuses on identifying patterns in complex data although traditional statistical methodology are also applied. The expectations are that big data will allow predictive modelling to identify high risk or high-cost patterns, facilitate population management and case finding, allow drug and medical device surveillance utilising eHR data and clinical registries to identify disease treatment heterogeneity. In terms of prescriptive analytics, the applicability to integrate omics platforms and integrate the systems biology approach with hard outcomes holds great promise.

Despite the potential, the challenges in utilising Big Data are many and have yet to translate into major advances for diabetes care specifically. The evidence base at the moment for benefit is still in its infancy. There are significant issues of data quality and data inconsistency to be overcome for this tool to have true impact. Data are still observational and subject to unmeasured bias as all observational studies are prone. Furthermore, the problem of missing data and imputation methodology at scale may impact the conclusions drawn. Then there are the additional challenges of patient privacy, consent, data security and other legal considerations. It would be reasonable to say that the promise of big data has yet to be realised in the field of diabetes.

1.3 Knowledge Gaps and The Utility of The Routinely Collected eHR

In summary, in the context of an increasing prevalence of diabetes and a need to further examine the heterogeneous disease that is type 2 diabetes, there are great opportunities provided by the growing adoption of eHR systems in healthcare to further

diabetes research. This is especially attractive given the cost and other limitations defined by the traditional gold standard approaches to inform clinical decision making such as the RCT. As mentioned, the promise of Big Data has yet to be realised for diabetes, and the utility of administrative databases, disease registries and the like are limited in the data they capture. It is the routinely collected clinical electronic medical record that, often overlooked, still holds great promise as a research tool. Specifically, the detailed patient data contained in the eHR has the potential to answer many different types of questions in diabetes (53). Disparate questions that would inform patient care, such as "are the risks for complications similar for different subgroups of diabetes patients?" to "can the electronic health record be used to inform public health measures and identify gaps in patient care?" could be potentially explored with this facility. That said, the utility of the routinely collected eHR as a research tool, given its relatively recent advent has not been greatly explored in diabetes. Thus, the studies undertaken in this thesis examine the overarching issue of the research utility of smaller datasets such as the routinely collected eHR from a single site in this context. The studies presented in this thesis leverage the advantage of access to data housed in a long established clinical eHR provided by the RPA Diabetes Centre. The RPAH Diabetes Centre were early adopters of the eHR and this dataset houses clinical information from over 30,000 patients collected over a greater than 20 year period. This is expanded on further in **Chapter 2**. The data have been collected in a standardised way which allows the full research potential of such an eMR from a single centre to be studied. If utility is proven, this would have significant implications given that worldwide implementation of the eHR is a recent phenomenon with as yet un-harnessed potential. So in addition to the promise of Big Data, if these smaller databases, all developed primarily for the management of our patients in medical

settings could be utilised to also provide data for meaningful research, this will have implications ongoing for diabetes care. Specifically, data managers and clinicians alike would be encouraged to design systems that in addition to routine patient care, facilitate data that can advance the field. This concept is a primary theme that underpins the studies presented herein.

Part II: General Aspects of Diabetes

1.4 The Global Burden of Diabetes

Diabetes Mellitus used to be considered a disease of affluent societies alone. This is no longer the case with 1 in 11 adults diagnosed with diabetes and an estimated total of 425 million people living with the disease globally, with the largest growth in developing countries (54). Globally, diabetes prevalence is projected to continue to increase, and thus diabetes is considered a priority non-communicable disease (NCD) for the World Health Organisation (WHO). NCD are chronic conditions that are not caused by infectious agents but may result from a combination of genetic, physiological, environmental and behavioural factors (55). These include apart from diabetes, cardiovascular diseases, cancer, and chronic respiratory diseases. Factors identified as having an impact on the development of these diseases are rapid urbanisation, unhealthy diets and lack of physical activity. These in turn are associated with raised blood pressure, increased blood glucose and lipids creating a milieu of metabolic risk. Diabetes is now responsible for 12% of global health expenditure ($727 billion) and this is projected to increase in line with prevalence (54). Moreover, diabetes is now the leading NCD in terms of causing premature death. The IDF states that diabetes is responsible for 10.7% of all-cause mortality and this is higher than the combined percentage of deaths from HIV/AIDs, tuberculosis and malaria (7).

1.5 Diagnosis of Diabetes and Pre Diabetes

The diagnosis of diabetes can be made on a number of tests of hyperglycaemia, either fasting plasma glucose, the 2-hour plasma glucose following a 75gm glucose load, random plasma glucose or by way of glycated haemoglobin (HbA1c).

This framework of systematically classifying hyperglycaemia thresholds as diabetes was first developed by the National Diabetes Data Group (NDDG) in 1979. This classification was endorsed by the World Health Organisation (WHO). In June 1997 an International Expert Committee released a report with revised recommendations for the classification and diagnosis of diabetes mellitus using data from epidemiologic studies that measured blood glucose levels and quantified retinopathy (56). These studies identified a point at which the levels of fasting and 2 hours glucose correlated with the prevalence of retinopathy increased linearly. This standardised framework for the diagnosis of diabetes has proven to be of great importance in epidemiological studies as it provides a uniform platform across many countries and different health systems, hence making the results comparable and relevant.

A fasting blood glucose level to determine the diagnosis of diabetes should be collected in the morning, after an overnight fast of at least 8 hours. To collect the 2 hour plasma glucose, an oral glucose tolerance test must be undertaken as prescribed by the WHO (57). This involves the consumption of 75 g of anhydrous glucose dissolved in water. In asymptomatic individuals, a second test in the diabetes range, taken on another day is required to confirm the diagnosis of diabetes. In patients who present with symptoms of diabetes (polyuria, polydipsia and unexplained weight loss) a single random blood glucose (that is a test carried out at any time of the day) ≥11.1 mmol/L (≥200mg/dl) is diagnostic of the disease.

An Expert Committee determination for the inclusion of HbA1c for diagnostic purposes was presented in 2009. The rationale for its inclusion was the poor reproducibility of the OGTT and the variance in the measurement of plasma glucose. The HbA1c test represents a weighted measure of glycaemia over the last 2-3 months and prior to 2009 was used to assess glycaemic control only in already diagnosed patients. Until recently the assay had not been standardised until the development of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference methodology allowing the standardisation and unified reporting of HbA1c in universal units (mmol/mol) (58; 59). This development paved the way for its use as a standalone diagnostic test for diabetes. The threshold determined for the diagnosis of diabetes using HbA1c is 6.5% (≥48 mmol/mol). It is above this measurement that the prevalence of retinopathy increases (56; 60). The caveats for its use include conditions affecting the red blood cell (RBC) turnover. HbA1c is not recommended to diagnose gestational diabetes nor type 1 diabetes.

The Australian Diabetes Society (ADS) current criteria for the diagnosis of diabetes in Australia are:

- HbA1c ≥6.5% (48 mmol/mol)
- Fasting glucose ≥7.0 mmol/L (≥ 126ml/dL)
- Random glucose ≥11.1 mmol/L (>200m/dl)
- 75 g oral glucose tolerance test: fasting glucose ≥7.0 mmol/L or 2 hr glucose ≥11.1 mmol/L

In an asymptomatic patient, the test should be repeated for the confirmation of the result and diagnosis. An abnormal result on 2 different diagnostic tests is also acceptable (61).

These criteria are in line with international societies such as the American Diabetes Association(62) and the World Health Organisation. Currently, the guidelines for testing are the same for adults as well as for children and adolescents. Studies have questioned the validity of HbA1C in paediatric populations and suggest that the oral glucose tolerance test or a fasting plasma glucose are more accurate, although there is no validation in paediatric populations for any of the tests (63; 64).

1.5.1 Prediabetes

This condition describes elevated blood glucose ranges but which are below that for diabetes. The condition is further split into those with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Management of prediabetes is largely by lifestyle measures although some studies have shown the benefit of pharmacological agents (65-71). IFG is diagnosed if fasting plasma glucose is 6.1-6.9mmol/l; IGT is the 2 hr plasma glucose is ≥ 7.8-11.1 mmol/L following a 75g 2hr OGTT. Prediabetes infers a higher risk of diabetes and an increased CVD risk. Confusingly, the ADA reduced the IFG diagnostic threshold from ≥ 6.1 mmol/L to ≥ 5.6 mmol/l, but this has not been widely accepted internationally. Neither is there a widely accepted HbA1c threshold for prediabetes. Specific recommendations for screening in children and adolescents are discussed in **Part III**.

1.6 Types of Diabetes

Traditionally, diabetes has been classified broadly into two main groups, type 1 and type 2 diabetes mellitus. However, of importance and relevant to the theme of this thesis, the clinical criteria that have been used to distinguish diabetes type in the past (age of onset, weight and insulin therapy requirement at diagnosis) have blurred

considerably in recent times. Furthermore, several more 'types' of diabetes have now been added to an aetiological classification of diabetes given that specific genetic defects have been identified as well as diabetes associated with other endocrinopathies, medications and other immune disorders. Table 1 is taken from American Diabetes Association position statement of 2014 (72) and shows the current understanding of the different subtypes of diabetes and underscores the complexity for physicians now in establishing the correct subtype of diabetes.

In the following, the main subtypes of diabetes mellitus are discussed briefly. As one of the specific aims in this thesis focuses on age of onset of type 2 diabetes, type 2 is discussed more fully here, and youth onset type 2 diabetes will be discussed separately in **Part III**.

Table 1: Etiologic Classification of Diabetes Mellitus. Adapted from the American Diabetes Association; From (72)

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
   A. Immune mediated
   B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

III. Other specific types
   A. Genetic defects of β-cell function
      1. MODY 3 (Chromosome 12, HNF-1α)
      2. MODY 1 (Chromosome 20, HNF-4α)
      3. MODY 2 (Chromosome 7, glucokinase)
      4. Other very rare forms of MODY (e.g., MODY 4: Chromosome 13, insulin promoter factor-1; MODY 6: Chromosome 2, *NeuroD1;* MODY 7: Chromosome 9, carboxyl ester lipase)
      5. Transient neonatal diabetes (most commonly ZAC/HYAMI imprinting defect on 6q24)
      6. Permanent neonatal diabetes (most commonly KCNJ11 gene encoding Kir6.2 subunit of β-cell K_{ATP} channel)
      7. Mitochondrial DNA
      8. Others
   B. Genetic defects in insulin action
      1. Type A insulin resistance
      2. Leprechaunism
      3. Rabson-Mendenhall syndrome
      4. Lipoatrophic diabetes
      5. Others
   C. Diseases of the exocrine pancreas
      1. Pancreatitis
      2. Trauma/pancreatectomy
      3. Neoplasia
      4. Cystic fibrosis
      5. Hemochromatosis
      6. Fibrocalculous pancreatopathy
      7. Others
   D. Endocrinopathies
      1. Acromegaly
      2. Cushing's syndrome
      3. Glucagonoma
      4. Pheochromocytoma
      5. Hyperthyroidism
      6. Somatostatinoma
      7. Aldosteronoma
      8. Others
   E. Drug or chemical induced
      1. Vacor
      2. Pentamidine
      3. Nicotinic acid
      4. Glucocorticoids
      5. Thyroid hormone
      6. Diazoxide
      7. β-Adrenergic agonists
      8. Thiazides
      9. Dilantin
      10. γ-Interferon
      11. Others
   F. Infections
      1. Congenital rubella
      2. Cytomegalovirus
      3. Others
   G. Uncommon forms of immune-mediated diabetes
      1. Stiff-man syndrome
      2. Anti-insulin receptor antibodies
      3. Others
   H. Other genetic syndromes sometimes associated with diabetes
      1. Down syndrome
      2. Klinefelter syndrome
      3. Turner syndrome
      4. Wolfram syndrome
      5. Friedreich ataxia
      6. Huntington chorea
      7. Laurence-Moon-Biedl syndrome
      8. Myotonic dystrophy
      9. Porphyria
      10. Prader-Willi syndrome
      11. Others

IV. Gestational diabetes mellitus

Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

1.6.1 Type 1 Diabetes

Type 1 diabetes accounts for 5-10% of all diabetes and is an autoimmune disease. It is characterised by the immune destruction of pancreatic beta cells resulting ultimately in a failure of endogenous insulin production, leading to ketoacidosis if exogenous insulin is not administered. This type of diabetes can affect any age group, but its classical age of onset is in childhood or young adults. The rate of beta cell loss is typically more fulminant in younger onset type 1 diabetes.

With respect to pathophysiology, there is a genetic component to the development of type 1 diabetes, although genetic influences are less than for type 2 diabetes. Type 1 diabetes is considered to be a polygenetic condition, with many genes of small effect size contributing to disease susceptibility. The risk of developing type 1 diabetes is ~5% if a parent is affected and higher if paternally inherited (73). Gene variants in the major histocompatibility locus human leukocyte antigen (HLA) contribute 50-60% to the variance, i.e. most of the genetic risk in type 1 diabetes and do so by modulating antigen presentation to immune cells. There are ~50 additional gene loci also implicated in type 1 diabetes.

Environmental influences also contribute to the development of type 1 diabetes (74; 75). The importance of environmental influences is evidenced by discordant diabetes rates in genetically identical twins and the regional variations in prevalence. The current paradigm for the pathogenesis of type 1 diabetes is for an environmental trigger or triggers acting in the context of an at-risk genetic background, culminating in the T cell mediated autoimmune destruction of beta cells. Some putative environmental triggers are enterovirus and other infections, the gut microbiome composition and dietary composition including gluten, milk proteins and cereal triggers (76; 77).

Temporally the autoimmune destruction of beta cells occurs well before the onset of clinical diabetes. Abnormal insulin secretion has been found at least 2 years before diabetes diagnosis and the decline in secretion accelerates proximate to clinically evident hyperglycaemia. Furthermore, there is a decline in the beta cell sensitivity to glucose following the same trajectory (78-81). There is further decline in insulin secretion, post-diagnosis, which is more rapid in younger patients.

In type 1 diabetes, circulating antibodies against insulin, glutamic acid decarboxylase (GAD) and protein tyrosine phosphatase (IA2) and Zinc transporter 8 (ZnT8), all markers of beta cell autoimmunity, can be detected in the early stages and even before the onset of clinical disease. The presence of two or more such antibodies in the context of either the presence of HLA risk alleles or a relative with type1 diabetes is associated with a 75% risk of developing type 1 diabetes within 10 years. Risk increases with increasing numbers of autoantibodies. The progression of type 1 diabetes can now be staged based on the presence of autoantibodies and symptoms as outlined in Table 2 below (73). Nevertheless, despite being able to stage type 1 diabetes and prognosticate, there are to date no successful therapeutic strategies that can prevent or reverse type 1diabetes.

From a clinical utility perspective, the presence of islet cell antibodies (GAD ab, IA2ab and ZnT8ab) can be used in diagnostic phenotyping, and their strong presence identifies an autoimmune basis for diabetes suggesting type 1 diabetes in terms of the etiological classification. Furthermore, plasma c-peptide is often low or undetectable in type 1 diabetes.

Table 2: Staging of type 1 diabetes – From (73)

Table 1—Staging of type 1 diabetes

	Stage 1	Stage 2	Stage 3
Phenotypic characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New onset • Hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No impaired glucose tolerance or impaired fasting glucose	• Multiple autoantibodies • Dysglycemia: impaired fasting glucose and/or impaired glucose tolerance • Fasting plasma glucose 100–125 mg/dL • 2-h glasma glucose 140–199 mg/dL • HbA_{1c} 5.7–6.4% or ≥10% increase in HbA_{1c}	• Clinical symptoms • Diabetes by standard criteria

1.6.2 Gestational Diabetes

Gestational diabetes mellitus (GDM) has been defined as hyperglycaemia first discovered during pregnancy. Over time, the definition of GDM and diagnostic criteria have changed. The landmark Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study demonstrated the linear association of fasting, I hr and 2hr post load diabetes and adverse foetal outcomes such as birthweight > 90th central, cord blood c-peptide primary caesarean section and neonatal hypoglycaemia (82; 83). Two other landmark studies, the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and a Multicentre Randomized Trial of Treatment for Mild Gestational Diabetes (84; 85) demonstrated efficacy in terms of reducing glycaemia and subsequently reducing poorer pregnancy outcomes. Following on from this evidence base, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) proposed new diagnostic criteria which have been supported by the WHO and taken on by most but not all expert bodies to date (86; 87). Furthermore, the category of more severe hyperglycaemia in pregnancy that would be consistent with diabetes outside of pregnancy is now termed ‘Diabetes in Pregnancy” or DIP and separate from GDM. DIP constitutes a higher risk group.

GDM is managed with controlled carbohydrate and caloric intake, gentle exercise and blood glucose monitoring. If these methods are not sufficient to control blood glucose, then insulin is used. Alternatively, the use of metformin has been an option with proven efficacy (88), and although sulfonylureas have been used, these agents have recently been shown to have unwanted sequelae (89; 90). Regarding the longer term outcomes of GDM, the developmental origins of human disease including gestational diabetes are increasingly recognised. These mothers have a higher risk of developing diabetes in later pregnancies and in later life, their offspring appear to be at higher risk of obesity and consequently developing diabetes as teenagers and young adults. This is relevant and discussed in **Part III**.

1.6.3 Maturity Onset Diabetes of the Young (MODY)

Maturity onset diabetes of the young (MODY) is a subtype of diabetes that results from a mutation in a single gene. It is part of the wider etiological group referred to as monogenic diabetes which represents <5% of all diabetes cases. Largely, the gene mutations involve genes that regulate beta-cell function and in rare instances insulin resistance.

Historically MODY was identified by characteristics such as diabetes diagnosed at less than 25 years of age and an autosomal dominant pattern of inheritance. The single abnormal gene causing diabetes resides on one of the 22 autosomal (non sex) chromosomes from either parent with a typical inheritance pattern of 50% affected offspring (91; 92). Thus, children of an affected parent with MODY have a 50% chance of inheriting the affected gene and developing MODY themselves.

The three most common MODY subtypes are mutations of i) *hepatocyte nuclear factor 1 alpha* (*HNF1α*, MODY3), which accounts for up to 61% of MODY cases in the United Kingdom ii) *Glucokinase* (*GCK*, MODY2) has been found to account for 22% of MODY and iii) hepatocyte nuclear factor 4 alpha *HNF4α* (MODY1) being rarer and accounting for ~4% of MODY (93).

Table 3: The table from Bishey *et al.* (94) gives a snapshot of the genetic and key clinical features common in the most prevalent types of diabetes.

2 Prevalence, genetic and key clinical features of the common forms of diabetes and subtypes of maturity onset diabetes of the young (MODY)

	Type 2 diabetes	Type 1 diabetes	Gestational diabetes	MODY1	MODY2	MODY3
Prevalence	1 in 13 people (~ 870 000 in Australia)	10% of all diabetes (~ 170 000 in Australia)	5–10% of all pregnancies	~ 5%*	10–60%*	20–50%*
Causative mutation	Multiple polymorphisms (eg, class II *HLA* genes)	Multiple polymorphisms	Multiple polymorphisms	*HNF4A*[7,8]	*GCK*[2]	*HNF1A*[10]
Clinical features	Older (usually > 45 years), overweight or obese, often family history, insulin resistance	Slim, family history of autoimmune disorders, usually childhood or early adolescence or adulthood (includes LADA)	Older (> 40 years); pre-pregnancy obesity (BMI, > 30 kg/m^2); family history (30%) and ethnicity; previous GDM; PCOS; macrosomic babies, diagnosed 24–28 weeks' gestation	Young age (< 25 years), strong family history of diabetes, absent antibodies, detectable C-peptide		
Diagnostic glucose and HbA_{1c}	75 g OGTT: fasting BGL, ≥ 7 mmol/L; random or 2-h postprandial BGL, ≥ 11.1 mmol/L; HbA_{1c}, ≥ 6.5% (48 mmol/mol)	Similar to type 2 diabetes	75 g OGTT: fasting BGL, 5.1–6.9 mmol/L; 1-h, ≥ 10 mmol/L; 2-h, 8.5–11 mmol/L[11]	As with type 2 diabetes; postprandial glucose excursions, ≥ 5 mmol/L	Fasting BGL, 5.4–8.3 mmol/L; postprandial glucose excursions, ≤ 3 mmol/L, HbA_{1c}, 5.8–7.6% (40–60 mmol/mol)	As for MODY1
Treatment	Diet, exercise, OHG, injectable GLP1 RA, insulin	Insulin	Diet, exercise, metformin, insulin	Respond to sulfonylureas, 30–40% apparent insulin-requiring	None required (controversial)	As for MODY1
Special features	Progressive β-cell dysfunction with development of micro- and macrovascular complications	Negative C-peptide and DKA without insulin (outside of honeymoon period), positive antibodies in majority to GAD, IA-2, ICA, IAA and ZnT8	Hyperglycaemia remits postpartum	Glycosuria common; develop micro- and macrovascular complications as in type 1 and 2 diabetes	Favourable lipid profile; lean; minimal or no micro- or macrovascular complications; minimal effect of treatment on glycaemic control	As for MODY1; strong family history of macrosomic babies

* Denotes approximate percentage prevalence of all MODY subtypes. DKA = diabetic ketoacidosis. GAD = glutamic decarboxylase autoantibody. *GCK* = glucokinase gene. GDM = gestational diabetes mellitus. GLP1 RA = glucagon-like peptide 1 receptor agonists. HLA = human leukocyte antigen. HNF1A = hepatocyte nuclear factor 1α gene. *HNF4A* = hepatocyte nuclear factor 4α gene. IA-2 = insulinoma-associated-2 autoantibody. IAA = insulin autoantibody. ICA = islet cell cytoplasmic autoantibody. LADA = latent

Table 3 taken from (94) gives a snapshot of the genetic and key clinical features common in the most prevalent types of diabetes. These features will allow differentiation between young onset type 2 diabetes and MODY, acknowledging that clinically the differences may be challenging without genetic analysis. In the past given reduced awareness and lack of genetic testing, MODY diabetes has often been misdiagnosed as either type 1 or type 2 diabetes.

1.6.4 Mitochondrial Diabetes

Diabetes is a common feature of mitochondrial disease. Specifically, and most commonly, mitochondrial diabetes arises from a specific mutation in the mitochondrial genome, 3243A >G. Mitochondrial DNA is maternally inherited, and this pattern of inheritance is an important distinguishing feature. Mitochondrial diabetes can present in youth and should be differentiated from both type 2 diabetes and type 1 diabetes. The occurrence of deafness, retinal changes, myopathy and lactic acidosis may be other indicators of mitochondrial disease. It should be noted that the severity of the clinical phenotype is determined by heteroplasmy (the amount and presence of abnormal mtDNA) which defines the burden of abnormal mitochondrial in any given cell. Thus, a high index of suspicion should be maintained as other organ effects may not be immediately obvious (95; 96).

Diabetes presenting in younger patients can also be part of clinical syndromes such as Laurence-Moon-Biedl syndrome and other endocrinopathies. These are not discussed here further but are usually clinically evident at diagnosis and are rare (Table 1).

1.7 Overview of Type 2 Diabetes Mellitus

1.7.1 Type 2 Diabetes

Type 2 diabetes is the most common type of diabetes but that said, it is a diagnosis of exclusion. Type 2 diabetes has famously been described as “a disease in search of a definition” and notably the esteemed diabetologist Edwin Gale (97) writes “*It has no hallmark clinical features, is generally diagnosed by default (no other cause for diabetes being evident), has very heterogeneous pathophysiological features, and varies widely*

between populations in clinical presentation and consequences. Despite this obvious heterogeneity, laboratory and clinical research is typically done as if type 2 diabetes were one disease entity with uniform characteristics, thus assuming standard causal mechanisms and universal treatment pathways". Nevertheless, type 2 diabetes is thought to arise from a combination of insulin resistance and inadequate insulin secretion. The pathophysiology is discussed more fully later. Type 2 diabetes predominantly affects adults but is increasingly being diagnosed in children and adolescents paralleling a rise in childhood obesity. Youth onset type 2 diabetes is described more fully in **Part III**.

As individuals with type 2 diabetes can still produce some insulin (albeit not of the best quality and produced in a dysregulated way), the disease can remain undiagnosed for many years. Nevertheless, the high glucose levels damage tissue cells, hence many patients at diagnosis already have microvascular complications (retinopathy, nephropathy and neuropathy) and macrovascular disease (coronary artery disease, peripheral arterial disease, and stroke). Type 2 diabetes is the most predominant form of diabetes, and in developing countries, it affects ~90% of people with diabetes, and although considered in the past a disease of the wealthy, it has had an exponential increase due to excess body weight, physical inactivity and poor nutrition widespread in the community. Other factors which play a role are ethnicity, family history of diabetes, obesity, past history of gestational diabetes and advancing age. Risk factors type 2 diabetes will be discussed more fully in **section 2.0.**

In the presence of diabetes, damage to the body tissues resulting from hyperglycaemia and other metabolic disturbances can lead to diabetes complications involving many organs with serious medico-economic consequences for both the individuals and the

community. The impact of diabetes on individual organs will be discussed later in this review.

In T2DM there is a gradual decline in beta cell function, and hyperglycaemia is present prior to the diagnosis of diabetes. A usual pathway would be moving through a diagnosis of pre-diabetes, which encompass two conditions, impaired fasting glucose (IGF) or impaired glucose tolerance (IGT) leading eventually to the full diagnosis of T2DM. This progressive process can take from 5 to 10 years to occur (98; 99) in the older patient with type 2 DM but in YT2DM is much shorter. D'Adamo *et al*. suggested an accelerated process in the paediatric population compared with adults (100), especially in the setting of obesity. Notably at the prediabetes stage, prevention studies in adult populations have shown success for diet and lifestyle and metformin (101-106). Other pharmacotherapies shown to prevent diabetes are acarbose (107), glargine (69) and rosiglitazone (108) but not Ramipril (68; 109).

1.8 Prevalence of Type 2 Diabetes in Australia

The Australian Bureau of Statistics (ABS) estimated the Australian population to be 24,127,200 people on the 30 June 2016 (110). Currently, there is not a single national data source to provide definitive prevalence data for diabetes in Australia. The following estimates come from various data sources. One of the latest estimates of diabetes prevalence was obtained from the National Health Survey (NHS) 2014-2015 conducted by the ABS (111). It is estimated that more than 1.2 million people aged 2 years and over have some form of diabetes in Australia, representing 5.1% of the population. The NHS relies on self-reported data; it asks the participants if they have ever been told by a health professional if they have diabetes, irrespective of whether

the person considered their diabetes to be current or long-term. By this methodology, type 2 diabetes in 2014-15 affected one million people (4.4% of the population overall, representing ~85% of the population with diabetes) whilst in the 2011-12 survey this number was 3.8%. These results are likely an underestimate given the nature of the data collection and the lack of biochemical testing (111), but even using these crude measures there is evidence for an increase in self-reporting of this condition.

There are three other national sources of information to estimate the prevalence of diabetes in Australia that importantly incorporate some biochemical measure of glucose tolerance. These are as follows:

1. The National Diabetes Services Scheme (NDSS) is a government funded national scheme that provides subsidised consumables for self-monitoring of blood glucose strips, insulin needles and insulin pump consumables. Using this administration database, there were 1,273,917 people (5.3% of the Australian population) (110) with diagnosed diabetes registered with this service at the 31/12/2017 (112); 1,108,301 people were reported with type 2 diabetes, representing 87% of the total sample which is in accordance with the NHS 2014-2015 estimates above. Of note, regarding this population sample, registration with the NDSS is voluntary, therefore there may be a subgroup of the population who have never registered as they did not perceive that this would be of benefit to them, i.e. they are not performing home blood glucose monitoring or requiring insulin, or they may have an individual objection to organisations having their name in this register. Again the implication here is that the NDSS data may also underestimate the true population prevalence.

2. The National Health Measures Survey 2011–13 (113) is considered the largest and most comprehensive health survey ever conducted in Australia and for the first time in

2011-13 included blood and urine samples from over 11,000 participants as well as health status, risk factors, health service usage and medications. Using two tests, fasting blood glucose and HbA1c (glycated haemoglobin ≥6.5% as the diagnostic criteria for diabetes) it found that 5.1% of the population over the age of 18 had diabetes, of these 0.9% were new cases and that men were more likely than women to have diabetes (6.3% vs 3.9%). The survey cut-offs used for each test to determine whether a person has diabetes or is at high risk of diabetes are shown in Table 4. Using these criteria, 3.1% of all surveyed were identified at high risk of developing diabetes. Oral glucose tolerance tests were not used for diabetes diagnosis in this study. So those with milder degrees of hyperglycaemia or conditions confounding the use of HbA1c that would otherwise be diagnosed as diabetes could have been missed. Please also note that the formal diagnostic type of diabetes are not reported in this study.

Table 4: Adapted from Australian Health Survey: Biomedical Results for Chronic Diseases, 2011-12 (55)

Cut-offs for Diabetes in the NHMS

	Fasting plasma glucose (mmol/L)(a)	HbA1c (%)(b)
Has diabetes	≥7.0	≥6.5
At high risk of diabetes	6.1 to <7.0	6.0 to <6.5
No diabetes	<6.1	<6.0

(a) Based on World Health Organization cut-offs for fasting plasma glucose.[3]
(b) An HbA1c level of greater than or equal to 6.5% is the WHO recommended cut-off point for diabetes.[4]

3 The Australian Diabetes, Obesity and Lifestyle study (AusDiab) (114) was conducted between 1999-2000 and for the first time used an oral glucose tolerance test (OGTT) considered the gold standard test to diagnose diabetes. The study included 11,247 adults (aged 25 years and above), and it estimated the prevalence of diabetes at 7.5%, numbers higher than the NDSS. Unfortunately, the authors of AusDiab did not report

the prevalence of type 2 and type 1 separately in their data. They state that the vast majority was classified as type 2.

The different sources of information described above rely on disparate methodologies such as self-reporting, non-mandatory registrations, HbA1c measurements only or using the gold standard method of the oral glucose tolerance test. Combining these measures one can estimate the prevalence of diabetes in Australia to be between 5.1% and 7.5% of the population and the prevalence of type 2 diabetes between 4.2% and 4.6 %.

1.8.1 Indigenous, Ethnic Specific and Migrant Population Prevalence of Diabetes in Australia

The above estimates are for the total Australian population; however, Australia is a multi-ethnic and multicultural society with migrants from high-risk ethnic groups, which is relevant for diabetes risk. Knowing the prevalence rates in our migrant communities and our own indigenous populations would be important; 28.5% of the estimated resident population was born overseas, or 6.9 million persons (115) and 686,800 people or 3% of the total Australian population identifies itself as Aboriginal and Torres Strait Islander in 2014 (116). Figure 3 shows the rise in the overseas born population in Australia over the years (115). Perhaps due to Australian immigration policies over the last few decades, 46% of Australians have at least one parent born overseas. Earlier migrants came predominantly from the United Kingdom, and UK migrants now account for 5.0% of Australia's total population as of the 30th of June 2016. Subsequent to this, migration from the eastern and southern European countries followed and then migration from the Middle East and Asia. Specifically, the ABS (115) notes that the number of migrants from Nepal, Pakistan, Brazil, India and Bangladesh have had the

highest rate of increase from 2006 to 2016. There have been progressively higher numbers of migrants from African countries in recent years and being geographically proximate, the Pacific Islands have also been a major source of migrants in the recent decade. Figure 4 shows the top 10 country of origin for overseas born people in Australia and the growth or decline of these groups of migrants in the years of 2006, 2011 and 2016.

Figure 3: Source Migration, Australia (cat. no. 3412.0)

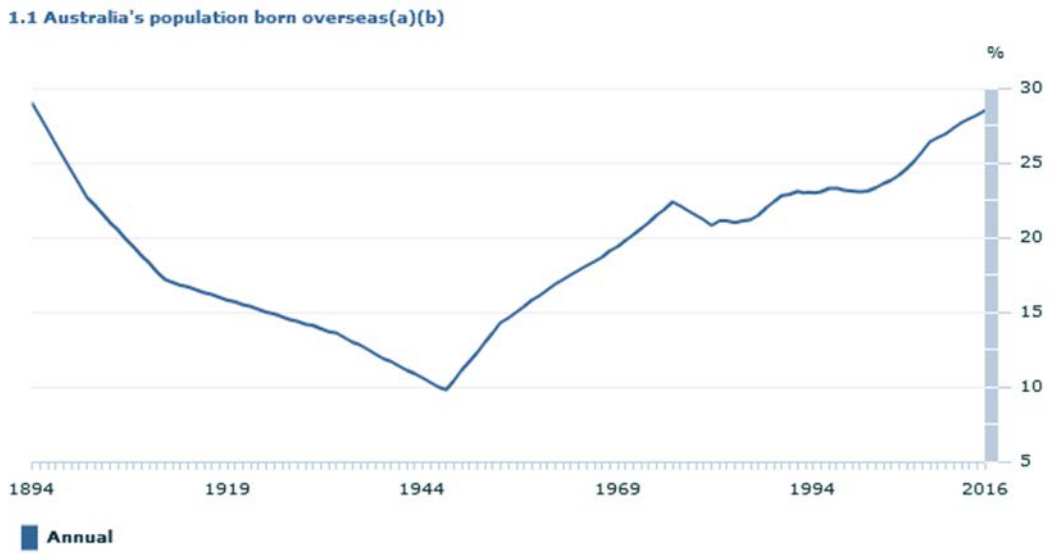
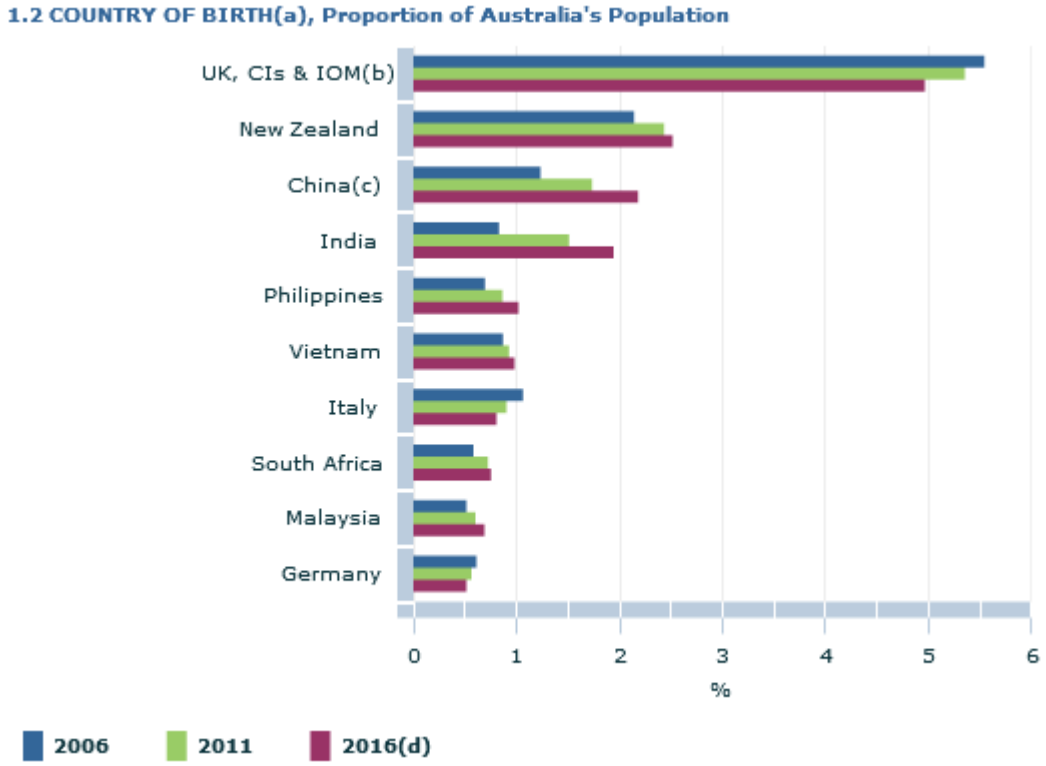


Figure 4: Top 10 country of origin for overseas born people in Australia and their growth or decline over 3 different years. Source: Migration, Australia (cat. no. 3412.0) (51)



The relevance is that diverse migrant groups are likely to be characterised by a differing susceptibility to diabetes and even different clinical manifestations of diabetes. Minority groups in Australia come from areas of the world with a high prevalence of type 2 diabetes signalling an ethnic specific increase in risk.

Additionally, the age structure of migrants also impacts on population risk for diabetes. For example, the ethnicities of the oldest migrant groups are shown in Table 5. It is likely that the ethnicities with a higher prevalence of older migrants have a higher prevalence of diabetes with perhaps a longer duration of pre-existing diabetes. Migrant and ethnic specific comparative data with respect to diabetes are discussed below.

Table 5: Oldest and youngest migrant groups, 2015 Source: The demographer's Christmas: countdown to the census: (117; 118)

Oldest and youngest migrant groups in Australia, 2015

Oldest	Country of birth	Median Age	Youngest	Country of birth	Median Age
1	Latvia	75.5	1	UAE	17.3
2	Slovenia	70.3	2	Saudi Arabia	24.6
3	Greece	70.3	3	Congo, Dem Rep	25.8
4	Italy	69.3	4	Nepal	28.7
5	Malta	67.6	5	South Sudan	29.9
6	Austria	67.4	6	Taiwan	30.3
7	Netherlands	66.7	7	Pakistan	30.5
8	Hungary	66.7	8	Sierra Leone	30.7
9	Germany	63.7	9	Estonia	30.8
10	Cyprus	63.3	10	Sudan	30.9

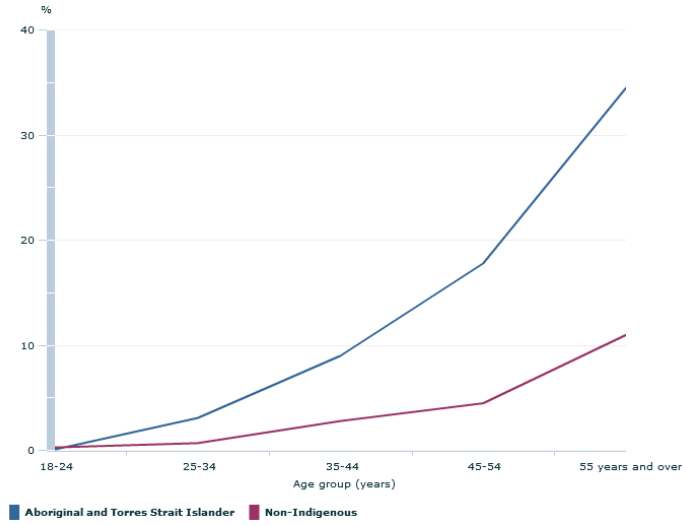
Source: KPMG Demographics based on ABS cat. 3412.0

Of note is that 686,800 people or 3% of the Australian population in 2014 identified itself as Aboriginal and Torres Strait Islander (116) and there is a relative dearth of data for this indigenous Australian group. However, all information available, when compared with the general population, shows that they carry a disproportional burden of diseases, including diabetes.

In 2014 the National Aboriginal and Torres Strait Islander Social Survey (NATSISS), 2014-15 (119) found that almost half of this indigenous group were under the age of 20 years. Importantly in this survey, the authors found the prevalence of diabetes to be 12.8%, much higher than the Australian average with most diabetes being type 2 diabetes in origin. However, the authors do acknowledge that their methodology was not robust enough to provide secure prevalence data. They recommend 2012-13 National Aboriginal and Torres Strait Islander Health Survey (*NATSIHS)* (119; 120) data for this purpose. NATSIHS 2012-2013 is the largest biomedical survey conducted in Indigenous Australians and surveyed 3300 individuals over 18 years of age. It reported a prevalence of diabetes in this population of 11.1%, with a range of 9.4% in major cities and regional areas and 20.8% in remote areas. After adjusting for age differences, Aboriginal and Torres Strait Islander people were three times as likely as

non-Indigenous people to have diabetes. This survey noted that the age pattern for the prevalence of diabetes between indigenous and non-indigenous was similar but diabetes and newly diagnosed diabetes tended to occur at a younger age in indigenous Australians. The authors found that the rate of diabetes for indigenous people aged 35-44 years (9.0%) was equivalent to that of non-indigenous people aged 55-64 years (8.2%). Similarly, the rate for those aged 45-54 years (17.8%) was similar to those non-indigenous aged 65-74 years (15.0%). This is illustrated in Figure 5.

Figure 5: Proportion with Diabetes by Indigenous status and age (From: 4727.0.55.003 - Australian Aboriginal and Torres Strait Islander Health Survey: Biomedical Results, 2011-13)



Minges *et al.* in 2011 (121) performed a systematic review of the literature for studies that reported the diabetes prevalence in the Australian indigenous population. The studies were conducted between 1997 and 2010, and the diagnosis of diabetes was based on self-reports or standard diagnostic criteria. Minges found the prevalence of diabetes and impaired glucose tolerance (IGT) in Indigenous Australians to range between 3.5% to 33.1% in the 24 studies reviewed.

The current comparative data pertaining to migrant and ethnic specific diabetes prevalence are now discussed. Abouzeid *et al* (122) reported that using the NDSS registry and the 2006 Australian National Census data in the state of Victoria in

Australia, in all migrant groups, the odds of them developing type 2 diabetes versus those who were Australian born was higher, even after adjusting for age and socio-economic strata. In this study, the groups from the Pacific Islands, Southern and Central Asia, North Africa and Middle East had the highest odds ratio (OR) of diabetes compared to the reference group. For example, the OR for persons born in the Pacific Islands is 6.3 for men and 7.2 for women compared to the Australian born reference group. These are illustrated further in Tables 6 and 7.

Table 6: Crude and Adjusted prevalence rates for males with Type 2 diabetes. Table from Abouzeid *et al.* (114)

Table 2 Crude and adjusted prevalence rates (%) and prevalence odds ratios (OR) by region of birth, males

Region of birth	Victorian population size[a]	Observed	Age-adjusted[b]	Observed	Age-adjusted[b]	Age- and SES-adjusted[c]
	n	%	%	OR (95% CI)[d]	OR (95% CI)[d]	OR (95% CI)[d]
Oceania	39802	3.7	4.9	2.2 (2.1-2.3)	2.5 (2.4-2.7)	2.6 (2.5-2.8)
North-West Europe	141754	6.2	3.0	3.8 (3.7-3.9)	1. 5 (1.4-1.5)	1.5 (1.4-1.5)
Southern & Eastern Europe	142711	10.2	4.1	6.4 (6.3-6.6)	2.0 (2.0-2.1)	2.0 (2.0-2.1)
North Africa & Middle East	37540	7.7	7.1	4.7 (4.6-4.9)	4.0 (3.8-4.2)	4.0 (3.8-4.2)
South-East Asia	74102	4.4	5.9	2.6 (2.5-2.7)	3.2 (3.0-3.3)	3.1 (3.0-3.3)
North-East Asia	41127	2. 7	3.5	1.6 (1.5-1.7)	1.7 (1.6-1.8)	1.9 (1.8-2.0)
Southern & Central Asia	54555	6.3	8.4	3.8 (3.7-3.9)	5.0 (4.8-5.2)	5.2 (5.0-5.4)
Americas	19252	3.7	4.0	2.2 (2.0-2.4)	2.0 (1.8-2.2)	2.0 (1.9-2.2)
Sub-Saharan Africa	22072	4.7	5.3	2.8 (2.6-3.0)	2.8 (2.6-3.0)	2.9 (2.7-3.1)
Australia	1682160	1.7	2.1	Referent	Referent	Referent
TOTAL[e]	2421553	4.1	4.1	n/a	n/a	n/a
Overseas	572915	6.5	4.2	3.9 (3.9-4.0)	2.1 (2.1-2.2)	2.2 (2.1-2.2)
Pacific Islands	7829	7.7	10.1	4.7 (4.3-5.1)	6.5 (5.9-7.1)	6.3 (5.7-6.9)
New Zealand	31973	2.7	3.6	1.6 (1.5-1.7)	1.8 (1.7-1.9)	1.9 (1.7-2.0)

[a] based on 2006 Victorian census counts, [b] adjusted for age group; [c] adjusted for age group and SES quintile (n = 4997 missing data); [d] 95% confidence interval; [e] includes region of birth unknown.

Table 7: Crude and Adjusted prevalence rates for females with Type 2 diabetes. Table from Abouzeid *et al.* (122)

Table 3 Crude and adjusted prevalence rates (%) and prevalence odds ratios (OR) by region of birth, females

Region of birth	Victorian population size[a]	Observed	Age-adjusted[b]	Observed	Age-adjusted[b]	Age- and SES-adjusted[c]
	n	%	%	OR (95% CI)[d]	OR (95% CI)[d]	OR (95% CI)[d]
Oceania	41062	3.1	4.4	2.2 (2.1-2.3)	2.9 (2.7-3.1)	3.0 (2.8-3.2)
North-West Europe	143311	5.1	2.6	3.7 (3.6-3.8)	1.6 (1.6-1.7)	1.7 (1.6-1.7)
Southern & Eastern Europe	146632	8.4	3.8	6.4 (6.3-6.6)	2.5 (2.4-2.5)	2.4 (2.4-2.5)
North Africa & Middle East	35047	6.6	6.7	4.9 (4.7-5.1)	4.8 (4.6-5.1)	4.7 (4.5-5.0)
South-East Asia	91986	4.3	5.9	3.1 (3.0-3.2)	4.1 (4.0-4.3)	4.0 (3.9-4.2)
North-East Asia	50406	2.4	3.5	1.7 (1.6-1.8)	2.3 (2.1-2.4)	2.6 (2.4-2.7)
Southern & Central Asia	44767	5.7	6.7	4.2 (4.0-4.4)	4.8 (4.6-5.0)	5.0 (4.8-5.2)
Americas	20967	3.1	3.7	2.2 (2.1-2.4)	2.4 (2.2-2.6)	2.4 (2.2-2.6)
Sub-Saharan Africa	22895	3.7	4.4	2.7 (2.5-2.9)	3.0 (2.8-3.2)	3.1 (2.9-3.3)
Australia	1754144	1.4	1.7	Referent	Referent	Referent
TOTAL[e]	2513054	3.5	3.5	n/a	n/a	n/a
Overseas	597073	5.4	3.8	4.0 (3.9-4.1)	2.5 (2.5-2.5)	2.5 (2.5-2.6)
Pacific Islands	9027	6.8	9.5	5.1 (4.6-5.5)	7.6 (6.9-8.3)	7.2 (6.6-7.9)
New Zealand	32035	2.0	2.9	1.4 (1.3-1.5)	1.8 (1.7-2.0)	1.9 (1.8-2.1)

[a] based on 2006 Victorian census counts; [b] adjusted for age group; [c] adjusted for age group and SES quintile (n = 4072 missing data); [d] 95% confidence interval; [e] includes region of birth unknown.

The authors in this work stated that the reference group, the Australian born group included Indigenous people, who are known to have a higher prevalence of diabetes, and thus may have artificially lowered the prevalence OR for other ethnicities reported. However, the authors further mention that they were unable to analyse the Indigenous group separately due to uncertainty over the demographic characteristics of this population in Victoria. They argue that the National Census for Victoria in 2006 only identified 0.6% of the population as Indigenous and thus their inclusion would not greatly impact on the overall prevalence OR reported. Furthermore, this work could only account for first generation migrants because the NDSS only records country of birth rather than ethnicity data. The implication is that many of the Australian born in the reference group would be second or more generation migrants, but the authors were not able to distinguish. This issue may also mean that the OR reported are an underestimate of the relative prevalence of diabetes in migrant and indigenous communities in Australia.

The origin of this migrant specific excess risk of diabetes is not entirely clear. Of course, genetic predisposition may account for differences in risk. It has also been postulated that an increase in BMI, as a result of greater economic prosperity achieved upon migration to Australia, may also be a factor (123; 124). Montesi *et al.* (125) suggest that lower the social, economic status in the country of origin the higher the risk of the population to become obese in the new country, further exacerbating any background ethnicity specific predispositions to diabetes.

In addition to the migrant prevalence data presented above, in terms of ethnicity alone irrespective of migrant status, there are few Australian data that examine this. McGill and Twigg (126) in 2012 pointed out in an audit of more than 9000 patients in Sydney that in all non-Caucasian groups, the diabetes diagnosis occurred at a significantly

younger age than in Caucasian groups and that they had poorer blood glucose control and higher rates of microvascular and in some cases macrovascular complications such as higher prevalence of retinopathy and ischaemic heart disease. In the Fremantle Diabetes Study, the prevalence of type 2 diabetes in Asian patients was similar to the background population; however, these Asian patients with diabetes were younger and less obese. The researchers also found that these patients had a higher prevalence of retinopathy despite accounting for similar diabetes control and duration; 27.3% for Asians vs 13.5% for Anglo-Celtic (127).

Despite the established multi ethnic composition of the Australian population, there are few data on the multi ethnic differences in diabetes outcomes in Australia and, in particular, mortality data are lacking. In this context, using a single centre eHR, ethnic specific differences in complications and survival are explored further in this thesis in **chapter 3**. The potential confounding from geographic variation in the treatment of diabetes and risk factors on mortality, in addition to variations in access to care, are attenuated by exploring data from a single site.

1.9 Pathophysiology of Type 2 Diabetes

Type 2 diabetes, like type1 diabetes, is considered to be a polygenic disease. The genetic factors are discussed more fully later in this chapter under risk factors. Briefly, using genome wide association studies the genetic architecture of type 2 diabetes has been assembled to a certain degree. What has been identified are that approximately 130 gene variants are associated with type 2 diabetes. Most of these genes, most of which are involved with beta cell function, only explain a small proportion (~15%) of the observed heritability of this condition (73). Nevertheless and in contrast to type 1

diabetes, the lifetime risk of type 2 diabetes is ~40% if one parent has type 2 diabetes and higher if the mother has the disease (128). The relative risk of siblings developing type 2 diabetes is 1 in 3. The identified risk gene alleles have been used to predict the risk of type 2 diabetes. Nevertheless, clinical risk factors such as family history, body mass index (BMI) and glucose levels continue to be the best predictive tools.

