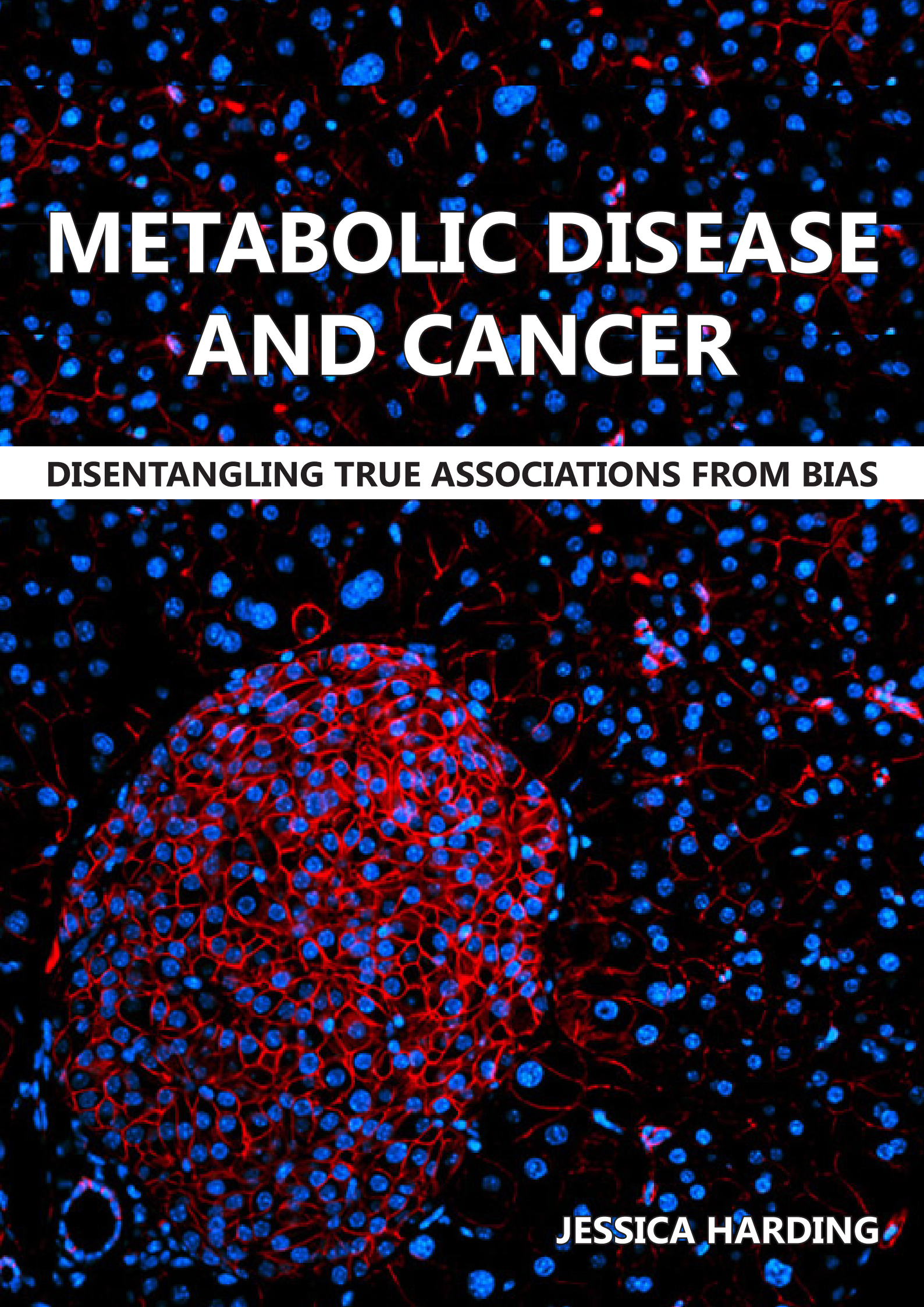

METABOLIC DISEASE AND CANCER

DISENTANGLING TRUE ASSOCIATIONS FROM BIAS

JESSICA HARDING

Metabolic Disease and Cancer
Disentangling true associations from bias

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BBioMedSci (Hons)

A thesis submitted in fulfilment of the requirements for the degree of

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SUMMARY

Background

Diabetes is one of the biggest challenges of the 21st century. In 2015, 415 million people worldwide were living with diabetes. In addition, one-quarter of the world's adult population have the metabolic syndrome (MetS) which directly increases the risk of diabetes, cardiovascular disease (CVD) and all-cause mortality. Diabetes and the MetS are becoming increasingly prevalent worldwide and both are thought to be associated with an increased incidence and mortality from many cancers. Cancer is the second leading cause of death in economically developed countries and the third leading cause of death in developing countries. Together, these are common diseases with a considerable impact on public health. Therefore, improving our understanding of risk factors and consequences of these diseases is of increasing importance to improve screening programs, identify preventive strategies and develop novel therapies.

The aim of this thesis is to contribute to current knowledge gaps in the association of diabetes and the MetS with cancer. Specifically, the three broad aims of this thesis are:

i. To examine secular trends in excess all-cause and cause-specific mortality in type 1 and type 2 diabetes compared with the general population, overall and by age-group;

ii. To quantify associations of type 1 and type 2 diabetes with cancer; and

iii. To quantify associations of the MetS and individual components of the MetS with cancer.

Further, this thesis aims to address methodological concerns not addressed in previous research of metabolic disease and cancer.

Methods

To adequately address these questions prospective, population-based studies with high quality databases and long follow-up time are needed. Publications included in this thesis pertain to results derived from analyses conducted using four national data sources: the *National Diabetes Service Scheme (NDSS)*; the *Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC)*; the *National Death Index (NDI)*; and the *Australian Cancer Database (ACD)*. The NDSS is a large-scale administrative database of Australians with diagnosed diabetes and the ANZDCC is a large pooled cohort comprised of 18 population-based cohort studies within Australia and New Zealand (ANZ). Both the NDSS and ANZDCC cohorts were linked to the ACD and the NDI to obtain incident cancer and mortality outcomes, respectively.

Key Findings

Several key findings have arisen from this work:

1. Age-standardised mortality rates (ASMRs) for all-cause, CVD and diabetes mortality have decreased in people with type 1 and type 2 diabetes in the last decade, while cancer ASMRs remain unchanged.
2. Improvements in mortality are seen among older age groups (40–60 and 60–80). However this is not seen across the entire age spectrum with younger ages (0–40) not experiencing the same declines in mortality and even more concerning, for type 2 diabetes, increases in all-cause and cancer mortality were noted in this age group.
3. Cancer is a leading cause of death in people with diabetes and the proportion of deaths due to cancer is increasing over time.
4. Using underlying cause of death to quantify the mortality burden among people with diabetes will underestimate by >50% of deaths attributed to CVD.
5. People with type 1 and type 2 diabetes are at increased risk for a number of site-specific cancers and risk estimates are similar between type 1 and type 2 diabetes.
6. Detection bias and reverse causation explain some, but not all, of the associations between diabetes and cancer.
7. The MetS is associated with an increased risk for overall and colorectal cancers and these associations are driven largely by obesity and hypertension. However, the MetS is not a useful tool for deciding who is and who is not likely to get cancer.
8. Measures of central and general obesity are similarly predictive of cancer risk, though stronger associations with central obesity suggest a key role in the pathogenesis of cancer.
9. Hypertension, both treated and untreated, is associated with a modest increased risk for cancer incidence and mortality. Similar risks in treated and untreated suggest the increased cancer risk is not due to anti-hypertensive treatment.

Conclusion

This thesis has added to the current evidence-base on the association between metabolic disease and cancer. This work has wide-ranging clinical and public health implications. These include insights into the potential mechanisms of cancer; assessment of the burden and consequences of metabolic disease; recommendations to clinicians to be vigilant in ensuring diabetes patients are up to date with cancer screening according to screening guidelines for the general population; aggressive management of risk factors among young-onset type 2 diabetes to prevent premature mortality; the need to adapt our health care systems to meet the changing needs of diabetes patients in the future and the need for lifestyle modification programs to prevent both type 2 diabetes and cancer. Considering the high prevalence of diabetes and the MetS, even a small increase in cancer risk could have severe consequences at the population level. Therefore, it is imperative that we use this and similar data to inform policies that will improve the health and care of people living with metabolic disease.

ASSOCIATED PUBLICATIONS, PRESENTATIONS & AWARDS

Publications by the candidate produced during candidature relevant to the thesis

Harding JL, Shaw JE, Peeters A, Davidson S & Magliano DJ. Age-specific trends from 2000-2011 in all-cause and cause-specific mortality in type 1 and type 2 diabetes: a cohort study of over one million people. *Diabetes Care*. Accepted Feb 2016 (Impact Factor 8.570)

Harding JL, Sooriyakumaran M, Anstey K, et al. Hypertension, anti-hypertensive treatment and cancer risk: a pooled collaborative analysis of 12 Australian and New Zealand cohorts. *Journal of Hypertension*. 2016; 34(1):149-55 (Impact Factor 4.72)

Harding JL, Sooriyakumaran M, Anstey K, et al. The metabolic syndrome and cancer: is the metabolic syndrome useful for predicting cancer risk above and beyond its individual components? *Diabetes and Metabolism*. 2015; 41(6): 463-469. (Impact Factor: 3.267)

Harding JL, Shaw JE, Anstey K, et al. Comparison of anthropometric measures as predictors of cancer incidence: A pooled collaborative analysis of 11 Australian cohorts. *International Journal of Cancer*. 2015; 137(7):1699-708 (Impact Factor: 5.085)

Harding JL, Shaw JE, Peeters A, Cartensen B, & Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes in Australia; disentangling true associations, detection bias and reverse causation. *Diabetes Care*. 2015; 38(2):264-70 (Impact Factor: 8.570)

Harding JL, Shaw JE, Peeters A, Guiver T, Davidson S & Magliano DJ. Mortality trends among people with type 1 and type 2 diabetes in Australia; 1997-2010. *Diabetes Care* 2014; 37(9):2579-86 (Impact Factor: 8.570)

Harding JL, Shaw JE, Koshkina V, Magliano DJ. Cohort profile: The Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC). *Australasian Epidemiologist* 2014; 21(2):51-7.

Additional publications by the candidate during candidature relevant to the thesis but not forming part of it

Magliano DJ, **Harding JL**, Shaw JE. Comment in 'Glycemic control and excess mortality in type 1 diabetes'. *New England Journal of Medicine*. 2015; 26; 372(9):880. doi: 10.1056/NEJMc1415677#SA3 (Impact Factor: 55.873)

Harding JL, Shaw JE, Magliano DJ (2014) Linking data to improve health outcomes (letter). *Medical Journal of Australia* 2014; 201(2): 91 (Impact Factor: 4.089)

Harding JL, Soderberg S, Shaw JE, et al. All-cause cancer mortality over 15 years in multi-ethnic Mauritius: The impact of diabetes and intermediate forms of glucose tolerance. *International Journal of Cancer* 2012; 131(10): 2385-93 (Impact Factor: 5.085)

Additional peer-reviewed publications by the candidate during candidature

Huo L, Peeters A, Wong E, **Harding JL**, Shaw JE, Magliano DJ. Burden of diabetes in Australia: life expectancy and disability-free life expectancy in adults with diabetes. *Diabetologia*. Accepted March 2016 (Impact Factor 6.671

Cartensen B, Read SH, Friis S, Sund R, Keskimaki I, Svensson AM, Ljung R, Wild SH, Kerssens JJ, **Harding JL**, Magliano DJ, Gudbjornsdottir S. Cancer incidence in persons with type 1 diabetes: a five-country study of cancers in type 1 diabetic individuals. *Diabetologia*. 2016; doi: 10.1007/s00125-016-3884-9 (Impact Factor 6.671)

Huo L, **Harding JL**, Peeters A, Shaw JE, Magliano DJ. Life expectancy of type 1 diabetic patients during 1997-2010: a national Australian registry-based cohort study. *Diabetologia*. 2016; doi: 10.1007/s00125-015-3857-4 (Impact Factor 6.671)

Magliano DJ, Cohen K, **Harding JL**, Huxley W, Davis W, Shaw JE. Excess risk of dying from infectious causes in those with type 1 and type 2 diabetes. *Diabetes Care*. 2015; doi: 10.2337/dc14-2820 (Impact Factor: 8.570)

Magliano DJ, Cohen K, **Harding JL**, Shaw JE. Residential Distance from Major Urban Areas, Diabetes and Cardiovascular Mortality in Australia. *Diabetes Research and Clinical Practice*. 2015; doi:10.1016/ (Impact Factor: 2.538)

Loh VHY, **Harding JL**, Koshkina V, Barr ELM, Shaw JE, Magliano DJ. The validity of self-reported cancer in an Australian population study. *Australian & New Zealand Journal of Public Health* 2014; 38(1); 35-38 (Impact Factor: 1.980)

Harding JL, Backholer K, Williams ED, Cameron A, Hare M, Peeters A, Shaw J, Magliano DJ. Psychosocial stress is positively associated with body mass index gain over 5 years: evidence from the longitudinal AusDiab Study. *Obesity*. 2013; 22(1):277-86. (Impact Factor: 3.734)

Wong E, Backholer K, Gearon E, **Harding JL**, Freak-Poli R, Stevenson C, Peeters A Diabetes and risk of physical disability in adults: a systematic review and meta-analysis. *The Lancet Diabetes and Endocrinology* 2013; 1(2):106-114 (Impact Factor: 9.185)

Magliano DJ, Loh VHY, **Harding JL**, Botton J, Shaw JE. Persistent organic pollutants and diabetes: A review of the epidemiological evidence. *Diabetes & Metabolism* 2013; 40(1):1-14 (Impact Factor: 3.267)

Harding JL, Freak-Poli R, Backholer K, Peeters A. Change in health-related quality of life amongst participants in a 4-month pedometer-based workplace health program. *Journal of Physical Activity and Health* 2012; 10(4): 533-43 (Impact Factor: 1.854)

Wong E, Backholer K, **Harding JL**, Gearon E, Stevenson C, Freak-Poli R & Peeters A. A systematic review and meta-analysis of diabetes and risk of physical disability and functional impairment - protocol. *Systematic Reviews* 2012; 1:47.

Non-peer-reviewed publications produced by the candidate during candidature

Magliano DJ, **Harding JL**, Shaw JE. Pancreatic cancer and diabetes: what is the link? *Diabetes Management*. 2015

Conference abstracts/presentations during candidature

Harding JL, Shaw JE, Magliano DJ. (December 2015) Overnight fasting is not associated with cancer risk. Accepted for guided poster presentation at the International Diabetes Epidemiology Group meeting, Vancouver, Canada

Harding JL, Nedkoff L, Shaw JE, Magliano DJ (on behalf of the ANZDCC group). (December 2015) Differences in absolute and relative risks for CVD mortality among various low and high risk groups: exploring the phenomenon. Accepted for oral presentation at the International Diabetes Epidemiology Group meeting, Vancouver, Canada

Harding JL, Shaw JE, Magliano DJ. (December 2015) Age-specific trends in all-cause and cause-specific mortality among type 1 and type 2 diabetes: a cohort study of over one million people. Accepted for guided poster presentation at the World Diabetes Congress, Vancouver, Canada

Harding JL, Shaw JE, Peeters A, Magliano DJ (October 2014). Cancer risk among type 1 and type 2 diabetes. Oral presentation at the Australasian Epidemiology Association, Auckland New Zealand

Harding JL, Shaw JE, Davidson S, Magliano DJ (August 2014). Mortality trends among type 1 and type 2 diabetes in Australia 2000-2010. Oral presentation at the Australian Diabetes Society Conference, Melbourne, Australia

Harding JL, Shaw JE, Magliano DJ (June 2013). Accurate estimation of CVD mortality in people with type 1 diabetes. Guided poster presentation at the American Diabetes Association Conference, Chicago, USA.

Harding JL, Peeters A, Shaw JE, Magliano DJ (on behalf of the ANZDCC collaborating group). (October 2013). Anthropometric measures of obesity and risk of cancer in Australia and New Zealand. Oral presentation at the Australian and New Zealand Obesity Society Conference, Melbourne, Australia.

Harding JL, Peeters A, Shaw JE, Guiver T, Magliano DJ (December 2013). Cancer risk in people with type 1 diabetes. Oral presentation at the World Diabetes Congress, Melbourne, Australia.

Harding JL, Shaw JE, Peeters A, Magliano DJ (on behalf of the ANZDCC collaborating group). (December 2013). Pre-diabetes is associated with incident cancer in a pooled Australian cohort. Oral presentation at the International Diabetes Epidemiology Group Meeting, Melbourne, Australia.

Harding JL, Shaw JE & Magliano DJ. (October 2012) Poster presentation at Alfred Research Week. Trends of cancer incidence and mortality in Australians with diabetes: 1997-2007

Awards

2015	Paul Korner Award (for outstanding achievement by a PhD student) ($2000)
	Monash University Early Career Research Best Paper ($500)
	Monash post-graduate publication award ($6,500)
	Friends of Baker IDI travel award ($5,000)
	IDEG travel grant ($2,000)
2014	Australasian Epidemiology Association travel grant ($500)
	Excellence in Teaching award, Monash University ($500)
	Baker IDI travel grant ($1,000)
	Monash University travel grant ($1,000)
	Baker IDI monthly research prize ($200)
	Finalist – Clinical Young investigators award Australian Diabetes Society
2013	Baker IDI travel grant ($750)
	Monash University travel grant ($1,125)
	Biostat Epi summer school scholarship (€550)
2012–2015	Australian Postgraduate Award (APA) scholarship
	Baker IDI Bright Sparks' scholarship

GENERAL DECLARATION

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

General Declaration

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

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

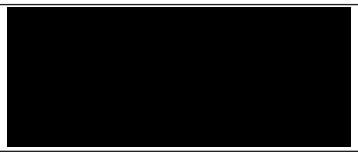
ii. This thesis includes six original papers published in peer reviewed journals and one unpublished publication. The core theme of the thesis is epidemiological associations between metabolic diseases and cancer. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Department of Clinical Diabetes and Epidemiology at Baker IDI Heart and Diabetes Institute under the supervision of A/Prof Dianna Magliano, A/Prof Jonathan Shaw and A/Prof Anna Peeters.

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

In the case of chapters 2–6, my contribution to the work involved the following:

Thesis chapter	**Publication title**	**Publication status**	**Nature and extent of candidate's contribution**
2.2	Cohort Profile: The Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC)	Published	Conceptualisation, manuscript development and preparation
3.1	Mortality trends among people with type 1 and type 2 diabetes in Australia; 1997-2010	Published	Data collection, data management, data analysis, and manuscript development and preparation
3.2	Age-specific trends from 2000-2011 in all-cause and cause-specific mortality among type 1 and type 2 diabetes: a cohort study of over one million people	Accepted	Data collection, data management, data analysis, and manuscript development and preparation
4	Cancer risk in type 1 and type 2 diabetes; disentangling true associations, detection bias and reverse causation	Published	Data collection, data management, data analysis, and manuscript development and preparation
5	The metabolic syndrome and cancer: is the metabolic syndrome useful for predicting cancer risk above and beyond its individual components?	Published	Data collection, data management, data analysis, and manuscript development and preparation
6.1	Comparison of anthropometric measures as predictors of cancer incidence: A pooled collaborative analysis of 11 Australian cohorts	Published	Data collection, data management, data analysis, and manuscript development and preparation
6.2	Hypertension, anti-hypertensive treatment and cancer incidence and mortality: a pooled collaborative analysis of 12 Australian and New Zealand cohorts	Published	Data collection, data management, data analysis, and manuscript development and preparation

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

Signature		Date: 31/03/2016

ABBREVIATIONS

ABSI	A Body Shape Index
ACD	Australian Cancer Database
AIHW	Australian Institute of Health and Welfare
ALSA	Australian Longitudinal Study of Ageing
ALSWH	Australian Longitudinal Study on Women's Health
ANBP2	The Second Australian National Blood Pressure Study
ANZ	Australia and New Zealand
ANZDCC	Australian and New Zealand Diabetes and Cancer Collaboration
ASMR	Age-standardised mortality rate
AusDiab	Australian Diabetes, Obesity and Lifestyle Study
BMES	Blue Mountains Eye Study
BMI	Body mass index
BP	Blood Pressure
CI	Confidence interval
COD	Cause of Death
CUDS	Crossroads Undiagnosed Disease Study
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DPP	Diabetes Prevention Program
DUBBO	Dubbo Study of the Elderly
FDS	Fremantle Diabetes Study
FLETCHER	Fletcher Challenge – University of Auckland heart and Health Study
FPG	Fasting plasma glucose
GOS	Geelong Osteoporosis Study
HC	Hip circumference
HDL	High-density cholesterol

HIMS	Health In Men Study
HR	Hazard ratio
HREC	Human Research Ethics Committee
ICD	International Classification of Disease
IDF	International Diabetes Federation
LIPID	Long-term intervention with Pravastatin in Ischaemic Disease Trial
MCCS	Melbourne Collaborative Cohort Study
MetS	Metabolic Syndrome
NDI	National Death Index
NEJM	New England Journal of Medicine
NDSS	National Diabetes Service Scheme
NHMRC	National Health and Medical Research Council
NWAHS	North West Adelaide Health Study
NZ	New Zealand
PATH	Personality and Total Health Through Life Project
PM	Post-menopausal
PY	Person-years
SBP	Systolic blood pressure
SD	Standard deviation
SIR	Standardised incidence ratio
SMR	Standardised mortality ratio
Trig	Triglycerides
WC	Waist circumference
WHR	Waist-to-hip ratio
WtHR	Waist-to-height ratio

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Firstly, to the many people involved in the data linkage component of this thesis: Susan Davidson and Darren Rae at Diabetes Australia; Tenniel Guiver, Barbara Chan, Catherine Lawrence, Kirk Hampel and Karen Bishop at the Australian Institute of Health and Welfare; and the ethics committees in each State and Territory of Australia for ensuring that this was an ethically sound project and for keeping me buried in paperwork. Second, to the funding bodies that have supported my PhD journey: an Australian Postgraduate Award awarded by Monash University, a Baker IDI Bright Sparks top-up and several travel grants. Without this funding I would not have had the opportunity to complete a PhD or to showcase my work at national and international conferences. I would also be slimmer than I am now because I would not have been able to afford food. Third, to all who co-authored papers with me, in particular the ANZDCC investigators for their support, input and guidance into these projects.

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CHAPTER 1

Introduction

Diabetes has become one of the biggest challenges of the 21st century.[1] In 2015, almost 415 million people worldwide were living with diabetes and this is expected to increase to 642 million by 2040 as a result of population growth, aging, unhealthy diets and sedentary lifestyles.[2] In addition, one-quarter of the world's adult population has the metabolic syndrome (MetS) which directly increases the risk of diabetes, cardiovascular disease (CVD) and all-cause mortality.[3,4] Diabetes and the MetS are becoming increasingly prevalent worldwide, and both are thought to be associated with an increased incidence and mortality from many cancers. Cancer is the second leading cause of death in economically developed countries and the third leading cause of death in developing countries.[5] Diabetes, the MetS and cancer are common diseases with a considerable impact on public health. Therefore, improving our understanding of risk factors and consequences of these diseases is of increasing importance to improve screening programs, identify preventive strategies and develop novel therapies.

This introductory Chapter will first define diabetes and the MetS, their risk factors and associated complications. Second, this Chapter will summarise the current body of evidence linking diabetes, the MetS and cancer, and highlight relevant paucities in the literature at the time of commencement of this PhD. Last, this Chapter will briefly summarise the main objectives of this thesis and the relevant publications that have arisen from this work. This Chapter provides the background for why this thesis has been necessary to advance our understanding of the association between metabolic diseases and cancer.

1.1 Metabolic Disease

Metabolism refers to the biochemical processes that allow us to grow, reproduce, repair damage and respond to our environment. Metabolic disease arises when these biochemical pathways are disrupted. This thesis will consider two key metabolic disorders: diabetes and the MetS.

1.1.1 Diabetes

Diabetes mellitus, more commonly referred to as diabetes, consists of a group of metabolic diseases characterised by hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin resistance, or both.[6] There are two main types of diabetes: type 1 diabetes and type 2 diabetes.

1.1.1.1 Type 1 Diabetes

Type 1 diabetes accounts for 5–10% of all people with diabetes[7] and is a state of absolute or near absolute insulin deficiency usually caused by autoimmune destruction of pancreatic β-cells.[8] People with type 1 diabetes therefore require insulin therapy for survival. The disease can affect people of any age but is usually diagnosed in children or young adults. Characteristic symptoms of uncontrolled hyperglycaemia include polyuria (excessive urination), polydypsia (excessive thirst), blurring of vision, weight loss and infections. The underlying cause of type 1 diabetes is unknown, though there are several postulated causes.

First, there is considerable geographic and ethnic variation in the risk of type 1 diabetes. For example, the incidence of type 1 diabetes varies from 0.73/100,000 per year in China[9], to 18/100,000 in Australia[10], to 60/100,000 in Finland[11]. This equates to a child in Finland being 100 times more likely to develop diabetes than a child in China. These variations suggest different pools of susceptibility genes, or different prevalence of causative environmental factors, or a combination of both. Second, there is evidence for marked variations in type 1 diabetes incidence by season. For example, declines in type 1 diabetes incidence have been noted in the warmer months, implicating a climatic factor, possibly exposure to vitamin D.[12] *In vitro* studies have shown vitamin D3 to be immunosuppressive and experimental models of autoimmunity have shown vitamin D to be protective for type 1 diabetes.[13] However, observational studies in humans are conflicting. A birth-cohort in Europe has reported a protective effect of vitamin D supplementation[14] while other studies have demonstrated no association.[15] It is also possible that seasonal variations in type 1 diabetes incidence may be explained by exposure to viral infections in people with autoimmunity.[16] Several viruses have been linked to type 1 diabetes, in particular the herpes virus, mumps, rubella and retroviruses.[17] Several studies also implicate enteroviruses in the pathogenesis of type 1 diabetes, though evidence is conflicting.[18] Lastly, family history of type 1 diabetes[19] and susceptibility genes, such as specific HLA geneotypes,[20] are also associated with an increased risk for type 1 diabetes. In addition, for unknown reasons, the incidence of type 1 diabetes has been increasing progressively over the last half century by 3–5% per year.[21-23] Hypotheses include changes in environmental risk factors including increased obesity, early events in the womb, diet early in life and/or viral infections.[24]

1.1.1.2 Type 2 Diabetes

Type 2 diabetes is the most common form of diabetes, accounting for 90–95% of all diabetes[7] and is characterised by disorders of insulin resistance and insulin secretion.[8] This leads to an inadequate, compensatory increased production of insulin, during early stages of type 2 diabetes, resulting in hyperinsulinaemia. In later stages of type 2 diabetes, pancreatic β-cells fail to produce adequate insulin, resulting in hyperglycaemia. Type 2 diabetes usually occurs in adults but is increasingly seen in children and adolescents.[25] Symptoms of type 2 diabetes may be minimal or even absent and therefore a diagnosis can be delayed for many years. In fact, it is estimated that close to half of all people with diabetes are unaware of their disease.[2] This is of considerable importance as in this time, excess glucose is causing damage and people are often not diagnosed until complications have already begun to develop. Indeed, several studies have found that many people with undiagnosed diabetes already have complications such as chronic kidney disease, heart failure, retinopathy and neuropathy.[26-28] Strategies to identify diabetes in its early stages may be warranted to prevent or reduce

the risk of developing complications. However, current evidence that screening will reduce diabetes-related is questionable. Evidence from the Diabetes Prevention Program (DPP), a 27-center randomised clinical trial, failed to show that intervention, either with lifestyle modifications or pharmalogical treatment (metformin), decreased miscrovascular outcomes.[29]

Although the reasons for developing type 2 diabetes are still not clear, there are several known risk factors. Obesity and weight gain have consistently been shown to be one of the strongest modifiable risk factors for diabetes.[30-32] It is estimated that 60–90% of people with type 2 diabetes are obese and obesity itself causes insulin resistance.[33] However, the majority of obese people do not develop diabetes and therefore obesity is only one factor that leads to the development of type 2 diabetes. Ethnicity is also a known risk factor for type 2 diabetes with considerable variations in diabetes prevalence among different ethnic groups. For example, in the US between 1988 and 2012, the prevalence was 1.9 and 2 times greater in African Americans and Latino Americans respectively, as compared with white Americans of the same age with prevalence estimates of 21.8% and 22.6% respectively, compared with 11.3% for white Americans.[34] Pima Indians and Pacific Island populations have the highest prevalence of diabetes in the world, with 40–50% of adults living with diabetes.[35-37] In Australia, Indigenous populations have an age-adjusted diabetes prevalence more than three times that of non-Indigenous Australian populations, with estimates of 18% and 5.1%, respectively.[38] The risk of type 2 diabetes also increases with age,[39] family history of diabetes[40] and lifestyle behaviours such as smoking[41], physical inactivity[42] and poor diet.[43] In fact, 80–90% of all causes of type 2 diabetes have been attributed to the unhealthy lifestyle practices that come with modern industrialised environments.[44]

In 2015, the global prevalence of diabetes was estimated to be 8.8%. This equates to 415 million people, with the majority of this burden being attributed to type 2 diabetes.[2] Consequently, type 2 diabetes and its complications, discussed below, have a considerable health and economic burden.[2] And most cases are preventable. Evidence from the DPP first demonstrated that intensive lifestyle intervention of weight loss and exercise decreased the incidence of diabetes by 58% in those who were at high risk for diabetes. This was considerably higher than the 31% of diabetes cases that were prevented in the pharmacological treatment arm.[45] This finding has now been replicated in several studies in various high risk populations.[46,47] Specific targets for diabetes prevention and halting the growth of obesity and diabetes is now high on the global action plan for the prevention and control of non-communicable diseases.

1.1.1.3 Other forms of diabetes

There are several other specific types of diabetes that are less common. These can be broadly classified into gestational diabetes (diabetes during pregnancy), genetic defects of β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas, infections, drug- or chemical-induced, endocrinopathies, immune-mediated diabetes and other genetic syndromes sometimes associated with diabetes.[8] These forms of diabetes will not be discussed further in this thesis.

1.1.1.4 Diabetes complications

People with diabetes are at risk of developing a number of diabetes complications. These are, in general, divided into microvascular and macrovascular complications. The microvascular complications of diabetes include nephropathy (kidney disease), retinopathy (blindness) and neuropathy (leading to amputations, joint problems and foot ulcers).[48] Strict glycaemic control, as shown in clinical trials, can reduce the incidence of microvascular complications.[49] The macrovascular complications of diabetes are underpinned by the process of atherosclerosis which leads to narrowing of the arterial walls throughout the body.[50] This process ultimately leads to an increased risk for CVD. In people with type 2 diabetes, the risk of having an incident myocardial infarction or stroke is increased 2- to 3-fold, independent of other known risk factors for CVD.[51] Type 1 and type 2 diabetes have a 5.2 and 4.9 increased risk for CVD mortality respectively, compared with people without diabetes.[52] In fact, CVD is the primary cause of death in people with either type 1 or type 2 diabetes[53,54] and accounts for the greatest component of health care expenditure in people with diabetes.[55] The benefits of improved glycaemic control are less clear with respect to macrovascular disease where large-scale clinical trials have shown that in patients with long duration of diabetes, strict glycaemic control may in fact be detrimental in some circumstances.[56,57]

Recently, evidence suggests that mortality from these 'traditional' complications of diabetes, in particular CVD, may be decreasing.[58-60] While these findings should be confirmed in other populations, these trends suggest improvements in the treatment and prevention of diabetes complications over time. However, with people with diabetes now less likely to die from CVD, attention has shifted to other non-traditional complications of diabetes, such as cancer. This is discussed in greater detail in Section 1.2 and in Chapter 3.

1.1.2 Metabolic Syndrome

The MetS is defined by a constellation of interconnected physiological, biochemical, clinical and metabolic factors that directly increase the risk of CVD, type 2 diabetes and all-cause mortality.[61] Features of the MetS include obesity (particularly central obesity), hypertension, dyslipidaemia (specifically hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol) and insulin resistance. The concept of the MetS was first described by Kylin in the 1920s[62] and by 1988, Reaven had established the importance of this syndrome and suggested a conceptual framework to link these apparently unrelated clinical and biochemical characteristics.[63] Today, the pathophysiological basis for the association between these factors remains unidentified. However, central obesity and insulin resistance are believed to be central to understanding the pathogenesis of the syndrome.[64]

Table 1.1 Harmonised criteria for identifying the metabolic syndrome

Measure	Categorical thresholds
Elevated waist circumference	Population and country-specific definitions
Elevated triglcyerides	≥1.7 mmol L^{-1} or drug therapy for hypertriglyceridemia
Reduced HDL-cholesterol	<1.0 mmol L^{-1} in men, <1.3 mmol L^{-1} in women or drug therapy for low HDL-cholesterol
Elevated blood pressure	Systolic ≥130 mmHg and/or diastolic ≥85 mmHg or drug therapy with a history of hypertension
Elevated fasting plasma glucose	≥5.6 mmol L^{-1} or glucose-lowering therapy

Source: Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009.120(16):1640-5

Different national and international organisations have produced various overlapping, but different, iterations of diagnostic criteria for the MetS over the last 15 years. To address recognised shortcomings in previous definitions, in 2009, a harmonised definition was generated by a working group on behalf of the International Diabetes Federation (IDF), National Heart Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society and the International Association for the Study of Obesity.[3] Currently, any three out of the five criteria listed in Table 1.1 constitutes a diagnosis of the MetS. Population and country specific definitions of elevated waist circumference (WC) reflect the inherent differences in ethnicity for definitions of central obesity.

The MetS confers a 5-fold increase in the risk of type 2 diabetes and 2-fold increase in risk of developing CVD over 5–10 years.[3] The MetS is currently used in clinical practice as a simple tool to predict future risk of developing type 2 diabetes and/or experiencing a CVD event.[65] However, the clinical utility of the MetS above and beyond its individual components has been controversial with sceptics arguing that the label of the MetS adds little to established methods for risk calculation for type 2 diabetes and CVD.[66-68] The MetS has also been implicated as a risk factor for cancer, discussed in detail in Chapters 1.3 and 5, but its utility in predicting cancer risk in also not clear.

1.2 Diabetes and Cancer: The Evidence

An association between diabetes and cancer has been recognised for many years. Epidemiologists first noted an association between diabetes and cancer in the early part of the 20th century when it was observed that diabetes and cancer were being diagnosed within the same individual more frequently than would be expected by chance.[69,70] However, until the 1990s much of the epidemiological findings were inconsistent due to many confounding risk factors that were not accounted for in previous research. Since then, a wealth of research has been conducted in the field of diabetes and cancer.

Numerous epidemiologic studies have identified associations between type 2 diabetes and several types of cancer in various populations. The large amount of literature on this topic has been summarised in several recent reviews.[69-71] While the literature indicates a strong and consistent association between type 2 diabetes and cancer, the magnitude and direction of the association depends on the specific site of the cancer.[72] The strongest relationships have been demonstrated for liver[73] and pancreatic[74] cancers, although these may also reflect some degree of reverse causality, with the cancer itself leading to the onset of type 2 diabetes. Risk of endometrial cancer appears to be doubled in women with diabetes[75] and risks of breast, colorectal, bladder, stomach, kidney and non-Hodgkin's lymphoma are approximately 20–40% higher in people with type 2 diabetes.[76-81] Interestingly, there appears to be a protective effect of diabetes for prostate cancer, in the neighbourhood of 15%, which is thought to be due, in part, to reduced levels of endogenous testosterone levels in men with type 2 diabetes.[82] On the other hand, although the number of studies is small, there appears to be no consistent association with lung,[83] thyroid[84] and ovarian[85] cancers.

Although many of these studies do not specifically record diabetes type, 90–95% of adults with diabetes have type 2 diabetes. Therefore, at least 90% of the populations in these studies would have type 2 diabetes. In contrast to type 2 diabetes, studies on the risk of type 1 diabetes and cancer have been few and largely inconsistent. This is most likely due to variability in definitions of type 1 diabetes and differences between cohort and case-control study designs. Nonetheless, some studies report increased risks for pancreatic, liver, mouth and pharyngeal, stomach, skin and ovarian cancer, as well as leukaemia in those with type 1 diabetes.[86] For other rarer malignancies and cancer-specific mortality, the number of studies is small, and more importantly, they usually lack adequate power to reliably explore these associations. The ability to tease out relationships of type 1 and type 2 diabetes with site-specific cancer (especially the magnitude of the association), is hampered largely by the lack of cohorts of sufficient size and long follow-up time.

1.2.1 Potential mechanisms linking diabetes and cancer

Biological mechanisms

A number of biologically plausible explanations exist for the observed association between diabetes and cancer, including metabolic derangements typical of diabetes, in particular hyperglycaemia or insulin resistance and hypersinulinaemia.[69,72] Evidence is accumulating that hyperinsulinaemia promotes tumour cell growth directly via the insulin receptor, or indirectly via the insulin-like growth factor I (IGF-I) receptor, both of which are expressed on many cancer cells.[87-89] High levels of circulating IGF-I are associated with increased risk of certain cancers including colorectal, breast and prostate cancers.[90-92] Alternatively, hyperglycaemia may drive associations between diabetes and cancer, though studies are inconclusive. It is well known that cancer cells take up glucose at a higher rate compared with non-cancerous cells. Therefore, it is plausible that an environment abundant in glucose, as is seen in diabetes, could promote the growth of cancer cells. A recent European study found that higher glucose levels were associated with increased risks for several cancers.[93] However, data from large randomised controlled trials of intensified glycaemic control suggest that cancer risk is not reduced by improving glycaemic control in type 2 diabetes which does not support the hypothesis that hyperglycaemia is causally linked to increased cancer risk.[94] It should be noted, however, that trials such as these

were not designed to examine cancer incidence as a primary outcome and all of the patients in these studies already had diabetes and therefore were all at potentially increased risk of cancer. Therefore, the jury is still out as to whether hyperglycaemia plays an important role in associations of diabetes and cancer. Nonetheless, hyperglycaemia occurs in both type 1 and type 2 diabetes, while insulin resistance and hyperinsulinaemia are much more prominent in type 2 diabetes. Therefore, investigating both diabetes types may shed light on the likely mechanistic pathway and the role of hyperglycaemia in these associations.

Shared risk factors

Diabetes and cancer share many common risk factors. Overweight and obesity are known to be associated with an increased incidence of several cancers including colorectal, endometrium, pancreas, oesophageal, kidney, gallbladder, ovarian, breast and liver cancers.[95-100] Obesity is a known risk factor for type 2 diabetes[33] and in countries where obesity prevalence is high, people with type 1 diabetes are also more likely to be obese.[24] Obesity leads to insulin resistance, which may partly explain associations with cancer.[101] Studies of visceral adiposity, a marker of insulin resistance, have shown increased risks for both type 2 diabetes[102] and certain cancers[103] independent of body mass index (BMI).

Poor dietary habits and physical inactivity are also important confounding factors to be considered in studies of diabetes and cancer as they may mediate cancer risk via insulin resistance and obesity[95,104] Similarly, tobacco smoking is more common in people with type 2 diabetes and is a risk factor for several cancers.[105] These primary modifiable risk factors are also closely associated with socioeconomic status, another potentially important factor to be considered in analysis of diabetes and cancer.[106] While exploring these factors in detail is not the aim of this thesis, they are important considerations in our understanding of associations between diabetes and cancer.

Competing risks

Another consideration is the potential impact of competing risks. The concept of competing risk suggests that among people with diabetes, an increased risk of death due to other causes, most notably CVD, would compete for the incidence of cancers, which may have a longer latency period.[72] For example, improvements in CVD risk reduction have led to reduced CVD mortality in the general population as well as the diabetic population.[107] It might be expected that, as life expectancy increases, we will see an increase in the number of cancer cases in the diabetic population, but we would only see an increase in cancer rates if the additional survivors are more susceptible to cancer, which is unlikely to be the case. However, if one competing risk (CVD, for example) decreases without change in the cancer rates, we will observe an increasing cumulative risk of cancer, and hence an apparent increase in the cancer burden.[72]

Detection bias and reverse causality

It is also possible that the observed risk estimates for diabetes and cancer risk may be due to methodological challenges in previous research. For example, detection bias has been suggested as a plausible explanation,

at least in part, for the observed association between diabetes and cancer risk.[72,108,109] Detection bias may occur when cancer is more likely to be observed for people with newly diagnosed diabetes compared to people without diabetes simply due to increased interaction with the health care system as a result of the new diagnosis. Alternatively, detection of diabetes may occur in people seeking medical care for symptoms related to cancer. It is this differential health care utilisation and use of screening tests that may lead to an overestimation of cancer risk for people with diabetes.

Alternatively, reverse causality could explain associations of diabetes and cancer. Dysfunction in insulin secretion as a consequence of cancer may be sufficient to induce hyperglycaemia, particularly in individuals with underlying insulin resistance.[72] This is of particular relevance for associations between diabetes and pancreatic cancer, which has been discussed in detail in Appendix 1. Cancer affecting similarly active metabolic organs such as the liver may also result in derangements of glycaemic control and cause diabetes onset. While reverse causality is a potential alternative hypothesis for the observed associations between diabetes, particularly type 2 and cancer, evidence suggests it is unlikely to explain the entirety of the association.[72] For example, studies have shown that observations of elevated pancreatic cancer risk persist up to ten years after diabetes onset. This is unlikely to be due to reverse causality as pancreatic cancer is rapidly progressive and generally fatal.[110] Therefore, pancreatic cancer is only likely to lead to diabetes in the short term (<6 months) and not for extended periods following diabetes diagnosis.

Thus, these relationships are complex and require the use of large, population-based datasets with long follow-up time and the application of advanced epidemiologic methods to disentangle true associations from bias.

1.3 Metabolic Syndrome and Cancer

There is emerging evidence that the MetS, a syndrome on the continuum between obesity and type 2 diabetes, may be an important etiologic factor in the development and progression of certain types of cancer and cancer mortality.[111] A 2012 meta-analysis reported that the MetS is associated with a low to modest increased risk for colorectal, post-menopausal (PM) breast, bladder, pancreatic, endometrium and liver cancers,[112] but for prostate cancer evidence is conflicting. Some studies report an increased risk,[113] others report a decreased risk[114] and others report no association with the MetS.[112] In addition, the association between the MetS and cancer differs betweens sexes, populations and varying definitions of the MetS making it difficult to make direct comparisons between studies.[112]

Mechanisms linking the MetS and cancer are not well understood. The MetS may be a surrogate marker for other cancer risk factors, such as decreased physical activity, consumption of high-calorie dense foods, high dietary fat intake, low fibre intake and oxidative stress.[3] It is also possible that the association may be mediated by obesity, insulin resistance and overt hyperglycaemia, which have been repeatedly associated with increased risks for some common cancers[115,116] and are important factors contributing to the prevalence of the MetS. There is also some evidence to suggest that elevated blood pressure (BP) is associated with an increased cancer risk[117] while HDL-cholesterol has been shown to have an inverse association with cancer.[118] It remains to be

elucidated if factors within the MetS act in synergy on the risk of cancer or if individual components are driving observed associations. This thesis will explore, in detail, associations of two individual MetS components, obesity and hypertension with cancer risk.

1.3.1 Obesity and cancer

Obesity is a well-established risk factor for cancer. Reports from the World Cancer Research Fund have confirmed that there is sufficient evidence to support causal associations between obesity and cancers of the oesophagus, pancreas, colon, rectum, gallbladder, kidney, breast [post-menopause (PM)], endometrium and ovaries.[95-100] Findings for prostate cancer, however, are mixed with some studies suggesting that there may be associations only in those with advanced prostate cancer.[119] Given the plausibility of the biological explanations (detailed below), the consistency of associations across studies, excluding prostate cancer, and the sufficiently long latency times between measurement of obesity and cancer occurrence, many of these associations are likely to be causal.[120] Additionally, recent studies of patients undergoing bariatric surgery for morbid obesity point to a reduction in cancer incidence associated with sustained weight loss[121,122] which adds further weight to a causal association between obesity and cancer risk.

Currently, findings suggest sex and cancer site-specific biological mechanisms underpin associations between obesity and cancer and it is unlikely that there is one single underlying mechanism.[120] The three most common pathways proposed are those involving insulin and IGF,[88] sex steroids[123,124] and adipokines and markers of chronic inflammation (all linked through insulin resistance).[125] The insulin-cancer hypothesis was postulated over a decade ago by Eyseen[126] and Giovannucci.[127] They suggest that hyperinsulinaemia may contribute to cancer developing through the growth-promoting effect of elevated levels of insulin. In its simplest form, prolonged hyperinsulinaemia reduces the production of IGF binding protein (IGFBP)-1 and IGFBP-2 (which normally binds to IGF-1 and inhibits its action). This results in an increase in levels of free or 'bioactive' IGF-I and concomitant changes in the cellular environment that favours tumour development.[120]

Over the past decade, it has also become clear that adipose tissue is a highly active and large source of endocrine and metabolic activity.[128] It is thought that most established risk factors for breast cancer probably act through oestrogen-related pathways and increased concentrations of circulating oestrogen-related hormones have been linked to breast cancer risk.[120] Experimental evidence from *in vitro* and animal models supports this finding demonstrating that oestrogens are mitogenic in normal and neoplastic mammary tissues. Adiposity is also inversely related to testosterone concentrations in men[115] but positively related in women.[129] Elevated blood concentrations of androgens have been associated with increased risk of breast cancer in women, though experimental evidence is conflicting as animal studies show that androgens actually inhibit breast tumour growth.[130]

Obesity also leads to altered expression profiles of various adipokines and cytokines including leptin, adiponectin, interleukin (IL)-6, tumour necrosis factor (TNF)-α and IL-1β.[131] The increased levels of leptin and decreased adiponectin secretion have been directly associated with cancer development in several studies.[131-133] Overall, research suggests most adipokines promote cancer cell progression via enhancement of cell proliferation and

migration, inflammation and anti-apoptosis pathways, which subsequently can promote cancer metastasis.[134] However, further research and longitudinal studies are needed to define the specific independent and additive roles of adipokines in cancer progression and reoccurrence.[135]

The majority of epidemiologic studies exploring associations between obesity and cancer use BMI as a marker of general adiposity or obesity. BMI is a useful tool in both clinical medicine and population health to predict health risk related to weight and is easily measured. However, BMI has known limitations. Namely, the inability to distinguish between muscle and fat accumulation and it does not reflect fat distribution.[136] Measures of central adiposity [e.g. waist circumference (WC) and waist-to-hip ratio (WHR)] have been shown to better reflect abdominal adiposity than BMI and have stronger associations with cardio-metabolic risk factors and outcomes.[137-140] However, for cancer, results are less clear. Central adiposity, as assessed by WC or WHR, has been associated with PM breast cancer in several studies, independent of BMI.[141-142] However, a more recent review showed that adjustment for BMI attenuated the relationship between WC or WHR and risk of PM breast cancer to the null.[143] Studies of colorectal cancer show WC and WHR are more strongly associated with cancer than BMI in men, but this has not been shown for women.[144] Studies of oesophageal,[145] endometrial[146] and pancreatic cancers[147] also suggest stronger associations with central adiposity than with BMI. For prostate cancer, several large studies have found an increased BMI to be associated with an increased risk for prostate cancer, though others have shown no association.[148] A Chinese study has shown that men in the highest quartile of WHR have a three-fold increased incidence of prostate cancer compared with men in the lowest quartile of WHR, but no association was seen for BMI.[149] Other studies show that central obesity may play a role only in advanced stages of prostate cancer.[119] However, an important caveat in all of these aforementioned studies is that including separate anthropometric measures in the same model can lead to difficulties in interpretation of results, because of the high degree of co-linearity between the anthropometric variables. To understand if central or general adiposity is driving the association with incident cancer, separate models need to be fitted and compared. This is yet to be done.