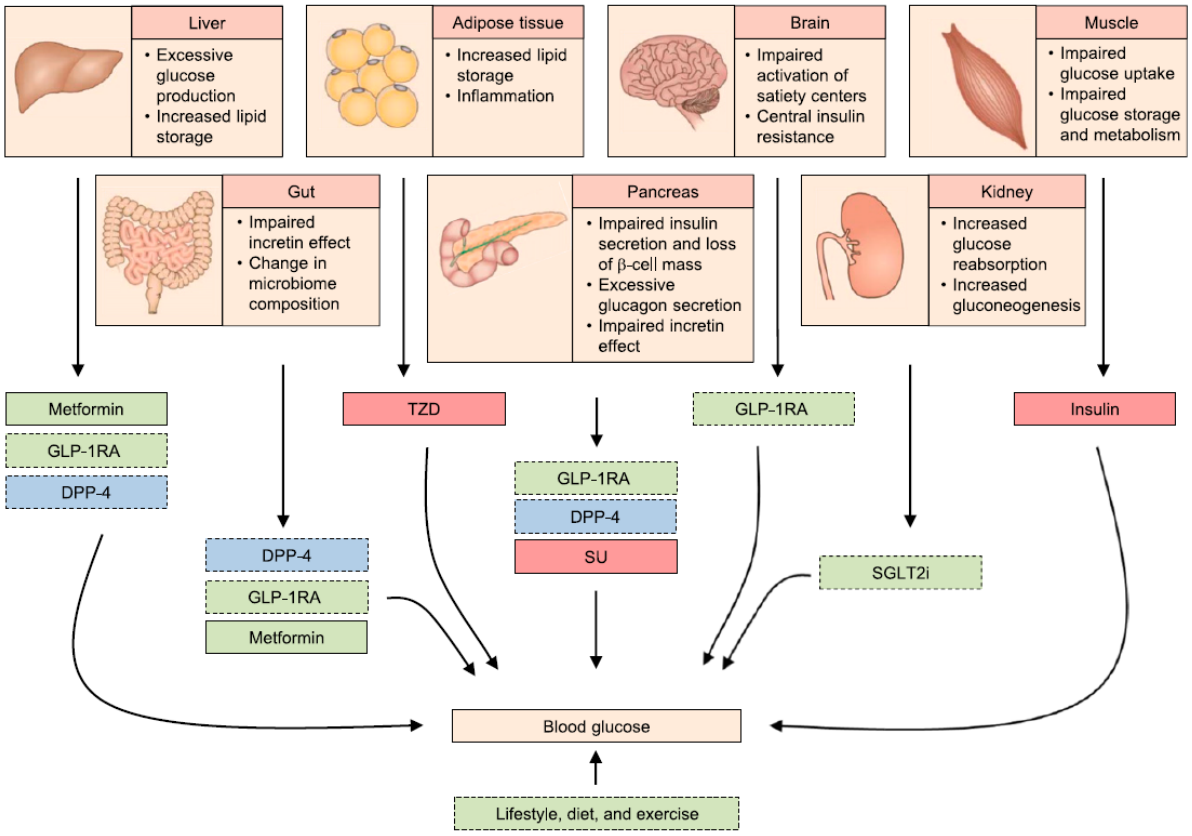
Genetics aside, type 2 diabetes develops when β-cells do not produce enough insulin to maintain blood glucose homeostasis as a result of the progressive destruction of the β-cell mass (129; 130) and/or its dysfunction (131). In type 2 diabetes beta cell dysfunction is also often found on a background of increased insulin resistance, mostly associated with obesity, a major risk factor in type 2 diabetes. Insulin resistance is associated with ectopic fat in the liver and muscle with evidence for causality. Furthermore, Van der Zijl *et al.* (132) observed that fat also accumulates in the pancreas and this may have a pathogenic effect on the β-cells contributing to dysfunction. It should be noted that this area of study is still developing due to difficulty in measuring accurately pancreatic fat. It is recognised that the ectopic visceral fat depots produce inflammatory cytokines, which impact both peripherally and centrally on insulin sensitivity and secretion. Not all obese patients develop diabetes, and diabetes presents in patients at quite different levels of BMI or body fat. This is particularly true for Asian populations, where the development of type 2 diabetes occurs at a much lower weight threshold and at higher levels of visceral fat for any given BMI (133).

That said, the pathogenesis is more complex than just beta cell dysfunction and increased insulin resistance in muscle and liver discussed above. Contemporary understanding includes known defects in many of the other organ systems that impact glucose homeostasis. The gut incretin system has been identified to be defective in type 2 diabetes with reduced levels of incretin peptides such as GLP1 (glucagon like

peptide 1) and GIP (gastric inhibitory polypeptide) which normally facilitate meal related insulin secretion (134; 135). The incretin system also modulates alpha cell glucagon outputs and gut motility. Incretins appear also to have central effects on satiety.

Furthermore, the kidney also plays a role in regulating glucose by gluconeogenesis and also by renal reabsorption of filtered glucose (136). This occurs via the SGLT2 transporters expressed on renal tubules. These transporters, paradoxically, have been found to be upregulated in type 2 diabetes resulting in a maladaptive increase in renal glucose reabsorption. The figure below (Figure 6) reproduced from (137) provides an overview of the defects involved in type 2 diabetes pathogenesis and also illustrates the site of action of modern pharmacotherapies for type 2 diabetes discussed more fully later. The central areas such as the ventral medial hypothalamus responsible for control of appetite and satiety as well as neural outputs also impact on glucose homeostasis and are targets for new drug therapy (137).

Figure 6: Pathophysiology and drug targets. Pleiotropic drug effects are illustrated by the frame and colour of the boxes. Green indicates body weight loss, blue indicates body weight neutrality, and red indicates body weight gain. A dotted frame indicates blood pressure reduction and a solid frame indicates blood pressure neutrality. Source (137)



2.0 Risk factors for Type 2 Diabetes

As discussed above, conceptually the development of type 2 diabetes may arise due to a non-modifiable inherited genetic susceptibility coupled with modifiable environmental and behavioural factors. These factors are further discussed below.

2.0.1 Genes

There is a large body of evidence to support that specific genes are implicated in the development of this disease (138). The strongest evidence base for this arises from twin studies where the concordance of type 2 diabetes in monozygotic twins (resulting

from the division of a single fertilized egg, which usually share a common chorion and placenta) is ~70% compared with 20 to 30 % in dizygotic twins (non-identical twins). The challenge has been in finding the specific genetic components that explain this familial risk. The complexity of type 2 diabetes, being a heterogeneous phenotype with many underlying aetiological and pathophysiological processes that encompass many organs and tissues, presents a difficulty. To date, a candidate gene approach has been unfruitful in identifying type 2 diabetes genes. With the advent of the Genome-wide association studies (GWAS) now over 80 risk loci (the position of a particular gene on a chromosome) have been identified from populations including Europids, South and East Asians, African-Americans and Hispanics (139; 140). The majority of the identified type 2 diabetes genes only have a small effect size; *TCF7L2* being the most common risk allele for Europeans. Researchers are currently studying isolated populations in order to research the idea that type 2 diabetes in these populations may have a more specific genetic aetiology (141; 142). These populations live in isolated geographical areas or have radical lifestyles or religions, which have helped to maintain cultural isolation. Examples of such isolated populations are those residents in Greenland who are descendants of a small group of Inuit whale hunters who arrived in a single migration wave. The Old Order Amish population is also an example of a religious community that did not integrate with the local community in Pennsylvania and continue to marry within the community. By studying these populations which have a simplified genetic background, the effect of a fewer number of genes for type 2 diabetes may be amplified and thus more easily identified (143).

As mentioned above, despite a large number of loci being identified, it remains that in large populations genes only explain about 15% of the estimated heritability of the disease. Other risk factors, some of these modifiable are discussed below.

2.0.2 Ethnicity

Type 2 Diabetes is prevalent in all ethnicities, but some groups are more affected than others. The Aboriginal and Torres Strait people, Australia's first nation groups, have a disproportionately high rate of diabetes (121; 144).

The propensity of the indigenous population being more at risk for diabetes (120) is not unique to Australia with similar findings reported for other international groups including the American Pima Indians, the Canada First Nation, and South Asian indigenous groups (145-153).

Additional information regarding differences in ethnicity and diabetes risk can be gleaned from The IDF Atlas which showed the top 10 countries with adult diabetes in 2015 (Table 8).

Table 8; Top Ten Countries/territories for number of people with diabetes (20-79), 2017 and 2045. Source The IDF Atlas (5)

2017			2045		
Rank	Country/territory	Number of people with diabetes	Rank	Country/ territory	Number of people with diabetes
1	China	114.4 million (104.1-146.3)	1	India	134.3 million (103.4-165.2)
2	India	72.9 million (55.5-90.2)	2	China	119.8 million (86.3-149.7)
3	United States	30.2 million (28.8-31.8)	3	United States	35.6million (33.9-37.9)
4	Brazil	12.5 million (11.4-13.5)	4	Mexico	21.8 million (11.0-26.2)
5	Mexico	12.0 million (6.0-14.3)	5	Brazil	20.3 million (18.6-22.1)
6	Indonesia	10.3 million (8.9-11.1)	6	Egypt	16.7million (9.0-19.1)
7	Russian Federation	8.5 million (6.7-11.0)	7	Indonesia	16.7million (14.6-18.2)
8	Egypt	8.2million (4.4-9.4)	8	Pakistan	16.1 million (11.5-23.2)
9	Germany	7.5 million (6.1-8.3)	9	Bangladesh	13.7 million (11.3-18.6)
10	Pakistan	7.5 million (5.3-10.9)	10	Turkey	11.2 million (10.1-13.3)

2.0.3 Family History

There has been a long-held belief that “diabetes seems to run in families “and twin studies have been used to support a genetic origin for diabetes as mentioned prior. However, a family history of type 2 diabetes conceptually represents a composite of both genetic epigenetic and environmental risk.

A positive first-degree family history is generally associated with an approximate 2 fold increased risk of future type 2 diabetes across the wide spectrum of diabetes prevalence globally (154; 155). For example, Harrison *et al*. in a comprehensive review

of this topic (156) reported that studies in the Pima Indians (a population with high risk for type 2 diabetes) showed that participants with one affected parent were 2.3 times more likely to progress to diabetes than participants who did not have affected parents (157). The Honolulu Heart Program, a study of Japanese-American men, similarly showed an increased risk of incident diabetes in those with a parental history of diabetes (158). In a report from the EPIC-InterAct (159), the world's largest study of incident T2DM, a case-cohort study within the pan-European EPIC study which has gathered 4 million person-years of follow-up (160) reported that a family history of type 2 diabetes was associated with a higher incidence of the condition with a hazard ratio of HR 2.72,(95% CI 2.48, 2.99), consistent with the Pima data.

Furthermore, there are parent of origin effects reported for diabetes. Groop *et al*. (128) showed that there is a lifetime risk of developing the disease of ~40% in offspring if one parent has type 2 diabetes, which is greater if the mother is affected. In Norway Bjornholt *et al.* (161) reported that in a study of men without diabetes followed for 22.5 years that 7.4% went on to develop diabetes. In this study the risk of developing diabetes associated with a maternal family history was greater than for a paternal family history; RR(95%CI) were 2.51 (1.55-4.07) and 1.41 (0.657-3.05) respectively. The San Antonio Heart Study examined a large cohort of Mexican Americans and non-Hispanic whites (162). In this study, there was a difference in parent of origin effects in men and women. In short, men with a parental history of diabetes had a higher prevalence of type 2 diabetes and impaired glucose tolerance, regardless of which parent had diabetes. In contrast, for women, only a maternal history of diabetes was associated with a higher prevalence of type 2 diabetes and impaired glucose tolerance.

In many studies and not unexpectedly, the risk for offspring is even greater if both parents are affected. For example, in the study reported by Groop *et al.* (128) the

lifetime risk of developing the disease was increased from 40% to 70% if both parents have diabetes. Similar findings have been seen in the Framingham Offspring Study (163) where the risk for type 2 diabetes among offspring with a single diabetic parent was increased 3.5 fold and for those with two diabetic parents was 6-fold higher compared with offspring without parental diabetes. Interestingly in this study, there was a strong signal that the younger the age of onset of the mother, the earlier the offspring were diagnosed (Table 9). Again from the EPIC-InterAct study (159), the greatest risk of type 2 diabetes was in those with both maternal and paternal history of type 2 diabetes (HR 5.14, 95% CI 3.74, 7.07) and those whose parents had diabetes diagnosed at a younger age (<50 years; HR 4.69, 95% CI 3.35, 6.58). This effect was more strongly associated with the maternal history of diabetes (164).

The underlying mechanism that might explain the parent of origin effects on diabetes risk are not yet fully elucidated. Suffice to say maternal diabetes, and especially having a mother with diabetes diagnosed at a young age, underscores the potential for epigenetic in utero effects of maternal diabetes on offspring (165-167). It is notable that even in monogenic diabetes, the maternal parent of origin infers a risk for earlier age of onset (168). The relationship of intrauterine hyperglycaemia and earlier onset of diabetes is of concern given the growing numbers of those with GDM and the poor outcomes for younger onset type 2 diabetes, discussed in **Part III**.

Table 9: From Meigs *et al.* (163); Offspring from young maternal diabetes age of onset are significantly younger at diagnosis

TABLE 4
Age at examination 5 and age of diagnosed diabetes onset by parental diabetes age of onset among 94 Framingham Offspring Study subjects with diagnosed type 2 diabetes and without bilineal parental diabetes

	Parental diabetes age of onset				
		Mother		Father	
	Neither	<50 years of age	≥50 years of age	<50 years of age	≥50 years of age
Subjects with type 2 diabetes (n)	49	3	22	5	15
Age at examination 5 (years)	64 ± 1.0	54 ± 4.2	68 ± 1.1	56 ± 3.3	57 ± 1.4
Age of diabetes onset (years)	59 ± 0.9	39 ± 4.8	61 ± 1.0	53 ± 3.7	49 ± 1.4
Age of diabetes onset, adjusted for age at examination 5 (years)	57 ± 0.7	47 ± 3.0*	57 ± 1.1	59 ± 2.3	54 ± 1.4

Data are means ± SE. *$P < 0.02$ for all pair-wise comparisons of offspring with young-onset maternal diabetes to those with no parental diabetes, older-onset maternal diabetes, or any paternal diabetes.

2.0.4 Age

Type 2 diabetes has been considered a disease of mature age and the highest incidence and prevalence are seen in older age groups (7; 169-172). The common understanding is that the risk of developing type 2 diabetes increases considerably after age 45 and this is the age at which distinguished bodies such as the ADA and ADS recommend testing for diabetes in the overweight and obese (62; 173).

It is notable, however, although still a minority, type 2 diabetes is being seen in younger age groups. Different ethnic groups behave considerably differently from Caucasian populations with younger age of onset of diabetes being well documented (147; 174-176). In the context of multicultural Australia with the potential for greater numbers of type 2 diabetes in the young, the question arises whether age of onset might have an impact on disease outcome. This is a question addressed by some studies in this thesis, the background is discussed more fully in **Part III**.

2.0.5 Obesity

Obesity is considered to be the key risk factor for the development of Type 2 diabetes (177). In Australia, the rate of obesity (28% of the population aged 15 and over) is fourth highest among 34 OECD countries, behind the United States (37%), Mexico (30%) and Hungary (29%). However, the rates of overweight and obesity in children and adolescents aged 5-17 have remained stable at 25% (178).

The SEARCH for Diabetes in Youth Study reported that the prevalence of overweight was 10.4% and obesity was 79.4% among the youth with T2DM (179). Moreover, within certain ethnicities, the prevalence of obesity in YT2DM seems to be higher than their background non-diabetic populations. For example, Non-Hispanic white, African American and Hispanic youth with T2DM were nearly 4 times more obese than their peers without diabetes. In fact, the issue of obesity and its associations including diabetes, hypertension, dyslipidaemia, the components of the metabolic syndrome, in the Asia Pacific has been well documented and has become a focus for governments due to the socio economic implications for the region (180). Hillier and Pedula described this phenomenon of earlier onset of diabetes which progressively increases with obesity, and subsequent work continues to observe this inverse relation between BMI and age at diagnosis of type 2 diabetes (181).

2.0.6 Metabolic Syndrome and Cardiovascular Risk Profile

As mentioned above, obesity is a common feature of type 2 diabetes and a significant risk factor in its pathogenesis. A concomitant of obesity are the other metabolic syndrome features such as dyslipidaemia and hypertension providing a milieu for the development of macrovascular disease. The ‘common soil” in all of this is thought to be

insulin resistance mediated largely by abdominal fat deposits, contributing obesogenic and inflammatory cytokines that antagonise insulin action. The importance of abdominal obesity is reflected in the more recent diagnostic criteria for the metabolic syndrome. There have been many different diagnostic criteria for the metabolic syndrome, all of which are largely constructs to dichotomise risk. The most widely accepted being the IDF definition of the metabolic syndrome for which abdominal obesity is *sine qua non* as shown in Table 10. The other diagnostic factors include hypertension, elevated fasting glucose, elevated plasma triglyceride and low high-density lipoprotein cholesterol (HDL) (182).

The corollary of these associations are that reduction in obesity, and especially abdominal adiposity should be a target for intervention, both in prevention of diabetes and in the management of diabetes, with a view to both improving glycaemic control and improving CVD risk factor profiles.

Table 10: Criteria for waist circumference thresholds for diagnosis of Metabolic Syndrome; Reproduced from Hillier *et al.* (181)

Table 2. Current Recommended Waist Circumference Thresholds for Abdominal Obesity by Organization

		Recommended Waist Circumference Threshold for Abdominal Obesity	
Population	Organization (Reference)	Men	Women
Europid	IDF (4)	≥94 cm	≥80 cm
Caucasian	WHO (7)	≥94 cm (increased risk) ≥102 cm (still higher risk)	≥80 cm (increased risk) ≥88 cm (still higher risk)
United States	AHA/NHLBI (ATP III)* (5)	≥102 cm	≥88 cm
Canada	Health Canada (8,9)	≥102 cm	≥88 cm
European	European Cardiovascular Societies (10)	≥102 cm	≥88 cm
Asian (including Japanese)	IDF (4)	≥90 cm	≥80 cm
Asian	WHO (11)	≥90 cm	≥80 cm
Japanese	Japanese Obesity Society (12)	≥85 cm	≥90 cm
China	Cooperative Task Force (13)	≥85 cm	≥80 cm
Middle East, Mediterranean	IDF (4)	≥94 cm	≥80 cm
Sub-Saharan African	IDF (4)	≥94 cm	≥80 cm
Ethnic Central and South American	IDF (4)	≥90 cm	≥80 cm

*Recent AHA/NHLBI guidelines for metabolic syndrome recognize an increased risk for CVD and diabetes at waist-circumference thresholds of ≥94 cm in men and ≥80 cm in women and identify these as optional cut points for individuals or populations with increased insulin resistance.

2.0.7 Obstructive Sleep Apnoea (OSA)

Sleep, sleep deprivation and sleep-related disorders have been linked to the development of insulin resistance and type 2 diabetes through multiple pathways. These include a deleterious effect on glucose homeostasis by increasing inflammation and an adverse effect on appetite regulation, leading to increased food intake, weight gain and ultimately obesity (183).

Sleep disturbances are common in the community; The 2016 Sleep Health Survey of Australian Adults surveyed 1,011adults aged over 18 years across Australia and reported that sleep disordered diseases affected 33-45% of adults in this study. Furthermore, this study found that a medical diagnosis for the most common sleep conditions already existed showing how prevalent disturbances of sleep affect our population. A medical diagnosis for obstructive sleep apnoea (OSA) was present in 8% of the sample size as well as other conditions including significant insomnia at 20% and restless legs at 18% in adults.

OSA is described as a condition where there is repetitive cessations of breathing (apnoea) or partial upper airways obstructions (hypopneas) occur.

For the diagnosis of OSA to occur these apnoeas or hypopneas need to occur five or more times per hour of sleep (183). Clinically, the diagnosis of OSA is suspected in patients that complain of snoring and disrupted sleep including daytime sleepiness. Once a sleep study confirms the diagnosis of OSA the current treatment is interventions related to weight reduction and the use of continuous positive airway pressure (CPAP).

The relationship between type 2 diabetes and OSA is well recognised and obesity and age are common risk factors for both. Patients with OSA are considered at high risk of developing diabetes. In a study of 8678 individuals, the incidence of diabetes was

14.9% over 5 years in those with severe OSA (184). In diabetes populations, OSA is a frequent comorbidity and prevalence of OSA have reported in the range of 23.8% -70% (185). Pathophysiologically speaking, patients with OSA and especially those with excessive daytime sleepiness (the severity of which is indicated by the Epworth Sleepiness scale and Multiple sleep latency test), had higher measures of insulin resistance when measured by the homeostatic model assessment (HOMA-IR) (186). It is unknown if the relationship is entirely due to obesity or if there are other significant factors contributing. Even in lean individuals, the presence of OSA increases insulin resistance (187; 188).

Additionally, OSA is associated with impaired beta cell function. Interestingly, pre-clinical studies (189) have linked periods of intermittent hypoxia to an increase in beta cell death resulting in overall beta cell secretory dysfunction. In these ways, OSA has been linked to the main pathophysiological processes leading to type 2 diabetes.

The impact of OSA on metabolic control has been examined, and the presence of OSA has been reported to increase the adjusted mean HbA1c in the range of 0.7-3.7% (185). In type 2 diabetes hyperglycaemia, as indexed by HbA1c, has been shown to be related to the degree of nocturnal hypoxaemia but not necessarily to the hypopnoea (190). Furthermore, treatment of OSA with CPAP in small non-controlled studies has been shown to improve insulin sensitivity and glycaemia (191), but there is conflicting evidence in the literature (192-196). Suboptimal adherence to CPAP therapy may account for variability in studies of treatment efficacy.

Interestingly, lifestyle intervention in type 2 diabetes improves OSA and specifically the Apnoea Hypopnoea Index (AHI), independent of loss of weight.

Not only is OSA associated with type 2 diabetes and glycaemia, the presence of OSA predicts the progression of some diabetic vascular complications. In a longitudinal study, patients with type 2 diabetes and OSA were more likely to develop advanced diabetic retinopathy after adjusting for confounding factors. The OR found was 6.6 (95%CI 1.2-35.1) (197). Similar findings were found in a study examining neuropathy associations with OSA with an OR of 2.82 (95%CI 1.44-5.52) reported (185). With respect to nephropathy, a study of those with type 2 diabetes, after adjustment for confounders demonstrated that the presence of OSA increased the incidence of albuminuria or reduced eGFR). Snoring, as a surrogate for OSA, was independently associated with microalbuminuria although data in this area are somewhat conflicting. There are fewer data available on the impact of OSA in macrovascular disease and type 2 diabetes The LOOK AHEAD study of lifestyle interventions in type 2 diabetes showed that the apnoea-hypopnoea index (a quantitative assessment of OSA (198)) was associated with self-reported stroke but not coronary ischaemia.

Thus, OSA is an important comorbidity of type 2 diabetes with increasing evidence of an impact on diabetes outcomes. Future studies are needed on the impact of therapeutic treatment on diabetes.

2.1 Contemporary concepts

2.1.1 Microbiome

There is growing evidence that environmental factors such as diet, viruses, bacteria and chemicals can influence the development of both type 1 and type 2 diabetes (199). Recent interest in gut microbiota, as one of these environmental factors, is predicated on evidence of gut microbiota dysbiosis in pre-clinical and human studies.

The human GI tract plays host to a large and complex collection of 10-100 trillion microorganisms. The bacteria are the largest group and the most diverse (200). The most common bacterial groups in the human GI tract are *Firmicutes* (gram-positive), *Bacteroidetes* (gram-negative) and *Actinobacteria* (gram-positive) [Figure 7]. The colonisation of intestinal bacteria in humans begins immediately after birth, and it becomes a stable ecosystem around the age of 2 to 3 years. However, the load and diversity continue to increase as we get older and its size and composition vary between individuals and during periods of disease.

The complex microbiota contribute over 100-fold more unique genes than the human genome and this genetic potential in our GI tract can impact strongly on health and disease. This collective genome has been dubbed the metagenome. The advent of high-throughput sequencing of the metagenome (metagenomic analysis) allows investigators to analyse all the intestinal microbiota of an individual instead of culturing individual microbes. In recent times, metagenomic analysis has been combined with the clinical data in metagenome-wide association studies (MGWAS) also including studies of diabetes.

The microbiome is larger than the human genome (200), and it is referred to as an "organ" that contributes to overall metabolism and plays a role in converting food into nutrients and energy in the human body. There is evidence from pre-clinical studies in mice of a causal relationship between certain intestinal micro-organisms and obesity. Turnbaugh and colleagues (201) performed microbiota transplantation experiments in mice and showed that the microbiome of obese mice have a greater capacity to yield energy from the diet. Furthermore, this capacity is transferrable because when the "obese microbiota" was transplanted in mice with "lean microbiota" these mice had a

significant increase in total body fat and the type of micro-organisms changed in the "lean" animal's biota.

In humans, the micro-organisms appear to have a causal role in decreasing insulin resistance, and this was shown by experiments undertaken by Anne Vrieze *et al.* (202). The researchers used the knowledge that the small intestine has an important role in carbohydrate and fat uptake. They infused microbiota from lean donors into obese recipients, and after six weeks, the insulin sensitivity of recipients increased as well as the levels of butyrate-producing intestinal microbiota. It has been suggested that butyrate, a free fatty acid, prevents the transfer of endotoxins which have been shown to cause insulin resistance (203). Furthermore, butyrate has been shown to prevent and treat diet-induced obesity and insulin resistance in mouse models. In 2013, two pivotal MGWAS studies published, in Nature, strengthen the knowledge how intestinal microbes are implicated in obesity, metabolic syndrome and type 2 diabetes. The first study by Karlsson *et al.* (204) used shotgun sequencing (sequencing long DNA strands) to characterise the faecal metagenome of 145 European women with normal, impaired or diabetic glucose control. They report observing compositional and functional alterations in the metagenome of women with type 2 diabetes, and then developed a mathematical model based on metagenomics profile that identified type 2 diabetes with high accuracy. When they applied the model to women with impaired glucose tolerance, they were able to identify who had a more specific "blood plasma markers" hence being at high risk of developing type 2 diabetes.

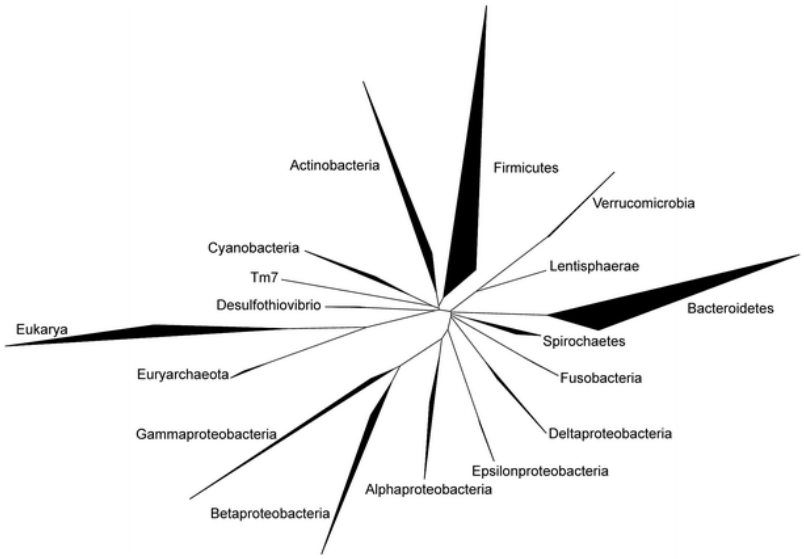
The second study by Qin *et al.* (205) also in Nature found similar correlations for specific intestinal microbes and their genes with type 2 diabetes. This group studied a total of 345 Chinese T2D patients and non-diabetic controls using a case-control MGWAS based on deep next-generation shotgun sequencing of DNA of stool samples.

Qin *et a*l. showed that patients with type 2 diabetes have a specific microbiota signature which is characterised by a decrease in some universal butyrate-producing bacteria and an increase in various opportunistic pathogens and other microbial functions including sulphate reduction and oxidative stress resistance. An analysis of 23 additional individuals demonstrated that these gut microbial signatures had utility in identifying those with type 2 diabetes, an area for further investigation. De Vos *et al.* (206) in an editorial in Nature points out that both researchers found the presence of fewer *Clostridiales* bacteria that produce the short-chain fatty acid butyrate (*Roseburia* species and *Faecalibacterium prausnitzii*) and this was highly discriminant of T2D.

Nevertheless, there were several differences with the Karlsson cohort having high *Lactobacillus gasseri* and *Streptococcus mutans*, usually found in the mouth and upper intestinal tract, in their T2D cohort, whereas Qin *et al*. found mainly *Proteobacteria*, which may produce inflammatory lipopolysaccharides that lead to endotoxaemia. De Voss *et al.* assert that these two studies support a model in which when our healthy gut bacteria are undermined by infections, use of antibiotics, unhealthy diet and lifestyle, the composition of the gut micro-organisms are changed (Figure 8). In Type 2 diabetes, these changes affect insulin sensitivity of the liver and muscles.

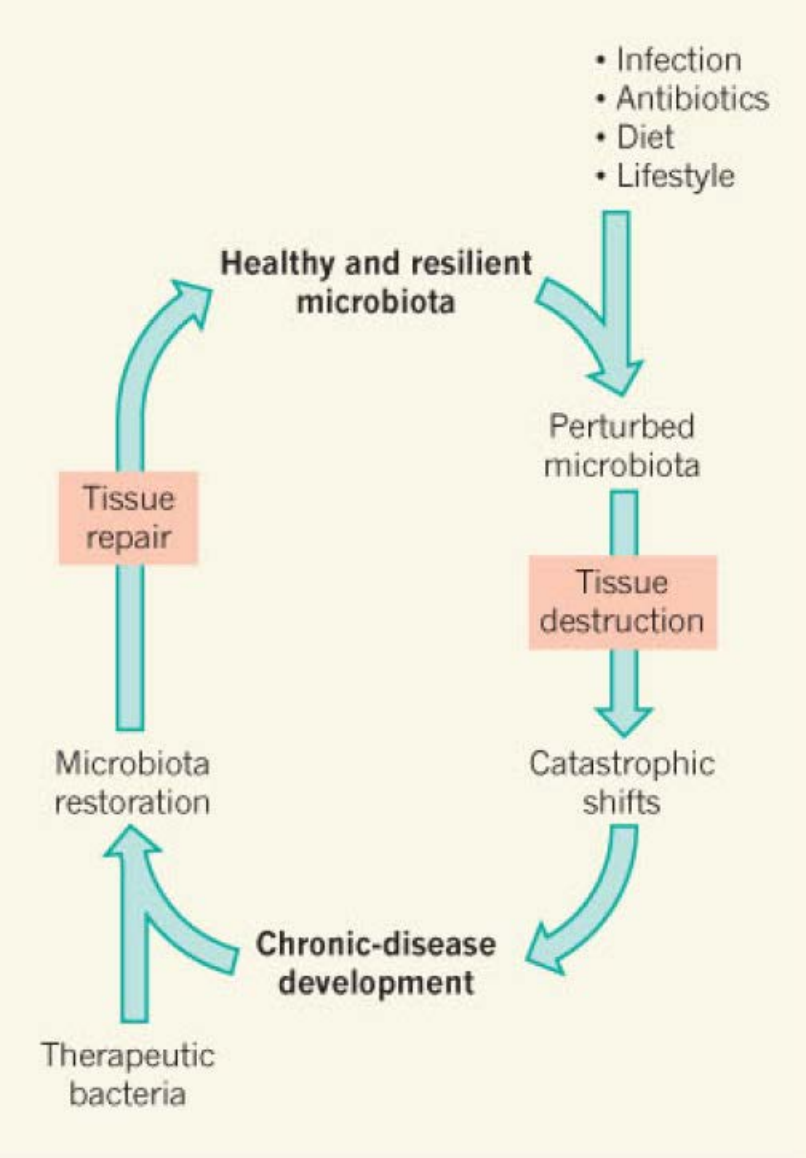
Furthermore, these two studies highlight the need for more information in multi-ethnic cohort studies, to further establish, if there are major differences in the gut biome of different ethnic groups. These new studies will also need to take age and gender into account as they have a significant impact in the ecosystems of the human biota. It is not clear if abnormal microbiota signatures will be used as a predictive/diagnostic tool or lead to the development of pro and pre biotics as a therapeutic tool. Nevertheless, studies using MGWAS are taking a step closer to personalising therapy to delay, treat or even maybe cure Type 2 diabetes.

Figure 7: Phylogenetic tree representing the groups of bacteria most frequently detected in human faeces using 16S rRNA gene sequencing. The extent of the bold areas indicate diversity and abundance of the bacterial groups



Reproduced from Vrieze *et al.* (200)

Figure 8: Microbiota in Health and Disease; Reproduced from de Vos



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"A model of how the composition of gut microorganisms can influence the health of an individual. The model proposes that external factors such as infection or diet alter the healthy, resilient microbial composition to which can cause tissue destruction, and ultimately chronic disease. If this occurs, it is possible that healthy microbial diversity can be restored, and damaged tissue repaired, only by delivery of specific 'therapeutic' bacteria"; Reproduced from de Vos (206)

2.1.2 Omics

Personalised therapy is the goal of every clinician; to be able to deliver for patients the best-targeted clinical management plan for their condition. The great hope of personalised and precision medicine has been the study of systems biology and "omics". Wikipedia (207) states the "…*word **omics** informally refers to a field of study in biology ending in -**omics**, such as genomics, proteomics or metabolomics. The related suffix -ome is used to address the objects of study of such fields, such as the genome, proteome or metabolome respectively*…". Therefore, precision medicine can be defined as when the clinical and the omic data combine to lead to better health outcome for our patients. Understanding this new paradigm and linking it to the clinical information has provided clinicians with opportunities to step outside generic clinical treatment guidelines and be able to provide precision diagnosis in some types of diabetes, e.g., monogenic diabetes. Genetic analysis allows the precise identification of these patients with specific molecular defects and avoid their incorrect classification as type 1 or type 2 diabetes, often for many decades. The most striking example of this are patients who have MODY1 and MODY3; these patients have a monogenic defect affecting insulin-related transcription factors and are clinically sensitive to sulphonylureas. Many of these patients have used insulin for many years only to find out that oral therapy such as sulphonylureas are just as effective in their treatment (208; 209).

Another advance has been in the optimisation of treatments in our patients by using pharmacogenomics or the study of how genes affect our response to drugs. This major work has led to ways to reduce adverse drug reactions in patients or in identifying why some patients respond to some drugs and others not. For example, Metformin is

considered the first line of treatment in diabetes. It has major clinical advantages over other therapies because of its safety record, it does not induce hypoglycaemia or weight gain, and has possible cardiovascular benefits (210). The most common side effect of metformin treatment is gastrointestinal (GI) upset, which occurs in ~30% of patients. In~5%of patients treated with metformin, GI symptoms are so extreme that the drug is ceased (211). Dujic *et al*. (212), studied the impact of genetic factors on the gastrointestinal intolerance to metformin treatment in the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) study. The authors examined the genotype of two genes, one with potential involvement in metformin absorption (the organic cation transporter 1 (OCT1) and a gene involved in enterocyte serotonin (serotonin reuptake transporter (SERT). The authors showed the link between a SERT polymorphism and metformin gastrointestinal intolerance in 1,356 tolerant and 164 extreme metformin-intolerant patients. The number of low-expressing SERT S* alleles significantly increased the odds of metformin intolerance. Moreover, there was a multiplicative interaction between the OCT1 and SERT genotypes, suggesting a complex genetic control of metformin intolerance. These results show how precision medicine could inform our management of patients at the front line of drug management in diabetes.

The fundamental manner in which our genome, transcriptome and proteome impact on every human structure and can cause pathogenic processes that impact in our health is now better understood.

Big data initiatives have been embraced in science and health care communities with the human genome scientists leading the way in many ways. Fundamentally, under big data projects the disparate knowledge of the human genome is harnessed in an

organised way. These data combined with clinically routine collected data can lead to faster and more precise clinical and public health solutions (213; 214).

To this point, Floyd and Psaty (215) in a review of the application of genomics in diabetes, point out that for genomic information to be integrated into clinical practice it requires strategies to ensure that both clinicians and patients understand how these data can enhance clinical outcomes. Furthermore, it is important to understand some of the limitations of electronic health care data that can impact directly on genomic data. For example, disease diagnostic codes associated with each health care encounter are assigned for billing and clinical description of the encounters. Data collected in the electronic health record is representative only of the required information to dispense clinical care in an occasion of service, and it may not include a complete medical history. Neither of these data are collected for research purposes; hence, the use of it without further validation in studies including the human genome may be fraught with problems. Notwithstanding, electronic health records need to be developed in a way where research is an integral part of the clinical encounter and the data collected is able to be harvested in a standardised and meaningful manner.

2.2 Treatment of Type 2 Diabetes

Guidelines for the medical management of type 2 diabetes are widespread and expert bodies including the European Association for the Study of Diabetes (EASD), American Diabetes Association (ADA) and Australian Diabetes Society (ADS) have published guidance in this regard (216-219). These have been reviewed recently by all expert bodies in light of new data from cardiovascular outcome trials. This section provides an overview of the medical management of type 2 diabetes. Lifestyle management,

including medical nutrition therapy as a component of lifestyle intervention, is recommended with individualised eating styles and calorie intake in the context of exercise and activity and body weight goals established in the context of personal and cultural preferences. Pharmacotherapy is advised either following a period of lifestyle modification or at diagnosis.

Practitioners are encouraged to elect an individualised HbA1c glycaemic target. The generic target is ≤ 7% (≤ 53 (mmol/mol) with lower targets considered depending on duration of disease, life expectancy and hypoglycaemic risk. Similarly, more relaxed targets for those with long standing disease, high CVD burden, risk of hypoglycaemia and reduced lifespan are recommended. Adherence, occupation and patient preference are also considerations (219).

In terms of pharmacotherapy treatment options are diverse. The preferred initial agent in most guideline algorithms is metformin and second line agents are added if HbA1c targets are not reached. Other therapeutic options are sulphonylurea agents, thiazolidinediones and acarbose. More recently, newer classes of agents have become available. The dipeptidyl peptidase-4 (DPP-4) inhibitor and glucagon-like peptide-1 receptor agonists (GLP1 RA) agents are active on the incretin system with pleiotropic effects including glucose lowering, reducing blood pressure, reducing glucagon release, increasing satiety and reducing gastric motility. The sodium-glucose co-transporter 2 inhibitors (SGLT2-i) class of medications act to reduce renal tubular reabsorption of glucose to lower HbA1c and have the added effect of reducing body weight and blood pressure.

It is notable that most recent cardiovascular outcome trials for DPP-4 show no effect on major adverse cardiac/cardiovascular events (MACE) outcomes however so far GLP-

1RA and SGLT2-I cardiovascular outcome trials (CVOTs) have shown significant benefit for MACE outcomes independent (largely) of glycaemic control. Trials of newer agents are ongoing, and these findings are likely to change treatment algorithms, especially for those with increased CV risk. In addition to pharmacotherapy, bariatric surgery has shown benefit over medical therapy across a short timespan (220).

2.3 Treatment Efficacy

The UKPDS investigated outcomes for type 2 diabetes in those with high or lower glucose (intensive therapy achieving an HbA1c of 7%). At the end of the 10 year, study there was an approximate 25% reduction in microvascular endpoints in the intensive therapy group. In the epidemiological follow-up study, despite a loss of glycaemic differences after study close out, a continued reduction in microvascular risk was found for the intensively treated group (which was deemed to be a legacy effect of intensive treatment), and emergent benefits were seen in respect to mortality and MI.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE)(221), Action to Control Cardiovascular Risk in Diabetes (ACCORD) (222) and Veterans Affairs Diabetes Trial (VADT) (223) studies were set up to investigate the question of whether excellent control by further lowering glucose is of particular benefit in established high risk type 2 diabetes. These studies confirmed the microvascular benefit seen in the UKPDS study, but the results on macrovascular risk and mortality were largely disappointing. The ACCORD study was terminated early with the finding of an excess of deaths in the intensive treatment arm, which is still unexplained. These trials have had added to the impetus to individualise HbA1c targets especially for those with high CVD risk.

In addition to hyperglycaemic management, management of blood pressure has been shown to delay diabetes related complications, especially renal related complications. The achievement of LDL lowering with statins and ezetimibe is recommended, and arguably, fenofibrate has been considered in the context of hypertriglyceridemia, especially for secondary prevention. The Steno diabetes trial confirmed that this combined risk factor approach has a significant positive impact on survival in high risk patients (224).

2.4 The Complications of Diabetes

Diabetes complications are diseases or conditions that can be broadly divided into macrovascular complications; disease of the large blood vessels leading to cerebrovascular, cardiovascular and peripheral vascular disease and microvascular complications; disease of the small blood vessels which typically include retinopathy, nephropathy and neuropathy. People with diabetes are at higher risk of complications with increasing duration of the disease. What follows is an overview of the general field of diabetic complications that can occur in diabetes in the next few pages and with particular emphasis on diabetic retinopathy, a topic for study in this thesis.

2.4.1 Microvascular Complications

2.4.1.1 Diabetic Retinopathy

2.4.1.1.1 Epidemiology, Prevalence and Incidence

Diabetic retinopathy (DR) is a common complication of diabetes which causes considerable morbidity. It is a specific microvascular complication of both type 1 and type 2 diabetes. In the landmark UKPDS study of newly diagnosed type 2 diabetes, 1

in 3 patients had a diagnosis of retinopathy at baseline (225) and the IDF atlas (7) states “that DR affects over one-third of all people with diabetes and is the leading cause of vision loss in working-age adults”. Wong *et al.* (226) in a review of DR states that whilst diabetic retinopathy is present in 30% of people with diabetes, only 5 to 10% of them will develop the sight-threatening states of proliferative DR and diabetic macular oedema (DMO). Furthermore, in two seminal Wisconsin epidemiologic studies of diabetic retinopathy, it was calculated that the lifetime risk of developing DR was 50-60% in type 2 and up to 90% in type 1 diabetes (227; 228). It is postulated that these risks are an overestimation as management of retinopathy has significantly changed since these papers were published. Yau *et al* (229) in a meta-analysis of 35 studies with 22,896 individuals with both type 1 and 2 diabetes, from the U.S., Australia, Europe and Asia, after controlling for methodologies and outcome definitions, reported that the age-standardized prevalence was 35.4% for any DR, 7.24% for proliferative diabetic retinopathy (PDR), 7.48% for DMO, and 11.7% for vision-threatening diabetic retinopathy (VTDR). The authors then extrapolated these prevalence rates against the 2010 world diabetes population, and estimated that 92.6 million adults had any type of DR, 17.2 million had PDR, 20.6 million had DME, and 28.4 million had VTDR. The size of the problem worldwide is alarming considering that diabetes eye disease has a significant impact on an individual’s health and well-being and given many are unable to work as a result. Furthermore, DR has a significant impact on the health budgets of individual countries as diabetes is still the primary reason for blindness globally (7; 229).

The incidence and progression of DR is of considerable importance as it can guide policy in relation to appropriate screening of populations. To this end, there have been a number of studies worldwide that have informed this particular issue. Burger *et al.* (230) studied a population of 231 young type 1 patients (mean age 17.6± 4.0 years)

with a mean duration of diabetes of 8.5 ± 4.9 years for a period of 5 years. At the study end, the authors reported that 47% of the participants with no DR at baseline had developed retinal changes and found that the median interval between the 'onset' of retinopathy, (as indicated by the finding of a few microaneurysms and background retinopathy) was 5 years. In the Wisconsin study, it was reported that the 10 year incidence of DR in type 1 was 74% increased 97% to after 25 years (231). In type 2 diabetes one of the largest incident studies published was done in England where Jones *et al.* (232) followed 20,686 people with type 2 diabetes, managed in primary care, who underwent annual retinal photography up to 14 times between the years of 1990 and 2006 in a community screening programme. The authors found that the 5 year cumulative incidence in T2DM patients (calculated by dividing the number of new cases of a disease in a population during a specific period of time (the numerator) by the total number of people at risk of developing the disease in that population during the same period of time (the denominator) with no DR at baseline to pre-proliferative DR was 4% and it increased at 10 years to 16.4%. In Australia, the Blue Mountains Eye Study undertaken by Cikamatana *et al.* (233) examined 3654 residents of the Blue Mountains area aged 49 years and above. Of these, 284 had diabetes (mostly type 2 diabetes) and after 5 years of follow up 150 patients were re-examined. The difference in subject numbers was accounted for by those who had died (24.3%) or were lost to follow up. The authors reported a 5 year cumulative incidence rate for DR of 22.2% (see Table 11) and the rate of DR progression was reported to be 25.9% in this cohort. In Hong Kong, Song and colleagues reported a 4 year cumulative incidence of 15.2% in 5,160 patients with type 2 diabetes mellitus who attended at least two diabetic retinopathy screening sessions.

Overall, there are differences in the prevalence and incidence of DR amongst all studies, and these can be attributed to differences in methodologies used, such as a handheld ophthalmoscope, non-stereoscopic photographs vs non-mydriatic retinal photography as well as the number of subjects involved in the studies. Nevertheless, more recent studies point to a reduction in the prevalence and incidence of DR particularly in type 1 diabetes (234-236). This may be attributed to a better understanding of the causes of DR and more targeted treatment of diabetes risk factors, specifically, hyperglycaemia, hypertension and lipids. Public health campaigns by diabetes organisations may have contributed to a better understanding of the need to seek treatment earlier and the need to screen all patients for retinopathy at diagnosis and thereafter at regular intervals. One important caveat in this picture is that for patients in rural areas and in poorer countries the access to screening is limited or non-existent, leaving these patients still at high risk of developing significant DR (237; 238).

Table 11: Table from the Blue Mountains Eye Study (233): CI calculated only on those patients that the study examiners had both images at baseline and 5 years later

Table 3 Progression of retinopathy in 139 diabetic participants examined at both baseline and 5-year visits with retinal photographs available from both examinations

		Retinopathy level at the 5-year follow-up visit				
Baseline retinopathy level	*n*	*DR absent (%)*	*NPDR questionable, minimal, or mild (%)*	*NPDR moderate or severe (%)*	*PDR (%)*	*Macular oedema (%)*
DR absent	90	77.8	22.2	—	—	
NPDR—quest, min, mild	39	30.8	56.4	12.8	—	
NPDR—moderate, severe	9	—	22.2	55.6	22.2	
PDR	1				100	
Total	139					
Macular oedema (%)	5.3					4.0

Abbreviations: DR, diabetic retinopathy; n, number of participants with gradable photos; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; quest, questionable diabetic retinopathy.

2.4.1.1.2 Retinopathy Risk Factors

Long standing duration of diabetes, hyperglycaemia and hypertension are considered the most recognised and studied risk factors for DR (225; 226; 237; 239-241). It is interesting that despite persistent hyperglycaemia not all patients with long standing diabetes go on to develop DR, hence hyperglycaemia and hypertension may not be the only factors involved in this process, and there may be unknown protective factors. Most of the literature states that >90% of patients with type 1 diabetes, after 20 years of diabetes, will develop some form of DR (227; 228) and this is in the context of hyperglycaemia, but Keenan *et al.* (242) studied a group of patients that had more than 50 years of diabetes. These patients were identified from the 50-Year Medal Program of the Joslin Diabetes Centre, and against a background of a long duration of hyperglycaemia, only 47.9% of these survivors were found to have retinopathy. The remainder without diabetic retinopathy were older, had longer diabetes duration, and had lower triglyceride levels. Although a survival bias could explain these results, i.e. those with retinopathy would have died earlier, these results also suggest that other factors must be at play in the development of DR.

Nevertheless, hyperglycaemia has long been associated with the development of DR in pre-clinical and clinical studies. In ground-breaking clinical trials such as the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and the United Kingdom Prospective Diabetes Trial (UKPDS) for type 2 diabetes patients, participants were randomised to intensive treatment or conventional treatment. In both studies the intensive treatment arm showed reduced amounts of retinopathy; in the DCCT(243; 244) there was a 76% reduction in the mean risk of development of retinopathy whilst in the UKPDS (239) there was a 21% risk reduction to the progression of retinopathy (245).

Interestingly, in both trials after study closeout, in both the intensive and conventional groups, diabetes control as measured by HbA1c converged. In the case of the DCCT (236), the conventional group HbA1c improved, and in the UKPDS the intensive group regressed towards the conventional treatment arm. When both groups were surveyed years later the intensive groups in both trials continued to develop retinopathy at a lower rate than their counterparts. This gave rise to the concept of "metabolic memory" and "legacy effect" leading to a change in the paradigm of diabetes management; clinicians now aim to intensify treatment from diagnosis and to maintain the lower HbA1c by a more intensive management of oral and injectable treatments. This same occurrence has now been observed in pre-clinical studies of retinopathy in different animals models (246). Studies of epigenetic regulation in the development of retinopathy show that detrimental effects associated with hyperglycaemia persist despite subsequent normalisation of glucose. Such studies are in support of the metabolic memory and legacy effects seen in human studies.

Without a doubt, the management of hyperglycaemia has a central role in the prevention and treatment of diabetes eye disease, but dyslipidaemia has also been considered to play an important role (247) although the evidence is less conclusive. The Wisconsin Epidemiology study of diabetic retinopathy (248) originally reported an association between total cholesterol and hard exudates. In a follow up study of these patients, 30 years later, published in 2015 (249) the authors reported that there was no association between total cholesterol and HDL in the incidence of DR and macular oedema and concluded that the type of serum lipids studied may not be implicated in the development of DR and DMO. However several other studies both in type 1 and type 2 diabetes report that patients with severe visual loss have persistently higher TC, triglycerides and LDL. This is the case for the Early Treatment Diabetic Retinopathy

Study (ETDRS) (250) original study, and subsequent follow-up study as well as the Pittsburgh Epidemiology of Diabetes Complications (EDC) (251). In the DCCT cohort, Miljanovic *et al.* (252) reported that the total cholesterol to HDL ratio and LDL could predict the development of clinically significant macular oedema and hard exudates. However, the authors also found that once adjusted for glycaemic control lipid profile could not predict the progression and development of DR. In an up-to-date review of lipids and diabetic retinopathy, Modjtahedi *et al* (253) suggest that apolipoprotein subclasses may be more sensitive than conventional lipid profiles in detecting a relationships with retinopathy and may be more implicated in the pathogenesis of DR. This may occur by transient damage occurring to the blood retina barrier allowing for lipoproteins to escape to the intra-retinal environment where they are remodelled causing damage into this space, contributing to the development of DR.

Hypertension control was examined as an independent risk factor for DR in the UKPDS study. It reported that tight blood pressure control showed a clinically significant risk reduction in the progression of DR (239; 245). Do *et al.* (254) undertook a Cochrane Review on the topic of blood pressure control for diabetic retinopathy and found some mixed evidence. They found that treating blood pressure may prevent DR for up to 4 to 5 years but also found that there is a lack of evidence with regard to retarding the progression of DR.

These findings suggest that there must be several mechanisms involved in the development of DR with the primary cause being the metabolic effects of long standing hyperglycaemia which leads to vascular changes and subsequent retinal injury and ischemia. Nevertheless, hyperglycaemia may only explain up to10% of the risk of developing DR (255), and hypertension and dyslipidaemia combined may explain <10% risk. Clearly, there are some less defined risk factors for retinopathy yet to be identified.

In addition, puberty and pregnancy are also important risk factors in the development of DR especially in type 1 diabetes (256; 257). At puberty Mitchell *et al* (258) suggests that the marked increase in growth hormone (GH) is the underlying cause of development of DR. In pregnancy Mallika *et al.* (259) suggested that retinal autoregulation may be modified by the pregnancy-related hormonal changes, and volume and cardiac output increases leading to the worsening of retinopathy.

2.4.1.1.3 Pathophysiology of DR

Diabetes retinopathy is a complex progressive condition that can be dormant for many years without any clinical symptoms and when discovered can be quite advanced. Thus far, molecular and biochemical pathways have been described and shown to be involved in this disease development, but the actual mechanism by which the disease develops is still not fully known.

The biochemical pathways in DR, mostly linked to glycaemia that have been established are as follows:

Polyol or sorbitol pathway: Responsible for metabolising excessive glucose. This pathway is under the control of two enzymes. The first is the aldose reductase enzyme that converts excessive glucose to sorbitol. The second enzyme is sorbitol dehydrogenase which has the role of converting sorbitol to fructose. Sorbitol is not soluble, and the process of converting sorbitol to fructose is slow and leads to the accumulation in the retinal cells which cause damage.

Advanced glycation end products (AGEs): When proteins are exposed to glucose for a significant amount of time it leads to a reaction where the glucose becomes attached to the protein and through cross-linking damages the protein and produces AGEs. The

production of these products is accelerated in the presence of diabetes due to the high level of glucose. AGEs, when found in retinal membranes, is associated with most complications including DR.

Protein kinase C (PKC): Hyperglycaemia causes an increase in diacylglycerol (DAG) which in turns increases the expression of PKC. PKC then increases the expression of transforming growth factor beta (TGFB) and endothelial growth factor (VEGF). These two products are implicated in the development of macular oedema and new vessel formation.

Oxidative stress: This condition occurs when there is an imbalance between the reactive oxygen species (ROS) and the ability of the cells to neutralise the ROS using antioxidants. Oxidative stress damages cells and contributes to the development of many diseases such as DR.

Hexosamine pathway: This pathway is triggered when there is an excess of intracellular glucose that cannot be dissipated by glycolysis. When glucose is high in the cells, glucose is converted to glucose-6-phosphate and subsequently leading to an increased flux of fructose-6- phosphate to the hexosamine pathway. Activation of hexasamine is implicated in retinal capillary apoptosis by altering protein function and gene expression.

Inflammation: Early and late stages of retinopathy appear to be related to an inflammatory process in the retina (260). It is known that hyperglycaemia, oxidative stress and AGEs contribute to the inflammatory process but inflammation per se then creates a self-propagating cycle that keeps stimulating the other pathways. Chronic inflammation also involves the production of vascular endothelial growth factor (VEGF) in the retina leading to angiogenesis of new weak vessels which have a propensity to

leak. This leads to the appearance of haemorrhages in the retina and leukostasis (leukocyte adhesion to endothelial cells) which causes capillary obstruction and non-perfusion.

Overall, there are many biochemical and molecular pathways that lead to the development of DR; it is not the result of a single common pathway. Nevertheless, to date, the established, most effective treatment is the use of anti-VEGF therapy. This will be discussed further on.

2.4.1.1.4 Evaluation of the Retina in Diabetes

The retina in diabetes can be visualised using a hand-held ophthalmoscope after applying dilating drops or by taking colour photographs of the fundus using a camera or slit lamp. In the ETDRS study 7 standard field colour photographs, using 35 mm colour film able to visualise 30 degrees of the fundus each was used. Since then, photographs have become a validated international standard for the classification of DR. From this study, what has been termed “the modified Airlie House” classification of diabetic retinopathy has been the accepted method for determining severity and grading DR. In more recent times, ultra-wide field colour photographs and fluorescein angiograms can now capture over 80% of the retina in a single image giving an assessment of what is happening in the periphery of the retina. Silva *et al* (261) showed that in a cohort of 200 eyes (100 participants) in a longitudinal prospective study that the presence and severity of peripheral lesions is predictive of worsening DR. The use of retinal photographs to visualise the retina at a cellular level is also now available using adaptive optics technology (262). Studies using this type of technology have allowed for the imaging of early vascular changes that have not been able to be captured on standard images or ophthalmoscopy.

Optical coherence tomography (OCT) is another tool for monitoring retinal changes in patients. OCT uses interferometry (techniques in which electromagnetic waves are superimposed causing interference in order to extract information) to differentiate individual retinal layers. It allows for the measurement of retinal thickness and morphologic changes in eyes including DR and DMO.

A newer wave of screening tools in the diabetic eye include electroretinography that can demonstrate abnormalities in retinal electro signalling. These devices such as RETeval-DR (263) use 3 parameters to assess normality or abnormality in the retina. RETeval-DR first measures the implicit time that it takes the retina to respond to each flash of lighting. As the eyes become more ischaemic the time response increases. It also measures the amplitude of the response or the strength of the response to the flashlight. The amplitude will decrease with disease progression. Lastly, it looks at change in pupil size between the dimmest and brightest flash. As disease progresses, the pupils will change less. Overall, electroretinography devices are currently not sensitive or specific enough for DR or DMO grading, but they are a useful tool in screening by streamlining referral of patients to eye services when digital photographs are not available.

2.4.1.1.5 Classification of DR

DR is classified in two broad categories; the early stage referred to as non-proliferative DR (NPDR), or the advanced stage referred to as proliferative DR (PDR). NPDR clinical features include microaneurysms, retinal haemorrhages, intra-retinal microvascular abnormalities (IRMA) and venous calibre changes. PDR, on the other hand, is characterised by new blood vessel growth (neovascularisation), which can lead to severe complications and blindness.

Diabetes macular oedema (DMO) is a condition that can occur in both NPDR and PDR, and is the leading cause of vision impairment with diabetes and occurs when fluid accumulates leading to abnormal retinal thickening and cystoid oedema in the macula.

2.4.1.1.6 Treatment

Minimising vision loss in the presence of severe retinopathy is the holy grail of diabetes eye management. Overall, we have few treatment modalities to use, and these include:

Laser photocoagulation: Argon-Laser retinal photocoagulation therapy was introduced in the 1960s and was the first treatment that provided an effective mean of preventing visual loss and has been the standard treatment for PDR and DMO (264). The use of this methodology was underpinned by 2 randomised clinical trials, the Diabetic Retinopathy Study (DRS) (265) and the Early Treatment Diabetic Retinopathy Study (ETDRS) (266). The DRS showed a reduction in risk of severe vision loss from 33% down to 13.9% at 5 years in patients with proliferative or severe non-proliferative DR whilst the ETDRS showed a risk reduction from 24% down to 12% on those with clinically significant DMO. The mechanism of action of laser on the retina is not fully understood (226), but the authors postulate that the laser scars lighten hypoxia and this, in turn, affects the haemodynamics of the retina. The goal of patients receiving laser has been to preserve useful vision and prevent blindness. Reversal of visual loss is rare, and laser photocoagulation has significant side effects. In a paper by Deschler *et al.* (267) a comprehensive review of side effects was undertaken by the authors. Some of these included severe pain during the procedure, worsening of macular oedema following laser therapy, loss of peripheral visual fields and reduction in night vision, decreased colour vision and contrast sensitivity. Moreover, there is a high

chance for laser burns to be deployed to other sites in the macula leading to damage of the macular and of other structures nearby such as lens etc.

Intravitreous steroid: The intraocular injection of steroids became part of the suite of treatments for DR and DMO in the 2000s as a way of trying to suppress inflammation and was particularly directed at those patients who were not responding to laser therapy. This form of treatment is mostly directed at patients with chronic DMO and who have undertaken previous cataract extraction as the use of steroids increase the risk of cataract. In 2011, Elman *et al.* (268) reported in a clinical trial that the benefits of intravitreal triamcinolone did not persist beyond 1 year, and by 2 years the visual outcome was generally not better than laser photocoagulation. Moreover, there are considerable adverse events with the use corticosteroids; more cataracts as mentioned but also glaucoma and an increased risk to eye infections due to the immunosuppressive properties of the drug.

Intravenous injections of anti-VEGF: This type of injectable therapy has been highly effective in regressing PDR and can be considered a turning point in the treatment of severe DR and DMO. Anti-VEGF therapy works by restoring the integrity of the blood-retinal barrier by stopping the formation of small, leaky, abnormal blood vessels in the eye (269). This drug in clinical trials has been shown to have achieved the same visual acuity (VA) as the subjects treated with laser photocoagulation at the end of the 2 year trial (241; 270). Furthermore, it is reported that patients achieved a better average VA, less peripheral visual field loss, decreased rates of new DMO onset and fewer vitrectomies over the 2 year period. Nevertheless, some patients find it difficult to adhere to the treatment routine of monthly injections into the eye.

Vitreoretinal Surgery: Although new modalities of treatments such as laser and anti-VEGF therapy appeared to have been the answer to so many patients with very severe eye disease, for a smaller group that has not responded pars plans vitrectomies are an option (271). These group of surgeries are conducted in patients where vitreous haemorrhages do not get reabsorbed or who have retinal detachments mainly due to the fibrous bands that appear with the onset of new vessels on the retina or require peeling of the epiretinal membrane amongst others conditions.

The current guidelines for the management of DR and DMO have been evolving with the introduction of therapies such as anti-VEGF. This is most relevant in those with DMO, and where it involves the fovea, and there is vision loss, anti-VEGF is the first line of treatment. Laser therapy remains still an important tool in DMO not involving the central vision and in PDR with steroid therapy being the last resort therapy (226).

Despite improvements in glycaemic and blood pressure control of our patients and an overall better understanding of the management of complications in diabetes, DR continues to be diagnosed, and it will continue to increase as more people are diagnosed with diabetes. This is particularly important in countries in Asia and Africa where health resources are scarce, and there is less chance for early screening of DR. In countries such as Australia it is important to continue to develop systems where the screening of our patients in the community is integrated in the ehealth record so that gaps in clinical care are minimised. This is the focus of a study presented in **Chapter** 7.

2.4.1.2 Diabetic Nephropathy

Diabetic nephropathy occurs in approximately 30% of patients with type 1 diabetes and up to 40% of individuals with diabetes (272; 273) and is the leading cause of chronic kidney disease (CKD) worldwide.

CKD refers to all kidney conditions that are present for ≥3 months, and the most severe form of this condition is referred to as end-stage kidney disease (ESKD). At this stage patients will require dialysis or kidney transplantation to survive. In Australia in 2014, there were around 22,100 people with treated ESKD—55% of patients were on dialysis while 45% were living with a transplanted organ (274). CKD can be asymptomatic with up to 90% of all kidney function lost before patients become aware of symptoms (274). The diagnosis of CKD is considered when persistently abnormal urine albumin excretion, defined as urine ACR > 2.5 mg/mmol in males or > 3.5 mg/mmol in females and/or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 is found (273) .

CKD is categorised into 5 stages where 1 is the least amount of kidney disease, and 5 is the highest. These categories are arrived at by using biological markers such as the blood and albumin in the urine described above. Table 12 (275) shows the different categories and levels of markers required for categorisations.

The pathophysiology of diabetes related CKD is complex and with molecular and biological pathways described. It includes glomerular hyperfiltration caused by haemodynamic changes related to systemic blood pressure changes or at the local level within the kidney. The haemodynamic changes occur due to alterations in the metabolic milieu with the release of vasoactive factors, alterations in cell signalling and others. These changes in diabetes lead to glomerular hypertrophy, glomerulosclerosis, and tubule-interstitial inflammation and fibrosis (272; 276).

2.4.1.2.1 Treatment

In addition to excellent glycaemic control being the major preventative factor and a means of retarding the progression of CKD, control of blood pressure is also of paramount importance. Renin-angiotensin-aldosterone system (RAAS) blockade is first

line therapy in the context of diabetes and Ca antagonists have shown benefit. Newer agents such as the SGLT2i show some renal benefit but these observations are awaiting RCT outcomes for confirmation these data needs to be updated in light of recent renal outcome trials. It is clear from the ONTARGET study the ARB and ACEi combination therapy is not of benefit and may accelerate renal function decline.

Table 12: CKD categories. From AIHW (275)

Box B5: Stages of chronic kidney disease

Stage 1: Kidney damage with normal kidney function (eGFR ≥ 90 mL/min/1.73 m²)
Usually no symptoms but high blood pressure is more frequent than for patients without CKD. Patients also had albuminuria.

Stage 2: Kidney damage with mild loss in kidney function (eGFR 60–89 mL/min/1.73 m²)
Most patients have no symptoms but high blood pressure is frequent. Patients also had albuminuria.

Stage 3a and b: Mild—moderate loss of kidney function (eGFR 45–59 mL/min/1.73 m²) (3a), or moderate–severe loss of kidney function (eGFR 30–44 mL/min/1.73 m²) (3b)
Possibly no symptoms, or may experience an increased need to urinate during the night (nocturia), a mild feeling of being ill and loss of appetite. Common complications include high blood pressure, mineral and bone disorders, anaemia, sleep apnoea, restless legs, CVD, malnutrition and depression.

Stage 4: Severe loss of kidney function (eGFR 15–29 mL/min/1.73 m²)
Symptoms are as for Stage 3, plus nausea, itching skin, restless legs and shortness of breath. Common complications of this stage are also as for Stage 3, along with electrolyte disturbances such as raised blood levels of phosphate and potassium and increased acidity of the blood.

Stage 5: End-stage kidney disease (eGFR <15 mL/min/1.73 m2 or on dialysis)
Symptoms are as for Stage 4. Additional common complications include inflammation of the tissue layers surrounding the heart, bleeding in the gastrointestinal tract, altered brain function and structure, and disturbances or structural or functional changes in the peripheral nervous system.

Source: Adapted from Kidney Health Australia 2007; Kidney Health Australia 2012a.

2.4.1.3 Diabetic Neuropathy

Neuropathy is a group of disorders that can affect up to 50% of patients with diabetes (277). Diabetic neuropathy can be divided into acute reversible neuropathy and persistent neuropathies. Persistent neuropathies form a large group of pathologies that cause considerable morbidity and mortality and can be broadly divided into two categories: distal symmetrical or peripheral neuropathy, which can be subdivided into focal and generalised; and autonomic neuropathy. The focal and multifocal

neuropathies include carpal tunnel syndrome, ulnar nerve compression at the elbow, and diabetic amyotrophy of the femoral nerve, III and VI cranial nerves and truncal.

Autonomic neuropathy can include orthostatic hypotension, erectile dysfunction and gastroparesis. Peripheral neuropathy can be asymptomatic in up to 50% of patients and if not recognised and managed, patients are at high risk of suffering devastating foot injuries and amputations (278).

The main clinical features of distal symmetrical or peripheral neuropathy include bilateral symptoms, predominantly loss of sensation in the distal lower extremities, and neuropathic pain. To date, the only strategy to prevent or delay nerve damage in neuropathy is to tighten glycaemic control conceding that it will not prevent nerve cell loss. The evidence for tightening glycaemic control is stronger in type 1 diabetes and only moderate for type 2 diabetes (279-281). Currently, Pregabalin and Duloxetine are the two pharmacologic drugs recommended for the treatment of neuropathic pain (279).

Papanas and Zigler (280) in a review of risk factors and comorbidities in diabetic neuropathy list duration of diabetes, hyperglycaemia, age, hypertension, dyslipidaemia and obesity as the major risk factors and cite additional risks as height, smoking, insulin resistance and hypo-insulinaemia. Furthermore, the authors suggest that hyperglycaemia, hypertension, dyslipidaemia, smoking and obesity are the only modifiable risk factors currently for patients to minimise this complication.

ADA (279) recommends that a medical history and clinical tests should be done in all patients with type 1 diabetes with >=5 years duration and all patients with type 2 diabetes annually for peripheral neuropathy. These tests assess both the small and large nerve fibres function and how insensate the feet are. They help predict future risk of complications and the presence or absence of an abnormality or impairment in the

feet. Screening and monitoring of patients with peripheral neuropathy is the cornerstone of managing our patients. Small fibre function can be monitored by using pinprick and temperature sensation, and for large fibre function, vibration perception, ankle reflexes and the 10g monofilament is used. The 10g monofilament is the suggested test to estimate the loss of protective sensation.

2.4.2 Macrovascular Complications

Macrovascular disease are diseases of the circulatory system and affect the heart and any large blood vessels in the human body.

2.4.2.1 Cardiovascular Disease

Cardiovascular diseases (CVD), broadly includes stroke, transient ischemic attacks (TIA), angina, myocardial infarction, claudication, and critical limb ischemia and are major healthcare issues in both developed and developing countries. Cardiovascular disease appears to have decreased in the last decades, and this has been attributed to better health care including the use of statins and aspirin (282-284). WHO states that in 2015 CVD was the number one cause for deaths implicated in 31% of all deaths globally (285).

The risk factors for CVD include non-modifiable ones such as age, gender and family history and life long behavioural issues such as tobacco and alcohol use, physical inactivity, and poor diet amongst others. These risk factors lead to the diagnosis of hypertension, dyslipidaemia, obesity and diabetes and in an individual the greater the number of these risk factors the higher the chance of heart attack or stroke. Diabetes is associated with an increased risk of CVD due primarily to atherosclerosis, i.e. deposits of plaque lining the artery (282; 284; 286; 287). The mechanism by which

atherosclerosis develops is unclear, but it appears to be the result of chronic inflammation and injury to the arterial walls. This process leads to the narrowing of all the artery walls in the human body resulting in a decrease in blood flow to heart muscles (leading to heart attack), brain (leading to stroke) and to the extremities (leading to pain, poor healing of foot ulcers and later amputation).

2.4.2.2 Cerebrovascular Disease - Stroke

Cerebrovascular disease or stroke is the leading cause of disability worldwide and the second primary cause of death in people aged >60 years and in those aged 15 to 59 years, the fifth leading cause of death (288). The disabilities that patients suffer from stroke include paralysis, loss of vision and confusion.

Stroke occurs when a) a clot either obstructs blood flow to the brain referred to as ischaemic stroke or b) when a blood vessel ruptures and prevents blood flow to the brain referred to as haemorrhagic stroke. Transient ischaemic attacks (TIA) are temporary partial blockages of the blood vessels and predispose patients to having strokes.

There is a plethora of information in epidemiologic studies that indicate that diabetes is an independent but modifiable risk factor for both ischemic and haemorrhagic stroke and it confers a higher mortality in a diabetic population (289-292).

2.4.2.3 Peripheral Vascular Disease

Peripheral vascular disease (PVD) or peripheral artery disease (PAD) is defined as narrowing of the lumen of arteries causing a reduction in circulation and in the arteries to the legs, pelvis and less commonly the arms. PAD is linked with an increased risk of lower extremity amputation.

Data from the UKPDS showed that the glycaemic control and duration of DM are significant predictors of both the incidence and the extent of PAD. In this study, each 1% increase in HbA1c was correlated with a 28% increase in the incidence of PAD, and higher rates of death, microvascular complications and major amputation (293; 294).

The usual symptom of this condition is pain in the legs whilst undertaking some physical exertion, and this is relieved by rest. Simple tests such as an assessment of pedal pulses and ankle brachial index in conjunction with history taking for symptoms can be undertaken to assess for PAD.

2.4.3 Non Traditional Complications

2.4.3.1 Cognitive Dysfunction

It is known that the brain represents only 2% of the body weight but its primary metabolic fuel is glucose and in adults, the energy intake of the brain accounts for 25% of the total body glucose consumption (295) to maintain its function. In recent years a body of evidence underpinned by studies using MRI has identified subtle structural and functional changes to the brain in the setting of long term diabetes referred to as "diabetic encephalopathy", usually presenting itself by cognitive dysfunction and dementia (296; 297). These findings are present in both in type 1 diabetes and type 2 diabetes (296; 298), and the cognitive domains most affected include attention and executive function, processing speed, perception and memory (296; 297). Elizabeth Seaquist (299) in an editorial titled "The final frontier: how does diabetes affect the brain?" suggests that persistent hyperglycaemia has negative impacts especially in cognitive function evidenced most recently in the ACCORD study. Here those with type 2 diabetes and an elevated HbA1c showed the most unfavourable performance in

neurocognitive testing. Koekkoek *et al.* in a review of the literature states that in T2DM patients the speed of cognitive decline is twice as fast compared with normal ageing subjects (298; 300-302). In type 1 diabetes the DCCT is the only randomised trial where cognition was included as an outcome measure. After 18 years of follow up, it reported that there was no clear deterioration of overall performance except in the subgroup with advanced diabetic microvascular disease and this showed an accelerated cognitive decline (303). This cognitive decline in epidemiological studies shows itself as vascular dementia and Alzheimer's disease and are more common in patients with type 2 diabetes, after adjusting for risk factors such as previous cardiovascular disease, history of hypertension and dyslipidaemia in aged matched controls (304).

Diabetic encephalopathy appears to share many underlying pathophysiologic mechanisms with other forms of dementia. Some of these mechanisms include the impairment of insulin signalling, the presence of low-grade inflammation and the amassing of AGEs and increase oxidative stress. The presence of amyloid plaques and neurofibrillary tangles are present in the hippocampus of patients with diabetes (305) examined at autopsy, but these changes are augmented in patients with both AD and DM (297). In a person with diabetes Simo *et al.* (306) propose that it is possible for diabetes to be an accelerator for the development of Alzheimer's disease. Nevertheless, the co-occurrence in diabetes of cerebrovascular disease leading to neurodegeneration and development of progressive cognitive impairment and dementia make it difficult to tease out which comes first (307). Of note, severe hypoglycaemia is also a well-known independent risk factor for cognitive impairment and dementia in elderly patients with type 2 diabetes (308; 309).

To date, there is little that can be done to treat patients to prevent DM related dementia. The most robust evidence is for aerobic exercise and dietary interventions (310; 311). Both of these are also helpful in diabetes, but to date, most of the treatments are ineffective at breaking through the blood brain barrier (297). Imaging of the brain in our patients is not helpful as it does not provide enough precision and omics has not provided us with any clear indicators to target our patients at high risk. However, cognitive dysfunction and dementia are clearly present in our clinics and can have grave consequences as patients are unable to self-care as shown by their poor glycaemic control, increased number of hypoglycaemia episodes in the home leading to hospital admissions. To date, it is important that in our clinics, apart from spotting self-care issues during the consultation, or by relatives or partners reporting odd behaviours, the application of self-administered questionnaires are a solution to screen and identify patients with early cognitive behaviours in the clinic. Some of these include the Mini-Mental state examination (MMSE) (312), Test your Memory (TYM) (313), Self–Administered Gero-cognitive examination (SAGE) and the diabetes-specific dementia risk score (DSRRS); a dementia predictive risk score for the prediction of 10 years dementia risk in T2DM patients (314).

2.4.3.2 Liver and Pancreas

Non-traditional complications of diabetes would not be complete without a mention of the growing numbers with non-alcoholic fatty liver disease (NAFLD). Although not specific to diabetes, it is reported to be present in between 21% to 67% of patients with type 2 diabetes, depending on the methodology used to measure liver fat (315). Ectopic liver fat in itself is thought to trigger a cascade of local changes, which potentiate hepatocellular injury. A proportion of those with NAFLD progress to non-alcoholic

steatohepatitis (NASH) with the ultimate endpoint of cirrhosis hepatocellular carcinoma and liver failure (316). To date, weight loss is recommended as well as maintaining excellent glycaemic control. Currently, there is no compelling evidence for any pharmacotherapy in NAFLD or NASH. Ectopic fat in the pancreas similarly is thought to play a role in beta cell decline although the study and imaging of pancreatic fat is still in its infancy.

Summary

Overall diabetes, and specifically type 2 diabetes, remains a challenging chronic disease with gaps in knowledge across the spectrum of pathogenesis, optimal treatment and complications. Anyone of these areas could be studied to test our hypothesis that the eHR can provide new knowledge, nevertheless specifically in this thesis, the areas chosen are the issues of diabetes complications and mortality in specific phenotypes of diabetes defined variously by ethnicity and age of onset. One of the specific areas studied is the relatively new phenomenon of youth onset type 2 diabetes, which is now discussed in **Part III**.

Part III: Young Onset Type 2 Diabetes Mellitus (YT2DM)

The studies presented in **Chapters 4 and 5** examine routinely collected eHR to provide information on whether age of onset impacts on diabetes outcomes and specifically whether young onset type 2 diabetes behaves differently to type 1 diabetes of a similar age or to type 2 diabetes of usual age of onset. In this context, **Part III** of the literature review pertains to young onset type 2 diabetes (variously described also as youth onset type 2 diabetes, YT2DM) as relevant background to these studies.

2.5 Introduction

Youth is no longer just the domain of type 1 diabetes (T1DM). Superimposed on the alarming upward global trajectory of diabetes prevalence are the increasing numbers with type 2 diabetes (T2DM) being diagnosed before the age of 40 years of age (317-319). The global incidence of T1DM is also increasing, and taken together, the net result is one, where clinicians will be faced with greater numbers of youth with diabetes of either type. Indeed, recent predictions for the US population are for a greater than threefold increase in the numbers of youth with T1DM and a fourfold increase in the young-onset T2DM (YT2DM), especially amongst minority youth (320-322). A rarity until recently, little was known of YT2DM, its clinical associations and outcomes. The US epidemiological SEARCH for Diabetes in Youth Study and the landmark Treatment Options for Type 2 diabetes in Adolescents and Youth (TODAY) study have illuminated this area considerably, and the results are sobering, with evidence for a high complications risk and an aggressive clinical course (323-329).

2.6 Epidemiology

There have been many reports in the literature since 1979 (330-332) of increasing numbers with YT2DM, and there is little doubt now that the incidence of YT2DM in youth has increased since then, at least in the US (320). One of the most accurate perspectives come from the SEARCH for Diabetes in Youth Study (SEARCH) which is essentially a US based registry of youth aged less than 20 years, who have been diagnosed with either type 1 or type 2 diabetes. SEARCH started in five American Centres in 2000 to determine the prevalence and annual incidence of youth-onset diabetes. From this collection, it has been ascertained that the prevalence of YT2DM between 2001 and 2009 increased by 30.5% from 0.37 per 1000 (95% CI, 0.34-0.40) to 0.48 per 1000 (95% CI, 0.45-0.51) in the United States (320). Over the same period, the incidence of YT2DM increased by about 37%. US estimates are in the order of up to 5000 new cases per annum.

Globally, there appears to be considerable variation in prevalence and incidence, with the lowest rates in Europe. However, the numbers are notably high in Asia and India (133). For example, using the China Health and Nutrition Survey (CHNS), a large, household-based and longitudinal survey in China and the NHANES survey data for America, Yan *et al* (333), reported that the prevalence of diabetes was higher in Chinese adolescents than in US adolescents at 1.9% vs 0.9% respectively using data from the 1999-2006 National Health and Nutrition Examination Survey for the United States (334). They also compared their adolescent data with South Korea (0.1%) and Taiwan (<0.0%) suggesting a higher diabetes prevalence in China. Xu *et al.* from the Chinese Centre for Disease Control and Prevention (CDC's) National Disease Surveillance Point System reported that the prevalence of type 2 diabetes was 4.5 % in

people aged 18 to 20 years and 6.6% in those aged 30-39 years. The assumption here given the populations reported is that these are patients with type 2 diabetes, however, diabetes type was not ascertained specifically.

Indigenous children also seem to be disproportionately affected. American Indians have the highest rated of youth onset type 2 diabetes in the US (335). In Australia using two administrative datasets, the Australian Institute of Health and Welfare reported in 2014 the prevalence of YT2DM in Australia; estimating that there were 881,000 Australians aged 10 years and over with type 2 diabetes with a calculated estimated prevalence of 4.5 % of Australians in this age group (Table 13). Among those aged 10 – 39, there were nearly 31,000 people (3.5% of all those over 10 with type 2 diabetes and 0.3% of this age group of the Australian population) with type 2 diabetes (336).

In addition to the US data, the global increase in YT2DM has been observed in all age groups except those younger than 4 years (28). Prevalence increases with increasing age with a tripling of numbers from 10-14 years to 15-18 years reported (320). Although YT2DM is not common under the age of 10 years, in the SEARCH Study involving a population of 1.2 million, 19 children with T2DM were aged between 5-9 years old. In the 10-14 years age group, 215 children were identified, and in the 15-19 years age group, a total of 296 with YT2DM were identified (322). Recently in the USA a young girl aged 3 was diagnosed with YT2DM (337). At the time of diagnosis, she was 35 kg. Similarly, in Australia, the youngest reported person diagnosed with YT2DM was a 5 year old from a remote indigenous community (338) and similarly weighing 36kg with a height of 1.23m.

Table 13: Prevalence of type 2 diabetes; Table from (336)

Table 3.9: Number of people aged 10 years and over, with derived type 2 diabetes, as at 30 June 2012

	Males			Females			Persons		
Age group (years), as at 30 June 2012	Number	Per cent	Proportion with type 2 diabetes in the population (%)	Number	Per cent	Proportion with type 2 diabetes in the population (%)	Number	Per cent	Proportion with type 2 diabetes in the population (%)
10–14	35	0.01	0.00	71	0.02	0.01	106	0.01	0.01
15–19	231	0.05	0.03	363	0.09	0.05	594	0.07	0.04
20–24	592	0.13	0.07	919	0.22	0.12	1,511	0.17	0.09
25–29	1,504	0.32	0.18	2,104	0.51	0.25	3,608	0.41	0.21
30–34	3,712	0.79	0.47	4,494	1.10	0.57	8,206	0.93	0.52
35–39	7,983	1.69	1.03	8,988	2.19	1.15	16,971	1.93	1.09
10–39	*14,057*	*2.98*	*0.30*	*16,939*	*4.13*	*0.37*	*30,996*	*3.52*	*0.33*
40+	456,936	97.02	8.98	392,851	95.87	7.25	849,791	96.48	8.09
Total (10+)	**470,993**	**100.00**	**4.81**	**409,790**	**100.00**	**4.10**	**880,787**	**100.00**	**4.45**

Notes:

1. Excludes people who have been identified as deceased (unless their date of death was after 30 June 2012).
2. Excludes people who were born, diagnosed or registered after 30 June 2012.
3. Prevalence based on the ABS Australian estimated resident population at 30 June 2012 (preliminary estimates).
4. Subcomponents may not add to totals due to a small number of cases with missing gender.

Source: AIHW analyses of NDSS and APEG records (see 'Data sources' in Appendix B).

2.7 Defining Youth Onset Type 2 Diabetes

Currently, most authors agree that YT2DM refers to the diagnosis of diabetes in children, adolescents and young adults. Nevertheless, there is no universally accepted definition in the literature regarding the age threshold for making the diagnosis of YT2DM. This is a challenge when reviewing the literature. As mentioned previously type 2 diabetes is extremely rare in pre-pubertal children. In the SEARCH study, the median age at diagnosis of diabetes was 13.5 years for girls and one year later for boys (322; 325). The SEARCH Study used the age of 20 as the upper threshold defining YT2DM, but some older studies have used age of onset only up to age 15 as the cutoff. A number of other studies from adult groups have used as high as 45 years old as the threshold below which YT2DM is defined (339). In the studies described in this thesis,

we have arbitrarily defined YT2DM as those diagnosed in the 15-30 age range. It is likely that the age definitions selected for various studies would have a major impact on the prevalence, demography and outcomes and need to be taken into consideration when interpreting the results.

In addition to the specific age thresholds, the distinction between type 1 diabetes and YT2DM has not been systematically addressed. In the past, the age of 30 or 40 years at diabetes diagnosis was broadly used as the threshold to distinguish type 1 from type 2 diabetes. Due to the increasing overlap in the age of diabetes onset, the distinction between YT2DM and type 1 diabetes may be less clear and becomes an important issue for individual patients and also for studies of the type described in this thesis. Furthermore, as background rates of obesity are rising in the general population the utility of BMI in defining diabetes type in youth may not be as robust as previously. Clinically, the presence of low c-peptide in the face of hyperglycaemia and the presence of anti-islet cell antibodies are helpful and support an autoimmune aetiology. Nevertheless, islet cell antibodies are not always positive in clinically phenotypic type 1 diabetes, and conversely, there is also a population background of positive antibody status in many people without diabetes. Suggestions have been made to replace the categories of type 1 and type 2 diabetes with a more etiologic approach to classification of diabetes types in youth, based on the combination of autoimmunity and insulin resistance status. This has yet to be widely adopted but would be a step forward. It should be recognised that many studies have the caveat that the diagnosis of type 2 diabetes was based on clinical phenotype alone.

2.8 Screening for YT2DM

Widespread screening for diabetes is not recommended although various expert bodies have recommended screening in high risk individuals. The current approach outlined by the American Diabetes Association (ADA) consensus report "Type 2 Diabetes in Children and Adolescents" are summarised in the table below (173). It is not known how widely this is put in to practice in the community. Nevertheless, these targeted screening recommendations capture the known risks for YT2DM being overweight and obesity, family history, at risk ethnicity and exposure to maternal dysglycaemia in utero as well as clinical signs of insulin resistance.

Table 14: Type 2 Diabetes in Children and Adolescents - Source: Classification and Diagnosis of Diabetes, American Diabetes Association Diabetes Care 2015 Jan; 38(Supplement 1): S8-S16. http://dx.doi.org/10.2337/dc15-S005 (173)

Criteria for Testing for type 2 diabetes or prediabetes in asymptomatic children*
• Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
Plus any two of the following risk factors:
• Family history of type 2 diabetes in first- or second-degree relative
• Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
• Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidaemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)
• Maternal history of diabetes or GDM during the child's gestation
Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age

Criteria for Testing for type 2 diabetes or prediabetes in asymptomatic children*
Frequency: every 3 years
* Persons aged ≤18 years.

2.9 Pathophysiology of Youth Onset Type 2 Diabetes

The pathophysiology of type 2 diabetes in youth differs from that of type 1 diabetes and resembles the pathophysiology seen in older onset type 2 diabetes; arising from the admixture of varying degrees of beta cell dysfunction and insulin resistance. There are, however, differences that are notable for youth. The TODAY study (Treatment Options for type 2 Diabetes in Adolescents and Youth) (323) was a multicentre randomised controlled trial examining treatment options for 600 youth with type 2 diabetes. Patients were randomised to 3 treatment arms; metformin, metformin plus rosiglitazone or metformin plus intensive lifestyle intervention. This study has illuminated the rapid beta cell decline seen in youth with type 2 diabetes as compared to adult onset disease. This was especially evident when compared with results from the ADOPT trial, a similar RCT but involving usual age of onset diabetes and the landmark UKPDS trial of newly diagnosis type 2 diabetes. Beta cell failure rates for youth (the proxy being medication failure rates) are shown in the figure below (Figure 9) and are clearly most rapid for youth in the TODAY trial (340-343). This rapid β-cell failure has also been shown to occur in their obese pre-diabetes phase at a rate of 15% per year with the mean transition time from prediabetes to overt diabetes at about 2.5 years (344-346).

Figure 9: Beta cell failure rates adults vs youth: From (343)

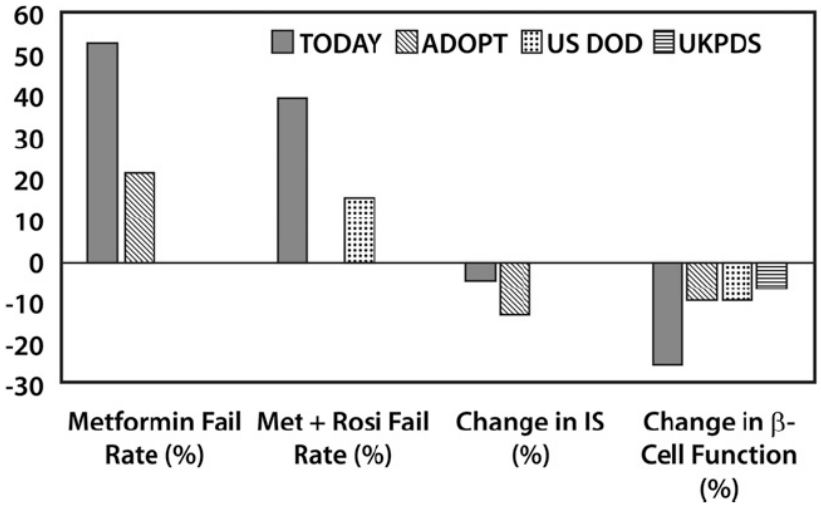


Figure 2—β-Cell failure rates in adults versus youth with type 2 diabetes. A comparison of medication treatment failure rates and percent change in surrogate measures of insulin sensitivity and β-cell function as reported in the TODAY study (youth) versus adult studies (A Diabetes Outcome Progression Trial [ADOPT], U.S. Department of Defense Database [US DOD], and UK Prospective Diabetes Study [UKPDS]). Note that the studies had different primary end points and therefore this is an approximate comparison, as there have been no head-to-head comparisons (11,12,14–16,67,68). Met, metformin; Rosi, rosiglitazone.

In addition to the greater beta cell abnormalities identified for YT2DM, modifiable risk factors for insulin sensitivity such as adiposity, excess visceral fat, ectopic liver and intramyocellular fat, physical activity, diet, sleep and stress may all impact and have generally been found to be abnormal in youth with type 2 diabetes (343).

It is notable that normal puberty is associated with a transient reduction in insulin sensitivity (an increase in insulin resistance); this is in the order of 50% in lean non obese healthy children. There is a compensatory increase in insulin secretion, and hyperglycaemia may ensue arising from low beta cell reserve. This beta cell reserve may be genetically, epigenetically and environmentally determined and thus puberty may be a high risk time for susceptible individuals. Diabetes onset in puberty may be reversible in youth due to this transient nature of insulin resistance (343).

3.0 Glycaemic Control and Psychosocial Aspects in YT2DM

In concert with the above observations of faster beta cell decline is the reduced durability of glycaemic control in YT2DM. This was clearly seen in the TODAY study mentioned above (347). For example, the monotherapy metformin glycaemic control failure rate was 50% by 3 years which is much more rapid than we see in adults (348). In many studies of older vs younger onset disease, glycaemic control appears to be worse in the younger age of onset groups. In a study involving the RPA Diabetes Centre data from 2840 patients, Hsieh *et al.* (349) noted worse glycaemic control in youth irrespective of diabetes duration and treatment. This in itself heralds a potentially increased risk for complications discussed further in this chapter.

Apart from biological differences there are now documented challenges with respect to psychosocial aspects including self-management in YT2DM, contributing (at least in their adolescent phase) to poor glycaemic control. In contrast to young individuals with type 1 diabetes, individuals with YT2DM are not acutely sick, they are generally are not treated in a specialised clinic dedicated to their condition, and they are in a phase of life characterised by a propensity to avoid parental supervision. Browne *et al.* undertook an online study in Australia where a random sample of the National Diabetes Services Scheme registrants with Type 2 diabetes were surveyed, aged 18 to 39 years (350). The self-reported results indicated that 63% of respondents had severe diabetes-related distress and 27% had impaired general emotional wellbeing. Lack of motivation, feeling burned out and being time poor were identified as top barriers to self-management. It was perceived that YT2DM had different healthcare needs than their older counterparts (68%) and that most T2DM information/services were aimed at older adults.

In addition to the psychological disadvantages noted above, globally those populations at risk for early onset type 2 diabetes may also be those who are socioeconomically disadvantaged. Thus, the challenges for YT2DM are more than metabolic, and there is very little research around the needs and concerns of young people with YT2DM (351; 352).

3.1 YT2DM: Chronic Complications and Mortality

Given the long duration of diabetes ahead of those with early onset type 2 diabetes and the challenges to achieving good glycaemic control noted above, one would predict a high lifetime risk for diabetes complications. An exploration of the complications in youth with type 2 diabetes, in comparison to type 1 diabetes and older onset type 2 diabetes follows.

3.1.1 Chronic Complications for YT2DM vs Type 1 Diabetes

How do those who develop T2DM in adolescence and young adulthood fare in the long term and in comparison with their age counterparts with T1DM? This question is further explored for traditional chronic complications of diabetes

Other than recent reports that DKA presentations in YT2DM are declining but remain significant for T1DM (353), comparative data on acute complications are still limited. Similarly for less classical complications (e.g. hepatic steatosis, periodontal disease, cognition) which are therefore not reviewed here.

3.1.1.1 Microalbuminuria, Nephropathy and Renal Failure

3.1.1.1.1. Microalbuminuria at Presentation

Microalbuminuria is more prevalent at presentation in YT2DM than in T1DM. Dart *et al*. compared complications ascertained by healthcare utilisation codes for 342 YT2DM (onset <18 years and a high proportion of First Nation Canadians) and 1011 T1DM subjects (354). Albuminuria at diagnosis was more prevalent in the YT2DM cohort (27.1 vs 13.5 %), despite a similar hypertension prevalence. In the multi-ethnic SEARCH study, within 12 months of diagnosis, the prevalence of an elevated albumin/creatinine ratio (ACR) was 16.3 vs 9.9 % in 374 YT2DM and 2885 T1DM subjects, respectively (355). These findings are consistent with earlier reports in other ethnicities; albuminuria at diagnosis of YT2DM was present in 22 % of Pima and 14 % of Maori peoples (356). The majority at diagnosis are in the microalbuminuric range. Although some of these data are based on single assessments for albuminuria Taken together, the prevalence of elevated urinary albumin is in the order of 15–27 % at diagnosis for YT2DM, heralding an increased cardiovascular and nephropathy risk and a strong argument for screening at presentation. It is recognised that albuminuria can precede diabetes as a component of the metabolic syndrome and may have common origins. The presence of albuminuria at this stage could represent early incipient diabetic nephropathy or an obesity-related glomerulonephropathy, the origins and prognosis of which are less clear (357).

3.1.1.1.2 Higher Prevalence of Excess Urinary Albumin at Various Disease Time Points for YT2DM than T1DM

The SEARCH study found that after a shorter duration, the prevalence of elevated ACR was still in excess for YT2DM than for T1DM (22.2 % and 9.2 %) and there was a

prevalence ratio of 2.4 for excess albuminuria noted for YT2DM (355). In the SEARCH cohort, the association of type of diabetes and elevated ACR persisted after adjustments for glycaemia. Further, insulin resistance parameters (BP, LDL, HDL, Tg and BMI) accounted for 19 % of the excess prevalence in YT2DM, with little additional information provided by the addition of inflammatory markers to the model (fully adjusted odds ratio (OR) 1.68 for YT2DM vs T1DM for elevated ACR). A similar excess in the prevalence of microalbuminuria and macroalbuminuria was seen in Manitoba. The higher prevalence of microalbuminuria and nephropathy is seen in YT2DM despite their shorter disease duration and lower mean baseline HbA1c (354).

These data together support the conclusion that the risk of excess albuminuria at any time point is increased more than twofold for YT2DM over T1DM and the differences highlight the impact of metabolic syndrome factors over and above glycaemia. These data also imply a residual excess risk for albuminuria for YT2DM not captured by usual clinical measures. There is, however, a need for a longer-term perspective on the implications of this.

3.1.1.1.3 Evidence for an Increased Rate of Progression of Albuminuria and a Shorter Time to ESRD for YT2DM Compared with T1DM

A current debate in nephrology is whether albuminuria in diabetes, particularly at microalbuminuria levels, is a risk factor (the modification of which will affect the disease process) or a risk marker (not necessarily causally related) for later renal disease (358). It is now recognised that microalbuminuria can regress and estimated glomerular filtration rate (eGFR) can decline with no change in albuminuria status. Therefore, the presence of microalbuminuria does not exclusively confirm the presence of kidney disease and, indeed, the cross-sectional data described above do not consistently show

a difference in eGFR/creatinine clearance between the two youth-onset groups. A key question is whether the cross-sectional observations of higher rates of excess albuminuria truly represents an accelerated time course and translate into a higher risk for established renal disease. More recent data do now give us a perspective on the rate of progression of albuminuria and to end-stage renal disease (ESRD) in these groups. In the prospectively followed YT2DM TODAY study cohort, the prevalence of albuminuria continued to increase, and the progression to new-onset albuminuria in this study was 2.6 % per year in the context of optimised clinical care offered in a trial setting and aggressive therapy to maintain BP and renin-angiotensin-aldosterone system (RAAS) blockade (326). Dart and colleagues found that the time-based risk of renal failure (composite outcomes including all chronic kidney disease codes and end-stage kidney disease) for YT2DM was increased fourfold compared with T1DM after controlling for age at diagnosis, HbA1c, BMI Z score and era of diagnosis. Notably, estimated SES status was not an independent predictor of renal outcomes in this study (354). These findings are consistent with earlier data from Japan that reported an increased rate ratio of 2.74 for YT2DM and the development nephropathy (359).

3.1.1.2 Retinopathy

The data are less clear if there is an excess risk of retinopathy in youth with T1DM vs YT2DM. Retinopathy has been noted at diagnosis of YT2DM. In a Manitoba study, the prevalence of retinopathy was higher in type 1 vs type 2 (13.8 vs 11.7 %) at a median duration of 7.9 and 7.4 years, respectively, and higher mean HbA1c for T1DM. This pattern of excess retinopathy in T1DM was in contrast to the other microvascular complications in the same study. Retinopathy free survival analysis for YT2DM appeared more reduced ~10 years from diagnosis, but differences were not statistically

significant (360). In the SEARCH pilot study, diabetic retinopathy was assessed by two 45° field retinal photographs. The prevalence of diabetic retinopathy was 17 % for T1DM and 42 % for YT2DM with a short mean follow-up (6.8 years in YT2DM) (361). Notably, the prevalence of retinopathy in YT2DM assessed using similar methods and criteria was much less in the TODAY study, than in the SEARCH study (13.7 vs 42 %). For the TODAY study cohort, the retinopathy assessment was performed in the final year of the trial. The SEARCH cohort had a longer duration of diabetes (mean 4.9 vs 7.2 years) and did not have the benefit of trial-based intensive glycaemic and BP interventions. Whether these factors alone can account for the differences seen in retinopathy prevalence is not clear. Interestingly, in the TODAY study, a higher BMI tertile was independently associated with a lower risk of retinopathy, and it is suggested that retinal insulin resistance may have a paradoxically protective effect (329).

3.1.1.3 Neuropathy

There are a few studies comparing neuropathy in YT2DM with T1DM. A pilot study from the SEARCH investigators found that the prevalence of peripheral neuropathy assessed by the Michigan Neuropathy Screening Instrument was 25.7 % in YT2DM vs 8.2 % in YT1DM. The unadjusted OR of neuropathy was fourfold increased for YT2DM, the difference not only largely accounted for by age and duration but also metabolic syndrome variables (362). Dart *et al*. also found that the raw prevalence of neuropathy conveyed by health codes was highest in YT2DM compared to T1DM and statistically significant differences were noted by approximately 5 years of known duration (360). Whether these are clinically significant differences remains to be seen, and there are no data on painful vs insensate forms of neuropathy. These data coupled with the observation of an increased prevalence of neuropathy in association with the metabolic

syndrome (363) would predict a heightened risk for adverse neuropathy outcomes in YT2DM. Definitive prospective evidence is needed, similarly for autonomic disease.

3.1.1.4 Macrovascular Disease and Risk Factors

Cardiovascular disease (CVD) remains the leading cause of death for both T1DM and YT2DM and risk factors for cardiovascular or macrovascular disease are similar for both: overweight, dyslipidaemia, hypertension, gender, hyperglycaemia and renal disease (364). A higher prevalence of adverse CVD risk factors compared with controls or T1DM has been consistently seen in YT2DM (6; 365-367). We observed significantly less favourable lipid and BP indices for T2DM vs T1DM at similar age, duration and glycaemic control, despite a higher prevalence of antihypertensive and statin treatment. These long-term observations are consistent with the progression of CVD risk factors in the face of treatment seen prospectively in the TODAY study (328). The heightened renal risk of YT2DM and previously unrecognised adverse lipid subpopulations in YT2DM predict adverse clinical outcomes in YT2DM (368). Prior studies of intermediates for cardiovascular disease, such as IMT, arterial stiffness and diastolic dysfunction, have shown early preclinical abnormalities not only in YT2DM but also in T1DM (369; 370). The SEARCH study demonstrated significantly increased arterial stiffness measures in YT2DM over T1DM, largely explained by differences in abdominal adiposity and hypertension (371). At the time of planning of these studies in this thesis, there were no data on the long term macrovascular complications in YT2DM vs T1DM and this area is examined in the study presented in *Chapter 4*.

3.1.2 Time Trends and Mortality Observations for YT2DM vs Type 1 Diabetes

T1DM diabetes remains the seventh leading cause of death in the USA and on the top 10 causes of death globally (372; 373). Here, we examine the more recent mortality trends for T1DM and, where possible, compare the mortality experience with that of YT2DM

In the wake of the landmark, DCCT study and the advent of improved cardiovascular and glycaemic management, the outcomes for T1DM have improved significantly. The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study and the community-based Allegheny County T1DM Registry (ACR) established in the 1970s have both provided valuable and unequivocal evidence of a significant secular decline in mortality for T1DM in regional America. Mortality rates in childhood-onset T1DM have declined by 34 % over 15 years, and there has been a 15-year increase in life expectancy for those diagnosed in 1965–1980 vs. 1950–1964 (374; 375). The greatest reductions are seen in mortality from acute complications, renal disease and to a lesser extent cardiovascular disease.

Recent data extend these observations internationally and are inclusive of older-onset age groups, with nationwide studies from Finland, Denmark, Australia and Japan all confirming significant mortality benefits over time, largely attributable to a reduction in chronic complications (376-379). These benefits have not reached all T1DM populations, and poorer risks and outcomes persist for some minority groups and comparatively for women (375; 380). Of concern is a report from Finland that found increasing mortality rates for T1DM diagnosed aged 15–29 years, driven by a higher proportion of alcohol-related deaths and deaths from acute diabetic complications (376). Smaller studies have also reported differential excess mortality dependent on

age of onset, which together highlights the increased vulnerability associated with the development of a chronic disease in adolescence and young adulthood (381). More contemporary standard mortality ratios (SMR) reported for T1DM populations still range from 2.8 to 5.8. Although mortality improvements are seen in diabetes, there is still an excess residual risk as background mortality rates improve (376; 380; 381). Studies from FinnDiane, the EDC and more recently Denmark suggest that this excess risk is due to renal disease, in the absence of which mortality rates in T1DM are almost at background. However, there also remains a significant mortality from acute complications that are also potentially preventable (377; 382; 383).

On this background are some comparative mortality data with respect to Type 1 diabetes vs YT2DM. The large prospective population-based study Diabetes Incidence Study in Sweden (DISS) (384) examined mortality in 6771 incident cases of diabetes in the 15–34 age group with an average follow up time of 8.5 years. The SMR compared to the general population for the YT2DM group was higher than for T1DM at 2.9 and 1.8, respectively, with a greater percentage of circulatory disease being the underlying cause of death in YT2DM (58 vs 28 %). From the Southern Community Cohort Study in the USA, Conway *et al*. examined mortality in youth with diabetes over a shorter mean period of 3.9 years stratified by treatment rather than by diabetes type; the HR for death compared to the non-diabetic population were 4.3 for those using insulin alone, 4.2 insulin plus hypoglycaemic agents and 2 for those not on insulin therapy (385). These studies are of short to medium term. At the time of planning this thesis, long term data on these outcomes were not yet available, but such a perspective is important given that patients are young at disease onset. This is the focus of the study presented in **Chapter 4.**

3.1.3 Chronic Complications in YT2DM vs Older Onset Type 2 Diabetes

There is precedence for the idea that age of onset may impact on complications risk in diabetes. In type 1 diabetes a number of studies have investigated the concept of whether the onset of type1 diabetes in puberty or before affects complications risk with some studies suggesting that the early pre-pubertal years are protective (386; 387). Nevertheless, the situation for type 2 diabetes is less clear with a relative paucity of data, at least up to the point when the studies in this thesis were planned. In the section following are the data on specific chronic complications in early onset disease, i.e. YT2DM in comparison to later onset type 2 diabetes.

3.1.3.1 Microalbuminuria and Nephropathy

As noted prior, there have been several studies now which report an increased prevalence of albuminuria in Y2TDM at presentation (356; 359; 388). The rate of progression seems to be rapid in young type 2 diabetes in general. In studies of Pima Indian youth with type 2 diabetes, the rate of albuminuria reported increased from a base of 22% to 58% with many progressing to macroalbuminuria by 10 years (389). Krakoff *et al.* examined the incidence of diabetic nephropathy in early and later onset diabetes and did not find a difference (390). The study population were Pima Indian and included 1359 subjects aged 20-39 with type 2 diabetes, and 971 between 40-59 followed up for over 25 years.

Nevertheless, a less sensitive measure of nephropathy, the protein/ creatinine ratio was the marker used, and albuminuria was not compared in this early study. Examining ESRD incidence showed an excess in youth and this was largely accounted for by a longer disease duration (391). One of the best known studies is that by Hillier and

Pedula who interrogated the Kaiser Permanente database in the US and studied over 7000 patients with type 2 diabetes (339). The YT2DM group (identified as age less than 45 years old) did have a higher risk of microalbuminuria as compared to older onset disease with an HR of 1.2 (95% CI1.1-1.4). Whether this translates into an excess risk of ESRF is not confirmed at this point.

3.1.3.2 Retinopathy

The prevalence of retinopathy at presentation of young onset type 2 diabetes appears to be less than for albuminuria. In a Japanese study of YT2DM, ~ 9% had retinopathy noted at first visit and retinopathy prevalence was in the order of 18% after 5 years (392). In a robust study using formal seven field photography to grade retinopathy, an Australian group found that only 4% of YT2DM had retinopathy after 2 years of diabetes duration (365). Similarly, the prevalence of background retinopathy was 4% after 3 years of diabetes in youth with type 2 diabetes in a study from New Zealand(393).