1.3.2 Hypertension and cancer

Epidemiologic evidence points to the possibility that high BP, or hypertension, is also a significant risk factor for cancer. Several prospective studies have demonstrated clearly that hypertension is a risk factor for incident cancer,[117,150-155] though only few studies have explored associations with cancer mortality and these have been inconsistent.[154,156,157] In addition, these studies are often hampered by small sample sizes and/or lack of information on important confounders, such as smoking habits and obesity.

If we assume a causal relationship between hypertension and cancer, three main hypotheses have been proposed to explain the observed associations. First, medications used in the treatment of hypertension may cause cancer by directly promoting carcinogenesis, accelerating other carcinogens or impeding defence mechanisms.[158] Some studies report that anti-hypertensive medication, in particular diuretics, may be associated with an increased cancer risk even in those who are normotensive.[159,160] The mechanisms underpinning these associations, however, are not well understood and continue to be investigated. In addition, a 2011 meta-analysis concluded that diuretics or any other single anti-hypertensive medication are not associated with an increased cancer risk, though it cannot

be ruled out that a combination of anti-hypertensive drugs may confer an increased risk for overall cancer.[161] Second, there may be a common mechanism linking BP regulation and cancer development, independent of anti-hypertensive treatment.[154] For example, it has been speculated that the association between hypertension and cancer may be mediated via abnormalities in vascular smooth muscle cells.[162] These abnormalities result in increased apoptosis and proliferation as well as a shortened cell cycle and lead to enhanced cell turnover. This increased cell turnover becomes the target of degeneration and of neoplasia (cancer).[162,163] Third, it is also possible that cancer itself may lead to hypertension.[117] Earlier work by Rees suggests that tumour cells secrete hormones that lead to BP elevation.[164] This is supported by elevated adrenocortical hormones found in the blood of patients with a variety of cancers.[117] Buck et al. also found an elevated cancer incidence among new hypertensives, consistent with the hypothesis that certain sites of cancer are capable of producing hormones that raise BP.[117] Alternatively, the association between hypertension and cancer may be confounded by factors such as central obesity, which might not have accurately been adjusted for in previous studies.[153]

Most previous studies have recognised that it is difficult to disentangle the separate effects of hypertension and anti-hypertensive treatment as they are highly correlated. Other key deficiencies in previous work include small sample sizes and a lack of information on key confounding factors for hypertension and cancer.

Disentangling these associations has important clinical implications for the pharmacological management of people with hypertension. If anti-hypertensive medication is indeed found to be causally linked with cancer, a review of current guidelines for the use of anti-hypertensive medication, even in light of their known CVD benefits, may be warranted.

1.4 Thesis Aims

Against this backdrop of evidence and current knowledge gaps, this thesis specifically aims to address the following:

i. To examine secular trends in excess all-cause and cause-specific mortality in people with type 1 and type 2 diabetes compared with the general population, overall and by age group

ii. To quantify associations of type 1 and type 2 diabetes with cancer

iii. To quantify associations of the MetS and individual components of the MetS with cancer

To adequately address these questions, prospective, population-based studies with high quality databases and long follow-up time are needed. Understanding the epidemiologic links between metabolic disease and cancer and determining the mechanisms through which these conditions are linked is a research priority in order to prevent and treat cancers that are more likely to occur in those with diabetes and/or the MetS.

References

1. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. *The Lancet Diabetes and Endocrinology.* 2014;2(1):56-64.

2. International Diabetes Federation. *Diabetes Atlas Seventh Edition*. International Diabetes Federation. 2015.

3. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* 2009;120(16):1640-1645.

4. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. http://www.idf.org/metabolic-syndrome. Accessed 28th October 2015.

5. World Health Organization. *The global burden of disease: 2004 update*. WHO; 2008.

6. Report of a WHO Study Group on Diabetes Mellitus. Geneva: World Health Organization. 1985.

7. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice.* 2010;87(1):4-14.

8. Magliano DJ, Zimmet PZ, Shaw JE. Classification of diabetes mellitus and other categories of glucose intolerance. In: DeFronzo R, Ferrannini E, Alberti KG, Zimmet PZ, eds. *International Textbook of Diabetes Mellites*. 4th ed. Chichester, West Sussex, UK: John Wiley & Sons Ltd; 2015:3-16.

9. Zhang H, Xia W, Yu Q, et al. Increasing incidence of type 1 diabetes in children aged 0-14 years in Harbin, China (1990-2000). *Primary Care Diabetes.* 2008;2(3):121-126.

10. Haynes A, Bulsara MK, Bower C, Jones TW, Davis EA. Cyclical variation in the incidence of childhood type 1 diabetes in Western Australia (1985-2010). *Diabetes Care.* 2012;35(11):2300-2302.

11. Harjutsalo V, Sjoberg L, Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. *Lancet.* 2008;371(9626):1777-1782.

12. Kostraba JN, Gay EC, Cai Y, et al. Incidence of insulin-dependent diabetes mellitus in Colorado. *Epidemiology.* 1992;3(3):232-238.

13. Mathieu C, Laureys J, Sobis H, Vandeputte M, Waer M, Bouillon R. 1,25-Dihydroxyvitamin D3 prevents insulitis in NOD mice. *Diabetes.* 1992;41(11):1491-1495.

14. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet.* 2001;358(9292):1500-1503.

15. Simpson M, Brady H, Yin X, et al. No association of vitamin D intake or 25-hydroxyvitamin D levels in childhood with risk of islet autoimmunity and type 1 diabetes: the Diabetes Autoimmunity Study in the Young (DAISY). *Diabetologia.* 2011;54(11):2779-2788.

16. Steck A, Rewers M. Epidemiology and risk factors for type 1 diabetes mellitus. In: DeFronzo RA, Ferrannini E, Alberti KG, Zimmet PZ, eds. *International Textbook of Diabetes Mellitus*. 4th ed. Chichester, West Sussex: John Wiley & Sons Ltd; 2015:17-28.

17. Conrad B, Weidmann E, Trucco G, et al. Evidence for superantigen involvement in insulin-dependent diabetes mellitus aetiology. *Nature.* 1994;371(6495):351-355.

18. Coppieters KT, Boettler T, von Herrath M. Virus infections in type 1 diabetes. *Cold Spring Harbor Perspectives in Medicine.* 2012;2(1):a007682.

19. Redondo MJ, Jeffrey J, Fain PR, Eisenbarth GS, Orban T. Concordance for islet autoimmunity among monozygotic twins. *New England Journal Medicine.* 2008;359(26):2849-2850.

20. Rewers M, Bugawan TL, Norris JM, et al. Newborn screening for HLA markers associated with IDDM: diabetes autoimmunity study in the young (DAISY). *Diabetologia.* 1996;39(7):807-812.

21. Patterson CC, Gyurus E, Rosenbauer J, et al. Trends in childhood type 1 diabetes incidence in Europe during 1989-2008: evidence of non-uniformity over time in rates of increase. *Diabetologia.* 2012;55(8):2142-2147.

22. Diabetes Epidemiology Research International Group. Secular trends in incidence of childhood IDDM in 10 countries. *Diabetes.* 1990;39(7):858-864.

23. EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. *Lancet.* 2000;355(9207):873-876.

24. Gale EA. The rise of childhood type 1 diabetes in the 20th century. *Diabetes.* 2002;51(12):3353-3361.

25. Rosenbloom AL, Joe JR, Young RS, Winter WE. Emerging epidemic of type 2 diabetes in youth. *Diabetes Care.* 1999;22(2):345-354.

26. Flores-Le Roux JA, Comin J, Pedro-Botet J, et al. Seven-year mortality in heart failure patients with undiagnosed diabetes: an observational study. *Cardiovascular Diabetology.* 2011;10:39.

27. Plantinga LC, Crews DC, Coresh J, et al. Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. *Clinical Journal of the American Society of Nephrology.* 2010;5(4):673-682.

28. Spijkerman AM, Dekker JM, Nijpels G, et al. Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general practice: the hoorn screening study. *Diabetes Care.* 2003;26(9):2604-2608.

29. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *The Lancet Diabetes and Endocrinology*. 2015; 3(11):866–875

30. Haffner SM. Epidemiology of type 2 diabetes: risk factors. *Diabetes Care.* 1998;21 Suppl 3:C3-6.

31. Knowler WC, Saad MF, Pettitt DJ, Nelson RG, Bennett PH. Determinants of diabetes mellitus in the Pima Indians. *Diabetes Care.* 1993;16(1):216-227.

32. O'Dea K. Obesity and diabetes in "the land of milk and honey". *Diabetes/Metabolism Research and Reviews*. 1992;8(4):373-388.

33. Felber JP, Golay A. Pathways from obesity to diabetes. *International Journal of Obesity and Related Metabolic Disorders*. 2002;26 Suppl 2:S39-45.

34. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. *The Journal of the American Medical Association*. 2015;314(10):1021-1029.

35. Zimmet PZ, King H, Taylor R, et al. The high prevalence of diabetes mellitus, impaired glucose tolerance and diabetic retinopathy in Nauru-the 1982 survey. *Diabetes Research*. 1984;1(1):13-18.

36. King H, Finch C, Collins A, et al. Glucose tolerance in Papua New Guinea: ethnic differences, association with environmental and behavioural factors and the possible emergence of glucose intolerance in a highland community. *The Medical Journal of Australia*. 1989;151(4):204-210.

37. Collins VR, Dowse GK, Toelupe PM, et al. Increasing prevalence of NIDDM in the Pacific island population of Western Samoa over a 13-year period. *Diabetes Care*. 1994;17(4):288-296.

38. Australian Bureau of Statistics. *Australian health survey: First results, 2011–12. ABS cat. no. 4364.0.55.001*. Canberra: Australian Bureau of Statistics;2012.

39. Qiao Q, Williams DE, Imperatore G, Narayan KMV, Tuomilehto J. Epidemiology and geography of type 2 diabetes mellitus. In: DeFronzo R, Ferrannini E, Alberti KG, Zimmet PZ, eds. *International Textbook of Diabetes Mellitus*. 4th ed. Chichester, West Sussex: John Wiley & Sons Ltd; 2015:29-51.

40. InterAct Consortium, Scott RA, Langenberg C, et al. The link between family history and risk of type 2 diabetes is not explained by anthropometric, lifestyle or genetic risk factors: the EPIC-InterAct study. *Diabetologia*. 2013;56(1):60-69.

41. Facchini FS, Hollenbeck CB, Jeppesen J, Chen YD, Reaven GM. Insulin resistance and cigarette smoking. *Lancet*. 1992;339(8802):1128-1130.

42. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS, Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *New England Journal of Medicine*. 1991;325(3):147-152.

43. Hu FB, van Dam RM, Liu S. Diet and risk of Type II diabetes: the role of types of fat and carbohydrate. *Diabetologia*. 2001;44(7):805-817.

44. Mozaffarian D, Kamineni A, Carnethon M, Djousse L, Mukamal KJ, Siscovick D. Lifestyle risk factors and new-onset diabetes mellitus in older adults: the cardiovascular health study. *Archives of Internal Medicine*. 2009;169(8):798-807.

45. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;374(9702):1677-1686.

46. Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet*. 2008;371(9626):1783-1789

47. Lindstrom J, Ilanne-Parikka P, Peltonen M, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet*. 2006;368(9548):1673-1679.

48. Forbes JM, Harcourt B. Complications of diabetes: general and microvascular. In: DeFronzo R, Ferrannini E, Alberti KG, Zimmet PZ, eds. *International Textbook of Diabetes Mellitus*. 4th ed. Chichester, West Sussex, UK: John Wiley & Sons Ltd.; 2015:875-888.

49. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine* 1993;329(14):977-986.

50. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *The Journal of the American Medical Association*. 2002;287 2570-2581.

51. Almdal T, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Archives of Internal Medicine*. 2004;164(13):1422-1426.

52. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Similarity of the impact of type 1 and type 2 diabetes on cardiovascular mortality in middle-aged subjects. *Diabetes Care*. 2008;31:714-719.

53. Laing SP, Swerdlow AJ, Slater SD, et al. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia*. 2003;46(6):760-765.

54. Wilson PW. Diabetes mellitus and coronary heart disease. *American Journal of Kidney Disease*. 1998;32:S89-S100.

55. Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. *Diabetes Care*. 2003;26:917-932.

56. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *New England Journal of Medicine*. 2008;358:2560-2572.

57. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *New England Journal of Medicine*. 2008;358:2545-2559

58. Alleman S, Saner C, Zwahlen M, Christ ER, Diem P, Stettler C. Long-term cardiovascular and non-cardiovascular mortality in women and men with type 1 and type 2 diabetes mellitus: A 30-year follow-up in Switzerland. *Swiss Medical Weekly*. 2009;139(39-40):576-583.

59. Ford ES. Trends in the risk for coronary heart disease among adults with diagnosed diabetes in the US. *Diabetes Care*. 2011;34:1337-1343.

60. Gregg EW, Cheng YJ, Saydah S, et al. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006. *Diabetes Care*. 2012;35:1252-1257.

61. Kaur J. A comprehensive review on metabolic syndrome. *Cardiology Research and Practice*. 2014;2014:943162.

62. Kylin E. Studien ueber das Hypertonie-Hyperglyka¨mie-Hyperurika¨miesyndrom. *Zentralblatt fuer Innere Medizin*. 1923;44:105- 127.

63. Reaven G. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595-1607.

64. Miranda PJ, DeFronzo RA, Califf RM, Guyton JR. Metabolic syndrome: definition, pathophysiology, and mechanisms. *American Heart Journal*. 2005;149(1):33-45.

65. Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care*. 2005;28(7):1769-1778.

66. Gale EA. Should we dump the metabolic syndrome? Yes. *British Medical Journal*. 2008;336(7645):640.

67. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2005;48(9):1684-1699.

68. Woodward M, Tunstall-Pedoe H. The metabolic syndrome is not a sensible tool for predicting the risk of coronary heart disease. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2009;16(2):210-214.

69. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. *Endocrine-related Cancer*. 2009;16(4):1103-1123.

70. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care*. 2010;33(7):1674-1685.

71. Tsilidis KK, Allen NE, Appleby PN, et al. Diabetes mellitus and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *International Journal of Cancer*. 2015;136(2):372-381.

72. Johnson JA, Carstensen B, Witte D, et al. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. *Diabetologia*. 2012;55(6):1607-1618.

73. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. *Diabetes/Metabolism Research and Reviews*. 2012;28(2):109-122.

74. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *British Journal of Cancer*. 2005;92(11):2076-2083.

75. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia*. 2007;50(7):1365-1374.

76. Yoon JM, Son KY, Eom CS, Durrance D, Park SM. Pre-existing diabetes mellitus increases the risk of gastric cancer: a meta-analysis. *World Journal of Gastroenterology.* 2013;19(6):936-945.

77. Larsson SC, Wolk A. Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. *Diabetologia.* 2011;54(5):1013-1018.

78. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *Journal of the National Cancer Institute.* 2005;97(22):1679-1687.

79. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia.* 2006;49(12):2819-2823.

80. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *International Journal of Cancer.* 2007;121(4):856-862.

81. Chao C, Page JH. Type 2 diabetes mellitus and risk of non-Hodgkin lymphoma: a systematic review and meta-analysis. *American Journal of Epidemiology.* 2008;168(5):471-480.

82. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention.* 2006;15(11):2056-2062.

83. Hall GC, Roberts CM, Boulis M, Mo J, MacRae KD. Diabetes and the risk of lung cancer. *Diabetes Care.* 2005;28(3):590-594.

84. Shih SR, Chiu WY, Chang TC, Tseng CH. Diabetes and thyroid cancer risk: literature review. *Experimental Diabetes Research.* 2012;2012:578285.

85. Weiderpass E, Ye W, Vainio H, Kaaks R, Adami HO. Diabetes mellitus and ovarian cancer (Sweden). *Cancer Causes & Control.* 2002;13(8):759-764.

86. Gordon-Dseagu VLZ, Shelton N, Mindell JS. Epidemiological evidence of a relationship between Type 1 diabetes mellitus and cancer: A review of the existing literature. *International Journal of Cancer.* 2013;132:501-508.

87. Pollak M. The insulin receptor/insulin-like growth factor receptor family as a therapeutic target in oncology. *Clinical Cancer Research.* 2012;18(1):40-50.

88. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet.* 2004;363(9418):1346-1353.

89. Novosyadlyy R, Lann DE, Vijayakumar A, et al. Insulin-mediated acceleration of breast cancer development and progression in a nonobese model of type 2 diabetes. *Cancer Research.* 2010;70(2):741-751.

90. Rowlands MA, Gunnell D, Harris R, Vatten LJ, Holly JM, Martin RM. Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis. *International Journal of Cancer.* 2009;124(10):2416-2429.

91. Rinaldi S, Cleveland R, Norat T, et al. Serum levels of IGF-I, IGFBP-3 and colorectal cancer risk: results from the EPIC cohort, plus a meta-analysis of prospective studies. *International Journal of Cancer*. 2010;126(7):1702-1715.

92. Endogenous Hormones and Breast Cancer Collaborative Group, Key TJ, Appleby PN, Reeves GK, Roddam AW. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. *The Lancet Oncology*. 2010;11(6):530-542.

93. Stocks T, Rapp K, Bjorge T, et al. Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (Me-Can): analysis of six prospective cohorts. *PLoS Mmedicine*. 2009;6(12):e1000201.

94. Johnson JA, Bowker SL. Intensive glycaemic control and cancer risk in type 2 diabetes: a meta-analysis of major trials. *Diabetologia*. 2011;54(1):25-31.

95. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: AICR;2007.

96. World Cancer Research Fund/American Institute for Cancer Research. *Continuous update project report. Food, nutrition, physical activity, and the prevention of breast cancer*. World Cancer Research Fund and American Institute for Cancer Research;2010.

97. World Cancer Research Fund/American Institute for Cancer Research. *Continuous update project report. Food, nutrition, physical activity, and the prevention of colorectal cancer*. World Cancer Research Fund and American Institute for Cancer Research;2011.

98. World Cancer Research Fund/American Institute for Cancer Research. *Continuous update project report. Food, nutrition, physical activity, and the prevention of pancreatic cancer.*: World Cancer Research Fund and American Institute for Cancer Research;2012.

99. World Cancer Research Fund/American Institute for Cancer Research. *Continuous update project report. Food, nutrition, physical activity, and the prevention of endometrial cancer*. World Cancer Research Fund and American Institute for Cancer Research2013.

100. World Cancer Research Fund/American Institute for Cancer Research. *Continuous update project report. Food, nutrition, physical activity, and the prevention of ovarian cancer*. World Cancer Research Fund and American Institute for Cancer Research;2014.

101 Psaty BM, Koepsell TD, Lin D, Weiss NS, Siscovick DS, Rosendaal FR, et al. Assessment and control for confounding by indication in observational studies. *Journal of the American Geriatrics Society*. 1999; 47(6):749-754

102 Wei M, Gaskill SP, Haffner SM, Stern MP. Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans—a 7-year prospective study. *Obesity Research*. 1997; 5:16–23

103 Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T Tjonneland A, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Journal of the National Cancer Institute*. 2006; 98(13): 920-931

104 Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P, et al. Glycemic index, glycemic load, and chronic disease risk- a meta-analysis of observational studies. The *American Journal of Clinical Nutrition*. 2008; 87(3):627-637

105 Sasco AJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. *Lung Cancer*. 2004; 45(Suppl 2):S3-S9

106 Clark AM, Raine K, Pahpael D. The American Cancer Society, American Diabetes Association and American Heart Association Joint Statement on preventing cancer, cardiovascular disease and diabetes: where are the social determinants? *Diabetes Care*. 2004; 27:3024

107 Rewers M. Why do people with diabetes die too soon? *Diabetes Care*. 2008; 31:830-831

108. Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. *Diabetologia*. 2011;54(9):2263-2271.

109. Colmers IN, Majumdar SR, Yasui Y, Bowker SL, Marra CA, Johnson JA. Detection bias and overestimation of bladder cancer risk in type 2 diabetes: a matched cohort study. *Diabetes Care*. 2013;36(10):3070-3075.

110. Luke C, Price T, Karapetis C, Singhal N, Roder D. Pancreatic cancer epidemiology and survival in an Australian population. *Asian Pacific Journal of Cancer Prevention*. 2009;10(3):369-374.

111. Zhou JR, Blackburn GL, WA. W. Symposium introduction: metabolic syndrome and the onset of cancer. *The American Journal of Clinical Nutrition*. 2007;86:s817-s819.

112. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care*. 2012;35:2402-2411.

113. Pelucchi C, Serraino D, Negri E, et al. The metabolic syndrome and risk of prostate cancer in Italy. *Annals of Epidemiology*. 2011;21:835-841.

114. Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. *American Journal of Epidemiology*. 2006;164:1094-1102.

115. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population based cohort study of 5.24 million UK adults. *The Lancet*. 2014;384:755-765.

116. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *The Journal of the American Medical Association*. 2005;293(2):194-202.

117. Buck C, Donner A. Cancer incidence in hypertensives. *Cancer*. 1987;59:1386-1390.

118. Jafri H, Alsheikh-Ali AA, Karas RH. Baseline and on-treatment high-density lipoprotein cholesterol and the risk of cancer in randomized controlled trials of lipid-altering therapy. *Journal of the American College of Cardiology.* 2010;55:2846-2854.

119. Pasco JA, Nicholson GC, Brennan SL, Kotowicz MA. Prevalence of obesity and the relationship between the body mass index and body fat: cross-sectional, population-based data. *PLoS ONE.* 2012;7(1):e29580

120. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annual Review of Medicine.* 2010;61:301-316.

121. Renehan AG. Bariatric surgery, weight reduction, and cancer prevention. *The Lancet Oncology.* 2009;10(7):640-641.

122. Sjostrom L, Gummesson A, Sjostrom CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *The Lancet Oncology.* 2009;10(7):653-662.

123. Derby CA, Zilber S, Brambilla D, Morales KH, McKinlay JB. Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones: the Massachusetts Male Ageing Study. *Clinical Endocrinology.* 2006;65(1):125-131.

124. Kaaks R, Rinaldi S, Key TJ, et al. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. *Endocrine-Related Cancer.* 2005;12(4):1071-1082.

125. Kelesidis I, Kelesidis T, Mantzoros CS. Adiponectin and cancer: a systematic review. *British Journal of Cancer.* 2006;94(9):1221-1225.

126. McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer epidemiology, Biomarkers & Prevention.* 1994;3(8):687-695.

127. Giovannucci E. Insulin and colon cancer. *Cancer Causes and Control.* 1995;6(2):164-179.

128. Fischer-Posovszky P, Wabitsch M, Hochberg Z. Endocrinology of adipose tissue - an update. *Hormone and Metabolic Research.* 2007;39(5):314-321.

129. Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *Journal of the National Cancer Institute.* 2003;95(16):1218-1226.

130. Renehan AG. *Hormones, Growth Factors and Tumor Growth.* Oxford, UK: Oxford Univ. Press;2007.

131. Khan S, Shukla S, Sinha S, Meeran SM. Role of adipokines and cytokines in obesity-associated breast cancer: therapeutic targets. *Cytokine and Growth Factor Reviews.* 2013;24(6):503-513.

132. Raucci R, Rusolo F, Sharma A, Colonna G, Castello G, Costantini S. Functional and structural features of adipokine family. *Cytokine.* 2013;61(1):1-14.

133. Arner E, Forrest AR, Ehrlund A, et al. Ceruloplasmin is a novel adipokine which is overexpressed in adipose tissue of obese subjects and in obesity-associated cancer cells. *PloS One.* 2014;9:e80274.

134. Lee CH, Woo YC, Wang Y, Yeung CY, Xu A, Lam KSL. Obesity, adipokines and cancer – an update. *Clinical Endocrinology.* 2015;83(2):147-156.

135. Booth A, Mangnuson A, Fouts J, M. F. Adipose tissue, obesity and adipokines: role in cancer promotion. *Hormone Molecular Biology and Clinical Investigation.* 2015;21(1):57–74.

136. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obesity Reviews.* 2012;13(3):275-286.

137. Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0.5 could be a suitable global boundary value. *Nutrition Research Reviews.* 2010;23(2):247-269.

138. Pouliot MC, Despres JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *The American Journal of Cardiology.* 1994;73(7):460-468.

139. Rankinen T, Kim SY, Perusse L, Despres JP, Bouchard C. The prediction of abdominal visceral fat level from body composition and anthropometry: ROC analysis. *International Journal of Obesity and Related Metabolic.* 1999;23(8):801-809.

140. Huang Z, Willett WC, Colditz GA, et al. Waist circumference, waist:hip ratio, and risk of breast cancer in the Nurses' Health Study. *American Journal of Epidemiology.* 1999;150(12):1316-1324.

141. Schapira DV, Kumar NB, Lyman GH, Cox CE. Abdominal obesity and breast cancer risk. *Annals of Internal Medicine.*1990;112(3):182-186.

142. Harvie M, Hooper L, Howell AH. Central obesity and breast cancer risk: a systematic review. *Obesity Reviews.* 2003;4(3):157-173.

143. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Annals of Internal Medicine.* 1995;122(5):327-334.

144. Steffen A, Schulze MB, Pischon T, et al. Anthropometry and esophageal cancer risk in the European prospective investigation into cancer and nutrition. *Cancer Epidemiology, Biomarkers & Prevention.* 2009;18(7):2079-2089.

145. Friedenreich C, Cust A, Lahmann PH, et al. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. *Cancer Causes & Control.* .2007;18(4):399-413.

146. Aune D, Greenwood DC, Chan DS, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. *Annals of Oncology.* 2012;23(4):843-852.

147. Freedland SJ, Aronson WJ. Examining the relationship between obesity and prostate cancer. *Reviews in Urology.* 2004;6(2):73-81.

148. Hsing AW, Deng J, Sesterhenn IA, et al. Body size and prostate cancer: a population-based case-control study in China. *Cancer Epidemiology, Biomarkers & Prevention.* 2000;9(12):1335-1341.

149. Prabhat P, Tewari R, Natu SM, et al. Is central obesity, hyperinsulinemia and dyslipidemia associated with high-grade prostate cancer? A descriptive cross-sectional study. *Indian Journal of Urology.* 2010;26(4):502-506.

150. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL, Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. T*he Journal of the American Medical Association.* 2004;291(20):2441-2447.

151. Cowey S, Hardy RW. The metabolic syndrome: A high-risk state for cancer? *The American Journal of Pathology.* 2006;169(5):1505-1522.

152. Stocks T, Lukanova A, Johansson M, et al. Components of the metabolic syndrome and colorectal cancer risk; a prospective study. *International Journal of Obesity.* 2008;32(2):304-314.

153. Stocks T, Van Hemelrijck M, Manjer J, et al. Blood pressure and risk of cancer incidence and mortality in the Metabolic Syndrome and Cancer Project. *Hypertension.* 2012;59(4):802-810.

154. Rosengren A, Himmelmann A, Wilhelmsen L, Branehog I, Wedel H. Hypertension and long-term cancer incidence and mortality among Swedish men. *Journal of Hypertension.* 1998;16(7):933-940.

155. Goon PK, Stonelake PS, Lip GY. Hypertension, anti-hypertensive therapy and neoplasia. *Current Pharmaceutical Design.* 2007;13(25):2539-2544.

156. Grossman E, Messerli FH, Boyko V, Goldbourt U. Is there an association between hypertension and cancer mortality? *The American Journal of Medicine.* 2002;112(6):479-486.

157. Dyer AR, Stamler J, Berkson DM, Lindberg HA, Stevens E. High blood-pressure: a risk factor for cancer mortality? *Lancet.* 1975;1(7915):1051-1056.

158. Grossman E, Messerli FH, Goldbourt U. Antihypertensive therapy and the risk of malignancies. *European Heart Journal.* 2001;22(15):1343-1352.

159. Corrao G, Scotti L, Bagnardi V, Sega R. Hypertension, antihypertensive therapy and renal-cell cancer: a meta-analysis. *Current Drug Safety.* 2007;2(2):125-133.

160. Schmieder RE, Delles C, Messerli FH. Diuretic therapy and the risk for renal cell carcinoma. *Journal of Nephrology.* 2000;13(5):343-346.

161. Bangalore S, Kumar S, Kjeldsen SE, et al. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. *Lancet Oncology.* 2011;12(1):65-82.

162. Hamet P. Cancer and hypertension: a potential for crosstalk? *Journal of Hypertension.* 1997;15(12 Pt 2):1573-1577.

163. Lindgren A, Pukkala E, Nissinen A, Tuomilehto J. Blood pressure, smoking, and the incidence of lung cancer in hypertensive men in North Karelia, Finland. *American Journal of Epidemiology.* Sep 1 2003;158(5):442-447.

164. Rees LH. The biosynthesis of hormones by nonendocrine tumours. *Journal of Endocrinology.* 1975;67:143-175.

CHAPTER 2

Data Sources

Publications included in this thesis pertain to results derived from analyses conducted using four national data sources: the *National Diabetes Service Scheme* (NDSS); the *Australian and New Zealand Diabetes and Cancer Collaboration* (ANZDCC); the *National Death Index* (NDI); and the *Australian Cancer Database* (ACD). The NDSS is a large-scale administrative database of Australians with diagnosed diabetes and the ANZDCC is a large pooled cohort comprised of 18 population-based cohort studies within Australia and New Zealand (ANZ). Both the NDSS and ANZDCC cohorts were linked to the ACD and the NDI to obtain incident cancer and mortality outcomes, respectively. One NZ study included in the ANZDCC was linked to the respective NZ cancer and mortality registries but will not be discussed in detail. All data received by the Clinical Diabetes and Epidemiology unit at the Baker IDI Heart and Diabetes Institute was de-identified. A summary of these data sources is provided below.

2.1 The National Diabetes Service Scheme

The NDSS is an Australian government initiative established in 1987 and administered by Diabetes Australia. The NDSS delivers education and information services to people with diabetes. It also provides a range of diabetes products, such as glucose testing strips and insulin syringes, at a subsidised cost.[1] Registration is free and open to all Australians with diagnosed diabetes. Registration onto the NDSS, including specification of diabetes type, must be certified by a registered medical practitioner, or by a credentialed diabetes educator. NDSS registrants include those with diagnosed type 1, type 2, gestational diabetes, or diabetes caused by a genetic defect, pancreatic disease, hormonal abnormality or exposure to certain drugs and chemicals. Diagnoses of pre-diabetes or impaired glucose tolerance are not included on the registry.[1]

For the studies outlined in this thesis, over one million individuals with a diagnosis of type 1 or type 2 diabetes registered on the NDSS between 1997 and 2011 were included. However, due to migration from the terms insulin (IDDM) and non-insulin dependent diabetes (NDDM) to type 1 or type 2 during this time period, there is some misclassification of diabetes type. Therefore, for this thesis, type 1 diabetes status was assigned to registrants who were recorded as type 1 on the NDSS registry, were diagnosed <45 years of age and were taking insulin. Registration date was used as a proxy for diagnosis date as a large proportion of registrants (54.4% type 1 and 32.8% type 2) were missing date of diagnosis, many of whom registered in the early years of the operation of the NDSS and had had diabetes for a number of years. We chose 45 years as the cut-off to minimise the number of people with type 1 diabetes that we would miss, without misclassifying significant numbers of people with type 2 as type 1.[2] Additionally, registrants who were recorded as type 2 on the registry, were diagnosed before the age of 30 and taking insulin within one year of diagnosis date were reclassified as type 1 diabetes. All others were classified as type 2 diabetes.

There are several inherent strengths and limitations in using administrative databases such as the NDSS for research purposes. These have been discussed briefly in Chapters 3.1, 3.2, 4 and in detail in Chapter 7.2 *Strengths and Limitations*.

2.2 The Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC)

The ANZDCC is a pooled cohort comprised of all longitudinal cohorts in Australia and New Zealand (ANZ) from 1983 onwards with information on diabetes, hypertension, anthropometry and the metabolic syndrome (MetS) and with a sample size ≥1000. This pooled cohort is the largest study to ever examine the relationship between diabetes, hypertension, anthropometry, the MetS and cancer with individual-level data. It includes 153,025 men and women from a population-based sample of ANZ adults.

The purpose of the ANZDCC, the study sample and the strengths and weaknesses of this pooled cohort have been detailed in the following publication, included at the end of this chapter:

Harding JL, Shaw JE, Koshkina V, Magliano DJ. Cohort profile: The Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC). *Australasian Epidemiologist* 2014; 21(2):51-7

Additional discussion on the key strengths and limitations of this data source has also been provided in Chapters 5, 6.1, 6.2 and in detail in Chapter 7.2 *Strengths and Limitations*.

2.3 National Death Index

The NDI is a database, housed at the Australian Institute of Health and Welfare (AIHW), which contains records of all deaths occurring in Australia since 1980. The data is obtained from the Registrars of Births, Deaths and Marriages in each State and Territory.

The NDI database comprises the following variables for each deceased person: name, date of birth, age at death, sex, date of death, State/Territory of death registration. Cause of death information is coded according to the International Classification of Disease coding 10th Revision (ICD-10) and includes the underlying cause of death (the disease or injury that initiated the events resulting in death) and all other contributory causes of death specified according to whether they appear in Part I (events leading to final death event with Part IA referring to the final disease or condition resulting in death) or Part II (all other conditions contributing to death but not resulting in the underlying cause given in Part I) of the death certificate.

2.4 Australian Cancer Database

The ACD, also housed at AIHW, is a data collection of all primary, malignant cancers diagnosed in Australia since 1982. It is a statutory requirement to notify the registry of all cases of malignant neoplasms. Only the first occurrence of a cancer is included; recurrences and metastases are not included. Tumours diagnosed as benign, of borderline malignancy or *in situ* are also not included. In addition, basal cell carcinomas and squamous cell carcinomas of the skin are not included because they are not notifiable diseases.

2.5 Data Linkage

The NDSS and Australian participants of the ANZDCC cohort were linked to the NDI and ACD databases. This data was linked from 1997 and 1983 for the NDSS and ANZDCC, respectively, up until 2011. This linkage was conducted by AIHW using the general framework of Fellegi and Sunter.[3] Linkage of the Fremantle Diabetes Study (FDS), a cohort of people with diabetes included in the ANZDCC cohort, was linked by the Western Australian Data linkage unit using similar methodology. First name, second name, third name, sex and date of birth were used to conduct the linkage.

The record linkage methodology assigns each compared pair of records a record pair comparison weight. For results derived from NDSS data, we set a match link rate of 98.1% (true matches/correct links) with link accuracy of 98.2% (1.8% expected to be false positive links). For results derived from ANZDCC data, we set a match link rate of 97.70% with link accuracy of 97.92% (2.08% expected to be false positive links).[4] NZ participants of the ANZDCC cohort, those from the Fletcher Challenge Study, were linked to the NZ Cancer Registry and mortality database using National Health Index numbers, unique identifiers assigned to every person who uses health and disability support services in New Zealand.

References

1. Diabetes Australia. The National Diabetes Service Scheme. 2015; https://www.ndss.com.au/ Accessed Saturday 28th August, 2015.
2. Kenny SJ, Aubert RE, LS. G. *Prevalence and incidence of non-insulin-dependent diabetes*. 2nd ed. Washington, DC, U.S. Govt. Printing Office 1995.
3. Fellegi IP, Sunter AB. A Theory for Record Linkage. *Journal of the American Statistical Association*. 1969;40:1183-1210.
4. Blakely T, Salmond C. Probabilistic record linkage and a method to calculate the positive predictive value. *International Journal of Epidemiology*. 2002;31:1246-1252.

Declaration for Thesis – Chapter 2

Harding JL, Shaw JE, Koshkina V, Magliano DJ. Cohort profile: The Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC). *Australasian Epidemiologist* 2014; 21(2):51-7

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

Nature of contribution	**Extent of contribution**
Acquisition of data, data management, analysis and interpretation of data, conceptualisation and writing of manuscript, critical revision, corresponding author	80%

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

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Jonathan Shaw	Conceptualisation, critical revision, approval of final draft for publication	
Vira Koshkina	Data management, approval of final draft for publication	
Dianna Magliano	Conceptualisation, data acquisition, critical revision, approval of final draft for publication	

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

Candidate's Signature		Date: 31/03/2016
Main Supervisor's Signature	[redacted]	Date: 31/03/2016

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

Current Work in Australasian Epidemiology

Cohort profile: The Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC)

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Abstract

There is now a wealth of data supporting a link between diabetes, and obesity, with cancer. While the data strongly suggests an association, there is less clarity about site-specific cancers. This is often due to limitations in sample size. Additionally, many studies do not consider important confounding variables such as central adiposity, smoking, and physical activity. In 2010, we initiated the Australian New Zealand Diabetes and Cancer Collaboration (ANZDCC) in order to create a large pooled cohort to investigate factors of diabetes, pre-diabetes, obesity, metabolic syndrome, and hypertension, with cancer risk. We included all longitudinal cohorts in Australia and New Zealand from 1983 onwards with information on diabetes, hypertension, anthropometry, and with a sample size ≥1000. These baseline data (n=153,025) were linked to the national cancer and mortality registries to obtain longitudinal follow-up of cancer and mortality outcomes for all participants in the pooled cohort. This study will provide insights into the potential mechanisms of cancer; allow a better and fuller assessment of the likely burden and consequences of diabetes and obesity; and in the Australia/New Zealand context, inform clinical practice about the appropriate care of patients with diabetes and obesity.

How did the study come about?

In 2013, an estimated 382 million people had diabetes worldwide, and this number is expected to increase to 592 million by 2030 as a result of population growth, unhealthy diets and sedentary lifestyles.[1] In Australia, approximately one million people were living with diabetes in 2011–12[2], with an annual cost of approximately $6 billion.[3] For obesity, the figures are equally alarming: in 2011–12, the prevalence of overweight and obesity for adults aged 18 and over was 62.8%[2], with the total direct cost estimated at $21 billion (2005).[4] Both diabetes and obesity are associated with significant morbidity and mortality from several chronic illnesses, including cardiovascular diseases (CVD), eye disease, neuropathy, lower limb amputations, and chronic kidney disease. There is also now a large body of epidemiological evidence to show that diabetes[5], and obesity[6], along with the metabolic syndrome (MetS)[7] and hypertension[8], are associated with cancer.

There is a wealth of data supporting a link of diabetes with cancer, especially in westernised populations. This evidence is derived from meta-analyses and pooling projects from various part of the world. While the data strongly suggests a link, there is less clarity around particular site-specific cancer. The key deficiencies are that not all studies include an assessment of important confounding variables such as physical activity, waist circumference (WC) or hip circumference (HC), which are key confounding factors for diabetes, pre-diabetes, and cancer. To date there are few data on diabetes, pre-diabetes, obesity, MetS, hypertension, and cancer in Australia and New Zealand.

In 2010, we initiated the Australian New Zealand Diabetes and Cancer Collaboration (ANZDCC) in order to create a large pooled cohort to investigate factors of diabetes, obesity, MetS, and hypertension, with cancer risk. We included all longitudinal cohorts from 1983 onwards with information on diabetes, hypertension, anthropometry, and with a sample size ≥1000, in Australia/New Zealand. These baseline data were linked to the national cancer and mortality registries to obtain longitudinal follow-up of cancer and mortality outcomes for all participants in the pooled cohort.

The coordinating centre for this project is at the Department of Clinical Diabetes and Epidemiology, Baker IDI Heart and Diabetes Institute, Melbourne, Australia. The ANZDCC project was approved by the Alfred Health Human Research Ethics Committee (HREC), the Australian Institute for Health and Welfare (AIHW) HREC, and all state and territory cancer registry HRECs.

The purpose of ANZDCC

To determine whether diabetes, pre-diabetes, obesity, MetS, and/or hypertension are associated with an increased risk of all cause and site specific cancer in Australia/New Zealand populations, after adjusting for potential confounding factors.

Figure 1. Map with location of sub-cohorts included in the ANZDCC

Who is in the sample?

The distribution of studies across Australia/New Zealand is shown in *Figure 1*. The individual studies and their recruitment methods are detailed below. In total, the pooled ANZDCC includes 153,025 participants across Australia and New Zealand. All participants self-completed questionnaires and underwent clinical assessment, including measured anthropometry (excluding one study which was self-reported). The questionnaires included information pertaining to lifestyle factors and various topics of specific interest for each study. Available data for key variables differed by study (*Table 1*). Where required, variables were harmonised to reflect consistent categories across studies. Diet intake was also collected, but only in a subset of the studies.

Australian Longitudinal Study of Ageing (ALSA)

ALSA is a longitudinal study aimed at 'identifying factors that contribute to, and predict, the health and social well-being of older Australians'.[9] Participants aged 70 years and over were randomly selected from the State Electoral Database, which includes all residents over 18-years-old, in the Adelaide, South Australia Statistical Division. Spouses (aged 65 and over) or co-residents (aged 70 and over) were also invited to participate.[9] A total sample of 2,705 individuals drawn from the electoral roll (registration to vote is compulsory for adults in Australia) were eligible for inclusion in the study, of which 1,477 agreed

Table 1. Baseline observations and data coverage of ANZDCC cohorts

Variable	ALSA	ALSWH	ANBP2	AUSDIAB	BMES	CUDS	DUBBO	FLETCHER	FDS
Year of baseline examination	1992–93	1996	1995–98	1999–2000	1992–93	2001–02	1988–89	1992–93	1993–96
Men	1,056	0	2,910	5034	2,101	635	1,233	7,581	708
Women	1,031	26,096	3,084	6171	2,719	819	1,572	2,944	715
All	2,087	26,096	5994	11,205	4,820	1,454	2,805	10,525	1423
Age range	65 – 103	43 – 76	65 – 85	25 – 95	49 – 97	25 – 96	60 – 98	16 – 18	11 – 97
Age (mean±SD)	78.7 ± 6.7	59.4 ± 12.6	72.8±4.9	51.5 ± 14.5	64.9 ± 9.7	52.9 ± 15.6	69.2 ± 7.0	43.6 ± 15.1	62.1 ± 13.3
Ascertainment of DM status	SR & TRT	SR	SR & TRT	FPG, HbA1C, SR & TRT	FPG, SR & TRT	FPG, SR & TRT	SR & FPG	SR & TRT	SR, FPG & HbA1C
Diabetes (n (%))	182 (8.8)	1,509 (5.8)	292 (4.9)	675 (6.0)	327 (7.6)	106 (7.3)	172 (6.2)	223 (2.1)	1,423 (100)
Body Mass Index (mean±SD)	26.0±4.1	25.6±4.8	27.1±4.2	27.0±5.0	26.7±4.8	27.9±5.2	26.0±4.3	26.4±4.2	29.3±5.5
Waist circumference (mean±SD)									
Men	96.8±9.8	N/A	100±10.1	97.6±11.5	No data	101±11.6	No data	No data	98.9±13.2
Women	86.6±11.4	89.7±13.9	89.4±11.3	85.5±13.5	No data	89.5±13.9	No data	No data	98.8±13.2
Hip circumference (mean±SD)									
Men	102.6±7.5	N/A	105.3±7.8	104.3±7.7	No data	106.5±8.0	No data	No data	109.3±11.6
Women	103.0±10.3	No data	105.6±10.4	105.3±11.6	No data	107.8±12.5	No data	No data	109.2±11.6
Current smoker (%)	7.5	13.2	7.1	15.8	14.9	17.9	15.4	23.6	16.0
Physical activity (% sufficient)	2.1	41.8	47.5	52.1	36.4	2.9	48.6	72.9	No data
Blood Pressure (mean±SD)									
Systolic	148.8±23.4	No data	157.7±18.1	129.4±18.9	144.6±21.4	131.8±22.4	147.5±24.3	12.5.9±16.9	149±24.0
Diastolic	76.5±12.4	No data	85.8±10.0	70.1±11.8	83.8±10.5	72.2±10.1	79.1±12.1	76.8±11.0	80.0±11.2
Cholesterol (mean±SD)									
HDL	1.3±0.4	No data	1.4±0.5	1.4±0.4	1.4±0.4	1.4±0.4	1.3±0.4	No data	1.1±0.3
LDL	4.3±1.1	No data	No data	4.0±1.0	4.24.0±1.0	3.6±0.9	4.9±1.2	No data	3.4±0.9
Triglycerides (mean±SD)	1.6±1.00	No data	No data	1.6±1.1	1.7±1.1	1.5±1.1	1.8±1.2	No data	2.3±2.6

SR: self-report; TRT: diabetes treatment; FPG: fasting plasma glucose; HbA1C: glycated haemoglobin A1C; ALSA: Australian Longitudinal Study of Aging; ALSHW: Australian Longitudinal Study on Women's Health; ANBP2: The Second Australian National Blood Pressure Study; AusDiab: Australian Diabetes, Obesity and Lifestyle Study; BMES: Blue Mountains Eye Study; CUDS: Crossroads Undiagnosed Disease Study; DUBBO: Dubbo Study of the Elderly; Fletcher: Fletcher Challenge – University of Auckland Heart and Health Study; FDS: Fremantle Diabetes Study

to participate. A further 879 spouses were identified as eligible for inclusion in the study, of whom 597 were recruited. A total of 2,087 persons participated giving response rates of 55% for primary subjects, and 68% for identified spouses and other household members.[9]

Australian Longitudinal Study on Women's Health (ALSWH)

This is a longitudinal study of factors that affect the health and well-being of more than 40,000 women across Australia.[10] Three national cohorts of women born in 1973–78 (young); 1946–51 (middle-age); and 1921–26 (older) were randomly selected in 1996 from the Medicare health insurance database, with overrepresentation of women living in rural and remote areas. After adjustment for those known to be non-contactable or ineligible, response rates were 41.0%, 53.5%, and 35.5% for the young, mid-age, and older cohorts respectively.[11] For this study, we only included the middle-age and older cohorts (n=26,147), as it is unlikely that the young cohort would have had enough follow-up time for the development of cancer.