If one examines the issue of young vs older onset diabetes by direct comparison, early studies from Pima again noted a lower prevalence of retinopathy in the younger onset cohort and a lower risk of retinopathy for young onset disease, after adjusting for gender, glycaemia and BP (390). Hillier and Pedular in the study mentioned above did not find an excess of retinopathy for youth although follow up duration was short. In contrast, Chuang *et al.* (394), in a study from Asia involving multiple sites did show an excess of risk for retinopathy in young onset diabetes and this was determined to be largely due to a longer duration of disease. A study of data from our unit, after accounting for duration and HbA1c as an index of glycaemic exposure, found an excess prevalence of retinopathy in younger age of onset groups suggesting a greater susceptibility to retinopathy for youth (395).

3.1.3.3 Neuropathy

There is a paucity of data on neuropathy specifically in YT2DM.

In the study above by Chuang *et al.* (394) the prevalence of neuropathy measured by various modalities were similar in young vs older onset groups with a prevalence in the older of 26% for both. The SEARCH Study reported that the prevalence of peripheral neuropathy was significantly higher in those with type 2 (25.7%) versus type 1 (8.2%) and Jaiswal *et al.* (362) concluded that the prevalence of peripheral neuropathy amongst the youth with type 2 was similar to the reported numbers in older adults with type 2 diabetes (396-398). Nevertheless, there is a great need for long term comparative data for this complication.

3.1.3.4 Macrovascular disease

The data again are sparse in this area with many studies looking primarily at surrogate markers for vascular disease. The high prevalence of microalbuminuria, an independent risk factor for vascular disease, heralds an increased vascular risk at a young age. In a cardiac echo study, septal wall thickness was increased in YT2DM (399) which would be in keeping with studies that showed higher BP measurements compared to non-diabetic controls (366). Furthermore, reduced nocturnal BP dipping, a negative prognostic factor has been found in studies of youth with type 2 diabetes (400). A Japanese study reported increased atherosclerotic disease and measures of aortic pulse wave velocity in a small study of YT2DM compared to controls (401; 402). In the comparison of younger (less than 45 years of age) vs older onset type 2 diabetes Hillier and Pedula found a 14 fold increase in the risk of myocardial infarction compared to non-diabetic background populations and a 4 fold increase for older onset diabetes against background. For any macrovascular complication, the HR were 7.9 (95% CI

4.8 –13.0) for the younger onset group in contrast to the HR 3.8 (95% CI 3.4–4.2) for older onset groups. Providing a different perspective, Chuang *et al.* found that older age of onset, once duration was accounted for (but not age), increases the risk of macrovascular disease. Collectively, the data seem to imply that the absolute risk of macrovascular disease is highest for older onset groups, largely due to the effects of an older age *per se*, however, the relative impact of diabetes on macrovascular risk compared to those of similar age without diabetes is greater for youth. One assumes this might be so because of the low background risk in younger people. Whether these findings would persist for longer periods of observation and whether this would imply differential effects of age of onset on survival is unknown and the focus of the study presented in **Chapter 5**.

3.1.3.5 Mortality in YT2DM vs usual onset type 2 diabetes

Similar to the T1DM situation, advances in survival for general T2DM populations are also being reported (403; 404). However, studies in Pima Indians first suggested adverse mortality outcomes for YT2DM (391). The lack of long-term data in other populations prompted an interesting study by Rhodes *et al*. (405). By using a Markov modelling approach to predict the life course for a hypothetical cohort with YT2DM aged between 15 and 24 years, they projected a 15-year loss of life expectancy, along with the onset of chronic complications by the 40s for those with YT2DM. At the time of this study plan little was known about survival at all in YT2DM, especially given the difficulty in obtaining long term data. Furthermore, being a relatively recent phenomenon, prospective longitudinal data on survival are lacking.

3.2 Knowledge Gaps Regarding Young Onset Type 2 Diabetes.

There remain significant gaps in the understanding of youth onset type 2 diabetes as an entity distinct from usual onset type 2 diabetes and type 1 diabetes in youth. The poorer glycaemic control, faster monotherapy failure rate and decline in beta cell function heralds a significant increased risk for diabetes complications. At this point, it is still unclear how to preserve beta cell function in YT2DM and the most optimal treatment for YT2DM pharmacologically. At the time of planning the studies, these newer agents, such as the SGLT2i and GLP1RA, have not been extensively trialled in YT2DM.

Although early studies do suggest a high burden of complications and high prevalence of obesity and adverse CVD risk factors, little is known of the longer-term complications for YT2DM, especially in comparison to type 1 diabetes. With this realisation, a question arising is how do those who develop T2DM in adolescence and young adulthood fare in the longer term and in comparison with their age counterparts with T1DM? One might well ask, what utility would such a long term comparative perspective offer? Of course, assessing the modern burden of disease and the characteristics of diabetes at a younger age is essential to healthcare planning and delivery. However, such insights also have relevance at the clinical coalface. The traditional focus of diabetes in youth is on T1DM and clinicians are well versed in these challenges; the differences in outcome for YT2DM are not immediately obvious. Prior comparisons of outcome between T1DM and T2DM of usual onset have always been hampered by either the older age of the typical T2DM patient or, if age is accounted for, the much longer disease duration of the T1DM patient, resulting in seemingly poorer outcomes for T1DM. Until recently, little has existed in the literature to refute this

assumption for youth, and as a consequence, historically younger patients with YT2DM may not have been treated optimally (402; 406). By the comparison of YT2DM with T1DM of similar age, the confounders of disparate age and duration on outcomes can now be attenuated.

Additionally, a unique and informative perspective as to the degree to which glycaemia (common to both types) and insulin resistance/metabolic syndrome features (more likely to be represented in YT2DM) contribute to diabetes outcomes can be examined. With the changing landscape of diabetes, it is timely that a comparative perspective is offered to help clinicians prioritise and prognosticate more appropriately. The available evidence suggests that YT2DM is a more aggressive phenotype, but long term data remain lacking and especially in regard to survival. This aspect is examined in the study presented in **Chapter 4**.

Furthermore, the impact of diabetes in youth compared to older onset in terms of mortality and CVD mortality has not been fully elucidated. It does appear that CVD risk factors are present early in YT2DM but whether this translated into worse long term survival than older onset disease is not known. These aspects are explored in **Chapter 5** presented in this thesis. Furthermore, research is needed to better understand complications risk. If there is truly an inherent susceptibility in youth is not known but would inform treatment strategies. The prevalence of other “non-traditional” complications of diabetes such as NAFLD, OSA and cognitive decline is an area for further study.

CHAPTER 2:

General Description of the Database (eHR) Used in the Studies of this Thesis

The Royal Prince Alfred Hospital (RPAH) Diabetes Database is the eHR that holds clinical information on patients attending the diabetes service since 1986. It is our third attempt at computerising diabetes data. The first two, between 1979 and 1985 were abandoned because the operating systems became obsolete and the programs were also difficult to modify according to demands caused by rapid changes in the expanding knowledge of diabetes. The software used to generate data for this thesis is Clinical Reporting System (CRS) (407), and the hardware is located at a secured offsite location within the hospital. The CRS system allows usage, as a clinical database for multiple health care professionals to record simultaneously clinical findings of patients. However, with research always an integral part of our overall aim, we designed the program to conform to a relational database format. This allows different types of information about a patient to be stored in and extracted when required from discrete but related tables (Figure 10). This relational design minimises redundancy and inconsistency of the data fields in comparison with a flat file design such as an Excel spreadsheet, which requires a new and repeating data entry for each patient visit and is more cumbersome for different data to be linked for analysis. Of note, the overall design of the RPAH eHR database allows it to serve the two overlapping but distinct purposes of clinical care and research.

For research purpose, depending on the questions being asked, relevant information can then be extracted from the various tables and linked for analysis. For example, a

question on the impact of ethnicity and socio-economic status on diabetes complications and foot ulceration can be extracted from two tables (Figure 10). CRS database uses a query language to access required data from one or more tables, and an example of a query is shown in Figure 11 illustrating how a cohort of YT2DM with age of onset between 15-30 years with available data after 1st January 2015 identified, and their clinical status examined. Figure 12 shows an example of the results of the query in a format suitable for export for analysis.

At the outset 30 years ago we chose to retain paper copies of patient data (both structured and unstructured) in parallel with the electronic data. Amongst other reasons, this decision was largely due to the fact that computer systems were not as reliable at that time, the paper format was still the standard medico-legal requirement, and clinicians were anxious to maintain direct interaction with patients during the consultation, rather than being distracted by the point of care data entry. While more labour intensive the use of these paper documents in all clinical encounters helps to minimise omissions made during clinical assessment and to standardise information collected, facilitating cross-sectional and longitudinal comparisons. With current technology and changes in community attitudes and regulatory requirements of utilising computer data, our decision may be substantially different. Because of this historical decision, data collection in our system has traditionally been based on the entry of data during the consultation into the paper forms with subsequent transcription into the electronic database. The paper documents contain fields for both structured and unstructured data. Data such as family history and status of retinopathy which need to be collected for every patient in a standardised way is entered by a series of structured tick boxes by staff making the appropriate choice. An example is shown in Figure 13. Information which varies more widely between individual patients and which are not

highly relevant to diabetes are entered in free form text as unstructured data. An example is shown in Figure 14.

Therefore, a great deal of judgement is used during the design of the database to determine whether the collection of particular information warrants a structured format. In line with this philosophy, a structured tick box would be created for a condition such as IHD which is always relevant to diabetes whereas conditions such as the previous cholecystectomy would be entered in an unstructured format. Some items such as medications are collected in both structured and unstructured formats. Of course, this type of decision needs to be reviewed regularly as our knowledge of diabetes evolves. A prominent example of the requirement for change is the emerging understanding of hepatic disease as an important complication of diabetes in the last 2-3 decades.

Some of the relevant forms are shown in Appendix 5. The use of our database has been approved by the Institutional Ethics Committee. In addition, each patient at first presentation is asked to give consent for their data to be stored in this manner.

Functions of the RPAH eHR:

As mentioned above, the database underpins both clinical and research activities of the Diabetes Centre. It also serves an administrative role in identification and tracking of every patient who attends the service and enables the preparation of detailed reports such as monthly statistics for hospital and government requirements. Additionally and importantly, it is the backbone of our communication with referring doctors. For a clinical encounter, the data in the database is automatically extracted to become the first (and factual) part of a hybrid letter and merged with freehand (and advisory) comments made by the treating clinicians. A typical example of such a hybrid letter is

shown in Figure 15. The hybrid letter is always checked by the responsible clinicians and health professionals during which mistakes or omissions in data entry can be rectified. As any correspondence cannot be generated without prior data entry, this process has the added advantage of ensuring that data have been appropriately entered. We also participate in national data collections such as the Australian National Diabetes Audit, allowing our data with that of other centres in Australia to be compared.

Figure 10: Example of related tables and the information gathered.

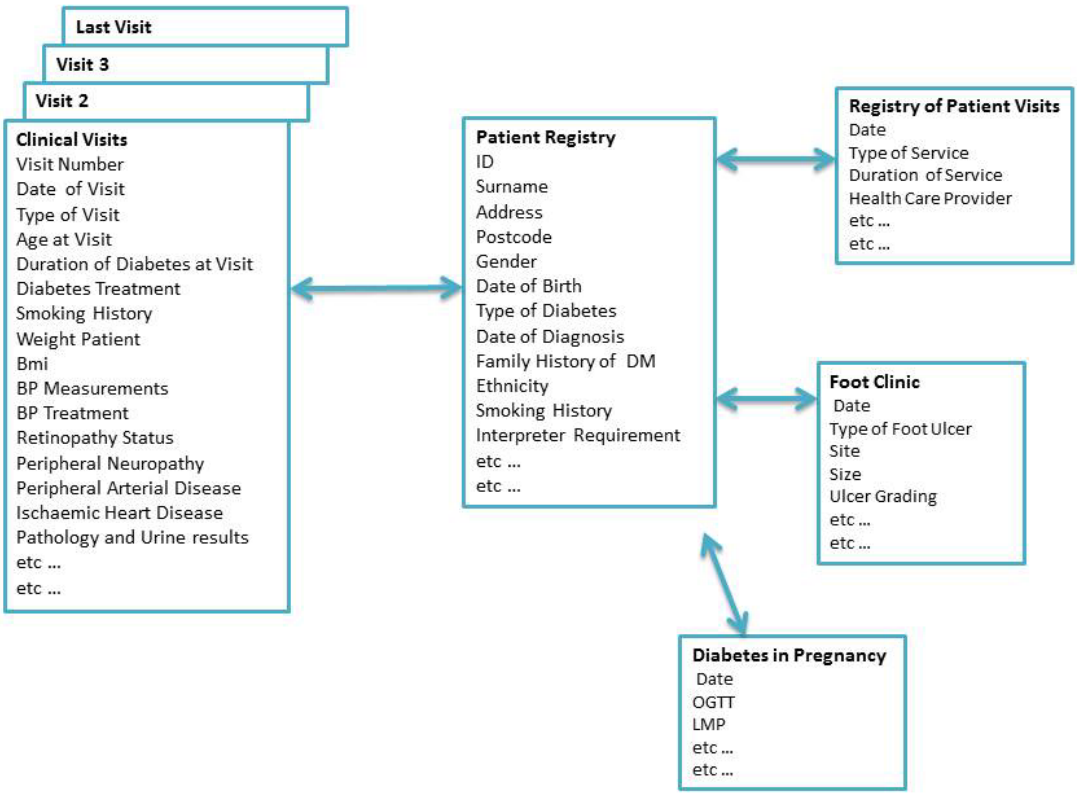


Figure 11: An Example of a Query on the CRS Interface Screen

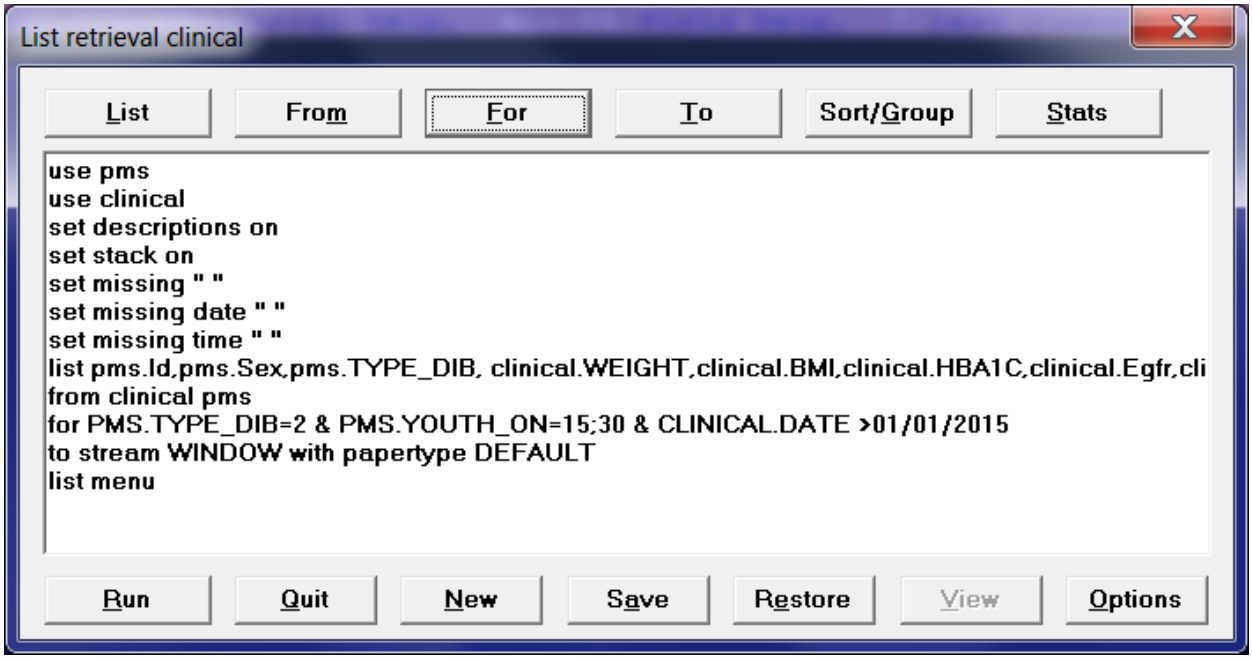


Figure 12: An Example of the Result of a Query

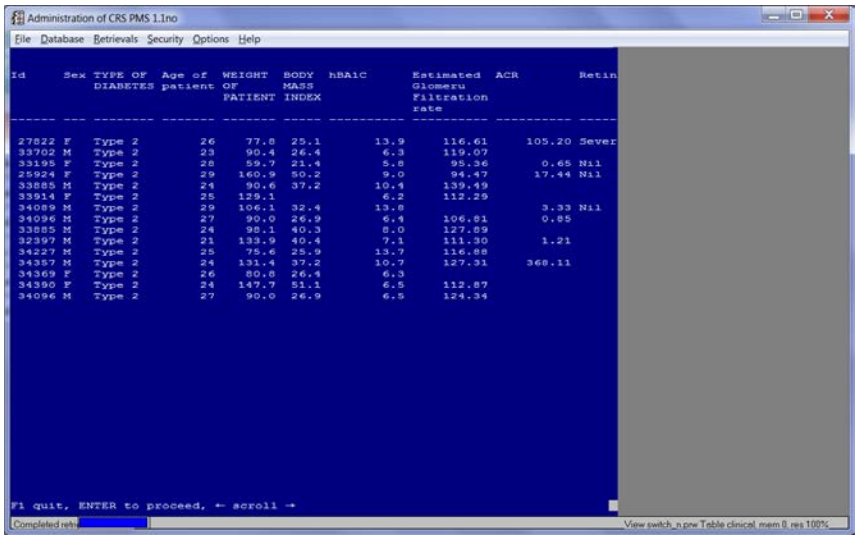
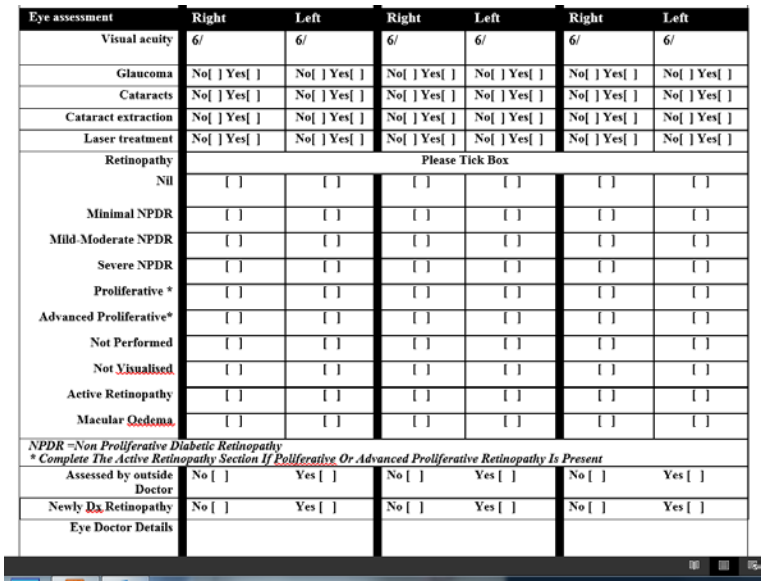


Figure 13: Example of Structured Data

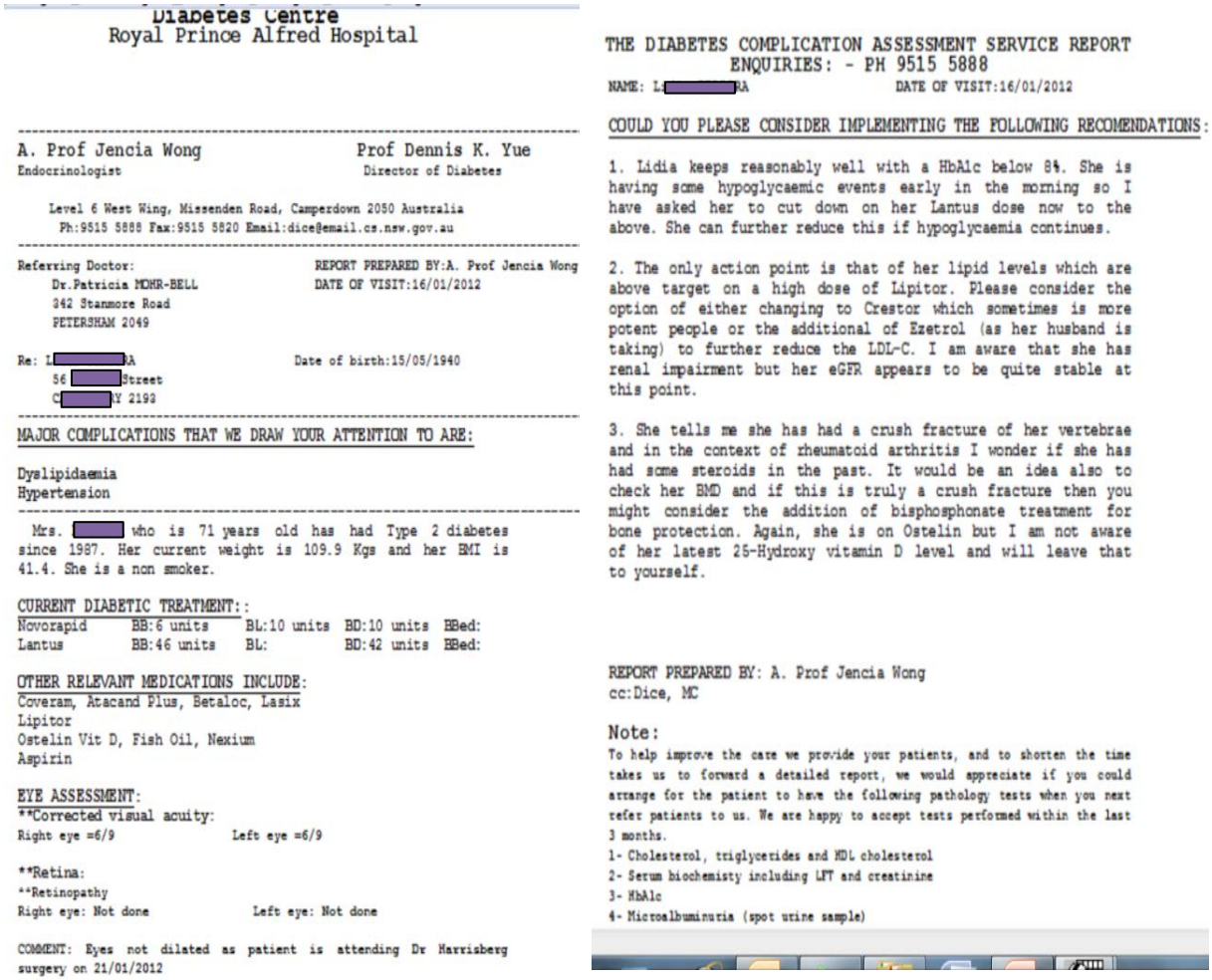


Eye assessment	Right	Left	Right	Left	Right	Left
Visual acuity	6/	6/	6/	6/	6/	6/
Glaucoma	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Cataracts	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Cataract extraction	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Laser treatment	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Retinopathy	Please Tick Box					
Nil	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Minimal NPDR	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Mild-Moderate NPDR	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Severe NPDR	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Proliferative *	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Advanced Proliferative*	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Not Performed	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Not Visualised	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Active Retinopathy	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Macular Oedema	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
NPDR =Non Proliferative Diabetic Retinopathy ** Complete The Active Retinopathy Section If Poliferative Or Advanced Proliferative Retinopathy Is Present*						
Assessed by outside Doctor	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Newly Dx Retinopathy	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Eye Doctor Details						

Figure 14: Example of unstructured data

Major Procedures and Investigations	Results	Year

Figure 15: Example of correspondence to referring physician



Diabetes Centre
Royal Prince Alfred Hospital

A. Prof Jencia Wong
Endocrinologist

Prof Dennis K. Yue
Director of Diabetes

Level 6 West Wing, Missenden Road, Camperdown 2050 Australia
Ph:9515 5888 Fax:9515 5820 Email:dice@email.cs.nsw.gov.au

Referring Doctor:
Dr.Patricia MOHR-BELL
342 Stanmore Road
PETERSHAM 2049

REPORT PREPARED BY:A. Prof Jencia Wong
DATE OF VISIT:16/01/2012

Re: L[redacted]A
56 [redacted]Street
C[redacted]W 2193

Date of birth:15/05/1940

MAJOR COMPLICATIONS THAT WE DRAW YOUR ATTENTION TO ARE:

Dyslipidaemia
Hypertension

Mrs. [redacted] who is 71 years old has had Type 2 diabetes since 1987. Her current weight is 109.9 Kgs and her BMI is 41.4. She is a non smoker.

CURRENT DIABETIC TREATMENT::

Novorapid	BB:6 units	BL:10 units	BD:10 units	BBed:
Lantus	BB:46 units	BL:	BD:42 units	BBed:

OTHER RELEVANT MEDICATIONS INCLUDE:
Coveram, Atacand Plus, Betaloc, Lasix
Lipitor
Ostelin Vit D, Fish Oil, Nexium
Aspirin

EYE ASSESSMENT:
**Corrected visual acuity:
Right eye =6/9 Left eye =6/9

**Retina:
**Retinopathy
Right eye: Not done Left eye: Not done

COMMENT: Eyes not dilated as patient is attending Dr Harrisberg surgery on 21/01/2012

THE DIABETES COMPLICATION ASSESSMENT SERVICE REPORT
ENQUIRIES: - PH 9515 5888

NAME: L[redacted]A DATE OF VISIT:16/01/2012

COULD YOU PLEASE CONSIDER IMPLEMENTING THE FOLLOWING RECOMENDATIONS:

1. Lidia keeps reasonably well with a HbAlc below 8%. She is having some hypoglycaemic events early in the morning so I have asked her to cut down on her Lantus dose now to the above. She can further reduce this if hypoglycaemia continues.

2. The only action point is that of her lipid levels which are above target on a high dose of Lipitor. Please consider the option of either changing to Crestor which sometimes is more potent people or the additional of Ezetrol (as her husband is taking) to further reduce the LDL-C. I am aware that she has renal impairment but her eGFR appears to be quite stable at this point.

3. She tells me she has had a crush fracture of her vertebrae and in the context of rheumatoid arthritis I wonder if she has had some steroids in the past. It would be an idea also to check her BMD and if this is truly a crush fracture then you might consider the addition of bisphosphonate treatment for bone protection. Again, she is on Ostelin but I am not aware of her latest 25-Hydroxy vitamin D level and will leave that to yourself.

REPORT PREPARED BY: A. Prof Jencia Wong
cc:Dice, MC

Note:
To help improve the care we provide your patients, and to shorten the time takes us to forward a detailed report, we would appreciate if you could arrange for the patient to have the following pathology tests when you next refer patients to us. We are happy to accept tests performed within the last 3 months.
1- Cholesterol, triglycerides and HDL cholesterol
2- Serum biochemisty including LFT and creatinine
3- HbAlc
4- Microalbuminuria (spot urine sample)

Data Quality

A core issue in the use of databases is the maintenance of data quality. This is especially important in a system, such as ours, with multiple internal users and sometimes deriving input from external sources.

From the perspective of the internal vs external source of data, training of staff, well-designed data collection instruments and regular auditing are safeguards to minimise errors. For example, in our system when a clinical encounter is created for a patient, it cannot be saved without entering an appropriate date. Some fields such as height

would also have built-in upper and lower limits outside which the user will be asked to confirm the entry. The accuracy and completeness of data are facilitated by the use of the template during clinical encounters and is checked at a daily staff clinical meeting when patient files are reviewed. The routine checking of data by the reading of the 'hybrid' letters has been alluded to in the previous section. The generation of various administrative reports and research queries also offer additional opportunities to correct discrepancies. The stability and completeness of the electronic data for important indices of diabetes, captured at our clinical services over the years, are shown in Table 15.

As outlined in Table 15, data are complete for many fields however there are missing data noted for a number of complications. With respect to the studies that are outlined in this thesis, only files with complete data with respect to the complication of interest were analysed. This is evidenced as the denominator changes between the different studies. There was no attempt to use imputation methodology to account for such missing data in the studies described in this thesis.

From an external perspective, it would be more difficult to implement any quality assurance for data derived from outside sources. For example, we have confronted particular difficulties in maintaining completeness and accuracy of retinopathy data because, in the current health care system, this information was progressively being derived from external sources. This led to the study described in **Chapter 7** of this thesis in which the difficulties encountered in improving the quality of diabetes eye data capture was described.

Table 15: The stability and Completeness of Data Capture

Data items	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients with complications assessments	783	810	785	923	953	1084	1143	1283	1219	1431	10414
Gender											
Female	39%	37%	40%	40%	42%	43%	42%	41%	41%	42%	40%
Male	61%	63%	60%	60%	58%	57%	58%	59%	59%	58%	59%
Missing	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Ethnicity											
Anglo	40%	41%	40%	41%	42%	42%	42%	43%	44%	44%	42%
Other	60%	58%	60%	58%	58%	58%	57%	56%	56%	56%	56%
Missing	1%	1%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Type of Diabetes											
Type 1	8%	10%	9%	10%	9%	12%	11%	12%	10%	9%	10%
Type 2	90%	89%	90%	88%	89%	87%	88%	86%	89%	90%	88%

Data items	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Other	2%	1%	1%	2%	2%	1%	1%	1%	1%	1%	1%
Missing	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Date of Diagnosis											
Missing	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Visual Acuity											
Missing	7%	12%	12%	11%	9%	12%	7%	8%	7%	7%	9%
Retinopathy											
Missing/Not done	20%	24%	20%	23%	12%	15%	8%	11%	10%	10%	14%
Weight											
Missing	1%	0%	1%	1%	1%	11%	0%	0%	1%	1%	1%
Height											
Missing	1%	8%	1%	1%	0%	2%	1%	2%	4%	1%	1%
Vibration Perception Threshold											

Data items	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Missing	3%	5%	4%	5%	4%	7%	3%	3%	4%	4%	4%
HbA1c											
Missing	1%	1%	0%	1%	1%	1%	1%	1%	1%	1%	1%
Microalbuminuria											
Missing	12%	13%	16%	14%	19%	20%	16%	13%	13%	10%	14%
Serum Creatinine											
Missing	4%	5%	3%	5%	5%	9%	6%	7%	7%	6%	6%
Systolic Blood Pressure											
Missing	3%	4%	3%	4%	3%	3%	2%	2%	2%	3%	3%
Estimated glomerular filtration rate											
Missing	4%	5%	3%	5%	5%	9%	6%	7%	7%	6%	6%
Cholesterol											

Data items	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Missing	8%	7%	5%	6%	7%	10%	6%	7%	5%	4%	6%
HDL											
Missing	19%	15%	13%	14%	14%	19%	16%	15%	14%	15%	15%
Triglycerides											
Missing	8%	7%	6%	6%	7%	10%	6%	7%	6%	5%	7%

Chapter 3: Presented as publication

Ethnic Specific Differences In Survival Of Patients With Type 2 Diabetes: Analysis Of Data Collected From An Australian Multi-Ethnic Cohort Over A 25 Year Period (2)

DIABETES RESEARCH AND CLINICAL PRACTICE 107 (2015) 130–138

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Ethnic specific differences in survival of patients with type 2 diabetes: Analysis of data collected from an Australian multi-ethnic cohort over a 25 year period

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ARTICLE INFO

Article history:
Received 1 July 2014
Received in revised form
5 September 2014
Accepted 15 September 2014
Available online 6 October 2014

Keywords:
Type 2 diabetes
Complication
Mortality
Ethnicity

ABSTRACT

Aims: To examine the survival of patients with type 2 diabetes from 7 ethnic groups, living in the shared environment of an Australian city.

Methods: Hazard ratio of death (HR) after diagnosis of diabetes was compared between Anglo-Celtic ($n = 5433$), Indigenous Australian ($n = 439$), Pacific Islander ($n = 354$), Mediterranean ($n = 3138$), Arabic ($n = 768$), Indian ($n = 702$) and Chinese ($n = 1632$) patients who live in metropolitan Sydney. Mortality was ascertained by data-linkage with the Australian National Death Index. The modulating effects of glycaemic control, diabetes/vascular complications and risk factors, year of diabetes diagnosis and duration of diabetes on ethnic differences were analysed by Cox regression. Socio-economic status and competence in English were also examined.

Results: There were significant differences in survival between the ethnic groups; the Indigenous Australians had the highest HR for death (2.3, 95% CI 1.7–3.0) and the Chinese the lowest (0.4, 95% CI 0.4–0.5). The survival of the Anglo-Celtics (HR 1) was surprisingly poorer than for Indian (0.6, 95% CI 0.5–0.8), Arab (0.7, 95% CI 0.6–0.8) and Mediterranean groups (0.8, 95% CI 0.7–0.9). Prevalence of smoking and albuminuria were strongly associated with HR. The better survival of Chinese and Arab and the worse survival of Indigenous Australians remained after adjustment of risk factors. Need for an interpreter was a favourable risk factor for survival.

Conclusions: Ethnicity is a significant determinant of survival in type 2 diabetes and this is substantially but not completely mediated by smoking and vascular risk factors. The favourable impact associated with less competence in English may represent a Healthy-migrant effect.

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http://dx.doi.org/10.1016/j.diabres.2014.09.037

1. Introduction

Diabetes mellitus is one of the most common non-communicable diseases globally and the fourth or fifth leading cause of death in developed countries. It is undoubtedly one of the greatest challenges to health care in the 21st century. Furthermore, type 2 diabetes is well recognised to be a heterogeneous disorder comprised of varying phenotypes, thus a better understanding of the variables in regards to outcome is of great importance. It is well documented that ethnicity is a significant factor, not only for the development of type 2 diabetes and its related complications, including mortality [1]. However, comparative information on the impact of ethnicity on mortality is often obtained from different countries and at different points in time, therefore the findings would be confounded by other factors including the effects of varying standards of health care and socio-economic conditions.

Australia has been an increasingly multi-cultural society since the end of the second world war. With more migration to Australia, many different ethnic groups now share the same environment with equivalent health care access due to universal medicare. Thus a multi-ethnic mortality study in an Australian context, minimises these confounding factors. Further to this end, a comprehensive systemically collected clinical and demographic database has been maintained for the last three decades at the Diabetes Centre of Royal Prince Alfred Hosptial(RPAH). This longitudinal data offers the opportunity to examine the relationship between ethnicity and survival in people with type 2 diabetes and allows the impact of clinical and demographic factors on any ethnic differences to be analysed.

The aim of this study is therefore to examine differences in survival of people with type 2 diabetes from seven ethnic groups attending a metropolitan diabetes centre in Australia.

2. Material and methods

2.1. Patients and clinical management

The Diabetes Centre of Royal Prince Alfred Hospital is a conjoint hospital and university facility situated about 5 km from the centre of the city. Patients are referred by their primary care physician and can receive either diabetes education or also for clinical care. Sixty eight percent of patients are from the local health district which has a population of about half a million people. However, according to Australian Health Care regulations, any person from other districts can also be referred. The distinction of type 2 vs type 1 diabetes was made on clinical grounds as the collection of data commenced before the popular availability of immunological testing. For categorisation of individuals according to ethnicity, the patients' self reported ethnicity was used and subjects of mixed ethnicity were not included. Approximately 40% of patients are of Anglo-Celtic origin with the rest made up of Mediterranean 13%, Chinese 13%, Arabic 4%, Indian 4%, Indigenous Australians 2% and Pacific Islanders 2%. These are therefore the 7 ethnicities studied. About 50% of the population speak a language other than English at home. The need for an interpreter during the initial consultation is usually requested by the referring doctor (about 70% of the time) and by the patients (about 30% of the time). Socio-economic status(SES) of the patients was assessed by using the Index of Relative Socio-economic Disadvantage (IRSD) generated by the Australian Bureau of Statistics [2]. IRSD is a score derived from a range of information about the economic and social conditions of people and households within a post code area. The score is provided in deciles with a lower score indicative of greater disadvantage. For the purpose of our study, the IRSD scores were analysed in tertiles.

One of the main formats of clinical care provided by the Diabetes Centre is the performance of a packaged comprehensive diabetes complication assessment [3]. In brief, retinopathy was assessed by direct fundoscopy with pupils dilated or in recent years, by digital retinal photography; albuminuria was determined by collection of spot urine samples and considered abnormal if albumin concentration was greater than 30 mg/L or if the urine albumin/creatinine ratio was greater than 3.5 and 2.5 mg/mmol for females and males, respectively; neuropathy assessment was by examination of ankle reflexes and testing of vibration perception threshold (VPT, volts) with a biothesiometer adjusted for age by expressing data as a Z score; and macrovascular disease and risk factors were assessed by clinical history of past events or relevant symptoms, collection of blood for lipid profile and measurement of sitting blood pressure. Renal function was assessed by calculated eGFR using the MDRD formula. The degree of hyperglycaemia was assessed by measurement of HbA1c using a HPLC method.

2.2. Diabetes database

The Diabetes Centre Computerised Clinical Database is purpose built. It contains the demographic data of every patient attending since 1986 but clinical information only for the 77% who also attended for comprehensive clinical care and complications assessment. The RPAH Ethics Committee gave permission for the computer data to be analysed.

2.3. Data on mortality

A total of 24,415 names of patients from our database were submitted to the National Death Index (NDI) of the Australian Institute of Health and Welfare (AIH&W), which contains records of all deaths occurring in Australia since 1980. An NDI standard linkage protocol was followed to match individuals from the databases using the following fields: ID number, surname, first given name, second given name, third given name, gender, date of birth, date of last contact and state of residency. This linkage protocol has been well validated and reported to have a sensitivity and specificity of 94% and 100%, respectively [4]. In cases where matching was ambiguous, mortality was confirmed by checking with the area wide hospital database, general practitioners and in some cases also family members. Due to the time lag in data entry by the AIH&W, data on death was only available to 30th June 2011 which was the date of censor for survival analysis and the cause of death only available till

2008. For deaths in and after 1997, causes of death are coded according to ICD10. For deaths prior to 1997, the underlying cause of death was coded according to ICD9, then aligned to ICD10 for the purposes of this work.

We excluded from this study patients who had transplant related diabetes or who were seen at the Diabetes Centre while inpatients and then died within 8 months. These patients were considered to have serious co-morbidities that would distort the assessment of the natural history and death of our patients with type 2 diabetes. Patients with gestational diabetes were also excluded as they represent a transient form of diabetes in the context of this study and would again distort the calculation of survival after diabetes diagnosis. Since this study is examining only type 2 diabetes, patients with type 1 diabetes and secondary diabetes were excluded. Altogether, this process provided the names of 15,769 individuals, of which 12,466 belonged to the seven ethnic groups being studied for survival after the diagnosis of diabetes. The remaining 3303 patients belonged to more than 20 other ethnic groups and were not included in this study. To reduce the impact of selection bias arising from studying only patients who had survived diabetes for sufficient (and variable) time to attend the diabetes centre, a subset of 4756 patients who presented within one year of diabetes onset was also analysed for their survival. Due to the time lag in updating the NDI database mentioned above and that some patients only came for education and did not have detailed clinical data, the relationship between death and clinical data was only examined in 8484 subjects. Clinical data captured at the patient's last visit were chosen for studying their impact on mortality because they would likely have the greatest impact on mortality outcomes.

2.4. Statistical methods

Data was analysed using NCSS 2007. Continuous data were checked for normality and presented as mean ± SD or median (interquartile range). Skewed data such as triglycerides were log transformed. The ANOVA or Kruskal–Wallis test was used to compare means or medians of the different ethnic groups. Bonferroni or Kruskal–Wallis Z test was used to adjust for multiple comparisons. Categorical data were presented as percentage and the Chi-square test was used to compare groups. Kaplan–Meier survival curve with adjustment of individual age at first contact was used to determine the time based survival rate between the 7 ethnic groups. Cox regression analysis was used to find predictors for death with age as the time variable. Variables included in the initial model were ethnicity, smoking, systolic BP, diastolic BP, Hba1c, cholesterol, triglycerides, retinopathy, body mass index (BMI), history of ischemic heart disease (IHD), gender, albuminuria, duration of diabetes, interpreter use and socio-economic status. To adjust for possible secular trend over the three decades of observation, the year of diabetes diagnosis was also examined as a variable. Significant variables were included in the final model to generate the hazard ratio (HR) of death at an earlier age. Significance level was accepted as $p < 0.05$.

3. Results

3.1. Survival and cause of death according to ethnicity

The age at diagnosis of diabetes, first visit to the Diabetes centre and death and all cause mortality for the different ethnicities after a similar mean follow up duration of 9.6–11.8 years are shown in Table 1. All ethnic groups, with the exception of the Mediterranean groups, had diabetes diagnosed at a younger age than the Anglo-Celtic reference group. There were a total of 5035 deceased individuals from the 24,415 names submitted. Of these 3337 (26%) were from the 12,466 individuals of the seven ethnic groups studied. On average, Indigenous Australians died at a comparatively younger age and conversely the Chinese died at a relatively older age with the reference Anglo-Celtic group's age of death in an intermediate position.

The HR of death and the Kaplan–Meier survival curves showed the same pattern of ethnic differences (Table 1 and Fig. 1). There were significant differences in survival between the ethnic groups; the Indigenous Australians had the highest HR (2.3, 1.7–3.0) and the Chinese the lowest (0.4, 0.4–0.5). The survival of the Anglo-Celtics (HR 1) was surprisingly poorer than for Indian (0.6, 0.5–0.8), Arab (0.7, 0.6–0.8) and Mediterranean groups (0.8, 0.7–0.9). The HR of death and the survival of the various ethnic groups did not change significantly even if analysis was confined only to the 4756 subjects who presented within one year of diabetes diagnosis (Table 1 and Supplementary Fig. 1).

With respect to the cause of death (Table 1), despite differences in the average age of death spanning over 15 years amongst the ethnic groups, the percentage of IHD as a primary cause of death was similar. By contrast, the Chinese and Mediterranean group who had the highest longevity had a higher cancer related mortality. The Pacific Islanders had the highest prevalence of renal disease as the combined primary or secondary cause of death.

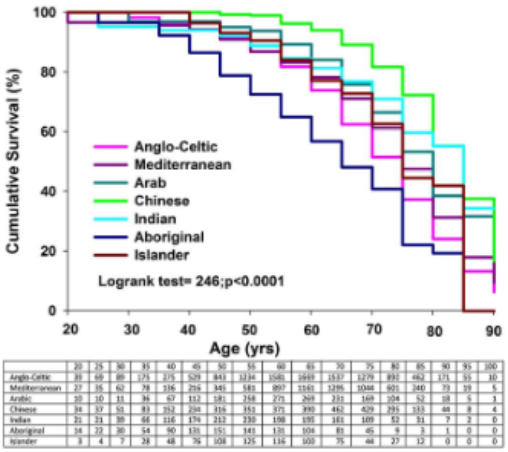
3.2. Clinical factors determining survival by ethnicity

The clinical factors and their relationship with survival were examined in the cohort of 8484 subjects who presented for clinical treatment and therefore had recorded clinical parameters (Table 2). The mean HbA1c level was suboptimal (7.5–9.0% [58–75 mmol/mol]) in all groups. In accordance with their poor survival, the Indigenous Australians had poor indices in glycaemic control, cholesterol levels, prevalence of smoking and albuminuria whereas the Chinese had the most favourable risk parameters. These vascular risk factors were reflected in the ethnic specific prevalence of IHD although there were only minor differences in their modality of treatment for diabetes, dyslipidemia and hypertension. Amongst the various ethnic groups, a strong univariate correlation was found between the HR of death and prevalence of smoking (Fig. 2a) and albuminuria status (Fig. 2b) but not with HbA1c ($r = 0.5$, $p = 0.3$). The HR of death of various ethnic groups as determined by Cox regression analysis after adjustments for significant risk factors including albuminuria, BMI, total and HDL cholesterol and Triglyceride levels,

Table 1 – Demographic and mortality data for the total cohort.

Ethnicity (n = 12,466)	Mean age (yrs)			Duration of follow up	All cause mortality (total 3337) n (%)	HR for death & (CI)	HR for Death & (CI) (<1 yr DM duration at presentation) n=4756	Primary cause of death (%)		Combined primary and secondary cause of death (%)
	Diagnosis	First visit	Death					IHD[¶]	Cancer[¶]	Renal[¶]
Anglo-Celtic n = 5433	53.7 ± 12.7	59.3 ± 12.3	74.1 ± 10.6	9.6 4.9–14.6	1811(33.3)	1.0	1.0	42	21	10
Indigenous Australians n = 439	42.6 ± 12.2*	48.5 ± 11.9	60.8 ± 12.0*	11.1* 6.3–15.3	109(24.8)	2.3* (1.7–3.0)	2.1* (1.2–3.4)	47	15	9
Pacific Islanders n = 354	46.6 ± 10.8*	51.8 ± 11.2	64.9 ± 12.2*	9.8 4.9–16.0	55(15.5)	1.0 (0.8–1.3)	1.2 (0.7–2.0)	35	8	24*
Mediterranean n = 3138	54.3 ± 11.6	61.2 ± 11.3	74.7 ± 9.6	10.5* 5.4–15.4	898(28.6)	0.8* (0.7–0.9)	0.8 (0.7–0.9)	38	25*	10
Arabic n = 768	49.0 ± 11.3*	55.8 ± 11.9	72.1 ± 10.5	11.6* 6.0–16.7	154(20.1)	0.7* (0.6–0.8)	0.6* (0.4–0.7)	41	21	11
Indian n = 702	44.8 ± 11.3*	50.5 ± 12.7	66.8 ± 15.0*	11.8* 5.9–16.3	77(11.0)	0.6* (0.5–0.8)	0.8 (0.5–1.1)	46	15	11
Chinese n = 1632	52.2 ± 12.4*	58.4 ± 13.3	77.6 ± 9.3*	9.7 5.4–13.3	233(14.1)	0.4* (0.4–0.5)	0.4* (0.3–0.5)	41	31*	11

* $p < 0.05$ versus Anglo-Celtic.
¶ χ^2 $p < 0.05$.



	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
Anglo-Celtic	30	69	89	175	275	529	843	1234	1581	1669	1537	1279	892	462	171	55	10
Mediterranean	27	35	62	78	116	256	345	581	897	1141	1295	1044	601	240	73	19	5
Arabic	10	10	11	36	67	112	181	268	271	269	231	169	104	52	18	3	1
Chinese	34	37	53	83	152	294	316	351	371	390	462	429	295	133	44	8	4
Indian	21	21	39	66	116	174	212	230	198	195	161	109	53	31	7	2	0
Aboriginal	14	22	30	54	90	131	151	141	131	104	85	45	9	3	1	0	0
Islander	3	4	7	28	48	76	108	125	116	100	75	44	27	12	0	0	0

Fig. 1 – Kaplan–Meier survival curves for the 7 ethnic groups of the total cohort. The number of individuals at each time point is shown in the accompanying table.

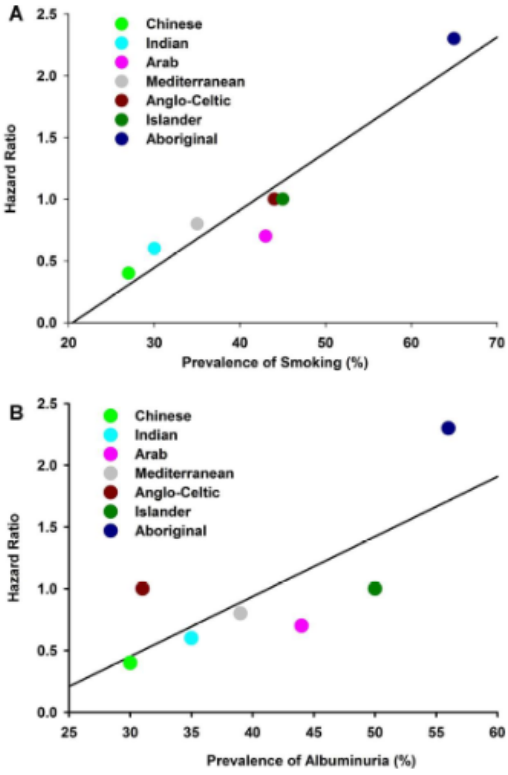


Fig. 2 – (a) Correlation between prevalence of smoking by ethnicity with HR of death ($r = 0.9$, $p = 0.001$). Fig. 2 (b) Correlation between prevalence of albuminuria by ethnicity with HR of death ($r = 0.8$, $p = 0.046$).

Table 2 – Clinical and socio-economic data of the ethnic groups at the last visit.

N = 8484	Anglo-Celtic (N = 3608)	Mediterranean (N = 2217)	Arabic (N = 493)	Chinese (N = 1109)	Indian (N = 485)	Indigenous Australian (N = 345)	Pacific Islander (N = 227)	p-Value
Age at the last visit	62.5 ± 12.0	64.8 ± 11.0*	58.9 ± 12.0*	62.4 ± 12.6*	54.0 ± 12.7*	52.7 ± 12.3*	55.0 ± 11.2*	p < 0.001
Number visits	3.3 ± 3.4	3.6 ± 3.6	3.3 ± 3.5	4.3 ± 5.0*	3.4 ± 5.5	3.2 ± 3.2	2.9 ± 3.2	p < 0.001
Male (%)	57.8	56.4	62.1	50.4	62.3	43.5	50.2	p < 0.001
BMI(kg/m^2)	33.3 ± 9.9	31.5 ± 8.4*	33.3 ± 8.9	28.5 ± 6.4*	27.7 ± 7.0*	32.3 ± 9.2	37.8 ± 10.2*	p < 0.001
HbA1c (%)	7.6 ± 1.8	7.7 ± 1.6	8.0 ± 1.8*	7.5 ± 1.5	8.1 ± 1.8*	8.5 ± 2.1*	9.0 ± 2.4*	p < 0.001
HbA1c(IFCC) (mmol/mol)	60 ± 19	61 ± 18	64 ± 19	59 ± 16	65 ± 20	70 ± 23	75 ± 26	p < 0.001
Retinopathy (%)	15.1	22.9	24.9	19.3	22.7	24.7	30.2	p < 0.001
Albuminuria (%)	30.5	38.7	44.0	29.6	35.2	55.9	50.2	p < 0.001
eGFR	71 ± 18	73 ± 18	73 ± 18	69 ± 19	73 ± 17	73 ± 19	65 ± 20	p < 0.001
Z score for foot sensation	2.0 ± 1.3	1.9 ± 1.2	1.8 ± 1.1*	2.0 ± 0.9	1.8 ± 1.1*	2.0 ± 1.2	2.6 ± 1.3*	p < 0.001
Cholesterol (mmol/L)	4.9 ± 1.3	4.8 ± 1.2	5.0 ± 1.3	4.8 ± 1.1*	5.1 ± 1.3	5.1 ± 1.4	5.1 ± 1.6	p < 0.001
Triglycerides (mmol/L)	1.9 [1.3–2.7]	1.7* [1.2–2.5]	1.9 [1.3–2.8]	1.5* [1.1–2.2]	1.8 [1.2–2.6]	2.1* [1.5–3.2]	1.7 [1.2–2.7]	p < 0.001
HDL (mmol/L)	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.5	1.3 ± 0.4*	1.2 ± 0.3	1.1 ± 0.4	1.2 ± 0.3	p < 0.001
Diabetes treatment								p < 0.001
Diet	24.5	20.4	21.0	23.1	23.5	22.6	11.3	
Oral agents	50.6	52.2	50.3	58.2	54.4	51.4	58.9	
Insulin	24.8	27.4	28.7	18.7	22.1	26.0	29.8	
Statin Rx (%)	54	53	53	45	48	49	39	p < 0.001
Systolic (mmHg)	135 ± 19	137 ± 19	130 ± 16*	129 ± 18*	127 ± 18*	131 ± 18*	133 ± 19	p < 0.001
Diastolic (mmHg)	78 ± 10	77 ± 11*	77 ± 10	76 ± 9*	77 ± 10	79 ± 10	81 ± 11*	p < 0.001
BP Rx (%)	68	68	61	59	50	71	62	p < 0.001
IHD (%)	22	21	23	10	16	24	11	p < 0.001
Stroke (%)	8	8	5	4	3	7	3	p < 0.001
PVD (%)	10	11	11	6	6	9	8	p = 0.002
Ever smoked (%)	43.7	35.2	43.0	26.9	29.8	65.1	44.9	p < 0.001
Death (%)	29.0	25.6	17.8	14.5	10.5	25.2	14.1	p < 0.001
Socio-economic score (deciles)	6.9 ± 2.9	6.7 ± 2.7	5.3 ± 3.0*	6.4 ± 3.1*	6.2 ± 2.1	5.5 ± 3.0*	5.7 ± 3.0*	p < 0.001

* p < 0.05 versus Anglo-Celtic.

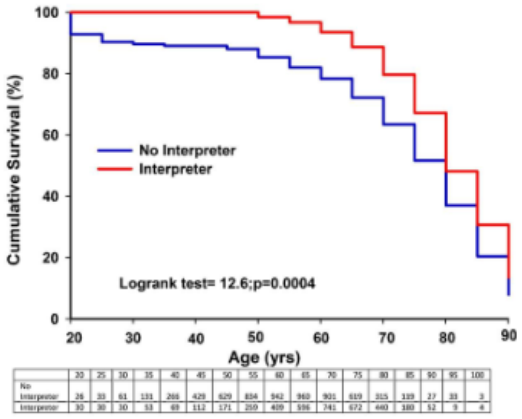


Fig. 3 – Kaplan–Meier survival curves of Interpreter vs No-interpreter groups for the five ethnicities in which English was not the primary language. The number of individuals at each time point is shown in the accompanying table.

gender, smoking status, and co-existing complications of retinopathy and IHD disease is shown in Supplementary Table 1. The Chinese and the Indigenous Australian ethnicities remained a significant factor as determinants of their, respectively decreased and increased HR for death of 0.7 (0.6–0.9) and 2.0 (1.6–2.6). The Arabs also had a lower HR for death although less significant than that of the Chinese.

3.3. *Social economic factors determining survival by ethnicity*

The HR of death were 1.1 (0.9–1.1), 0.9 (0.8–1.0) and 1 for the highest, middle and lowest socio-economic tertiles, respectively, not significantly different (logrank = 5, $p = 0.08$). The differences were minor between ethnicities with all groups falling in the middle tertile (Table 2). The Kaplan–Meier survival curves of the three strata showed no significant differences (Supplementary Fig. 2). When SES status was added as a variable to the Cox regression analysis above, there was no independent effect of SES status on survival.

3.4. *Language, acculturation and survival*

The relationship between competence in the English language as an index of acculturation to Australian society and mortality was examined. For each of the five ethnicities in which English is not the primary language, the subjects who could not understand English sufficiently and therefore required an interpreter during their attendance at the Diabetes Centre had lower HR of death (0.8 vs 1.0 $p < 0.0004$). The corresponding Kaplan–Meier survival curves showing the different survival between the Interpreter requiring vs Non-interpreter requiring groups are shown in Fig. 3. This trend of better survival in the Interpreter requiring group is evident for all ethnicities (Supplementary Table 2). The socio-economic status of the Interpreter vs Non-interpreter groups were not different (6.2 ± 2.9 and 6.3 ± 2.9, respectively).Overall, the interpreter requiring group was characterised by older age at diabetes diagnosis, more female representation, less smoking history and a lower BMI. When added as a factor to the Cox regression analysis, the need for an interpreter was just short of statistical significance as an independent predictor of mortality ($p < 0.07$).

4. Discussion

Our study confirms the existence of differences in mortality amongst type 2 diabetes subjects from seven ethnic groups living in Australia. Three factors have facilitated this survival study. First, the presence of so many ethnic groups and in substantial numbers living in proximity allows analysis of seven ethnicities whereas many other studies have concentrated on two or three groups [5–7]. Second, a comprehensive, standardised and long established database was used, allowing for survival to be more closely linked to the clinical status of the patients. Thirdly, although the type and quality of health care received by individuals depends on many personal factors, health care is universally available in Australia and generally of good standard. Thus the chances of access and standard of care playing a predominant role in affecting mortality is minimised.

In comparison with the WHO Study on ethnic differences in diabetes reported up to 1988 [1], our patients with type 2 diabetes are surviving to a more advanced age, by about 20 years and this is similar to that observed in other more recent studies [8,9]. This improved survival should be considered in the context of increased longevity in developed countries worldwide. Over the last decade, the median age of all deaths in the State of New South Wales where our study was conducted has increased by 3 years to 82 years [10]. Important factors in the improvement in survival of our cohort with diabetes are likely to include more intensive treatment of dyslipidemia and hypertension. It is well established that the

Indigenous Australians fare much less well in health status compared with other Australians and alarmingly our study has confirmed this discordance, even in an urban based population [11]. What was less expected is that the Anglo-Celtic group with type 2 diabetes appeared to survive less well than many of their non Anglo-Celtic counterparts. This pattern of better survival in ethnicities who had migrated in more recent times has also been observed in other studies [5,7]. By contrast, the 2003 Australian report of the AIHW showed a higher standardised mortality ratio of Australians with diabetes who were born overseas [12]. Based on the findings of their Fremantle Study in Western Australia, Tan et al. had also previously pointed out this inconsistency because they also found better survival of their Asian diabetic patients [13]. Selection bias due to varying severity, duration and definition of diabetes may have contributed to these differences.

The explanation for the ethnic differences in mortality remains speculative but is likely to be due to variance in the known risk factors for cardiovascular death. The Indigenous Australian and Islander groups died predominately of cardiac and renal causes, despite their death at an earlier age. Indeed these groups had the highest rates of smoking, albuminuria and relatively low statin use given their cardiovascular risk factors. Pacific Islanders had the highest BMI and together with Indigenous Australian groups had the worst glycaemic control of all ethnicities. In multivariate analysis there remains a residual risk for an earlier mortality for the Indigenous Australian group not captured by these known risk factors or duration of diabetes. Conceptually, the persistence of ethnicity being a significant factor suggests that some relevant environmental, clinical or genetic factors are either unknown or not measured and therefore not adequately adjusted. Whilst a younger age of onset may explain some of the excess hazard for the Indigenous Australian people, the same cannot be true for the Chinese, who despite a young age of onset, died at a relatively older age. Further the impact of socio-economic status seems to be not a significant influence in this Australian cohort. However, we did not have detailed socio-economic information of individuals but relied on the post code of their residence, an index which may not be sufficiently sensitive in this context. It is still possible that the some of the excess risk seen in Indigenous Australian is a result of such unmeasured socio-demographic factors. Nevertheless, despite the unknowns, these data clearly suggest that targeting known risk factors such as smoking, albuminiuria and statin treatment will go a way toward closing the mortality gap for this at risk cohort.

Conversely, despite a relatively younger age of diagnosis of diabetes, those of Chinese ethnicity survived for longer. This phenomenon has been reported previously [5,7]. As would be predicted, Chinese with diabetes had the lowest BMI, smoking rates and most favourable lipid profiles and glycaemic control of all ethnicities. Again the survival advantage of the Chinese is incompletely explained and remained evident even after adjustment of known risk factors.

A few other relevant remarks can be made about our observations of ethnic differences. In terms of targeting at risk populations, it is important to recognise that the Anglo-Celtic group had a worse survival than many of the ethnic groups. It is theoretically possible that our hospital, being a government funded and free health care provider, would be preferentially attended by more Anglo-Celtic patients of lower socio-economic status whereas the socio-economic status of the ethnic groups was more evenly distributed. However, this possibility is not reflected by our data on socio-economic status. It is notable that the Anglo-Celtic group had higher systolic or diastolic blood pressure compared with all but one other ethnic group, the Pacific Islanders (Table 2). Their smoking rate is also higher. Together these factors may contribute to the relatively worse outcomes of the Anglo-Celtics. Certainly, smoking and blood pressure represent potentially reversible or preventable risk factors that should be addressed. In this regard, the generally lower prevalence of smoking observed in our other ethnic groups is not typical of the situation in their native countries such as has been noted in previous studies [5,6], suggesting an element of migration selection. The traditional use of the Mediterranean diet may contribute to the better survival of this particular ethnic group. The Mediterranean diet is thought to act primarily by minimizing vascular risk factors and certainly the reduced hazard for death seen in our Mediterranean populations is attenuated after adjustment of such risk factors.

An interesting and perhaps counter-intuitive finding in our study is that a requirement for interpreter conveyed survival benefits. These results could be explained by the "health migrant" bias, i.e. only those older with favourable health profiles migrate. Additionally, as English language competence can be considered a crude measure of acculturation, these data suggest that factors such as length of stay in Australia, maintenance of a traditional lifestyle and other cultural practices could be important in determining survival outcomes.

The advantage of performing this study based on our clinical database has been discussed previously but possible limitations inherent in this system need to be considered. Although the data were collected and recorded prospectively, the comparative analysis was retrospective and patient selection criteria were not a priori. It raises the possibility of a selection bias due to studying only the subset of patients who had survived diabetes for sufficient time to attend the Diabetes Centre. In this scenario, the observed ethnic differences could be due to varying degrees of survival time bias between the ethnic groups. However, when our analysis was restricted to patients who had diabetes only for the short period of less than 12 months, the same trend in ethnic differences in death was demonstrable, indicating that our overall conclusion on ethnic differences in survival is likely to be robust. Fortunately, the period of follow up after presentation for the various ethnic groups were also quite similar at about 10 years. The 12 year gap between the youngest (Indigenous Australian) and the oldest (Mediterranean) groups at presentation and cannot be eliminated as a factor unless a sub-population of each ethnicity is studied. It is also well established that the diagnosis of type 2 diabetes is often delayed. Our own results (data not shown) derived by extrapolating the prevalence of retinopathy against known duration of diabetes indeed showed a delay in diabetes diagnosis of 2.5 years for Anglo-Celtics and 4–5 years for the other ethnic groups. This would exclude the possibility that the ethnic groups such as the Chinese that had a better survival, do so because of more

prompt diagnosis and treatment. Being a referral centre, it is also possible that our patient cohorts are not representative of those in the community, although one of our previous studies has indicated this to be not the case [14]. The possibility remains that the ethnic specific mortality differences we observed are a reflection different population characteristics in the wider non diabetic community. Despite these limitations, we believe our method of data collection and analysis, although not perfect, is a valuable alternative to provide meaningful data for hypothesis generation.

In conclusion, ethnic differences in survival can be demonstrated in patients with type 2 diabetes and is largely but incompletely explained by differences in known risk factors for cardiovascular mortality which are suboptimal in higher risk ethnicities. Therefore, targeted intervention measures are required to move towards equity of outcome within multiethnic populations. Further, for Indigenous Australians and Chinese with type 2 diabetes, there remain unquantified detrimental and favourable factors, respectively that impact their disparate mortality risk. This would be an important field for further clinical, genetic, sociological and medico-economic studies.

Acknowledgments

The authors have no relevant conflicts of interest to declare. MC is the guarantor of the data. Author Contributions: TA, MC, JW, DKY researched the data and wrote manuscript; LM researched the data and reviewed the manuscript; TW and SMT reviewed and edited the manuscript and contributed to discussion. We wish to acknowledge the support of The NSW Ladies Bowl for Others Association and thank Professor Adel Mishriky for expert statistical advice. We would also like to gratefully acknowledge the assistance of the Australian Institute of Health and Welfare for their support and expertise with the mortality data linkage.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2014.09.037.

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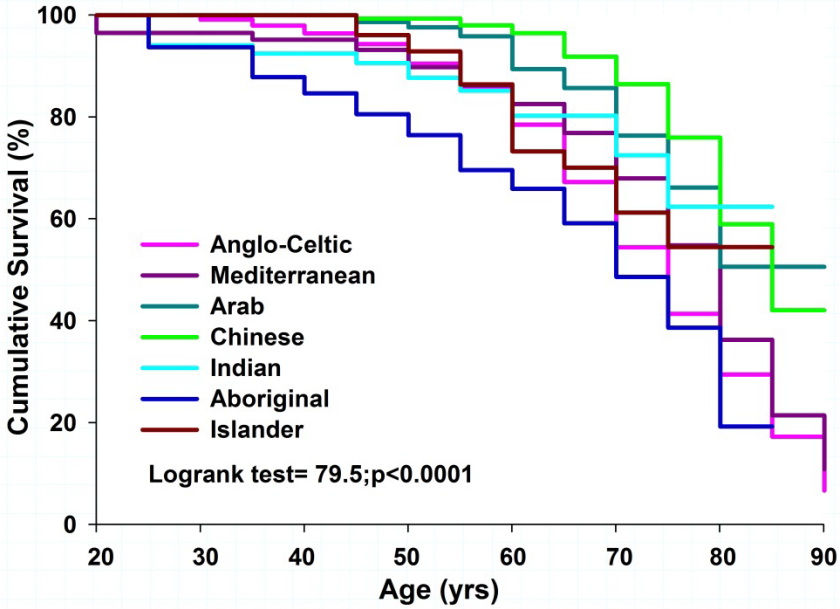
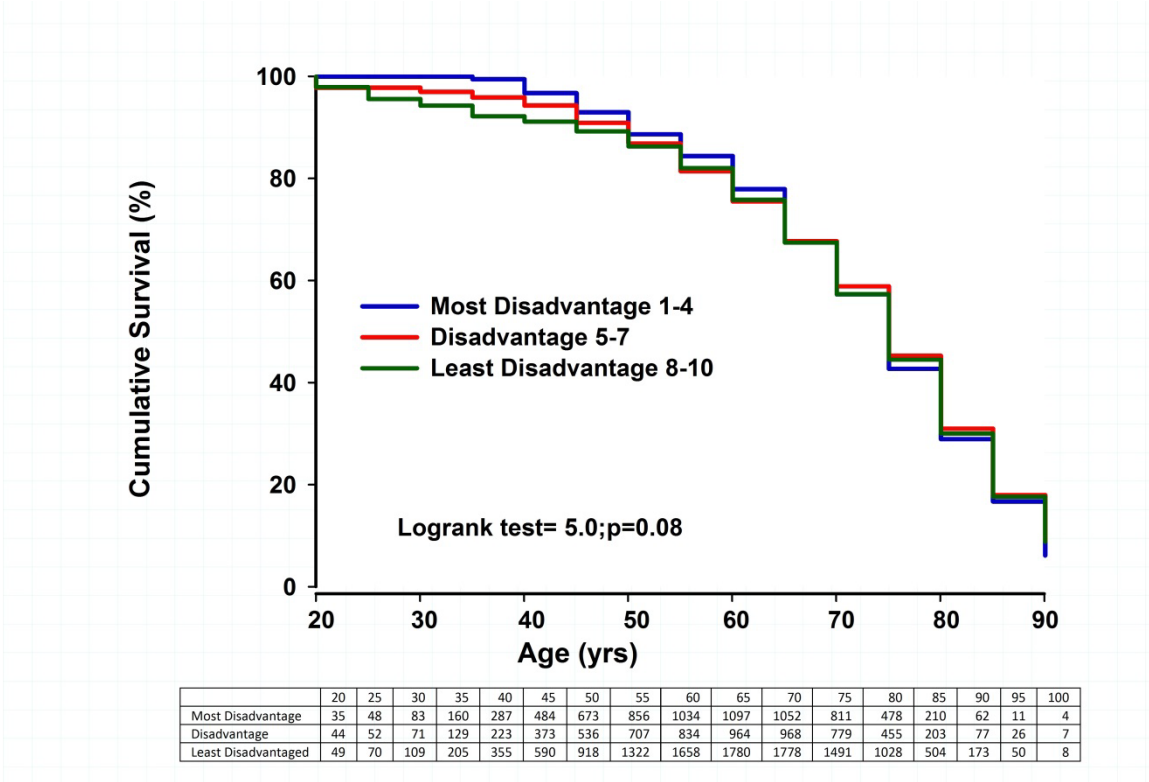
Supplementary figures



	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
Anglo-Celtic	37	58	68	128	194	353	485	636	716	703	587	438	302	162	58	17	4
Mediterranean	27	31	52	61	98	121	166	234	329	383	431	304	172	55	15	1	0
Arabic	7	7	8	35	45	61	82	112	109	86	63	33	22	10	5	2	1
Chinese	32	34	45	76	112	137	166	156	140	128	125	100	54	23	8	3	2
Indian	18	18	42	49	84	97	95	90	58	47	40	20	10	4	1	0	0
Aboriginal	11	14	17	30	50	59	64	53	40	29	22	12	2	1	0	0	0
Islander	3	4	24	24	33	50	62	60	51	32	20	13	8	3	0	0	0

Supplementary Figure 1: Kaplan-Meier survival curves of subjects with diabetes duration <1 yr at presentation. The number of individuals at each time point is shown in the accompanying table.



	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
Most Disadvantage	35	48	83	160	287	484	673	856	1034	1097	1052	811	478	210	62	11	4
Disadvantage	44	52	71	129	223	373	536	707	834	964	968	779	455	203	77	26	7
Least Disadvantaged	49	70	109	205	355	590	918	1322	1658	1780	1778	1491	1028	504	173	50	8

Supplementary Figure 2: Kaplan-Meier survival curves according to socio-economic status. (Log rank test=5; p=0.08). The number of individuals at each time point is shown in the accompanying table

Supplementary Table 1: Cox regression analysis of factors determining mortality

	P value	HR	95% CI
Anglo-Celtic		1	
Mediterranean	0.5	1	0.8-1.1
Arabic	<0.01	0.7	0.6-0.9
Chinese	<0.001	0.7	0.6-0.9
Indian	0.06	0.7	0.5-1.1
Indigenous Australian	<0.001	2.0	1.6-2.6
Pacific Islander	0.6	1.1	0.8-1.7
Albuminuria	<0.001	1.1	1.1-1.2
BMI	<0.001	1.01	1.0-1.1
Cholesterol	<0.001	1.1	1.1-1.2
HDL	<0.04	0.8	0.8-0.9
No IHD	<0.001	0.9	0.8-0.9
Triglycerides	<0.006	1.1	1.1-1.3
Retinopathy	<0.04	1.1	1.3-1.5
Males	<0.001	1.1	1.1-1.2
Smoking	<0.001	1.1	1.1-1.2

Supplementary Table 2: Impact of Need for Interpreter on Mortality

Ethnicity n=4353	HR of death when Interpreter needed n=1601	HR of death when No Interpreter needed n=2752
Mediterranean n=2130	0.9 (0.8-1.1)	1.0
Arabic n=471	0.6* (0.4-0.9)	1.0
Chinese n=1075	0.9 (0.6-1.3)	1.0
Indian n=463	0.6 (0.2-1.5)	1.0
Pacific Islander n=214	0.3 (0.7-1.5)	1.0

*p <0.05 versus Interpreter

Chapter 4: Presented As Publication

Comparison Of Complications And Mortality Of YT2DM And YT1DM : Long-Term Complications And Mortality In Young-Onset Diabetes Type 2 Diabetes Is More Hazardous And Lethal Than Type 1 Diabetes (1)

On publication, this paper was editorialised. This is presented in Appendix 2

ORIGINAL ARTICLE

Long-Term Complications and Mortality in Young-Onset Diabetes

Type 2 diabetes is more hazardous and lethal than type 1 diabetes

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OBJECTIVE—To evaluate long-term clinical outcomes and survival in young-onset type 2 diabetes (T2DM) compared with type 1 diabetes (T1DM) with a similar age of onset.

RESEARCH DESIGN AND METHODS—Records from the Royal Prince Alfred Hospital Diabetes Clinical Database, established in 1986, were matched with the Australian National Death Index to establish mortality outcomes for all subjects until June 2011. Clinical and mortality outcomes in 354 patients with T2DM, age of onset between 15 and 30 years ($T2DM_{15–30}$), were compared with T1DM in several ways but primarily with 470 patients with T1DM with a similar age of onset ($T1DM_{15–30}$) to minimize the confounding effect of age on outcome.

RESULTS—For a median observation period of 21.4 (interquartile range 14–30.7) and 23.4 (15.7–32.4) years for the T2DM and T1DM cohorts, respectively, 71 of 824 patients (8.6%) died. A significant mortality excess was noted in $T2DM_{15–30}$ (11 vs. 6.8%, $P = 0.03$), with an increased hazard for death (hazard ratio 2.0 [95% CI 1.2–3.2], $P = 0.003$). Death for $T2DM_{15–30}$ occurred after a significantly shorter disease duration (26.9 [18.1–36.0] vs. 36.5 [24.4–45.4] years, $P = 0.01$) and at a relatively young age. There were more cardiovascular deaths in $T2DM_{15–30}$ (50 vs. 30%, $P < 0.05$). Despite equivalent glycemic control and shorter disease duration, the prevalence of albuminuria and less favorable cardiovascular risk factors were greater in the $T2DM_{15–30}$ cohort, even soon after diabetes onset. Neuropathy scores and macrovascular complications were also increased in $T2DM_{15–30}$ ($P < 0.0001$).

CONCLUSIONS—Young-onset T2DM is the more lethal phenotype of diabetes and is associated with a greater mortality, more diabetes complications, and unfavorable cardiovascular disease risk factors when compared with T1DM.

Diabetes Care 36:3863–3869, 2013

Type 2 diabetes (T2DM) in youth is coming increasingly into focus given its rising incidence and prevalence, tracking together with childhood obesity. For those with young-onset T2DM, the increased lifetime exposure to hyperglycemia predicts a high complications risk over time (1). Moreover, there is evidence for an increased inherent susceptibility to complications, namely retinopathy in diabetes presenting earlier rather than later in life (2). Furthermore, the results from the recent TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) study, which examines optimal treatment regimens in young-onset T2DM (3), illustrate the difficulty in achieving and maintaining good glycemic control in youth, highlighting the lifelong metabolic challenges of early onset T2DM. Together, these observations predict a poorer prognosis for young-onset T2DM. Nevertheless, T2DM in youth is a relatively new problem, and there are few data on long-term survival or complications to substantiate this prediction. Such long-term outcomes from this point would take many decades to collect. Therefore, we interrogated a systematically maintained clinical database, with data spanning >20 years, and cross-referenced it to the Australian National Death Index (NDI) to examine the long-term case fatality and cause of death in young-onset T2DM. Long-term complications data were also examined in this group.

In clinical practice, a diagnosis of T2DM as opposed to type 1 diabetes (T1DM) in a young person often is met with relief because T2DM is perceived as the milder form. Again, little exists in the literature to substantiate this assumption. Given that the traditional focus of diabetes in youth has been on T1DM and that established morbidity and mortality data exist for this group (4,5), a comparison was made with T1DM. Accurate comparisons of outcome between T1DM and T2DM of usual onset have always been confounded by either older age of the typical T2DM patient or if age is accounted for, the much longer disease duration of the T1DM patient. By comparing only young-onset groups in this study, we were able to examine the long-term effects T2DM compared with T1DM, minimizing the otherwise unavoidable confounding effects of age differences on morbidity and mortality outcomes.

RESEARCH DESIGN AND METHODS

Clinical database

The Royal Prince Alfred Hospital (RPAH) Diabetes Database holds clinical information collected by standardized protocol on patients attending the diabetes service since 1986 (6). Patients are referred from a wide area, with the majority from metropolitan Sydney, Australia, but the catchment also extends rurally. Complications assessments are performed as previously outlined (6), usually on an annual basis. In brief, retinopathy was assessed by direct fundoscopy under

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Received 25 November 2012 and accepted 8 May 2013.
DOI: 10.2337/dc12-2455
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-2455/-/DC1.
A slide set summarizing this article is available online.

See accompanying commentary, p. 3857.

mydriasis or, in recent years, by retinal photography. Albuminuria was determined by collection of spot urine samples, and a urine albumin/creatinine ratio (ACR) >2.5 mg/mmol in males and >3.5 mg/mmol in females (or an albumin concentration >30 mg/L if ACR unavailable) was considered abnormal. Peripheral neuropathy assessment involved testing vibration perception threshold by biothesiometer, with results expressed as a *Z* score adjusting for age. Macrovascular disease and risk factors were assessed by clinical history, symptoms, sitting blood pressure (BP), and lipid profiles. Ischemic heart disease included a history of myocardial infarction or angina or ischemia noted on electrocardiogram or during stress testing. Renal function was assessed by estimated glomerular filtration rate (eGFR) (Modification of Diet in Renal Disease equation) (7). Complications data are available on >80% of subjects for all complications. Glycemic exposure was quantified by the calculation of the updated HbA_{1c}, which accounts for the time between visits and the number of measurements (8,9). All measurements (mean ± SD) of HbA_{1c} up to the last clinic visit were included (4.6 ± 4.4 and 5.4 ± 4.6 for the T2DM and T1DM groups, respectively). HbA_{1c} methodology was not standardized because of the time span over which the data were collected and because different pathology providers were used to analyze samples in an ambulatory clinic setting. Smoking history was ascertained by patient report. Smoking scored as current, ever, or never and pack-year estimates were recorded.

Mortality data

Mortality was ascertained by submitting patient data from the RPAH Diabetes Database to the Australian Institute of Health and Welfare for matching with the NDI, a centralized national mortality registry of all deaths occurring in Australia since 1980. Matching was performed by a standardized probabilistic linkage protocol with the following data items: ID number, surname, first given name, second given name, third given name, sex, date of birth, and date and state of residence at last contact. This linkage protocol is well validated and reported to have a sensitivity and specificity of 94% and 100%, respectively (10). Additionally, matching ambiguities were adjudicated by two authors (M.I.C., A.A.-S.) blinded to age of diabetes onset by cross-referencing with area-wide hospital records or confirmation provided by family members or primary care physicians. Death data were censored to 30 June 2011. The NDI is subject to delays in data acquisition, and as a result, information regarding the primary cause of death was available to 2008 so that cause of death is available for 72% of deaths. Cause of death was classified according to ICD-10 from 1997 onward. For the deaths occurring before 1997, causes of death were converted from ICD-9 to ICD-10 for analysis.

Identification and comparison of young-onset cohorts

A total of 24,415 records were available in the RPAH Diabetes Database. We identified 354 patients with young-onset T2DM defined as T2DM diagnosed between 15 and 30 years of age ($T2DM_{15–30}$). We examined the outcome of this early onset T2DM cohort with patients with T1DM in several ways. For the primary analysis, data from the $T2DM_{15–30}$ subjects were compared with data from all T1DM patients in the database who were diagnosed between 15 and 30 years of age ($T1DM_{15–30}$) (n = 470) . The two cohorts were compared with respect to clinical characteristics, cardiovascular risk factors, and the presence of complications evident at the last clinical visit. To examine for differences in clinical parameters that may have been present early in the disease, clinical data were also compared for a subset for whom there was the full complement of complications information at a time point of 2–5 years post diagnosis. Long-term survival outcomes between the $T2DM_{15–30}$ and the $T1DM_{15–30}$ cohorts were examined.

For supplementary analyses, we analyzed the entire T1DM cohort diagnosed before 30 years of age (n = 870) as a comparator. We also compared complications prevalence by 1:1 matching of the $T2DM_{15–30}$ cohort with the $T1DM_{15–30}$ cohort (n = 354 each) for age of onset to attenuate the confounding effects of diabetes duration on the presence of complications. The data from the matched cohort are presented in Table 1.

Statistical methods

Data were analyzed with NCSS 2007 (11) and ACCorD (Analysis of Censored and Correlated Data) (12). Continuous data were checked for normality and presented as mean or median. The two-sample *t* test or the Mann-Whitney *U* test were used to compare means or medians. Categorical data were represented as percentages. The χ^2 test was used to compare groups. Logistic regression was used to examine the determinants of macrovascular complications. The independent variables were the following: diabetes type, age, systolic BP, diastolic BP, BMI, HbA_{1c}, cholesterol level, triglyceride level, sex, ethnicity, albuminuria, smoking status, and lipid-lowering treatment.

A Kaplan-Meier survival curve was constructed to determine the time-based survival rate between the groups. A Cox regression analysis was performed to examine the relationship between mortality as the dependent variable and duration of diabetes as the time variable. The independent variables used in this analysis were the following: diabetes type, age, systolic BP, diastolic BP, HbA_{1c}, cholesterol level, triglyceride level, sex, ethnicity, albuminuria, smoking status, and lipid-lowering treatment. Significance was accepted at $P < 0.05$.

For the supplementary analysis involving a matched T1DM cohort, the NCSS Greedy (13) data-matching algorithm based on propensity scores was used. As described previously, patients with $T2DM_{15–30}$ were matched 1:1 according to age of diagnosis with patients with $T1DM_{15–30}$. A propensity score was calculated for the matching procedure with the use of logistic regression. Sum of rank distances, including the propensity score, were used to calculate the distance between the groups. Pairwise tests were used for all matched data.

RESULTS

Subject characteristics

For the primary analysis of 354 $T2DM_{15–30}$ and 470 $T1DM_{15–30}$ patients, the age of diabetes onset was 25.6 ± 3.7 and 22.0 ± 4.3 years ($P < 0.01$), respectively, and duration of diabetes was 11.6 vs. 14.7 years ($P = 0.001$), respectively. There was an excess of males found in both groups, particularly in the $T1DM_{15–30}$ cohort (50.6 vs. 60.0%, $P = 0.007$). Patients in the $T1DM_{15–30}$ group were mainly of Anglo-Celtic background (77.8%), and by contrast, the $T2DM_{15–30}$ group was of a more multiethnic background (28.1% Anglo-Celtic) (Table 1). Within 5 years of diagnosis, the majority of $T2DM_{15–30}$ subjects were treated with diet or oral hypoglycemic agents, and only 7% were being treated with insulin alone. With relevance to the concern of excess myocardial infarction in patients treated with rosiglitazone, only one subject had been treated with this agent. The $T2DM_{15–30}$ group had a

Table 1—*Complications status and risk factor profile at last clinical visit for study cohorts*

	$T2DM_{15-30}$	$T1DM_{15-30}$	*P* value
n	354	470	
Age (years)	40.4 ± 12.5	38.9 ± 10.9	0.07
Duration of diabetes (years)	11.6 (4.5–22.6)	14.7 (8.2–23.6)	0.001
Year of diagnosis (range)	1942–2011	1948–2010	0.09
Ethnicity			
Anglo-Celtic	97 (28.1)	358 (77.8)	<0.0001
Mediterranean	12.8	11.1	
Arab	6.4	2.0	
Southeast Asian	15.4	1.5	
East Asian	8.7	1.5	
Aborigine	13.6	1.5	
Islander	2.6	0.4	
Other	12.5	4.1	
BMI (kg/m^2)	32.2 ± 7.6	25.6 ± 4.5	<0.0001
eGFR	98 ± 39	93 ± 30	0.09
Retinopathy	131 (37)	192 (41)	0.3
Albuminuria	137 (47.4)	58 (15.3)	<0.0001
ACR (mg/mmol)	2.2 (0.8–12.8)	0.7 (0.4–1.6)	<0.0001
VPT *Z* score	2.3 ± 1.3	1.8 ± 1.3	<0.0001
Stroke	13 (4.3)	3 (0.7)	0.002
Ischemic heart disease	38 (12.6)	10 (2.5)	<0.0001
Any macrovascular disease	46 (14.4)	25 (5.7)	<0.0001
Updated HbA_{1c} (%)	8.1 ± 1.6	8.1 ± 1.6	0.9
Antihypertensive treatment	148 (49.3)	96 (24.6)	<0.0001
Systolic BP (mmHg)	126 ± 17	122 ± 16	0.003
Diastolic BP (mmHg)	78 ± 10	74 ± 9	<0.0001
Statin treatment	114 (38.3)	81 (21.0)	<0.0001
Cholesterol (mmol/L)	5.2 ± 1.5	4.9 ± 1.1	0.0008
Triglycerides (mmol/L)	1.9 (1.3–3.0)	1.0 (0.7–1.4)	<0.0001
HDL (mmol/L)	1.2 ± 0.4	1.5 ± 0.5	<0.0001
LDL (mmol/L)	3.0 ± 1.1	2.7 ± 0.9	0.06
Ever smoked	126 (39)	189 (45)	0.1
Pack-year	12 (6–22)	11 (7–20)	0.1

Data are mean ± SD, median (interquartile range), *n* (%), or %. VPT, vibration perception threshold.

significantly higher BMI; however, both groups were in the overweight to obese range (32.2 ± 7.6 vs. 25.6 ± 4.5 kg/m^2 for $T2DM_{15-30}$ and $T1DM_{15-30}$, respectively, $P < 0.0001$). There were no significant differences in the calendar year of diagnosis between the two study groups ($P = 0.09$), excluding a significant cohort effect. Of note, the updated HbA_{1c} as a measure of glycemic exposure was similar between the groups (8.1 ± 1.6% for both, $P = 0.9$).

Cardiovascular risk factors

For the primary analysis, at the final clinical visit, less favorable cardiovascular risk factors were found in the T2DM cohort, with significantly higher levels of serum triglyceride levels, lower HDL levels, higher BP readings, and higher use of antihypertensive and statin treatment (Table 1). With respect to mortality, smoking prevalence was not different between the two cohorts. To explore whether these adverse risk factors were present early in the disease process, we examined clinical data within 2–5 years of diagnosis. Clinical data were available for 92 $T2DM_{15-30}$ subjects and 148 $T1DM_{15-30}$ subjects (Table 2). Again, we found that the presence of cardiovascular disease (CVD) risk factors, such as BMI, albuminuria, dyslipidemia, systolic and diastolic BP, were significantly more unfavorable in the $T2DM_{15-30}$ group ($P < 0.02$ for all). There is already a high prevalence of abnormal albuminuria present at this early stage in $T2DM_{15-30}$ patients (39 vs. 7.9%, $P = 0.001$). These less favorable risk factor profiles were found early in the disease (average age of 29 years) before any clinical evidence of macrovascular complications (Table 2).

Diabetes complications

Data comparing the prevalence of diabetes complications are presented in Table 1. Despite a statistically shorter duration of diabetes and remarkably similar glycemic exposure, there was a significant excess of complications in the $T2DM_{15-30}$ cohort. Specifically, the ACR, prevalence of abnormal albuminuria, and biothesiometer *Z* scores were significantly increased ($P < 0.0001$ for all indices). However, there were no differences found between the groups with regard to the prevalence of retinopathy or renal function assessed by eGFR. A marked excess of macrovascular disease was found in the $T2DM_{15-30}$ cohort, with a higher prevalence of ischemic heart disease (12.6 vs. 2.5%, $P < 0.0001$), stroke (4.3 vs. 0.7%, $P = 0.002$), and the composite end point of any macrovascular disease (14.4 vs. 5.7%, $P < 0.0001$). Findings are similar for the matched cohorts, where duration of diabetes is similar (Supplementary Table 1).

Logistic regression analyses based on data from all available T1DM patients ($n = 870$) and young T2DM subjects ($n = 354$) showed a significant independent relationship between a diagnosis of T2DM and the presence of macrovascular disease (odds ratio 5.4 [95% CI 2.7–10.5], $P < 0.0001$). Other significant independent variables were diabetes duration, albuminuria, male sex, and smoking history. Ethnicity was not a significant variable.

Survival analyses

After a similar median observation period of >20 years for both groups (21.4 [14.0–30.7] vs. 23.4 [15.7–32.4] years for $T2DM_{15-30}$ and $T1DM_{15-30}$, respectively, $P = 0.002$), altogether, 71 of 824 patients (8.6%) died. A significant excess case fatality rate of 39 deaths in 354 $T2DM_{15-30}$ subjects (11%) compared with 32 deaths in 470 $T1DM_{15-30}$ patients (6.8%) was noted ($P = 0.03$). Deaths in the $T2DM_{15-30}$ cohort occurred after a significantly shorter disease duration (26.9 [18.1–36.0] vs. 36.5 [24.4–45.4] years, $P = 0.01$), and subjects died at a relatively young age in both groups (52.9 ± 14.7 and 57.4 ± 12 years for $T2DM_{15-30}$ and $T1DM_{15-30}$, respectively). The Kaplan-Meier analysis shows that cumulative survival was decreased for a given diabetes duration in the $T2DM_{15-30}$ compared with the $T1DM_{15-30}$ cohort (Fig. 1*A*), with separation of the survival curves appearing after ~15 years of diabetes duration. The hazard ratio (HR) for death was increased significantly in the $T2DM_{15-30}$ cohort to 2.0 (95% CI

Table 2—*Cardiovascular risk factors present after 2–5 years of known diabetes*

	T2DM	T1DM	*P* value
n	92	148	
Age (years)	29.4 ± 3.4	27.5 ± 3.9	0.0004
Duration of diabetes (years)	3.9 (3.0–4.6)	4.0 (3.0–4.7)	0.4
Average year of diagnosis	1997	1999	0.006
BMI (kg/m^2)	31.2 ± 7.2	24.8 ± 3.9	<0.0001
eGFR	86.7 ± 10.0	84.0 ± 19.6	0.6
Albuminuria	39.0	7.9	0.001
ACR (mg/mmol)	1.5 (0.7–3.7)	0.6 (0.3–0.9)	0.0004
Systolic BP (mmHg)	120 ± 15	115 ± 13	0.02
Diastolic BP (mmHg)	78 ± 10	73 ± 9	0.0001
Antihypertensive treatment	17.0	5.3	0.03
Statin treatment	17.0	5.3	0.03
Cholesterol (mmol/L)	5.4 ± 1.2	4.7 ± 0.9	0.0005
Triglycerides (mmol/L)	2.3 (1.5–3.6)	0.9 (0.7–1.3)	<0.0001
HDL (mmol/L)	1.1 ± 0.3	1.6 ± 0.6	<0.0001
Ever smoked	25.0	34.5	0.1
Pack-year	8 (3–14)	10 (7–11)	0.9

Data are mean ± SD, median (interquartile range), or %.

1.2–3.2, $P = 0.003$) compared with the T1DM matched cohort. Because ethnicity varied significantly between the two groups, we also examined outcomes for the Anglo-Celtic groups only ($n = 97$ for $T2DM_{15–30}$, $n = 358$ for $T1DM_{15–30}$). This analysis still showed that the more unfavorable risk factors and a higher mortality rate were seen in the $T2DM_{15–30}$ cohort (18.6 vs. 7.5%, $P = 0.001$), and Kaplan-Meier analysis showed that survival was also reduced in this group (Supplementary Fig. 1).

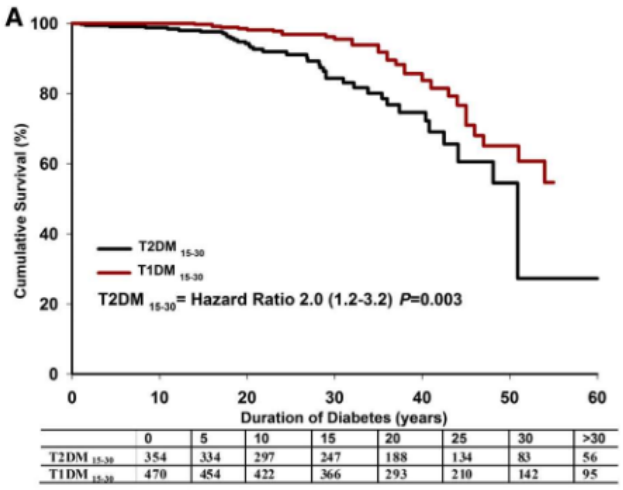
This excess risk for death in $T2DM_{15–30}$ subjects was still seen when the cohort was compared with the larger unmatched T1DM population diagnosed at <30 years of age ($n = 870$), yielding an HR of 2.7 (95% CI 1.6–4.4, $P = 0.0001$) (Fig. 1*B*). Additionally, Cox regression analysis of this larger cohort showed a significantly increased risk of death for the $T2DM_{15–30}$ cohort (2.1 [1.1–3.8], $P = 0.02$) together with an independent impact of diastolic BP (1.06 [1.03–1.09], $P = 0.0002$) and albuminuria (2.0 [1.1–3.7], $P = 0.03$) on mortality.

The predominant primary causes of death were cardiovascular (ICD-10 code I11-I80) for both cohorts, but there was a notable excess of cardiovascular deaths in the $T2DM_{15–30}$ cohort (50.0 vs. 30.3%, $P < 0.053$) (Fig. 2). Kaplan-Meier survival analysis for vascular mortality showed for both cohorts that the first vascular deaths occurred in the third decade of life, with an increased HR for vascular death for the $T2DM_{15–30}$ cohort of 3.5 (1.4–8.5, $P = 0.004$). Self-harm, ketoacidosis, and accidents were not listed as a major cause of death for this cohort. Causes of death are listed in Supplementary Table 2.

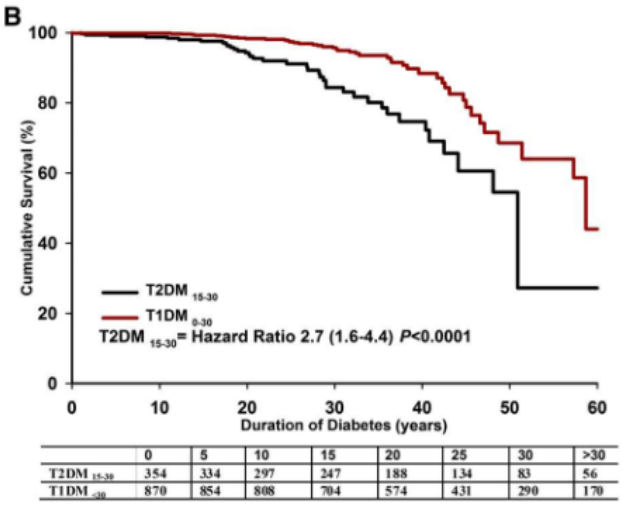
CONCLUSIONS—This analysis of systematically collected data provides a unique opportunity to examine the future burden of a disease that, until recently, has been a relatively rare phenomenon. Such information on mortality and long-term complications will require several decades of observation to examine prospectively, underscoring the value of the data. We found that case fatality is increased twofold in young-onset T2DM compared with T1DM of a similar age and duration. This increased death rate is driven primarily by cardiovascular deaths occurring in the prime of life, and these results give substance to the notion that young-onset T2DM is an aggressive disease, even more so than T1DM. Because T1DM itself carries an increased mortality risk, with standardized mortality ratios in the order of 4 (14,15) compared with the general population, the present findings give a disquieting perspective on the long-term mortality risk of $T2DM_{15–30}$ and a sobering glimpse of the future for patients, such as those in the TODAY study cohort.

In recognition of the paucity of data on survival in young-onset T2DM and that it will take decades from this point to understand the long-term mortality risk, Rhodes et al. (16) used a Markov modeling approach to project survival outcomes in this group, predicting that these patients lose ~15 years from an average remaining life expectancy compared with the average 20-year-old. Only a few previous studies have looked at comparative mortality in T1DM and T2DM onset in patients <30 years of age. In a Swedish study of patients with diabetes aged 15–34 years compared with a general population, the standardized mortality ratio was higher for the T2DM than for the T1DM cohort (2.9 vs. 1.8) (17). A study of mortality in a multiethnic, low-income population with diabetes onset before age 30 found that the excess mortality was greatest for the insulin-treated cohort, but the investigators were unable to differentiate between T1DM and T2DM requiring insulin therapy (18). Recently, Dart et al. (19) examined survival in youth aged 1–18 years with T2DM versus T1DM. Kaplan-Meier analysis revealed a statistically significant lower survival probability for the youth with T2DM, although the number at risk was low after 10 year's duration. Taken together, these findings are in keeping with the present observations and are supportive evidence for a higher mortality in young-onset T2DM than in T1DM.

The majority of deaths appear to be from cardiovascular causes and significantly more so for young T2DM. This would be predicted from the higher prevalence of macrovascular disease in the $T2DM_{15–30}$ cohort seen during the last follow-up period. Indeed, other studies have predicted this outcome, with surrogate measures of arterial stiffness found to be higher in young T2DM patients than in T1DM patients (20). However, with the results of the present study, we now have confirmatory evidence of more concrete outcomes of clinically apparent vascular disease and death. The presence of less favorable cardiovascular risk factors and higher prevalence of macrovascular disease evident in the $T2DM_{15–30}$ cohort is a contributing factor in the survival outcomes. These more adverse risk factors seen at the last visit were also evident even as early as 2–5 years from diagnosis. The constellation of higher BMI, diabetic dyslipidemia, BP, and urine ACR, all seen in the 20-year age-group, is alarming, particularly in the context of the patients' youth. Others too have found a high incidence of cardiovascular risk factors, including microalbuminuria in young-onset T2DM, particularly in some ethnicities such as Maori, Pima, Japanese, Hispanic, and African American populations (21–24). Most recently, Dart et al. (19) examined renal outcomes in young-onset



	0	5	10	15	20	25	30	>30
T2DM 15-30	354	334	297	247	188	134	83	56
T1DM 15-30	470	454	422	366	293	210	142	95



	0	5	10	15	20	25	30	>30
T2DM 15-30	354	334	297	247	188	134	83	56
T1DM 0-30	870	854	808	704	574	431	290	170

Figure 1—*A: Kaplan-Meier survival curve for T2DM$_{15–30}$ (n = 357) and T1DM$_{15–30}$ (n = 470) patients. B: Kaplan-Meier survival curve for T2DM$_{15–30}$ and all T1DM (age of onset <30 years) (n = 870) patients.*

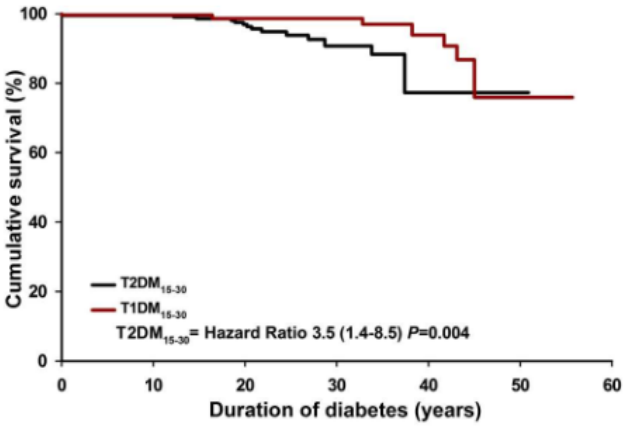
T2DM subjects compared with T1DM and normal control subjects and found a high burden of kidney disease and a fourfold risk of renal failure over T1DM subjects.

The observation of less favorable neuropathy scores in the T2DM cohort is a novel finding. Dyslipidemia has been implicated in the pathogenesis of diabetic neuropathy, and it is possible that less favorable lipid profiles in the T2DM$_{15–30}$ cohort are contributory (20). In contrast to albuminuria, the prevalence of retinopathy is very similar for T1DM and T2DM. Perhaps for the retinal vasculature, glycemia is the main contributor to the development of retinopathy, whereas in the kidney, obesity and hypertension demonstrably present early in the genesis of young-onset T2DM have a much greater impact on the development of albuminuria in concert with other CVD risk factors.

The evidence presented underscores that metabolic syndrome features are a frequent and early accompaniment in young-onset T2DM and that common factors may be involved in their pathogenesis. The higher prevalence of macrovascular disease in the present patients with T2DM was evident despite a shorter or equivalent duration of disease and glycemic exposure. The implication of this observation is that control of glycemia alone at an early stage would not be enough to attenuate the excess vascular risk in early onset T2DM. Although the uptake of established CVD-protective therapies, such as ACE inhibitor/angiotensin receptor blocker and statin use is higher in the present T2DM$_{15–30}$ cohort than in the T1DM$_{15–30}$ cohort, the overall use of these therapies is low given the abnormalities that already exist. It is important to note that CVD risk reduction is largely dictated by results derived from adult populations. For example, in most statin intervention trials, the lower age entry criterion is 40 years. It is assumed that pharmaceuticals such as statins and ACE inhibitors/angiotensin receptor blockers have equivalent benefits in this younger age group because larger intervention trials have not systematically included such young patients with either type of diabetes. However, assuming that such treatments are efficacious in youth, there are issues regarding teratogenicity during childbearing years. Furthermore, in Australia, age is an arbiter for which patients are eligible for a national subsidy of pharmaceuticals such as statins, with older age-groups given priority preference because of their higher absolute risk. Such barriers add to the treatment gap and residual risk in young-onset T2DM patients that need to be addressed more fully.

One of the strengths of this study is the long duration of observation, allowing sufficient events to have accumulated for overall mortality and complications risk to be evaluated. In this context, the study provides a robust platform on which to compare outcomes that have been systematically collated. However, several limitations should be discussed. The subjects were referred to a diabetes center in a large metropolitan teaching hospital. It is possible that only severe cases of T2DM with high cardiovascular risk were referred, resulting in a selection bias toward less

Youth T2DM is more lethal than T1DM



	0	5	10	15	20	25	30	>30
$T2DM_{15-30}$	329	311	275	226	171	118	72	47
$T1DM_{15-30}$	445	429	397	342	272	193	126	81

Figure 2—*Kaplan-Meier curve for cardiovascular deaths.*

favorable outcomes in T2DM patients. Although this could be a confounder, we are reassured by studies that have screened for T2DM in youth in the community that also reported similar risk profiles of obesity, hypertension, and albuminuria, thus arguing against a selection bias as a significant contributor to the present findings (25). Differences in ethnicity and socioeconomic factors could account for poorer outcomes for the T2DM patients in this study. However, access to care for our services in a public hospital is free, so any impact of socioeconomic status resulting in a financial barrier to health care would be minimized. Although differences in complications risk may cosegregate with ethnicity, ethnicity was not a significant independent risk factor for either macrovascular complications or earlier mortality. Of note, even when only Anglo-Celtic groups are compared, T2DM patients still fared worse than their T1DM counterparts. Male sex often is associated with a higher mortality; however, in this study, the slight excess of males is seen in the T1DM cohort and, therefore, unlikely to have negatively biased the results. Although the age of onset of T1DM diabetes is usually in little doubt because of a more abrupt presentation, it is possible that the age of onset of T2DM was in fact earlier than recognized. With a previously published method for estimating time delay until diagnosis of T2DM (26) by plotting the prevalence of retinopathy against duration and extrapolating to a point of zero retinopathy, we found that there is no difference in the slope and intercept of this relationship between the T2DM and the T1DM cohorts (Supplementary Fig. 2). These data are reassuring in that delay in diagnosis is unlikely to be an explanation for the differences in observed outcome. Moreover, the survival analysis that used as a comparator an unmatched cohort of 870 T1DM patients who as a group had an earlier onset of diabetes still showed an excess mortality in those with T2DM. Because of the long time span over which the data were collected, many of the patients studied did not have autoantibodies measured. However, we are reassured by the low prevalence of early insulin use in the young-onset T2DM cohort, so any possible misclassification bias would be expected to be low. Finally, causes of death are derived from death certificates, which have recognized inaccuracies applicable to both types of diabetes.

In conclusion, this study highlights young-onset T2DM as a high-risk phenotype requiring intensive intervention directed not only toward the treatment of glycemia, but also toward cardiovascular risk factors that often are concurrent early in the course of diabetes. From the CVD risk management point of view, strategies for this patient group cannot necessarily be extrapolated from the adult situation. Therefore, the benefits, optimal timing, and mode of delivery of risk-lowering interventions in this high-risk group remain to be determined, with teratogenic risk a significant consideration. Additionally, given the severity of the young-onset T2DM phenotype and in the context of burgeoning numbers, if today we are to protect against tomorrow's outcomes as predicted by this study, there is an urgent need for efforts to be redoubled toward diabetes prevention targeted to youth.