The Second Australian National Blood Pressure Study (ANBP2)

The ANBP2 was a comparative outcome trial, using a prospective, randomised, open-label design, with blinded assessments of end points.[12] The primary objective was to determine, in hypertensive subjects aged 65–84 years, whether there is any difference in cardiovascular events (non-fatal and fatal) over five years between two treatment regimens: angiotensin-converting enzyme (ACE) inhibitor and diuretic treatment. Specific inclusion and exclusion criteria are listed elsewhere.[12] The study was conducted at 1,594 family medical practices throughout Australia. A total of 54,288 subjects presented for the initial screening visit. Of these, 48,205 were either ineligible for the study, or did not agree to participate. 6,083 subjects (95% of whom were white) were subsequently randomly assigned over a three-year period to the ACE-inhibitor group (3,044 subjects) or the diuretic group (3,039 subjects).[12]

Table 1 continued. Baseline observations and data coverage of ANZDCC cohorts

Variable	GOS	HIMS	LIPID	MCCS	NEWCASTLE	NWAHS	PATH	RFP	Total
Year of baseline examination	1993–97; 2001–06	1996–98	1990–92	1991–94	1983; 1988–89; 1994	1999–2000; 2002–03	1999–2002	1989 & 1994	1983–2006
Men	1,534	12,119	7,498	17,045	2,954	1924	3360	1902	69,594
Women	1,721	0	1,516	24,469	2,980	2110	3558	1926	83,431
All	3,255	12,119	9,014	41,514	5,934	4034	6918	3828	153,025
Age range	19 – 96	65 – 80	31 – 75	27 – 76	21 – 77	17 – 90	20 – 66	20 – 70	11 – 104
Age (mean±SD)	52.9 ± 20.4	71.6 ± 4.3	61.5 ± 8.4	55.3 ± 8.7	51.7 ± 10.5	50.2 ± 16.4	43.9 ± 16.1	46.0 ± 13.6	57.1 ± 14.1
Ascertainment of DM status	SR, FPG & TRT	SR & TRT	SR, FPG & TRT	SR, FPG & TRT	SR	SR & FPG	SR & TRT	SR	SR, FPG, TRT & HbA1C
Diabetes (n (%))	169 (5.2)	1,444 (11.9)	820 (9.1)	2,335 (5.6)	122 (3.5)	206 (5.1)	245 (3.6)	129 (3.4)	10,379 (6.9)
Body Mass Index (mean±SD)	26.8±5.0	26.9±3.7	26.8±3.8	26.9±4.4	26.7±4.5	27.8±5.5	25.7±5.1	27.5±5.2	26.6±4.6
Waist circumference (mean±SD)									
Men	97.2±11.4	100.6±10.4	No data	93.5±10.0	No data	99.9±13.0	No data	92.9±10.9	97.0±11.1
Women	84.5±12.9	N/A	No data	80.0±11.8	No data	89.8±14.1	No data	79.5±11.6	84.0±13.4
Hip circumference (mean±SD)									
Men	100.6±8.9	103.2±7.2	No data	101.1±7.1	104.0±7.4	105.7±9.3	No data	102.6±7.0	102.9±7.7
Women	105.0±11.7	N/A	No data	101.6±10.0	105.0±11.5	107.2±12.9	No data	103.3±10.1	103.3±10.9
Current smoker (%)	16.0	11.0	9.6	11.3	23.0	22.2	19.3	21.0	14.2
Physical activity (% sufficient)	No data	21.8	No data	26.4	No data	35.2	85.2	58.4	38.4
Blood Pressure (mean±SD)									
Systolic	129.2±21.1	157.1 ±21.2	134.1±19.1	137.0±19.2	132.4±19.7	127.8±18.5	128.8±19.1	129.3±21.3	137.4±21.9
Diastolic	78.2±12.4	89.9±11.7	80.5±10.8	76.3±11.7	80.2±11.0	80.6±10.2	79.3±10.8	78.2±12.1	78.8±12.4
Cholesterol (mean±SD)									
HDL	No data	No data	1.0±0.2	1.4±0.4	1.3±0.4	1.4±0.4	No data	1.3±0.4	1.3±0.4
LDL	No data	No data	4.4±0.8	4.0±1.1	No data	3.6±1.0	No data	4.0±1.1	4.1±1.0
Triglycerides (mean±SD)	No data	No data	1.8±0.9	1.3±0.8	No data	1.5±1.0	No data	1.3±1.0	1.6±1.1

SR: self-report; TRT: diabetes treatment; FPG: fasting plasma glucose; HbA1C: glycated haemoglobin A1C; #: data could not be harmonised; GOS: Geelong Osteoporosis Study; HIMS: Health in Men Study; LIPID: Long-Term Intervention with Pravastatin in Ischaemic Disease; MCCS: Melbourne Collaborative Cohort Study; NEWCASTLE: Newcastle MONICA; NWAHS: North West Adelaide Health Study; PATH: Personality and Total Health Through Life Project; RFP: Perth Risk Factor Prevalence Cohort Studies

Australian Diabetes, Obesity, and Lifestyle Study (AusDiab)

The AusDiab study is a population-based cross-sectional survey of national diabetes prevalence and associated risk factors in people aged ≥25 years across Australia.[13] A stratified cluster sample method was used involving seven strata (six states and the Northern Territory), and clusters based on census collector districts (the smallest geographic unit defined by the Australian Bureau of Statistics, with an average of 225 dwellings in each). In total, 25,984 households across 42 clusters were approached, of which 17,129 households were confirmed as containing at least one eligible participant and 20,347 eligible participants were interviewed. Of those who participated in the household interview, 11,247 (response rate: 55.3%) additionally took part in the biomedical examination.[13]

Blue Mountains Eye Study (BMES)

BMES is a population-based study of vision designed to assess the prevalence of visual impairment, and blindness, and their causes and risk factors, in a representative urban, Australian population of men and women aged 50 years and older.[14] Two urban postcode areas in the Blue Mountains area (west of Sydney, in New South Wales) were selected as the target population. This region has a slightly older age distribution than that for Australia, and is geographically well-defined, enhancing potential for community support and publicity for the study. Of 4,433 eligible residents, 3,654 (82.4%) participated in the examinations, of which 97% were white.[14] After five years, a repeat door-to-door census of the same area conducted in 1999 identified 1,378 additional eligible permanent residents who had moved into the area or were now aged 50 years or older. Of these, 1,174 (85.2%) were examined in 1999-2000.[15] In total, the BMES sample included in the ANZDCC cohort is 4,828.

Crossroads Undiagnosed Disease Study (CUDS)

CUDS was established to 'compare the prevalence of various chronic diseases in rural Victoria, where access to general practice is known to be low'.[16] Households were randomly selected from residential address lists in one regional centre (Shepparton-Mooroopna) and six surrounding 'Shire capitals' in the Goulburn Valley. Households were visited between June 2001 and March 2003 until a response was received(16). All residents' aged ≥25 years who completed a household census were invited to participate in the CUDS with an initial response rate of 70.3%. Among these, 61.3% (n=1,454) attended a clinic to collect biomedical measurements.[16]

Dubbo Study of the Elderly (DUBBO)

Given Australia's ageing population, DUBBO was established to 'identify predictors of mortality, hospitalisation, and placement in long-term care facilities, and to study risk factors for chronic disease and disability in the elderly'.[17] Dubbo, in New South Wales, was chosen as the study site because it has a relatively small, stable population which is relatively younger than Australia as a whole, with the proportion of adults older than 60 years lower than the national average. Identification of non-institutionalised subjects 60 years and over (born before 1 January 1930) was via confidential examinations of records from 21 general practitioners in the Dubbo area. 3,860 eligible subjects were identified, of whom 2,805 agreed to participate, giving a response rate of 72.7%.[17]

Fletcher Challenge – University of Auckland Heart and Health Study (FLETCHER)

FLETCHER is a prospective observational study designed to 'determine the relationships of socio-demographic factors, psychological factors, and several factors measured in blood, with the risk of coronary heart disease in a New Zealand population'.[18] Participants were recruited from two sources; employees of the Fletcher Challenge Group's New Zealand operation, and individuals listed on the general electoral roll of the Auckland metropolitan region. A total of 14,118 individuals were invited to participate, and 10,529 were enrolled (8,011 from Fletcher Challenge, and 2,518 from the electoral roll), yielding a response rate of 74.6%. Overall, 72% of the study sample were men (80% among Fletcher Challenge participants) and 15% identified as Māori or Pacific Islanders.[18]

Fremantle Diabetes Study (FDS)

The FDS is a longitudinal, community-based, observational study of people with known diabetes from an urban postcode-defined population in Fremantle, Western Australia.[19] The study consists of two phases, of which data from Phase I is included in the ANZDCC cohort. The aim of FDS Phase I was to identify all people with known diabetes and examine clinically relevant aspects of diabetes, such as clinical management, metabolic control, complications, and cost.[19] In total, 2,258 people with diabetes were identified between April 1993 and July 1996 from the Fremantle Hospital clinic and inpatient lists, local physician referrals, allied health facilities, pharmacies, opticians, advertising in local media and word of mouth. Of these, 1,426 (90.7% type 2 diabetes) were recruited into the study.[19]

Geelong Osteoporosis Study (GOS)

The Geelong Osteoporosis Study (GOS) began as a population-based study designed to investigate the epidemiology of osteoporosis in Australia.[20] Initially the GOS comprised only women; men were recruited later. Participants were recruited from the Barwon Statistical Division, situated in southeastern Australia. Individuals were selected at random from the electoral roll using an age-stratified sampling method to ensure at least 100 women and 100 men in each five-year age group from 20 to 69 years, and 200 of each sex for age groups 70–79 and 80+. During the years 1993–97, 2,390 women were invited to participate, of which 1,494 (77%) were eligible and agreed to participate. A new sample of 246 women listed as aged 20–29 years on the 2005 electoral roll were recruited in 2006–08, giving a total sample of 1,740 women. During the years 2001–06, 3,273 men were invited to participate, of which 1,540 (67%) were eligible and agreed to participate.[20]

Health in Men Study (HIMS)

The HIMS study arose out of a population-based randomised trial of screening for abdominal aortic aneurysms (AAAs) conducted in Perth, Western Australia in 1996–99.[21] Only men aged 65 years and over were recruited into the trial as AAAs are uncommon below this age and are six times more common in men than women. The aim of the trial was to assess whether screening reduced mortality from AAA. Secondary outcomes included assessments of the impact of screening on all-cause mortality and quality of life, and a study of the rates of expansion of screen-detected AAAs. After exclusion of 2,296 men dying prior to invitation, 19,352 men were invited and 12,203 (63.1%) attended baseline screening.[21]

Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)

LIPID was a multicentre double-blind randomised placebo-controlled trial comparing the effects of pravastatin, a cholesterol-lowering drug, with placebo, given for up to five years.[22] The primary objective of this trial was to compare coronary heart disease mortality in the two treatment arms, with secondary endpoints including total mortality, incidence of acute myocardial infarction, total hospitalisation, serum lipid fractions, and relationship of changes in these outcomes to changes in coronary mortality. Participants were aged 31–75 years at baseline with total cholesterol levels of 4.0 to 7.0mmol/L and with a history of acute myocardial infarction, or hospitalisation for unstable angina pectoris within the preceding three months to three years. From April 1990 to September 1992, 11,106 patients were registered. Following the run-in phase and after exclusions, 9,014 were randomised (5,958 from Australia; 3,056 from New Zealand) from a total of 87 centres.[22]

Melbourne Collaborative Cohort Study (MCCS)

The MCCS is a prospective cohort study of 41,528 participants, ages 27 to 75 years at recruitment from 1990 to 1994 (almost all were ages 40–69 years), and includes 5,425 migrants from Italy and 4,535 from Greece.[23] Southern Europeans (born in Italy or Greece) were deliberately over-sampled to increase the variety of dietary intake and genetic variability.[23] Subjects were recruited via electoral rolls advertisements, and community announcements in local media (e.g. television, radio, and newspapers). Comprehensive lists of Italian and Greek surnames were also used to target southern European migrants listed in the phone books and on electoral rolls.

Newcastle MONICA

The MONICA Project was a World Health Organization study MONitoring trends and determinants of CArdiovascular disease.[24] Thirty-two MONICA Collaborating Centres from 21 countries were involved in the study from the mid-1980s to the mid-1990s. Australia participated in the Project with two centres, one in Newcastle, New South Wales, the other in Perth, Western Australia.[25] The population for the MONICA project in Newcastle was residents aged 25 to 69 years from five local government areas of Newcastle, Lake Macquarie, Port Stephens, Maitland, and Cessnock. Participants were randomly selected from the electoral roll. Three cross-sectional surveys of risk factors were conducted during the study period, the first in 1983 (n=2,464), the second in 1988 and 1989 (n=1,067), and the third in 1994 (n=1,675) giving a total sample of 5,934.[25]

North West Adelaide Health Study (NWAHS)

The NWAHS was formulated in 1997 in response to a lack of longitudinal biomedical data on chronic conditions in South Australia.[26] The main aim of this study was to collect measured information on diabetes, asthma, and chronic obstructive pulmonary disease, and health related risk factors. All non-institutionalised households in the northern and western areas of Adelaide with a telephone connected and a telephone number listed in the electronic white pages were eligible for selection. Within each household, the person who had their birthday last and was aged 18 years or over was selected for interview and invited to attend the clinic for a biomedical examination. Of the initial sample of 10,096, 8,213 (81.3%) were eligible. Of these, 4,060 were interviewed and agreed to attend the clinic (2,523 were recruited from December 1999 to December 2000; 1,537 were recruited from August 2002 to July 2003), yielding an overall response rate of 49.4%.[26]

Personality and Total Health (PATH) Through Life Project

The PATH project was established in 1999 to 'explore factors influencing the development of, and recovery from mental disorders over the adult age span'(27). PATH is based on three cohorts (birth years: 1975–79, 1956–60, and 1937–41). At the start of the study, these cohorts were aged 20–24 years, 40–44 years, and 60–64 years, respectively. The sample for this study was drawn from the electoral rolls of the three federal electorates that makeup the Australian Capital Territory, and the electoral containing Queanbeyan, a neighbouring town in the adjoining state of New South Wales. Participation numbers and response rates from the random sampling are as follows: 20–24years: n=2,404; 58.6%, 40–44 years: n=2,530; 64.6%, 60–64 years: 2,551; 58.3%, giving a total sample size of 7,485.[27]

Perth Risk Factor Prevalence Cohort Studies

A series of five standardised population surveys of coronary risk factors were conducted in Perth (1980, 1983, 1989, 1994, 1999) sponsored either by the National Heart Foundation of Australia, or by the Perth MONICA (Multinational MONItoring of trends and determinants in Cardiovascular disease) Project.[28,29] The 1989 (n=1,966, response rate 74%) and 1994 (n=1,907), response rate 73%) surveys included adults aged 20–69 years randomly selected from the electoral roll living within the Perth metropolitan area. Detailed descriptions of the methods have been given elsewhere.[28,30]

Outcome ascertainment

Australian participants of the pooled cohort were linked to the Australian Cancer Database (ACD) and the National Death Index (NDI) up to and including 31 August 2011. This provided follow-up of cancer and mortality endpoints for all participants. These registries are maintained by AIHW with 100% capture of all cancers from 1982 onwards.[31] Tumours diagnosed as benign, of borderline malignancy, or in situ were not included.

Linkage to the ACD and NDI used the general framework of Fellegi and Sunter[32] using first name, second name, last name, gender, and date of birth to conduct the linkage. This record linkage methodology assigns each compared pair of records a record pair comparison weight. Based on clerical review of a sample of these links, it is expected that links with a weighting of 'low', 'medium' and 'high' correspond to a link accuracy (positive predictive value) of 96.75%, 98.97% and 99.90%, respectively. A total of 351 pairs of duplicates were identified during the linkage process whereby individuals had participated in more than one study. One of each pair of duplicates was chosen at random and maintained in the cohort. Additionally, 593 participants across the original cohorts were lost to follow-up, were missing information on key identifiable variables, or did not consent to participate in future studies, and were subsequently not linked.

New Zealand participants of the pooled cohort were linked to the NZ Cancer Registry and mortality database using National Health Index numbers, unique identifiers assigned to every person who uses health and disability support services in New Zealand. All recorded cancers and deaths are coded according to the International Classification of Diseases Tenth revision (ICD-10), and were recoded from ICD-9 to ICD-10 where appropriate.

Strengths and weaknesses

The key strength of this study that distinguish it from previous work is that it will be the largest study to ever examine the relationship between diabetes, obesity, MetS, hypertension, and cancer. We have individual unit record data available from all significantly large studies in Australian and New Zealand populations, with adequate follow-up time. The 18 cohort studies have breadth in the range of variables collected, not seen in any other pooled cancer studies, thus allowing adjustment for confounding factors such as physical activity and smoking. Lastly, the use of high-quality national registers for follow-up of subjects is an additional strength. Limitations of the project are a lack of detailed data on tumour characteristics and cancer treatment, and that measurements of risk factors differ between cohorts.

Significance

Diabetes, obesity and cancer, are growing epidemics in both developed and developing countries, and therefore understanding the full range of their consequences is of increasing importance. Should this study show that diabetes and central (rather than total) obesity are risk factors for the development of certain cancers, it will: provide insights into the potential mechanisms of cancer; allow a better and fuller assessment of the likely burden and consequences of diabetes and obesity; in the Australian and New Zealand context inform clinical practice about the appropriate care of patients with diabetes and obesity; provide evidence to suggest that cancer screening should be added to the micro and macro-vascular complications of diabetes for which diabetic patients currently undergo annual screening; and add further weight to the need for lifestyle modification programs to prevent obesity, type 2 diabetes, metabolic syndrome and hypertension.

Where can I find out more?

Further information about cohorts in ANZDCC can be found in the reference list.

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Conflicts of Interest

None declared

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References

1. International Diabetes Federation. IDF Diabetes Atlas, 6th edn. Brussels, Belgium: International Diabetes Federation, 2013.
2. ABS. Australian health survey: First results, 2011–12. ABS cat. no. 4364.0.55.001. Canberra: Australian Bureau of Statistics, 2012.
3. **Colagiuri S, Colagiuri R, Conway B, Davey P, Grainger D.** DiabCost Australia – Assessing the Burden of Type 2 Diabetes in Australia Canberra: Diabetes Australia, 2003.
4. **Colagiuri S, Lee CM, Colagiuri R, Magliano D, Shaw JE, Zimmet PZ, et al.** The cost of overweight and obesity in Australia. *Med J Aust.* 2010;192(5):260-4.
5. **Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R.** Diabetes and Cancer. *Endocrine-Related Cancer.* 2009;16:1103-23.
6. **Wolin KY, Carson K, Colditz GA.** Obesity and cancer. *The Oncologist.* 2010;15(6):556-65.
7. **Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D.** Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care.* 2012;35(11):2402-11.
8. **Stocks T, Van Hemelrijck M, Manjer J, Bjorge T, Ulmer H, Hallmans G, et al.** Blood pressure and risk of cancer incidence and mortality in the Metabolic Syndrome and Cancer Project. *Hypertension.* 2012;59(4):802-10.
9. **Andrews G.** The Australian Longitudinal Study of Ageing and a Collaborative *Study of Aging in the US and Australia.* Adelaide: Flinders University of South Australia, 1992.
10. **Brown WJ, Bryson L, Byles JE, Dobson AJ, Lee C, Mishra G, et al.** Women's Health Australia: recruitment for a national longitudinal cohort study. *Women & Health.* 1998;28(1):23-40.
11. **Lee C, Dobson AJ, Brown WJ, Bryson L, Byles J, Warner-Smith P, et al**. Cohort Profile: the Australian Longitudinal Study on Women's Health. Int J *Epidemiol.* 2005;35(4):987-91.
12. **Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, et al.** A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med.* 2003;348(7):583-92.
13. **Dunstan DW, Zimmet PZ, Welborn TA, Cameron AJ, Shaw J, de Courten M, et al.** The Australian Diabetes, Obesity and Lifestyle Study (AusDiab)-methods and response rates. *Diabetes Res Clin Pract.* 2002;57(2):119-29.
14. **Attebo K, Mitchell P, Smith W.** Visual acuity and the causes of visual loss in Australia. The Blue Mountains Eye Study. *Ophthalmology.* 1996;103(3):357-64.
15. **Foran S, Wang JJ, Mitchell P.** Causes of visual impairment in two older population cross-sections: The Blue Mountains Eye Study. *Ophthalmic Epidemiol.* 2003;10(4):215-25.
16. **Simmons D, McKenzie A, Eaton S, Shaw J, Zimmet P.** Prevalence of diabetes in rural Victoria. *Diabetes Res Clin Pract.* 2005;70(3):287-90.
17. **Simons LA, McCallum J, Simons J, Powell I, Ruys J, Heller R, et al.** The Dubbo study: an Australian prospective community study of the health of elderly. *Aust NZ J Med.* 1990;20(6):783-9.
18. **MacMahon S, Norton R, Jackson R, Mackie MJ, Cheng A, Vander Hoorn S, et al.** Fletcher Challenge-University of Auckland Heart & Health Study: design and baseline findings. *New Zeal Med J.* 1995;108(1013):499-502.
19. **Davis TM, Bruce DG, Davis WA.** Cohort profile: the Fremantle Diabetes Study. *Int J Epidemiol.* 2013;42(2):412-21.
20. **Pasco JA, Nicholson GC, Kotowicz MA.** Cohort profile: Geelong Osteoporosis Study. *Int J Epidemiol.* 2012;41(6):1565-75.
21. **Norman PE, Flicker L, Almeida OP, Hankey GJ, Hyde Z, Jamrozik K.** Cohort Profile: The Health In Men Study (HIMS). *Int J Epidemiol.* 2009;38(1):48-52.
22. **The LIPID Study Group.** Design features and baseline characteristics of the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) Study: a randomised trial in patients with previous acute myocardial infarction and/or unstable angina pectoris. *Am J Cardiol.* 1995;76(7):474-9.
23. **Giles GG, English DR.** The Melbourne Collaborative Cohort Study. *IARC Scientific Publications.* 2002;156:69-70.
24. **Tunstall-Pedoe H, for the WHO MONICA Project.** The World Health Organization MONICA Project (Monitoring Trends and Determinants in Cardiovascular Disease): A major international collaboration. *J Clin Epidemiol.* 1988;41:105-14.
25. **Dobson A, Jamrozik KD, Hobbs M, Heller RF, Steele PL, Parsons R, et al.** Medical care and case fatality from myocardial infarction and coronary death in Newcastle and Perth. *Aust NZ J Med.* 1993;23:12-8.
26. **Grant JF, Chittleborough CR, Taylor AW, Dal Grande E, Wilson DH, Phillips PJ et al.** The North West Adelaide Health Study: detailed methods and baseline segmentation of a cohort for selected chronic diseases. *Epidemiologic Perspectives & Innovations.* 2006;3:4.
27. **Anstey KJ, Christensen H, Butterworth P, Easteal S, Mackinnon A, Jacomb T, et al.** Cohort profile: the PATH through life project. *Int J Epidemiol.* 2012;41(4):951-60.
28. **Bennett SA, Magnus P.** Trends in cardiovascular risk factors in Australia. Results from the National Heart Foundation's Risk Factor Prevalence Study, 1980–1989. *Med J Aust.* 1994;161:519-27.
29. **Hobbs MS, Knuiman MW, Briffa T, Ngo H, Jamrozik K.** Plasma cholesterol levels continue to decline despite the rising prevalence of obesity: population trends in Perth, Western Australia, 1980–1999. *Eur J Cardiov Prev R.* 2008;15:319-24.
30. **McElduff P, Dobson A, Jamrozik K, Hobbs M.** The WHO MONICA Study, Australia, 1984–93: A summary of the Newcastle and Perth MONICA Projects. AIHW Cat. No. CVD 11. Canberra: Australian Institute of Health and Welfare (Cardiovascular Disease Series No. 13). 2000.
31. AIHW (Australian Institute of Health and Welfare) & AACR (Australasian Association of Cancer Registries). Cancer in Australia: an overview. Canberra: AIHW: Australian Institute of Health and Welfare, 2008 Contract No.: Report No.: AIHW Cat. no. CAN 42.

CHAPTER 3

Contemporary Trends in Mortality Among People with Diabetes

Diabetes increases mortality, with evidence suggesting that this excess risk is mainly attributable to cardiovascular disease (CVD). However, patterns of mortality may be changing. Marked declines in mortality among the general population, primarily from CVD, have been noted in the past four decades, with some evidence that mortality in type 2 diabetes may be approaching that of the general population, particularly at older ages. However, little is known about the extent to which mortality from different causes of death (COD) in people with diabetes have changed over time, or which age groups have primarily been affected.

The following Chapter explores contemporary total and cause-specific mortality patterns among people with type 1 and type 2 diabetes.

Chapter 3.1 examines secular trends in excess all-cause mortality rates in type 1 and type 2 diabetes compared with the general population in Australia and assesses the change in the proportion of cause-specific deaths over time. Key findings include a decrease in all-cause mortality rates among both type 1 and type 2 diabetes and a narrowing of the mortality gap between people with diabetes and the general population. However, there is still a 3 and 1.2 relative excess risk for all-cause mortality in people with type 1 and type 2 diabetes, respectively, compared with the general population. This chapter also reports a shift in the distribution of COD among people with diabetes: the proportion of deaths from CVD has decreased over time and consequently, the proportion of deaths attributed to cancer has increased. Last, this Chapter also reports that a large proportion of CVD deaths are potentially underestimated using standard underlying COD coding methods and this has direct implications for the interpretation of CVD mortality among people with diabetes.

This work was published in Diabetes Care in June 2014. An erratum to this work was published thereafter and this is also included at the end of this chapter. In addition, a comment on limitations of using death certificate data in diabetes was published in the New England Journal of Medicine (NEJM), 2015, Appendix 2. This commentary was written in response to a paper that was published in the NEJM by Lind et al. entitled 'Glycaemic control and excess mortality in type 1 diabetes'. Here, myself and co-authors highlight that Lind et al. may not have adequately captured the true burden of deaths due to CVD as their categorisation of deaths was based on the underlying COD only.

Chapter 3.2 builds upon this work by exploring mortality rates of cause-specific death over time, by age group. Examining age-specific trends in mortality identifies which age groups are driving observed changes in mortality. This is important data to inform government to prioritise where prevention and treatment efforts are most needed. This original research article was accepted for publication in Diabetes Care in February 2016.

Overall findings presented in Chapter 3.2 show declines in age-standardised rates of mortality from all-cause, CVD and diabetes, while cancer mortality remains unchanged. These trends suggest continued success in the

treatment of diabetes and its complications. However, improvements in mortality are not consistently seen across the age spectrum, with younger ages (<40) not experiencing the same declines in mortality as older populations and even more concerning, for type 2 diabetes, increases in all-cause and cancer mortality rates was noted in age-groups 0–40. Efforts to rectify this disparity are needed. In addition, the absence of a decline in cancer mortality among people with diabetes is likely to lead a higher burden of cancer among people with diabetes. This warrants urgent attention.

Declaration for Thesis – Chapter 3.1

Harding JL, Shaw JE, Peeters A, Guiver T, Davidson S & Magliano DJ. Mortality trends among people with type 1 and type 2 diabetes in Australia; 1997-2010. *Diabetes Care* 2014; 37(9):2579-86

In the case of Chapter 3.1, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Acquisition of data, data management, analysis and interpretation of data, conceptualisation and writing of manuscript, critical revision, corresponding author	70%

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

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Jonathan Shaw	Conceptualisation, critical revision, approval of final draft for publication	
Anna Peeters	Critical revision, approval of final draft for publication	
Tenniel Guiver	Data linkage	
Susan Davidson	Data provision	
Dianna Magliano	Conceptualisation, data acquisition, critical revision, approval of final draft for publication	

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

Candidate's Signature	[redacted]	Date: 31/03/2016
Main Supervisor's Signature	[redacted]	Date: 31/03/2016

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

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Mortality Trends Among People With Type 1 and Type 2 Diabetes in Australia: 1997–2010

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OBJECTIVE

With improvements in cardiovascular disease (CVD) rates among people with diabetes, mortality rates may also be changing. However, these trends may be influenced by coding practices of CVD-related deaths on death certificates. We analyzed trends of mortality over 13 years in people with diabetes and quantified the potential misclassification of CVD mortality according to current coding methods.

RESEARCH DESIGN AND METHODS

A total of 1,136,617 Australians with diabetes registered on the National Diabetes Services Scheme between 1997 and 2010 were linked to the National Death Index. Excess mortality relative to the Australian population was reported as standardized mortality ratios (SMRs). Potential misclassification of CVD mortality was determined by coding CVD according to underlying cause of death (COD) and then after consideration of both the underlying *and* other causes listed in part I of the death certificate.

RESULTS

For type 1 diabetes, the SMR decreased in males from 4.20 in 1997 to 3.08 in 2010 ($P_{trend} < 0.001$) and from 3.92 to 3.46 in females ($P_{trend} < 0.01$). For type 2 diabetes, the SMR decreased in males from 1.40 to 1.21 ($P_{trend} < 0.001$) and from 1.56 to 1.22 in females ($P_{trend} < 0.001$). CVD deaths decreased from 35.6 to 31.2% and from 31.5 to 27.2% in males and females with type 1 diabetes, respectively ($P_{trend} < 0.001$ for both sexes). For type 2 diabetes, CVD decreased from 44.5 to 29.2% in males and from 45.5 to 31.6% in females ($P_{trend} < 0.001$ for both sexes). Using traditional coding methods, ~38 and 26% of CVD deaths are underestimated in type 1 diabetes and type 2 diabetes, respectively.

CONCLUSIONS

All-cause and CVD mortality has decreased in diabetes. However, the total CVD mortality burden is underestimated when only underlying COD is considered. This has important ramifications for understanding mortality patterns in diabetes.

Diabetes increases mortality, with this excess mainly being attributable to cardiovascular disease (CVD) (1). However, patterns of mortality may be changing (2,3). Marked declines in mortality among the general population, primarily from CVD, have been noted in the past 4 decades (4), with some evidence that mortality in type 2 diabetes may be approaching that of the general population, particularly at older ages (2,3,5). Studies of type 1 diabetes are, however, inconsistent, with some reporting a decrease in all-cause mortality over time (6–8), while others report no

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change (9–11). Furthermore, little is known about the extent to which mortality from different causes of death (CODs) in people with diabetes has changed over time. Evidence suggests a reduction in mortality from complications of diabetes (6,12,13), an increase in cancer mortality (3), and no change in mortality from acute complications of diabetes (3,14). However most of these studies are based on small sample sizes and do not distinguish between type 1 and type 2 diabetes.

Although examining cause-specific mortality is of significant value, limitations in using death certificate data are well recognized (15–17). Most of the attention in this area has focused on whether or not death certificates in people with diabetes refer to diabetes at all (17–19). It is also possible that due to an increasing recognition of the role of diabetes, the underlying COD may be given as diabetes when the death was primarily caused by CVD. This may lead to misclassification, whereby deaths due to CVD in people with diabetes are not classified as CVD deaths, but as diabetes deaths, leading to an underestimate of the impact of CVD.

The aims of the current study, using a cohort of Australians registered on the National Diabetes Services Scheme (NDSS) followed from 1997–2010, are to

i. examine secular trends in excess all-cause mortality in type 1 and type 2 diabetes compared with the general population,
ii. examine secular trends in proportions of cause-specific deaths in type 1 and type 2 diabetes, and
iii. explore the potential underestimation of CVD deaths in people with diabetes.

RESEARCH DESIGN AND METHODS

The NDSS was set up in 1987 to deliver diabetes-related products at subsidized prices and provide information to people with diabetes. Registration of patients is free and is completed by a medical practitioner or credentialed diabetes nurse educator. The NDSS captures 80–90% of all Australians with known diabetes (20).

We included all people with type 1 or type 2 diabetes who were on the NDSS between 1997 and 2010. 1997 was chosen as the start date, as this time period followed a unification of state-based registries as well as an improvement in data quality. After excluding 944 registrants, because registration date and date of death were the same, the sample size for these analyses was 1,136,617. Diabetes type is classified by the health practitioner completing registration. However, for the current study, type 1 diabetes status was assigned to registrants who were classified as type 1 on the NDSS and were diagnosed before the age of 30 years, and the time between diagnosis date and date of first insulin use was less than 1 year. For those missing data on date of diagnosis or insulin initiation date (many of whom registered in the early years of the operation of the NDSS and had had diabetes for a number of years), we classified people as type 1 diabetes if they were recorded as type 1 on the registry, were taking insulin, and were registered at $\leq$45 years of age. We chose 45 years as the cutoff to minimize the number of people with type 1 diabetes that we would miss, without misclassifying significant numbers of people with type 2 as type 1 (21). All others were classified as type 2 diabetes.

The NDSS was linked to the National Death Index (NDI) using data up to and including 31 December 2010, and the general framework of Fellegi and Sunter (22) was used. First name, second name, third name, sex, and date of birth were used to conduct the linkage. The record linkage methodology assigns each compared pair of records a record pair comparison weight. Based on clerical review of a sample of these links, it is expected that links with a weighting of low, medium, and high correspond to a link accuracy (positive predictive value) of 96.75, 98.97, and 99.90%, respectively (23). For this study, we chose a medium cutoff point with a predictive value of 98.97%. Sensitivity analyses were also conducted using the high and low cutoffs.

Statistical Analysis

Individuals were followed from 1 January 1997, or registration date if thereafter, to 31 December 2010 or date of death, whichever occurred first. Annual mortality rates were calculated by direct standardization. In brief, 5-year age-specific mortality rates of those with diabetes were applied to the equivalent age strata from the Australian population of 2001, obtained from the Australian Institute of Health and Welfare. For type 1 diabetes, this was 0–75 years of age, and for type 2, it was all ages. Among the general population, mortality rates were also age-standardized to the 2001 Australian population.

All-cause mortality by year, 5-year age group (0–85+ years), and sex was calculated among people with diabetes. Year-, age-, and sex-specific mortality rates from the general Australian population, obtained from the Australian Institute of Health and Welfare, were applied to the diabetes population. The number of people in each age group of the diabetes population was multiplied by the age (in 5-year age groups), sex, and year-specific mortality rates in the general population to obtain the expected number of deaths and then summed to give a total expected number of deaths. Standardized mortality ratios (SMRs) were calculated by comparing the observed and expected mortality. An SMR of 1 indicates equivalent mortality risk to the age-matched general population, and 95% CIs were calculated using limits for a Poisson distributed variable.

For the assessment of changes in all-cause mortality over time, annual SMRs were fitted separately for each type of diabetes using a Poisson regression model using age as the time scale and including sex and calendar year as covariates, with P_{trends} reported. To examine changes in all-cause mortality over time by age group, we grouped data from the calendar years 1997–2003 and 2004–2010 together.

COD was classified according to underlying COD codes as follows: CVD I10-I25, I60-I69; diabetes E10-E14; cancer C00-C97; respiratory J00-J99; infections A00-B99; renal diseases N00-N21, N25-N26; and all remaining "other" codes. In a second analysis, deaths with an underlying COD corresponding to "uncomplicated diabetes" (E10.9, E11.9, E12.9, E13.9, E14.9) or "diabetes with circulatory complications" (E105, E11.5, E12.5, E13.5, E14.5) where a CVD code *also* appeared in the first part of the death certificate were reclassified to CVD. These recoded deaths are thought to be reflective of *real* CVD

deaths, as it is unlikely that people die of "uncomplicated diabetes" or "diabetes with circulatory complications," but rather, the CVD death, as described in part I of the death certificate, is a consequence of diabetes.

Binary outcomes were created for each cause-specific death, categorized into, for example, CVD or "other death" and individual logistic regression analyses (crude and age-adjusted) were performed to observe trends in the proportion of deaths attributed to each category, with P_{trends} reported. Trends in the proportions of underestimated CVD deaths over time were also reported using logistic regression with the binary outcome "misclassified" or "not misclassified." Statistical significance was established at $P < 0.05$. All analysis used STATA version 12.1 (StataCorp, College Station, TX). This study was approved by the Alfred Health Human Ethics Committee and the Australian Institute of Health and Welfare Ethics Committee.

RESULTS

This study included 1,136,617 (7.6% type 1) individuals with type 1 or type 2 diabetes who were registered on the NDSS between 1997 and 2010. In brief, there were a greater proportion of males with type 1 and type 2 diabetes compared with females, 52.4 and 53.8%, respectively; median age at diagnosis was 21.1 and 60.0 years for type 1 and type 2 diabetes, respectively; average follow-up time was 10.5 and 6.9 years for type 1 and type 2 diabetes, respectively; and 21.7% of people with type 2 diabetes were on insulin.

Among 86,250 people with type 1 diabetes, a total of 6,134 deaths occurred during 908,730 person-years (PY) of follow-up between 1997 and 2010; crude mortality rate was 6.8 per 1,000 PY. Age-standardized (0–75 years) mortality rates decreased among the type 1 diabetes population from 9.5 per 1,000 to 6.3 per 1,000 PY over the follow-up period, and from 3.3 per 1,000 to 2.3 per 1,000 among the general population for the same age group. The SMR for males decreased from 4.20 (95% CI 3.66–4.82) in 1997 to 3.08 (95% CI 2.77–3.42) in 2010 ($P_{trend} < 0.001$) and for females from 3.92 (95% CI 3.19–4.82) to 3.46 (95% CI 3.01–3.97; $P_{trend} < 0.01$) (Fig. 1).

Among 1,060,367 people with type 2 diabetes, a total of 211,082 deaths occurred during 7,263,618 PY of follow-up for the same time period; crude mortality rate was 29 per 1,000 PY. Age-standardized (0–75 years) mortality rates decreased among the type 2 diabetes population from 9.4 per 1,000 to 5.5 per 1,000 PY over the follow-up period. The SMR for males decreased from 1.40 (95% CI 1.36–1.44) in 1997 to 1.21 (95% CI 1.19–1.23) in 2010 ($P_{trend} < 0.001$) and for females from 1.56 (95% CI 1.51–1.61) to 1.22 (95% CI 1.19–1.24; $P_{trend} < 0.001$) (Fig. 2).

Age-specific SMRs in 1997–2003 and 2004–2010 are presented in Table 1. In general, SMRs for type 1 diabetes were

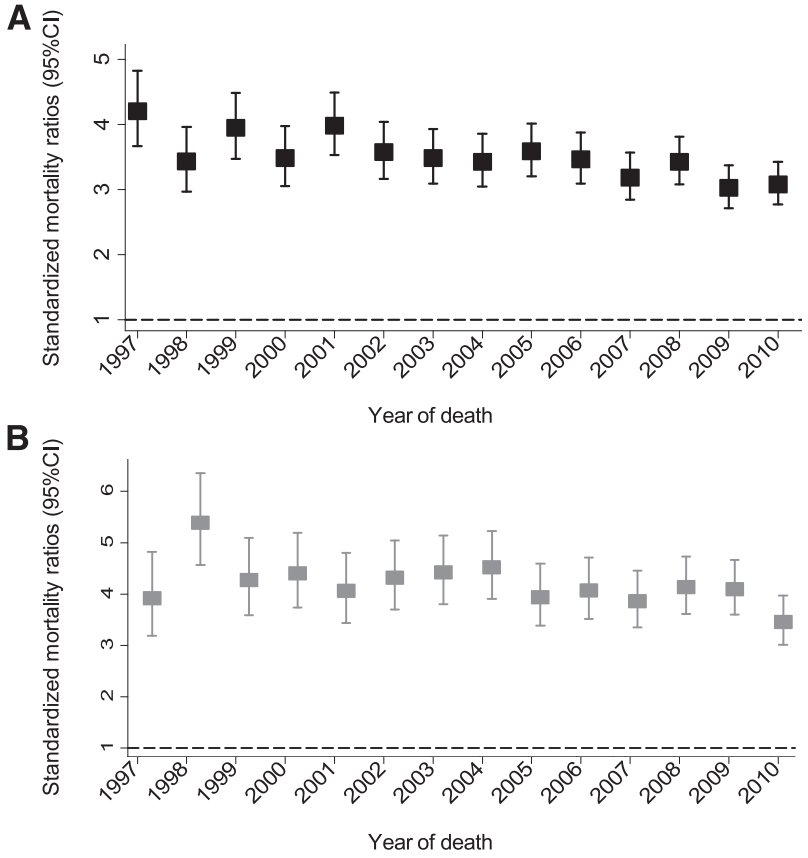

Figure 1—All-cause SMRs in males (*A*) and females (*B*) with type 1 diabetes compared with the general population between 1997 and 2010.

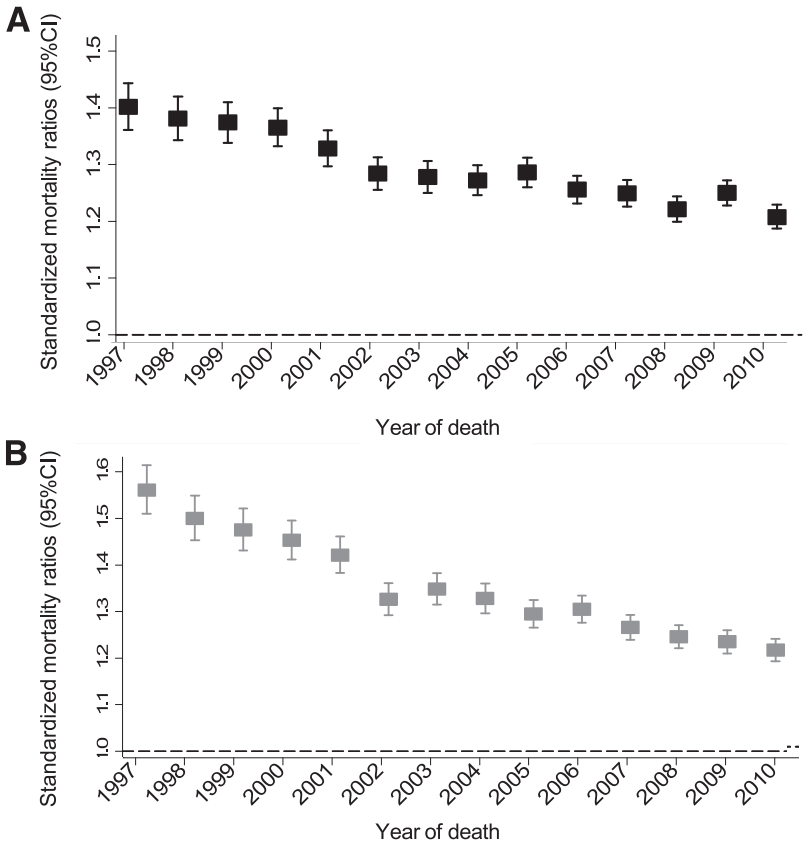

Figure 2—All-cause SMRs in males (*A*) and females (*B*) with type 2 diabetes compared with the general population between 1997 and 2010.

almost double across all age groups compared with those for type 2 diabetes in 1997–2003 and 2004–2010. Females generally had higher SMRs compared with males, and SMRs generally decreased from 1997–2003 to 2004–2010 for males and females with type 2, but not type 1, diabetes.

COD data were available for 85.8% (n = 5,261) of all deaths among type 1 diabetes and for 95.3% (n = 201,156) among type 2 diabetes. Using the standard underlying COD data, Fig. 3 shows that in type 1 diabetes, the percentage of crude deaths due to CVD fell between 1997 and 2010 (significant only for females), while the percentage due to cancer increased. Age-adjustment resulted in the CVD decline between 1997 and 2010 becoming significant in males also. Figure 3 also shows that there were similar findings for type 2 diabetes, both crude and age-adjusted (significant in males and females).

After recoding relevant "uncomplicated diabetes" deaths and "diabetes with circulatory complications" deaths to CVD, the proportion of deaths for the total time period among those with type 1 diabetes attributed to CVD increased from 22.3 to 35.7% in males and from 18.9 to 31.6% in females (Table 2). For both males and females, the amount of underestimation increased over time ($P_{trend} < 0.05$), and subsequently, decreases in the proportion of deaths attributed to CVD over time were overestimated. Similar findings were seen for type 2 diabetes.

Separate sensitivity analyses using NDI cutoffs with linkage rates of 99.9 and 96.75% and using a cutoff date of age <40 at registration for classification as type 1 diabetes among those missing data on age at diagnosis did not change the overall pattern of results (data not shown).

CONCLUSIONS

Our findings of an analysis of mortality trends among Australians with diabetes are threefold. First, we observed a significant decline in excess all-cause mortality among both males and females for type 1 and type 2 diabetes between 1997 and 2010. This decrease in excess risk over time was underpinned by decreases in mortality for both the diabetes and general population groups, though decreases in mortality were greater among the diabetes population, making the relative difference between the two groups smaller over time. However, people with type 1 and type 2 diabetes still experience a 3 and 1.2 times increased risk of excess all-cause mortality, respectively, compared with the general population. Second, we observed a decline in the proportion of deaths attributed to CVD among type 1 diabetes and type 2 diabetes and for both males and females. Finally, we observed that a large proportion of deaths from CVD are potentially underestimated using standard underlying COD coding methods, and this proportion has increased over time.

Table 1—Age group– and sex-specific SMRs (95% CI) from 1997–2003 and 2004–2010 in type 1 and type 2 diabetes

Age group, years	1997–2003						2004–2010					
	Male			Female			Male			Female		
	Deaths (*n*)	SMR	95% CI	Deaths (*n*)	SMR	95% CI	Deaths (*n*)	SMR	95% CI	Deaths (*n*)	SMR	95% CI
Type 1 diabetes												
0–9	2	0.75	0.19–2.99	1	0.56	0.08–4.00	3	1.21	0.39–3.74	3	1.73	0.56–5.36
10–19	37	3.26	2.36–4.49	41	7.77	5.72–10.56	32	3.06	2.16–4.32	20	3.98	2.57–6.17
20–29	101	2.56	2.11–3.11	80	5.91	4.75–7.36	95	2.95	2.41–3.61	81	6.91	5.56–8.59
30–39	258	4.09	3.62–4.62	159	4.57	3.92–5.34	236	4.08	3.59–4.653	137	4.95	4.19–5.85
40–49	582	4.69	4.33–5.09	315	4.72	4.23–5.27	505	4.39	4.02–4.79	313	4.22	3.77–4.71
50–59	533	3.75	3.45–4.08	284	4.36	3.88–4.89	780	3.37	3.14–3.61	467	4.02	3.67–4.40
60–69	55	2.01	1.54–2.62	30	2.52	1.76–3.60	402	2.60	2.36–2.87	237	3.40	3.00–3.87
70–79	47	2.10	1.58–2.41	28	2.81	1.99–3.95	80	2.25	1.81–2.80	64	3.12	2.44–3.98
80–89	23	2.42	1.61–3.64	18	2.25	1.42–3.57	46	2.13	1.59–2.84	34	2.53	1.81–3.54
Type 2 diabetes												
0–9	—	—	—	—	—	—	—	—	—	—	—	—
10–19	4	14.26	5.35–38.0	2	7.75	1.94–31.0	2	3.57	0.89–14.28	1	2.40	0.34–17.02
20–29	10	2.06	1.11–3.84	15	1.82	1.10–3.02	23	4.00	2.66–6.02	21	4.59	3.00–7.04
30–39	134	3.16	2.67–3.74	99	1.60	1.32–1.95	192	3.02	2.62–3.48	164	2.93	2.52–3.42
40–49	650	2.26	2.09–2.44	407	2.43	2.20–2.67	1,250	2.65	2.51–2.80	793	2.63	2.45–2.82
50–59	3,491	2.14	2.07–2.21	1787	2.51	2.40–2.63	4,890	1.97	1.91–2.02	2,527	2.23	2.14–2.32
60–69	9,504	1.69	1.66–1.73	5224	2.07	2.02–2.13	13,724	1.63	1.60–1.65	7,122	1.90	1.86–1.95
70–79	17,441	1.40	1.38–1.42	11,726	1.70	1.67–1.73	25,562	1.36	1.34–1.37	16,361	1.56	1.54–1.59
80–89	12,501	0.98	0.96–1.00	13,694	1.08	1.05–1.09	29,917	0.99	0.98–1.00	31,844	1.03	1.02–1.04

The dash indicates that there were no deaths among people with diabetes for this age group.

Comparison With the Literature

Our results for the risk of excess all-cause mortality are consistent with other studies. Lind et al. (2) show that in a large diabetes population in Ontario, Canada, the mortality rate ratios decreased from 1.90 in 1996 to 1.51 in 2009 compared with people without diabetes and from 2.14 to 1.65 in a diabetes population from the U.K. for the same time period. However, this study did not distinguish diabetes type and may explain why the rate ratios lie somewhere between our estimates for type 1 and type 2 diabetes. Gregg et al. (13) showed that between 1997 and 2006, all-cause and CVD death rates declined by 23 and 40%, respectively, in a population of U.S. adults with diabetes, and there were no differences between males and females. This study also did not discriminate between type 1 diabetes and type 2 diabetes. Allemann et al. (6) examined type 1 and type 2 diabetes separately and showed that SMRs for all-cause and CVD mortality decreased significantly over 30 years of follow-up in Switzerland. In that study, SMRs for type 1 and type 2 diabetes from 1974 to 2005 were 4.5 and 3.5, respectively, and were higher for females than males. These SMRs are much higher than those reported here, most likely due to the fact that the Swiss study began in the 1970s when mortality from diabetes

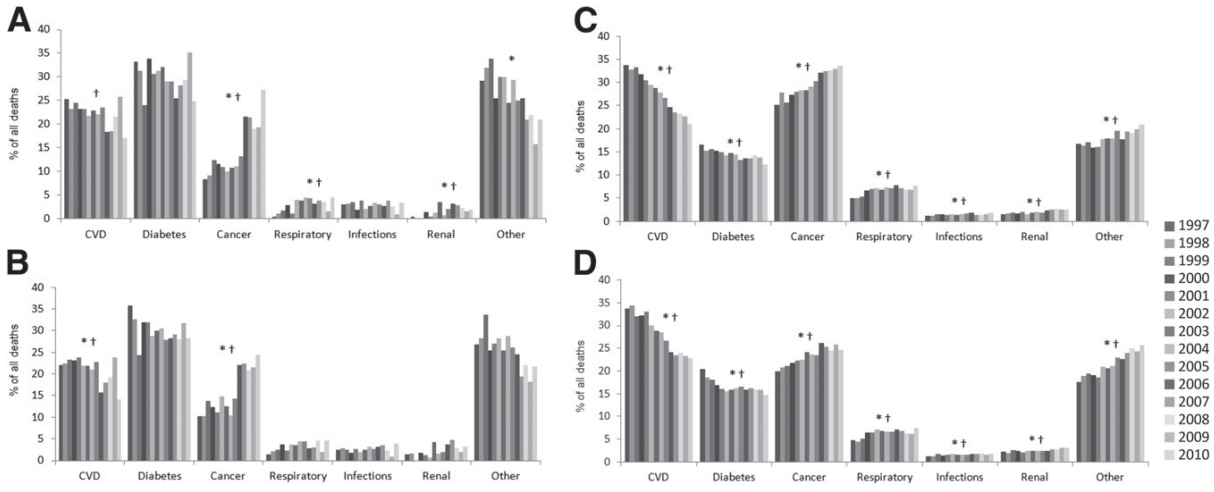

Figure 3—Cause-specific mortality in males (*A*) and females (*B*) with type 1 diabetes and males (*C*) and females (*D*) with type 2 diabetes using traditional coding between 1997 and 2010. *crude $P_{trend} < 0.001$; †age-adjusted $P_{trend} < 0.001$.