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

M.I.C., D.K.Y., and J.W. researched the data and wrote and edited the manuscript. L.M., F.L.-G., A.A.-S., and C.L. researched the data and reviewed the manuscript. T.W. and S.M.T. reviewed and edited the manuscript. M.I.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in an oral session at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, 8–12 June 2012.

The authors thank Profs. V. Gebski, A. Keech, and S. Colagiuri, University of Sydney, for their expert advice. The authors acknowledge the support of the Endocrinology and Diabetes Research Foundation of the University of Sydney and The NSW Ladies Bowl for Others Association. They also acknowledge the Australian Institute of Health and Welfare for support and expertise with the mortality data linkage.

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SUPPLEMENTARY DATA

Supplementary Table 1. Complications status and risk factor profile at last clinical visit for youth onset cohorts matched 1:1 for age of diagnosis

	Type 2 Diabetes	Type 1 Diabetes	p-value
N	354	354	
Duration of diabetes (yrs)	11.6 [4.5-22.6]	14.0 [7.3-22.2]	0.06
Ethnicity			
Anglo-Celtic n (%)	97 (28.1)	264 (76.3)	<0.0001
Mediterranean(%)	12.8	11.6	
Arabic(%)	6.4	2.0	
SE Asian(%)	15.4	1.4	
E Asian(%)	8.7	2.0	
Aborigine(%)	13.6	1.7	
Islander(%)	2.6	0.6	
Other(%)	12.5	4.3	
BMI Kg/m^2	32.2 ± 7.6	25.9 ± 4.3	0.0001
eGFR	98 ± 39.2	93 ± 32	0.3
Retinopathy n(%)	131(37)	141(40)	0.5
Albuminuria n(%)	137 (47.4)	38 (13.1)	<0.0001
ACR mg/mmol	2.2 [0.8-12.8]	0.7 [0.4-1.5]	<0.0001
VPT Z score	2.3 ± 1.3	1.8 ± 1.3	<0.0001
Stroke n(%)	13 (4.3)	2 (0.6)	0.002
IHD n(%)	38 (12.6)	5 (1.6)	<0.0001
Any Macrovacsular Disease n(%)	46 (14.4)	14 (4.2)	<0.0001
Updated HbA1c (%)	8.16 ± 1.6	8.16 ± 1.6	1.0
Antihypertensive Treatment n (%)	148 (49.3)	72 (24.6)	<0.0001
Systolic BP (mm Hg)	126 ± 17	122 ± 17	0.02
Diastolic BP (mm Hg)	78± 10	75 ± 9	<0.0001
Statin treatment n (%)	114 (38.3)	66 (22.5)	<0.0003
Cholesterol (mmol/L)	5.2 ± 1.5	4.9 ± 1.2	0.007
Triglycerides (mmol/L)	1.9 [1.3-3.0]	1.0 [0.7-1.5]	<0.0001
HDL (mmol/L)	1.2 ± 0.4	1.5 ± 0.4	<0.0001
LDL (mmol/L)	3.0 ± 1.1	2.8 ± 0.9	0.2
Ever smoked n(%)	126 (39)	141 (44)	0.2
Pack Years	12 [6-22]	12 [10-20]	0.4

Data are mean±SD or median [IQR] unless otherwise specified

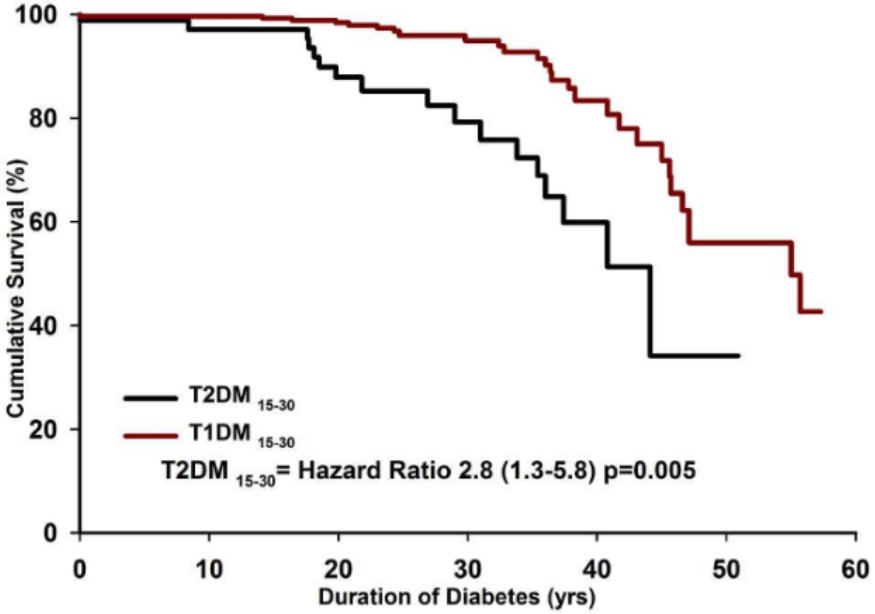
SUPPLEMENTARY DATA

Supplementary Table 2. Causes of Death

	Type 2 Diabetes	**Type 1 Diabetes**
n	354	470
Primary cause of death available for analysis (n)	28	23
Causes of Death n (%)		
Ischaemic/ vascular	14 (50.0)	7 (30.4)
Malignant neoplasm	2 (7.1)	3 (13.0)
Endocrine	6 (21.4)	12 (52.2)
Alcohol related	1 (3.6)	
Disease of the nervous System	1 (3.6)	
Congenital Malformation Syndrome	1 (3.6)	
Car accident	1 (3.6)	
Accidental respiratory blockage	1 (3.6)	
Accidental poisoning	1 (3.6)	
Diseases of the Digestive System		1 (4.3)

SUPPLEMENTARY DATA

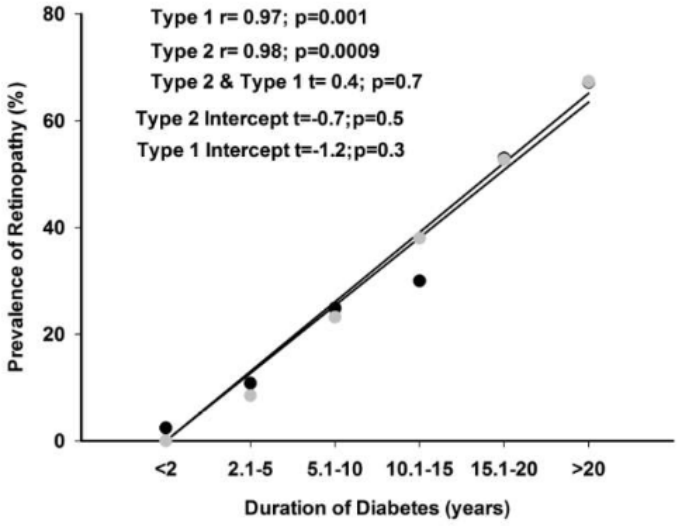
Supplementary Figure 1. Kaplan Meier Curve for Anglo-Celtic only



	0	5	10	15	20	25	30	>30
T2DM 15-30	97	91	81	67	47	38	28	22
T1DM 15-30	358	345	324	282	235	166	115	79

SUPPLEMENTARY DATA

Supplementary Figure 2. Plot of retinopathy prevalence by duration of diabetes for $T2DM_{15\text{-}30}$ (n=354) and $T1DM_{15\text{-}30}$ (n=470) primary cohorts to show equivalent duration of diabetes at a zero prevalence of retinopathy, suggesting no difference in the time to diagnosis between the two groups



Type 1 (Y= -6.2 + 2.9*Duration) (duration of 2.1 years = 0 retinopathy)
Type 2 (Y= -3.2 + 2.8*Duration) (duration of 1.1 years = 0 retinopathy)

Chapter 5: Presented as publication

Comparison of Complications of YT2DM vs. older onset T2DM: An Inverse Relationship Between Age Of Type 2 Diabetes Onset With Complications Risk And Mortality: The Impact Of Youth-Onset Type 2 Diabetes (6)

An Inverse Relationship Between Age of Type 2 Diabetes Onset and Complication Risk and Mortality: The Impact of Youth-Onset Type 2 Diabetes

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Diabetes Care 2016;39:823–829 | DOI: 10.2337/dc15-0991

OBJECTIVE

This study compared the prevalence of complications in 354 patients with T2DM diagnosed between 15 and 30 years of age ($T2DM_{15–30}$) with that in a duration-matched cohort of 1,062 patients diagnosed between 40 and 50 years ($T2DM_{40–50}$). It also examined standardized mortality ratios (SMRs) according to diabetes age of onset in 15,238 patients covering a wider age-of-onset range.

RESEARCH DESIGN AND METHODS

Complication status was assessed according to a standard protocol and extracted from our electronic database. Survival status was ascertained by data linkage with the Australian National Death Index. SMRs were calculated in comparison with the background Australian population and analyzed according to age of onset.

RESULTS

After matching for duration, despite their younger age, $T2DM_{15–30}$ had more severe albuminuria ($P = 0.004$) and neuropathy scores ($P = 0.003$). $T2DM_{15–30}$ were as commonly affected by metabolic syndrome factors as $T2DM_{40–50}$ but less frequently treated for hypertension and dyslipidemia ($P < 0.0001$). An inverse relationship between age of diabetes onset and SMR was seen, which was the highest for $T2DM_{15–30}$ (3.4 [95% CI 2.7–4.2]). SMR plots adjusting for duration show that for those with $T2DM_{15–30}$, SMR is the highest at any chronological age, with a peak SMR of more than 6 in early midlife. In contrast, mortality for older-onset groups approximates that of the background population.

CONCLUSIONS

The negative effect of diabetes on morbidity and mortality is greatest for those diagnosed at a young age compared with T2DM of usual onset. These results highlight the growing imperative to direct attention toward young-onset T2DM and for effective interventions to be applied before middle age.

Type 2 diabetes is well recognized to be a heterogeneous disorder, and its effect on morbidity and mortality may not be identical within this diagnosis. No longer just a disorder of mature age, there is now a well-recognized trend toward younger people presenting with this disease, particularly for some ethnic groups. Adolescents accounted for less than 4% of incident type 2 diabetes cases in the U.S. 15 years ago, but in a more

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Received 10 May 2015 and accepted 27 October 2015.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-0991/-/DC1.

A.H.A.-S. and M.I.C. contributed equally to this work.

recent report, 45% of new cases were in this category. The net result is a widening of the clinical spectrum, with age of diabetes onset increasingly recognized as an important factor in the heterogeneity of risk within this diagnosis.

The landmark Search for Diabetes in Youth (SEARCH) and Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) studies, among others, have contributed to an understanding that type 2 diabetes presenting at a young age is of a particularly aggressive nature and have highlighted the challenges in the management of this patient group (1,2). Young people with type 2 diabetes are likely to be obese, with a clustering of unfavorable cardiometabolic risk factors all present at a very early age (3,4). In adolescents with type 2 diabetes, a 10–30% prevalence of hypertension and an 18–54% prevalence of dyslipidemia have been found, much greater than would be expected in a population of comparable age (4). In another study of patients with type 2 diabetes younger than 20 years of age, aortic pulse wave velocity was already higher than that of age-matched control subjects, indicating an increased degree of arterial stiffness (5). Most recently, results from the TODAY study have clearly documented the progression of cardiovascular disease (CVD) risk factors despite optimal within-trial interventions (6,7). These all portend a poor long-term prognosis, but there are still relatively limited data on long-term complication status and mortality risk in youth with type 2 diabetes.

Only a few studies have looked at the question of complications according to age of disease onset. More specifically, few data are available to assess whether the risk is truly in excess of that seen in diabetes presenting in the more usual middle age and beyond, after accounting for disease duration. Hillier and Pedula (8) reported a higher relative risk of macrovascular disease in those diagnosed with type 2 diabetes between 18 and 44 years of age than in those identified after 45 years of age, when each group was compared with an age-matched population without diabetes. Similarly, Song and Hardisty (9) showed that in cohorts with type 2 diabetes with disease onset before and after 40 years of age, by the sixth decade of life, a substantially higher risk of CVD is seen in those with the earlier onset of diabetes. Whether the excess risk seen in younger cohorts is simply the result of a longer diabetes duration at any attained age or whether there is an underlying enhanced susceptibility to complications is less clear.

Similarly, few data are available on the survival of individuals with young-onset type 2 diabetes, and this lack of robust clinical data has prompted the use of a Markov modeling approach by investigators. Extrapolating from the UK Prospective Diabetes Study cohort, Rhodes et al. (10) project a shortening of life expectancy by 15 years for type 2 diabetes in adolescents. Narayan et al. (11) used the same modeling approach to examine data from the National Health Interview Survey in the U.S. They similarly found that non-Hispanic white individuals diagnosed with diabetes at the age of 20 years would lose 15.3 years of life expectancy (11). We have found that for individuals with young-onset type 2 diabetes, survival is worse than for type 1 diabetes of similar age of onset (3,12). Given that young patients with type 2 diabetes are still a relatively new clinical cohort, a comparative perspective on long-term mortality has hitherto been lacking.

In this two-part study, we examined the effect of age of onset on *1*) diabetes complications after controlling for diabetes duration and *2*) the standardized mortality ratio (SMR). In the first part, prospectively collected clinical complications data from 354 patients with young-onset type 2 diabetes diagnosed between the ages of 15 and 30 years ($T2DM_{15–30}$) were compared with 1,062 subjects with type 2 diabetes onset between the ages of 40 and 50 years ($T2DM_{40–50}$), after matching for duration of known diabetes. Groups with older age were not used for direct comparison to minimize the additional confounding effect of chronological age on macrovascular complications. In the second part, we ascertained the mortality status of 15,238 patients with type 2 diabetes by linkage with the Australian National Death Index and related the findings to the age of diabetes onset. The effect of diabetes on mortality according to age of onset is difficult to compare directly given the confounder of intrinsically higher mortality rates related to age itself. Thus, this study standardized mortality rates to the general Australian population and stratified by age of onset of diabetes. In this way, the relative effect of diabetes beginning at different life stages can be more clearly compared.

RESEARCH DESIGN AND METHODS

Diabetes Database and Collection of Clinical Information

The Royal Prince Alfred Hospital Diabetes electronic database contains demographic and clinical information from patients who have attended the Royal Prince Alfred Diabetes Centre in Sydney Australia since 1986. Diabetes was defined by World Health Organization criteria (13). The diagnosis of type 2 diabetes was made on clinical grounds by the treating physician. Age-of-onset data are available for all patients in this study. The age of onset was taken from the primary care correspondence or from the date of the defining laboratory test. If neither was available, patient recall was relied on. If only the year of diagnosis was known, the default date of 1 January was used to calculate age of onset. All patients reported in this complications component of the study had a clinical and complications assessment via a standardized protocol and data entered in a purpose built database (14). Data quality is linked to the model of care; data were frequently reviewed as the clinical correspondence is linked to data entry and previously described and evaluated (14,15).

In brief, retinopathy was assessed by direct funduscopy with pupils dilated or by digital retinal photography in recent years. Albuminuria was determined by collection of spot urine samples and considered abnormal if the albumin concentration was greater than 30 mg/L or if the urine albumin-to-creatinine ratio was greater than 3.5 and 2.5 mg/mmol for females and males, respectively. Neuropathy assessment was by examination of ankle reflexes and testing of vibration perception threshold (volts) with a biothesiometer adjusted for age by expressing data as a Z score. Macrovascular disease and risk factors were assessed by clinical history of events or relevant symptoms and measurements of sitting blood pressure and lipid profiles. The degree of hyperglycemia was assessed by measurement of HbA_{1c} using the high-performance liquid chromatography method, and long-term glycemic control was documented by the calculation of updated HbA_{1c}, adjusting for the time between visits and the number of measurements (16).

Complications

To examine the differential effect of age of onset on clinical parameters and diabetes, the complication status of 354 patients with $T2DM_{15–30}$ was identified from the database and compared with a 1:3 matched sample of 1,062 patients with $T2DM_{40–50}$ with the same duration of known diabetes. Unadjusted mortality rates and cause of death are also presented for this cohort.

Mortality and SMR

A total of 24,415 names of patients, including 15,238 with type 2 diabetes from our database, were submitted to The National Death Index (NDI) of the Australian Institute of Health and Welfare, which contains records of all deaths occurring in Australia since 1980. An NDI standard linkage protocol was followed to match individuals from the two databases using the following fields: ID number, surname, first given name, second given name, third given name, sex, date of birth, date of last contact, and state of residency. When matching was ambiguous, mortality was confirmed by checking with the area-wide hospital database. This protocol has been validated in other populations and found to have a high sensitivity in determining survival (17). Because of a time lag in the updating of the NDI database, the primary cause of death was only available in 3,630 records, and data from these individuals were used to examine the specific cause of death. For deaths in and after 1997, all causes of death are available and are coded according to ICD-10. For deaths before 1996, the underlying cause of death was coded according

Table 1—Clinical profile and mortality of patients with T2DM (*N* = 1,416) grouped by age of diagnosis and matched for diabetes duration

	$T2DM_{15–30}$ *n* = 354	$T2DM_{40–50}$ *n* = 1,062	Test statistics *P* value
Age diagnosed (years)	25.6 ± 3.7	45.2 ± 2.9	<0.0001
Duration of diabetes at last visit (years)	11.6 (4.5–22.6)	11.4 (4.5–21.7)	Matched
Male (%)	50.6	50.6	Matched
Age at last visit (years)	40.4 ± 12.6	59.1 ± 10.7	<0.0001
Family history of diabetes (%)	80.9	67.1	<0.0001
Number of family members affected with diabetes	2.4 ± 2.0	2.0 ± 1.6	0.02
Updated HbA_{1c}			
Percentage (%)	8.1 ± 1.6	8.0 ± 1.7	0.3
IFCC (mmol/mol)	65.5 ± 17.7	64.3 ± 18.2	0.3
Diabetes treatment (%)			0.0002**
Diet	9.6	8.2	
Tablets	37.3	49.9	
Insulin	53.1	41.9	
BMI (kg/m^2)	32.2 ± 7.6	31.2 ± 7.4	0.04
Blood pressure (mmHg)			
Systolic	126 ± 17	132 ± 19	<0.0001
Diastolic	78 ± 10	77 ± 11	0.2
Blood pressure treatment (%)	49.3	68.1	<0.0001
Cholesterol (mmol/L)	5.2 ± 1.5	4.8 ± 1.2	<0.001
Triglyceride (mmol/L)	1.9 (1.3–3.0)	1.6 (1.2–2.5)	0.001
Statin treatment (%)	38.1	51.5	0.0001
Smoking (%)	41.3	45.3	0.2
Retinopathy (%)	37.0	35.4	0.5
Vibration perception threshold Z score*	2.3 ± 1.3	2.0 ± 1.2	0.003
Albuminuria (%)	47.4	41.1	0.07
Urine albumin concentration (mg/L)	19.1 (6.0–114.1)	14.5 (6.5–49.0)	0.004
Any macrovascular disease (%)	14.4	23.7	<0.0001
Peripheral arterial disease (%)	3.8	6.5	0.07
Ischemic heart disease (%)	12.6	17.5	0.02
Stroke (%)	4.3	7.0	0.1
Death, *n* (%)	39 (11.0)	204 (19.2)	<0.0001
Age at the time death (years)	52.9 ± 4.7	68.6 ± 12.4	<0.0001
Duration of diabetes at the time of death (years)	26.9 (18.1–36.0)	25.1 (15.3–32.0)	<0.0001
Cause of death (%)			0.7**
Vascular	50.0	42.8	
Cancer	7.1	10.1	
Other	42.9	47.1	

Results are presented as mean ± SD, as median (IQR), or as indicated. IFCC, International Federation of Clinical Chemistry and Laboratory Medicine. *Vibration perception threshold is tested by biothesiometer adjusted for age by expressing data as a Z score. **P for differences in the distribution of the three categories between groups.

to ICD-9 and then aligned to ICD-10 for the purposes of this work. Cause of death was only examined for the matched cohort.

For the mortality analysis, individuals were monitored from 1986 or, if they presented later, from the time of the first clinic registration date, to the date of death or death censor on 6 January 2011. To establish the expected mortality rate of the diabetes population defined by age of diagnosis, the following procedure was undertaken. The age structure of each population with diabetes was established for each year of follow-up, and the expected mortality rates of the clinic population were calculated from the age- and sex-specific annual mortality rates of the general Australian population, published by the Australian Institute of Health and Welfare (18). SMRs were calculated by the ratio of the observed mortality rate of the clinic population/the calculated expected mortality. Thus an SMR of 1 indicates an equivalent mortality risk compared with an age-matched general Australian population.

Statistics

For the analysis of complications, data were analyzed using NCSS 2007 and ACCorD software (version 2.0.10; Boffin Software, Sydney, Australia). An NCSS data-matching procedure was used to match 1:3 $T2DM_{15–30}$ case subjects to $T2DM_{40–50}$ control subjects for the duration of diabetes. A propensity score was calculated for the matching procedure using logistic regression. Sum of rank distances, including the propensity score, was used to calculate the distance between the groups for matching. Continuous data are presented as medians or means. Categorical data are presented as percentage. Matched data were compared using paired analysis, generalized estimating equations (ACCorD). Significance was accepted as $P < 0.05$.

A Poisson regression model was used to calculate SMRs and the corresponding 95% CI. SMRs were analyzed with a Poisson regression model using log-expected deaths as the offset. The patient follow-up data were split into 1-year intervals, with each interval recording the current age and diabetes duration in years. For each interval, we merged the corresponding overall population mortality rates (18) (matched by age-group, sex, and calendar year) and computed the expected number of deaths. SMR was analyzed with current age (in years), duration of diabetes, and the interaction of age and diabetes duration as the independent variables. The mortality analysis was done using SAS 9.3 software.

RESULTS

Clinical Features and Complications

The clinical characteristics, complications, and mortality rates of $T2DM_{15–30}$ and $T2DM_{40–50}$ are reported in Table 1. The $T2DM_{15–30}$ group was more likely to have a positive family history of diabetes ($P < 0.0001$) and diabetes involving more members of the family ($P = 0.02$). After the same duration of diabetes, ~11 years, the $T2DM_{15–30}$ group were more likely to be treated with insulin but achieved a similar updated HbA_{1c}. The prevalence of retinopathy was similar, but the $T2DM_{15–30}$ group had higher urine albumin concentration and vibration perception thresholds ($P \leq 0.004$), despite their younger age. The $T2DM_{15–30}$ group was also more obese and had higher cholesterol and triglyceride but was less frequently treated with a statin or antihypertensive agent. Although macrovascular disease was less clinically evident in the younger-onset group ($P < 0.0001$ for any vascular disease), vascular deaths nevertheless predominated and were equivalent in percentage terms to the older cohorts. The age of death was significantly lower in the $T2DM_{15–30}$ group by ~15 years.

Mortality

The number of observed and expected deaths and the SMR for the different age-of-onset groups are given in Table 2. There were 15,238 patients with type 2 diabetes, contributing 156,804 person-years of follow-up, equating to an average follow-up time of 10 years until death or date of censure. Males comprised 57% of the population. Among the 15,238 patients with type 2 diabetes studied, 4,169 deaths occurred in a 25-year period. The crude mortality rate for the entire cohort was 27.2 deaths (95% CI 26.4–28.1) per 1,000 patient-years and was lowest for the younger age-of-onset group, a consequence of their still relatively young achieved age.

As reported in Table 2, with the age structure of the population accounted for, the SMR is highest for the youngest-onset group with a threefold increase compared with the general population (3.4 [95% CI 2.7–4.2]). The SMR of the older-diabetes-onset groups falls progressively toward 1, trending toward a negligible effect on mortality above the general population (Fig. 1 and Table 2).

The SMR at each age, adjusted for duration, for each age-of-onset group is shown in Fig. 2 and for males and females in Supplementary Figs. 1 and 2. The peak SMR is the highest for the youngest-onset group; the highest SMR of more than 6 is seen in the fourth decade of life and is highest for females. The SMRs for these younger-onset groups still remain elevated above background until extreme old age. In contrast, the peak SMR for those diagnosed after 50 years of age is at most twofold increased and declines with aging compared to that of the background population.

CONCLUSIONS

The characteristics of young-onset type 2 diabetes have been the subject of a growing number of reports. The higher insulin use for similar glycemic indices seen in our cohort is in accordance with the results of the TODAY study, in which a rapid loss of glycemic

Table 2—SMR for each age-of-onset group

Age of onset (years)	N	Deaths (n)		SMR	95% CI
		Observed	Expected		
15–29	588	79	23	3.4	2.7–4.2
30–39	2,022	306	123	2.5	2.2–2.8
40–49	3,891	772	439	1.8	1.6–1.9
50–59	4,583	1,265	860	1.5	1.4–1.6
60–69	2,960	1,119	1,000	1.2	1.1–1.2
>69	1,194	628	633	1.0	0.9–1.1

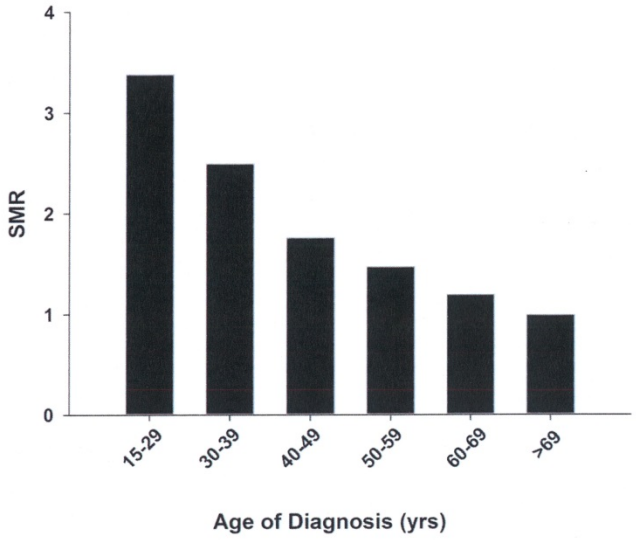

Figure 1—SMR for each age-of-onset cohort.

control and β-cell decline was observed (19). Our study also provides additional information on the relative effect of the age of diagnosis of diabetes on complications prevalence and the long-term mortality relative to the background population. Compared with type 2 diabetes of typical onset in middle age and older, younger-onset patients have a greater risk of renal and nerve complications and a higher standardized mortality. The greatest excess mortality is seen by the age of ~40. These perspectives on the effect of type 2 diabetes occurring at a young age are particularly important moving forward in considering how best to derive strategies for management of this high-risk patient group.

Duration of diabetes is one of the strongest determinants of complication risk, and our study is one of the few that minimizes the effect of duration by matching directly rather than using statistical adjustments for duration. In so doing, our data provide a more robust perspective of the underlying "inherent" morbidity of having type 2 diabetes at a younger age, particularly because differences in glycemic exposure were not evident in our cohorts. Once duration is equated, the younger-onset group has a higher prevalence of albuminuria and neuropathy scores than the later-onset group. There was less clinically evident macrovascular disease in the early-onset group, and taken together with the finding of an equivalent burden of cardiovascular deaths, introduces the possibility that subclinical/unrecognized CVD might be more prevalent in younger-onset groups and perhaps that the first manifestation of ischemic heart disease is more likely to be fatal. These

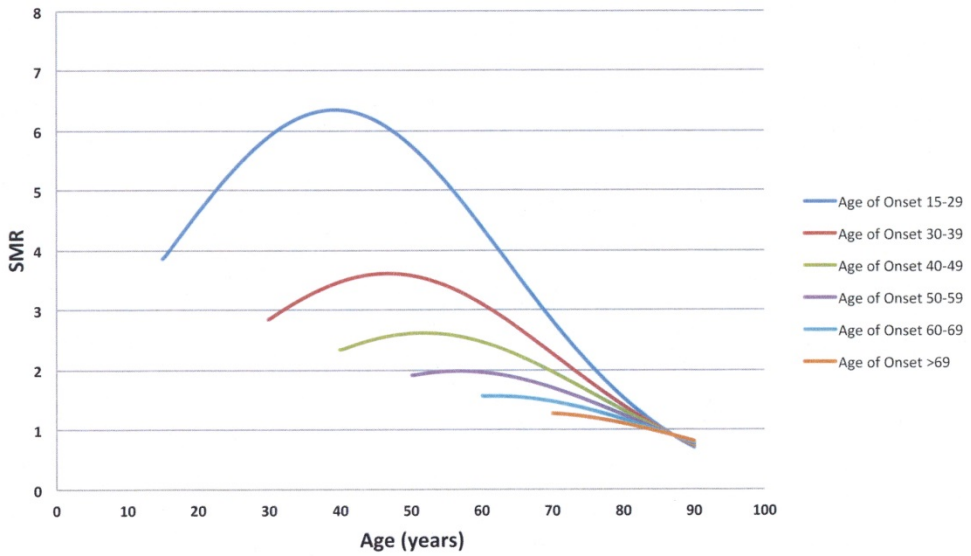

Figure 2—SMR plots for attained age for each age-of-onset cohort.

data imply that for youth with type 2 diabetes, their poorer complications outcomes, at least for renal complications and neuropathy, are not simply a result of a lead-time bias given their longer duration of disease. In contrast to neuropathy and albuminuria, we did not find differences in the prevalence of retinopathy between the age-of-onset groups. Data from Hillier and Pedula (8) showed a slight decrease in susceptibility to retinopathy in young adults with early-onset diabetes, and the TODAY study suggested that obesity might be a protective factor in the development of retinopathy. In both studies, however, diabetes duration was much shorter than here (20). We previously found an excess risk of retinopathy in younger-onset type 2 diabetes (aged <45 years) compared with older-onset groups with equivalent glycemic exposure, a finding that was not seen here. Our previous analysis did not specifically examine the groups with very young onset. It included much older age-of-onset cohorts monitored for a longer duration and had a wider range of glycemic exposure than in this study (21).

A shortened life expectancy associated with diabetes has been recognized for decades, but few previous studies have examined the relative effect of age of diagnosis in this regard. To generate a true perspective of the effect of age of diagnosis of diabetes, it is not possible to just examine mortality by using standard Kaplan-Meier survival analyses, because chronological age in itself is such a dominant factor in determining mortality. We thus used the calculation of SMR and also examined the SMR by attained age. Our data are in keeping with a U.S. study of diabetic versus nondiabetic mortality that found a more than threefold relative increase in mortality among individuals with diabetes between the ages of 25 and 44 (22). Our data highlight this phenomenon in a more general sense by showing the progressive and inverse relationship between age of onset and the SMR. Notably, an adverse effect is seen more with early-onset disease, where peak excess mortality at the attained age of 40 and thereabouts is approximately sixfold increased above that of the background population. In contrast in diabetes of onset at a later age, the total SMR and SMR at any attained age more closely approximates that of the general population.

A strength of our study on complications is the comprehensive documentation of individual demographic profile, glycemic control, cardiovascular risk factors, and the micro- and macrovascular complication status over a long period of time, using a set of standardized clinical criteria and an electronic database (14). The almost identical updated HbA_{1c} in the two cohorts was fortuitous but added strength to our conclusions. The ability to cross-reference our data with actual mortality recorded in a national database also provided a unique opportunity to link to outcomes. By taking a total SMR and the SMR by attained age approach, we have been able to assess not only the effect of the age of onset of disease on mortality but also the timing of any such adverse effect.

Some limitations of this study should be acknowledged. The study is from a single center, and the numbers of individuals with youth-onset type 2 diabetes are relatively low. There were no consistent measures of anti-GAD or other relevant antibody measurements to define better the types of diabetes, but the risk of misclassification is probably small because most patients with younger-onset diabetes were not treated with insulin in the first 5 years of diabetes.

Although the data were entered prospectively, they were not collected according to a prespecified time schedule. Many of the individuals did not present immediately after their diagnosis of diabetes, with the potential for "immortal time bias" to be favoring survival. In other words, patients would have had to survive long enough to reach our clinic. This bias, if present, would mean that our SMR calculations may have even underestimated the true mortality for our youth-onset groups. As for all such analyses, we recognize that the mortality data provided for the general population by the Australian Institute of Health and Welfare will also contain individuals with diabetes, and so the expected mortality rate calculations cannot be assumed to be from those completely disease free. The cohorts studied were not population based and therefore were susceptible to selection bias. Differential referral of more severe patients could potentially affect the mortality rates by age of diagnosis; however, the effects on the findings would depend on whether the bias was seen only in some age-of-onset groups. It is reassuring to note that the total SMRs in our study are of a similar magnitude to those seen in a recent mortality study of diabetes in Australia using data from national administration databases where selection bias would be less likely (23). Despite these limitations, the data obtained provide information that would otherwise take several decades to gather.

The clinical implications of our results are profound for the clinicians managing younger patients with type 2 diabetes. The observation that the relative morbidity and mortality risk in the younger-onset group is not only high but also early should prompt interventions to control glycemia and CVD risk factors before middle age. Existing absolute risk calculators used to aid treatment decisions are likely not to adequately capture the risk for our younger-onset patients. At the population level, enormous resources are presently directed toward the prevention and treatment of diabetes. In view of our findings, direction of these limited resources needs to be prioritized toward those at a younger age. The challenges identified by the landmark TODAY study showing the progression of adverse cardiovascular risk factors and glycemia, despite intensive interventions, will render this no easy task (24). Currently, we have no specific evidence of how to successfully prevent CVD in the young because trials of interventions, such as statin treatment and blood-pressure lowering, have not included young people with type 2 diabetes.

Furthermore, there is little specific evidence to guide how to prevent diabetes in the young. In the context of rising rates of obesity largely driving type 2 diabetes in younger age groups, research into effective and diverse strategies, including modifying in utero glycemic exposure, public health policy, addressing social disadvantage, and urban planning, are needed to tackle this. There is now some urgency to develop an evidence base in this regard and to determine the optimal timing of such interventions more closely. Our results highlight the growing imperative to prevent diabetes in youth and, if not possible, at least to delay

the development of diabetes to an older age.

Acknowledgments. The support of the Endocrinology and Diabetes Research Foundation of the University of Sydney and the NSW Women's Bowl for Others Club is gratefully acknowledged. The authors also thank Val Gebski (NHMRC Clinical Trials Centre, Sydney Medical School, The University of Sydney) for helpful statistical advice.

Funding. A.H.A.-S. was supported by the Riyadh Military Hospital.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.H.A.-S., M.I.C., L.M., D.K.Y., and J.W. researched and analyzed the data and wrote the manuscript. M.D'S. performed the statistical analysis and reviewed the manuscript. F.L.-G. and C.L. reviewed records and collected data. T.W. and S.M.T. reviewed the manuscript and contributed to discussion. M.I.C. and J.W. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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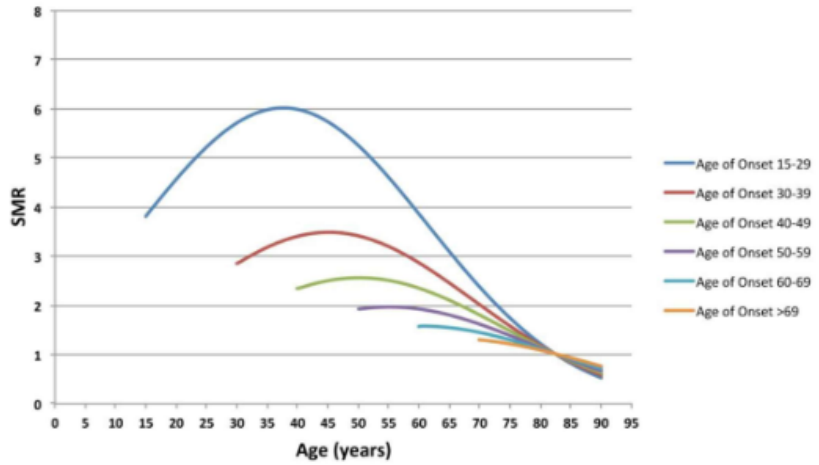
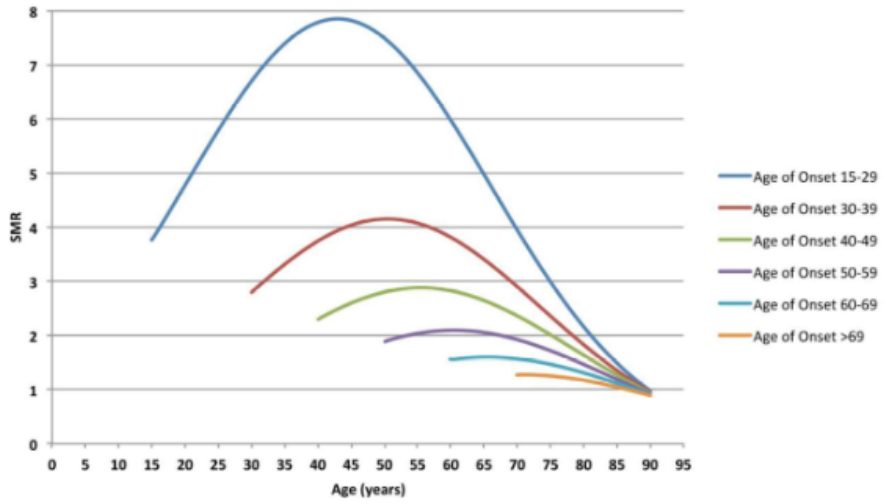
SUPPLEMENTARY DATA

Supplementary Figure 1. Males Standardised Mortality Ratio plots for attained age, for each age of onset cohort



SUPPLEMENTARY DATA

Supplementary Figure 2. Females Standardised Mortality Ratio plots for attained age, for each age of onset cohort



Chapter 6: Presented as publication

Data Collection On Retinopathy As A Public Health Tool: The Hubble Telescope Equivalent Of Looking Back In Time (4)

Journal of Diabetes and Its Complications 31 (2017) 721–725

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Data collection on retinopathy as a public health tool: The Hubble telescope equivalent of looking back in time

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ARTICLE INFO

Article history:
Received 27 October 2016
Received in revised form 14 December 2016
Accepted 17 December 2016
Available online 21 January 2017

Keywords:
Retinopathy
HbA1c
Type 2 diabetes
Public health
Complications

ABSTRACT

Objective: To test whether the rate of diabetic retinopathy development in a population calculated from the prevalence of retinopathy and duration of diabetes can be used to assess their prior glycemic control.
Research Design and Methods: 9281 patients with type 2 diabetes (T2DM) were grouped by duration of diabetes and plotted against the % of retinopathy in each band. The slope was used to calculate retinopathy development/year (RD/y). We correlated the RD/y with updated HbA1c within groups of different ethnicity, age of diabetes onset, year of the eye examination, socio-economic status and fluency in English.
Results: Differences in ethnicity, age of diabetes onset and year of the eye examination affect RD/y to a degree predictable from their respective updated HbA1c. No such relationship with updated HbA1c was evident when a factor has no apparent effect on RD/y.
Conclusions: This relationship between prevalence of retinopathy and duration of diabetes can be used to assess future retinopathy burden. Perhaps more intriguing, the camera can be reversed to allow an estimate of prior glycemic control of a population from its retinopathy prevalence. Health care organizations can use this method to project future needs and to assess adequacy of prior glycemic control.

1. Introduction

Diabetic retinopathy (DR) is an important complication of diabetes which causes considerable morbidity and also associated with significant increase in mortality of those affected. At an individual level, the presence of retinopathy is best predicted, although far from perfectly, by the duration of diabetes and the overall glycemic exposure of the individual in the previous years (Klein, Klein, Moss, & Cruickshanks, 1994; Nathan, Singer, Godine, Harrington, & Perlmuter, 1986; Wong, Molyneaux, Constantino, Twigg, & Yue, 2008; Nordwall et al., 2015). By contrast to the relatively poor predictability at an individual level, investigators have previously demonstrated a strong linear relationship between duration of diabetes and prevalence of retinopathy at a population level, e.g., in a Wisconsin and a Western Australian population (Harris, Klein, Welborn, & Knuiman, 1992). The slope of such relationship between prevalence of retinopathy and duration of diabetes is a measure of the rate of retinopathy development per unit time for that population. We used patient information stored in our electronic database to test the hypothesis that the rate of retinopathy development calculated in this manner can be used to estimate the prior glycemic control of the population.

Our electronic database collected information including retinopathy status, duration of diabetes and glycemic control of our patients over more than two decades (McGill, Molyneaux, Yue, & Turtle, 1993). We used these data to construct the linear relationship between duration of diabetes and prevalence of retinopathy. As duration of diabetes is already accounted for in the *x*-axis, the slope of the linear regression should correlate well with the prior glycemic control of the individual group being examined. The implication being that, if this assumption is proven, cross-sectional data of retinopathy prevalence at various duration of diabetes in a defined population can be used to retrospectively assess the adequacy of glycemic control of that population in the preceding years. Health Maintenance Organizations and some community screening programs could have information on the status of retinopathy and duration of diabetes of their participants but not serial measurements of HbA1c (Scanlon, Aldington, & Stratton, 2014). Their data could be analyzed by our method to serve as an indirect measurement of the average glycemic control of their patients in the preceding 1–2 decades. By examining data of patients with defined criteria (e.g., according to their ethnicity or age of diabetes onset), the prior glycemic control of specifically defined groups of diabetic patients can be compared. Our

Conflicts of interest: The authors have no relevant conflicts of interest to declare.

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http://dx.doi.org/10.1016/j.jdiacomp.2016.12.016
1056-8727/

method which only requires cross-sectional and retrospective data could be a simple but useful public health tool.

2. Methods

The findings of this study were derived from a total cohort of 9281 patients with T2DM who had information collected prospectively during clinical consultations over a period of approximately two to three decades. For this study, the following data from each patient were retrieved from our electronic database: retinopathy status, HbA1c, ethnicity, date of diabetes diagnosis, date of last consultation with documented retinopathy data, socio-economic status and fluency in English. Retinopathy was detected by direct fundoscopy or in recent years by retinal photography and graded by a modified Airlie House Classification System into categories of no retinopathy or minimal, mild and moderate, severe non-proliferative retinopathy and proliferative retinopathy. All grades of retinopathy were pooled as "Any retinopathy" for analysis and the two most severe grades were also grouped as "Vision Threatening Retinopathy" for a separate analysis. For patients who had multiple visits, the eye data of the last visit were studied. HbA1c was measured by high performance liquid chromatography and updated HbA1c calculated according to the UKPDS formula (Stratton et al., 2000). Although the last eye data of each patient was used for analysis of retinopathy status, the updated HbA1c was calculated from all their visits and on average each patient had 4 measurements of HbA1c during follow up. Ethnicity was determined by self-reporting. Socio-economic strata were determined by the Index of Relative Socio-economic Disadvantage (IRSD) generated by the Australian Bureau of Statistics. The IRSD is a score derived from a range of information about economic and social conditions of people within a postcode area. Fluency in English was determined by the need for an interpreter during consultation and this was jointly determined by the patients and health professionals.

The prevalence of retinopathy of the total cohort was plotted against the duration of diabetes divided into four bands of 5 years up to 20 years. The median durations of diabetes for the four bands were 1.5, 7.3, 11.9 and 16.8 years respectively. Our study on mortality showed that after 20 years the mortality of patients with retinopathy became disproportionately higher and would lead to an under-estimation of the retinopathy prevalence. The slope of the regression line was calculated to derive the rate of retinopathy development per year. For validation purpose, in addition to each patient's last available eye data used for this study, we also determined the extent that calculated retinopathy development rate varied when using the data from the first or a randomly selected visit.

In addition to the study of the total cohort, patient data according to the following criteria were extracted for additional analysis:

(i) Ethnicity: Seven ethnic groups were studied including Anglo Celtic ($n = 3384$), Indigenous Australian ($n = 319$), Pacific Islander ($n = 236$), Mediterranean ($n = 1924$), Arabic ($n = 444$), Chinese ($n = 1040$) and Indian ($n = 456$). These ethnicities accounted for 78% of the total patient cohort attending the Diabetes Centre.
(ii) Age of diabetes onset: <30 y. ($n = 259$); 30-49 y. ($n = 3376$); ≥50 y. ($n = 5645$)
(iii) Year of the eye examination: between 1988 and 1997 ($n = 2864$); between 1998 and 2003 ($n = 2872$); after 2003 ($n = 3544$)
(iv) Socio-economic strata: Least disadvantaged ($n = 3837$); mid-disadvantaged (2337); most disadvantaged ($n = 2882$)
(v) Fluency in English: required an interpreter ($n = 1751$); not required an interpreter ($n = 6635$)

The linear regression equation between prevalence of retinopathy and duration of diabetes for each of the above studied group was constructed in the same way used for the total cohort. The slope of the regression was similarly used to calculate the rate of retinopathy development per year and results correlated with their respective updated HbA1c levels.

The ability of HbA1c and duration of diabetes and other factors (age, gender, blood pressure, and smoking status) to predict the presence of retinopathy in individuals of the 9281 subjects in the total cohort was determined by logistic regression. The rates of retinopathy development of different groups within a selection criteria were compared using multiple regression. Interaction terms were calculated between the groups and duration of diabetes, to establish any significant differences in the slope. ANOVA was used to detect differences in updated HbA1c between various subgroups with Bonferroni post-hoc test to adjust for multiple groups.

The collection of data from patients and its storage in our electronic database is approved by the Hospital Database Committee and approved by the Human Ethics Committee of the Area Health Service.

3. Results

Diabetes duration and updated HbA1c were relatively poor predictors for the presence of retinopathy in individuals. These two factors only accounted for 13.8% of the variance for the presence of retinopathy in individuals in the total cohort of 9281 patients. Other factors examined including age of diagnosis, blood pressure, smoking status and gender did not add to the prediction of retinopathy in individuals. By contrast, as shown in Fig. 1A and B, the relationship between duration of diabetes and group prevalence of retinopathy was extremely strong for both any retinopathy ($r = 0.99$) and vision threatening retinopathy ($r = 0.98$). From the slope of the regression, the rate of any retinopathy development for the total cohort can be calculated to be 2.62% per year and for vision threatening retinopathy 0.66% per year. Validation studies showed that the CV for the rate of retinopathy development calculated using the last or first or randomly selected visits of the patients was 4.3%.

The rates of retinopathy development/year for each of the criteria used in selecting patients and the corresponding updated HbA1c are shown in Table 1. These data indicate that patients of different ethnicity have differing rates of retinopathy development/year, to a degree strongly correlated with their updated HbA1c (Fig. 2A). The same pattern of results can also be observed on patients selected according to the year of eye examination (Fig. 2B) or according to the age of diabetes diagnosis (Fig. 2C). By contrast, there was no difference in retinopathy development among the subgroups for patients selected according to socio-economic status or language fluency and also no correlation with their respective updated HbA1c.

4. Discussion

It is well accepted that glycemic control and duration of diabetes are the major determinants for the presence of DR, but their predictive power for individual patients is only modest (Nathan, 2014; Group TDCaCTR, 1995). In our cohort these two factors only account for 13.8% of the variance of retinopathy, underlying the importance of routine screening in clinical practice. A less appreciated but the fundamental basis of our study is that, in contrast to the situation for individuals, duration of diabetes, even by itself, is an extremely powerful factor in predicting the prevalence of retinopathy in a group of individuals (Leal, Hayes, Gray, Holman, & Clarke, 2013). The slope of this relationship is a cross-sectional measure of the rate of retinopathy development for that population. The linear correlation coefficients between these two parameters in our study were always very strong. This relationship underpins the analysis made in the current study. The information in Table 1 provides examples of this. Knowing the trajectory of retinopathy development in any population facilitates the prediction for future burden due to retinopathy. Additionally, this type of data is also useful in assessing many other questions of potential public health importance. For example, our data revealed

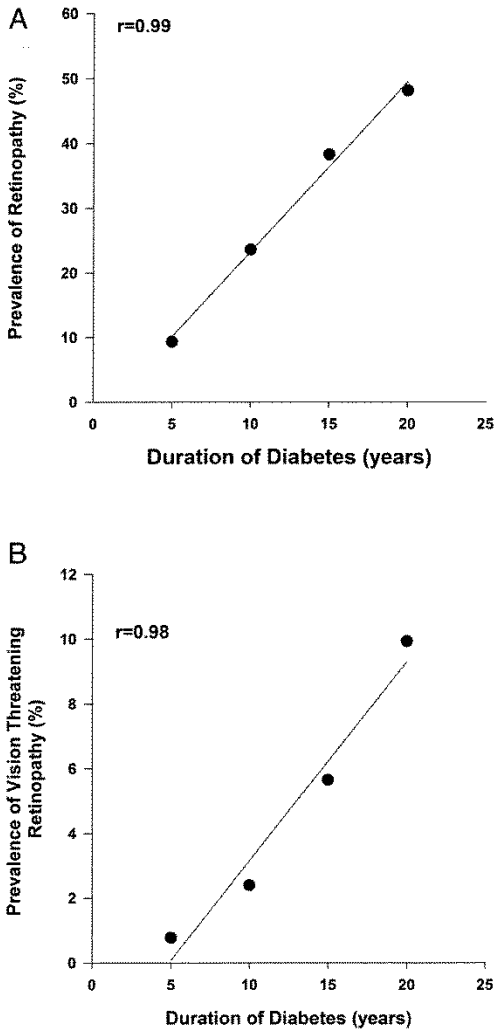


Fig. 1. A: Prevalence of any retinopathy according to diabetes duration for the total cohort. The slope is a measure of retinopathy development/year. B: Prevalence of vision threatening retinopathy according to diabetes duration for the total cohort.

different rates of retinopathy development in some ethnic groups, allowing further hypothesis generation. Our data also showed that the rate of retinopathy development over a couple of decades has decreased and this trend could be evidence supporting that improved care in diabetes has generated quantifiable benefits. The observation that younger age of diabetes onset has a progressively more detrimental effect on rate of retinopathy development supports previous report of increased susceptibility in the younger age group to this complication (Wong et al., 2008). On the other hand, the fact that language fluency and socio-economic status did not have any impact on the retinopathy development rate is consistent with the tenor that

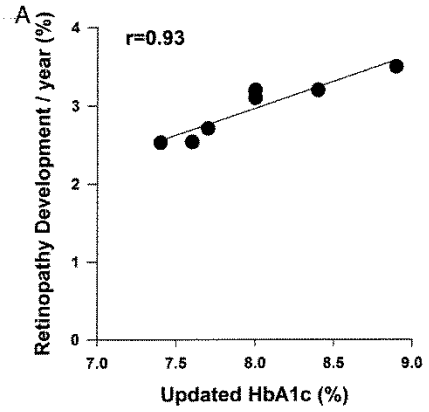
Table 1
Rates of development of retinopathy and updated HbA1c in various groups of patients with diabetes.