Table 2—Proportion of CVD deaths misclassified using traditional coding in males and females with type 1 and type 2 diabetes

	Men			Women		
Year of death	% of CVD deaths[a]	% of CVD deaths after recoding[b]	% of CVD deaths underestimated	% of CVD deaths[a]	% of CVD deaths after recoding[b]	% of CVD deaths underestimated
Type 1 diabetes						
1997	25.3	34.7	27.1	14.6	28.1	48
1998	23.2	34.1	31.7	21.4	32.1	33.3
1999	24.5	33.9	27.8	21.0	33.1	36.6
2000	23.2	38.0	39.0	23.2	34.1	31.9
2001	23.2	36.3	36.1	24.8	39.4	54.0
2002	21.7	33.6	35.3	21.9	29.0	24.4
2003	22.9	35.5	35.5	20.2	28.6	29.2
2004	22.1	35.3	37.5	19.4	32.8	40.7
2005	23.6	37.4	36.9	21.7	32.9	34.0
2006	18.4	30.8	40.4	12.2	24.5	50.0
2007	18.5	34.6	46.5	16.6	33.1	50.0
2008	21.6	35.8	39.8	15.7	26.4	40.5
2009	25.7	41.6	38.1	20.6	31.5	34.6
2010	17.1	31.2	45.3	9.9	26.5	62.5
Total	22.3	35.3	36.8[c]	18.9[d]	30.9	38.7[c]
Type 2 diabetes						
1997	33.8	43.8	22.7	33.7	44.6	24.3
1998	32.7	42.2	22.5	34.3	44.8	23.3
1999	33.3	42.7	22.0	32.0	42.1	23.9
2000	31.7	40.8	22.2	32.2	40.9	21.3
2001	30.5	39.4	22.6	33.1	42.3	21.7
2002	29.4	37.6	21.7	30.0	38.7	22.5
2003	28.8	37.8	23.9	28.9	38.4	24.6
2004	27.7	36.6	24.3	28.5	37.8	24.5
2005	26.6	35.8	25.6	26.6	37.0	28.1
2006	24.6	32.8	24.8	24.1	33.0	27.1
2007	23.5	31.5	25.3	23.5	32.2	27.1
2008	23.2	31.6	26.7	23.9	32.3	25.9
2009	22.6	30.5	25.7	23.3	32.0	27.3
2010	21.1	28.2	25.2	22.8	30.9	26.1
Total	26.7	35.3[d]	24.1[c]	27.2[d]	36.3[d]	25.1[c]

[a]Proportion of deaths using traditional ICD coding using underlying COD only. [b]Proportion of deaths after recoding diabetes to CVD where it was suspected CVD was the true underlying COD. [c]Significant increase between 1997 and 2010 ($P_{trend} < 0.05$). [d]Significant decrease between 1997 and 2010 ($P_{trend} < 0.05$).

was much higher compared with the general population.

In our study, we show that the second largest contributor to mortality among people with diabetes is now cancer, which increased substantially between 1997 and 2010. While there is now a plethora of epidemiological evidence supporting a strong association between diabetes and many types of cancer (24), only one other study that we are aware of has shown increasing trends of mortality from cancer over time in people with diabetes. In this study, the proportion of deaths attributed to cancer increased from ~23% in 1970 to 27% in 1990 (3). This is similar to our results where we show that the proportion of deaths attributed to cancer among type 1 diabetes is now 27%, but we show a higher proportion among people with type 2 diabetes, with 33% of all deaths in people with diabetes attributed to cancer in 2010. This is of significant importance in light of the increasing prevalence of diabetes, coinciding with an ageing population, an inherent risk factor for both diabetes and cancer.

Mortality ICD codes are widely used in epidemiological research to assess the health of populations, direct the allocation of funds, and inform appropriate health care policy. But as we, and others, have shown, misclassification of COD can have major implications for the conclusions drawn from epidemiological research (25). In this study, we show that the proportion of CVD deaths potentially underestimated by using underlying COD was ~39 and 26% for type 1 and type 2 diabetes, respectively. We also show that the proportion has increased over time. It is most likely that this reflects an increasing awareness among doctors that diabetes is a key etiological factor in the development of CVD. Our findings are supported by a study by Harriss et al. (26), which adjudicated 750 deaths from an Australian longitudinal cohort and found that of 54 deaths with an underlying ICD code listed as "diabetes," almost 60% were primarily due to CVD. Our somewhat lower estimates are most likely explained by our conservative approach, whereby only those diabetes cases that were "diabetes with circulatory complication" or "uncomplicated diabetes" were recoded. Additionally, our study distinguished between diabetes types and had a different age distribution. Our data show that when death from CVD is attributed to diabetes (often correctly) on the death certificate, it can significantly

obscure patterns of CVD mortality if only underlying COD is used to attribute COD. Similar issues may also apply to other chronic diseases and their complications. We suggest that when considering mortality data, particularly for diabetes populations, the current reliance on the underlying COD coding may be misleading.

Strengths and Limitations

The main strength of this study is that it is population based with a large sample size, a long follow-up time, and the ability to distinguish between type 1 and type 2 diabetes. There are several limitations, however, that should be acknowledged. Firstly, the NDSS is an administrative database, and there are inherent limitations with using administrative databases for research purposes (27). Namely, for our study, the lack of precise information about type of diabetes for all registrants was not available. The classification of diabetes, particularly in young patients, is challenging, and misclassification can occur. However, the proportions of type 1 and type 2 diabetes in this study (7.6 vs. 92.4%) are similar in other Australian data (28). Further, the proportion of type 2 diabetic patients who were also on insulin is consistent with other studies (29). Given these well-known demographics and our very large sample size, we believe that any misclassification in this study will not alter our results.

The NDSS is considered among the best available national data sources for estimating overall prevalence of diagnosed diabetes in Australia (20). However, the NDSS does not capture those with undiagnosed diabetes. Recent Australian data show that for every four cases of known diabetes, there is one undiagnosed case (30). The NDSS also may underestimate the total number of people with diet-controlled diabetes, as the diabetes-related products provided through the scheme may not be needed (30). In Australia, the proportion of known diabetes controlled by diet only was estimated to be 28% in 2000 (31). It is possible, therefore, that using the NDSS is reflective of the more serious diabetes cases. However, the NDSS coverage of type 1 diabetes is known to be very high as access to insulin-related products is through the NDSS (20). Further, we believe the coverage of type 2 diabetes is adequately reflective of people with type 2 diabetes in Australia given that the age distribution and the median age at diagnosis are similar to that seen in other populations (29). We therefore do not believe this potential source of bias will significantly impact our findings. Obtaining vital status and COD information can also be difficult for large-scale studies such as this in Australia where unique health identifiers are not available. Therefore, linkage is based on probabilistic algorithms that a given name, address, and date of birth will correctly link records belonging to the same individual. Again, this may introduce misclassification. However, for all primary analyses, we applied cutoffs that have a 98.97% positive match rate. Further, we performed sensitivity analyses using cutoffs with positive match rates of 99.9 and 96.75%, respectively, and our conclusions regarding patterns of mortality over time were unchanged.

Lastly, although the NDSS provides the largest data set for people with diagnosed diabetes, our findings are limited by a lack of covariates in the data set. Therefore, we were unable to explore the extent to which improvements in quality of care, medical treatments, and/or self-management behaviors contributed to the reductions in mortality over time. Furthermore, ethnicity is known to have a strong association with type 2 diabetes such that migrant populations have a higher prevalence of diabetes compared with Australian-born individuals (32,33). It is not known if ethnicity would impact on SMR estimates. Unfortunately, we were not able to explore this further due this information not being available in the general population.

Conclusion

We have shown that excess all-cause mortality in males and females with type 1 and type 2 diabetes has decreased over the past decade in Australia. These trends suggest continued success in the treatment of diabetes and its complications, though there is still a significant amount of excess mortality experienced among people with diabetes compared with the general population, and continued efforts to rectify this disparity are needed. Additionally, improvements in CVD-related mortality are offset by increases in the proportion of deaths attributed to cancer among people with diabetes. One of our most important and novel findings is that a substantial and increasing proportion of CVD deaths among people with diabetes are attributed to diabetes on death certificates, leading to underestimates in the CVD mortality burden among people with diabetes. If confirmed in other data collections, this has important ramifications for the understanding of mortality patterns.

Acknowledgments. Data for this project were sourced from the NDSS, an initiative of the Australian government administered by Diabetes Australia since 1987. Mortality data were sourced from the NDI, a database housed at the Australian Institute of Health and Welfare that contains records of all deaths registered in Australia since 1980.

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

Author Contributions. J.L.H. wrote the manuscript, had full access to all the data, and conducted the analyses. J.E.S. and D.J.M. contributed to conceptualization and discussion and reviewed/edited the manuscript. A.P. contributed to discussion and reviewed/edited the manuscript. T.G. and S.D. assisted in data preparation and data linkage and reviewed/edited the manuscript. D.J.M. 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.

References

1. Seshasai SR, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–841

2. Lind M, Garcia-Rodriguez LA, Booth GL, et al. Mortality trends in patients with and without diabetes in Ontario, Canada and the UK from 1996 to 2009: a population-based study. Diabetologia 2013;56:2601–2608

3. Thomas RJ, Palumbo PJ, Melton LJ 3rd, et al. Trends in the mortality burden associated with diabetes mellitus: a population-based study in Rochester, Minn, 1970-1994. Arch Intern Med 2003;163:445–451

4. Sarti C, Rastenyte D, Cepaitis Z, Tuomilehto J. International trends in mortality from stroke, 1968 to 1994. Stroke 2000;31:1588–1601

5. Preis SR, Pencina MJ, Hwang SJ, et al. Trends in cardiovascular disease risk factors in individuals with and without diabetes mellitus in the Framingham Heart Study. Circulation 2009;120:212–220
6. Allemann S, Saner C, Zwahlen M, Christ ER, Diem P, Stettler C. Long-term cardiovascular and non-cardiovascular mortality in women and men with type 1 and type 2 diabetes mellitus: a 30-year follow-up in Switzerland. Swiss Med Wkly 2009;139:576–583
7. Nishimura R, LaPorte RE, Dorman JS, Tajima N, Becker D, Orchard TJ. Mortality trends in type 1 diabetes. The Allegheny County (Pennsylvania) Registry 1965-1999. Diabetes Care 2001;24:823–827
8. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study experience. Diabetes 2006;55:1463–1469
9. Waernbaum I, Blohmé G, Östman J, et al. Excess mortality in incident cases of diabetes mellitus aged 15 to 34 years at diagnosis: a population-based study (DISS) in Sweden. Diabetologia 2006;49:653–659
10. Burnet DL, Cooper AJ, Drum ML, Lipton RB. Risk factors for mortality in a diverse cohort of patients with childhood-onset diabetes in Chicago. Diabetes Care 2007;30:2559–2563
11. Skrivarhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006;49:298–305
12. Ford ES. Trends in the risk for coronary heart disease among adults with diagnosed diabetes in the U.S.: findings from the National Health and Nutrition Examination Survey, 1999-2008. Diabetes Care 2011;34:1337–1343
13. Gregg EW, Cheng YJ, Saydah S, et al. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006: findings from the National Health Interview Survey. Diabetes Care 2012;35:1252–1257
14. Harjutsalo V, Forsblom C, Groop PH. Time trends in mortality in patients with type 1 diabetes: nationwide population based cohort study. BMJ 2011;343:d5364
15. Adair T, Rao C. Changes in certification of diabetes with cardiovascular diseases increased reported diabetes mortality in Australia and the United States. J Clin Epidemiol 2010;63:199–204
16. Will JC, Vinicor F, Stevenson J. Recording of diabetes on death certificates. Has it improved? J Clin Epidemiol 2001;54:239–244
17. Fuller JH, Elford J, Goldblatt P, Adelstein AM. Diabetes mortality: new light on an underestimated public health problem. Diabetologia 1983;24:336–341
18. Cheng WS, Wingard DL, Kritz-Silverstein D, Barrett-Connor E. Sensitivity and specificity of death certificates for diabetes: as good as it gets? Diabetes Care 2008;31:279–284
19. Vauzelle-Kervroëdan F, Delcourt C, Forhan A, Jougla E, Hatton F, Papoz L. Analysis of mortality in French diabetic patients from death certificates: a comparative study. Diabetes Metab 1999;25:404–411
20. Australian Institute of Health and Welfare. *Diabetes Prevalence in Australia. An Assessment of National Data Sources*. Canberra, Australian Institute of Health and Welfare, 2009
21. Kenny SJ, Aubert RE, Geiss LS. *Prevalence and Incidence of Non-Insulin-Dependent Diabetes*. 2nd ed. Washington, DC, U.S. Govt. Printing Office, 1995
22. Fellegi IP, Sunter A. A theory for record linkage. J Am Stat Assoc 1969;64:1183–1210
23. Blakely T, Salmond C. Probabilistic record linkage and a method to calculate the positive predictive value. Int J Epidemiol 2002;31:1246–1252
24. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer 2009;16:1103–1123
25. Pekkanen J, Sunyer J, Chinn S. Nondifferential disease misclassification may bias incidence risk ratios away from the null. J Clin Epidemiol 2006;59:281–289
26. Harriss LR, Ajani AE, Hunt D, et al. Accuracy of national mortality codes in identifying adjudicated cardiovascular deaths. Aust N Z J Public Health 2011;35:466–476
27. Hoover KW, Tao G, Kent CK, Aral SO. Epidemiologic research using administrative databases: garbage in, garbage out. Obstet Gynecol 2011;117:729–730; author reply 729–730
28. Australian Institute of Health and Welfare. *Diabetes Prevalence in Australia: Detailed Estimates for 2007-08*. Canberra, Australia, AIHW, 2011
29. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care 2004;27:17–20
30. Australian Bureau of Statistics. *Australian Health Survey: Biomedical Results for Chronic Diseases, 2011-2012*. Canberra, Australia, Australian Bureau of Statistics, August 2013 (cat. no. 4364.0.55.005)
31. Dunstan DD, Zimmet PZ, Welborn TA, et al. Diabesity & Associated Disorders in Australia - 2000: The Australian Diabetes, Obesity and Lifestyle Study. Melbourne, International Diabetes Institute, 2001
32. Abouzeid M, Philpot B, Janus ED, Coates MJ, Dunbar JA. Type 2 diabetes prevalence varies by socio-economic status within and between migrant groups: analysis and implications for Australia. BMC Public Health 2013;13:252
33. Shamshirgaran SM, Jorm L, Bambrick H, Hennessy A. Independent roles of country of birth and socioeconomic status in the occurrence of type 2 diabetes. BMC Public Health 2013;13:1223

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Erratum

Jessica L. Harding, Jonathan E. Shaw, Anna Peeters, Tenniel Guiver, Susan Davidson, and Dianna J. Magliano

Mortality Trends Among People With Type 1 and Type 2 Diabetes in Australia: 1997–2010. Diabetes Care 2014;37:2579–2586

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The authors of the article cited above noticed an error in the way they had described their definitions of type 1 and type 2 diabetes in the RESEARCH DESIGN AND METHODS section.

The description as published is as follows:

> Diabetes type is classified by the health practitioner completing registration. However, for the current study, type 1 diabetes status was assigned to registrants who were classified as type 1 on the NDSS and were diagnosed before the age of 30 years, and the time between diagnosis date and date of first insulin use was less than 1 year. For those missing data on date of diagnosis or insulin initiation date (many of whom registered in the early years of the operation of the NDSS and had had diabetes for a number of years), we classified people as type 1 diabetes if they were recorded as type 1 on the registry, were taking insulin, and were registered at ≤45 years of age. We chose 45 years as the cutoff to minimize the number of people with type 1 diabetes that we would miss, without misclassifying significant numbers of people with type 2 as type 1 [Kenny et al., 1995]. All others were classified as type 2 diabetes.

Amended description is as follows:

> Diabetes type is classified by the health practitioner completing registration. However, for the current study, type 1 diabetes status was assigned to registrants who were recorded as type 1 on the NDSS registry, were registered at <45 years of age, and were taking insulin. Registration date was used as a proxy for diagnosis date as a large proportion of registrants (59.1% with type 1 diabetes and 36.1% with type 2 diabetes) were missing date of diagnosis, many of whom registered in the early years of the operation of the NDSS and had had diabetes for a number of years. We chose 45 years as the cutoff to minimize the number of people with type 1 diabetes that we would miss, without misclassifying significant numbers of people with type 2 diabetes as type 1 diabetes [Kenny et al., 1995]. In addition, registrants who were recorded as having type 2 diabetes on the registry, were diagnosed before the age of 30 years, and were taking insulin within 1 year of diagnosis date were reclassified as having type 1 diabetes. All others were classified as having type 2 diabetes.

Had the authors analyzed the data according to how the definition reads in the article, they would have excluded approximately 13% of those with type 1 diabetes. These patients were all insulin treated and were all registered on the NDSS before the age of 45 years, and the majority were registered with the NDSS in the early years of its existence and therefore did not have an age at diagnosis available. The authors believe that the most appropriate classification of these patients is type 1 diabetes and that the published results, in which they were classified as type 1 diabetes, are therefore the appropriate ones. Nevertheless, the authors have examined the effect of differential coding by conducting some analyses using both the method that appeared in the RESEARCH DESIGN AND METHODS section and the amended method. These results and comparisons are shown in Supplementary Tables 1 and 2. Supplementary Table 1 highlights the all-cause standardized mortality ratios (SMRs), by year, for type 1 and type 2 diabetes. The authors show a magnitude of

difference between the two sets of results of less than 10% for type 1 diabetes and even less for type 2 diabetes, with overlapping 95% CI suggesting that the two versions of results are not statistically different. The proportions of cause-specific deaths attributed to cardiovascular disease, diabetes, and cancer are also immaterially different between the two definitions (Supplementary Table 2).

Changing the description of the definition does not require any change to the results.

Supplementary Data

Supplementary Table 1. All-cause SMRs in men and women with type 1 and type 2 diabetes compared to the general population; comparing the two different definitions of diabetes

		Type 1 diabetes				Type 2 diabetes			
		Correct DM definition*		Incorrect DM definition		Correct DM definition*		Incorrect DM definition	
Year	Sex	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
1997	Men	4.20	(3.66-4.82)	4.56	(3.97-5.24)	1.40	(1.36-1.44)	1.40	(1.36-1.44)
1998	Men	3.43	(2.97-3.96)	3.74	(3.22-4.34)	1.38	(1.34-1.42)	1.35	(1.31-1.38)
1999	Men	3.94	(3.47-4.48)	3.97	(3.45-4.57)	1.37	(1.34-1.41)	1.34	(1.30-1.37)
2000	Men	3.48	(3.05-3.97)	3.26	(2.80-3.80)	1.37	(1.33-1.40)	1.33	(1.30-1.37)
2001	Men	3.98	(3.53-4.49)	4.08	(3.57-4.67)	1.33	(1.30-1.36)	1.29	(1.26-1.33)
2002	Men	3.57	(3.16-4.04)	3.70	(3.23-4.25)	1.28	(1.26-1.31)	1.25	(1.22-1.28)
2003	Men	3.48	(3.09-3.92)	3.18	(2.76-3.67)	1.28	(1.25-1.31)	1.26	(1.23-1.28)
2004	Men	3.42	(3.04-3.86)	3.38	(2.95-3.88)	1.27	(1.25-1.30)	1.25	(1.23-1.28)
2005	Men	3.58	(3.20-4.01)	3.40	(2.98-3.88)	1.29	(1.26-1.31)	1.27	(1.25-1.30)
2006	Men	3.46	(3.09-3.87)	3.34	(2.93-3.80)	1.26	(1.23-1.28)	1.24	(1.22-1.27)
2007	Men	3.18	(2.84-3.57)	2.96	(2.59-3.38)	1.25	(1.23-1.27)	1.24	(1.21-1.26)
2008	Men	3.42	(3.08-3.81)	3.39	(3.01-3.83)	1.22	(1.20-1.24)	1.21	(1.19-1.23)
2009	Men	3.02	(2.71-3.37)	2.93	(2.58-3.33)	1.25	(1.23-1.27)	1.24	(1.22-1.26)
2010	Men	3.08	(2.77-3.42)	2.95	(2.61-3.33)	1.21	(1.19-1.23)	1.20	(1.18-1.22)
1997	Women	3.92	(3.19-4.82)	4.12	(3.33-5.10)	1.56	(1.51-1.61)	1.55	(1.50-1.61)
1998	Women	5.39	(4.57-6.36)	5.81	(4.88-6.91)	1.50	(1.45-1.55)	1.47	(1.42-1.51)
1999	Women	4.28	(3.59-5.10)	4.22	(3.46-5.14)	1.48	(1.43-1.52)	1.44	(1.40-1.49)
2000	Women	4.40	(3.73-5.19)	4.75	(3.96-5.69)	1.45	(1.41-1.49)	1.42	(1.38-1.46)
2001	Women	4.06	(3.44-4.80)	4.07	(3.36-4.93)	1.42	(1.38-1.46)	1.39	(1.35-1.43)
2002	Women	4.32	(3.70-5.04)	4.42	(3.70-5.27)	1.33	(1.29-1.36)	1.29	(1.26-1.33)
2003	Women	4.42	(3.81-5.14)	4.56	(3.84-5.40)	1.35	(1.32-1.38)	1.33	(1.29-1.36)
2004	Women	4.52	(3.91-5.23)	4.81	(4.09-5.65)	1.33	(1.30-1.36)	1.31	(1.27-1.34)
2005	Women	3.94	(3.38-4.59)	3.79	(3.17-4.53)	1.30	(1.27-1.33)	1.28	(1.25-1.31)
2006	Women	4.10	(3.52-4.71)	4.00	(3.39-4.73)	1.31	(1.28-1.33)	1.29	(1.26-1.32)
2007	Women	3.86	(3.35-4.46)	3.66	(3.10-4.32)	1.27	(1.24-1.29)	1.26	(1.23-1.28)
2008	Women	4.13	(3.61-4.73)	4.10	(3.52-4.78)	1.25	(1.22-1.27)	1.23	(1.21-1.26)
2009	Women	4.10	(3.60-4.67)	4.01	(3.46-4.66)	1.24	(1.21-1.26)	1.23	(1.20-1.25)
2010	Women	3.46	(3.01-3.97)	3.44	(2.94-4.02)	1.22	(1.19-1.24)	1.21	(1.18-1.23)

*These are the results as presented in the current published paper

Supplementary Table 2. CVD-, diabetes-, and cancer-related mortality in men and women with type 1 and type 2 diabetes, by year; comparing the two different definitions of diabetes

		Type 1 diabetes				Type 2 diabetes			
		Men (% of all deaths)		Women (% of all deaths)		Men (% of all deaths)		Women (% of all deaths)	
Year	Mortality outcome	Correct dm definition*	Incorrect dm definition	Correct dm definition*	incorrect dm definition	Correct dm definition*	incorrect dm definition	Correct dm definition*	incorrect dm definition
1997	**CVD**	25.25	24.75	14.61	14.29	33.84	33.91	33.74	34.11
1998		23.24	22.22	21.43	21.26	32.72	33.23	34.33	34.75
1999		24.46	23.44	20.97	19.59	33.28	33.73	32.04	32.27
2000		23.15	20.75	23.19	21.55	31.71	32.07	32.17	32.16
2001		23.22	23.11	24.82	20.75	30.47	30.43	33.1	33.24
2002		21.74	20.6	21.94	17.5	29.44	29.55	29.98	30.06
2003		22.9	23.5	20.24	18.94	28.76	28.74	28.92	28.84
2004		22.06	20.49	19.44	19.73	27.74	27.76	28.54	28.13
2005		23.57	25.00	21.74	18.64	26.63	26.7	26.61	26.61
2006		18.38	16.79	12.23	10.00	24.62	24.64	24.05	24.08
2007		18.54	18.75	16.55	16.83	23.5	23.43	23.47	23.53
2008		21.55	21.71	15.72	14.63	23.16	23.06	23.93	23.93
2009		25.74	25.71	20.61	19.67	22.62	22.54	23.25	23.21
2010		17.07	16.67	9.93	11.11	21.11	21.04	22.79	22.68
1997	**Diabetes**	33.17	33.84	41.57	42.86	16.56	16.68	20.46	20.5
1998		31.35	32.75	34.29	35.43	15.19	15.56	18.56	18.67
1999		24.03	25.52	25.00	27.84	15.49	15.44	18	18.02
2000		33.80	38.36	28.99	32.76	15.22	15.24	16.92	17.05
2001		30.71	33.02	34.31	36.79	14.98	14.81	16.01	15.94
2002		31.23	32.16	24.52	26.67	14.31	14.2	15.52	15.29

2003		32.06	34.97	26.79	30.3	14.76	14.59	15.8	15.36
2004		29.04	33.66	32.78	33.33	14.35	14.06	16.28	16.11
2005		28.96	28.7	26.09	28.81	13.21	12.86	16.5	16.15
2006		25.41	27.48	31.65	35.00	13.57	13.35	15.91	15.69
2007		28.29	27.78	31.65	31.68	13.65	13.44	16.24	16.14
2008		29.31	28.00	26.42	29.27	14.28	14.14	15.81	15.67
2009		35.15	39.29	28.48	31.15	13.7	13.54	15.94	15.83
2010		24.88	25.64	33.11	34.19	12.26	12.18	14.75	14.57
1997	**Cancer**	8.42	8.08	14.61	13.10	25.18	24.85	19.86	19.29
1998		9.19	8.77	11.43	10.24	27.84	27.02	20.78	19.84
1999		12.45	11.98	16.13	13.40	25.66	25.01	21.01	20.73
2000		11.57	8.81	13.77	11.21	27.24	26.89	21.71	21.27
2001		10.86	9.43	11.68	13.21	28.01	28.32	22.26	22.48
2002		9.88	9.55	23.23	24.17	28.36	28.44	22.46	22.65
2003		10.69	9.84	15.48	17.42	28.34	28.37	24.07	24.44
2004		11.03	9.76	9.44	10.88	29.12	29.42	23.59	23.94
2005		13.13	12.5	16.15	15.25	30.22	30.6	23.52	23.79
2006		21.62	21.37	22.3	23.00	32.08	32.32	26.12	26.37
2007		21.46	19.44	23.74	21.78	32.45	32.56	25.29	25.52
2008		18.97	19.43	23.27	21.95	32.53	32.69	24.51	24.6
2009		19.31	15.00	24.85	24.59	32.94	33.09	25.78	25.91
2010		27.32	25.00	19.87	17.95	33.63	33.66	24.55	24.77

*These are the results as presented in the current published paper

Declaration for Thesis – Chapter 3.2

Harding JL, Shaw JE, Peeters A, Davidson S & Magliano DJ. Age-specific trends from 2000-2011 in all-cause and cause-specific mortality in type 1 and type 2 diabetes: a cohort study of over one million people. *Diabetes Care*. Accepted Feb 2016

In the case of Chapter 3.2, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Acquisition of data, data management, analysis and interpretation of data, conceptualisation and writing of manuscript, critical revision, corresponding author	80%

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

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Jonathan Shaw	Conceptualisation, design of protocol, interpretation and approval of final draft for publication	
Anna Peeters	Critical revision, approval of final draft for publication	
Susan Davidson	Data provision	
Dianna Magliano	Conceptualisation, data acquisition, critical revision, approval of final draft for publication	

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

Candidate's Signature		Date: 31/03/2016
Main Supervisor's Signature		Date: 31/03/2016

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

Age-Specific Trends from 2000–2011 in All-Cause and Cause-Specific Mortality in Type 1 and Type 2 Diabetes: A Cohort Study of Over One Million People

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ABSTRACT

Background

We analysed changes in all-cause and cause-specific mortality rates from 2000-2011 in people with diabetes, by age-group.

Methods

1,189,079 (7.3% type 1) Australians with diabetes registered on the National Diabetes Service Scheme between 2000 and 2011 were linked to the National Death Index. Mortality rates in the total population were age-standardised to the 2001 Australian population. Mortality rates were calculated for the following age-groups: 0 to <40; ≥40 to <60; ≥60 to ≤85. Annual mortality rates were fitted using a Poisson regression model including calendar year as a covariate and age and sex where appropriate, with p_{trends} reported.

Results

For type 1, all-cause, CVD, and diabetes age-standardised mortality rates (ASMR) decreased each year by 0.61, 0.35 and 0.14 per 1,000 person-years (PY), respectively, between 2000 and 2011, $p_{trend}<0.05$, while cancer mortality remained unchanged. By age, significant decreases in all-cause, CVD and diabetes mortality rates were observed in all age-groups, excluding diabetes mortality in age-group 0-40. For type 2, all-cause, CVD and diabetes ASMRs decreased per year by 0.18, 0.15 and 0.03 per 1,000 PY, respectively, $p_{trend}<0.001$, while cancer remain unchanged. By age these decreases were observed in all age-groups, excluding 0-40 where significant increases in all-cause and cancer mortality were noted and no change for CVD and diabetes mortality.

Conclusion

All-cause, CVD and diabetes ASMRs in type 1 and type 2 diabetes decreased between 2000 and 2011, while cancer mortality remains unchanged. However, younger populations are not benefiting from the same improvements as older populations. The absence of a decline in cancer mortality warrants urgent attention.

People with diabetes have higher all-cause mortality rates compared to people without diabetes, mainly attributable to cardiovascular disease (CVD).[1] However, some evidence suggests that patterns of mortality may be changing.[2,3] Declines in age-standardised all-cause and CVD mortality rates have been noted among people with type 2 diabetes with some evidence that mortality may be approaching that of the general population, particularly at older ages.[2-4] For type 1 diabetes, data are inconsistent, with some studies reporting a decrease in all-cause and CVD mortality over time,[5-8] while others report no change.[9-11]

Data on the effects of diabetes on other causes of death over time is mixed with studies reporting increased, unchanged or reduced mortality for complications of diabetes,[5,12,13] cancer mortality,[3,8] and acute complications of diabetes.[3,14] Many of these studies are based on small sample sizes and do not distinguish between type 1 and type 2 diabetes. To date, there have been no age-specific analyses of trends in cause-specific mortality among people with diabetes. Examining age-specific trends in mortality identifies which age-groups are driving observed changes in mortality. These are important data to inform public health to prioritise where prevention and treatment efforts are most needed.

Using a large cohort of Australians registered on the National Diabetes Service Scheme (NDSS), we examine trends in age-specific mortality rates for all-cause, and the three most common causes of death, CVD, diabetes and cancer, among people with type 1 and type 2 diabetes.

Research Design & Methods

The NDSS was set up in 1987 to deliver diabetes-related products at subsidised prices and provide information to people with diabetes. Registration of patients is free, and is completed by a medical practitioner or credentialed diabetes nurse educator. The NDSS captures 80-90% of all Australians with known diabetes.[15]

We included all people with type 1 or type 2 diabetes who were registered on the NDSS between 2000 and 2011 (including all those registered before 2000, and still alive on January 1 2000). 2000 was chosen as the start date, as it followed a unification of state-based registries, as well as an improvement in data quality. After excluding 833 registrants, because registration date and date of death were the same, the sample size for these analyses was 1,189,079. Diabetes type is classified by the health practitioner completing registration. However, for the current study, type 1 diabetes status was assigned to registrants who satisfied all three of the following conditions: were recorded as type 1 on the NDSS registry, were diagnosed <45 years of age and were taking insulin. Registration date was used as a proxy for diagnosis date as a large proportion of registrants (54.4% type 1 diabetes and 32.8% type 2 diabetes) were missing date of diagnosis, many of whom registered in the early years of the operation of the NDSS and had had diabetes for a number of years. We chose 45 years as the cut-off to minimize the number of people with type 1 diabetes that we would miss, without misclassifying significant numbers of people with type 2 as type 1.[16] Additionally, registrants who were recorded as type 2 on the registry, were diagnosed before the age of 30 and were taking insulin within 1 year of diagnosis date were reclassified as type 1 diabetes. All others were classified as type 2 diabetes.

The NDSS was linked to the National Death Index (NDI) using data up to and including 31 December 2011, and used the general framework of Fellegi and Sunter.[17] First name, second name, third name, gender, and date of birth were used to conduct the linkage. We set a match link rate of 98.63% (true matches/correct links) with link accuracy of 98.97% (1.03% expected to be false positive links).

Cause of death (COD) was classified according to the International Classification of Diseases 10th revision (ICD-10). Deaths were attributed to CVD if the underlying COD was coded I10-I25 or I60-I69. In addition, participants with a COD of 'uncomplicated diabetes mellitus' (ICD-10 codes E109, E119, E12.9, E13.9 or E149) or 'diabetes with circulatory complications' (E105, E11.5, E12.5, E13.5, E14.5), and where a CVD code also appeared in the first line of the death certificate, were attributed a CVD code for COD. Diabetes and cancer deaths were defined by underlying ICD-10 codes E10-E14 and C00-C97, respectively.

Statistical Analysis

Individuals were followed from 1 January 2000, or registration date if thereafter, to 31 December 2011 or date of death, whichever occurred first. Age-specific mortality rates and 95% confidence intervals (95%CI) were calculated using a Poisson regression model, with a Poisson error distribution, a log link function and the natural log of population treated as an 'offset'.[18] This was done for the following age-groups: 0 to <40; ≥40 to <60; ≥60 to ≤85 in the total population and in men and women separately. We also examined smaller age-groups of: 0 to <40; ≥40 to <50; ≥50 to <60; ≥60 to <70; ≥70 to ≤85 in the total population to tease out mortality patterns in more specific age groups. For analyses of the total population, we calculated age-standardised mortality rates (ASMR), standardised to the 2001 Australian population, obtained from the Australian Institute of Health and Welfare.

For the assessment of changes in all-cause, and cause-specific mortality over time, annual mortality rates were fitted using a Poisson regression model including calendar year as a covariate and age and sex where appropriate, with p_{trends} reported. For each annual percentage change estimate, the corresponding 95%CI was

calculated. Statistical significance was established at $p<0.05$.

All analysis used STATA version 12.1 (StataCorp, College Station, TX, USA). Graphs were generated using GraphPad Prism version 6.0 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com). This study was approved by the Alfred Health Human Research Ethics Committee (HREC) and the Australian Institute for Health and Welfare HREC.

Results

This study included 1,189,049 (7.3% type 1) individuals with type 1 or type 2 diabetes who were registered on the NDSS between 2000 and 2011. There was a greater proportion of males with type 1 and type 2 diabetes compared to females, 52.6% and 53.9% respectively; median age at diagnosis was 20.1 years (inter quartile range (IQR): 11.1—30.4) and 58.5 years (IQR: 49.3—67.8) for type 1 and type 2 diabetes, respectively; median follow-up time was 15.2 years and 7.2 years for type 1 and type 2 diabetes, respectively; and 27.9% of people with type 2 diabetes were on insulin.

Among 87,047 people with type 1 diabetes, a total of 5,578 deaths occurred during 825,777 person years (PY) of follow-up between 2000 and 2011; ASMR was 16.2 per 1,000 PY. In the total type 1 diabetes population, all-cause, CVD, and diabetes ASMRs significantly decreased each year by 0.61, 0.35 and 0.14 per 1,000 PY, respectively, between 2000 and 2011 ($p_{trend}<0.05$, Figure 1A and Supplementary Table 1), while cancer ASMRs remain unchanged. When examined by age, significant decreases in all-cause, CVD and diabetes mortality rates were observed in all age-groups, excluding diabetes mortality in age-group 0-40 years (Table 1). No declines in cancer mortality rates were observed in any age-group. The largest declines in mortality rates were consistently observed in the 60-85 year age-groups with declines per year of 0.08, 0.11 and 0.10 per 1,000 PY for all-cause, CVD and diabetes, respectively. Similar patterns were observed in men and women.

When examined in smaller age-groups, all-cause mortality significantly decreased in all age-groups, excluding 70-85 with a borderline significant 0.03 per 1,000 PY decrease in the annual rate ($p_{trend}=0.098$, Table 2). Significant improvements in CVD mortality were noted in all age-groups with annual rate declines between 0.05 and 0.09 per 1000 PY. For diabetes mortality, significant decreases in mortality were observed in age-groups 50-60 and 60-70 and no change in mortality for age-groups 0-40, 40-50 and 70-85 . Significant decreases in cancer mortality rates were observed in age-group 40-50, $p_{trend}=0.023$, but this trend was not observed in any other age-group.

Among 1,102,002 people with type 2 diabetes, a total of 206,974 deaths occurred during 7,309,921 PY of follow-up between 2000 and 2011; ASMR was 8.6 per 1000 PY. In the total population with type 2 diabetes, all-cause, CVD and diabetes ASMRs significantly decreased per year by 0.18, 0.15 and 0.03 per 1000 PY, respectively, between 2000 and 2011 (Figure 1B and Supplementary Table 1), while cancer ASMRs remained unchanged. By age, significant decreases in all-cause, CVD, diabetes and cancer mortality rates were observed in all age-groups, excluding age-group 0-40 where significant increases in mortality were observed for all-cause and cancer, and no change for CVD and diabetes mortality (Table 3). The largest declines in mortality rates were consistently observed in the 40-60 year age-groups with annual rate declines of 0.02, 0.05, 0.05 and 0.03 per 1000 PY for all-cause, CVD, diabetes and cancer, respectively. Similar patterns were observed in men and women , however diabetes mortality in women aged 0-40 could not be estimated due to too few observations to derive meaningful trends. By smaller age-groups, in those aged 40-50 there was no change in mortality rates from all-cause and diabetes, while significant increases in cancer mortality rates were noted (Table 4). Significant declines in mortality from all-cause, CVD, diabetes and cancer were noted in all age-groups >50 with the greatest declines consistently observed in the 50-60 and 60-70 age-groups.

Discussion

Summary

Our findings of an analysis of age-specific mortality trends among Australians with diabetes are three-fold. First, ASMRs for all-cause, CVD, and diabetes mortality have decreased in people with type 1 and type 2 diabetes in the last decade, while cancer ASMRs remains unchanged. Second, improvements in mortality are not consistently seen across the age spectrum, with younger ages (<40) not experiencing the same declines in mortality as older populations and even more concerning, for type 2 diabetes, increases in all-cause and cancer mortality rates was noted in age-groups 0-40. Last, declines in cancer mortality rates were observed for older age-groups in type 2, but not in type 1 diabetes.

Comparison to the literature

Our observed declines in all-cause and CVD mortality are consistent with trends in other developed nations. For example, in a population of U.S. adults with diabetes, Gregg et al. showed that between 1997 and 2006, all-cause and CVD death rates declined by 23% and 40%, respectively, comparable to our observed declines of 17.9% and 51.7% in type 2 diabetes, respectively. Declines in all-cause and CVD mortality have also been noted in non-diabetes populations with declines of 40% and 62% between 1950 and 2005, respectively, though evidence suggests the rate of decline is greater in diabetes with declines of 48% and 69%, respectively, for the same time period.[4] These declines in mortality may be explained, at least in part, by earlier detection and by improvements in diabetes

care, and in CVD treatments and risk factors.[19-21] However, previous work by our group using the NDSS data, has shown that people with type 1 and type 2 diabetes still experience a 200% and 20% increased risk of excess all-cause mortality, respectively, compared to the general population[8], similar to findings in the UK and Canada.[2,22] Excess CVD mortality is in the realm of 50-110%, and 300-400% for type 2[23,24] and type 1 diabetes[22], respectively, compared with non-diabetes populations. Therefore, while data presented here suggest improvements in the mortality experience among diabetes, much room exists for additional improvements.

Previous studies on mortality from diabetes and cancer are conflicting. For diabetes, we report overall declines of 18.5% and 38.5% in type 1 and 2 diabetes, respectively. National data from the USA recently reported relative declines of 64% between 1990 and 2010 for mortality due to hyperglycaemic crisis among type 2 diabetes.[25] These estimates are higher than those reported here most likely due to the longer time frame of the US study and the specific exploration of hyperglycaemic crisis. For type 1 diabetes, a Finnish study found increases in mortality due to (all) acute complications of diabetes between 1970-1989[26], while a Japanese study of patients with diabetes diagnosed before 18 years of age observed an 80% decrease (from 421 to 83 deaths per 100,000 persons) between 1965-1980[27], though more contemporary estimates for type 1 diabetes are lacking. Improvements in mortality from diabetes may be attributed to changes to practice guidelines for diabetes management over the last decade which have emphasised the need for aggressive control of blood pressure, lipid levels and hyperglycaemia in patients with diabetes.[28]

For cancer, we observed no change in ASMRs between 2000 and 2011 among people with type 1 and type 2 diabetes. However, among type 2 diabetes, we did observe significant decreases in cancer mortality among 40-60 and 60-85 age-groups, though these improvements were not noted for younger age-groups, and in fact, we noted an increase in cancer mortality in those aged 0-40. One of the key reasons for our findings is likely to be competing mortality. We have previously reported that the proportion of deaths attributed to cancer is increasing over time, in part due to improvements in treatment of CVD. Thus, people with diabetes are surviving longer and not dying from diseases such as CVD and then develop other outcomes such as cancer.[29] Cancer is now a leading cause of death among diabetes, accounting for 27 and 33% of all deaths in people with type 1 and type 2 diabetes, respectively.[29] Only one other study that we are aware of has also shown that the proportion of deaths attributed to cancer among people with type 2 diabetes has increased from 23% in 1970 to 27% in 1990.[3] This increase in the proportion of deaths attributed to cancer is similar to what is being observed in the general population.[30] However, the increase in the proportion of deaths attributed to cancer among the general population coincides with decreases in absolute mortality rates from cancer.[31,32] declines in cancer mortality rates among the general population may be attributed to increased uptake of screening and improved treatments. The absence of a decline in cancer mortality rates among those with diabetes may to be due to a range of reasons including a rise in cancer incidence, later presentations and diagnosis and poorer responses to therapy..[33]

To our knowledge, this is the first time that trends in absolute cause-specific mortality rates in diabetes have been explored by age-group. This is possibly because large study sizes are needed to obtain precise estimates, especially among younger age-groups where fewer deaths occur. We show significant declines in mortality from all-cause, CVD and diabetes in older age-groups, but this is not seen in those less than 40 years old. In fact, significant increases in mortality were observed for all-cause and cancer among younger people with type 2 diabetes and no change for CVD or diabetes mortality. There are several potential explanations for no improvement, and an increase in mortality rates among younger age-groups. These include a low number of CVD and diabetes events in these age groups which may result in a Type II error, the worsening or lack of improvement in risk factors, as well as possible misclassification of type 1 and type 2 diabetes which may differ over time. For example, the incidence of young-onset type 2 diabetes is increasing, and it is possible, that young people with type 2 diabetes are being incorrectly misclassified as type 1 diabetes and this may drive the higher mortality rates in this age-group. However, in those with type 1 diabetes, we show mortality is decreasing. Therefore, we believe that the more likely explanation is that young-onset type 2 diabetes represents a more severe form of diabetes. Our data support recently published studies suggesting that young-onset type 2 diabetes is the more lethal phenotype of diabetes and is associated with a greater mortality, more diabetes complications, unfavourable cardiovascular disease risk factors and greater difficulty in achieving glycaemic control, even compared with type 1 diabetes.[34-37] Given the increasing incidence of young-onset type 2 diabetes and its severity, there is an urgent need for diabetes prevention efforts to be targeted toward youth.

Strengths and limitations

The main strength of this study is that it is disease-registry based with a large sample size, long follow up time and the ability to distinguish between type 1 and type 2 diabetes. There are several limitations, however, that should be acknowledged. Firstly, the NDSS

is an administrative database and there are inherent limitations with using administrative databases for research purposes.[38] Namely, for our study, the lack of precise information about type of diabetes for all registrants was not available. The classification of diabetes, particularly in young patients, is challenging and misclassification can occur. However, the proportions of type 1 and type 2 diabetes in this study (7.3% vs. 92.7%) are similar in other Australian data.[39] Further, the proportion of type 2 diabetes who were also on insulin is consistent with other studies.[40] Given these well known demographics, and our very large sample size, we believe that any misclassification in this study will not alter our results.

Second, the NDSS is considered among the best available national data sources for estimating overall prevalence of diagnosed diabetes in Australia.[15] However, the NDSS does not capture those with undiagnosed diabetes. Recent Australian data show that for every five cases of known diabetes, there are four undiagnosed cases.[41] The NDSS also may underestimate the total number of people with diet-controlled diabetes as the diabetes-related products provided through the scheme may not be needed.[41] In Australia, the proportion of known diabetes controlled by diet only was estimated to be 28% in 2000.[42]. It is possible, therefore, that using the NDSS is reflective of the more serious diabetes cases. However, the NDSS coverage of type 1 diabetes is known to be very high as access to insulin-related products is through the NDSS scheme.[15] Further, we believe the coverage of type 2 diabetes is adequately reflective of people with type 2 diabetes in Australia given that the age distribution and median age at diagnosis is similar to that seen in other populations.[40] We therefore do not believe this potential source of bias will significantly impact our findings.

Last, although the NDSS provides the largest dataset for people with diagnosed diabetes, our findings are limited by a lack of covariates in the dataset. Therefore, we were unable to explore the extent to which improvements in quality of care, medical treatments, and/or self-management behaviours contributed to the reductions in mortality over time.

Conclusions

We have shown that ASMRs from all-cause, CVD and diabetes in type 1 and type 2 diabetes have decreased over the last decade in Australia, while cancer ASMRs remain unchanged. These trends suggest continued success in the treatment of diabetes and its complications. However, these improvements are not seen across the entire age spectrum, with younger populations not benefiting from the same improvements as older populations and continued efforts to rectify this disparity are needed. In addition, the absence of a decline in cancer mortality rates among diabetes is likely to lead a higher burden of cancer among people with diabetes. This warrants urgent attention.

Author's contributions

JLH, BBioMedSci(Hons) (Baker IDI Heart and Diabetes Institute; Monash University) wrote the manuscript, had full access to all the data, and conducted the analyses. AP, PhD (Deakin University) contributed to discussion and reviewed/edited the manuscript. SD, BHSc (Diabetes Australia) provided data. JES, FRACP (Baker IDI Heart and Diabetes Institute; Monash University) & DJM, PhD, (Baker IDI Heart and Diabetes Institute; Monash University) contributed to conceptualisation, discussion and reviewed/edited manuscript. DJM 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.

Acknowledgments

Data for this project were sourced from the National Diabetes Service Scheme (NDSS) – an initiative of the Australian Government administered by Diabetes Australia since 1987. Mortality data were sourced from the National Death Index, a database, housed at the Australian Institute of Welfare, which contains records of all deaths registered in Australia since 1980.

Conflict of Interest

None

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Figure Legends

Figure 1 Age-standardised mortality rates in people with type 1 (A) and type 2 (B) diabetes between 2000 and 2011. Note: Rates were standardised to the 2001 Australian population. *$p_{trend} < 0.05$

References

1. The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *New England Journal of Medicine*. 2011;364:829-841.
2. Lind M, Garcia-Rodriguez LA, Booth GL, et al. Mortality trends in patients with and without diabetes in Ontario, Canada and the UK from 1996 to 2009: a population-based study. *Diabetologia*. 2013;DOI 10.1007/s00125-013-2949-2.

3. Thomas RJ, Palumbo PJ, Melton J, et al. Trends in the mortality burden associated with diabetes mellitus. *Archives of internal medicine*. 2003;163:445-451.
4. Preis SR, Pencina MJ, Hwang SJ, et al. Trends in cardiovascular disease risk factors in individuals with and witout diabetes mullitus in the Framingham Heart Study. *Circulation*. 2009;120:212-220.
5. Alleman S, Saner C, Zwahlen M, Christ ER, Diem P, Stettler C. Long-term cardiovascular and non-cardiovascular mortality in women and men with type 1 and type 2 diabetes mellitus: A 30-year follow-up in Switzerland. *Swiss Medical Weekly*. 2009;139(39-40):576-583.
6. Nishimura R, LaPorte RE, Dorman JS, Tajima N, Becker D, Orchard TJ. Mortality trends in type 1 diabetes. *Diabetes care*. 2001;24:823-827.
7. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year national history of type 1 diabetes complications. *Diabetes*. 2006;55:1463-1469.
8. Diabetes Australia. The National Diabetes Service Scheme. 2015; https://www.ndss.com.au/ Accessed Saturday 28th August, 2015.
9. Waernbaum I, Blohmé G, Östman J, et al. Excess mortality in incident cases of diabetes mellitus aged 15 to 34 years at diagnosis: a population-based study (DISS) in Sweden. *Diabetologia*. 2006;49:653-659.
10. Burnet DL, Cooper AJ, Drum ML, Lipton RB. Risk factors for mortality in a diverse cohort of patients with childhood-onset diabetes in Chicago. *Diabetes care*. 2007;30:2559-2563.
11. Skrivarhaug T, Bangstead HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. *Diabetologia*. 2006;49:298-305.
12. Ford ES. Trends in the risk for coronary heart disease among adults with diagnosed diabetes in the US. *Diabetes care*. 2011;34:1337-1343.
13. Gregg EW, Cheng YJ, Saydah S, et al. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006. *Diabetes care*. 2012;35:1252-1257.
14. Harjutsalo V, Forsblom C, PH. G. Time trends in mortality in patients with type 1 diabetes: nationwide population based cohort study. *British Medical Journal*. 2011;343:d5364.
15. Australian Institute of Health and Welfare. *Diabetes prevalence in Australia. An assessment of national data sources*. Australian Institute of Health and Welfare, Canberra; 2009.
16. Kenny SJ, Aubert RE, LS. G. Prevalence and incidence of non-insulin-dependent diabetes. 2nd ed. Washington, DC, U.S. Govt. Printing Office 1995.
17. Fellegi IP, AB. S. A Theory for Record Linkage,. *Journal of the American Statistical Association*. 1969;40:1183-1210.
18. Breslow NE, Day NE. Fitting Models to Grouped Data. Statistical methods in cancer research. II: The design and analysis of cohort studies. Lyon: IARC Scientific Publications No. 82; 1987.
19. Kromhout D, Bloemberg B, Feskens E, Menotti A, A. N. Saturated fat, vitamin C and smoking predict long-term population all-cause mortality rates in the Seven Countries Study. *International journal of epidemiology*. 2000;29(2):260-265.
20. Hertog MG, Kromhout D, Aravanis C, et al. Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. *Arch Intern Med*. 1995;155(4):381-386.
21. Sytkowski PA, D'Agostino RB, Belanger A, Kannel WB. Sex and time trends in cardiovascular disease incidence and mortality: the Framingham Heart Study, 1950-1989. *American Journal of Epidemiology*. 1996;43(4):338-350.
22. Livingstone SJ, Looker HC, Hothersall EJ, et al. Risk of Cardiovascular Disease and Total Mortality in Adults with Type 1 Diabetes: Scottish Registry Linkage Study. *PLoS medicine*. 2012;9:e1001321.
23. Romon I, Rey G, Mandereau-Bruno L, et al. The excess mortality related to cardiovascular diseases and cancer among adults pharmacologically treated for diabetes--the 2001-2006 ENTRED cohort. *Diabetic medicine: a journal of the British Diabetic Association*. Aug 2014;31(8):946-953.
24. Barnett KN, Ogston SA, McMurdo ME, Morris AD, Evans JM. A 12-year follow-up study of all-cause and cardiovascular mortality among 10,532 people newly diagnosed with Type 2 diabetes in Tayside, Scotland. *Diabetic medicine: a journal of the British Diabetic Association*. Oct 2010;27(10):1124-1129.
25. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. *New England Journal of Medicine*. 2014;370(16):1514-1523.
26. Harjutsalo V, Forsblom C, Groop PH. Time trends in mortality in patients with type 1 diabetes: nationwide population based cohort study. *British Medical Journal*. 2011;343:d5364.
27. Nishimura R, Matsushima M, Tajima N, et al. A major improvement in the prognosis of individuals with IDDM in the past 30 years in Japan. *Diabetes care*. 1996;19:758-760.
28. American Diabetes Association. Standards of medical care in diabetes. *Diabetes care*. 2011;34(Suppl. 1):S11-S61.

29. Harding JL, Shaw JE, Peeters A, Guiver T, Davidson S, Magliano DJ. Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997-2010. *Diabetes care*. Sep 2014;37(9):2579-2586.
30. AIHW. *Cancer in Australia: an overview 2014*. Canberra: AIHW2014.
31. Marshall DC, Webb TE, Hall RA, Salciccioli JD, Ali R, Maruthappu M. Trends in UK regional cancer mortality 1991-2007. *British journal of cancer*. Jan 14 2016.
32. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA: a cancer journal for clinicians*. Jan-Feb 2015;65(1):5-29.
33. Srokowski TP, Fang S, Hortobagyi GN, Giordano S, H. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. *Journal of clinical oncology*. 2009;27(13):2170-2176.
34. Constantino MI, Molyneaux L, Limacher-Gisler F, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes care*. Dec 2013;36(12):3863-3869.
35. Rhodes ET, Prosser LA, Hoerger TJ, Lieu T, Ludwig DS, Laffel LM. Estimated morbidity and mortality in adolescents and young adults diagnosed with Type 2 diabetes mellitus. *Diabetic medicine: a journal of the British Diabetic Association*. Apr 2012;29(4):453-463.
36. Yeung RO, Zhang Y, Luk A, et al. Metabolic profiles and treatment gaps in young-onset type 2 diabetes in Asia (the JADE programme): a cross-sectional study of a prospective cohort. The lancet. *Diabetes & endocrinology*. Dec 2014;2(12):935-943.
37. Group TS, Zeitler P, Hirst K, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med*. Jun 14 2012;366(24):2247-2256.
38. Hoover KW, Guoyu T, Kent CK, SO. A. Epidemiologic research using administrative databases: Garbage in, garbage out. *Obstetrics and Gynecology*. 2011;117(3):729-730.
39. Australian Institute of Health and Welfare. *Diabetes prevalence in Australia: detailed estimates for 2007-08*. Canberra, Australia: AIHW 2011.
40. Koro CE, Bowlin SJ, Bourgeois N, DO. F. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. *Diabetes care*. 2004;27:17-20.
41. Valentine NA, Alhawassi TM, Roberts GW, Vora PP, Stranks SN, Doogue MP. Detecting undiagnosed diabetes using glycated haemoglobin: an automated screening test in hospitalised patients. *The Medical journal of Australia*. Feb 21 2011;194(4):160-164.
42. Dunstan DD, ., Zimmet P, Welborn T, et al. *Diabesity & Associated Disorders in Australia - 2000: The Australian Diabetes, Obesity and Lifestyle Study*. Melbourne: International Diabetes Institute;2001.

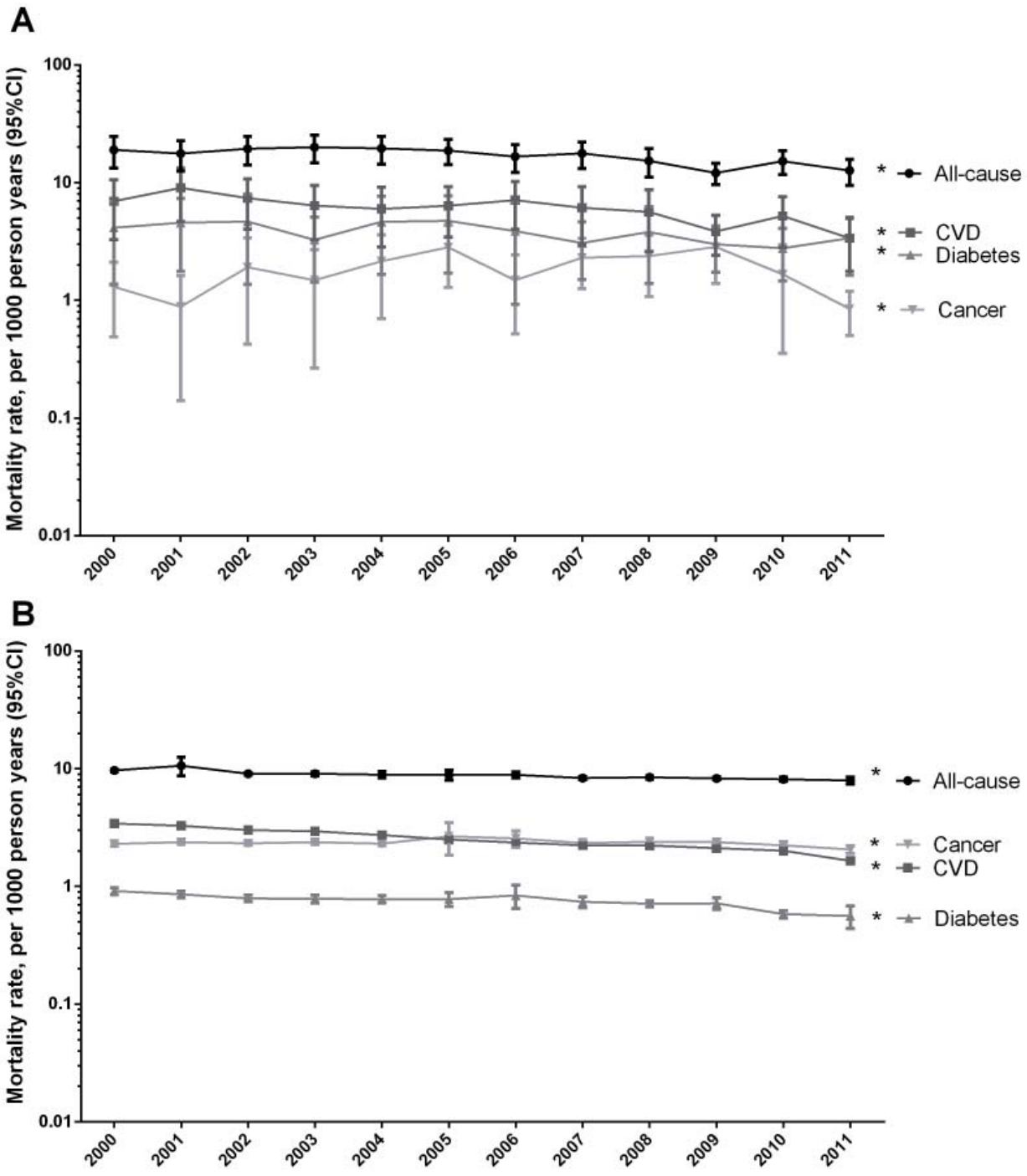

Figure 1 Age-standardised mortality rates (95%CI) in type 1 (A) and type 2 (B) diabetes between 2000 and 2011. Rates were standardised to the 2011 Australian population. *p_{trend}<0.05

Table 1 All-cause, CVD, diabetes and cancer mortality rates between 2000 and 2011, by age group, among the total type 1 diabetes and in men and women separately

		Year														
	Age group	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Annual change in rate (95%CI)	% change 2000-2011†	P_{trend}
Men and women combined																
All-cause	*0-40*	2.48	2.71	2.54	2.15	2.52	2.11	2.30	1.85	2.33	2.36	1.88	1.96	-0.03 (-0.04, -0.01)	-21.00	0.006
	40-60	10.00	10.94	10.21	10.41	9.79	10.03	9.55	9.36	10.16	9.24	8.73	7.41	-0.02 (-0.09, -0.06)	-25.90	<0.001
	60-85	61.43	46.96	52.23	51.18	42.34	33.71	31.49	28.82	27.75	24.35	25.95	26.31	-0.08 (-0.09, -0.06)	-57.20	<0.001
CVD	*0-40*	0.42	0.48	0.27	0.29	0.37	0.23	0.36	0.14	0.27	0.23	0.10	0.25	-0.08 (-0.13, -0.03)	-40.10	0.003
	40-60	3.50	3.82	3.17	3.31	3.02	3.28	2.35	2.94	2.75	3.29	2.32	1.77	-0.04 (-0.06, -0.02)	-49.40	<0.001
	60-85	25.29	26.41	26.12	20.47	16.02	12.48	12.85	9.77	11.42	8.06	7.81	9.09	-0.11 (-0.14, -0.08)	-64.10	<0.001
Diabetes	*0-40*	0.66	0.69	0.77	0.64	0.57	0.51	0.55	0.68	0.64	0.75	0.69	0.55	-0.01 (-0.04, 0.03)	-16.70	0.691
	40-60	2.26	2.55	2.12	2.31	2.23	2.11	2.06	1.74	2.27	2.15	1.73	1.65	-0.02 (-0.05, -0.00)	-27.00	0.022
	60-85	14.45	11.74	9.95	8.53	10.30	5.83	4.50	5.37	4.72	5.10	4.88	4.24	-0.10 (-0.14, -0.05)	-70.70	<0.001
Cancer	*0-40*	0.18	0.24	0.41	0.29	0.11	0.23	0.17	0.14	0.21	0.13	0.25	0.13	-0.05 (-0.11, 0.01)	-27.80	0.116
	40-60	1.45	1.43	1.56	1.42	1.17	1.27	1.63	1.23	1.47	1.23	1.51	1.21	-0.01 (-0.03, 0.02)	-16.60	0.541
	60-85	7.23	1.47	4.97	3.41	5.15	7.49	5.14	7.33	5.12	5.92	4.46	3.76	-0.03 (-0.08, 0.02)	-48.00	0.247
Men																
All-cause	*0-40*	2.65	3.89	3.21	2.25	3.28	2.47	2.69	2.08	2.68	2.90	2.29	2.43	-0.03 (-0.05, -0.02)	-8.30	0.032
	40-60	11.86	13.67	12.02	12.25	11.03	12.66	11.98	11.75	12.45	10.61	11.22	9.30	-0.02(-0.03, -0.01)	-21.60	0.006
	60-85	75.91	40.79	55.37	64.10	44.07	38.23	32.90	29.19	31.44	24.95	27.95	29.07	-0.08 (-0.10, -0.05)	-61.80	<0.001
CVD	*0-40*	0.44	0.56	0.36	0.36	0.46	0.22	0.49	0.11	0.21	0.40	0.15	0.38	-0.06 (-0.12, 0.01)	-13.60	0.098
	40-60	4.32	5.17	4.05	4.04	3.55	4.46	3.38	4.19	3.94	4.11	3.21	2.45	-0.03 (-0.06, -0.01)	-43.30	0.002
	60-85	25.30	22.94	27.69	25.34	18.03	12.98	12.83	8.46	14.01	8.60	9.72	10.19	-0.10 (-0.14, -0.06)	-59.70	<0.001

Diabetes	*0-40*	0.69	0.99	0.91	0.77	0.69	0.62	0.55	0.90	0.88	0.95	0.88	0.62	-0.00 (-0.04, 0.04)	-10.10	0.948
	40-60	2.59	2.66	2.59	2.76	2.43	2.84	2.55	1.65	2.79	2.46	1.95	2.14	-0.02 (-0.05, 0.01)	-17.40	0.124
	60-85	22.14	10.20	10.65	11.93	9.02	6.49	4.46	6.77	5.81	5.45	4.86	4.03	-0.11 (-0.17, -0.06)	-8.20	<0.001
Cancer	*0-40*	0.19	0.25	0.48	0.24	0.17	0.28	0.22	0.11	0.21	0.05	0.24	0.14	-0.07 (-0.15, 0.02)	-26.30	0.121
	40-60	1.49	1.77	0.98	1.41	1.38	1.36	1.72	1.33	1.52	1.07	1.95	1.26	0.00 (-0.03, 0.04)	-15.40	0.918
	60-85	9.49	2.55	6.39	4.47	6.01	8.66	5.58	7.62	5.13	6.31	5.35	4.88	-0.03 (-0.09, 0.03)	-48.60	0.366
Women																
All-cause	*0-40*	2.32	1.61	1.90	2.06	1.76	1.75	1.90	1.61	1.97	1.78	1.44	1.43	-0.03 (-0.05, 0.00)	-39.70	0.085
	40-60	7.77	7.75	8.13	8.36	8.42	7.21	6.98	6.89	7.85	7.86	6.26	5.55	-0.02 (-0.04, -0.01)	-28.80	0.004
	60-85	42.13	55.33	47.83	33.89	40.02	27.54	29.56	28.31	22.75	23.55	23.25	22.64	-0.07 (-0.10, -0.04)	-46.30	<0.001
CVD	*0-40*	0.41	0.40	0.17	0.23	0.28	0.23	0.22	0.17	0.33	0.05	0.05	0.11	-0.12 (-0.20, -0.03)	-73.20	0.008
	40-60	2.53	2.24	2.15	2.48	2.45	2.01	1.28	1.64	1.54	2.47	1.44	1.11	-0.05 (-0.08, -0.02)	-56.10	0.001
	60-85	25.28	31.12	23.91	13.95	13.34	11.80	12.89	11.55	7.89	7.34	5.24	7.64	-0.14 (-0.18, -0.09)	-69.80	<0.001
Diabetes	*0-40*	0.64	0.40	0.63	0.52	0.45	0.40	0.56	0.44	0.38	0.54	0.48	0.48	-0.02 (-0.07, 0.04)	-25.00	0.576
	40-60	1.87	2.41	1.60	1.81	2.01	1.32	1.54	1.84	1.74	1.84	1.50	1.17	-0.03 (-0.06, 0.00)	-37.40	0.081
	60-85	4.21	13.83	8.97	3.99	12.01	4.92	4.55	3.47	3.25	4.63	4.91	4.53	-0.07 (-0.14, 0.01)	7.60*	0.073
Cancer	*0-40*	0.17	0.23	0.35	0.34	0.06	0.17	0.11	0.17	0.22	0.22	0.27	0.11	-0.03 (-0.12, 0.06)	-78.70	0.511
	40-60	1.41	1.03	2.23	1.43	0.94	1.18	1.54	1.12	1.42	1.39	1.06	1.17	-0.02 (-0.06, 0.02)	-17.00	0.311
	60-85	4.21	0.00	2.99	1.99	4.00	5.90	4.55	6.93	5.11	5.41	3.27	2.26	-0.03 (-0.11, 0.05)	-46.30	0.467

†% change is calculated as: (2000 rate– 2011 rate)/2000 rate*100. A negative percent change indicates a decline in rate between 2000 and 2011. *Indicates an increase in mortality rate between 2000 and 2011

Table 2 All-cause, CVD, diabetes and cancer mortality rates between 2000 and 2011 among type 1 diabetes in smaller age-groups

		Year														
	Age group	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Annual change in rate (95%CI)	% change 2000-2011†	P_{trend}
All-cause	*0-40*	2.48	2.71	2.54	2.15	2.52	2.11	2.30	1.85	2.33	2.36	1.88	1.96	-0.03 (-0.04, -0.01)	-20.97	0.006
	40-50	7.69	7.94	7.51	7.76	7.19	7.56	6.95	7.04	6.57	6.27	6.17	5.33	-0.03 (-0.04, -0.01)	-30.72	0.001
	50-60	14.60	16.18	14.44	14.23	13.34	13.25	12.79	12.19	14.46	12.71	11.68	9.77	-0.03 (-0.04, -0.01)	-33.10	<0.001
	60-70	53.41	28.04	23.81	29.23	31.70	21.95	25.07	23.41	24.10	20.46	22.39	24.00	-0.05 (-0.07, -0.03)	-55.05	<0.001
	70-85	78.20	87.25	112.3	120.1	94.37	113.9	87.48	89.56	77.29	86.22	89.32	69.96	-0.03 (-0.06, 0.00)	-10.54	0.098
CVD	*0-40*	0.42	0.48	0.27	0.29	0.37	0.23	0.36	0.14	0.27	0.23	0.10	0.25	-0.08 (-0.13, -0.03)	-40.48	0.003
	40-50	2.18	2.56	2.50	2.05	1.78	2.01	1.30	2.00	1.58	2.23	1.29	1.00	-0.05 (-0.08, -0.03)	-54.32	0.001
	50-60	6.15	6.01	4.21	5.12	4.72	4.93	3.67	4.09	4.14	4.53	3.51	2.66	-0.05 (-0.07, -0.02)	-56.77	<0.001
	60-70	18.69	17.25	10.99	12.37	12.40	9.07	8.95	7.71	10.15	6.65	6.33	8.30	-0.09 (-0.12, -0.06)	-55.60	<0.001
	70-85	39.10	45.92	58.12	45.96	33.70	35.81	46.86	32.84	28.63	30.59	34.15	24.12	-0.06 (-0.10, -0.01)	-38.31	0.03
Diabetes	*0-40*	0.66	0.69	0.77	0.64	0.57	0.51	0.55	0.68	0.64	0.75	0.69	0.55	-0.01 (-0.04, 0.03)	-16.67	0.691
	40-50	1.73	1.75	1.65	1.99	1.54	2.18	1.83	1.35	1.58	1.58	1.70	1.23	-0.02 (-0.05, 0.01)	-28.94	0.252
	50-60	3.33	3.94	2.87	2.78	3.17	2.00	2.35	2.22	3.09	2.82	1.76	2.13	-0.04 (-0.08, -0.01)	-36.15	0.006
	60-70	16.02	6.47	7.33	4.50	8.96	3.34	3.58	4.26	3.38	4.02	4.12	3.32	-0.08 (-0.13, -0.03)	-79.28	0.003
	70-85	11.17	22.96	15.50	21.21	16.85	22.79	12.50	17.91	22.90	22.25	18.39	21.71	0.02 (-0.05, 0.09)	94.33*	0.576
Cancer	*0-40*	0.18	0.24	0.41	0.29	0.11	0.23	0.17	0.14	0.21	0.13	0.25	0.13	-0.05 (-0.11, 0.01)	-27.78	0.116
	40-50	1.47	1.12	0.79	1.14	0.95	0.71	1.00	0.76	0.76	0.94	0.88	0.59	-0.05 (-0.09, -0.01)	-60.28	0.023
	50-60	1.41	1.97	2.77	1.82	1.46	2.00	2.43	1.79	2.32	1.58	2.23	1.93	0.00 (-0.03, 0.04)	36.78*	0.818
	60-70	10.68	0.00	3.66	3.37	2.76	5.73	5.01	6.65	4.23	4.90	4.42	3.83	-0.01 (-0.07, 0.04)	-64.14	0.646
	70-85	0.00	4.59	7.75	3.54	16.85	19.53	6.25	14.93	17.18	22.25	5.25	2.41	0.03 (-0.06, 0.13)	0.00	0.511

†% change is calculated as: (2000 rate– 2011 rate)/2000 rate*100. A negative percent change indicates a decline in rate between 2000 and 2011. *Indicates an increase in mortality rate between 2000 and 2011

Table 3 All-cause, CVD, diabetes and cancer mortality rates between 2000 and 2011, by age-group, among the total type 2 diabetes and in men and women separately

		Year												Annual change in rate (95%CI)	% change 2000 and 2011†	p_{trend}
	Age group	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011			
Men and women combined																
All-cause	*0-40*	1.49	1.19	1.72	2.20	1.83	2.09	2.48	1.90	2.13	2.48	2.48	3.50	0.05 (0.02, 0.07)	134.40*	<0.001
	40-60	8.25	7.73	7.20	7.20	6.90	6.67	6.53	6.79	6.51	6.54	6.50	6.08	-0.02 (-0.02, -0.01)	-26.29	<0.001
	60-85	44.29	43.00	42.20	41.58	41.00	39.84	40.09	40.02	40.82	39.34	38.66	35.31	-0.01 (-0.02, -0.01)	-20.27	<0.001
CVD	*0-40*	0.17	0.21	0.40	0.31	0.16	0.23	0.27	0.35	0.31	0.19	0.23	0.23	-0.02 (-0.08, 0.05)	32.34*	0.558
	40-60	2.38	2.28	1.84	1.86	1.65	1.63	1.49	1.36	1.42	1.38	1.43	1.16	-0.05 (-0.06, -0.04)	-51.28	<0.001
	60-85	16.72	16.36	15.14	14.90	14.26	13.09	12.43	12.00	12.14	11.57	10.83	9.17	-0.05 (-0.05, -0.05)	-45.13	<0.001
Diabetes	*0-40*	0.04	0.04	0.08	0.35	0.19	0.27	0.31	0.19	0.16	0.27	0.08	0.15	0.00 (-0.07, 0.08)	252.82*	0.922
	40-60	0.75	0.71	0.42	0.37	0.41	0.40	0.41	0.46	0.42	0.40	0.42	0.31	-0.05 (-0.07, -0.03)	-58.51	<0.001
	60-85	4.35	4.09	4.01	3.82	3.92	3.72	3.70	3.75	3.89	3.60	3.09	2.78	-0.03 (-0.03, -0.03)	-36.21	<0.001
Cancer	*0-40*	0.26	0.25	0.24	0.47	0.12	0.19	0.50	0.19	0.54	0.58	0.46	0.71	0.08 (0.03, 0.14)	179.38*	0.004
	40-60	2.65	2.70	2.82	2.76	2.72	2.53	2.41	2.49	2.36	2.34	2.08	2.02	-0.03 (-0.04, -0.02)	-23.62	<0.001
	60-85	10.44	10.56	10.37	10.55	10.52	10.52	10.71	10.59	10.61	10.57	10.44	9.03	-0.01 (-0.01, -0.00)	-13.53	<0.001
Men																
All-cause	*0-40*	2.66	2.72	3.98	5.03	3.28	3.59	3.99	3.10	2.49	4.07	2.89	4.87	0.01 (-0.02, 0.04)	82.96*	0.425
	40-60	9.57	8.83	8.55	8.59	8.53	8.17	7.54	8.14	7.92	7.76	8.02	7.17	-0.02 (-0.02, -0.01)	-25.07	<0.001
	60-85	48.18	46.49	45.77	44.57	43.78	42.84	42.30	42.21	42.45	41.52	39.97	37.07	-0.02 (-0.02, -0.02)	-23.06	<0.001
CVD	*0-40*	0.57	0.68	1.07	0.42	0.26	0.37	0.23	0.44	0.31	0.19	0.27	0.43	-0.09 (-0.018, 0.00)	-25.09	0.058
	40-60	3.15	2.86	2.59	2.46	2.29	2.16	2.01	1.96	2.04	1.84	1.97	1.61	-0.05 (-0.06, -0.04)	-48.93	<0.001
	60-85	17.91	16.85	16.07	15.78	14.93	13.92	13.17	12.60	12.64	12.13	10.90	9.47	-0.05 (-0.05, -0.05)	-47.10	<0.001
Diabetes	*0-40*	0.00	0.17	0.31	0.98	0.39	0.37	0.35	0.55	0.21	0.49	0.09	0.34	-0.01 (-0.11, 0.08)	n/a	0.775
	40-60	0.90	0.81	0.46	0.49	0.50	0.43	0.47	0.48	0.43	0.49	0.44	0.31	-0.06 (-0.09, -0.04)	-65.90	<0.001
	60-85	4.33	4.37	4.17	3.95	3.88	3.55	3.60	3.65	3.66	3.46	2.86	2.71	-0.04 (-0.04, -0.03)	-37.41	<0.001

Cancer	*0-40*	0.38	0.34	0.61	0.84	0.13	0.37	0.82	0.22	0.41	1.07	0.63	1.03	0.08 (-0.00, 0.16)	169.65*	0.051
	40-60	2.95	2.78	3.10	2.98	3.08	2.89	2.51	2.75	2.69	2.46	2.31	2.21	-0.03 (-0.04, -0.02)	-24.82	<0.001
	60-85	12.61	12.81	12.54	12.30	12.44	12.69	12.40	12.46	12.42	12.42	12.36	10.68	-0.01 (0.01, -0.01)	-15.33	<0.001
Women																
All-cause	*0-40*	1.15	0.71	0.92	1.09	1.22	1.41	1.73	1.25	1.92	1.42	2.18	2.42	0.09 (0.05, 0.12)	109.49*	<0.001
	40-60	6.57	6.35	5.52	5.52	4.95	4.88	5.36	5.23	4.90	5.13	4.76	4.82	-0.02 (-0.03, -0.01)	-26.68	<0.001
	60-85	40.08	39.22	38.31	38.33	37.97	36.55	37.66	37.58	38.99	36.87	37.18	33.29	-0.01 (-0.01,-0.01)	-16.95	<0.001
CVD	*0-40*	0.05	0.05	0.16	0.27	0.11	0.17	0.29	0.30	0.31	0.19	0.20	0.07	0.06 (-0.04, 0.15)	22.22*	0.254
	40-60	1.40	1.56	0.92	1.13	0.89	1.01	0.87	0.66	0.71	0.85	0.82	0.64	-0.06 (-0.08, -0.04)	-54.42	<0.001
	60-85	15.43	15.84	14.13	13.95	13.53	12.18	11.61	11.33	11.58	10.93	10.74	8.82	-0.05 (-0.05, -0.04)	-42.80	<0.001
Diabetes	*0-40*	0.05	0.00	0.00	0.11	0.11	0.23	0.29	0.00	0.12	0.13	0.07	0.00	0.03 (-0.09, 0.17)	-100.00	0.580
	40-60	0.57	0.57	0.36	0.24	0.30	0.37	0.34	0.45	0.40	0.31	0.40	0.32	-0.02 (-0.05, 0.01)	-43.85	0.129
	60-85	4.38	3.80	3.83	3.68	3.96	3.92	3.81	3.87	4.14	3.75	3.36	2.86	-0.02 (-0.03, -0.01)	-34.82	<0.001
Cancer	*0-40*	0.22	0.22	0.11	0.33	0.11	0.11	0.35	0.18	0.62	0.26	0.33	0.47	0.09 (0.01, 0.16)	113.89*	0.030
	40-60	2.27	2.59	2.46	2.49	2.30	2.10	2.29	2.19	1.99	2.21	1.80	1.80	-0.03 (-0.04, -0.02)	-20.69	<0.001
	60-85	8.09	8.12	8.02	8.63	8.43	8.13	8.86	8.51	8.57	8.49	8.24	7.13	-0.01 (-0.01, -0.00)	-11.92	0.018

†% change is calculated as: (2000 rate– 2011 rate)/2000 rate*100. A negative percent change indicates a decline in rate between 2000 and 2011. *Indicates an increase in mortality rate between 2000 and 2011; n/a: % change cannot be estimated

Table 4 All-cause, CVD, diabetes and cancer mortality rates between 2000 and 2011 among type 2 diabetes in smaller age-groups

		Year														
	Age group	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Annual change in rate (95%CI)	% change 2000-2011†	P_{trend}
All-cause	*0-40*	1.49	1.19	1.72	2.20	1.83	2.09	2.48	1.90	2.13	2.48	2.48	3.50	0.05 (0.02, 0.07)	134.40*	<0.001
	40-50	3.89	3.94	4.04	4.54	4.46	4.16	4.90	4.31	4.14	4.29	4.18	3.79	-0.00 (-0.01, 0.01)	-2.58	0.64
	50-60	10.29	9.55	8.74	8.51	8.10	7.89	7.33	8.02	7.68	7.64	7.64	7.18	-0.02 (-0.03, -0.02)	-30.19	<0.001
	60-70	21.28	19.38	18.46	18.44	17.59	16.62	15.99	16.53	15.70	15.14	14.22	13.37	-0.04 (-0.04, -0.04)	-37.18	<0.001
	70-85	62.76	61.49	60.43	59.07	58.48	56.96	57.62	57.13	59.09	56.93	56.33	51.09	-0.01 (-0.01, -0.01)	-18.61	<0.001
CVD	*0-40*	0.17	0.21	0.40	0.31	0.16	0.23	0.27	0.35	0.31	0.19	0.23	0.23	-0.02 (-0.08, 0.05)	32.34*	0.558
	40-50	1.06	0.78	0.86	1.06	1.01	1.06	1.10	0.82	0.79	0.78	0.72	0.58	-0.04 (-0.06, -0.02)	-45.80	0.001
	50-60	3.00	3.00	2.32	2.25	1.97	1.91	1.68	1.62	1.73	1.67	1.78	1.44	-0.06 (-0.07, -0.05)	-51.93	<0.001
	60-70	7.10	6.33	5.74	5.59	5.05	4.71	4.02	4.10	3.89	3.63	3.35	2.84	-0.08 (-0.09, -0.08)	-60.07	<0.001
	70-85	24.43	24.22	22.37	21.95	21.14	19.27	18.54	17.75	18.14	17.34	16.22	13.72	-0.05 (-0.05, -0.04)	-43.83	<0.001
Diabetes	*0-40*	0.04	0.04	0.08	0.35	0.19	0.27	0.31	0.19	0.16	0.27	0.08	0.15	0.00 (-0.07, 0.08)	252.82*	0.922
	40-50	0.25	0.24	0.21	0.19	0.28	0.23	0.30	0.30	0.31	0.28	0.27	0.25	0.02 (-0.03, 0.06)	-2.58	0.461
	50-60	0.99	0.93	0.51	0.46	0.47	0.49	0.46	0.54	0.47	0.46	0.50	0.34	-0.06 (-0.08, -0.04)	-65.12	<0.001
	60-70	2.21	1.74	1.63	1.48	1.41	1.23	1.24	1.27	1.13	1.19	0.77	0.78	-0.08 (-0.08, -0.07)	-64.70	<0.001
	70-85	6.07	5.93	5.83	5.59	5.80	5.56	5.49	5.56	5.89	5.35	4.77	4.21	-0.02 (-0.03, -0.02)	-30.67	<0.001
Cancer	*0-40*	0.26	0.25	0.24	0.47	0.12	0.19	0.50	0.19	0.54	0.58	0.46	0.71	0.08 (0.03, 0.14)	179.38*	0.004
	40-50	0.98	1.49	1.35	1.47	1.44	1.19	1.42	1.35	1.15	1.07	1.08	1.09	-0.02 (-0.04, -0.00)	-11.43*	0.023
	50-60	3.43	3.27	3.53	3.39	3.35	3.18	2.89	3.05	2.96	2.97	2.56	2.47	-0.03 (-0.04, -0.02)	-27.94	<0.001
	60-70	6.98	6.59	6.46	6.79	6.64	6.36	6.18	6.45	6.24	6.00	5.76	5.31	-0.02 (-0.02, -0.02)	-23.98	<0.001
	70-85	13.21	13.67	13.38	13.39	13.42	13.58	14.01	13.61	13.79	13.90	13.81	11.70	-0.00 (-0.01, -0.00)	-11.47	0.001

†% change is calculated as: (2000 rate– 2011 rate)/2000 rate*100. A negative percent change indicates a decline in rate between 2000 and 2011. *Indicates an increase in mortality rate between 2000 and 2011

Supplementary Data

Supplementary Table 1 Age-standardised all-cause, CVD, diabetes and cancer mortality rates (95%CI) between 2000 and 2011 according to type of diabetes

	Type 1 diabetes				Type 2 diabetes			
Year	All-cause	CVD	Diabetes	Cancer	All-cause	CVD	Diabetes	Cancer
2000	19.0 (13.3, 24.8)	6.9 (3.3, 10.6)	4.1 (1.4, 6.9)	1.3 (0.5, 2.1)	9.7 (9.4, 9.9)	3.4 (3.3, 3.5)	0.9 (0.9, 1.0)	2.3 (2.2, 2.4)
2001	17.7 (12.5, 22.8)	9.0 (4.7, 13.3)	4.6 (1.8, 7.4)	0.9 (0.1, 1.6)	10.6 (8.7, 12.5)	3.3 (3.2, 3.4)	0.9 (0.8, 0.9)	2.4 (2.3, 2.5)
2002	19.4 (14.2, 24.7)	7.4 (4.0, 10.8)	4.7 (1.4, 8.0)	1.9 (0.4, 3.4)	9.1 (8.8, 9.3)	3.0 (2.9, 3.1)	0.8 (0.7, 0.8)	2.3 (2.2, 2.4)
2003	20.0 (14.7, 25.3)	6.4 (3.3, 9.5)	3.3 (1.4, 5.1)	1.5 (0.3, 2.7)	9.1 (8.7, 9.4)	2.9 (2.8, 3.0)	0.8 (0.7, 0.8)	2.4 (2.3, 2.5)
2004	19.5 (14.3, 24.7)	6.0 (2.8, 9.1)	4.6 (1.7, 7.6)	2.1 (0.7, 3.6)	8.9 (8.4, 9.5)	2.7 (2.6, 2.8)	0.8 (0.7, 0.8)	2.3 (2.2, 2.4)
2005	18.7 (14.2, 23.3)	6.4 (3.5, 9.3)	4.7 (1.7, 7.8)	2.8 (1.3, 4.4)	8.9 (8.0, 9.7)	2.5 (2.4, 2.6)	0.8 (0.7, 0.9)	2.7 (1.8, 3.5)
2006	16.7 (12.2, 21.1)	7.1 (4.0, 10.2)	3.9 (0.9, 6.8)	1.5 (0.5, 2.4)	8.9 (8.3, 9.4)	2.4 (2.3, 2.4)	0.8 (0.6, 1.0)	2.6 (2.1, 3.0)
2007	17.7 (13.2, 22.3)	6.1 (3.0, 9.3)	3.1 (1.5, 4.6)	2.3 (1.3, 3.4)	8.3 (8.1, 8.6)	2.2 (2.2, 2.3)	0.7 (0.7, 0.8)	2.3 (2.2, 2.5)
2008	15.3 (11.1 19.2)	5.6 (2.6, 8.7)	3.8 (1.4, 6.2)	2.4 (1.1, 3.7)	8.5 (8.2, 8.8)	2.2 (2.2, 2.3)	0.7 (0.7, 0.8)	2.4 (2.2, 2.6)
2009	12.1 (9.6, 14.6)	3.8 (2.4, 5.3)	3.0 (1.7, 4.3)	2.8 (1.4, 4.3)	8.3 (8.0, 8.5)	2.1 (2.0, 2.2)	0.7 (0.6, 0.8)	2.4 (2.2, 2.5)
2010	15.2 (11.7, 18.7)	5.2 (2.8, 7.6)	2.8 (1.5, 4.1)	1.7 (0.4, 3.0)	8.1 (7.8, 8.4)	2.0 (1.9, 2.1)	0.6 (0.5, 0.6)	2.2 (2.1, 2.4)
2011	12.7 (9.5, 15.8)	3.4 (1.8, 5.0)	3.4 (1.6, 5.1)	0.8 (0.5, 1.2)	7.9 (7.4, 8.5)	1.7 (1.6, 1.7)	0.6 (0.4, 0.7)	2.1 (1.9, 2.2)
Annual change in rate	-0.61	-0.35	-0.14	0.04	-0.18	-0.15	-0.03	-0.01
(95%CI)	(-0.91, -0.31)	(-0.52, -0.19)	(-0.24, -0.03)	(-0.09, 0.17)	(-0.25, -0.11)	(-0.16, -0.13)	(-0.03, -0.02)	(-0.04, 0.02)
% change†	-33.48	-51.41	-18.51	-34.97	-17.91	-51.72	-38.53	-10.3
p_{trend}	0.001	0.001	0.014	0.481	<0.001	<0.001	<0.001	0.352

†% change is calculated as: (2000 rate– 2011 rate)/2000 rate*100. A negative percent change indicates a decline in rate between 2000 and 2011.

CHAPTER 4

Cancer Risk in Type 1 and Type 2 Diabetes: Disentangling True Associations, Detection Bias and Reverse Causation

In Chapter 3.1 we observed an increasing proportion of deaths attributable to cancer among people with diabetes, likely due, at least in part, to large reductions in cardiovascular disease (CVD) mortality and smaller reductions (and/or stability) in cancer mortality rates over time among people with type 1 and type 2 diabetes. There is also a large body of research suggesting that people with type 2 diabetes are at increased risk for several types of cancer including pancreas, liver, endometrium, breast and colorectal cancers. For type 1 diabetes, rare cancer outcomes and cancer mortality, studies are often limited by small sample sizes that cannot reliably explore associations between these rare diseases.

A number of potential explanations exist for the observed association between diabetes and cancer. Most notable are shared risk factors such as smoking and obesity; and biologically plausible relationships, including metabolic derangements such as insulin resistance. However, it is also possible that the observed risk for diabetes and cancer may be due to challenges in the way previous research was conducted or interpreted. For example, detection bias has been suggested as a plausible explanation, at least in part, for the observed associations between diabetes and cancer risk. Detection bias may occur when cancer is more likely to be observed among newly diagnosed diabetes compared with those without diabetes, simply due to more attention and interaction with the health care system as a result of the new diagnosis. It is also possible, particularly for pancreatic cancer, that reverse causation may explain some of this excess risk whereby dysfunction in insulin secretion as a consequence of tumour growth may be sufficient to induce hyperglycaemia.

To explore associations of type 1 diabetes and type 2 diabetes with cancer while reducing the potential impact of methodological challenges such as detection bias and reverse causation, we need extremely large population datasets. Registry-based data, therefore, provides a unique opportunity to explore these associations.

Using the National Diabetes Service Scheme (NDSS) registry, we report here the excess risk of site-specific cancer incidence and mortality among people with type 1 and type 2 diabetes, compared with the general Australian population. Additionally, we explore the potential contribution of detection bias and reverse causation to these observed risk estimates. This original research article was published in Diabetes Care in February 2015. An erratum to this work, similarly mentioned in Chapter 3, was published thereafter and this is also included at the end of this chapter. A detailed discussion pertaining to the unique association between diabetes and pancreatic cancer was also published in Diabetes Management Journal, 2015, Appendix 1.

The main finding from this work is that people with type 1 and type 2 diabetes have similar increased risks for a number of site-specific cancers, as compared with the general population. This is important as type 1 and type 2 diabetes have different disease aetiologies with respect to insulin availability, yet similar risk estimates for cancer, and this knowledge may therefore help disentangle underlying causal pathways. For example, data

presented in this paper suggest that hyperglycaemia (common to both type 1 and type 2 diabetes) may be the causal pathway linking diabetes and cancer and not endogenous hyperinsulinaemia (found only in type 2) as has previously been hypothesised. This suggests that management of hyperglycaemia in diabetes patients may be key to cancer prevention.

In addition, by comparing incidence and mortality risk in time segments within two years of diabetes diagnosis, we were able to minimise the impact of detection bias and reverse causation on the excess risk of cancer among people with diabetes. This finding is of particular relevance to other researchers in this field to ensure they take into account other possible reasons for their findings. Collectively, these findings suggest that screening for cancers in diabetes patients, according to standard protocols for the general population, should be emphasised in clinical practice as early detection will be key to preventing premature mortality from cancer. It is also likely that the prevention of key risk factors such as smoking, obesity, physical inactivity and poor diet will be important in the prevention of cancer, though the extent to which these risk factors contribute to the observed associations between diabetes and cancer could not be explored in this Chapter.

Declaration for Thesis – Chapter 4

Harding JL, Shaw JE, Peeters A, Cartensen B, & Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes in Australia. *Diabetes Care.* 2015; 38(2):264-70

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

Nature of contribution	**Extent of contribution (%)**
Acquisition of data, data management, analysis and interpretation of data, conceptualisation and writing of manuscript, critical revision, corresponding author	70%

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

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Jonathan Shaw	Conceptualisation, critical revision, approval of final draft for publication	
Anna Peeters	Critical revision, approval of final draft for publication	
Bendix Cartensen	Statistical advice, approval of final draft for publication	
Dianna Magliano	Conceptualisation, data acquisition, critical revision, approval of final draft for publication	

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

Candidate's Signature	[redacted]	Date: 31/03/2016
Main Supervisor's Signature	[redacted]	Date: 31/03/2016

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

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Cancer Risk Among People With Type 1 and Type 2 Diabetes: Disentangling True Associations, Detection Bias, and Reverse Causation

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OBJECTIVE

Evidence indicates an increased risk of certain cancers among people with type 2 diabetes. Evidence for rarer cancers and for type 1 diabetes is limited. We explored the excess risk of site-specific cancer incidence and mortality among people with type 1 and type 2 diabetes, compared with the general Australian population.

RESEARCH DESIGN AND METHODS

Registrants of a national diabetes registry (953,382) between 1997 and 2008 were linked to national death and cancer registries. Standardized incidence and mortality ratios (SIRs/SMRs) are reported.

RESULTS

For type 1 diabetes, significant elevated SIRs were observed for pancreas, liver, esophagus, colon and rectum (females only [F]), stomach (F), thyroid (F), brain (F), lung (F), endometrium, and ovary, and decreased SIRs were observed for prostate in males. Significantly increased SMRs were observed for pancreas, liver, and kidney (males only), non-Hodgkin's lymphoma, brain (F), and endometrium. For type 2 diabetes, significant SIRs were observed for almost all site-specific cancers, with highest SIRs observed for liver and pancreas, and decreased risks for prostate and melanoma. Significant SMRs were observed for liver, pancreas, kidney, Hodgkin's lymphoma, gallbladder (F), stomach (F), and non-Hodgkin's lymphoma (F). Cancer risk was significantly elevated throughout follow-up time but was higher in the first 3 months postregistration, suggesting the presence of detection bias and/or reverse causation.

CONCLUSIONS

Type 1 and type 2 diabetes are associated with an excess risk of incidence and mortality for overall and a number of site-specific cancers, and this is only partially explained by bias. We suggest that screening for cancers in diabetic patients is important.

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There is now a large body of evidence indicating a strong and consistent increased risk of incident cancer associated with diabetes (1). For type 2 diabetes, the strength of the association depends on the specific cancer site, with the strongest relationships observed for liver and pancreatic cancers, followed by endometrial, postmenopausal breast, colorectal, bladder, non-Hodgkin's lymphoma, and kidney cancer (2). For stomach cancer, there was an increased risk in a Japanese population (3), but it is not known if this extends to other populations, most of which have a much lower incidence of stomach cancer. The literature also consistently demonstrates a 10–20% decreased risk of prostate cancer among men with diabetes, due, in part, to the reduced levels of circulating testosterone levels in these individuals (4). For other, rarer malignancies, the number of studies is small, and more importantly, they usually lack adequate power to reliably explore these associations. Similarly, for studies of cancer mortality, positive associations have been shown for cancers of the pancreas, liver, colon and rectum, and bladder (5). However there is little data for mortality of rare cancer outcomes.

For type 1 diabetes, evidence is limited and variable. Cohort studies have shown a 10–37% increased risk for the incidence of all cancers combined, whereas case-control studies showed no association (6). Studies are rarely large enough to explore site-specific cancer incidence. However, there is evidence to suggest an increased risk for cancers of the pancreas, liver, and stomach (6). The evidence of cancer-specific mortality among type 1 diabetic cohorts is even more limited.