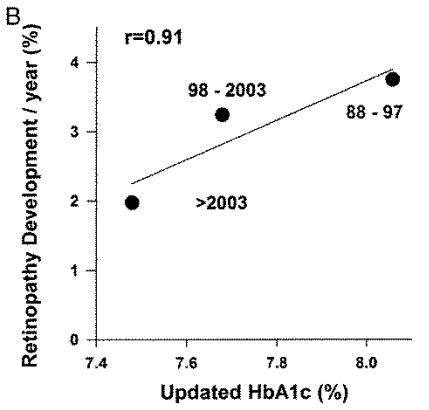
n = 9281	n	Development of retinopathy per year. (%)	Updated HbA1c (%/mmol/mol)
Ethnic groups (n = 7803)			
Anglo-Celtic	3384	2.5	7.6 ± 1.6/60 ± 17.5
Indigenous Australian	319	3.2*	8.4 ± 1.9/68 ± 20.8*
Pacific Islanders	236	3.5*	8.9 ± 2.0/74 ± 21.9*
Mediterranean	1924	2.7	7.7 ± 1.5/61 ± 16.4
Arabic	444	3.1	8.0 ± 1.7/64 ± 18.6*
Indian	456	3.2*	8.0 ± 1.6/64 ± 17.5*
Chinese	1040	2.5	7.4 ± 1.4/57 ± 15.3
Age of diabetes onset (n = 9280)			
Age < 30 years	259	4.1	8.6 ± 2.0/70 ± 21.9
Age 30–49 years	3376	3.4	8.0 ± 1.7/64 ± 18.6**
Age ≥ 50 years	5645	2.1**	7.5 ± 1.5/58 ± 16.4**
Year of eye examination (n = 9280)			
Between 1988 and 1997	2864	3.74	8.1 ± 1.9/65 ± 20.5
Between 1998 and 2003	2872	3.24	7.7 ± 1.5/60 ± 16.9***
After 2003	3544	1.97***	7.5 ± 1.4/58 ± 15.0***
Socio-economic strata (n = 9056)			
Disadvantage 1–4 (most disadvantaged)	2882	2.9	7.9 ± 1.6/63 ± 17.5
Disadvantage 5–7 (disadvantaged)	2337	2.6	7.7 ± 1.5/61 ± 16.4†
Disadvantage 8–10 (least disadvantaged)	3837	2.7	7.7 ± 1.6/61 ± 17.5†
Language fluency (n = 8386)			
Interpreter	1751	2.6	7.7 ± 1.6/61 ± 17.5
No interpreter	6635	2.8	7.7 ± 1.6/61 ± 17.5

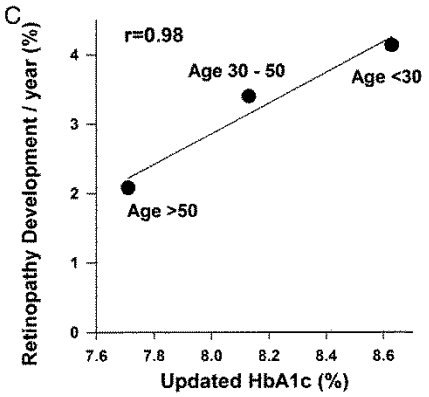
* Different to Anglo-Celtics, $p < 0.05$.
** Different to age of diagnosis <30 years, $p < 0.05$.
*** Different to year of eye examination made between 1988 and 1997, $p < 0.05$.
† Different to most disadvantaged group, $p < 0.05$.

the universal health care system in the patient population we serviced is providing equitable care for these strata of the society. The impact of many other factors such as smoking status, gender, differing models of diabetes care, and health insurance status can be similarly examined.

Another important observation is that the rate of retinopathy development of diabetic patients grouped according to certain criteria tends to correlate well with their respective updated HbA1c levels. Examples for ethnicity, age of diabetes onset and years of eye examination are shown in Fig. 2A, B and C respectively. The other side of the coin for this phenomenon is that groups of diabetic patients with retinopathy development rates which are not different showed no such correlation with their updated HbA1c levels. These observations are in a sense not unexpected because once duration is accounted for (on the x axis of the plot), previous glycemic control is the only other factor that affects retinopathy development. However, our observations raise the intriguing possibility that for any groups of individuals in which the relationship of retinopathy prevalence and duration of diabetes is known, the data can be used to estimate and compare retrospectively their glycemic control in previous years. This is in a way similar to the ability of the Hubble telescope to look back in time. Potentially many health care organizations would have data that can be analyzed by this technique. For example, in Australia some health insurance companies offer eye screening for people with diabetes. The retinopathy status and duration of diabetes would be available but not the details of glycemic control over the years. Researchers and health care planners can analyze the database of the insurance company with our method to assess if the glycemic control of any subgroups (e.g., by postcode of residence) in the preceding decades was more or less favorable than others. Programs such as The NHS Diabetic Eye Screening Program of United Kingdom (Scanlon, 2008) and some national telehealth eye







screening programs could similarly use our method to analyze regional and socio-economic differences in diabetes care.

It should be emphasized that the results of our study are not meant to be definitive proofs of causal relationships but only examples showing that public health relevant information can be generated in this manner for further in depth analysis and hypothesis generation. We are also not claiming that our results, being derived from a single hospital database, are necessarily numerical equivalents of what occur in the wider community, but just an illustration how the method can be utilized to compare groups within a population. It could also be argued that the same information we have generated can be obtained by studying retinopathy status of different groups of patients after a standardized and long duration of diabetes, e.g., 20 years. However, patients often present at different times after diagnosis of diabetes for eye examination and it would take longer and a defined research type protocol to accumulate sufficient subjects of the specified diabetes duration. Instead, relying on construction of a linear relationship using patients with any duration of diabetes, our method allows for a more rapid accumulation of data for analysis. Moreover, using retinopathy data only from patients with long duration of diabetes would also be biased by the increased mortality known to be associated with this complication (Kramer, Rodrigues, Canani, Gross, & Azevedo, 2011; Brownrigg et al., 2016). We have been able to minimize this impact of bias from mortality by including patients with shorter duration of diabetes and by only studying patients up to a known diabetes duration of 20 years. Additionally, our method only requires cross sectional data and does not need lengthy follow-up with the inevitable dropouts which would confound analysis. It is also independent of the timing of when a patient presents for eye examination after the diagnosis of diabetes, a factor which is typically quite variable in clinical practice. These features make our method easier to collect information in a non-protocol driven manner.

Some other caveats of this method should be mentioned. For our method to provide consistent results, it is necessary for patient selection to be unbiased or at least taken into consideration. In our analysis (results not shown as being submitted for another publication), if only patients whose data were obtained from ophthalmologists were analyzed, a much higher rate of retinopathy development would be found whereas those who consulted optometrists for general eye examination have a much lower rate of retinopathy development. Inevitably, over the years the primary method used in detecting retinopathy has changed and this might have affected the absolute number of retinopathy. However, we were more interested to compare retinopathy development between groups whose data were collected in parallel and their comparisons should not be greatly affected by methodological changes in retinopathy screening. However, our comparative data on retinopathy development over the last two to three decades would potentially be affected by changes in availability of ophthalmic health professionals and retinal photography in the general community. It should also be noted that we have only used the eye data of each patient once (their last available eye examination) because patients known to have retinopathy would obviously have more frequent eye examination and inclusion of all their data would distort the relationship between retinopathy and duration. There is also theoretically some doubt about the accuracy of self-reported duration of diabetes. The delay in diagnosis could explain why Porta et al. (2014). had found a slightly curvilinear relationship between retinopathy and duration of diabetes within the range where the duration of diabetes is relatively short. However, a systematic delay in diagnosis would not significantly affect the slope of the relationship which is the main focus of this study.

Fig. 2. A: Rate of retinopathy development in different ethnic groups as a function of their updated HbA1c. B: Rate of retinopathy development in patients with eye examination performed in different years as a function of their updated HbA1c. C: Rate of retinopathy development in patients with different age of diabetes onset as a function of their updated HbA1c.

In conclusion, studying the relationship between prevalence of retinopathy and duration of diabetes in groups of patients can be a useful tool for health care assessment and planning, both prospectively and retrospectively. The type of data required can be collected as part of ongoing clinical documentation. It is also the data often available to many government and health care organizations (Soto-Pedre, Hernaez-Ortega, & Piniés, 2007). These features make this method potentially applicable for widespread application.

Acknowledgments

We wish to acknowledge the support of the NSW Ladies Bowl for Others Association.

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CHAPTER 7:

The Impact of Data Quality on an Electronic Database: The Triple O (Outside Ophthalmologists And Optometrists) Retinopathy Study: Evidence of The Need For Standardised Reporting of Diabetic Retinopathy Status

Publication arising: Letter to the Editor (Appendix 3)

7.1.1 Introduction

The early detection and treatment of diabetic retinopathy remains an important component of modern diabetes care (240; 408). Due to resource limitations, many hospital-based ophthalmology clinics can no longer perform routine eye examination and follow-up for the majority of patients. As there is no nationwide retinopathy screening program in Australia, the task of organising regular eye examinations is left to the individual doctor or institution. For more than two decades, treating endocrinologists at Royal Prince Alfred Hospital Diabetes Centre have documented retinopathy status by routinely examining fundi as part of diabetes complications assessment. However, screening for diabetic retinopathy is now increasingly undertaken by outside ophthalmologists and optometrists (O-O&O). The basis for this trend stems from the increasing availability of retinal photography in the community and also the emphasis of modern treatment guidelines on completing cycles of care at the general practice level. This has resulted in the phenomenon of our staff having to frequently chase up eye results from O-O&O. Our experience has highlighted two key issues in that retrieving eye information from O-O&O can be laborious, unrewarding and the information retrieved is often difficult to interpret and apply clinically. The outcome is a communication barrier between health professionals. This compromise care of people with diabetes because the setting of individualised glycaemic targets and urgent triaging of care cannot be made in a timely manner.

Moreover and particularly relevant in the context of this thesis, a major consequence is that eye information entered into our database may be incomplete, inaccurate and unrepresentative. The primary aim of this study is, therefore, to evaluate objectively the deficiencies of the current communication process on data quality. The results pertaining to communications between health care providers are published in our

communication to the official Journal of the Australian and New Zealand College of Ophthalmologist shown in appendix 3. Additional data on the representativeness of the data from O-O&O are also included in this Chapter.

7.1.2 Methods

7.1.2.1 Communication Between Health Care Providers

It is the standard practice at the Diabetes Centre for the treating physician to perform retinal assessment either by direct ophthalmoscopy with pupillary dilatation or by retinal photography. The findings are graded clinically by the physician according to an adaptation of the Airlie House classification shown in Figure 16 (409). These data are entered into the database, which currently contains approximately 15,000 records collected over two decades. For patients who had a recent retinal assessment performed by an O-O&O, the majority preferred to have their report obtained from the relevant O-O&O, rather than having their examination repeated in-house. The relevant O-O&O is, therefore, usually contacted for a report.

For the purpose of the study examining the correspondence received from O-O&O, the retinopathy status described in the report is interpreted by one of the two endocrinologists involved in the study and coded according to the template in Figure 17. Where there is ambiguity in the interpretation of the report, a grade is assigned at the discretion of the assessor on the basis “beyond reasonable doubt”. In addition, the suitability of each letter in conveying crucial clinical information pertinent to diabetic retinopathy care was determined by the endocrinologist. Items examined included whether the report allowed coding for severity of retinopathy (if present), the presence or absence of macular pathology and whether the eye(s) affected could be determined

(Figure 18). As the main aim of our study is to examine the utility and clarity of transmitted reports between professionals, rather than the prevalence or severity of retinopathy in our community, we did not attempt to cross check the accuracy of reports generated by one group of health professionals against the others, as the results would not impact on the central conclusion to be reached.

Altogether, written reports from 683 consecutive patients who attended O-O&O over the preceding three years were available for analysis. If more than one report from the O-O&O was identified for an individual patient, only the first one was assessed. To minimise bias, each individual O-O&O was limited to a total of 15 patients (mean 2.3 per O-O&O) for the data analysis. This resulted in 355 letters (266 from Ophthalmologists and 89 from Optometrists) being analysed. The findings are shown in the published correspondence in the Result section.

7.1.3 Representativeness of the O-O&O data

In addition to the above, to study whether the retinopathy status of patients of the O-O&O is representative of the total clinic population, the prevalence of their retinopathy was compared with 10,000 patients for whom eye data were generated in-house. For this purpose, patients were divided into 5-year bands according to diabetes duration and the percentage with retinopathy calculated accordingly. Results are shown in Figure 19.

7.1.4 Results

Results of the 355 O-O&O letters coded for individual items of interest are shown in the published correspondence. A detailed breakdown of the results is shown in Figure 18.

For any duration of diabetes, more patients from ophthalmologists had retinopathy compared to the RPAH cohort (Figure 19). By contrast, patients screened by optometrists had a very low prevalence of retinopathy in the first 15 years of diabetes compared to the other two groups. However, the difference in prevalence between the groups diminished over time with the longer duration of diabetes.

7.1.5 Discussion

It is universally accepted that screening for retinopathy and delivery of appropriate monitoring and treatment are vital components of diabetes management. Australia does not have a national screening program for diabetic retinopathy. Although there are existing guidelines for the timing and frequency of eye examination for people with diabetes, their implementation is often variable and dependent on individual practices. A diabetic eye examination is increasingly performed by non-hospital based O-O&O and reports generated by them are often directed to a doctor who is the referrer but not the principal diabetes carer. This often leaves the principal diabetes care provider in the situation of having to make a clinical decision in the absence of eye data. There are several reasons contributing to this trend. Firstly, due to high case volume of diabetes in the presence of limited resources, it is now very difficult for public hospital clinics to meet the demand for routine diabetes eye care even for its own patients, let alone those looked after at the primary care level in the community. Secondly, patients commonly have more than one GP, and the O-O&O may have communicated with only the referring GP and not necessarily the other doctors or the diabetes specialist. Thirdly, optometrists do not require a referral, and a summary of relevant eye findings is not always communicated to the other healthcare providers. Irrespective of the cause, the lack of eye information eventuates in the cumbersome process of retrieving information

on retinopathy status from multiple disparate sources. It is a common experience that despite many attempts to contact the O-O&O, there is not always success in receiving a response.

Moreover, patients are often unsure of the name of the O-O&O they had seen, or the nature of the eye examination performed and the findings. This hurdle can be even more daunting when trying to source information from hospital eye clinics. The lack of pivotal clinical eye information at an important point of diabetes care is an obstacle to efficient triaging of cases for urgent ophthalmic intervention and to the establishment of individualised glycaemic targets and monitoring schedules. Obviously, the time taken by a clinician to seek out a report could be better utilised for more rewarding direct patient contact and clinical care.

Our study highlights deficiencies in the methods by which findings on fundal examination are recorded for transmission. Even when reports from O-O&O are available, a significant proportion omits vital information such as the severity of retinopathy, which is the predominant factor governing the need for urgent referral and treatment. A related issue frequently encountered is the use of descriptive terms such as “severe” to describe retinopathy in correspondence. It is often uncertain whether it was intended as a descriptive term rather than necessarily stipulating the grade of “severe retinopathy” which carries well-defined morphological features and prognostic implications (258). This distinction can be critical as the latter term implies that a more rapid deterioration is imminent and mandates vigilant monitoring and prompt intervention. Public ophthalmology clinic records display the same difficulties and have the additional (though not unique) problem of the extensive use of abbreviations and in-house notations to record findings that are usually beyond the scope of a non-eye specialist to decipher or interpret.

Moreover, despite increased recognition of the medical significance of macular oedema and the advancing techniques for its detection (e.g. Optical Coherence Tomography) and treatment (e.g. anti-VEGF injections), its documentation in medical correspondence is ambiguous or even omitted in almost half of the reports analysed. As we have only analysed the first report, if more than one is available, we cannot exclude the possibility that relevant information may have been included in subsequent correspondence. However, this simulates the usual clinical scenario where only one letter would often be retrieved from O-O&O.

The information in the report from O-O&O, as well as its dissemination to appropriate clinicians, can have significant implications for a patient's diabetes care. Treating doctors rely on it when individualising a patient's glycaemic target. For example, detection of early retinopathy may trigger an intensification of glucose-lowering therapy and mandate closer follow-up of that individual patient. Similarly, a report that clearly delineates the absence of significant retinopathy in an elderly patient might allow the treating doctor to relax the HbA1c target, lessening the risk of hypoglycaemia. By O-O&O facilitating smooth transmission of precise information to relevant clinicians, unnecessary repetition of eye examinations can be minimised, reducing the strain on individual patient as well as healthcare resources such as public ophthalmology clinics.

Additionally, many patients are reluctant to have further eye appointments because of the costs involved. If the treating doctor knows that a patient has vision-threatening retinopathy requiring intervention (rather than just monitoring) and conveys this message clearly, the patient may be more willing to do so. Our clinical experience and the data presented clearly emphasise that these challenges, in varying combinations, often present significant barriers to efficient diabetes management in a health care system working under significant strain.

Apart from clinical care, our study also has important implications for data collection and research in a hospital clinic setting. For example, if one relied purely on the subset of patients with outside ophthalmologist data to determine the prevalence of retinopathy, a higher prevalence of retinopathy than what is really the case would be found. In contrast, if most of the data were obtained from optometrists, the opposite conclusion would be drawn. These observations are obviously due to selection bias as patients with retinopathy or at higher risk of retinopathy are more likely to be referred to ophthalmologists while patients at low risk are more likely to present to an optometrist for a general eye assessment. These confounding factors due to selection bias have the potential to distort the results of retinopathy surveys and limit their generalisability. This highlights the importance of well-conducted epidemiological survey such as the Blue Mountain Study (410). In the absence of such, the distortion due to the representativeness of patient population in a survey of retinopathy prevalence must be taken into consideration.

Resource constraints, an increasing burden of disease and sub-specialisation of health professionals, have led to fragmentation of diabetes care becoming inherent in our current medical system. Although far from perfect, written correspondence remains the major vehicle for communication between health professionals and various studies have demonstrated that the content of letters is often not tailored to the needs of the recipients. For example, the difficulties of inter-disciplinary communication have been documented in medical oncology where 80% of GPs surveyed wanted information on patient prognosis, but only 20% of specialists' letters conveyed this information (411). To our knowledge, the current study is the first to investigate this aspect of communication in the diabetes setting on clinical care and data collection. Moreover, it

is likely that contemporary changes in technology and health care models in other fields of medicine have also led to the type of difficulties we have encountered.

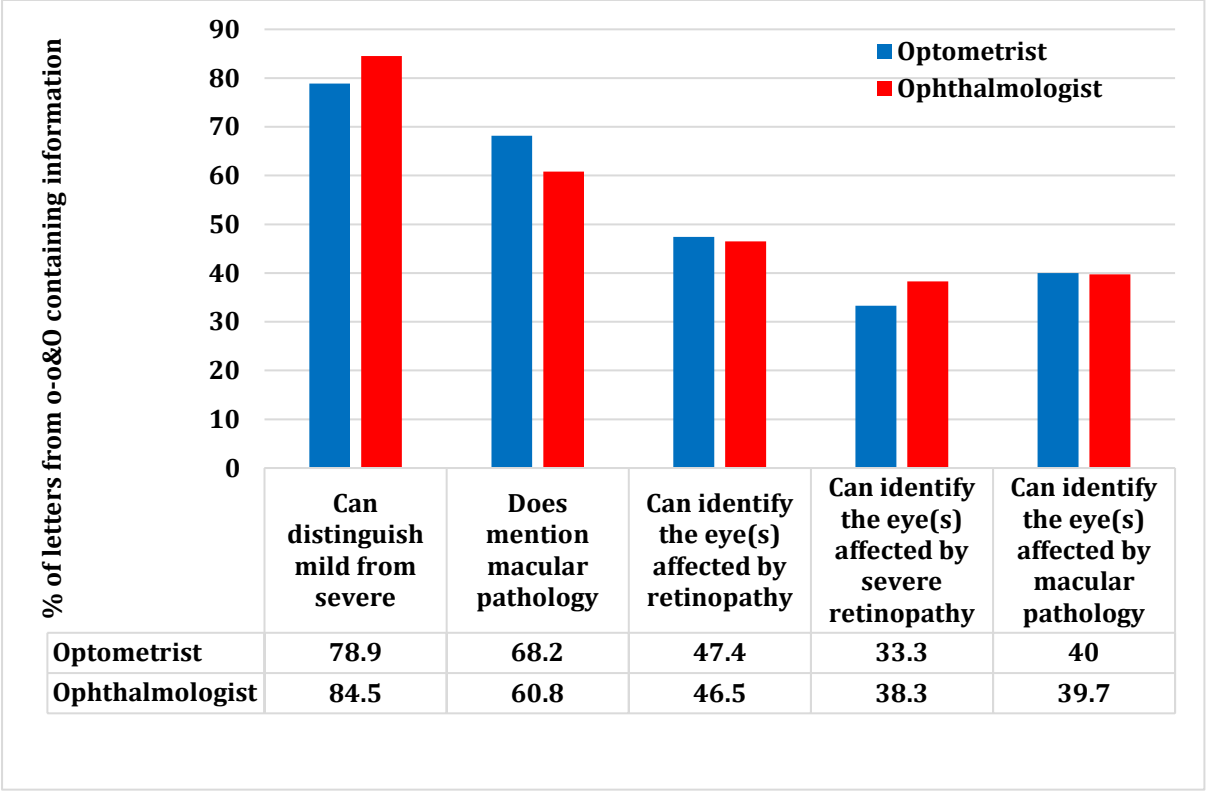
Figure 16: Modified Airlie House Retinopathy Grading Template

Eye assessment	Right	Left
Visual acuity	6/	6/
Glaucoma	No[ ] Yes[ ]	No[ ] Yes[ ]
Cataracts	No[ ] Yes[ ]	No[ ] Yes[ ]
Cataract extraction	No[ ] Yes[ ]	No[ ] Yes[ ]
Laser treatment	No[ ] Yes[ ]	No[ ] Yes[ ]
Retinopathy		
Nil	[ ]	[ ]
Minimal NPDR	[ ]	[ ]
Mild-Moderate NPDR	[ ]	[ ]
Severe NPDR	[ ]	[ ]
Proliferative *	[ ]	[ ]
Advanced Proliferative*	[ ]	[ ]
Not Performed	[ ]	[ ]
Not Visualised	[ ]	[ ]
Active Retinopathy	[ ]	[ ]
Macular Oedema	No[ ] Yes[ ]	No[ ] Yes[ ]
Report by outside Ophthalmologist	No [ ]	Yes [ ]
Report by outside Optometrist	No [ ]	Yes [ ]
Doctor Details		

Figure 17: Template for coding letters of correspondence from O-O&O

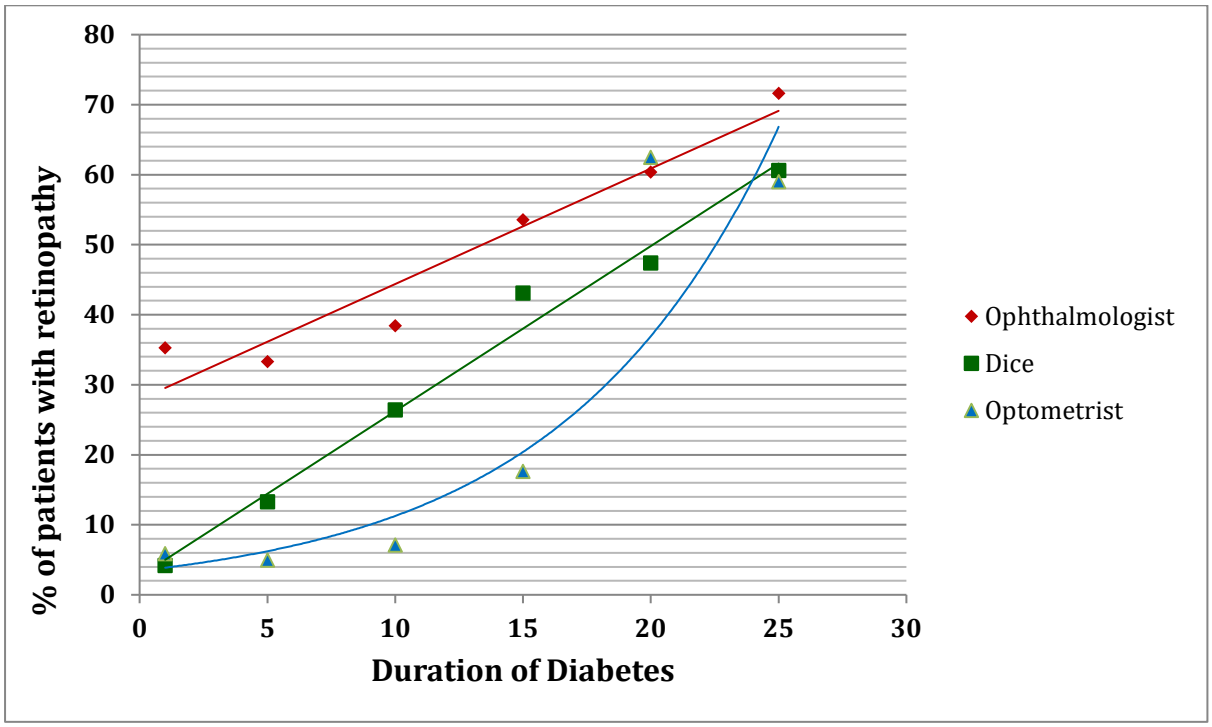
If Retinopathy is present, does the report allow coding for severity of retinopathy?	
Can distinguish milder retinopathy from vision-threatening retinopathy (Severe NPDR or Proliferative Retinopathy)	**No[ ] Yes[ ] N/A [ ]**
Does it mention specifically macular pathology	**No[ ] Yes[ ] N/A [ ]**
If retinopathy is present, does the report allow coding of both eyes?	
For any retinopathy	**No[ ] Yes[ ] N/A [ ]**
For severe NPDR and proliferative retinopathy (if present)	**No[ ] Yes[ ] N/A [ ]**
For macular pathology	**No[ ] Yes[ ] N/A [ ]**

Figure 18: Proportion of eye reports from O-O&O identifying key parameters relevant to the grading of diabetic retinopathy



	Can distinguish mild from severe	Does mention macular pathology	Can identify the eye(s) affected by retinopathy	Can identify the eye(s) affected by severe retinopathy	Can identify the eye(s) affected by macular pathology
Optometrist	**78.9**	**68.2**	**47.4**	**33.3**	**40**
Ophthalmologist	**84.5**	**60.8**	**46.5**	**38.3**	**39.7**

Figure 19: The relationship between diabetes duration and prevalence of retinopathy according to service provider



Chapter 8 General Discussion and Conclusion

Publication arising: Morbidity and Mortality in Young-Onset Type 2 Diabetes in Comparison to Type 1 Diabetes: Where Are We Now?

Components of this chapter have been published (Appendix 1)

The overriding postulate examined in this thesis is that with appropriate planning, routinely collected clinical data within an electronic health record (eHR) over time can provide new valuable information with respect to diabetes and has utility in terms of health decision making. This is relevant both in the context of public health delivery and for personalised and precision medicine. This thesis illustrates this by describing a series of studies using a longstanding electronic health record. We have chosen to examine diabetes subgroups stratified by ethnicity or by age of onset to be the focus of our investigations. The choice of ethnicity and age of diabetes onset is made pragmatically with the knowledge that our eHR contains relevant records of both data fields, which can be linked to mortality and complications. By making use of these resources, it has been possible to generate meaningful information, or at least observations, to facilitate further hypothesis testing.

Given the two aspects for discussion are 1) the clinical results of each study and 2) the practical challenges and learnings arising from using the eHR for research, these are addressed separately.

Prior to discussing the individual studies, it should be emphasised that the data arise from the clinical eHR described in detail in Chapter 2, which underscores the cohesive nature of studies in this thesis. Briefly, the database holds prospectively collected clinical data from patient encounters at the Royal Prince Alfred Diabetes Centre, Sydney Australia. With respect to the population studied, this single clinical facility is based in Metropolitan Sydney and is a secondary and tertiary referral centre for diabetes. The district population is predominantly white Australian but also other ethnicities from New Zealand, Europe and Asia are represented. This multiethnic cohort also include a significant number of people who were born overseas. There are a small proportion of people of Australian Aboriginal and Torres Strait Islander descent.

Patients were seen at the Centre following referral mainly from their primary care general practitioner (GP). With respect to data collection, as mentioned there is a standardised approach to this at the RPA Diabetes Centre which has been previously described (412). This approach is emphasised to clinical staff in regular team meetings and the centre participates in a National Benchmarking Audit, which provides feedback on data completeness and targets. This clinical model has been described in the publication by W Cheung et al (413). Briefly, this model of care consists largely of a one-visit review and structured complications screening and is underscored by a shared-care philosophy where the GP undertakes the major decisions regarding referral, timing and adjustment of diabetes medication. The Clinic makes recommendations regarding management of both metabolic abnormalities and diabetes complications. It is the prerogative of the GP to implement these recommendations and to refer the patients again when they judge necessary.

With specific reference to the grading of retinopathy within the Diabetes Centre, this has been, until recently performed by a single clinician (DKY) who has published on his grading ability in alignment with ophthalmologists (414). Retinopathy grading is by modified ETDRS when performed in-house . It should be noted that in more recent years, retinopathy assessments are performed by various other professionals as outlined the study presented in Chapter 6. It should be recognised then that any retinopathy assessments within the database may lack the precision of earlier years.

In the study presented in **Chapter 3** on the influence of ethnicity on survival of patients with type 2 diabetes, we found that, in a population of 12,466 patients from 7 ethnic groups attending our Diabetes Centre, that the Anglo-Celtic population have a much

higher HR for death than most other ethnic groups over a very similar median follow-up period of about 10 years. The Chinese had the lowest HR of 0.4 (95% CI 0.4-0.5), with the hazard for patients of Indian, Arabic, Mediterranean and Pacific Islander descent rising progressively. This pattern is somewhat surprising as it would seem logical to surmise that migrants from arguably more disadvantaged countries, having grown up in a less public health conscious environment and less well-established health care system, would have worse survival outcomes. The healthy migrant effect may be at play here, i.e. there may be a potential selection bias towards healthier migrants allowed into Australia. This bias may be due to regulatory pressures or the self-imposed exclusion from migration of less healthy individuals.

In contrast and as commonly documented for similar comparisons in other countries, the Indigenous Australians had the highest HR for death, of 2.3 (95% CI 1.7-3.0), and the worse outcomes remain even after adjustment for risk factors. Our data supports that much needs to be done for Australian Indigenous peoples, even in the urban context of metropolitan Sydney. The existence of as yet unmeasured factors will also need to be addressed if we are to improve the relative health and diabetes related life expectancy for Aboriginal peoples.

Interestingly, inability to speak English fluently as indicated by the need for interpreter services was found to be a favourable factor in determining survival, somewhat contrary to the common clinical impression (and frustration) that it is difficult to change the (often erroneous) health care beliefs of individuals in the presence of a language barrier. Alternatively, the lack of English fluency may signal a lack of acculturation towards a Westernised lifestyle which in and of itself may be beneficial. Also counter intuitively, socioeconomic status as defined by postcode was found not to be an important factor in determining survival. It is possible that the universal health care system of Australia, by

providing its citizens equal access to care has resulted in equity in survival as determined by the area of residency.

The type of information provided by our study on diabetes mortality and its relationship with clinical factors in a multi-ethnic population living in the same city and in similar socio-demographic environments is relatively rare in the literature. In support of our data, the comprehensive review on the Health Status of Migrants in Australia by Anikeeva *et al.* in 2010 (415), also found that many migrant groups have better health status according to several measures. However, information on diabetes was quite scanty and mainly related to the prevalence of diabetes rather than long-term outcomes.

The limitations with respect to the data collection are discussed later in this Chapter. Nevertheless, future studies of the potential factors over and above known risk factors for poor outcomes would be the next step to further identify intervention targets in our multiethnic population. It is envisaged that similar analysis of detailed datasets so linked may help clinicians and administrators better plan strategies to overcome demonstrable inequity in the Australian universal healthcare setting.

In the two subsequent studies presented in **Chapter 4 and 5**, on the impact of diabetes on mortality and complications, we focussed on comparing YT2DM with respectively (i) Type 1 diabetes and with (ii) Type 2 diabetes of an older age of onset. YT2DM was selected for special attention given their increasing prevalence in many parts of the world and their well-documented difficulty in achieving good metabolic control, thus the higher potential for a detrimental impact of diabetes. The standout feature of the YT2DM vs. Type 1 diabetes study was that, because of the availability of our eHR, we were able to compare patients with the same age of onset, i.e. 15-30 years of age. This

revealed a higher mortality and prevalence of vascular complications for YT2DM than Type 1 diabetes, a finding which at the time was against what would generally be accepted as clinical dogma. This finding was also contrary to epidemiological information derived from examining the standard mortality rate (SMR) of Type 1 diabetes and Type 2 diabetes of usual (older) age of onset. This seeming contradiction may be explained by methodological differences. In previous studies which measured the SMR of Type 1 and Type 2 diabetes, the death rate for each type of diabetes at any age group was compared with a background population without diabetes. As type 1 diabetes tends to present at an earlier age, part of the higher SMR associated with type 1 diabetes can be attributed to the fact that at any age group studied, the type 1 diabetic patients are likely to have on average a longer duration of diabetes than their counterparts with type 2 diabetes. Thus, prior SMR comparisons of type 1 and type 2 diabetes will have been affected by a lead-time bias. By matching the age of diabetes onset, our study presented in **Chapter 4** overcame this methodological issue. Our finding of a 2 fold excess of all-cause mortality for YT2DM compared to type 1 and other results presented have been editorialised, have generated a high number of citations, and discussed in the diabetes literature and correspondence (10; 416-418). Some readers have been disturbed by the impression that our findings conveyed the notion that type 2 diabetes is a more serious disease than type 1 diabetes and diminished the importance of type 1 diabetes. This is a legitimate concern, however, it would be important to note that this observation does not take anything away from the understanding of the potentially grave consequences of type 1 diabetes. Rather, these data serve to highlight to clinicians, and they can no longer reassure the YT2DM that they have a milder form of diabetes. Both types of diabetes are serious conditions especially when they affect young people in the most productive phase of their lives.

Both need support at an individual and community level, although the nature of help they need may be different.

The study presented in **Chapter 5** compared the mortality of YT2DM with type 2 diabetes of older age onset. As age, itself is a significant determinant of mortality as well as the duration of diabetes, a simple comparison of mortality rates would again not distinguish the impact of diabetes versus ageing alone. Therefore a Poisson regression model was used to include age of onset and age attained as factors in the calculation of the SMR, using the age matched Australian general population as background. Such a method was previously described in the mortality study of patients attending the Steno Diabetes Centre (419). The results again confirmed a higher SMR of patients with younger onset of type 2 diabetes, at any given age or at any given duration of diabetes. Thus, the impact of type 2 diabetes on mortality is higher in young onset type 2 diabetes than for later onset disease. In other words, the increased SMR attributable to type 2 diabetes became progressively less significant with a higher age of onset of diabetes. Indeed diabetes which first appeared at an age older than 60 years had a negligible impact on SMR.

In our opinion, these findings may have important public health implications. Much of our efforts in increasing community awareness of diabetes and finding cases of undiagnosed diabetes tend to be directed towards the older population. This has resulted in discovering many cases of diabetes in the older age groups, however, our studies suggest that their life expectancy is less impacted by diabetes as age becomes the main determinant of their overall survival. This is not to say that older onset diabetes should be ignored as it should be noted that our patients were all treated which would have contributed to survival. However, our results argue for finding

practical ways of focussing our limited health resources on at-risk younger patients to prevent or delay the onset of diabetes.

In this regard, it is pertinent to note that our studies have confirmed that individuals with YT2DM had severe cardiovascular risk factors even within a few years of onset of diabetes, suggesting a need to begin treating dyslipidaemia and hypertension at a very early age. This is particularly problematic as the young age group is generally not considered as high risk and therefore not included in pivotal, event rate driven cardiovascular clinical trials. The potential for pregnancy in young women further compounds this consideration as statins are contradicted in pregnancy. Thus there is little objective evidence on how this group of young individuals with type 2 diabetes should be treated for their cardiovascular risk factors. Therefore the treatment guidelines of various learned bodies have tended to only make general rather than specific recommendations of this facet of diabetes care. Recently more specific guidance has been published by expert bodies with the two publications arising from this thesis cited in evidence of the need for early and aggressive intervention in young onset type 2 diabetes (420-422). These results have also been discussed in a published review article presented in Appendix 1. It is notable also that since the publication of these studies several larger data linkage studies have published similar findings for young onset type 2 diabetes confirming a higher impact of mortality than older onset diabetes (170) and in comparison type 1 diabetes (404).

The future direction for studies of young onset type 2 diabetes should address the question as to how to prevent type 2 diabetes in young people. This may need to include in utero interventions such as aggressively managing weight gain and glycaemia thought to drive early onset type 2 diabetes risk in offspring. Further studies should also address the challenge of achieving excellent glycaemic control in this

subgroup and interventions that halt the rapid beta cell decline. Reasons for the greater prevalence of complications compared to type 1 diabetes should be further examined and may provide clues to effective intervention. Overall however it should now be more widely recognised, particularly in primary care settings that YT2DM is not a benign condition and aggressive management of CVD risk factors are in order. Currently, new guidelines for YT2DM have been published with this aim in mind (420; 421).

In addition to the above studies, we have also tested a novel application for the use of the routinely collected eHR in the study of diabetes. In previous sections of the thesis and indeed in the broader literature, the general tenor tends to be an examination of factors that affect diabetes complications and mortality. In **Chapter 6** we took a different approach by testing whether the prevalence of diabetic retinopathy, the best defined and the most specific of the diabetes complications in a population, can inform and compare the previous status of diabetes and overall treatment between populations. For this purpose, we used two factors to our advantage. First, our eHR includes comprehensive data on retinopathy status of individuals. This is relatively uncommon in clinical databases because eye assessment is usually performed by another speciality, making difficult the routine collection of data. Second, although the presence of retinopathy in individuals is quite unpredictable even when in possession of their relevant clinical data (such as HbA1c and duration of diabetes), the overall prevalence of retinopathy in a population is very dependent on the duration of diabetes and highly predictable. By exploiting these two factors in combination, we were able to show that the rate of change in retinopathy prevalence in a defined population (e.g. in young-onset type 2 diabetes) can be compared to another population (e.g. in older onset type 2 diabetes) and any difference noted could be used to explore factors that account for the difference. For example, in the study shown in **Chapter 6** the impact of

age of diabetes onset on retinopathy was found to be explainable by previous glycaemic control measured by calculation of updated HbA1c.

Similarly, the difference in retinopathy development in 7 ethnic groups could also be shown to correlate with updated HbA1c. By contrast, other factors such as socioeconomic status and fluency in English communication were found to be unimportant contributors in this regard. In essence, retinopathy has the advantage that it takes many years to develop and therefore acts as an integrator of the overall glycaemic control for the many years beforehand, making it superior to a single measurement of HbA1c which is only an integrator of glycaemic control for 3 months.

The eHR and Research: Advantages and Challenges

In addition to the clinical findings described above, aspects of using the eHR specifically for diabetes research deserve a separate mention. The work and findings of this thesis are substantially based on extracting and analysing data from over 20,000 individuals which have been stored over a period of 2-3 decades on an ongoing basis in the RPAH Diabetes Centre eHR. The systematically collected data serves as an individual repository of information on demographic profile, disease progression and other risk factors. The results described in this thesis showed that prospective collection of such edata could generate information, which improves the understanding of diabetes, helps in the development of strategies for patient care and can shape future research.

The advantages of research using such an eHR have been many fold. The studies herein have been cost effective as the data are already collected for other reasons. As the data are collected prospectively in real time, they are not affected by recall bias. Further, the large sample size provided by the systematic approach to clinical care in

our studies have allowed for increased power to provide high-resolution comparisons between subgroups. Furthermore, validity is provided by coded data for many outcomes in our dataset.

Our use of an eHR in studying diabetes is not unique, and there have been other national and international diabetes systems described in the literature that have advanced significantly the knowledge of the disease and its complications (45; 423; 424). However for many years, these systems have worked in silos, but now with the digital revolution extending across all facets of government and health care, technology has enabled (amongst other things) the linkage of data between disparate systems. The ability now to link datasets with granular clinical details to large administration databases with hard binary outcomes (i.e. death vs not dead or dialysis or no dialysis etc.) has enormous potential capacity. The studies presented in **Chapter 3, 4 and 5** relied on the ability to link our electronic medical records with the Australia National Death Index (425), a national registry of mortality. This data linkage offered a unique, opportunity to study the relationship between high-resolution clinical data that has been collected over many years with an accurate record of individual mortality in Australia. By high-resolution one means the detail provided by many clinical factors that could be utilised in adjusted modelling for the risk of death as in Chapter 3. The high impact nature of our findings should encourage future studies of linkage between other eHR with clinical data and administrative databases such as the NDI or another example might be the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) for renal outcomes. That this methodology can provide new knowledge has been underscored and evidenced by the studies in **Chapters 4 and 5**.

The study presented in **Chapter 6** widens our concept of using a clinical eHR for the study of diabetes and its management. Instead of, or in addition to, asking how

different types of diabetes or different approaches to diabetes management impact on outcomes, we can now use retinopathy development as a surrogate to compare retrospectively the overall glycaemic management delivered. Thus, the routinely collected retinopathy data can be used creatively to compare group outcomes, infer past quality care and predict for health needs into the future.

It is pertinent to bear in mind that relying on a single hospital eHR obviously has many inherent limitations which we must acknowledge in reaching any conclusion. The suitability of an eHR for the study of the type described in **Chapter 6** is naturally heavily dependent on the quality of eye data collected. The study described in **Chapter 7** and the publication arising illustrated how changes over time in technology (e.g. increased availability of retinal camera in the community) and model of diabetes care delivery (e.g. limitation in the resources of a public hospital eye clinic) can have great impact on the quality and suitability of eye data collected over time. There must be continued vigilance over such factors if the eHR is to be used for clinical or research purposes. Therefore users must be ever ready to modify work practice to ensure the quality of data collected. Nevertheless, overall it would be reasonable to surmise that assuming data quality is maintained, the electronic health record can be used to inform public health measures and identify gaps in patient care specifically looking at diabetic retinopathy data.

The need to keep the datasets up to date, in appropriate formats and in an accurate manner is essential to the utility of such datasets. For example, the standardised methodology applied to complications assessment and data dictionary as described in **Chapter 2** provided robustness to the data quality and to the conclusions derived. However, despite standardisation, there are some limitations of the routine data collections that still persist in self reported data. For example in the study presented in

 ethnicity is self-reported, and this can be ambiguous. In our experience, a Vietnamese of Chinese descent may nominate either ethnicity when questioned. Offspring of inter-racial marriages also pose a problem in coding. We attempted to minimise this type of data issue by grouping all the ambiguous cases as “others” and did not include them in the analysis.

Nevertheless, this in and of itself may have introduced some bias. Furthermore, the date of arrival to Australia of an individual who nominated a non-Anglo-Celtic ethnicity is not collected, and some patients may have been born in Australia, a trend likely to be increasing over the decades since the inception of the data collection. Thus, we were unable to differentiate ethnicity and migrant status completely.

Selection bias arising from data availability is minimised by a standardised approach to complications screening and the requirements for all data fields to be completed for each assessment as part of clinical care. Missing data has been less of an issue than it could have been if these processes were not in place. However, we cannot discount the effect of referral bias. Our patients are not selected on a population basis but dependent on referrals from primary care doctors who are themselves very heterogeneous in their practice and philosophy of referrals.

In addition, the problem of individuals joining the dataset at different disease time points has been challenging for our studies on mortality. For example, patients are referred to our Centre at variable times after the diagnosis of diabetes and therefore, by definition, patients referred must have survived that period of time. This creates the possibility of incurring “immortal time bias” in the analysis of this dataset (426). What is meant by this is that, as not all patients were seen from the time of diagnosis, some people had to have survived (Immortal Time) to have been seen at the diabetes Centre. Therefore,

the dataset may be enriched with those who are “survivors’ which potentially could have influenced the outcome. The impact of this on this dataset is unknown and should be acknowledged. It is also the policy of our clinic to not follow up every patient and only those perceived to have more problems are reviewed on an ongoing basis. It is therefore likely that our patient base would represent a more complex group of patients. In Australia, patients can also switch between the public and the private systems, depending on their socio-economic status and philosophical belief. These types of patient selection problems cannot be completely overcome at a technical level by better data collection and retrieval. Furthermore, unmeasured confounding such as unavailability of data on diet and physical activity may impact results. Therefore, any conclusions made based on a single hospital eHR must take these factors into consideration.

The eHR and Research: Future directions

Overall, the findings outlined confirm a positive role for the routinely collected data within the eHR as a meaningful research tool for diabetes care. Following on from this evidence, there are enormous potential research advantages for the use of the routinely collected eHR on a national basis. This is partially relevant with the advent of the ”My health record” in Australia being rolled out by the Australian Government with plans to be activated widely in 2019. However, if this research potential is to be realised, there are broader real world systematic challenges to be overcome, and these are discussed below.

By necessity, the eHR needs to cover a wide territory with many health-related fields, and the diabetes aspect may not be comprehensive enough for targeted research questions such as the ones we have posed. It is not a simple matter that can be addressed by adding more diabetes fields to the eHR because every major disease would demand the same depth of data. This would likely make the eHR instruments unwieldy and in turn, lead to unenthusiastic usage and poor data quality. One way to address this issue is for stakeholders of each major disease to develop a minimum dataset that should be collected at each patient encounter. A tiered structure of required information could then be progressively activated at different levels of diabetes severity and care. As a start, existing datasets such as that collected by the ANDA or our own can be further developed to form the basis of a national diabetes dataset. This ambition of a national tiered and shared eHR for clinical use and research would need enthusiastic input from learned societies and governments. Whatever the ultimate format adopted, in any broadly applicable eHR there will be more users under the umbrella of more institutions, magnifying the difficulties of maintaining data quality. An important strategy to help address this issue is to develop a national data dictionary and data standard. This would, in turn, allow for the comparison of national information about diabetes in a meaningful way.

There are also many other issues of developing a national eHR with research capability in diabetes. A transition to a specific eHR format would often necessitate the loss of legacy data already collected by different software systems over many years. This would require specific IT solutions to integrate existing systems. Other relevant issues requiring attention is in the designing of data access for research balancing the principle of “open data” vs privacy protection. In addition to ethical issues, considerations of privacy and safety are paramount. For example, questions to be addressed are

whether the use of data are appropriate, are there disclosure risks held in the data itself, are there settings on unauthorised use and are the statistical analysis set up for non-disclosure.

In summary, the novel studies within this thesis supports the notion that the routinely collected data held in the eHR can provide useful evidence for health decision making beyond that of the randomised controlled trial. However, the future utility of routinely collected clinical data depends on resolution of the privacy and access issues mentioned above and analytic processes adapted to account for the aforementioned data challenges. It will be then that existing data sources such ours can become better known, accessed and the promise of future opportunities provided by such data fully realised.

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Appendix 1

Morbidity and Mortality in Young-Onset Type 2 Diabetes in Comparison to Type 1 Diabetes: Where Are We Now? (3)

Curr Diab Rep (2015) 15:566
DOI 10.1007/s11892-014-0566-1

PEDIATRIC TYPE 2 DIABETES (PS ZEITLER, SECTION EDITOR)

Morbidity and Mortality in Young-Onset Type 2 Diabetes in Comparison to Type 1 Diabetes: Where Are We Now?

Jencia Wong · Maria Constantino · Dennis K. Yue

Abstract Increasingly, we recognise that type 2 diabetes in youth is a disease with an aggressive time course and a significant complication risk. On the other hand, outcomes for youth with type 1 diabetes appear generally to be improving. With increasing numbers of both types of diabetes in youth, it is timely that a comparative perspective is offered to help clinicians prognosticate more appropriately. Contemporary comparative studies add a new perspective to a consistent story, that for youth-onset type 2 diabetes, the development and progression of cardio-renal complications are increased and the survival prognosis is significantly worse than for type 1 diabetes. Here, we review this mounting evidence, highlight the importance of metabolic syndrome factors in the excess risk and underscore that there remains a significant mortality gap for youth with either type of diabetes, to be addressed as a matter of urgency.

Keywords Diabetes mellitus · Type 1 diabetes · Type 2 diabetes · Youth · Mortality · Diabetes complications

Introduction

Youth is no longer just the domain of type 1 diabetes (T1DM). Superimposed on the alarming upward global trajectory of diabetes prevalence are the increasing numbers with type 2 diabetes (T2DM) being diagnosed before the age of 40 [1–3]. The global incidence of T1DM is also increasing, and taken together, the net result is one where clinicians will be faced with greater numbers of youth with diabetes of either type. Indeed, recent predictions for the US population are for a greater than threefold increase in the numbers of youth with T1DM and fourfold increase in the young-onset T2DM (YT2DM), especially amongst minority youth [4•, 5, 6].

A rarity until recently, little was known of YT2DM, its clinical associations and outcomes. The US epidemiological SEARCH for diabetes in youth study and the landmark Treatment Options for Type 2 diabetes in Adolescents and Youth (TODAY) study have illuminated this area considerably and the results are sobering, with evidence for a high complications risk and an aggressive clinical course [7, 8••, 9–13]. With this realisation, a question arising is how do those who develop T2DM in adolescence and young adulthood fare in the long term and in comparison with their age counterparts with T1DM? This review will discuss the recent studies addressing morbidity and mortality with particular reference to YT2DM in comparison to T1DM.

One might well ask, what utility such a comparative perspective would offer? Of course, assessing the modern burden of disease and the characteristics of diabetes at a younger age is essential to healthcare planning and delivery. However, such insights also have relevance at the clinical coalface. The traditional focus of diabetes in youth is on T1DM and clinicians are well versed in these challenges; the differences in outcome for YT2DM are not immediately obvious. Prior comparisons of outcome between T1DM and T2DM of usual onset have always been hampered by either the older age of the typical T2DM patient or, if age is accounted for, the much longer disease duration of the T1DM patient, resulting in seemingly poorer outcomes for T1DM. Thus, a diagnosis of T2DM rather than T1DM is often taken with a sense of relief as T2DM has been generally perceived as the milder form, a

This article is part of the Topical Collection on *Pediatric Type 2 Diabetes*

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Published online: 11 November 2014

disease of lifestyle, more easily remediable and of a better prognosis. Until recently, little has existed in the literature to refute this assumption for youth, and as a consequence, historically younger patients with YT2DM may not have been treated optimally [14, 15•]. By the comparison of YT2DM with T1DM of similar age, the confounders of disparate age and duration on outcomes can now be attenuated. Additionally, a unique and informative perspective as to the degree to which glycaemia (common to both types) and insulin resistance/metabolic syndrome features (more likely to be represented in YT2DM) contributes to diabetes outcome can be examined. With the changing landscape of diabetes, it is timely that a comparative perspective is offered to help clinicians prioritise and prognosticate more appropriately.

Chronic Complications in Type 1 vs Young-Onset Type 2 Diabetes

Given their young age of onset, the lifetime risk of complications is high regardless of diabetes type. There is increasing recognition that the phenotype of YT2DM is more severe than our experience in older adults [16]. Further, even when risk factors are equated, the youth may be more susceptible to the development of some complications than their older-onset counterparts, perhaps by virtue of the interaction of their diabetes milieu, pubertal hormones or growth factors [16, 17]. On the other hand, chronic complications in T1DM appear to be declining over time [18, 19]. To effectively compare long-term outcomes in these two subtypes of diabetes, it is ideal if subjects are examined under the same healthcare conditions with equivalent access, rather than comparing outcomes across studies. Earlier comparative studies have been of a very short duration or confined to single ethnicities [20–23]. More recently, researchers have turned to meticulously maintained clinical databases to extract information on the prevalence of long-term complications in YT2DM and T1DM over a similar time course and health care conditions (Table 1).

Other than recent reports that DKA presentations in YT2DM are declining but remain significant for T1DM [23], comparative data on acute complications are still limited. Similarly for less classical complications (e.g. hepatic steatosis, periodontal disease, cognition) which are therefore not reviewed here.