Hyperglycemia, insulin resistance, hyperinsulinemia, and the effects of treatment for diabetes have all been suggested as possible mechanisms for cancer risk (7). Since insulin resistance and hyperinsulinemia are much more prominent in type 2 than type 1 diabetes, although hyperglycemia is more similar between the two, investigating both diabetes types may shed light on the likely mechanistic pathway. It has also been argued that the observed associations could be due to biases not adequately addressed by the majority of previous studies. Reverse causality is possible, particularly for pancreatic cancer, whereby dysfunction in insulin secretion as a consequence of tumor growth may be sufficient to induce hyperglycemia (2). Detection bias might also exist due to increased disease surveillance among diabetic patients, particularly in the period shortly after diabetes diagnosis (8). Finally, nonspecific systemic symptoms from a cancer may lead to earlier detection of diabetes, which also contributes to a relative overrepresentation of people with undiagnosed cancers among newly diagnosed diabetic patients.

We used an Australian diabetes register to investigate associations of diabetes and cancer. We also explored whether these estimates are impacted by reverse causation and detection bias.

RESEARCH DESIGN AND METHODS

Data Sources

The National Diabetes Services Scheme (NDSS) is an Australian government initiative established in 1987 to deliver diabetes-related products at subsidized prices and provide information to people with diabetes. Registration of patients is free and is completed by a medical practitioner or credentialed diabetes nurse educator. The NDSS captures 80–90% of all Australians with known diabetes (9).

We included all individuals with type 1 or type 2 diabetes who were on the NDSS between 1 January 1997 and 31 December 2008. The year 1997 was chosen as the start date, as this time followed a unification of state-based registries as well as an improvement in data quality. Diabetes type is classified by the health practitioner completing registration. However, for the current study, type 1 diabetes status was assigned to registrants who were classified as type 1 on the NDSS and were diagnosed before the age of 30 years, and the time between diagnosis date and date of first insulin use was $<$1 year. For those missing data on date of diagnosis (59.1% type 1 diabetes and 36.1% type 2 diabetes) or insulin initiation date (many of whom registered in the early years of the operation of the NDSS and had had diabetes for a number of years), we classified people as type 1 if they were recorded as type 1 on the registry, were taking insulin, and were registered at $\leq$45 years of age. We chose 45 years as the cutoff to minimize the number of people with type 1 diabetes that we would miss, without misclassifying significant numbers of people with type 2 as type 1 (10). All others were classified as type 2 diabetic.

The Australian Cancer Database (ACD) is a register of all primary, malignant cancers diagnosed in Australia since 1982. It is a statutory requirement to notify the registry of all cases of malignant neoplasms. Only the first occurrence of a site-specific cancer is recorded; recurrences and metastases are not. All recorded cancers were coded according to the ICD-10.

Data Linkage

The NDSS was linked to the National Death Index (NDI) and the ACD, using data up to and including 31 December 2008. NDI and ACD data beyond this date were not available at the time of linkage. Linkage was performed by the Australian Institute of Health and Welfare (AIHW) using first name, second name, last name, sex, and date of birth (11). The record linkage methodology assigns each compared pair of records a record pair comparison weight. Based on clerical review of a sample of these links, it is expected that links with a weighting of low, medium, and high correspond to a link accuracy (positive predictive value) of 96.75, 98.97, and 99.90%, respectively. For this study, we chose a medium cutoff point with a predictive value of 98.97% as this has shown to be a reliable cutoff in other, similar studies (12).

Statistical Analysis

Individuals were followed from 1 January 1997, or registration date if thereafter, to 31 December 2008, date of death, and date of event (death or cancer occurrence). Incidence of cancer was defined as the first occurrence of cancer, or death from cancer if that was the first time the cancer had been reported. For "overall cancer incidence," only the first reported cancer was included. Anyone with a previous nonfatal cancer diagnosis between 1982 and either 1997 or date of NDSS registration (whichever was the later) was excluded (n = 33,621). Observed cancer incidence and mortality rates by single calendar year, 5-year age-group, and sex were calculated among people with diabetes, to match the format of the available cancer incidence and mortality rates in the general population. Given that deaths at older ages can be

difficult to attribute to a single cause, we only analyzed follow-up until age 75 years.

Cancer incidence and mortality in the diabetic population was compared with the general Australian population using standardized incidence ratio (SIR) and mortality ratio (SMR), stratified by sex. The SIR/SMRs were computed by fitting a Poisson model for the number of events using the log of the expected number of events as offset. The expected number of events was computed using published cancer incidence and mortality rates as provided by AIHW. SIR/SMR estimates for breast cancer were calculated for total breast cancer and then stratified by pre- and postmenopausal status using age 50 years as a proxy for menopausal status.

To explore the possibility of detection bias and reverse causality, we split the follow-up time (for both incidence and mortality) into different time periods following NDSS registration date, at 3, 6, 12, and 24 months, and estimated separate rate ratios for each of the intervals. Time since NDSS registration was subdivided into intervals that were small shortly after diagnosis and longer later. This was motivated by other studies (8,13) that have shown a substantial variation in the hazard ratio by time since diabetes diagnosis, particularly shortly after diagnosis. This analysis was done among the total type 2 diabetic population (to increase power) and for cancers with an adequate number of outcomes. The number of cancer outcomes among type 1 diabetes was too low to split by follow-up time.

All analyses were done using STATA version 12.1 (StataCorp, College Station, TX). This study was approved by the Alfred Health Human Ethics Committee and the AIHW Ethics Committee.

RESULTS

This study included 953,382 NDSS registrants, 80,676 (8.5%) with type 1 diabetes and 872,706 (91.5%) with type 2 diabetes, whose baseline characteristics and total cancer outcomes are described in Table 1.

Table 1—Descriptive characteristics of the NDSS population, 1997–2008

	Type 1 diabetes	Type 2 diabetes
n	80,676	872,706
Males (%)	52.1	53.2
Median follow-up time (years)	12.0	5.8
Insulin use (%)	100	32.4
Age at diagnosis[a]	21.6 (11.6, 32.4)	59.5 (50.2, 69.2)
Age at registration[a]	27.4 (15.1, 36.6)	60.4 (51.1, 69.7)
Cancer (*n*)	2,079	70,406
Cancer deaths (*n*)	593	26,333

[a]Median (25th, 75th percentiles).

Figure 1*A* shows the overall SIRs for type 1 diabetes. For all cancers combined, the SIRs (95% CIs) were 1.02 (0.96–1.09) and 1.10 (1.04–1.17) for males and females, respectively. Among females, there were significant excess risks for cancers of the pancreas, liver, esophagus, colon and rectum, stomach, thyroid, brain, lung, ovary, and endometrium. The SIRs in males were generally increased for the same cancers, but fewer were significant, and a decreased risk for prostate cancer was also observed. For type 2 diabetes, SIRs for all cancers combined were 1.08 (1.07–1.09) and 1.22 (1.20–1.23) among males and females, respectively (Fig. 1*B*). Significant SIRs were observed for all cancers, excluding brain, anal (females), and testicular cancers, and esophageal cancer (females). Significant decreased risks were also observed for melanoma and prostate cancers. The highest excess risks were observed for cancers of the liver and pancreas. SIR values for type 1 and type 2 diabetes are detailed in Supplementary Tables 1 and 3 (for total population).

For type 1 diabetes, no significant SIRs were seen for all breast cancers combined or premenopausal breast cancer (data not shown). For type 2 diabetes, significant SIRs were seen for all breast cancers combined (data not shown) and postmenopausal breast cancer, but not premenopausal cancer. As the majority of breast cancer cases occurred after menopause, all subsequent results refer only to postmenopausal breast cancer.

Figure 2*A* shows overall SMRs for type 1 diabetes. For all cancers combined, the SMRs (95% CIs) were 1.19 (1.07–1.33) and 1.32 (1.17–1.49) for males and females, respectively. Significant SMRs were observed for cancers of the pancreas and liver, non-Hodgkin's lymphoma, and cancers of the kidney (males only) and brain (females only) and endometrial cancers. For type 2 diabetes, SMRs for all cancers combined were 1.03 (1.01–1.04) and 1.13 (1.11–1.15) among males and females, respectively (Fig. 2*B*). Significant SMRs were observed for cancers of the pancreas, liver, and kidney and Hodgkin's lymphoma. Significant SMRs were also observed for stomach, gallbladder, and non-Hodgkin's lymphoma among females only. SMR estimates are detailed in Supplementary Tables 2 and 3 (total population).

To explore the contribution of reverse causation and detection bias, we calculated SIRs and SMRs in type 2 diabetes over time. For SIRs, there was a clear elevation in risk for all cancer, and each site-specific cancer within the first 3 months of NDSS registration (Fig. 3*A* and Supplementary Table 4). Over time, excess risks reduced but remained significantly higher than the general population for all cancer, pancreas, liver, colon and rectum, kidney, bladder, non-Hodgkin's lymphoma, thyroid, breast, and endometrial cancers. Additionally, SIRs for prostate cancer were elevated in the first 3 months, but this became a significantly decreased risk from 12–24 months after NDSS registration.

For SMRs, there were no differences in estimates across different time periods following NDSS registration for all cancer, non-Hodgkin's lymphoma, and prostate and breast cancers (Fig. 3*B* and Supplementary Table 5). For kidney, colon and rectum, bladder, and lung cancers, point estimates in the early time periods following NDSS registration were protective. As time after NDSS registration increased, SMR estimates approached the null, and for kidney cancer were significantly elevated. For liver cancer, there was no increased risk of mortality within 3 months of NDSS registration, but there was a stable, elevated SMR from 3 months onwards. Last, for thyroid and pancreatic

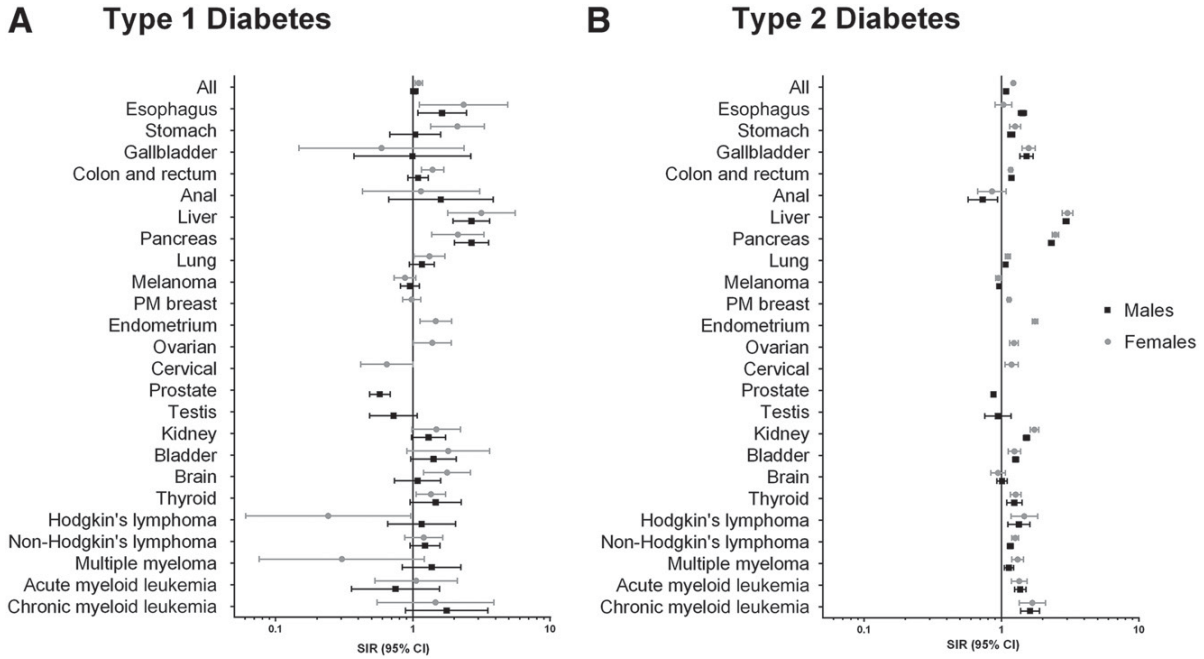

Figure 1—SIRs in males and females with type 1 (*A*) and type 2 (*B*) diabetes compared with the general population, 1997–2008.

cancers, early SMR estimates were high, and these became lower as time progressed but remained elevated relative to the general population.

Separate sensitivity analyses using NDI cutoffs with linkage rates of 99.9 and 96.75%, and using a cutoff date of age <40 years at registration for classification as type 1 diabetes among those missing data on age at diagnosis, did not change the overall pattern of results (data not shown).

CONCLUSIONS

In this study, we found excess risks of incidence and mortality for a number of cancers among both type 1 and type 2 diabetes, with the highest excess risks observed for pancreas, liver,

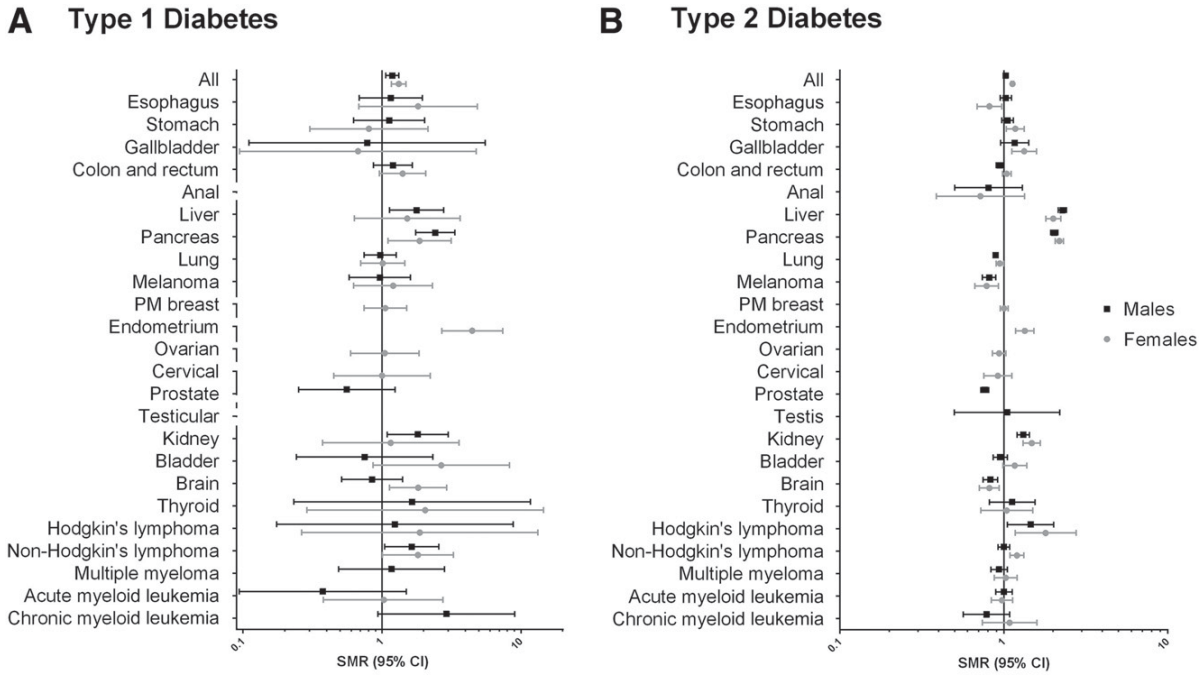

Figure 2—SMRs in males and females with type 1 (*A*) and type 2 (*B*) diabetes compared with the general population, 1997–2008.

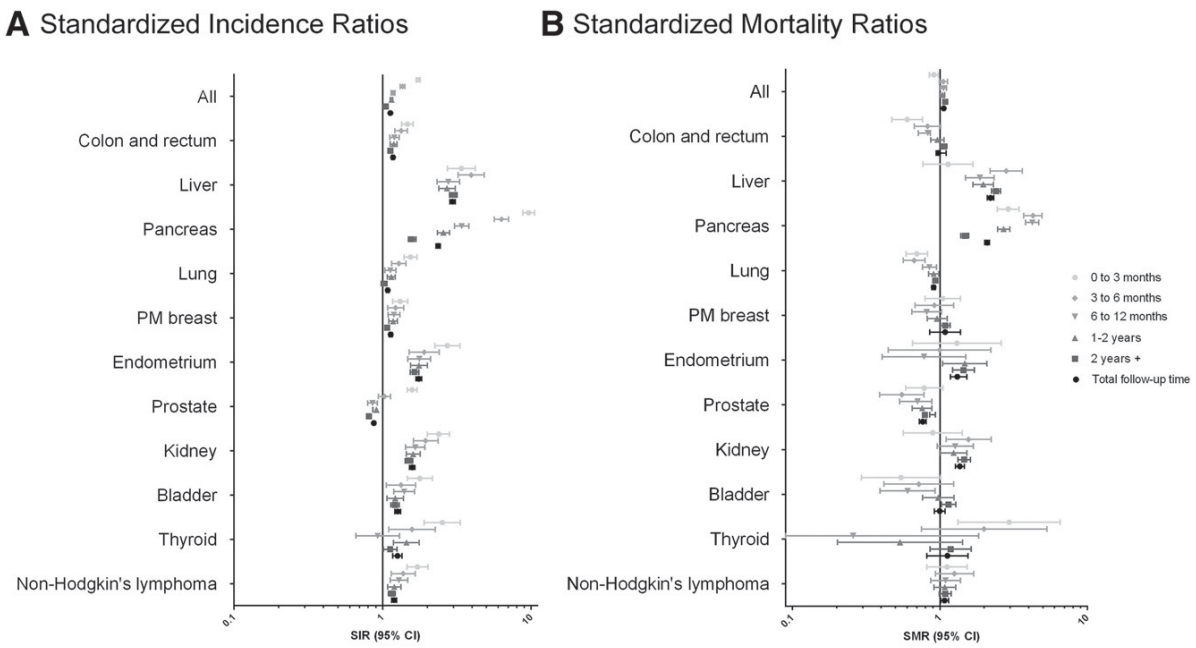

Figure 3—SIR (*A*) and SMR (*B*) at each site in the type 2 diabetic cohort compared with the general population, for different time periods following NDSS registration date.

endometrium, kidney, thyroid, chronic myeloid leukemia, and gallbladder cancers. Detection bias and/or reverse causation appear to explain some, but not all, of this excess risk, which often remains beyond 2 years after NDSS registration date.

Comparison With the Literature

Risk estimates for type 1 and type 2 diabetes in this study are lower compared with findings from other studies. A registry-based study in Denmark reported incident rate ratios for overall cancer of 1.2 and 1.4 for noninsulin and insulin users, respectively (13). Significant associations were also observed in that study for liver, pancreas, stomach, kidney, colon and rectum, endometrium, and lymphoma cancers, with rate ratios in the insulin group generally higher than the noninsulin group. Our lower estimates relative to this study may be attributed to the use of national population rates as the comparator (rather than a nondiabetic population). SIR estimates for type 2 diabetes obtained in our study are also comparable to previous meta-analyses performed on site-specific cancer incidence (4,14–20). We add to the current literature around type 2 diabetes and cancer incidence more precise risk estimates for some of the less common cancers. Our finding of a reduced risk of prostate cancer in type 1 diabetes suggests that factors other than obesity-induced low testosterone levels are responsible for the observation.

For cancer mortality outcomes in type 2 diabetes, estimates for all cancer, pancreas, liver, and bladder are similar to previous studies (21–24). We additionally show significant excess risks for mortality from cancers of the kidney, stomach, gallbladder, and endometrium, non-Hodgkin's lymphoma, and Hodgkin's lymphoma, which have previously not been shown. This study is one of the first studies to explore site-specific cancer mortality in type 1 diabetes. Estimates of risk were similar to those for type 2 diabetes, but fewer individual cancer types were significant. The lack of significant findings for type 1 diabetes and site-specific cancer mortality highlights the difficulty in assessing these relationships given the rarity of both of these conditions, the potentially long time lag between diabetes diagnosis and cancer death, and thus the need for extremely large cohort studies to explore these associations. Additionally, it should be noted that this is one of the first analyses of diabetes and cancer mortality whereby incident cancers were excluded prior to NDSS registration. Excluding prior incident cancers helps to disentangle the temporal association between diabetes and cancer incidence (and subsequent mortality).

Few studies to date have addressed the temporal relations between diabetes and cancer risk. A study by Johnson et al. (8) in Canada found a substantial degree of detection bias in the diabetic population, with elevated rate ratios reported in the first 3 months after diabetes diagnosis for all site-specific cancers, as did a Danish study (13). We also observed an initial elevated excess risk of cancer incidence at the time of NDSS registration, which fell over time but remained significantly elevated beyond 2 years for all but lung and prostate cancer. Even prostate cancer, for which diabetes is protective, had an increased SIR in the first 3 months. The SIRs clearly point toward increased cancer screening within the first few months of diabetes diagnosis due to increased medical attention, subsequently leading to earlier detection of any present and previously undiagnosed cancer, but also show the persistence of the relationship over time.

We noted three patterns of risk when modeling SMRs over time. The first, for bladder, lung, and colorectal cancers,

showed a protective SMR in the first few months after NDSS registration, which then became null over time. The low mortality risk in the first 3 months suggests either that diabetes diagnosis improves short-term cancer survival or that people with advanced cancer are less likely to appear on the NDSS. The latter is much more likely and could be due to weight loss reducing diabetes incidence or to a reluctance to diagnose diabetes or register a patient on the NDSS if the cancer is very advanced. The second pattern, observed for kidney, breast, endometrium, and non-Hodgkin's lymphoma, showed no difference in SMR estimates over time. Persisting elevation of SIR, but without an accompanying increase in SMR, suggests increased screening (detection bias) in people with diabetes. The failure of screening to translate into reduced mortality could be due to a lack of benefit of screening or to an offset of the benefits of screening by poorer responses to therapy (25) or by a real increase in incidence. Third, for pancreas, thyroid, and liver cancers, SMRs fell over time but remained elevated beyond 2 years for liver and pancreatic cancer, suggesting reverse causality only explains some of the relationship and that type 2 diabetes is a genuine risk factor for these two cancers. The varying relationships between SIR and SMR across cancers over time indicate a complex interplay of real effects of diabetes on cancer, detection bias, reverse causality, and cancer treatment factors.

Last, we show that the magnitudes of excess risk for type 1 and type 2 diabetes are generally similar, with overlapping 95% CIs; albeit fewer outcomes are significant for type 1 diabetes, most likely due to limited power. Given the different etiologies of these diseases with respect to insulin availability, if hyperinsulinemia was the driving force between diabetes and cancer, we would expect our results to be moderated by diabetes type. Our results, instead, support the concept that hyperglycemia, found in both type 1 and type 2 diabetes, may be the mechanistic driver between diabetes and cancer. Hyperglycemia can induce DNA damage (26), downregulate expression of antioxidants (27), and increase reactive oxygen species generation (28). Although biologically plausible, results from epidemiological studies are conflicting. The "hyperglycemia hypothesis" is supported by large inception cohort studies that demonstrate a strong relationship between elevated blood glucose and cancer incidence or mortality (24,29–31). However, a recent meta-analysis reported a nonsignificant pooled risk ratio for cancer incidence of 0.91 (95% CI 0.79–1.05) for subjects with improved glycemic control across three trials, compared with those in the control arms of the studies, suggesting that improved glycemic control does not confer a reduced risk of cancer among diabetic patients (32). Several other key mechanisms linking diabetes and cancer include poor diet, physical inactivity (33), genetic predisposition (34), and possibly some diabetes treatments, such as insulin (35). Information on these possibly modifying factors is not available for the entire population, and since this is a population-based study, the influence of these factors could not be explored further.

Strengths and Limitations

The main strength of this study is that it is population based with a large sample size, long follow-up time, and the ability to distinguish between type 1 and type 2 diabetes. There are several limitations, however, that should be acknowledged. First, the NDSS is an administrative database and hence lacks precise information about type of diabetes for all registrants. The classification of diabetes is challenging and misclassification can occur. However, the proportions of type 1 and type 2 diabetes in this study (8.5 vs. 91.5%) are similar to other Australian data (36). Further, the proportion of type 2 diabetes who were also on insulin is consistent with other studies (37). Second, the NDSS does not include undiagnosed diabetes, and the NDSS may underrepresent diet-controlled diabetes as the diabetes-related products provided through the scheme may not be needed. Third, the large sample size in this study enabled us to stratify results by sex, numerous cancer sites, and multiple time periods. By conducting multiple analyses on the same dataset, we have of course increased the possibility of chance findings if we were only using *P* values as guiding principle. Last, in a population-wide study, it is not possible to explore the extent to which obesity, smoking, socioeconomic position, family history of cancer, and/or pharmaceutical treatments contributed to the observed association between diabetes and cancer. However, studies based on cohorts with detailed information on type 2 diabetes that were able to account for obesity, lifestyle-related factors, and diabetes treatment have still observed elevated risks for a number of cancers (38,39). Therefore, it is unlikely that these factors explain the entire association between diabetes and cancer.

Conclusion

Using one of the largest diabetes registries in the world, we show that both type 1 and type 2 diabetes are associated with an excess risk of incidence and mortality for overall and a number of site-specific cancers. Detection bias and reverse causality may partly explain the stark increase in risk of cancer immediately following diabetes diagnosis, but they do not explain increased risks $>$2 years following diabetes diagnosis, particularly for cancers of the pancreas, liver, kidney, and endometrium. We suggest future analyses on type 2 diabetes and cancer should account for the presence of detection bias and reverse causation, particularly in the first 3 months after diabetes diagnosis. Screening for cancers, according to standard protocols for the general population, in diabetic patients should be emphasized in clinical practice, as early detection is key to preventing premature mortality.

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edited the manuscript. B.C. provided statistical advice and reviewed and edited the manuscript. D.J.M. 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.

References

1. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674–1685
2. Johnson JA, Carstensen B, Witte D, Bowker SL, Lipscombe L, Renehan AG; Diabetes and Cancer Research Consortium. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia 2012;55:1607–1618
3. Yamagata H, Kiyohara Y, Nakamura S, et al. Impact of fasting plasma glucose levels on gastric cancer incidence in a general Japanese population: the Hisayama study. Diabetes Care 2005;28:789–794
4. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2006;15:2056–2062
5. Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Møller H; Diabetes and Cancer Research Consortium. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia 2012;55:1619–1632
6. Gordon-Dseagu VLZ, Shelton N, Mindell JS. Epidemiological evidence of a relationship between type-1 diabetes mellitus and cancer: a review of the existing literature. Int J Cancer 2013;132:501–508
7. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet 2009;373:2215–2221
8. Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia 2011;54:2263–2271
9. Australian Institute of Health and Welfare. *Diabetes Prevalence in Australia. An Assessment of National Data Sources*. Canberra, Australia, Australian Institute of Health and Welfare, 2009
10. Kenny SJ, Aubert RE, Geiss LS. *Prevalence and Incidence of Non-insulin-Dependent Diabetes*. 2nd ed. Washington, DC, U.S. Govt. Printing Office, 1995
11. Fellegi IP, Sunter AB. A theory for record linkage. J Am Stat Assoc 1969;40:1183–1210
12. Loh V, Harding J, Koshkina V, Barr E, Shaw J, Magliano D. The validity of self-reported cancer in an Australian population study. Aust N Z J Public Health 2014;38:35–38
13. Carstensen B, Witte DR, Friis S. Cancer occurrence in Danish diabetic patients: duration and insulin effects. Diabetologia 2012;55:948–958
14. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 2007;121:856–862
15. Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia 2006;49:2819–2823
16. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005;97:1679–1687
17. Larsson SC, Wolk A. Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. Diabetologia 2011;54:1013–1018
18. Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 2005;92:2076–2083
19. Mitri J, Castillo J, Pittas AG. Diabetes and risk of non-Hodgkin's lymphoma: a meta-analysis of observational studies. Diabetes Care 2008;31:2391–2397
20. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006;4:369–380
21. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 2004;159:1160–1167
22. Lam EK, Batty GD, Huxley RR, et al. Associations of diabetes mellitus with site-specific cancer mortality in the Asia-Pacific region. Ann Oncol 2011;22:730–738
23. Morrison DS, Batty GD, Kivimaki M, Davey Smith G, Marmot M, Shipley M. Risk factors for colonic and rectal cancer mortality: evidence from 40 years' follow-up in the Whitehall I study. J Epidemiol Community Health 2011;65:1053–1058
24. Seshasai SR, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–841
25. Srokowski TP, Fang S, Hortobagyi GN, Giordano SH. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol 2009;27:2170–2176
26. Lorenzi M, Montisano DF, Toledo S, Barrieux A. High glucose induces DNA damage in cultured human endothelial cells. J Clin Invest 1986;77:322–325
27. Turturro F, Friday E, Welbourne T. Hyperglycemia regulates thioredoxin-ROS activity through induction of thioredoxin-interacting protein (TXNIP) in metastatic breast cancer-derived cells MDA-MB-231. BMC Cancer 2007;7:96
28. Robertson R, Zhou H, Zhang T, Harmon JS. Chronic oxidative stress as a mechanism for glucose toxicity of the beta cell in type 2 diabetes. Cell Biochem Biophys 2007;48:139–146
29. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194–202
30. Stocks T, Rapp K, Bjørge T, et al. Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts. PLoS Med 2009;6:e1000201
31. Pollak M. Do cancer cells care if their host is hungry? Cell Metab 2009;9:401–403
32. Johnson JA, Bowker SL. Intensive glycaemic control and cancer risk in type 2 diabetes: a meta-analysis of major trials. Diabetologia 2011;54:25–31
33. Kushi LH, Doyle C, McCullough M, et al.; American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin 2012;62:30–67
34. Slattery ML, Sweeney C, Murtaugh M, et al. Associations between apoE genotype and colon and rectal cancer. Carcinogenesis 2005;26:1422–1429
35. Karlstad O, Starup-Linde J, Vestergaard P, et al. Use of insulin and insulin analogs and risk of cancer - systematic review and meta-analysis of observational studies. Curr Drug Saf 2013;8:333–348
36. Australian Institute of Health and Welfare. *Diabetes Prevalence in Australia: Detailed Estimates for 2007-08*. Canberra, Australia, Australian Institute of Health and Welfare, 2011
37. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care 2004;27:17–20
38. Joh HK, Willett WC, Cho E. Type 2 diabetes and the risk of renal cell cancer in women. Diabetes Care 2011;34:1552–1556
39. Luo J, Beresford S, Chen C, et al. Association between diabetes, diabetes treatment and risk of developing endometrial cancer. Br J Cancer 2014;111:1432–1439

Supplementary Data

Supplementary Table 1 Standardised incidence ratios for males and females with type 1 and type 2 diabetes compared to the general Australian population: 1997-2008

Site-specific cancer	Type 1 Diabetes						Type 2 Diabetes					
	Males			Females			Males			Females		
	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI	N	SIR	95%CI
All cancers	1037	1.02	(0.96, 1.09)	1042	1.10	(1.04, 1.17)	43937	1.08	(1.07, 1.09)	26469	1.22	(1.20, 1.23)
Oesophagus	23	1.63	(1.08, 2.45)	7	2.34	(1.12, 4.91)	899	1.42	(1.33, 1.52)	204	1.03	(0.90, 1.18)
Stomach	21	1.04	(0.68, 1.60)	19	2.11	(1.34, 3.30)	1157	1.17	(1.11, 1.24)	448	1.25	(1.14, 1.38)
Gallbladder	4	0.99	(0.37, 2.64)	2	0.59	(0.15, 2.36)	314	1.52	(1.36, 1.69)	308	1.58	(1.41, 1.76)
Colorectal	130	1.09	(0.92, 1.29)	107	1.39	(1.15, 1.68)	6942	1.18	(1.15, 1.21)	3906	1.16	(1.13, 1.20)
Anal	5	1.60	(0.67, 3.84)	4	1.14	(0.43, 3.06)	63	0.73	(0.57, 0.93)	67	0.85	(0.67, 1.08)
Liver	41	2.67	(1.96, 3.62)	12	3.15	(1.79, 5.55)	1665	2.94	(2.81, 3.09)	480	3.02	(2.76, 3.30)
Pancreas	47	2.67	(2.01, 3.56)	20	2.12	(1.37, 3.29)	2009	2.30	(2.20, 2.41)	1395	2.46	(2.34, 2.60)
Lung	88	1.16	(0.94, 1.43)	57	1.32	(1.02, 1.71)	5334	1.07	(1.04, 1.10)	2318	1.11	(1.07, 1.16)
Melanoma	154	0.95	(0.81, 1.12)	117	0.88	(0.73, 1.05)	3573	0.96	(0.93, 0.99)	1752	0.95	(0.91, 0.99)
Breast (PM)	n/a			166	0.98	(0.84, 1.14)	n/a			6278	1.13	(1.11, 1.16)
Endometrial	n/a			55	1.47	(1.13, 1.91)	n/a			1796	1.75	(1.67, 1.83)
Ovarian	n/a			38	1.38	(1.01, 1.90)	n/a			792	1.23	(1.15, 1.32)
Cervical	n/a			20	0.65	(0.42, 1.00)	n/a			315	1.18	(1.06, 1.32)
Prostate	127	0.57	(0.48, 0.68)	n/a			11536	0.87	(0.86, 0.89)	n/a		
Testicular	24	0.72	(0.48, 1.08)	n/a			79	0.94	(0.75, 1.17)	n/a		
Kidney	47	1.30	(0.98, 1.73)	23	1.48	(0.98, 2.23)	1668	1.52	(1.45, 1.59)	772	1.73	(1.62, 1.86)
Bladder	26	1.41	(0.96, 2.07)	8	1.81	(0.90, 3.62)	1619	1.27	(1.21, 1.33)	371	1.24	(1.12, 1.37)
Brain	26	1.08	(0.74, 1.59)	25	1.77	(1.20, 2.63)	517	1.01	(0.93, 1.10)	266	0.94	(0.84, 1.06)
Thyroid	21	1.47	(0.96, 2.25)	63	1.35	(1.06, 1.73)	239	1.24	(1.09, 1.41)	471	1.27	(1.16, 1.39)
Hodgkin's lymphoma	12	1.16	(0.66, 2.04)	2	0.24	(0.06, 0.96)	112	1.34	(1.11, 1.61)	76	1.46	(1.17, 1.83)
NHL	62	1.23	(0.96, 1.57)	38	1.20	(0.87, 1.65)	1685	1.16	(1.10, 1.21)	1160	1.26	(1.19, 1.33)
Myeloma	16	1.37	(0.84, 2.24)	2	0.30	(0.08, 1.21)	613	1.13	(1.04, 1.22)	400	1.31	(1.19, 1.44)
AML	7	0.75	(0.36, 1.57)	8	1.05	(0.53, 2.11)	421	1.37	(1.24, 1.50)	220	1.34	(1.18, 1.53)
CML	8	1.76	(0.88, 3.52)	4	1.46	(0.55, 3.89)	152	1.61	(1.38, 1.89)	81	1.68	(1.35, 2.08)

Abbreviations: PM: Post-menopausal breast cancer; NHL: Non-Hodgkin's lymphoma; AML: Acute myeloid leukaemia; CML: Chronic myeloid leukaemia

Supplementary Table 2 Standardised mortality ratios for males and females with type 1 and type 2 diabetes compared to the general population; 1997-2008

Site-specific cancer	Type 1 diabetes						Type 2 diabetes					
	Males			Females			Males			Females		
	N	SMR	95%CI	N	SMR	95%CI	N	SMR	95%CI	N	SMR	95%CI
All	323	1.19	(1.07, 1.33)	270	1.32	(1.17, 1.49)	16628	1.03	(1.01, 1.04)	9705	1.13	(1.11, 1.15)
Oesophagus	14	1.15	(0.68, 1.95)	4	1.82	(0.68, 4.85)	614	1.03	(0.95, 1.11)	130	0.82	(0.69, 0.97)
Stomach	11	1.13	(0.62, 2.03)	4	0.81	(0.30, 2.14)	576	1.05	(0.97, 1.14)	240	1.17	(1.04, 1.33)
Gallbladder	1	0.78	(0.11, 5.55)	1	0.67	(0.09, 4.77)	97	1.16	(0.95, 1.42)	129	1.33	(1.12, 1.58)
Bowel	37	1.20	(0.87, 1.66)	26	1.41	(0.96, 2.07)	1737	0.94	(0.90, 0.99)	1023	1.04	(0.98, 1.11)
Anal	0			0			17	0.81	(0.50, 1.30)	10	0.72	(0.39, 1.34)
Liver	19	1.78	(1.13, 2.79)	5	1.52	(0.63, 3.65)	1089	2.28	(2.14, 2.41)	345	2.00	(1.80, 2.23)
Pancreas	36	2.42	(1.75, 3.35)	14	1.87	(1.11, 3.15)	1611	2.04	(1.94, 2.14)	1126	2.18	(2.06, 2.31)
Lung	54	0.97	(0.74, 1.27)	29	1.01	(0.70, 1.46)	3579	0.89	(0.86, 0.92)	1499	0.95	(0.90, 1.00)
Melanoma	15	0.96	(0.58, 1.60)	9	1.20	(0.63, 2.31)	440	0.81	(0.74, 0.89)	145	0.79	(0.67, 0.92)
Breast (PM)	n/a			31	1.06	(0.74, 1.50)	n/a			1247	1.00	(0.95, 1.06)
Endometrial	n/a			15	4.47	(2.69, 7.41)	n/a			233	1.34	(1.18, 1.53)
Ovarian	n/a			12	1.05	(0.60, 1.85)	n/a			440	0.94	(0.85, 1.03)
Cervical	n/a			6	1.00	(0.45, 2.23)	n/a			98	0.92	(0.75, 1.12)
Prostate	6	0.56	(0.25, 1.24)	n/a			1321	0.77	(0.73, 0.81)	n/a		
Testicular	0			n/a			7	1.05	(0.50, 2.20)	n/a		
Kidney	15	1.81	(1.09, 3.00)	3	1.16	(0.37, 3.58)	494	1.31	(1.20, 1.43)	256	1.48	(1.31, 1.67)
Bladder	3	0.75	(0.24, 2.32)	3	2.67	(0.86, 8.29)	392	0.95	(0.86, 1.05)	133	1.17	(0.98, 1.38)
Brain	15	0.85	(0.51, 1.41)	17	1.82	(1.13, 2.93)	377	0.83	(0.75, 0.92)	202	0.82	(0.71, 0.94)
Thyroid	1	1.65	(0.23, 11.69)	1	2.04	(0.29, 14.51)	37	1.12	(0.81, 1.55)	29	1.04	(0.72, 1.50)
HL	1	1.24	(0.17, 8.78)	1	1.87	(0.26, 13.29)	36	1.46	(1.05, 2.02)	21	1.80	(1.17, 2.76)
NHL	19	1.64	(1.05, 2.57)	11	1.82	(1.01, 3.28)	567	1.00	(0.92, 1.09)	411	1.20	(1.09, 1.33)
Myeloma	5	1.17	(0.49, 2.82)	0			284	0.94	(0.83, 1.05)	150	1.03	(0.87, 1.20)
AML	2	0.38	(0.09, 1.50)	4	1.03	(0.38, 2.75)	291	1.00	(0.89, 1.12)	172	0.97	(0.84, 1.13)
CML	3	2.91	(0.94, 9.01)	0			36	0.78	(0.56, 1.09)	26	1.08	(0.74, 1.59)

Abbreviations: PM: Post-menopausal breast cancer; NHL: Non-Hodgkin's lymphoma; AML: Acute myeloid leukaemia; CML: Chronic myeloid leukaemia

Supplementary Table 3 Standardised incidence and mortality ratios for people with type 1 and type 2 diabetes compared to the general Australian population: 1997-2008

	Incidence						Mortality					
	Type 1 diabetes			Type 2 diabetes			Type 1 diabetes			Type 2 diabetes		
Site-specific cancer	N	SIR	95%CI	N	SIR	95%CI	N	SMR	95%CI	N	SMR	95%CI
All	2079	1.06	1.02, 1.11	70406	1.13	1.12, 1.14	593	1.25	1.15, 1.35	26333	1.06	1.05, 1.07
Oesophagus	30	1.75	1.23, 2.51	1103	1.33	1.25, 1.41	18	1.26	0.79, 1.99	744	0.98	0.91, 1.06
Stomach	40	1.37	1.01, 1.87	1605	1.2	1.14, 1.25	15	1.02	0.61, 1.69	816	1.09	1.02, 1.16
Gallbladder	6	0.81	0.36, 1.8	622	1.54	1.43, 1.67	2	0.72	0.18, 2.89	226	1.25	1.10, 1.43
Colon and rectum	237	1.21	1.06, 1.37	10848	1.18	1.15, 1.2	63	1.28	1.00, 1.64	2760	0.98	0.94, 1.10
Anal	9	1.36	0.71, 2.61	130	0.79	0.66, 0.93	0			27	0.77	0.53, 1.13
Liver	53	2.76	2.11, 3.62	2145	2.96	2.84, 3.09	24	1.72	1.15, 2.56	1434	2.20	2.09, 2.32
Pancreas	67	2.48	1.95, 3.15	3404	2.37	2.29, 2.45	50	2.23	1.69, 2.95	2737	2.09	2.02, 2.17
Lung	145	1.22	1.04, 1.44	7652	1.08	1.06, 1.11	83	0.99	0.79, 1.22	5078	0.91	0.88, 0.93
Melanoma	271	0.92	0.81, 1.03	5325	0.96	0.93, 0.98	24	1.04	0.70, 1.55	585	0.81	0.74, 0.87
Breast (PM)	166	0.98	0.84, 1.14	6278	1.13	1.11, 1.16	31	1.06	0.74, 1.50	1247	1.00	0.95, 1.06
Uterine	55	1.47	1.13, 1.91	1796	1.75	1.67, 1.83	15	4.47	2.69, 7.41	233	1.34	1.18, 1.53
Ovarian	38	1.38	1.01, 1.90	792	1.23	1.15, 1.32	12	1.05	0.60, 1.85	440	0.94	0.85, 1.03
Cervical	20	0.65	0.42, 1.00	315	1.18	1.06, 1.32	6	1.00	0.45, 2.23	98	0.92	0.75, 1.12
Prostate	127	0.57	0.48, 0.68	11536	0.87	0.86, 0.89	6	0.56	0.25, 1.24	1321	0.77	0.73, 0.81
Testicular	24	0.72	0.48, 1.08	79	0.94	0.75, 1.17	0			7	1.05	0.50, 2.20
Kidney	70	1.35	1.07, 1.71	2440	1.58	1.52, 1.64	18	1.65	1.04, 2.63	750	1.37	1.27, 1.47
Bladder	34	1.49	1.06, 2.08	1990	1.26	1.21, 1.32	6	1.17	0.53, 2.60	525	1.00	0.91, 1.09
Brain	51	1.34	1.02, 1.76	783	0.99	0.92, 1.06	32	1.18	0.84, 1.67	579	0.82	0.76, 0.89
Thyroid	84	1.38	1.11, 1.71	710	1.26	1.17, 1.35	2	1.82	0.46, 7.29	66	1.09	0.85, 1.38
Hodgkin's lymphoma	14	0.75	0.44, 1.27	188	1.38	1.20, 1.6	2	1.49	0.37, 5.96	57	1.57	1.21, 2.03
NHL	100	1.22	1.00, 1.48	2845	1.2	1.15, 1.24	30	1.7	1.19, 2.43	978	1.08	1.01, 1.15
Myeloma	18	0.99	0.62, 1.56	1013	1.19	1.12, 1.27	5	0.76	0.32, 1.83	456	0.95	0.87, 1.04
AML	15	0.88	0.53, 1.47	641	1.36	1.26, 1.47	6	0.65	0.29, 1.45	441	1.01	0.92, 1.11
CML	12	1.65	0.94, 2.9	233	1.63	1.44, 1.86	3	1.85	0.60, 5.75	62	0.89	0.69, 1.14

Abbreviations: PM: Post-menopausal breast cancer; NHL: Non-Hodgkin's lymphoma; AML: Acute myeloid leukaemia; CML: Chronic myeloid leukaemia

Supplementary Table 4 Standardised incidence ratios (SIR) at each site in the type 2 diabetes cohort compared to the general population, for different time periods following NDSS registration date

Site-specific cancer	SIR by time since NDSS registration date											
	0 to 3 months		3 to 6 months		6 to 12 months		1 - 2 years		2 years +		Total follow-up time	
	SIR	95%CI	SIR	95%CI	SIR	95%CI	SIR	95%CI	SIR	95%CI	SIR	95%CI
All	1.74	(1.68, 1.79)	1.36	(1.31, 1.41)	1.18	(1.15, 1.21)	1.15	(1.13, 1.17)	1.05	(1.04, 1.06)	1.13	(1.12, 1.14)
Colorectal	1.47	(1.34, 1.60)	1.33	(1.21, 1.46)	1.20	(1.12, 1.29)	1.19	(1.13, 1.25)	1.13	(1.10, 1.16)	1.18	(1.15, 1.20)
Liver	3.39	(2.72, 4.21)	3.95	(3.22, 4.84)	2.77	(2.33, 3.30)	2.71	(2.38, 3.08)	2.99	(2.82, 3.17)	2.96	(2.84, 3.09)
Pancreas	9.61	(8.78, 10.51)	6.31	(5.64, 7.06)	3.40	(3.05, 3.80)	2.57	(2.34, 2.81)	1.58	(1.49, 1.67)	2.37	(2.29, 2.45)
Lung	1.54	(1.40, 1.70)	1.29	(1.15, 1.44)	1.13	(1.04, 1.23)	1.14	(1.08, 1.22)	1.03	(0.98, 1.05)	1.08	(1.06, 1.11)
Beast (PM)	1.31	(1.17, 1.48)	1.22	(1.08, 1.38)	1.19	(1.09, 1.31)	1.18	(1.10, 1.26)	1.07	(1.03, 1.11)	1.13	(1.11, 1.16)
Endometrial	2.72	(2.24, 3.31)	1.91	(1.51, 2.41)	1.77	(1.48, 2.11)	1.76	(1.54, 2.00)	1.64	(1.53, 1.75)	1.75	(1.67, 1.83)
Prostate	1.58	(1.47, 1.70)	1.03	(0.94, 1.13)	0.86	(0.79, 0.92)	0.91	(0.86, 0.86)	0.81	(0.79, 0.83)	0.87	(0.86, 0.89)
Kidney	2.39	(2.00, 2.83)	1.95	(1.61, 2.37)	1.66	(1.43, 1.93)	1.61	(1.44, 1.79)	1.50	(1.42, 1.59)	1.58	(1.52, 1.64)
Bladder	1.78	(1.47, 2.16)	1.33	(1.06, 1.67)	1.40	(1.19, 1.64)	1.21	(1.07, 1.38)	1.21	(1.14, 1.29)	1.26	(1.21, 1.32)
Thyroid	2.52	(1.91, 3.34)	1.58	(1.10, 2.25)	0.93	(0.66, 1.30)	1.45	(1.18, 1.76)	1.13	(1.01, 1.25)	1.26	(1.17, 1.35)
NHL	1.72	(1.46, 2.02)	1.38	(1.15, 1.65)	1.29	(1.12, 1.48)	1.20	(1.08, 1.33)	1.15	(1.10, 1.22)	1.20	(1.15, 1.24)

Abbreviations: PM: post-menopausal breast cancer; NHL: Non-Hodgkin's Lymphoma

Supplementary Table 5 Standardised mortality ratios (SMR) at each site in the type 2 diabetes cohort compared to the general population, for different time periods following NDSS registration date

Site-specific cancer	SIR by time since NDSS registration date											
	0 to 3 months		3 to 6 months		6 to 12 months		1 - 2 years		2 years +		Total follow-up time	
	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI	SMR	95% CI
All	0.91	(0.85, 0.97)	1.05	(0.99, 1.12)	1.06	(1.01, 1.11)	1.04	(1.01, 1.08)	1.09	(1.07, 1.10)	1.06	(1.05, 1.07)
Colorectal	0.60	(0.47, 0.76)	0.82	(0.67, 1.01)	0.83	(0.71, 0.86)	0.96	(0.87, 1.07)	1.06	(1.01, 1.12)	0.98	(0.94, 1.10)
Liver	1.14	(0.77, 1.68)	2.82	(2.19, 3.62)	1.87	(1.49, 2.34)	1.97	(1.68, 2.31)	2.40	(2.24, 2.57)	2.20	(2.09, 2.32)
Pancreas	2.91	(2.45, 3.45)	4.28	(3.71, 4.93)	4.23	(3.82, 4.69)	2.71	(2.46, 2.97)	1.48	(1.39, 1.57)	2.09	(2.02, 2.17)
Breast (PM)	1.04	(0.79, 1.38)	0.92	(0.68, 1.24)	0.81	(0.65, 1.03)	0.96	(0.82, 1.12)	1.09	(1.01, 1.17)	1.09	(0.85, 1.38)
Endometrial	1.30	(0.65, 2.61)	0.99	(0.45, 2.21)	0.78	(0.41, 1.50)	1.47	(1.04, 2.08)	1.45	(1.22, 1.72)	1.31	(1.18, 1.53)
Prostate	0.78	(0.59, 1.05)	0.55	(0.39, 0.78)	0.71	(0.53, 0.88)	0.76	(0.65, 0.88)	0.79	(0.93, 0.85)	0.77	(0.73, 0.81)
Kidney	0.89	(0.56, 1.42)	1.57	(1.10, 2.23)	1.27	(0.96, 1.68)	1.24	(1.01, 1.53)	1.46	(1.33, 1.62)	1.37	(1.27, 1.47)
Bladder	0.54	(0.29, 1.01)	0.72	(0.42, 1.24)	0.60	(0.39, 0.93)	0.97	(0.76, 1.24)	1.15	(1.02, 1.28)	1.00	(1.09, 0.91)
Thyroid	2.95	(1.32, 6.56)	1.99	(0.75, 5.32)	0.26	(0.04, 1.83)	0.54	(0.20, 1.43)	1.18	(0.86, 1.63)	1.12	(0.81, 1.55)
NHL	1.12	(0.82, 1.53)	1.26	(0.93, 1.69)	1.09	(0.87, 1.38)	1.08	(0.91, 1.28)	1.09	(0.99, 1.19)	1.08	(1.01, 1.15)

Abbreviations: PM: post-menopausal breast cancer; NHL: Non-Hodgkin's Lymphoma

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Erratum

Jessica L. Harding, Jonathan E. Shaw, Anna Peeters, Bendix Cartensen, and Dianna J. Magliano

Cancer Risk Among People With Type 1 and Type 2 Diabetes: Disentangling True Associations, Detection Bias, and Reverse Causation. Diabetes Care 2015;38:264–270

DOI: 10.2337/dc15-er04a

The authors of the article cited above noticed an error in the way they had described their definitions of type 1 and type 2 diabetes in the RESEARCH DESIGN AND METHODS section.

The description as published is as follows:

> Diabetes type is classified by the health practitioner completing registration. However, for the current study, type 1 diabetes status was assigned to registrants who were classified as type 1 on the NDSS and were diagnosed before the age of 30 years, and the time between diagnosis date and date of first insulin use was $<$1 year. For those missing data on date of diagnosis (59.1% type 1 diabetes and 36.1% type 2 diabetes) or insulin initiation date (many of whom registered in the early years of the operation of the NDSS and had had diabetes for a number of years), we classified people as type 1 if they were recorded as type 1 on the registry, were taking insulin, and were registered at $\leq$45 years of age. We chose 45 years as the cutoff to minimize the number of people with type 1 diabetes that we would miss, without misclassifying significant numbers of people with type 2 as type 1 [Kenny et al., 1995]. All others were classified as type 2 diabetic.

Amended description is as follows:

> Diabetes type is classified by the health practitioner completing registration. However, for the current study, type 1 diabetes status was assigned to registrants who were recorded as type 1 on the NDSS registry, were registered at $<$45 years of age, and were taking insulin. Registration date was used as a proxy for diagnosis date as a large proportion of registrants (59.1% with type 1 diabetes and 36.1% with type 2 diabetes) were missing date of diagnosis, many of whom registered in the early years of the operation of the NDSS and had had diabetes for a number of years. We chose 45 years as the cutoff to minimize the number of people with type 1 diabetes that we would miss, without misclassifying significant numbers of people with type 2 diabetes as type 1 diabetes [Kenny et al., 1995]. In addition, registrants who were recorded as having type 2 diabetes on the registry, were diagnosed before the age of 30 years, and were taking insulin within 1 year of diagnosis date were reclassified as having type 1 diabetes. All others were classified as having type 2 diabetes.

Had the authors analyzed the data according to how the definition reads in the article, they would have excluded approximately 13% of those with type 1 diabetes. These patients were all insulin treated and were all registered on the NDSS before the age of 45 years, and the majority were registered with the NDSS in the early years of its existence and therefore did not have an age at diagnosis available. The authors believe that the most appropriate classification of these patients is type 1 diabetes and that the published results, in which they were classified as type 1 diabetes, are therefore the appropriate ones. Nevertheless, the authors have examined the effect of differential coding by conducting some analyses using both the method that appeared in the RESEARCH DESIGN AND METHODS section and the amended method. These results and comparisons are shown in Supplementary Tables 1a and

2a. Standardized incidence ratios (SIRs) for type 1 and type 2 diabetes in men and women combined are presented in Supplementary Table 1a and in men and women separately are presented in Supplementary Table 2a. The authors observed a magnitude of difference between the two versions of results of less than 10% for type 1 diabetes and even less for type 2 diabetes, with overlapping 95% CIs. Stratified by sex, these differences are larger, probably driven by the small number of some cancers in the population with the type 1 diabetes.

Changing the description of the definition does not require any change to the results.

Supplementary Data

Supplementary Table 1a. Site-specific cancer SIRs in men and women (combined) with type 1 and type 2 diabetes compared to the general population; comparing the two different definitions of diabetes

	Type 1 diabetes						*Type 2 diabetes*					
	*Correct dm definition**			*Incorrect dm definition*			*Correct dm definition**			*Incorrect dm definition*		
Site-specific cancer	N	SIR	95% CI	N	SIR	95% CI	N	SIR	95% CI	N	SIR	95% CI
all	2079	1.06	(1.02 — 1.11)	1704	1.05	(1.00 — 1.10)	70406	1.13	(1.12 — 1.14)	68722	1.12	(1.11 — 1.13)
amleukemia	15	0.88	(0.53 — 1.47)	13	0.92	(0.53 — 1.58)	641	1.36	(1.26 — 1.47)	633	1.37	(1.27 — 1.48)
anal	9	1.36	(0.71 — 2.61)	7	1.27	(0.60 — 2.66)	130	0.79	(0.66 — 0.93)	127	0.78	(0.66 — 0.93)
bladder	34	1.49	(1.06 — 2.08)	24	1.36	(0.91 — 2.03)	1990	1.26	(1.21 — 1.32)	1952	1.27	(1.21 — 1.32)
bowel	237	1.21	(1.06 — 1.37)	196	1.24	(1.08 — 1.43)	10848	1.18	(1.15 — 1.20)	10611	1.17	(1.15 — 1.20)
brain	51	1.34	(1.02 — 1.76)	42	1.30	(0.96 — 1.76)	783	0.99	(0.92 — 1.06)	766	0.98	(0.92 — 1.06)
cmleukemia	12	1.65	(0.94 — 2.90)	10	1.63	(0.88 — 3.03)	233	1.63	(1.44 — 1.86)	226	1.62	(1.42 — 1.84)
gallbladder	6	0.81	(0.36 — 1.80)	5	0.84	(0.35 — 2.02)	622	1.54	(1.43 — 1.67)	604	1.53	(1.41 — 1.66)
hlymphoma	14	0.75	(0.44 — 1.27)	12	0.73	(0.42 — 1.29)	188	1.38	(1.20 — 1.60)	186	1.39	(1.21 — 1.61)
kidney	70	1.35	(1.07 — 1.71)	58	1.35	(1.05 — 1.75)	2440	1.58	(1.52 — 1.64)	2379	1.57	(1.51 — 1.64)
liver	53	2.76	(2.11 — 3.62)	42	2.68	(1.98 — 3.63)	2145	2.96	(2.84 — 3.09)	2082	2.93	(2.81 — 3.06)
lung	145	1.22	(1.04 — 1.44)	113	1.21	(1.01 — 1.45)	7652	1.08	(1.06 — 1.11)	7430	1.07	(1.05 — 1.10)
melanoma	271	0.92	(0.81 — 1.03)	240	0.96	(0.85 — 1.09)	5325	0.96	(0.93 — 0.98)	5230	0.96	(0.93 — 0.98)
myeloma	18	0.99	(0.62 — 1.56)	18	1.22	(0.77 — 1.93)	1013	1.19	(1.12 — 1.27)	994	1.20	(1.12 — 1.27)
nhlymphoma	100	1.22	(1.00 — 1.48)	77	1.12	(0.90 — 1.40)	2845	1.20	(1.15 — 1.24)	2769	1.19	(1.14 — 1.23)
oesophagus	30	1.75	(1.23 — 2.51)	22	1.60	(1.05 — 2.43)	1103	1.33	(1.25 — 1.41)	1072	1.32	(1.24 — 1.40)
pancreas	67	2.48	(1.95 — 3.15)	50	2.32	(1.76 — 3.06)	3404	2.37	(2.29 — 2.45)	3251	2.31	(2.23 — 2.39)
stomach	40	1.37	(1.01 — 1.87)	31	1.32	(0.97 — 1.87)	1605	1.20	(1.14 — 1.25)	1571	1.19	(1.14 — 1.25)
thyroid	84	1.38	(1.11 — 1.71)	69	1.34	(1.06 — 1.70)	710	1.26	(1.17 — 1.35)	698	1.26	(1.17 — 1.35)

*These are the results as they appear in the current published paper

Supplementary Table 2a. Site-specific cancer SIRs in men and women with type 1 and type 2 diabetes compared to the general population; comparing the two different definitions of diabetes

	Type 1 diabetes										*Type 2 diabetes*									
	*Correct dm definition**					*Incorrect dm definition*					*Correct dm definition**					*Incorrect dm definition*				
Site-specific cancer	*N*	*SIR*	*95%CI*			*N*	*SIR*	*95%CI*			*N*	*SIR*	*95%CI*			*N*	*SIR*	*95%CI*		
Men																				
all	1037	1.02	(0.96	—	1.09)	820	0.99	(0.93	—	1.06)	43937	1.08	(1.07	—	1.09)	42874	1.07	(1.06	—	1.08)
oesophagus	23	1.63	(1.08	—	2.45)	16	1.40	(0.86	—	2.29)	899	1.42	(1.33	—	1.52)	873	1.41	(1.32	—	1.51)
stomach	21	1.04	(0.68	—	1.60)	14	0.87	(0.51	—	1.46)	1157	1.17	(1.11	—	1.24)	1132	1.17	(1.11	—	1.24)
gallbladder	4	0.99	(0.37	—	2.64)	3	0.93	(0.30	—	2.89)	314	1.52	(1.36	—	1.69)	303	1.49	(1.33	—	1.67)
bowel	130	1.09	(0.92	—	1.29)	102	1.07	(0.88	—	1.30)	6942	1.18	(1.15	—	1.21)	6791	1.18	(1.15	—	1.21)
anal	5	1.60	(0.67	—	3.84)	3	1.16	(0.38	—	3.61)	63	0.73	(0.57	—	0.93)	61	0.72	(0.56	—	0.92)
liver	41	2.67	(1.96	—	3.62)	33	2.63	(1.87	—	3.70)	1665	2.94	(2.81	—	3.09)	1617	2.92	(2.78	—	3.06)
pancreas	47	2.67	(2.01	—	3.56)	33	2.35	(1.67	—	3.30)	2009	2.30	(2.20	—	2.41)	1926	2.25	(2.16	—	2.36)
lung	88	1.16	(0.94	—	1.43)	67	1.15	(0.90	—	1.46)	5334	1.07	(1.04	—	1.10)	5184	1.06	(1.03	—	1.09)
melanoma	154	0.95	(0.81	—	1.12)	128	0.94	(0.79	—	1.12)	3573	0.96	(0.93	—	0.99)	3506	0.96	(0.93	—	0.99)
prostate	127	0.57	(0.48	—	0.68)	100	0.58	(0.47	—	0.70)	11536	0.87	(0.86	—	0.89)	11324	0.87	(0.86	—	0.89)
testicular	24	0.72	(0.48	—	1.08)	21	0.73	(0.47	—	1.12)	79	0.94	(0.75	—	1.17)	78	0.94	(0.75	—	1.17)
kidney	47	1.30	(0.98	—	1.73)	38	1.27	(0.92	—	1.75)	1668	1.52	(1.45	—	1.59)	1624	1.51	(1.44	—	1.58)
bladder	26	1.41	(0.96	—	2.07)	19	1.34	(0.86	—	2.10)	1619	1.27	(1.21	—	1.33)	1588	1.27	(1.21	—	1.33)
brain	26	1.08	(0.74	—	1.59)	25	1.23	(0.83	—	1.82)	517	1.01	(0.93	—	1.10)	502	1.00	(0.92	—	1.09)
thyroid	21	1.47	(0.96	—	2.25)	18	1.49	(0.94	—	2.36)	239	1.24	(1.09	—	1.41)	231	1.22	(1.07	—	1.39)
hlymphoma	12	1.16	(0.66	—	2.04)	10	1.10	(0.59	—	2.04)	112	1.34	(1.11	—	1.61)	111	1.35	(1.12	—	1.62)
nhlymphoma	62	1.23	(0.96	—	1.57)	45	1.07	(0.80	—	1.43)	1685	1.16	(1.10	—	1.21)	1635	1.15	(0.80	—	1.43)
myeloma	16	1.37	(0.84	—	2.24)	16	1.70	(1.04	—	2.77)	613	1.13	(1.04	—	1.22)	602	1.13	(1.05	—	1.23)
amleukemia	7	0.75	(0.36	—	1.57)	6	0.77	(0.35	—	1.72)	421	1.37	(1.24	—	1.50)	417	1.38	(1.26	—	1.52)
cmleukemia	8	1.76	(0.88	—	3.52)	7	1.83	(0.87	—	3.84)	152	1.61	(1.38	—	1.89)	148	1.60	(1.36	—	1.88)
Women																				
all	1042	1.10	(1.04	—	1.17)	884	1.21	(1.20	—	1.23)	26469	1.22	(1.20	—	1.23)	25848	1.21	(1.20	—	1.23)
oesophagus	7	2.34	(1.12	—	4.91)	6	2.54	(1.14	—	5.66)	204	1.03	(0.90	—	1.18)	199	1.03	(0.90	—	1.18)
stomach	19	2.11	(1.34	—	3.30)	17	2.31	(1.43	—	3.71)	448	1.25	(1.14	—	1.38)	439	1.26	(1.14	—	1.38)
gallbladder	2	0.59	(0.15	—	2.36)	2	0.74	(0.18	—	1.76)	308	1.58	(1.41	—	1.76)	301	1.57	(1.41	—	1.76)

bowel	107	1.39	(1.15	—	1.68)	94	1.50	(1.22	—	1.83)	3906	1.16	(1.13	—	1.20)	3820	1.16	(1.13	—	1.20)
anal	4	1.14	(0.43	—	3.06)	4	1.36	(0.51	—	3.62)	67	0.85	(0.67	—	1.08)	66	0.86	(0.67	—	1.09)
liver	12	3.15	(1.79	—	5.55)	9	2.88	(1.50	—	5.54)	480	3.02	(2.76	—	3.30)	465	2.98	(2.72	—	3.27)
pancreas	20	2.12	(1.37	—	3.29)	17	2.27	(1.41	—	3.66)	1395	2.46	(2.34	—	2.60)	1325	2.39	(2.26	—	2.52)
lung	57	1.32	(1.02	—	1.71)	46	1.31	(0.98	—	1.75)	2318	1.11	(1.07	—	1.16)	2246	1.10	(1.06	—	1.15)
melanoma	117	0.88	(0.73	—	1.05)	112	0.99	(0.82	—	1.19)	1752	0.95	(0.91	—	0.99)	1724	0.95	(0.91	—	1.00)
breast - post	166	0.98	(0.84	—	1.14)	139	0.96	(0.81	—	1.14)	6278	1.13	(1.11	—	1.16)	6134	1.13	(1.10	—	1.16)
uterine	55	1.47	(1.13	—	1.91)	50	1.58	(1.20	—	2.09)	1796	1.75	(1.67	—	1.83)	1764	1.76	(1.68	—	1.84)
ovarian	38	1.38	(1.01	—	1.90)	32	1.38	(0.98	—	1.95)	792	1.23	(1.15	—	1.32)	771	1.22	(1.14	—	1.31)
cervical	20	0.65	(0.42	—	1.00)	19	0.72	(0.46	—	1.14)	315	1.18	(1.06	—	1.32)	308	1.17	(1.05	—	1.31)
kidney	23	1.48	(0.98	—	2.23)	20	1.54	(0.99	—	2.39)	772	1.73	(1.62	—	1.86)	755	1.73	(1.61	—	1.86)
bladder	8	1.81	(0.90	—	3.62)	5	1.45	(0.60	—	3.47)	371	1.24	(1.12	—	1.37)	364	1.24	(1.12	—	1.38)
brain	25	1.77	(1.20	—	2.63)	17	1.43	(0.89	—	2.29)	266	0.94	(0.84	—	1.06)	264	0.95	(0.85	—	1.08)
thyroid	63	1.35	(1.06	—	1.73)	51	1.29	(0.98	—	1.70)	471	1.27	(1.16	—	1.39)	467	1.27	(1.16	—	1.39)
hlymphoma	2	0.24	(0.06	—	0.96)	2	0.28	(0.07	—	1.10)	76	1.46	(1.17	—	1.83)	75	1.46	(1.17	—	1.83)
nhlymphoma	38	1.20	(0.87	—	1.65)	32	1.21	(0.85	—	1.71)	1160	1.26	(1.19	—	1.33)	1134	1.25	(1.18	—	1.33)
myeloma	2	0.30	(0.08	—	1.21)	2	0.37	(0.09	—	1.49)	400	1.31	(1.19	—	1.44)	392	1.31	(1.19	—	1.45)
amleukemia	8	1.05	(0.53	—	2.11)	7	1.09	(0.52	—	2.29)	220	1.34	(1.18	—	1.53)	216	1.35	(1.18	—	1.54)
cmleukemia	4	1.46	(0.55	—	3.89)	3	1.30	(1.32	—	2.05)	81	1.68	(1.35	—	2.08)	78	1.64	(1.32	—	2.05)

*These are the results as they appear in the current published paper

CHAPTER 5

The Metabolic Syndrome and Cancer: Is the Metabolic Syndrome Useful for Predicting Cancer Risk Above and Beyond Its Individual Components?

Diabetes is one of the most common, non-communicable diseases worldwide and undoubtedly one of the most challenging health problems of the 21st century. The metabolic syndrome (MetS) is also increasing worldwide with an estimated prevalence of approximately 20–25%. The MetS and diabetes are tightly connected insofar as they share common risk factors, namely increased body weight and insulin resistance. The MetS is also associated with a 3- to 4-fold increased risk for type 2 diabetes and the majority of people with type 2 diabetes also have the MetS. Chapters 3–4 provided evidence to support that diabetes is indeed a risk factor for cancer. Given the similar disease aetiologies between diabetes and the MetS, it is plausible that the MetS may also be a risk factor for cancer.

Emerging evidence supports an association between the MetS, individual components of the MetS and some cancers. However, it remains to be elucidated if factors within the MetS act in synergy on the risk of cancer or if individual components are driving observed associations. This Chapter reports the risks for overall, colorectal, breast and prostate cancer associated with components of the MetS, both separately and jointly. In addition, the utility of the MetS as a tool for predicting future cancer is determined. This work was published in Diabetes and Metabolism in May 2015.

Findings reported in this Chapter suggest that those with five components of the MetS are at an increased risk for overall and colorectal cancers and these associations appear to be driven largely by central obesity and elevated blood pressure (BP). However, discriminatory analyses suggest that the MetS is, at best, a moderate predictor of cancer risk and should not be considered for use in a clinical setting as a useful means to assess an individual's risk of developing overall, colorectal, breast or prostate cancer. Indeed, we show that the MetS is not a useful tool over and above standard considerations such as age, sex and smoking status in predicting cancer risk. The role of obesity and elevated BP are discussed in greater detail in Chapters 6.1 and 6.2, respectively.

Declaration for Thesis – Chapter 5

Harding JL, Sooriyakumaran M, Anstey K, et al. The metabolic syndrome and cancer: is the metabolic syndrome useful for predicting cancer risk above and beyond its individual components? *Diabetes and Metabolism*. 2015; 41(6): 463-469.

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

Nature of Contribution	**Extent of contribution (%)**
Acquisition of data, data management, analysis and interpretation of data, conceptualisation and writing of manuscript, critical revision, corresponding author	70%

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

Name	**Nature of Contribution**	**Extent of contribution (%) for student co-authors only**
Manoshyani Sooriyakumaran	Data analysis, writing of manuscript, critical revision	30%
Kaarin Anstey	Data provision and approval of final draft for publication	
Robert Adams	Data provision and approval of final draft for publication	
Beverley Balkau	Data provision and approval of final draft for publication	
Tom Briffa	Data provision and approval of final draft for publication	
Timothy Davis	Data provision and approval of final draft for publication	
Wendy Davis	Data provision and approval of final draft for publication	
Annette Dobson	Data provision and approval of final draft for publication	
Graham Giles	Data provision and approval of final draft for publication	
Janet Grant	Data provision and approval of final draft for publication	
Matthew Knuiman	Data provision and approval of final draft for publication	
Mary Luszcz	Data provision and approval of final draft for publication	
Paul Mitchell	Data provision and approval of final draft for publication	
Julie Pasco	Data provision and approval of final draft for publication	
Christopher Reid	Data provision and approval of final draft for publication	

David Simmons	Data provision and approval of final draft for publication	
Leon Simons	Data provision and approval of final draft for publication	
Andrew Tonkin	Data provision and approval of final draft for publication	
Mark Woodward	Data provision and approval of final draft for publication	
Jonathan Shaw	Conceptualisation, critical revision, approval of final draft for publication	
Dianna Magliano	Conceptualisation, data acquisition, critical revision, approval of final draft for publication	

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

Candidate's Signature	[redacted]	Date: 31/03/2016
Main Supervisor's Signature	[redacted]	Date: 31/03/2016

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

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Original article

The metabolic syndrome and cancer: Is the metabolic syndrome useful for predicting cancer risk above and beyond its individual components?

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Abstract

Aims. – The metabolic syndrome (MetS) is a risk factor for cancer. However, it is not known if the MetS confers a greater cancer risk than the sum of its individual components, which components drive the association, or if the MetS predicts future cancer risk.

Materials and methods. – We linked 20,648 participants from the Australian and New Zealand Diabetes and Cancer Collaboration with complete data on the MetS to national cancer registries and used Cox proportional hazards models to estimate associations of the MetS, the number of positive MetS components, and each of the five MetS components separately with the risk for overall, colorectal, prostate and breast cancer. Hazard ratios (HR) and 95% confidence intervals (95%CI) are reported. We assessed predictive ability of the MetS using Harrell's c-statistic.

Results. – The MetS was inversely associated with prostate cancer (HR 0.85; 95% CI 0.72-0.99). We found no evidence of an association between the MetS overall, colorectal and breast cancers. For those with five positive MetS components the HR was 1.12 (1.02-1.48) and 2.07 (1.26-3.39) for overall, and colorectal cancer, respectively, compared with those with zero positive MetS components. Greater waist circumference (WC) (1.38; 1.13-1.70) and elevated blood pressure (1.29; 1.01-1.64) were associated with colorectal cancer. Elevated WC and triglycerides were (inversely) associated with prostate cancer. MetS models were only poor to moderate discriminators for all cancer outcomes.

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Conclusions. – We show that the MetS is (inversely) associated with prostate cancer, but is not associated with overall, colorectal or breast cancer. Although, persons with five positive components of the MetS are at a 1.2 and 2.1 increased risk for overall and colorectal cancer, respectively, and these associations appear to be driven, largely, by elevated WC and BP. We also demonstrate that the MetS is only a moderate discriminator of cancer risk.

Keywords: Cancer; Epidemiology; Metabolic syndrome; Prediction

1. Background

The metabolic syndrome (MetS) is defined by a group of metabolic risk factors that have a tendency to cluster together in one individual-obesity (particularly central obesity), hypertension, dyslipidaemia and insulin resistance [1,2]. These factors, separately and jointly, have been associated with several chronic diseases, in particular cardiovascular disease (CVD) [3] and type 2 diabetes [4]. There is emerging evidence that the MetS may also be important in the development of some cancers [5].

A recent meta-analysis reported that the MetS is associated with low to modest increased risks for colorectal, post-menopausal breast, bladder, pancreas, endometrium and liver cancers [5], but for prostate cancer, evidence is conflicting. Some studies report an increased risk [6], others report a decreased risk [7], and others report no association with the MetS [5]. Mechanisms linking the MetS and cancer are not well understood. The association may partially be explained by the presence of obesity, and overt hyperglycaemia, both of which have been repeatedly associated with increased risks for some common cancers and a decreased risk for prostate cancer [8,9]. There is also some evidence to suggest that elevated blood pressure (BP) is associated with an increased cancer risk [10] while high-density lipoprotein (HDL) cholesterol has been shown to have an inverse association with cancer [11]. It is not yet known whether the strength of the association between the MetS and cancer is greater than the sum of its individual components, which individual components may be driving this association, or whether the MetS is a useful predictor of future cancer risk.

Using a large pool of prospective studies, we report the risks for overall, and the three most common site-specific cancers, colorectal, prostate and breast cancer associated with the components of the MetS, both separately and jointly. We additionally investigate whether the MetS is a useful measure for discriminating cancer risk.

2. Methods

2.1. Study population

The Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC) is a pooled cohort comprising 18 prospective studies in Australia and New Zealand with data on 153,025 men and women. All included cohorts were comprised of adults, except Fremantle Diabetes Study (FDS), a diabetes cohort, which also included some adolescents with type 1 diabetes. Details of sampling procedures, study designs, and methods for each of the studies have been described [12]. In brief, investigators of cohort studies conducted in the region from 1983 onwards with data on diabetes and the MetS, and with a minimum sample size of 1000 were invited to participate in the ANZDCC study. For the current analysis, we included studies that had collected data on all five MetS components in order to determine MetS status (five cohorts; $n = 59{,}630$). We further excluded participants with missing data on any of the five MetS components ($n = 37{,}392$); a cancer diagnosis prior to their baseline date ($n = 905$); and missing data on smoking and education status ($n = 305$). A total of 20,468 participants (men = 9437; women = 11,031) with complete data were included in the final data analysis.

2.2. Data linkage

The ANZDCC cohort was linked to the Australian Cancer Database (ACD), a register of all primary, malignant cancers diagnosed in Australia since 1982, and t*he National Death Index* (NDI). Linkage was performed by the Australian Institute of Health and Welfare (AIHW) and the Western Australian Data Linkage Unit (FDS only) using first name, second name, last name, gender, and date of birth [13]. Cancer status of the cohort was determined until 31 December 2008 for the Australian Diabetes Obesity and Lifestyle Study (AusDiab), Crossroads Undiagnosed Disease Study (CUDS) and the North West Adealaide Health Study (NWAHS); 31 August 2010 for the Melbourne Collaborative Cohort Study (MCCS); and 31 October 2012 for FDS. We set a match link rate of 97.70% (true matches/correct links) with link accuracy of 97.92% (1.08% expected to be false positive links). Twenty-seven percent of links underwent clerical review, performed by AIHW. This match link rate has shown to be a reliable cut-off in similar studies [14]. Cancer was defined using the International Classification of Disease 10th Revision (ICD-10) codes as follows: overall cancer (C00-C97, D45-D46, D47.1, D47.3); colorectal (C18-C20); prostate (C61); breast (C50).

2.3. Definition of covariates

All participants were measured for weight, height, waist circumference (WC), BP, fasting plasma glucose, serum HDL cholesterol and triglycerides by trained staff adhering to standardised protocols at baseline. Information on education and smoking status was collected by questionnaires. These risk

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Table 1
Criteria for a diagnosis of the metabolic syndrome.

Component	Cut-off points
Any three of	
Elevated waist circumference	Europid: men ≥ 94 cm; women: ≥ 80 cm
	South Asian and Chinese: men ≥90 cm; women ≥80 cm
	Japanese: men ≥90 cm; women ≥80 cm
	OR Body Mass Index ≥ 30 kg/m^2
Raised triglycerides	≥1.7 mmol/L
Reduced HDL-C	Men: <1.0 mmol/L; women: <1.3 mmol/L
Raised blood pressure	Systolic ≥ 130 and/or diastolic ≥ 85 mmHg or antihypertensive therapy (self-report)
Raised fasting plasma glucose	≥5.6 mmol/L or previously diagnosed diabetes (defined by self-report or anti-hyperglycaemic medication)

factors were harmonized across studies to reflect common categories as follows: smoking (current smoker, ex-smoker, never-smoker; education [high school or lower, above high school]).

2.4. Definition of the metabolic syndrome

The MetS was defined according to the current harmonized definition, Table 1 [2].

2.5. Statistical analysis

Individuals were followed from baseline date to census date of data linkage, date of death or date of cancer diagnosis, whichever occurred first. Incidence of cancer was defined as the first occurrence of cancer or death from cancer if that was the first time the cancer had been reported. For site-specific cancers, individuals with a diagnosis of a cancer at a site other than the one under consideration were censored at their date of diagnosis.

Differences in baseline characteristics were assessed using Pearson's Chi^2 test for proportions, Student's t-test for means from approximately continuous distributions and Wilcoxon's rank sum test for skewed data. Heterogeneity of studies was assessed by conducting a meta-analysis using a random effects model and statistical heterogeneity was estimated by the I^2 statistic [15]. Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% confidence intervals (95%CI) of cancer incidence associated with the MetS, the number of positive components of the MetS and the five component elements of the MetS. Proportional hazards assumptions were satisfied as assessed with graphs of log-log plots of the relative hazards by time for discrete variables and by scaled Schoenfeld residuals. All models were adjusted for sex, smoking, education and study cohort with age as the time scale. Sensitivity analyses were performed excluding the first two years of follow up, and excluding FDS.

To ascertain the best predictor of cancer incidence, we assessed the predictive capacity (discrimination) of models using Harrell's c-statistic. The models considered were: age and sex; MetS; the number of positive components for MetS; all individual MetS components in continuous form: all individual MetS components according to cut-offs. The c-statistic estimates the probability of concordance between predicted risk and the observed order of events from a randomly selected pair of participants while accounting for censored data [20]. A score of 1.0 indicates perfect discrimination and 0.5 indicates poor discrimination. The c-statistic and 95% CI's from each model were estimated and compared with the MetS model using the somersd package and lincom commands, respectively, in STATA (version 12.1, (StataCorp, College Station, TX, USA), as described elsewhere [16]. All models were adjusted for age and sex using follow-up time as the time scale.

This study was approved by the Alfred Health Human Research Ethics Committee (HREC), the Australian Institute for Health and Welfare HREC and the Western Australian Department of Health HREC.

3. Results

Those included in the MetS analysis ($n = 20{,}468$) were younger, less likely to be current smokers and had attained a higher level of education compared with those who were excluded ($n = 132{,}557$) (Table S1; see supplementary material associated with this article online). Over a median follow-up of 8.5 years 2827, 468, 651 and 549 cancers were identified for overall, colorectal, prostate and breast cancer, respectively. Baseline characteristics of the study population, by cancer and MetS status, are shown in Table 2. In brief, those who developed cancer were more likely to be men, older, less likely to be never smokers and have completed high school and more likely to manifest the MetS and its components, excluding triglycerides, compared with those who did not develop cancer. Similar patterns were observed among those with a diagnosis of the MetS as compared with those who did not have the MetS at baseline.

Information on the MetS and its components, by study, are shown in Table S2; see supplementary material associated with this article online. Similar proportions of participants with positive MetS components were observed across cohorts, except for FDS, a sample of people with diabetes, for which proportions were higher. No significant heterogeneity across studies was found ($I^2 = 12.6\%$).

Overall, the MetS was not associated with an increased risk of overall, or breast cancer, Table 3, and there was a non-significant borderline association with colorectal cancer, $P = 0.067$. Associations for overall and colorectal cancer were similar in men and women. A reduction in risk of prostate cancer was observed for the MetS (HR 0.85, 95% CI: 0.72-0.99). The HRs rose as the number of positive components rose, such that those with five positive MetS components were 1.12 (1.02-1.48) and 2.07 (1.26-3.39) times more likely to develop overall, and colorectal cancers, respectively, compared with those with no positive MetS components, $P_{trend} = 0.275$ and $P_{trend} = 0.006$ for overall and colorectal cancer, respectively (Fig. 1). There was an inverse association between the number of MetS components present and incident prostate cancer risk ($P_{trend} = 0.005$). No significant relationship with breast cancer was observed for the number of MetS components. Excluding the first two years of follow up

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Table 2
Baseline characteristics of participants according to cancer status and metabolic syndrome (MetS) status.

	Cancer status			Metabolic syndrome status		
	Cancer	No cancer	*P*-value	MetS	No MetS	*P*-value
n	2827	17,641		7923	12,545	
Men (%)	53.8	44.9	<0.001	53.4	41.5	<0.001
Mean age	61.1 (10.7)	51.3 (14.2)	<0.001	57.6 (12.7)	49.5 (14.1)	<0.001
Age range	14–91	11–96				
Education						
High school or lower	71.6	62.5	<0.001	71.4	59.0	<0.001
Above high school	28.4	37.5		28.6	41.0	
Smoking						
Never smoker	49.9	52.9	<0.001	47.6	55.6	<0.001
Ex-smoker	37.4	30.1		36.1	27.9	
Current smoker	12.7	17.0		16.3	16.4	
Metabolic syndrome variables						
Metabolic syndrome	47.7	37.3	<0.001			
WC (high risk)	64.8	62.8	0.043	93.3	44.0	<0.001
FPG (high risk)	47.6	32.2	<0.001	67.6	13.3	<0.001
BP (high risk)	73.6	51.7	<0.001	84.3	36.0	<0.001
HDL (high risk)	31.2	28.4	0.002	57.0	10.9	<0.001
TRIG (high risk)	31.0	29.9	0.240	64.0	8.7	<0.001
WC (men) (cm)	98.0 (11.3)	97.6 (11.9)	0.243	103.9 (10.4)	92.6 (10.3)	<0.001
WC (women) (cm)	86.0 (13.7)	86.4 (14.0)	0.316	96.7 (12.3)	81.2 (11.6)	<0.001
FPG (mmol/L)	6.1 (1.9)	5.7 (1.7)	<0.001	6.6 (2.3)	5.3 (1.0)	<0.001
Systolic BP (mmHg)	140.8 (21.0)	130.8 (20.1)	<0.001	142.5 (19.7)	125.7 (18.2)	<0.001
Diastolic BP (mmHg)	77.0 (12.2)	73.6 (12.2)	<0.001	78.7 (12.0)	71.2 (11.5)	<0.001
HDL cholesterol (mmol/L)	1.3 (0.4)	1.4 (0.4)	<0.001	1.2 (0.3)	1.5 (0.4)	<0.001
TRIG (mmol/L)[a]	1.3 (0.9, 1.9)	1.2 (0.9, 1.8)	<0.001	1.9 (1.4, 2.6)	1.0 (0.8, 1.3)	<0.001

Data are means (SD) or proportions.
WC: waist circumference; FPG: fasting plasma glucose; BP: blood pressure; HDL: high-density lipoproteins; Trig: triglycerides. Cut-off points for high risk by MetS component are detailed in Table 1.
[a] Median (25th, 75th percentile).

and excluding FDS had little effect on the magnitude of HR estimates (data not shown).

Of the five MetS components, WC was associated with an increased risk for colorectal cancer (1.38, 1.13-1.69) that was stronger in men (1.58, 1.19-2.10) compared with women (1.22, 0.91-1.65) and a decreased risk for prostate cancer 0.77 (0.66-0.91) (Table 4). Elevated BP was associated with an increased risk for overall cancer in men only (1.16, 1.02-1.33). Elevated BP was also associated with an increased risk for colorectal cancer (1.29, 1.01-1.64) with HRs higher for men than women, 1.38 vs 1.24, though analyses by sex were non-significant. Elevated triglycerides were protective against prostate cancer (0.78, 0.66-0.93) and elevated FPG and low HDL were not associated with any of the cancers.

C-statistics comparing prediction models were similarly moderate across all models for overall, colorectal, prostate and breast cancers with c-statistics ranging from 0.60 to 0.76 (Table 5). Models of age and sex had greater discriminative ability than the MetS for overall cancer, $P = 0.027$ (Table S3; see supplementary material associated with this article online). Models using the number of positive MetS components performed better than the MetS for the prediction

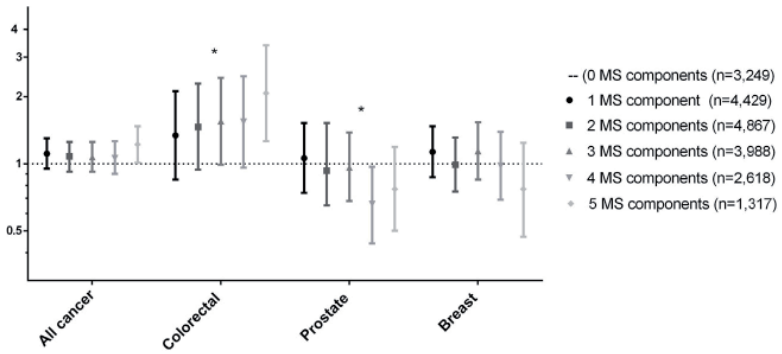

Fig. 1. Hazard ratios for cancer, with 95% confidence intervals, by the number of positive components of the metabolic syndrome. *Significant linear trend, $P < 0.05$.

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Table 3
Hazards ratios (HR) and 95% confidence intervals (95%CI) of the association between the metabolic syndrome and cancer.

	n events	Person-years	HR (95%CI)*
All cancer (total)	2827	187,794	1.01 (0.94–1.10)
All cancer (men)	1520	85,669	1.05 (0.94–1.16)
All cancer (women)	1307	103,125	1.03 (0.92–1.17)
Colorectal (total)	468	187,620	1.20 (0.99–1.45)
Colorectal (men)	242	84,609	1.22 (0.94–1.59)
Colorectal (women)	226	103,011	1.20 (0.91–1.60)
Prostate	651	84,582	0.85 (0.72–0.99)
Breast	549	102,992	1.00 (0.83–1.20)

*Model adjusted for sex (in models of total population), smoking, education and study name with age as the time scale.

of prostate and breast cancers, and models of all MetS components in continuous form and as cut-offs performed better than the MetS for the prediction of prostate cancer.

4. Discussion

Using a large pooled cohort of Australian adults, we show that the MetS is inversely associated with prostate cancer, but is not associated with overall, colorectal or breast cancer. Individuals who manifest all five components of the MetS are at a 1.2 and 2.1 times increased risk for overall and colorectal cancer, respectively, compared with those who have none. Elevated WC and BP are associated with a 1.4 and 1.3 times increased risk for colorectal cancer, respectively, and elevated WC and triglycerides are associated with decreased risks for prostate cancer. FPG was not associated with an increased risk for any cancer outcome. In discriminatory analysis, we show that all models were moderate discriminators but there was no clear driver for prediction of cancer.

4.1. Comparisons with literature

Our null findings of an association between the MetS and overall, breast and colorectal cancer were unexpected. For colorectal cancer, our risk estimates of 1.22 (0.94-1.59) for men and 1.20 (0.91-1.60)for women is similar to those published in the meta-analysis by Esposito et al. which estimated a 1.25 (1.19-1.32) and 1.34 (1.09-1.64) increased risk for men and women, respectively, with MetS defined in various ways, compared with those without MetS [5]. Our borderline non-significant finding might be due to the limited power in our study sample or a real null finding. The same meta-analyses concluded that women with MetS also have a 52% increased risk of post-menopausal breast cancer, but no association with total breast cancer [5]. For the current study, we combined pre-and post menopausal breast cancer as effect estimates between pre-and post menopausal breast cancer were not materially different (data not shown). The lack of significant findings here may be explained by a relatively young age of women at baseline with a mean age of 52 years. Previous studies have also shown no association between the MetS and breast cancer in middle-aged women, unless the MetS has been present for three to five years (HR 1.84, 95% CI 1.12-3.01) [17]. This suggests that the MetS may take time to manifest any deleterious effects on breast cancer development. For prostate cancer, we confirm previous studies that have shown the MetS to be protective such that men with MetS are approximately 15-25% less likely to develop prostate cancer compared with men without the MetS [7]. This is thought to be due to

Table 4
Hazards ratios (HR) and 95% confidence intervals (CI) for the association between individual components of the metabolic syndrome and cancer.

	n	Person-years	WC	FPG	BP	HDL	Trig
All cancer (total)	2827	187,794	1.02 (0.94–1.10)	1.00 (0.92–1.08)	1.07 (0.98–1.17)	1.06 (0.98–1.15)	1.00 (0.92–1.09)
All cancer (men)	1520	84,669	1.05 (0.95–1.18)	1.01 (0.90–1.12)	1.16 (1.02–1.33)	1.07 (0.95–1.19)	1.02 (0.91–1.13)
All cancer (women)	1307	103,124	1.03 (0.91–1.16)	1.02 (0.90–1.16)	1.06 (0.93–1.21)	1.07 (0.95–1.21)	1.06 (0.93–1.20)
Colorectal (total)	468	20,468	1.38 (1.13–1.70)	1.01 (0.83–1.24)	1.29 (1.01–1.64)	1.19 (0.97–1.45)	1.09 (0.89–1.34)
Colorectal (men)	242	84,609	1.58 (1.19–2.10)	0.86 (0.65–1.13)	1.38 (0.96–1.99)	1.13 (0.85–1.48)	1.18 (0.90–1.54)
Colorectal (women)	226	103,011	1.22(0.91–1.65)	1.24 (0.93–1.64)	1.24 (0.89–1.73)	1.29 (0.97–1.72)	1.01 (0.74–1.39)
Prostate	651	84,582	0.77 (0.66–0.91)	0.91 (0.79–1.04)	1.05 (0.88–1.25)	0.89 (0.76–1.04)	0.78 (0.66–0.93)
Breast	549	102,992	1.00 (0.84–1.20)	0.91 (0.75–1.11)	1.03 (0.86–1.25)	0.89 (0.73–1.09)	0.97 (0.78–1.21)

WC: waist circumference; FPG: fasting plasma glucose; BP: blood pressure; HDL: high-density lipoprotein cholesterol; Trig: triglycerides.
Effect estimates adjusted for sex (in models of total population) smoking and education with age as the timescale. HRs compare those at high risk for each component, compared with those not at high risk.

Table 5
Discrimination of cancer for five prediction models.

	Harrell's c statistic (95% CI)				
	Metabolic Syndrome	Age and sex	Continuous MetS components	Number of MetS components	Component cut-offs
All cancer	0.69 (0.69–0.71)	0.70 (0.69–0.71)[a]	0.70 (0.69–0.71)	0.70 (0.69–0.71)	0.70 (0.69–0.71)
Colorectal	0.75 (0.73–0.77)	0.75 (0.73–0.77)	0.75 (0.73–0.76)	0.75 (0.73–0.77)	0.75 (0.73–0.77)
Prostate	0.76 (0.74–0.77)	0.75 (0.74–0.77)[b]	0.76 (0.75–0.78)[a]	0.76 (0.75–0.77)[a]	0.76 (0.75–0.78)[a]
Breast	0.61 (0.59–0.63)	0.60 (0.58–0.62)[b]	0.60 (0.58–0.62)	0.62(0.60–0.64)[a]	0.60 (0.58–0.62)

[a] c-statistics significantly greater than MetS model, determined by estimating the differences in c-statistics, $P < 0.05$ (Supplementary Table 3).
[b] MetS better. All MetS models adjusted for age and sex.

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lower levels of circulating testosterone in overweight or obese men [18]. Future studies should explore these relationships by cancer grade as obese men are at a higher risk for more aggressive prostate cancers on diagnosis [19].

Mechanisms linking the MetS and cancer are not well understood. In this study, we have shown that high WC, a marker of visceral adiposity, is strongly associated with an increased risk for colorectal cancer. Visceral adiposity is an established risk factor for cancer, resulting in a chronic low-grade inflammatory state, which contributes to production of inflammatory cytokines [20]. We have also shown that BP is associated with colorectal cancer risk. High BP has shown to be associated with cancer by some studies [21] but data are conflicting. The Physician's Health Study showed that BP was not associated with an increased risk for colorectal cancer, though obesity and diabetes were [22]. It is possible that the association between high BP and cancer may, in part, be due to reverse causality whereby cancer gives rise to high BP [10]. But in our study, we excluded the first two years of follow-up and this did not materially change our results. The other key component thought to drive the association between the MetS and cancer is insulin resistance whereby levels of insulin-like growth factors (IGF) are influenced by circulating insulin levels. Increasing insulin leads to decreased levels of IGF-binding proteins 1 and 2, thus increasing the bioavailability of IGF, which in turn is thought to promote cell cycle progression and inhibition of apoptosis [23]. Unexpectedly, hyperglycaemia was not associated with overall, colorectal, breast or prostate cancers in our study. This may be because insulin resistance is more strongly associated with cancers of the pancreas, liver and endometrium, for which we were underpowered to investigate.

The utility of the MetS as a marker for future disease risk has been questioned in recent years. Commonly, the MetS has been a useful tool for predicting risk of CVD and type 2 diabetes. As the MetS is associated with cancer it seems intuitive that the MetS could also be used to predict an individual's risk of future cancer. On the other hand, studies of CVD have shown that while the MetS is strongly associated with increased risks for CVD, it is not a strong discriminator of CVD and therefore is not good at ranking people in terms of a future cardiovascular event [24]. To our knowledge, we are the first group to explore the utility of the MetS as a discriminator of cancer risk. Here, we find that the MetS is not a useful way of deciding who is or is not likely to get cancer. While people with the MetS are at a greater risk for certain cancers, the MetS is not likely to be a useful tool for predicting cancer risk in a clinical setting.

4.2. Strengths and weaknesses

Our study combined data from five large Australian population-based studies to investigate the association between MetS, individuals MetS components and risk of some common cancers. While studies have investigated the discriminative ability of MetS for CVD [24] this is the first time it has been assessed in terms of cancer risk. There are several limitations to this study that should be acknowledged. First, a large proportion of the ANZDCC population was excluded due to missing data on one or more of the MetS component variables. We assessed selection bias across a range of demographics and showed that those who were included in the study were more likely to be younger, never smokers and better educated than those who were not included. This may, therefore, limit the generalizability of our results. Second, because of our strict inclusion criteria that excluded any participant with missing data, it is possible that we were underpowered to detect true associations between the MetS and cancer, should they exist, and therefore increased our chance of type II errors. Third, the diagnosis of MetS was made on the basis of a single measure at a cross-sectional time point. It is possible, however, that the trajectory of MetS components, such as anthropometric measures and the duration of abnormalities, may influence cancer risk over time. Last, this is a pooled collaborative analysis and even though we did have lifestyle data such as physical activity and diet in some studies, these data were collected too differently across studies to derive sensible harmonized categories. Therefore, we could not further adjust our analyses for potential confounding effects of physical activity, diet and alcohol in a meaningful way.