Microalbuminuria, Nephropathy and Renal Failure

Microalbuminuria at Presentation

Microalbuminiuria is more prevalent at presentation in YT2DM than in T1DM. Dart et al. compared complications ascertained by healthcare utilisation codes for 342 YT2DM (onset <18 years and a high proportion of First Nation Canadians) and 1011 T1DM subjects [24•]. Albuminuria at diagnosis was more prevalent in the YT2DM cohort (27.1 vs 13.5 %), this despite a similar hypertension prevalence. In the multiethnic SEARCH study, within 12 months of diagnosis, the prevalence of an elevated albumin/creatinine ratio (ACR) was 16.3 vs 9.9 % in 374 YT2DM and 2885 T1DM subjects, respectively [25]. These findings are consistent with earlier reports in other ethnicities; albuminuria at diagnosis of YT2DM was present in 22 % of Pima and 14 % of Maori peoples [26]. The majority at diagnosis are in the microalbuminuric range.

Although some of these data are based on single assessments for albuminuria, taken together, the prevalence of elevated urinary albumin is in the order of 15–27 % at diagnosis for YT2DM, heralding an increased cardiovascular and nephropathy risk and a strong argument for screening at presentation. It is recognised that albuminuria can precede diabetes as a component of the metabolic syndrome and may have common origins. The presence of albuminuria at this stage could represent early incipient diabetic nephropathy or an obesity-related glomerulonephropathy, the origins and prognosis of which are less clear [27].

Higher Prevalence of Excess Urinary Albumin at Various Disease Time Points for YT2DM than T1DM

We interrogated prospectively collected data from a multiethnic population in Australia with T2DM and T1DM diagnosed between ages 15–30 years [28•]. After a median duration of >11.5 years, the prevalence of micro- and macroalbuminuria was greater for 354 YT2DM than 470 T1DM (47.4 vs 15.3 %). This excess albuminuria in YT2DM was also seen at an earlier time point, within 2–5 years of known diagnosis (39 vs 7 %). Glycaemic exposure measured by updated HbA1c was equivalent so that the excess seen may not be glycaemia driven. Although from a single centre, these data provide some of the longest-term published comparative prevalence data for multiethnic DM and are informative, as by design, the age of onset and duration were similar in the two groups compared. This is important given that residual confounding from incomplete adjustments for age and duration cannot be excluded in other analyses. Further, by restricting age of onset to a minimum of 15 years, the possibility of prepubertal years not contributing equally to complication risk in T1DM would be less relevant [29, 30]. These data are in keeping with the SEARCH study findings, albeit after a shorter duration, the prevalence of elevated ACR was still in excess for YT2DM (9.2 % and 22.2 %) and there was a prevalence ratio of 2.4 for excess albuminuria noted for YT2DM [25]. In the SEARCH cohort, the association of type of diabetes and elevated ACR persisted after adjustments for

Table 1 Complications in YT2DM vs T1DM: relative measures of prevalence and risk are presented as either odds ratios (OR), prevalence ratios or in the case of time-to-event analyses, as rate ratios (incidence) or hazard ratios (HR), dependent on study design

	Population country	Age of onset (years)	Cohort disease duration (years)[a]	Microalbuminuria (at diagnosis), %	Nephropathy macroalbuminuria (%)	Retinopathy (at diagnosis), %	Neuropathy (%)	Macrovascular disease (%)
Yokoyama et al. [14]	Japan	10<30						
Type 2 n=958			>30		44.4			
Type 1 n=620			>30		20.2			
Rate ratio T2DM vs T1DM					2.74 (95 % CI 1.17–6.4)			
Dart et al. [24•]	Manitoba Canada	1–18						
Type 2 n=342			1.6±1.5[b]	26.9 % (27.1 %)	4.7 %			
Type 1 n=1011			6.3±3.9[b]	12.7 % (13.5 %)	1.6 %			
HR T2DM vs T1DM					4.03 for renal failure (95 % CI 1.64–9.95)			
Dart et al. [35]	Manitoba Canada	1–18						
Type 2 n=342			6.5±5.6 (neuropathy)[b] 7.4±5.9 (retinopathy)			11.7 %	7.6 %	
Type 1 n=1011			9.8±4.9 (neuropathy)[b] 7.9±5.9 (retinopathy)			13.8 %	5.0 %	
HR T2DM vs T1DM								1.47 (95 % CI 1.02–2.12) for any complication
Maahs et al. [25]	US SEARCH for diabetes in youth	<20						
Type 2 n=374			1.9 (IQR 0.4–3.2)	22.2 (16.3)				
Type 1 n=2885			3.7 (IQR 0.5–5.7)	9.2 (9.9)				
Prevalence ratio T2DM vs T1DM				2.4 (95 % CI 1.9–3)				
Jaiswal et al. [38]	US SEARCH for diabetes in youth	<20						
Type 2 n=70			7.6±1.8				25.7	
Type 1 n=329			6.2±0.9				8.2	
OR T2DM vs T1DM							2.29 (95 % CI 1.05–5.02)	

Table 1 (continued)

	Population country	Age of onset (years)	Cohort disease duration (years)[a]	Microalbuminuria (at diagnosis), %	Nephropathy macroalbuminuria (%)	Retinopathy (at diagnosis), %	Neuropathy (%)	Macrovascular disease (%)
Mottl et al. [68]	US SEARCH for diabetes in youth	<20						
Antibody negative/ insulin resistant n=379				16				
Antibody+/insulin sensitive n=1351				9				
Luk et al. [15•]	HK Registry Chinese	<40						
Type 2 overweight n=1478			5 (1–12)	24.3	11.1	22.9	15.4	3.3 CHD
Type 2 normal weight n=636			7 (1–14)	20.5	8.8	23.3	17.9	1.6 CHD
Type 1 n=209			8 (2–12)	16.3	3.4	14.8	10.5	0.5 CHD
HR T2DM vs T1DM					5.4 (95 % CI 1.84–15.88) progression to ESRD			15.3 (95 % CI 2.08–112.4)
Constantino et al. [28•]	Multicthnic Australian	15–30						
Type 2 n=354			11.6 (4.5–22.6)	47.4		42		
Type 1 n=470			14.7 (8.2–23.6)	15.3		17		
OR T2DM vs T1DM								5.4 (95 % CI 2.7–10.5)
Mayer-Davis et al. [36]	US SEARCH for diabetes in youth	<20						
Type 2 n=43			7.2±0.93			42		
Type 1 n=222			6.8±.97			17		
OR T2DM vs T1DM						1.5 (95 % CI 0.58–3.88)		

CHD coronary heart disease

[a] Data are mean±SD or median (IQR)

[b] Mean duration at development of complication

glycaemia. Further, insulin resistance parameters (BP, LDL, HDL, Tg and BMI) accounted for 19 % of the excess prevalence in YT2DM, with little additional information provided by the addition of inflammatory markers to the model (fully adjusted odds ratio (OR) 1.68 for YT2DM vs T1DM for elevated ACR). A similar excess in the prevalence of microalbuminuria and macroalbuminuria was seen in Manitoba and in the Hong Kong Diabetes Registry of Chinese subjects. In both, the higher prevalence of microalbuminuria and nephropathy is seen in YT2DM despite their shorter disease duration and lower mean baseline HbA1c [15•, 24•].

These data together support the conclusion that the risk of excess albuminuria at any time point is increased more than twofold for YT2DM over T1DM and highlight the association of metabolic syndrome factors over and above glycaemia with the differences seen. These data also imply a residual excess risk for albuminuria for YT2DM not captured by usual clinical measures.

Evidence for an Increased Rate of Progression of Albuminuria and a Shorter Time to ESRD for YT2DM Compared with T1DM

A current debate in nephrology is whether albuminuria in diabetes, particularly at microalbuminuria levels, is a risk factor (the modification of which will affect the disease process) or a risk marker (not necessarily causally related) for later renal disease [31]. It is now recognised that microalbuminuria can regress and estimated glomerular filtration rate (eGFR) can decline with no change in albuminuria status. Therefore, the presence of microalbuminuria does not exclusively confirm the presence of kidney disease and, indeed, the cross-sectional data described above do not consistently show a difference in eGFR/creatinine clearance between the two youth-onset groups. A key question is whether the cross-sectional observations of higher rates of excess albuminuria truly represents an accelerated time course and translate into a higher risk for established renal disease. More recent data do now give us a perspective on the rate of progression of albuminuria and to end-stage renal disease (ESRD) in these groups.

In the prospectively followed YT2DM TODAY study cohort, the prevalence of albuminuria continued to increase and the progression to new-onset albuminuria in this study was 2.6 % per year in the context of optimised clinical care offered in a trial setting and aggressive therapy to maintain BP and renin-angiotensin-aldosterone system (RAAS) blockade [10]. Dart and colleagues found that the time-based risk of renal failure (composite outcome including all chronic kidney disease codes and end-stage kidney disease) for YT2DM was increased fourfold compared with T1DM after controlling for age at diagnosis, HbA1c, BMI *Z* score and era of diagnosis. Notably, estimated SES status was not an independent predictor of renal outcomes in this study [24•]. In Chinese, Luk et al. report an incidence for ESRD of 8.4 vs 2.2/1000 person years for YT2DM vs T1DM; adjusted hazard ratio (HR) of progression to ESRD was increased more than fivefold for overweight type 2 compared to T1DM [15•]. In this cohort, the excess risk of YT2DM for ESRD is largely accounted for after adjustment for BMI and insulin resistance parameters. These findings are consistent with earlier data from Japan that reported an increased rate ratio of 2.74 for YT2DM and the development nephropathy [22].

Perspective

Although studies using clinical databases have limitations, these data are consistent and large contemporary studies have allowed a greater examination of the factors contributing to the excess nephropathy risk of YT2DM over T1DM. These studies emphasise the same association of albuminuria with glycaemic control, which remains an important modifiable risk factor for all youth. However, glycaemia does not explain all of the differences in renal risk. These studies also show an association of albuminuria with insulin resistance parameters more prevalent in YT2DM and of greater magnitude. Thus a gluco-centric approach is likely to be insufficient to reduce the excess renal risk in YT2DM and attention to metabolic syndrome parameters will be extremely important for this group.

It is also possible that the overall poorer prognosis for YT2DM is due to the renal susceptibilities of some ethnicities in whom YT2DM is overrepresented [6, 32]. However, there is little evidence that ethnicity, independently above other known risk factors, contributed to the albuminuria risk in the SEARCH or TODAY studies, and differences are now seen within single ethnicities [10, 22, 25, 33]. These data also suggest a residual risk unaccounted for due to as-yet-unmeasured risk factors in some YT2DM populations, the discovery of which may be crucial to improving outcomes for this patient group. These may be socioeconomic, physiological, epigenetic or genetic in origin and prospective studies with these factors accounted for and bio-samples may offer some further clues to the discovery of novel biomarkers of renal risk.

It should also be noted that all renal disease in YT2DM may not be the typical renal disease associated with diabetes in adults. Sellers et al. have previously pointed to a lack of traditional diabetic nephropathy on biopsy in First Nation YT2DM [33]. Further, in adult populations, RAAS blockade in the presence of albuminuria has proven antihypertensive and reno-protective efficacy [34]. In the study by Dart et al., RAAS blockade use was associated with an unexpectedly higher risk of renal failure [24•]. Although it remains likely that RAAS blockade use is a marker for more severe disease, these results illustrate a point for further study in youth. The possibility remains that our adult standards for prevention and

treatment of diabetes-related renal disease may not be of equivalent benefit in younger patients and argues for youth-specific intervention trials rather than extrapolating from adult data. To this point, in the TODAY study, albuminuria and hypertension prevalence increased by nearly threefold despite best practice and single agent RAAS blockade to attenuate hypertension and albuminuria in YT2DM [10].

Retinopathy

The data are less clear as to whether there is an excess risk of retinopathy in youth with T1DM vs YT2DM. Retinopathy has been noted at diagnosis of YT2DM. In a Manitoba study, the prevalence of retinopathy was higher in type 1 vs type 2 (13.8 vs 11.7 %) at a median duration of 7.9 and 7.4 years, respectively, and higher mean HbA1c for T1DM. This pattern of excess retinopathy in T1DM was in contrast to the other microvascular complications in the same study. Retinopathy-free survival analysis for YT2DM appeared more reduced ~10 years from diagnosis but differences were not statistically significant [35]. These data are supported by our own long-term follow-up data that show that for youth with YT2DM and T1DM, there was an equivalent prevalence of retinopathy in the context of similar updated HbA1c and duration (37 vs 41 % T1DM, $p=0.3$) [28•]. Again, this pattern was in contrast to the findings in our study regarding other complications, e.g. albuminuria. Retinopathy was detected mostly by a mix of clinical examination and retinal photographs. By contrast, in a SEARCH pilot study, diabetic retinopathy was assessed by two 45° field retinal photographs. The prevalence of diabetic retinopathy was 17 % for T1DM and 42 % for YT2DM with a shorter mean follow-up (6.8 years in YT2DM) [36]. Findings were similarly of an excess in retinopathy for YT2DM in Chinese young diabetics [15•]. Notably, the prevalence of retinopathy in YT2DM assessed using similar methods and criteria was much less in the TODAY study, than in the SEARCH study (13.7 vs 42 %). For the TODAY study cohort, the retinopathy assessment was performed in the final year of the trial. The SEARCH cohort had a longer duration of diabetes (mean 4.9 vs 7.2 years) and did not have the benefit of trial-based intensive glycaemic and BP interventions. Whether these factors alone can account for the differences seen in retinopathy prevalence is not clear.

The different findings of these various studies may in part be due to the sensitivity of the methods used to detect retinopathy or may lie in the effects of varying periods of undiagnosed diabetes unaccounted for in YT2DM. To examine the latter, we estimated the time delay for YT2DM and T1DM cohorts utilising a previously published method and found that there was no differences in our youth cohort [28•, 37], although this issue cannot be entirely discounted in other studies. Possible also is that glycaemia over and above other metabolic syndrome factors has a greater impact on retinopathy as compared to albuminuria/nephropathy risk, so that the differential risk for retinopathy is not as great between the diabetes types. Interestingly, in the TODAY study, a higher BMI tertile was independently associated with a lower risk of retinopathy and it is suggested that retinal insulin resistance may have a paradoxically protective effect [13]. Whether this accounts for some of the conflicting risks is not known. Further, long-term study dedicated to retinopathy using sensitive measures is needed before definitive conclusions can be drawn.

Neuropathy

There are a few studies comparing neuropathy in YT2DM with T1DM. A pilot study from the SEARCH investigators found the prevalence of peripheral neuropathy assessed by the Michigan Neuropathy Screening Instrument was 25.7 % in YT2DM vs 8.2 % in YT1DM. The unadjusted OR of neuropathy was fourfold increased for YT2DM, the difference not only largely accounted for by age and duration but also metabolic syndrome variables [38]. We found a significant increase in the VPT Z score, used as a measure of vibration sensation, in YT2DM vs T1DM [28•]. Dart et al. also found that the raw prevalence of neuropathy conveyed by health codes was highest in YT2DM compared to T1DM and statistically significant differences were noted by approximately 5 years known duration [35]. Whether these are clinically significant differences remain to be seen and there are no data on painful vs insensate forms of neuropathy. These data coupled with the observation of an increased prevalence of neuropathy in association with the metabolic syndrome [39] would predict a heightened risk for adverse neuropathy outcomes in YT2DM. Definitive prospective evidence is needed, similarly for autonomic disease. Foot complications and amputations remain a significant morbidity for those with T1DM, and amputation rates appear not to be declining, although may be becoming less severe with fewer major amputations required [19].

Macrovascular Disease and Risk Factors

Cardiovascular disease (CVD) remains the leading cause of death for both T1DM and YT2DM and risk factors for cardiovascular or macrovascular disease are similar for both: overweight, dyslipdaemia, hypertension, gender, hyperglycaemia and renal disease [40]. A higher prevalence of adverse CVD risk factors compared with controls or T1DM has been consistently seen in YT2DM [21, 28•, 41, 42]. We observed significantly less favourable lipid and BP indices for

T2DM vs T1DM at similar age, duration and glycaemic control, despite a higher prevalence of antihypertensive and statin treatment. These long-term observations are consistent with the progression of CVD risk factors in the face of treatment seen prospectively in the TODAY study [12]. The heightened renal risk of YT2DM and previously unrecognised adverse lipid subpopulations in YT2DM predict adverse clinical outcomes in YT2DM [43]. Prior studies of intermediates for cardiovascular disease, such as IMT, arterial stiffness and diastolic dysfunction, have showed early preclinical abnormalities not only in YT2DM but also in T1DM [44, 45]. The SEARCH study demonstrated significantly increased arterial stiffness measures in YT2DM over T1DM, largely explained by differences in abdominal adiposity and hypertension [46]. Only a few studies have addressed the question of whether this translates to increased clinical disease for YT2DM over and above risks in T1DM.

We found a significant increase in the prevalence of CVD, including stroke, ischemic heart disease and any macrovascular disease (ascertained clinically, by medical history and records) in YT2DM; for YT2DM vs. T1DM, there was an OR of 5.4 for any macrovascular disease after adjusting for known risk factors. This excess prevalence of macrovascular/CVD in YT2DM is not fully accounted for by routine clinical factors and again, these suggest that unmeasured factors exist that need further discovery if differences are to be addressed.

Prospective data in Chinese show an increased incidence for CVD, including coronary artery disease, stroke and PVD and a 15-fold risk of macrovascular disease in overweight YT2DM <40 years of age vs T1DM [15•]. This risk declined to sixfold for lean T2DM and was not modified by controlling for HbA1c but was largely accounted for by the presence of metabolic syndrome factors. It should be noted that these were identified by hospital discharge diagnoses and thus may represent the more severe cases requiring admission.

Here, we now have cross-sectional and incident evidence of an excess in macrovascular disease for YT2DM compared with T1DM. As for renal complications, glycaemia remains an important risk factor; however, the differences seen in YT2DM vs T1DM are at least in part due to the presence of metabolic syndrome factors that are potentially modifiable. It is notable that differences in risk factors, such a serum lipids and BP, are seen early but differ only moderately, with medians in acceptable ranges [28•]. Therefore, the question has been raised as to whether even tighter goals are needed in high-risk youth [47]. This uncertainty highlights the lack of evidence base for treatment goals in both T1DM and YT2DM.

Mortality

It is well recognised that diabetes is associated with an increased risk of premature mortality, and despite the many recent therapeutic advances, diabetes remains the seventh leading cause of death in the USA and on the top 10 causes of death globally [48, 49]. Here, we examine the more recent mortality trends for T1DM and, where possible, compare the mortality experience with that of YT2DM.

Time Trends and Mortality Observations for T1DM

In the wake of the landmark DCCT study and the advent of improved cardiovascular and glycaemic management, the outcomes for T1DM have significantly improved. The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study and the community-based Allegheny County T1DM Registry (ACR) established in the 1970s have both provided valuable and unequivocal evidence of a significant secular decline in mortality for T1DM in regional America. Mortality rates in childhood-onset T1DM have declined by 34 % over 15 years and there has been a 15-year increase in life expectancy for those diagnosed in 1965–1980 vs. 1950–1964 [50, 51•]. The greatest reductions are seen in mortality from acute complications, renal disease and to a lesser extent cardiovascular disease.

Recent data extend these observations internationally and are inclusive of older-onset age groups, with nationwide studies from Finland, Denmark, Australia and Japan all confirming significant mortality benefits over time, largely attributable to a reduction in chronic complications [52–55]. These benefits have not reached all T1DM populations and poorer risks and outcomes persist for some minority groups and comparatively for women [50, 56]. Of concern is a report from Finland that found increasing mortality rates for T1DM diagnosed aged 15–29 years, driven by a higher proportion of alcohol-related deaths and deaths from acute diabetic complications [53]. Smaller studies have also reported differential excess mortality dependent on age of onset, which together highlights the increased vulnerability associated with the development of a chronic disease in adolescence and young adulthood [57].

More contemporary standard mortality ratios (SMR) reported for T1DM populations still range from 2.8 to 5.8. Although mortality improvements are seen in diabetes, there is still an excess residual risk as background mortality rates improve [53, 56, 57]. Studies from FinnDiane, the EDC and more recently Denmark suggest that this excess risk is due to renal disease, in the absence of which mortality rates in T1DM are almost at background. However, there also remains a significant mortality from acute complications that are also potentially preventable [52, 58, 59].

Mortality in Youth with YT2DM Compared with T1DM

Advances in survival for general T2DM populations are also being reported [55, 60]. However, studies in Pima Indians first suggested adverse mortality outcomes for YT2DM [61]. The

lack of long-term data in other populations prompted an interesting study by Rhodes et al. [62]. By using a Markov modelling approach to predict the life course for a hypothetical cohort with YT2DM aged between 15 and 24 years, they projected a 15-year loss of life expectancy, along with onset of chronic complications by the 40s for those with YT2DM. More recent studies support these predictions, which may be somewhat conservative.

The large prospective population-based study Diabetes Incidence Study in Sweden (DISS) [63] examined mortality in 6771 incident cases of diabetes in the 15–34 age group with an average follow up time of 8.5 years. The SMR compared to the general population for the YT2DM group was higher than for T1DM at 2.9 and 1.8, respectively, with a greater percentage of circulatory disease being the underlying cause of death in YT2DM (58 vs 28 %). From the Southern Community Cohort Study in the USA, Conway et al. examined mortality in youth with diabetes over a shorter mean period of 3.9 years stratified by treatment rather than by diabetes type; the HR for death compared to non-diabetic population were 4.3 for those using insulin alone, 4.2 insulin plus hypoglycaemic agents and 2 for those not on insulin therapy [64].

These studies are of short to medium term. To understand comparative long-term mortality in youth, we linked a long-standing diabetes database involving patients in multiethnic Australia to the Australian National Death Index. Mortality outcomes were examined for those with YT2DM and T1DM diagnosed between the age of 15 and 30. After a median >20 years with deaths censured in July 2011, a significant mortality excess was seen in the YT2DM group with a doubling of the risk of death compared with T1DM of similar onset. The primary cause of death was found to be cardiovascular in both groups but the HR for CVD mortality in YT2DM was greater than threefold that of T1DM. Data were from a single centre in Australia and reflect the usual practice in the time frames studied, so whether truly representative of risk to YT2DM in youth today remains to be seen. However it is notable that these findings are in keeping with a similar clinical long-term database study from Canada. Dart et al. found that the overall survival of T1DM vs YT2DM at 10 years was 99.5 and 91.4 %, respectively, which dropped to 97.6 and at 77.5 % at 20 years [24•]. Most recently, another Canadian study of diabetes in First Nation youth (likely to be T2DM) found a mortality rate after 25 years of 14.6 %, compared with a rate of 7.2 % for non-first Nation youth-onset diabetes [65].

Perspectives

Prior mortality studies of T1DM and T2DM not stratified by age of onset report a higher SMR for T1DM than for YT2DM. There are likely two reasons confounding these observations; firstly, the subject with T1DM has usually had diabetes for a much greater time and thus excess risk may simply be due to a longer duration of diabetes. Secondly, as the T1DM patient is generally younger, the mortality of the baseline general population is not as great, leading to a higher SMR. Thus, the results would appear to indicate that T1DM is associated with a higher mortality risk than type 2 diabetes. These more recent analyses of mortality confined to those with a similar age of onset minimise the confounders of age and duration and are likely to represent 'true' differences in outcome for the two types of diabetes in youth. Studies of mortality of T1DM in comparison of YT2DM are rare and these data provide some of the first glimpses of comparative long-term mortality outcomes for YT2DM and suggest a twofold excess in all-cause mortality for YT2DM and an even greater excess in cardiovascular mortality.

From these mortality data, it is difficult to gain a direct understanding of the early predictors of adverse outcomes in YT2DM. Socioeconomic status was not accurately assessed in these longer-term studies and one cannot completely discount these factors contributing to the differential outcomes observed. Taken in the context of continued excess mortality risk for T1DM above background populations, this is cause for alarm. Furthermore, although absolute numbers are small, we observed deaths are occurring in the 30s and 40s. It is clear that intervention will need to start early in the disease course to be effective.

A Problem of Typology: Insulin Resistance in Type 1 Diabetes

The categorisation of T1DM and YT2DM is less than perfect and made increasingly difficult as background rates of obesity rise. Much of the excess risk seen in YT2DM is associated with less favourable metabolic syndrome risk factors. It should be noted that insulin resistance can also develop in T1DM [66, 67]. The SEARCH investigators have explored diabetes outcomes on the basis of antibody status and insulin resistance in lieu of formal classification. They found that insulin resistance measures were strongly associated with albuminuria, irrespective of diabetes type [68]. Further data are awaited as to the utility of this approach, but it may be that those with seemingly classical T1DM who develop features of insulin resistance will be at equivalent risk as youth with YT2DM.

Conclusions: Closing the Gap: Treatment Challenges in Youth

It is clear that a focus on glycaemic management alone will not be sufficient to improve the differential outcomes between

YT2DM and T1DM. The studies reviewed here suggest that metabolic syndrome and CVD risk factor management should be a priority. Furthermore, studies such as TODAY have illustrated the challenges of management in YT2DM: progression of risk factors and complications, poorer response to pharmacotherapy and lifestyle interventions. Add to this a high prevalence of depression, a reduced quality of life, adherence challenges, the psychosocial demands of a chronic disease at an early age, often in the setting of economic disadvantage, teratogenicity and pregnancy-related considerations and it is clear that the challenges are great. There are research implications on a number of fronts and it is also clear that the adult benefits of a particular treatment cannot be assumed for YT2DM. From an evidence-based perspective, it may be some decades before we understand fully how to manage optimally, so the urgency therefore is for intervention trials to be youth-specific or at least extend to younger patients [69]. The clarion call here must be for clinicians to be aware of the risks and most importantly for prevention or even delay in T2DM onset. In older adults, lifestyle strategies have been shown to be effective but new data suggest traditional models to effect lifestyle change may not be effective in youth and remain a priority area for study. It is likely that interventions along these lines need to start in utero. Such are the challenges for this age group.

This focus on YT2DM should not detract from our challenges for youth with T1DM. The benefits of improved treatment and survival for T1DM are somewhat tempered by the rising incidence. There remain significant unattenuated risks and potentially preventable complications, both acute and chronic. Efforts directed specifically towards reno-protection would likely benefit mortality in this group. The relatively increased shorter-term mortality risk of T1DM onset in the adolescent years is of renewed concern and further characterisation of this observation is needed.

In summary, these data give new context to the growing body of evidence that onset of T2DM at a younger age is associated with a high early prevalence of metabolic syndrome risk factors, a more progressive course to the development of renal and cardiovascular complications and substantial mortality, all during the prime and reproductive years. Current evidence supports that the early risk for these events is at least twofold above that for childhood onset T1DM. This is on a background where risks for T1DM, although improving, are still in excess of the general population. The effects on quality of life, health care costs and demands both to the individual and community are yet to be fully realised, but projected to be significant [4•]. The findings are such that the imperative now is to recognise these risks and act on all fronts before prediction becomes reality.

Compliance with Ethics Guidelines

Conflict of Interest Jencia Wong, Maria Constantino and Dennis Yue declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Appendix 2 – Commentary on publication presented in Chapter 4

The Changing Face of Young-Onset Diabetes: Type 1 Optimism Mellowed by Type 2 Concerns

The Changing Face of Young-Onset Diabetes: Type 1 Optimism Mellowed by Type 2 Concerns

Until recently the outlook for a youth or young adult diagnosed with diabetes, which was almost universally type 1, was bleak. Indeed, using data from the National Health Interview Survey as recent as from 1984 to 2000, it was estimated that U.S. children diagnosed with diabetes at 10 years of age had a life expectancy approximately 19 years less than seen in the general population (1). However, more recent data from the Pittsburgh Epidemiology of Diabetes Complications (EDC) study suggest those diagnosed with childhood-onset diabetes between 1965 and 1980 have a life expectancy of almost 69 years, which is less than 4 years lower than the comparable U.S. population (2). This good news has been accompanied by the observation from the Finnish Diabetic Nephropathy (FinnDiane) study that virtually all of the excess mortality seen in type 1 diabetes is related to the development of micro- or macroalbuminuria (3). This seminal observation has been confirmed and extended for up to a 20-year period in the EDC population (4).

The improved prognosis, in terms of mortality, has been accompanied by a dramatic reduction (5) or delay (6) in the incidence of end-stage renal disease. Interestingly, the decline in cardiovascular disease (CVD), the leading cause of overall mortality in diabetes, is less marked (5). One cautionary note, however, has to be made concerning the improvement in mortality of patients with type 1 diabetes. In a recent analysis of over 17,000 individuals in Finland, diagnosed between 1970 and 1999, Harjutsalo et al. (7) compared the time trends of mortality for those diagnosed at an age less than 15 years to those diagnosed at an age of 15 through 29 years. Although a very significant fall was seen in mortality over time for the young-onset group, consistent with the Pittsburgh EDC population (who were all diagnosed before the age of 17), mortality for the older-onset group increased over time reflecting an increasing number deaths related to alcohol, drugs, and acute complications (7). This raises the possibility that type 1 diabetes mortality patterns may differ markedly by age of onset.

The picture becomes more confusing, and disturbing, when one considers the recent increased incidence of apparent type 2 diabetes occurring in youth and young adults (8). One major challenge is that of typology, or our ability to distinguish between type 1 and type 2 diabetes, which is particularly difficult in an overweight or obese young adult. The SEARCH for Diabetes in Youth (SEARCH) study has examined this issue in some depth and described four groups based on the presence or absence of diabetes autoantibodies and of insulin resistance (9). How well this schema would work in the future in terms of predicting outcome remains to be seen but it is likely to be quite relevant as a number of studies have suggested that even in clear type 1 individuals it is those with evidence of insulin resistance or an insulin resistance/type 2 diabetes family background that have increased cardiovascular and renal disease (10–15). The complexity of this issue is further demonstrated by the observation that many classic type 1 diabetic subjects may retain some residual β-cell function for many years after diagnosis (16), which may partly relate to the benign natural history seen in many of the patients from the Joslin 50-Year Medalist Study who have survived 50 years of type 1 diabetes (17).

So what do we know about the prognosis of type 2 diabetes in youth and young adults? A number of studies have suggested that individuals with type 2 diabetes have worse cardiovascular risk factors than similarly aged individuals with type 1 diabetes. Indeed, the SEARCH study has shown more adverse cardiovascular risk profiles, including blood pressure (18) and lipid levels (19), and a higher prevalence of microalbuminuria (20) in youth-onset type 2 diabetes compared with type 1. Up to now, however, there have been few data on mortality or major outcomes of diabetes comparing type 1 and type 2 diabetes where onset occurred in youth or young adulthood. Hillier and Pedula (21) some years ago suggested that type 2 diabetes with an onset between age 18 and 44 years ran a more aggressive course than cases diagnosed later, particularly in terms of relative impact compared with the age-matched general population. The results of the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study support such a conclusion in terms of metabolic deterioration and have been recently reviewed (22).

In this issue, Constantino et al. (23) now provide further data concerning young adult–onset type 2 diabetes. Using a diabetes clinical database, and matching to the Australian National Death Index, these investigators were able to compare clinical and mortality outcomes from 354 patients with type 2 diabetes and 470 with type 1 diabetes.

Strikingly there was a twofold greater mortality in the type 2 cohort predominantly due to an excess of cardiovascular deaths. Although the clinical data were largely collected through routine encounters, a standardized protocol was used and the data quality is thus likely to be generally high. Likewise, the linkage with the Australian National Death Index is validated and mortality ascertainment data are likely to be complete. A significant weakness of the study, however, is the reliance purely on death certificates alone for cause of death, which were only available for 72% of deaths at the time of analysis. A number of studies have demonstrated the pathways and contributors to death are quite complex in diabetes (24) and the study would be greatly enhanced by the investigation and standardized recording of causes of death. Nevertheless, these data are unique and extremely valuable and support the growing concern that type 2 diabetes with a youth/young adult–onset has a particularly high risk of adverse vascular outcomes. Some of the figures from Constantino et al. (23) are quite concerning with prevalence rates of ischemic heart disease reaching as high as 13% at an age of 40 years compared with only 3% in

the comparable group with type 1 diabetes whose mean age was 39 years.

In an interesting further analysis, the authors looked at the prevalence of risk factors 2–5 years after diabetes diagnosis when mean age was 28 years. Significant differences between the two types of diabetes were seen with the type 2 subjects having significantly higher blood pressures, lipids, and greater albuminuria. In contrast, smoking rates were marginally lower in those with type 2 diabetes. Finally, it should be noted that although the blood pressures and lipids were generally higher in type 2 diabetes than type 1 diabetes, they were only moderately elevated (e.g., mean blood pressures were 120/78 mmHg and total cholesterol was 210 mg/dL).

These data therefore raise very significant clinical questions that need urgent answers. First and foremost, it is important that we do not adopt the narrow "glucocentric" approach that for so many years dominated our approach to diabetes management and CVD prevention in type 2 diabetes. It should be noted these very divergent vascular outcomes in the current study's data occurred with an identical updated HbA_{1c} of 8.1% in both groups of subjects.

Second, we need to know more about the relative contribution of predictors of adverse outcomes in young-onset type 2 diabetes. Unfortunately the data from Constantino et al. on risk factors measured early on in the course of diabetes were available for only 29% of subjects thus precluding prospective, definitive multivariable risk modeling. Third, we need to address the lack of guidelines and evidence-based goals on which to base cardiovascular intervention. This has been a long-standing problem in type 1 diabetes because, with the exception of the Heart Protection Study (HPS) (25), there are no cardiovascular risk factor intervention trials in young-onset type 1 diabetes with clinical outcomes on which to base treatment goals and strategy. While clearly the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studies intensive insulin therapy intervention in early-onset type 1 is of great benefit, CVD still develops in the intervention group at a high rate (26) and, as noted earlier, CVD rates do not seem to be declining as rapidly as renal disease rates (5). It is thus quite possible that lower blood pressure and lipid goals may be more appropriate in type 1 diabetic subjects than now appear to be the case in older type 2 diabetic subjects, the group on which guidelines are loosely based. In the light of the recent Constantino et al. and TODAY (22) studies, data current guidelines and goals maybe even more out of tune for those with young-onset type 2 diabetes. Fourth, an implication of the results in Constantino et al. is the need to continue the search for other avenues to reduce the mortality and cardiovascular morbidity seen in diabetes in general. Clearly, the enhanced risk in type 2 diabetes may largely relate to insulin resistance itself, and as noted this is also an important risk factor in type 1 diabetes.

A further focus should be to better identify and target those with a genetic predisposition. Recent data concerning the combination of haptoglobin genotype 2–2 and diabetes (either type 1 or type 2) leading to enhanced coronary artery disease risk (27,28) and renal risk (in type 1 diabetes) (29) offers some hope in this regard. This is particularly encouraging as the CVD risk may be ameliorated by vitamin E therapy (so far tested only in type 2) (30). This is unlikely, however, to explain the differential risk between type 1 and type 2 diabetes.

So where do we go from here? While guidelines and CVD risk factor goals clearly need to be revisited in terms of their applicability to both young-onset type 1 and type 2 diabetes, they would be best based on clinical trial evidence. Thus, a CVD prevention trial evaluating both intensive blood pressure and lipid control versus current management would be helpful. The outcomes could also include renal disease while further randomized arms might address new approaches (e.g., insulin sensitization and/or vitamin E therapy in those with haptoglobin susceptibility). The target population should comprise young adults with either type 1 or type 2 diabetes though the former should have longer diabetes duration to provide comparable and sufficient event rates.

Constantino et al. (23) should serve not only as an alarm bell for the development of appropriate management strategies for young-onset type 2 diabetes but also—especially given the disappointing results of the TODAY study (22) of management of adolescent type 2 diabetes—a call to further our prevention efforts in terms of type 2 diabetes and insulin resistance in general. While we can probably still conclude that those with type 1 diabetes and an onset in youth may have a normal life expectancy, particularly if micro- or macroalbuminuria is avoided, it seems doubtful that the same optimism can be extended to those developing type 2 diabetes at a similarly young age.

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Acknowledgments—T.J.O. is funded by National Institutes of Health grants DK090809, DK034818, DK094157, DK048412, DK089028, DK081323, DK082900, DK096394 and has served as a consultant for Aegerion Pharmaceuticals, Inc., and the JDRF. No other potential conflicts of interest relevant to this article were reported.

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Appendix 3 – Letter to the Editor

Communication in the multidisciplinary care of diabetic eye disease ([5])

Clinical & Experimental Ophthalmology RANZCO
Clinical and Experimental Ophthalmology 2016; ••: ••–•• doi: 10.1111/ceo.12887

Letter to the Editor

Communication in the multidisciplinary care of diabetic eye disease

We conducted a study aiming to highlight the importance of clear and efficient communication in the multidisciplinary care of diabetic eye disease. In Australia, the screening and assessment of diabetic retinopathy is increasingly undertaken by ophthalmologists and optometrists outside of a hospital setting (O-O&O), even for patients attending public hospitals for their diabetes care. This trend is due to a combination of factors including higher patient volume, availability of retinal photography in the community and an emphasis on completing cycles of care at the general practice level. A more dynamic medical workforce, particularly at the primary care level has often necessitated the chasing up of eye reports directly from O-O&O. In our experience, this is a laborious process, and the information retrieved can be difficult to interpret. We have reviewed the written reports of O-O&O from 683 consecutive patients from our Diabetes Centre who had attended O-O&O over a 3-year period. If more than one report from the O-O&O was identified for an individual patient, only the first one was assessed. This resulted in 355 letters (266 from ophthalmologists and 89 from optometrists) being analysed. Two endocrinologists coded each letter for its ability to convey clinical information pertinent to diabetic retinopathy care. Important parameters included documentation of the severity of retinopathy (if present), the presence of macular pathology and the eye(s) affected.

Results showed that when retinopathy is present, 16.2% of O-O&O did not clearly differentiate vision-threatening retinopathy from milder forms of retinopathy and 38.3% of correspondence did not comment on the presence of macular pathology. If retinopathy was reported, only 53.3% of letters from O-O&O specified the affected eye(s).

Information in the report from O-O&O as well as its dissemination to appropriate clinicians can have significant implications for a patient's diabetes care. Treating doctors often rely on it when individualizing a patient's glycaemic target. With the current strain on healthcare resources, public eye clinic appointments can be utilized more efficiently so that patients in whom vision-threatening threating retinopathy is identified can access prompt intervention. Some patients with significant retinopathy fail to have regular follow-up eye consultations because of the time and costs involved. If the treating doctor knows that a patient has vision-threatening retinopathy likely to require intervention (rather than just monitoring) and conveys this message clearly, the patient may be more prepared to attend follow-up.

Our findings could serve as a stimulus for generating a dialogue between healthcare providers on what is the optimal format to convey pertinent eye care information in correspondence. A standardized reporting format and pathway would likely improve the chance of information being appropriately directed and acted upon. This is consistent with the stated aim of the National Diabetes Strategy. We would advocate using a numerical grading approach similar to the National Health Service Diabetes Eye Screening Programme of R0, R1, R2, M1 and M2 and so on.[1] The now widely adopted numerical Bethesda System for reporting thyroid cytology has greatly facilitated the interpretation of biopsy results.[2] The adoption of a numerical format should not undermine the importance of a more descriptive report with recommendations, but it will minimize ambiguity in what the eye care professionals think should be undertaken. Similarly, this framework is not intended to replace ongoing professional training or override local guidelines for referral but should ideally facilitate both processes. Another advantage of a numerical reporting system is the ability to foster the collection of uniform diabetes eye data for research.

We propose that a working party of ophthalmologists, optometrists, endocrinologists, diabetes educators, general practitioners and other interested parties be assembled to discuss the feasibility of moving in this direction.

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Received 13 November 2016; accepted 17 November 2016.

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2. Cibas ES, Syed AZ. The Bethesda System for Reporting Thyroid Cytopathology. *Am J Clin Pathol* 2009; **132**: 658–65.

Competing/conflicts of interest: None.
Funding sources: None.

Appendix 4 - Statement of Contributions by co-authors

Contributions of Maria I Constantino to the Publications included in this Thesis: Statements of the Co-authors

As co-authors for the paper "An Inverse Relationship between Age of Type 2 Diabetes Onset and Complication Risk and Mortality: The Impact of Youth-Onset Type 2 Diabetes" we confirm that Maria I Constantino's contribution to this paper is consistent with her being named as equal first author and corresponding author. In particular the candidate's contribution includes :

- Took part in hypothesis generation and discussion, extracted data, analysed and interpreted the data, and co-wrote and revised the manuscript with the senior authors

Journal : Diabetes Care		
Name	**Sign**	**Date**
Abdulghani H. Al-Saeed	[redacted]	
Lynda Molyneaux		
Mario D'Souza		
Franziska Limacher-Gisler		
Connie Luo		
Ted Wu		
Stephen M. Twigg		
Dennis K. Yue		
Jencia Wong		

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Journal : Diabetes Care		
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Abdulghani H. Al-Saeed		
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Mario D'Souza		
Franziska Limacher-Gisler		
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Ted Wu		
Stephen M. Twigg		
Dennis K. Yue		
Jencia Wong		

Contributions of Maria I Constantino to the Publications included in this Thesis: Statements of the Co-authors

As co-authors for the paper "Long-Term Complications and Mortality in Young-Onset Diabetes: Type 2 diabetes is more hazardous and lethal than type 1 diabetes" we confirm that Maria I Constantino's contribution to this paper is consistent with her being named first author and corresponding author. In particular the candidate's contribution includes :

- Undertook the mortality data linkage with the National Death Index and recoded the database in order to allow further studies, performed literature review, contributed to the development of the study hypothesis and discussion, researched and analysed the data and co-wrote and revised the manuscript with the authors

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Lynda Molyneaux	[redacted]	
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Abdulghani Al-Saeed		
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Stephen M. Twigg		
Dennis K. Yue		
Jencia Wong		

Contributions of Maria I Constantino to the Publications included in this Thesis: Statements of the Co-authors

As co-authors for the paper "Ethnic specific differences in survival of patients with type 2 diabetes: Analysis of data collected from an Australian multi-ethnic cohort over a 25 year period " we confirm that Maria I Constantino's contribution to this paper is consistent with her being named co-author and corresponding author. In particular the candidate's contribution includes :

- Undertook the mortality data linkage with the National Death Index and recoded the database, contributed to the research hypothesis and discussion, researched and analysed the data and co-wrote and revised the manuscript with the senior authors

Journal : Diabetes Research and Clinical Practice		
Name	**Sign**	**Date**
Turki J. Alharbi	[redacted]	
Lynda Molyneaux		
Ted Wu		
Stephen M. Twigg		
Dennis K. Yue		
Jencia Wong		

Contributions of Maria I Constantino to the Publications included in this Thesis: Statements of the Co-authors

As co-authors for the paper "Data collection on retinopathy as a public health tool: The Hubble telescope equivalent of looking back in time" we confirm that Maria I Constantino's contribution to this paper is consistent with her being named first author and corresponding author. In particular the candidate's contribution includes :

- Extracted the data, performed literature review , analysed and discussed the data, generated the graphic presentation of the data and co-wrote and revised the manuscript with the senior author DKY

Journal : Journal of Diabetes and its Complications		
Name	**Sign**	**Date**
L. Molyneaux	[redacted]	
T. Wu		
Stephen M. Twigg		
Jencia Wong		
Dennis Yue		

Contributions of Maria I Constantino to the Publications included in this Thesis: Statements of the Co-authors

As co-authors for the paper "Communication in the multidisciplinary care of diabetic eye disease: Communication in diabetic eye disease" we confirm that Maria I Constantino's contribution to this paper is consistent with her being named co-author. In particular the candidate's contribution includes:

- Contributed to the hypotheses generation and discussion of the study , undertook required data collection and coding of the database , extracted the data, researched and analysed the data, generated the graphic presentation of the data and co-wrote and revised the manuscript with co-authors

Journal : Clinical and Experimental Ophthalmology		
Name	**Sign**	**Date**
Eddy J Tabet	[redacted]	
Jencia Wong		
Dennis Yue		

Contributions of Maria I Constantino to the Publications included in this Thesis: Statements of the Co-authors

As co-authors for the paper "Morbidity and Mortality in Young-Onset Type 2 Diabetes in Comparison to Type 1 Diabetes: Where Are We Now? " we confirm that Maria I Constantino's contribution to this paper is consistent with her being named co-author. In particular the candidate's contribution includes:

- Undertook literature review and discussion, researched and co-wrote the manuscript with the senior author

Journal : Current Diabetes Reports		
Name	**Sign**	**Date**
Jencia Wong	[redacted]	
Dennis K Yue		

Appendix 5 - Data Forms

Royal Prince Alfred Hospital **Diabetes Ambulatory Care Centre**	**MRN:** **Fathers Full Name:** **Mothers Maiden Name:** **Medicare Number:** **Medicare Expiry Date & Eligibility** Date: Eligible[ ] Ineligible [ ] Reciprocal [ ] Unknown [ ]

Surname:	**Referring Doctor:**
First name:	
Address: **Post code:** **Phone: (H:)** **(W:)** **Mobile:**	**Address:** **Post code:** **Phone:** **Date of referral :**
Email:	

Personal details

D.O.B.:

Sex: Male [ ] Female [ ]

Ethnic origin:

Country of birth:

Interpreter: Yes [ ] No [ ] If yes, language:

Reason for this referral

Assessment / Comps [ ] Type 1 Service [ ] AIS [ ] Pain [ ]

Ward follow up [ ] Transplant follow up [ ] HRF [ ] Pregnancy [ ]

Referred by

Self [ ] LMO [ ] Rooms [ ] Clinic [ ] RPAH [ ] DKY [ ]

Type of diabetes & Diagnosis

Type 1 [ ] Type 2 [ ] GDM [ ] IGT [ ] SID [ ] CF [ ] Other [ ]

Date of Diagnosis: ____/____/_____

History of unconscious hypoglycaemia : Yes [ ] No [ ] GAD Positive: Yes [ ] No [ ]

Family history

Yes[ ] No [ ] *If Yes please print the number: ie: siblings [5]*

Maternal [ ] Paternal [ ] Grandpts [ ] Siblings [ ] Aunt/Uncle [ ] Children [ ]

Drug Allergies:

Name:

Social Background & Disease History

Social History

Occupation:	**If Not Working** **Past Occupation:**

Diabetes History

Research NO [ ]

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Name:

Medical and Surgical History (Year) & Major Procedures and Investigations	
Neurological:	**Ophthalmological:**
Endocrine (Non-Diabetes Related):	**Psychiatric:**
Respiratory:	**Musculoskeletal/Rheumatoid/Bone:**
Gastrointestinal/ Hepatobiliary:	**Haematological/Lymphatic:**
Dermatological:	**Renal/ Genitourinary:**
Neoplasia:	
MacroVascular/Cardiovascular:	
Other (Specify):	

Name:

Medication Chart Glucose Lowering Medications and Insulin Therapy		
Date	Before Assessment	After Assessment

AntiHypertensive Medication		
Date	Before Assessment	After Assessment

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Name:

Medication Chart Lipid Lowering Medications		
Date	**Before Assessment**	
Date	**Anti-Platelet Therapy** **Before Assessment**	**After Assessment**
Date	**Other Medications** **Before Assessment**	**After Assessment**

Name:

	Date:	Date:	Date:
Measurements			
Height:			
Weight:			
Waist:			
Hip:			
BP1			
BP2			
Pathology			
BSL			
HbA1c (Pathology Company:) %			
TSH (µmol/L)			
Hb			
Creatinine (µmol/L)			
eGFR			
Cholesterol (mmol/L)			
Triglycerides (mmol/L)			
HDL Cholesterol (mmol/L)			
LDL Cholesterol (mmol/L)			
Microalbuminuria (mg/L)			
Urinary protein (g/L)			
Urinary Creatinine (mmol/L)			
ACR			
Coeliac Screen			
Tests	**Date Signature**	**Date Signature**	**Date Signature**

Name:

	Date:		Date:		Date:	
Seen by:						
Doctor:						
Smoking Current	/day	yrs	/day	yrs	/day	yrs
Smoking Past	/day	yrs	/day	yrs	/day	yrs
Smoking Never	Yes[ ]		Yes[ ]		Yes[ ]	
ETOH (*If yes indicate grams per week*)	No[ ] Yes[ ]		No[ ] Yes[ ]		No[ ] Yes[ ]	
Hypoglycaemia: Please indicate number						
Symptomatic hypoglycaemia or BGL <=3.5 mmol/L						
Unconscious hypoglycaemia within the last year						
HBGM	No[ ] Yes[ ]		No[ ] Yes[ ]		No[ ] Yes[ ]	
HBGM Frequency (No weekly)						
Timing of HBGM	Pre[ ] Post[ ] Paired [ ]		Pre[ ] Post[ ] Paired [ ]		Pre[ ] Post[ ] Paired [ ]	
Eye assessment	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**
Visual acuity	6/	6/	6/	6/	6/	6/
Glaucoma	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Cataracts	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Cataract extraction	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Laser treatment	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Retinopathy	**Please Tick Box**					
Nil	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Minimal NPDR	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Mild-Moderate NPDR	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Severe NPDR	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Proliferative *	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Advanced Proliferative*	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Not Performed	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Not Visualised	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Active Retinopathy	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Macular Oedema	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
NPDR =Non Proliferative Diabetic Retinopathy ** Complete The Active Retinopathy Section If Poliferative Or Advanced Proliferative Retinopathy Is Present*						
Assessed by outside Doctor	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Newly Dx Retinopathy	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Eye Doctor Details						

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Name:

	Date:		Date:		Date:	
Foot Assessment	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**
Neuropathic pain	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Numbness	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Pins/needles	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Claudication [legs]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Bypass/angioplasty for PVD	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Amputation [note site if yes]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Past foot ulcer	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Current foot ulcer	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
If yes:	If Current Foot Ulcer Tick Site & Type					
Neuropathic	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Vascular	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Mixed	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Dry skin	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Corn/callus	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Biothesiometer						
Monofilament	Can feel [ ] Can't feel[ ]	Can feel [ ] Can't feel[ ]	Can feel [ ] Can't feel[ ]	Can feel [ ] Can't feel[ ]	Can feel [ ] Can't feel[ ]	Can feel [ ] Can't feel[ ]
Ankle Reflexes	Present [ ] Absent [ ]	Present [ ] Absent [ ]	Present [ ] Absent [ ]	Present [ ] Absent [ ]	Present [ ] Absent [ ]	Present [ ] Absent [ ]
Pedal Pulses	Present [ ] Absent [ ]	Present [ ] Absent [ ]	Present [ ] Absent [ ]	Present [ ] Absent [ ]	Present [ ] Absent [ ]	Present [ ] Absent [ ]
Doppler used	Yes [ ]	Yes [ ]	Yes [ ]	Yes [ ]	Yes [ ]	Yes [ ]
Newly Dx Vascular disease	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Newly Dx Neuropathy	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Autonomic Neuropathy						
Symptoms Of Autonomic Neuropathy Present?	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
If yes:	If Symptoms Of Autonomic Neuropathy Present Please Tick Box					
Gastroparesis	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Diarrhoea	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Urinary retention	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Gustatory Sweating	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
MacroVascular	**Right**	**Left**	**Right**	**Left**	**Right**	**Left**
Carotid bruit	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]	No[ ] Yes[ ]
Stroke	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Ischaemic heart disease	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
CAGS	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Stents/Angioplasty	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]
Erectile Dysfunction	No [ ]	Yes [ ]	No [ ]	Yes [ ]	No [ ]	Yes [ ]

Name:

Treatment Plan			
	Date:	**Date:**	**Date:**
Metabolic control Targets **FBGL** **PP BGL** **HbA1c**			
Blood Pressure/Renal Status			
Lipids			
Diet and exercise **Weight(kgs)** **Exercise(mins) days/wk**			
Eyes			
Feet			
Impotence			
Education			
NDSS			
Other			
Copies of Reports To			
Appointments	**Reason & Date**	**Reason & Date**	**Reason & Date**

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