5. Conclusions

This large pooled collaborative study has shown that the MetS is associated with a decreased risk for prostate cancer but is not associated with an increased risk for overall, colorectal or breast cancer. We have shown that those with five positive components of MetS are at a 1.2 and 2.1-fold increased risk for overall and colorectal cancer, respectively, and these associations appear to be driven, largely, by elevated WC and BP. We have also demonstrated that the MetS is only a moderate predictor of cancer risk and, thus, do not present strong evidence for the use of MetS in a clinical setting as a useful means for assessing an individual's risk for cancer. It may be more effective to identify high-risk individuals who might benefit from targeted treatment and prevention of high WC and BP to decrease future cancer risk.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Authors' contributions

J.L.H., BBiomedsci(hons), (Baker IDI Heart and Diabetes Institute; Monash University) and M.S., MBBS, (Baker IDI

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Heart and Diabetes Institute; Monash University) wrote the manuscript, had full access to all the data and conducted the analyses. J.E.S., FRACP, (Baker IDI Heart and Diabetes Institute; Monash University), and D.J.M., PhD, (Baker IDI Heart and Diabetes Institute; Monash University) contributed to conceptualisation, discussion and reviewed/edited manuscript. D.J.M. 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. All authors contributed to the collaboration and reviewed the manuscript and approved the final version.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2015.04.006.

References

[1] Aizawa Y, Kamimura N, Watanabe H, Aizawa Y, Makiyama Y, Usuda Y, et al. Cardiovascular risk factors are really linked in the metabolic syndrome: this phenomenon suggests clustering rather than coincidence. Int J Cardiol 2006;109:213–8.
[2] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–5.
[3] Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. J Am Coll Cardiol 2010;56(14):1113–32.
[4] Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care 2005;28:1769–78.
[5] Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care 2012;35:2402–11.
[6] Pelucchi C, Serraino D, Negri E, Montella M, Dellanoce C, Talamini R, et al. The metabolic syndrome and risk of prostate cancer in Italy. Ann Epidemiol 2011;21:835–41.
[7] Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. Am J Epidemiol 2006;164:1094–102.
[8] Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet 2014;384:755–65.
[9] Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194–202.
[10] Buck C, Donner A. Cancer incidence in hypertensives. Cancer 1987;59:1386–90.
[11] Jafri H, Alsheikh-Ali AA, Karas RH. Baseline and on-treatment high-density lipoprotein cholesterol and the risk of cancer in randomized controlled trials of lipid-altering therapy. J Am Coll Cardiol 2010;55:2846–54.
[12] Harding JL, Shaw JE, Koshkina V, Magliano DJ. Cohort profile: the Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC). Aust Epidemiol 2014;21:51–7.
[13] Fellegi IP, Sunter AB. A theory for record linkage. J Am Stat Assoc 1969;40:1183–210.
[14] Loh V, Harding J, Koshkina V, Barr E, Shaw J, Magliano D. The validity of self-reported cancer in an Australian population study. Aust N Z J Public Health 2014;38:35–8.
[15] Woodward M. Epidemiology: study design and data analysis. Third Edition ed. Boca Raton: CRC Press; 2014.
[16] Newson RB. Comparing the predictive powers of survival models using Harrell's C or Somers' D. Stata J 2010;10:339–58.
[17] Kabat GC, Kim M, Chlebowski RT, Khandekar J, Ko MG, McTiernan A, et al. A longitudinal study of the metabolic syndrome and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2009;18:2046–53.
[18] Freedland SJ. Obesity and prostate cancer: importance of race and stage of disease. J Urol 2007;178:1842–3.
[19] Freedland SJ, Aronson WJ. Examining the relationship between obesity and prostate cancer. Rev Urol 2004;6:73–81.
[20] Kelesidis I, Kelesidis T, Mantzoros CS. Adiponectin and cancer: a systematic review. Br J Cancer 2006;94:1221–5.
[21] Stocks T, Van Hemelrijck M, Manjer J, Bjorge T, Ulmer H, Hallmans G, et al. Blood pressure and risk of cancer incidence and mortality in the Metabolic Syndrome and Cancer Project. Hypertension 2012;59(4):802–10.
[22] Sturmer T, Buring JE, Lee IM, Gaziano JM, Glynn RJ. Metabolic abnormalities and risk for colorectal cancer in the physicians' health study. Cancer Epidemiol Biomarkers Prev 2006;15:2391–7.
[23] Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 2004;363:1346–53.
[24] Woodward M, Tunstall-Pedoe H. The metabolic syndrome is not a sensible tool for predicting the risk of coronary heart disease. Eur J Prev Cardiol 2009;16:210–4.

Please cite this article in press as: Harding J, et al. The metabolic syndrome and cancer: Is the metabolic syndrome useful for predicting cancer risk above and beyond its individual components? Diabetes Metab (2015), http://dx.doi.org/10.1016/j.diabet.2015.04.006

Supplementary Data

Supplementary Table 1 Baseline characteristics of participants included in MS analysis compared to those who were not

	Inclusion status		
	Not included	Included	P - value
n	132,557	20,468	
Men	45.4	46.1	0.053
Age	57.8 ± 14.5	55.8 ± 13.2	< 0.001
Smoking			
Never smoker	49.9	50.4	
Ex smoker	35.7	35.7	< 0.05
Current smoker	14.4	13.9	
Education			
High school or lower	65.9	64.8	
Above high school	34.1	35.2	< 0.001

Data are means ± SD or proportions

Supplementary Table 2 Baseline characteristics and follow-up data by study

	Australian Diabetes Obesity and Lifestyle Study	Crossroads Undiagnosed Study	Fremantle Diabetes Study	Melbourne Collaborative Cohort Study	Northwest Adelaide Health Study	Total
n	10,376	1,634	1,247	3,806	3,675	20,468
Year of baseline examination	1999-2000	2001-2002	1993-1996	1991-1994	1999-2000;2002-2003	1993-2003
Median follow-up (years)	8.7	6.8	14.9	16.6	8.1	8.5
% Men	45.0	44.3	49.6	47.1	47.6	46.1
Age (years)	51.0 ± 14.2	52.3 ± 15.5	62.2 ± 13.1	57.2 ± 8.5	49.5 ± 16.0	52.7 ± 14.2
Education (above high school)	37.1	25.2	11.7	27.5	55.2	36.2
Smoking (ever smoker)	45.0	49.1	55.3	43.6	55.4	47.5
WC (high risk)	61.4	72.4	81.6	52.0	69.7	63.1
FPG (high risk)	31.0	21.1	100.0	42.9	17.4	34.4
BP (high risk)	46.9	56.6	88.0	69.8	49.2	54.7
HDL (high risk)	24.7	24.9	64.6	28.6	29.7	28.8
TRIG (high risk)	31.4	28.7	55.9	20.8	27.8	30.1
MetS	35.3	35.1	88.3	38.9	32.6	38.7
N cancer events	831	94	295	1,356	251	2,827

Data are means ± SD or proportions. Abbreviations: WC: Waist Circumference; FPG: Fasting Plasma Glucose; BP: Blood Pressure; HDL: High Density Lipoproteins; TRIG: Triglycerides. Cut-off points for high risk by MetS component are detailed in Table 1

Supplementary Table 3 Coefficients and P - values for the difference in c-statistics between each model discriminative ability for cancer outcomes, as compared to MetS

	Coefficients and P - values							
	Age and sex		Continuous variables		Number of MetS components		Component cut-offs	
	Coef.	P - value	Coef.	P - value	Coef.	P - value	Coef.	P - value
All cancer	-0.0013	0.027	0.0054	0.213	-0.0001	0.868	-0.0001	0.616
Colorectal	-0.0006	0.597	0.0036	0.109	-0.0001	0.940	0.0006	0.754
Prostate	0.0032	< 0.01	-0.0078	< 0.001	-0.0038	< 0.01	-0.0056	< 0.001
Breast	0.0062	< 0.05	0.0020	0.678	-0.0172	< 0.01	0.0056	0.228

Note: A negative coefficient denotes that the model mentioned is a better discriminator than the MetS model; a positive coefficient denotes that the MetS model is a better discriminator. All MetS models adjusted for age and sex discriminators.

CHAPTER 6

Components of the Metabolic Syndrome and Cancer

Evidence provided in Chapter 5 suggests that observed associations between the MetS and cancer are largely driven by high blood pressure (BP) (hypertension) and waist circumference (WC), a marker of central obesity. Chapters 6.1 and 6.2, each including peer-reviewed publications, explore associations between obesity, BP and cancer in more detail.

Obesity is a well established risk factor for cancer. However, the majority of previous studies use body mass index (BMI) as a marker of obesity, which has known limitations, namely the inability to distinguish between muscle and fat, and to accurately reflect fat distribution. Measures of central adiposity (e.g. WC and waist-to-hip ratio (WHR)) have been shown to better reflect abdominal adiposity compared with BMI and have stronger associations with cardiometabolic risk factors and outcomes. However, for cancer, results are less clear. Chapter 6.1 explores which of general adiposity, as measured by BMI, or central adiposity (e.g. WC) has stronger associations with cancer. This original research article was published in the International Journal of Cancer in October 2015 and demonstrated that all anthropometric measures were associated with cancer and WC discriminating marginally better than BMI. This suggests that central obesity may be an important driver of cancer risk. However, all anthropometric measures were only moderately predictive of cancer risk and thus evidence in Chapter 6.1 does not support a recommendation for one anthropometric marker over another for assessing an individual's risk of cancer in clinical practice.

Emerging evidence suggests that other metabolic abnormalities, such as hypertension, may also be associated with an increased risk for cancer. Two main hypotheses have been proposed to explain the observation that cancer is higher among those with hypertension: medications used in the treatment of hypertension may cause cancer directly; or there may be a common mechanism linking BP regulation and cancer development, independent of anti-hypertensive treatment. Chapter 6.2 disentangles these associations by exploring associations between hypertension and cancer, stratified by anti-hypertensive treatment use. This original research article was published in the Journal of Hypertension in January 2016. This paper reports increased risks for cancer incidence and mortality in those with hypertension compared with those without hypertension. Similar risks in treated and untreated hypertension suggest that the increased cancer risk is not explained by the use of anti-hypertensive treatment, even after adjustment for several important confounders such as obesity, smoking, education and age, though residual confounding may still exist.

Declaration for Thesis – Chapter 6.1

Harding JL, Shaw JE, Anstey K, et al. Comparison of anthropometric measures as predictors of cancer incidence: A pooled collaborative analysis of 11 Australian cohorts. *International Journal of Cancer*. 2015; 137(7):1699-708

In the case of Chapter 6.1, the nature and extent of my contribution to the work was the following:

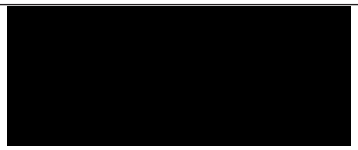
Nature of contribution	Extent of contribution (%)
Acquisition of data, data management, analysis and interpretation of data, conceptualisation and writing of manuscript, critical revision, corresponding author	70%

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

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Jonathan Shaw	Data provision, critical revision, approval of final draft for publication	
Kaarin Anstey	Data provision and approval of final draft for publication	
Robert Adams	Data provision and approval of final draft for publication	
Beverley Balkau	Critical revision, statistical advice and approval of final draft for publication	
Sharon Brennan-Olsen	Data provision and approval of final draft for publication	
Tom Briffa	Data provision and approval of final draft for publication	
Timothy Davis	Data provision and approval of final draft for publication	
Wendy Davis	Data provision and approval of final draft for publication	
Annette Dobson	Data provision and approval of final draft for publication	
Leon Flicker	Data provision and approval of final draft for publication	
Graham Giles	Data provision and approval of final draft for publication	
Janet Grant	Data provision and approval of final draft for publication	
Rachel Huxley	Critical revision approval of final draft for publication	
Matthew Knuiman	Data provision and approval of final draft for publication	

Mary Luszcz	Data provision and approval of final draft for publication	
Robert MacInnis	Data provision and approval of final draft for publication	
Paul Mitchell	Data provision and approval of final draft for publication	
Julie Pasco	Data provision and approval of final draft for publication	
Christopher Reid	Data provision and approval of final draft for publication	
David Simmons	Data provision and approval of final draft for publication	
Leon Simons	Data provision and approval of final draft for publication	
Andrew Tonkin	Data provision and approval of final draft for publication	
Mark Woodward	Data provision and approval of final draft for publication	
Anna Peeters	Conceptualisation, critical revision, approval of final draft for publication	
Dianna Magliano	Conceptualisation, data acquisition, critical revision, approval of final draft for publication	

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

Candidate's Signature		Date: 31/03/2016
Main Supervisor's Signature		Date: 31/03/2016

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

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Comparison of anthropometric measures as predictors of cancer incidence: A pooled collaborative analysis of 11 Australian cohorts

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Obesity is a risk factor for cancer. However, it is not known if general adiposity, as measured by body mass index (BMI) or central adiposity [*e.g.*, waist circumference (WC)] have stronger associations with cancer, or which anthropometric measure best predicts cancer risk. We included 79,458 men and women from the Australian and New Zealand Diabetes and Cancer Collaboration with complete data on anthropometry [BMI, WC, Hip Circumference (HC), WHR, waist to height ratio (WtHR), A Body Shape Index (ABSI)], linked to the Australian Cancer Database. Cox proportional hazards models assessed the association between each anthropometric marker, per standard deviation and the risk of overall, colorectal, post-menopausal (PM) breast, prostate and obesity-related cancers. We assessed the discriminative ability of models using Harrell's c-statistic. All anthropometric markers were associated with overall, colorectal and obesity-related cancers. BMI, WC and HC were associated with PM breast cancer and no significant associations were seen for prostate cancer. Strongest associations were observed for WC across all outcomes, excluding PM breast cancer for which HC was strongest. WC had greater discrimination compared to BMI for overall and colorectal cancer in men and women with c-statistics ranging from 0.70 to 0.71. We show all anthropometric

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measures are associated with the overall, colorectal, PM breast and obesity-related cancer in men and women, but not prostate cancer. WC discriminated marginally better than BMI. However, all anthropometric measures were similarly moderately predictive of cancer risk. We do not recommend one anthropometric marker over another for assessing an individuals' risk of cancer.

What's new?

The accumulation of excess fat around the abdomen is a well-known risk factor for cardiovascular and metabolic diseases and is associated with a variety of cancers. While measures that reflect central adiposity, namely waist circumference (WC) and waist-to-hip ratio (WHR), are strongly associated with cardiometabolic disease risk, their ability to predict cancer risk is unclear. In this study, overall cancer risk and risk of colorectal and obesity-related cancers were associated with multiple anthropometric measures—not only WC or WHR. An exception was prostate cancer, which was not significantly associated with any anthropometric marker.

Obesity is a well established risk factor for cancer. Reports from the World Cancer Research Fund have confirmed that there is sufficient evidence to support causal associations between obesity and cancers of the oesophageal adenocarcinoma, pancreas, colon, rectum, gallbladder, kidney, breast [post-menopause (PM)], corpus uteri (endometrium) and ovarian.[1–6] Findings for prostate cancer, however, are mixed with some studies suggesting that there may be associations only in those with advanced prostate cancer.[7]

The majority of epidemiologic studies exploring this association use body mass index (BMI) as a marker of general adiposity. BMI is a useful tool in both clinical medicine and population health to predict health risk related to weight and is easily measured. However, BMI has known limitations, namely the inability to distinguish between muscle and fat accumulation and it does not reflect fat distribution.[8] Measures of central adiposity [*e.g.,* waist circumference (WC) and waist-to-hip ratio (WHR)] have been shown to better reflect abdominal adiposity than BMI and have stronger associations with cardiometabolic risk factors and outcomes.[9–12] However, for cancer, results are less clear.

Some studies have found central adiposity to be an independent predictor of post-menopausal (PM) breast cancer risk, beyond the risk attributed to BMI alone, but a recent systematic review has suggested that this is not the case.[13] Another recent review demonstrated that BMI, but not measures of central adiposity, was associated with an increased risk for ovarian cancer.[14] Studies of colorectal cancer show WC and WHR are more strongly associated with cancer than is BMI in men, but this has not been shown for women.[15] Whilst numerous studies have explored the risk of cancer using multiple measures of adiposity, only one other study has compared the discriminative ability of multiple anthropometric measures for the risk of colorectal cancer.[16] In this study of US adults, Keimling *et al.* concluded that compared with BMI, measures of central adiposity did not materially influence colon cancer prediction models. To date, no studies have compared multiple anthropometric measures across multiple cancer outcomes. Further, many of the aforementioned studies do not explore the potential role of smoking as an effect modifier in the association between obesity and cancer.

Using a large pooled study with detailed information on relevant covariates, we aimed to estimate the risk of cancer incidence, in particular, overall, breast, colorectal, prostate and obesity-related cancers, with selected anthropometric measures and compare the discriminative ability of each measure for the risk of incident cancer.

Methods

Study population

The Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC) is a pooled study comprised of 18 prospective studies in Australia and New Zealand with data on 153,025 men and women. Details of sampling procedures, study designs and methods for each of the respective studies have been described elsewhere.[17] In brief, the chief investigators of epidemiological studies conducted from 1983 onwards with data on diabetes, obesity and the metabolic syndrome and with a minimum sample size of 1,000 were invited to participate in the ANZDCC study. For the current study, we included studies that had collected data on all anthropometric indicators for obesity (11 Australian cohorts; $n = 86{,}913$). Participants with a cancer diagnosis prior to baseline date ($n = 4{,}572$) or who were underweight at baseline (BMI: <18.5 kg/m^2; $n = 615$) were excluded to minimize the possibility of reverse causality. Additionally, participants with missing data on smoking status, education, weight, height, WC and hip circumference (HC) were excluded ($n = 2{,}268$). A total of 79,458 participants (40,734 men; 38,724 women) were included in the final data analysis on overall, breast, colorectal and prostate cancer incidence. Those who were excluded due to missing data were significantly older (68.4 *vs.* 57.4 years) and more likely to be male (51.3 *vs.* 45.5%) compared to those who were included in the final analysis. For the analyses of obesity-related cancer, participants from

the Melbourne Collaborative Cohort Study (MCCS) were excluded due to unavailable data for this level of specificity. The final sample size for this sub-analysis was $n = 39{,}565$ (24,229 men; 15,336 women).

Data linkage

The ANZDCC data were linked to the Australian Cancer Database (ACD), a register of all primary, malignant cancers diagnosed in Australia since 1982, and the National Death Index (NDI). Linkage was performed by the Australian Institute of Health and Welfare (AIHW) and the Western Australian Data Linkage Unit (for Fremantle Diabetes Study (FDS) only) using first name, second name, last name, gender and date of birth.[18] Cancer status of the cohort was determined until December 31, 2008 for nine of the 11 cohorts and until 31 August 2010 for MCCS and 31 October 2012 for FDS. We set an arbitrarily high match link rate of 97.70% (true matches/correct links) corresponding with an equally high link accuracy of 97.92% (1.08% expected to be false positive links). 27% of links underwent clerical review, performed by AIHW. This match link rate has shown to be a reliable cut-off in other, similar studies.[19]

Definition of anthropometric measures. All participants had weight, height, WC and HC measured at baseline by trained staff adhering to standardised protocols. For the majority of studies, WC was measured at the midpoint between the lowest rib and the iliac crest. For studies which measured WC as the narrowest point between the ribs and the hips, WC was adjusted to reflect the main method of measurement using methods outlined in Wang *et al.*[20] HC was measured at the maximal hip circumference. BMI was computed as weight (kg) divided by the square of height (m). The other ratios were similarly computed: WHR: WC to HC (cm/cm); waist to height ratio (WHtR): WC to height (cm/cm). The calculation of a body shape index (ABSI) was based on WC adjusted for weight and height, defined as follows: $\text{ABSI} = \text{WC} \times \text{weight}^{-2/3} \times \text{height}^{5/6}$.[21] ABSI is a new measure, based on WC and independent of height, weight and BMI, and has been found to predict overall mortality.[21]

Baseline covariates. Information on education and smoking status was collected by questionnaires. These risk factors were harmonized across studies to reflect common categories as follows: smoking [current smoker, ex-smoker, never smoker (ex and current smokers were combined into a single category of "ever" smokers)]; education (high school or lower, above high school). Diabetes was defined by self-report, fasting plasma glucose $\geq$126 mg/dl (7.0 mmol/L) or use of anti-hyperglycaemic medication.

Definition of cancer outcomes. Cancer was defined using the International Classification of Disease 10th Revision (ICD-10) codes as follows: overall cancer (C00–C97, D45–D46, D47.1, D47.3); breast (C50), colorectal (C18–C20), prostate (C61). Obesity-related cancers were defined separately for men and women according to previously known associations between obesity and site-specific cancers[22] as follows: *Men*: pancreas (C25), gallbladder (C23), colon (C18), rectum (C20), oesophageal adenocarcinoma (C15), kidney (C64), *Women*: pancreas, gallbladder, colon, rectum, oesophageal adenocarcinoma, kidney, PM breast (diagnosed $\geq$50 years of age), corpus uteri (C54) and ovarian (C56).

Statistical analysis

Individuals were followed from baseline date to date of data linkage, date of death or date of cancer diagnosis, whichever occurred first. Incidence of cancer was defined as the first occurrence of cancer or death from cancer if that was the first time the cancer had been reported. Individuals with a diagnosis of a cancer at a site other than those under consideration were censored at diagnosis date.

Differences in baseline characteristics, by cancer outcome, were assessed using Pearson's χ^2 test for proportions and Student's *t*-tests for means. Heterogeneity of studies was explored by conducting a meta-analysis using a random effects model and statistical heterogeneity was estimated by the I^2 statistic.[23] Cox proportional hazards models were used to compute hazard rate ratios (HRs) and 95% confidence intervals (95% CI) of cancer incidence, per standard deviation (SD) increase of each anthropometric measurement, calculated per study and per sex. Linearity of each relationship was evaluated by inclusion of a quadratic term in the models. Proportional hazards assumptions were satisfied as assessed with graphs of log–log plots of the relative hazards by time for discrete variables and by scaled Schoenfeld residuals. All models were adjusted for smoking status, education and study cohort with age from baseline as the time scale. Similar analyses were performed excluding the first three years of follow-up, adjusting for diabetes and excluding FDS, a sample of people with diabetes.

We tested for interactions between age groups ($<$50 years and $\geq$50 years; $<$65 and $\geq$65 years; $<$70 years and $\geq$70 years), smoking, diabetes and each anthropometric measure on cancer incidence. Given the lack of statistical power inherent in interaction tests, we considered interactions to be significant when $p < 0.2$, and in such cases present stratified analyses.[24] All analyses were performed separately for men and women.

To ascertain the best predictor of cancer incidence, we assessed the predictive capacity (discrimination) of models using Harrell's c-statistic. The models considered were: (Model 1) age, education, smoking and study cohort; Model 1 + each of the anthropometric measures in isolation. The c-statistic estimates the probability of concordance between predicted risk and the observed order of events from a randomly selected pair of participants while accounting for censored data.[23] A score of 1.0 indicates perfect discrimination and 0.5 indicates poor discrimination. The c-statistic and 95% CI's were estimated and compared using the somersd

package and lincom commands, respectively, in STATA (version 12.1, (StataCorp, College Station, TX), as described elsewhere.[25] All models were fitted for men and women separately and adjusted for age, smoking status, education and study cohort using follow-up time as the time scale.

This study was approved by the Alfred Health Human Research Ethics Committee (HREC), the Australian Institute for Health and Welfare HREC and the Western Australian Department of Health HREC.

Results

Over a median follow-up of 11.1 and 16.0 years 8,872 and 4,832 cancers were identified for men and women, respectively. Baseline characteristics of the study population, by cancer outcome, are shown in Table 1. In brief, men and women who developed cancer were older, less likely to have completed high school or above, and more likely to have diabetes than those who did not develop cancer. Men who developed cancer were also more likely to have a history of smoking than were men who remained cancer-free. These patterns were similar when obesity-related cancer was the outcome.

Mean values of each anthropometric measurement at baseline, by study, for men and women, are shown in Supporting Information Tables 1 and 2, respectively. Similar means and SDs for each anthropometric measurement, by sex, were observed across the cohorts, except for FDS, a sample of people with diabetes, for which means were slightly higher. No significant heterogeneity across studies was found in men and women, $I^2 = 12.2\%$ and $I^2 = 0.0\%$, respectively.

For men, all anthropometric markers were associated with overall, colorectal and obesity-related cancers, excluding ABSI for obesity-related cancers (Table 2). The strongest associations across all outcomes were observed for WC, and the weakest for ABSI. No statistically significant associations were observed between any anthropometric marker and prostate cancer incidence. Excluding the first three years of follow-up, adjusting for diabetes or excluding FDS had little effect on the magnitude of HR estimates (data not shown).

A significant interaction with smoking status was observed for all anthropometric measures and cancer, and therefore results were stratified by smoking status (Table 3). Among never smokers, the strongest associations were consistently observed for WC and the weakest for ABSI. For ever smokers, similar patterns were observed, though fewer associations were statistically significant, and the magnitude of effect was smaller than for never smokers. No significant interactions between anthropometry and age (50, 65, 70) or diabetes status and cancer were observed.

For women, BMI and HC were significantly associated with overall, PM breast and obesity-related cancers, but not colorectal cancer; WC was significantly associated with all cancer outcomes; WHR and WtHR were significantly associated with overall, colorectal and obesity-related cancers, but not PM breast; and ABSI was significantly associated with

Table 1. Baseline characteristics among men and women who developed cancer during follow-up compared to those that did not

	All Cancer						Obesity-related cancer					
	Men			Women			Men			Women		
	No cancer	Cancer	*p* values	No cancer	Cancer	*p* values	No cancer	Cancer	*p* values	No cancer	Cancer	*p* values
N	31,862	8,872		33,892	4,832		23,273	956		14,635	701	
Age	58.1±13.7	65.6±9.4	<0.001	54.3±12.6	59.8±10.6	<0.001	62.3±15.1	70.3±7.7	<0.001	54.5±16.9	65.3±11.6	<0.001
Education												
≤ High school	66.3	73.9	<0.001	72.3	75.9	<0.001	72.5	82.7	<0.001	59.9	64.2	<0.05
Above high school	33.7	26.1		27.7	24.2		27.5	17.3		40.1	35.8	
Smoking												
Never-smoker	39.3	31.1	<0.001	65.6	65.3	0.182	35.4	27.6	<0.001	59.9	64.1	<0.01
Ever smoker	60.7	68.9		34.4	34.8		64.6	72.4		25.5	25.7	
Diabetes status												
No diabetes	90.5	88.9	<0.001	94.5	92.4	<0.001	88.9	85.6	<0.001	92.1	87.8	<0.001
Diabetes	9.5	11.1		5.5	7.6		11.1	14.4		7.9	12.2	

Data are means ± SD or proportions.

Table 2. Hazards ratios (HR) and 95% confidence intervals (CI) of the association between each anthropometric measure (per one SD increase) and cancer

	Population at risk	Person-years at risk	*N* cancer outcomes	BMI	WC	HC	WHR	WtHR	ABSI
Men									
All cancer	40,734	462,705	8,872	1.03 (1.01–1.05)	1.06 (1.04–1.08)	1.04 (1.02–1.06)	1.05 (1.02–1.07)	1.02 (1.01–1.05)	1.03 (1.01–1.06)
Colorectal	40,734	462,705	1,204	1.14 (1.08–1.21)	1.19 (1.13–1.26)	1.13 (1.07–1.19)	1.16 (1.10–1.23)	1.14 (1.08–1.21)	1.10 (1.04–1.16)
Prostate	40,734	462,705	2,866	0.99 (0.95–1.03)	0.99 (0.96–1.03)	1.01 (0.97–1.04)	0.98 (0.94–1.01)	0.95 (0.92–0.99)	0.96 (0.92–1.00)
Obesity-related	24,229	214,319	956	1.12 (1.05–1.20)	1.14 (1.07–1.22)	1.15 (1.08–1.22)	1.06 (1.00–1.13)	1.10 (1.03–1.17)	1.05 (0.98–1.12)
Women									
All cancer	38,724	525,174	4,832	1.07 (1.04–1.10)	1.09 (1.06–1.12)	1.08 (1.05–1.11)	1.05 (1.02–1.09)	1.05 (1.02–1.08)	1.04 (1.01–1.07)
Colorectal cancer	38,724	525,174	714	1.06 (0.98–1.14)	1.11 (1.03–1.19)	1.06 (0.98–1.14)	1.10 (1.02–1.18)	1.08 (1.00–1.17)	1.09 (1.01–1.17)
PM breast cancer	38,724	525,174	1,323	1.06 (1.01–1.12)	1.06 (1.01–1.12)	1.09 (1.03–1.15)	1.01 (0.95–1.07)	1.02 (0.97–1.08)	0.98 (0.93–1.04)
Obesity-related	15,336	150,672	701	1.12 (1.04–1.20)	1.13 (1.04–1.21)	1.12 (1.04–1.20)	1.06 (1.00–1.15)	1.10 (1.02–1.18)	1.02 (0.95–1.11)

Abbreviations: BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; WtHR: Waist-to-height ratio; ABSI: A body shape index; PM: Post-menopause. All models adjusted for baseline smoking status, education and study cohort using age as the timescale.

Table 3. Hazards ratios (HR) and 95% confidence intervals (CI) of the association between each anthropometric measure (per one SD increase) and cancer, by smoking status in men

	Population at risk	Person-years at risk	*N* cancer outcomes	BMI	WC	HC	WHR	WtHR	ABSI
All cancer									
Never smokers	15,282	181,378	2,758	1.07 (1.03–1.11)	1.08 (1.05–1.13)	1.08 (1.04–1.12)	1.06 (1.02–1.10)	1.07 (1.02–1.11)	1.04 (1.01–1.08)
Ever smokers	25,452	281,328	6,114	1.00 (0.98–1.03)	1.04 (1.01–1.07)	1.01 (0.99–1.05)	1.04 (1.01–1.07)	1.00 (0.98–1.03)	1.03 (1.01–1.06)
Colorectal									
Never smokers	15,282	181,378	365	1.20 (1.09–1.33)	1.24 (1.12–1.37)	1.17 (1.06–1.29)	1.20 (1.08–1.32)	1.21 (1.09–1.35)	1.13 (1.10–1.26)
Ever smokers	25,452	281,328	839	1.12 (1.05–1.20)	1.17 (1.10–1.26)	1.11 (1.05–1.19)	1.14 (1.07–1.23)	1.11 (1.04–1.19)	1.07 (1.00–1.15)
Prostate									
Never smokers	15,282	181,378	1,088	1.03 (0.96–1.09)	1.03 (0.97–1.10)	1.04 (0.98–1.11)	1.00 (0.94–1.07)	1.01 (0.95–1.08)	1.00 (0.94–1.07)
Ever smokers	25,452	281,328	292	0.97 (0.92–1.02)	0.97 (0.93–1.02)	0.99 (0.94–1.04)	0.96 (0.92–1.01)	0.93 (0.88–0.97)	0.94 (0.89–0.98)
Obesity-related									
Never smokers	8,508	77,294	264	1.17 (1.04–1.32)	1.21 (1.07–1.36)	1.20 (1.07–1.35)	1.12 (0.99−1.26)	1.18 (1.04–1.33)	1.12 (0.99–1.27)
Ever smokers	15,721	137,024	692	1.10 (1.02–1.18)	1.12 (1.03–1.20)	1.12 (1.05–1.21)	1.04 (0.97–1.12)	1.07 (0.99–1.16)	1.03 (0.95–1.11)

Abbreviations: BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; WtHR: Waist-to-height ratio ABSI: A body shape index. All models adjusted for baseline smoking status, education and study cohort using age as the timescale.

overall and colorectal cancers, but not PM breast or obesity-related cancers (Table 2). The strongest associations across all outcomes were observed for WC, except PM breast whereby HC had the strongest association, and the weakest for ABSI. Excluding the first 3 years of follow-up, adjusting for diabetes or excluding FDS had little effect on the magnitude of HR estimates (data not shown).

Among never smokers, the strongest associations were observed between WC and colorectal and obesity-related cancer, and between HC and overall PM breast cancer (Table 4). Among ever smokers, significant associations were observed between WC, WHR, ABSI and overall cancer. All other associations were not statistically significant. No significant interactions between anthropometry and age (50, 65, 70) or diabetes status and cancer were observed.

C-statistics comparing prediction models in men and women were similar across all models for overall, colorectal, PM breast, prostate and obesity-related cancers (Table 5). All models had greatest discriminatory ability for colorectal cancer in men and women, and the lowest for PM breast cancer in women. Compared to Model 1, including age, education, smoking and study cohort, the addition of BMI, WC and HC, separately, improved the predictive ability for overall, colorectal, prostate, PM breast and obesity-related cancers in men and women ($p < 0.05$; change in c-statistic not shown). Compared with BMI, models of WC had a significantly greater discriminative ability for overall and colorectal cancer in both men and women, and HC had significantly greater discriminative ability than BMI for overall cancer in men (Supporting Information Table 6).

Discussion

In this large pooled cohort of Australian adults, we show that all anthropometric markers tested (BMI, WC, HC, WHR, WtHR and ABSI) were associated with the development of overall, colorectal and obesity-related cancers in men and women (excluding ABSI in women). BMI, WC and HC were associated with PM breast cancer but no statistically significant associations were observed for prostate cancer with any anthropometric measure. The magnitude of these associations was greatest for WC with 19% and 13% increased risk per SD for colorectal cancer in men and obesity-related cancer in women, respectively. The effect estimates of anthropometric measures on cancer risk were larger in never smokers than that in ever smokers. In discriminatory analysis, all measures had moderate discriminative ability for cancer risk with c-statistic values between 0.60 and 0.71. For men, compared with BMI, WC and HC were superior in predicting overall and colorectal cancer risk. For women, WC was the only measure significantly better at discriminating cancer risk than BMI for overall and colorectal cancer.

Whilst there is evidence to suggest that WC and other measures of central adiposity are better predictors of cardiovascular disease (CVD) than BMI,[26,27] less is known for the role of central adiposity in cancer risk. Of studies that use

Table 4. Hazards ratios (HR) and 95% confidence intervals (CI) of the association between each anthropometric measure (per one SD increase) and cancer, by smoking status in women.

	Population at risk	Person-years at risk	*N* cancer outcomes	BMI	WC	HC	WHR	WtHR	ABSI
All cancer									
Never smokers	25,393	351,662	3,153	1.08 (1.05–1.12)	1.10 (1.06–1.14)	1.11 (1.07–1.15)	1.04 (1.00–1.08)	1.06 (1.02–1.10)	1.02 (0.98–1.06)
Ever smokers	13,331	173,511	1,679	1.03 (0.98–1.08)	1.06 (1.01–1.11)	1.01 (0.97–1.06)	1.08 (1.03–1.14)	1.04 (0.99–1.09)	1.07 (1.02–1.12)
Colorectal									
Never smokers	25,393	351,662	482	1.12 (1.03–1.22)	1.16 (1.06–1.27)	1.13 (1.03–1.23)	1.11 (1.02–1.21)	1.13 (1.03–1.24)	1.08 (0.99–1.18)
Ever smokers	13,331	173,511	232	0.93 (0.81–1.07)	1.00 (0.88–1.14)	0.92 (0.80–1.05)	1.09 (0.96–1.24)	0.99 (0.68–1.13)	1.11 (0.98–1.27)
PM Breast									
Never smokers	25,393	351,662	901	1.07 (1.01–1.15)	1.08 (1.02–1.16)	1.11 (1.04–1.18)	1.01 (0.95–1.08)	1.04 (0.97–1.11)	1.00 (0.93–1.07)
Ever smokers	13,331	173,511	422	1.04 (0.94–1.15)	1.02 (0.93–1.13)	1.04 (0.95–1.15)	0.98 (0.89–1.09)	0.99 (0.89–1.09)	0.95 (0.86–1.05)
Obesity-related									
Never smokers	9,212	90,290	450	1.14 (1.04–1.25)	1.16 (1.05–1.27)	1.15 (1.05–1.26)	1.07 (0.97–1.18)	1.13 (1.03–1.24)	1.03 (0.93–1.137)
Ever smokers	6,124	60,382	251	1.07 (0.94–1.21)	1.08 (0.96–1.23)	1.07 (0.94–1.21)	1.06 (0.93–1.204)	1.05 (0.92–1.19)	1.03 (0.90–1.17)

Abbreviations: BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; WthR: Waist-to-height ratio; ABSI: A body shape index; PM: Post-menopause. All models adjusted for baseline smoking status, education and study cohort using age as the timescale.

Table 5. Comparison of the discriminative ability of each adiposity measure for the prediction of incident cancer in men and women

	Harrell's C statistic (95% CI) for each anthropometric measure						
	Model 1	Model 1+BMI	Model 1+WC	Model 1+HC	Model 1+WHR	Model 1+Waist-to-height ratio	Model 1+ABSI
Men							
All cancer	0.7001 (0.6951–0.7051)	0.7002 (0.6952–0.7052)	0.7009 (0.6959–0.7059)*	0.7006 (0.6956–0.7056)*	0.7005 (0.6955–0.7055)	0.7002 (0.6952–0.7052)	0.7005 (0.6954–0.7055)
Colorectal	0.7052 (0.6924–0.7180)	0.7089 (0.6962–0.7216)	0.7129 (0.7002–0.7256)*	0.7090 (0.6961–0.7218)*	0.7115 (0.6988–0.7241)	0.7094 (0.6967–0.7222)	0.7081 (0.6953–0.7209)
Prostate	0.6851 (0.6769–0.6934)	0.6852 (0.6769–0.6934)	0.6851 (0.6768–0.6933)	0.6852 (0.6769–0.6934)	0.6851 (0.6769–0.6933)	0.6853 (0.6771–0.6936)	0.6854 (0.6772–0.6936)
Obesity–related cancer	0.6750 (0.6599–0.6901)	0.6784 (0.6634–0.6934)	0.6795 (0.6646–0.6943)	0.6808 (0.6656–0.6958)	0.6764 (0.6615–0.6913)	0.6776 (0.6626–0.6926)	0.6762 (0.6612–0.6913)
Women							
All cancer	0.6386 (0.6308–0.6466)	0.6396 (0.6318–0.6434)	0.6403 (0.6325–0.6481)*	0.6401 (0.6323–0.6479)	0.6392 (0.6314–0.6470)	0.6392 (0.6314–0.6470)	0.6388 (0.6310–0.6466)
Colorectal cancer	0.7083 (0.6903–0.7264)	0.7086 (0.6906–0.7266)	0.7103 (0.6922–0.7284)*	0.7087 (0.6907–0.7267)	0.7105 (0.6924–0.7286)	0.7094 (0.6914–0.7274)	0.7101 (0.6920–0.7283)
PM breast cancer	0.5989 (0.5854–0.6124)	0.6010 (0.5873–0.6150)	0.6009 (0.5872–0.6145)	0.6026 (0.5889–0.6163)	0.5989 (0.5854–0.6125)	0.5993 (0.5858–0.6129)	0.5991 (0.5856–0.6126)
Obesity–related cancer	0.6955 (0.6794–0.7115)	0.6991 (0.6828–0.7154)	0.7005 (0.6842–0.7168)	0.6996 (0.6934–0.7157)	0.6969 (0.6807–0.7131)	0.6987 (0.6824–0.7149)	0.6958 (0.6797–0.7118)

Abbreviations: BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; WtHR: Weight-to-height ratio; ABSI: A body shape index; PM: Post-menopause. Model 1: Age, education, smokingand study cohort. All models adjusted for age, smoking status, education and study cohort using follow-up time as the time scale.*C-statistics significantly greater than BMI, determined by estimating the differences in c-statistics, $p < 0.05$ (Supporting Information Table 6).

multiple anthropometric markers to assess cancer risk, most examine site-specific cancers, with mixed effect sizes. Central adiposity, assessed by WC or WHR, has been associated with PM breast cancer in several studies, independent of BMI, with relative risks ranging from 1.28 to 2.85 depending on how measures were categorised.[28,29] However, a more recent review showed that adjustment for BMI attenuated the relationship between WC or WHR and risk of PM breast cancer to the null. This work did however show that there was evidence that central obesity may be important for premenopausal breast cancer.[13] Moghaddam *et al.*[30] pooled risk estimates from 31 studies to estimate associations of general and central adiposity with colorectal cancer incidence. They showed higher estimates for measures of central adiposity (HR: 1.44 (95% CI: 1.32–1.58) than BMI (1.19, 1.11–1.29) in obese compared to non-obese, but this was only statistically significant in men. Studies of oesophageal,[31] endometrial[32] and pancreatic cancers[33] also suggest stronger associations with central adiposity than with BMI. For prostate cancer, several large studies have found an increased BMI to be associated with an increased risk of the development of prostate cancer, while others have shown no such association.[7] For central adiposity, a Chinese study showed that men in the highest quartile of WHR had a three-fold increased incidence of prostate cancer compared with men in the lowest quartile of WHR, but no association was seen for BMI.[34] Other studies show that central obesity may play a role only in advanced stages of prostate cancer.[35] We did not have data on cancer stage to explore this in the current study.

An important caveat in all of these aforementioned studies is that including separate anthropometric measures in the same model can lead to difficulties in interpretation of results, because of the high degree of co linearity between the anthropometric variables. To understand if central or general adiposity is driving the association with incident cancer, separate models need to be fitted and compared. To our knowledge, we are the first group to compare the discriminative ability of each anthropometric measure for predicting the risk of multiple cancer outcomes. We show that addition of BMI, WC and HC to models of age, education and smoking significantly improved the predictive ability of models, though the impact was small. Additionally, among anthropometric measures, we show that WC, a measure of central adiposity, had statistically greater discrimination than BMI for overall and colorectal cancers. However, these differences were only in the order of approximately 1% and therefore, are unlikely to be clinically relevant. Additionally, given all anthropometric measures had similar discriminative ability we show that there is no one stand out measure for the prediction of cancer.

At present, the biological mechanisms that link adiposity to cancer are poorly understood. Current findings implicate sex- and cancer site-specific biological mechanisms underpinning these associations and it is unlikely that there is a one single underlying mechanism.[36] The three most common pathways proposed are; insulin and insulin-like growth factors,[37] sex steroids,[38,39] adipokines and markers of chronic inflammation.[40] We did not have data on these biological markers to disentangle these mechanisms further. Our data suggest that central adiposity, which is more active in terms of metabolic and inflammatory cytokines, appears to be more strongly related to cancer than is general adiposity.

Strengths and Weaknesses

Our study combined data from 11 large Australian population-based studies, with sufficient power to investigate the association between anthropometric measurements and risk of cancer incidence and is the first large scale analysis of obesity and cancer in Australia. While many studies have compared the discriminative ability of anthropometry for CVD,[9,10,26] this is the first time a large range of markers have been compared in terms of magnitude and discriminative ability for various cancer outcomes. This is also the first time that the ABSI has been examined for predicting cancer risk. ABSI has been shown to be a useful measure for predicting all-cause mortality,[21] but we show here that it is not useful for cancer.

There are several limitations to this study that should also be acknowledged. First, for outcomes of obesity-related cancers we included malignancies where there is internationally recognised "sufficient evidence" for associations with obesity. However, given the paucity of data on some rare site-specific cancers, it is possible that some cancers that may be driven by excess adiposity have not been included here. Nevertheless, their contribution to overall obesity-related cancers is likely to be very small. It is also known that associations between obesity and colorectal cancer differ by site, that is, colon *vs.* rectum.[41] Unfortunately, we were unable to stratify by these cancer sites. Second, there is potential for reverse causality from weight loss that may have been due to illness, or weight gain that may have been the result of quitting smoking. We have, however, attempted to address this by excluding people in the first three years of follow-up and performing stratified analyses in ever smokers and never smokers. With these sensitivity analyses, our conclusions were not altered. Third, this is a pooled collaborative analysis and even though we did have lifestyle data such as physical activity and diet in some studies, these data were collected too differently across studies to derive sensible harmonized categories. Therefore, we could not further adjust our analyses for potential confounding effects of physical activity, diet and alcohol in a meaningful way. Last, we did not have data on hormone replacement therapy, a factor shown in some studies to modify associations between obesity and cancer.[42,43] It is possible, therefore, that there may be some residual confounding of HRT on the association between obesity and cancer.

Conclusions

This large pooled collaborative study has shown that anthropometric measures are associated with the development of overall, colorectal, PM breast and obesity-related cancer in

men and women in Australia. Measures of central adiposity performed marginally better than BMI in discriminatory analyses of overall and colorectal cancers. However, all anthropometric measures were similarly moderately predictive of cancer risk. Therefore, at this stage we do not present strong evidence for the choice of one anthropometric marker over another for assessing an individuals' risk of cancer.

Conflicts of Interest

MW is a consultant to Amgen on a research grant awarded to the University of Alabama at Birmingham and to Sanofi on a research grant awarded to Mount Sinai School of Medicine, New York. He is also on a data monitoring committee for Novartis.

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Authors' Contributions

J.L.H., BBiomedsci(Hons), (Baker IDI Heart and Diabetes Institute; Monash University) wrote the manuscript, had full access to all the data, and conducted the analyses. J.E.S., FRACP, (Baker IDI Heart and Diabetes Institute; Monash University), A.P., Ph.D, (Baker IDI Heart and Diabetes Institute; Monash University) and D.J.M., Ph.D, (Baker IDI Heart and Diabetes Institute; Monash University) contributed to conceptualisation, discussion and reviewed/edited manuscript. D.J.M. 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. All authors contributed to the collaboration and reviewed the manuscript and approved the final version.

References

1. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: AICR, 2007.
2. World Cancer Research Fund/American Institute for Cancer Research. Continuous update project report. Food, nutrition, physical activity, and the prevention of breast cancer. World Cancer Research Fund and American Institute for Cancer Research, 2010.
3. World Cancer Research Fund/American Institute for Cancer Research. Continuous update project report. Food, nutrition, physical activity, and the prevention of colorectal cancer. World Cancer Research Fund and American Institute for Cancer Research, 2011.
4. World Cancer Research Fund/American Institute for Cancer Research. Continuous update project report. Food, nutrition, physical activity, and the prevention of pancreatic cancer. World Cancer Research Fund and American Institute for Cancer Research, 2012.
5. World Cancer Research Fund/American Institute for Cancer Research. Continuous update project report. Food, nutrition, physical activity, and the prevention of endometrial cancer. World Cancer Research Fund and American Institute for Cancer Research, 2013.
6. World Cancer Research Fund/American Institute for Cancer Research. Continuous update project report. Food, nutrition, physical activity, and the prevention of ovarian cancer. World Cancer Research Fund and American Institute for Cancer Research, 2014.
7. Freedland SJ, Aronson WJ. Examining the relationship between obesity and prostate cancer. *Rev Urol* 2004;6:73–81.
8. Pasco J, Nicholson A, Brennan GC, Kotowicz SLMA. Prevalence of obesity and the relationship between the body mass index and body fat: cross-sectional, population-based data. *PLoS ONE* 2012;7:e29580
9. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obesity Rev* 2012;13:275–86.
10. Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0.5 could be a suitable global boundary value. *Nutr Res Rev* 2010;23: 247–69.
11. Pouliot MC, Despres JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994;73:460–8.
12. Rankinen T, Kim SY, Perusse L, et al. The prediction of abdominal visceral fat level from body composition and anthropometry: ROC analysis. *Int J Obes Relat Metab Disord* 1999;23: 801–9.
13. Harvie M, Hooper L, Howell AH. Central obesity and breast cancer risk: a systematic review. *Obes Rev* 2003;4:157–73.
14. Aune D, Navarro Rosenblatt DA, Chan DS, et al. Anthropometric factors and ovarian cancer risk: a systematic review and nonlinear dose-response meta-analysis of prospective studies. *Int J Cancer* 2015;136:1888–98.
15. Giovannucci E, Ascherio A, Rimm EB, et al. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med* 1995; 122:327–34.
16. Keimling M, Renehan AG, Behrens G, et al. Comparison of associations of body mass index, abdominal adiposity, and risk of colorectal cancer in a large prospective cohort study. 2013;22: 1383–94.
17. Harding JL, Shaw JE, Koshkina V, et al. Cohort profile: the australian and new zealand diabetes and cancer collaboration (ANZDCC*). Aust Epidemiol* 2014;21:51–7.
18. Fellegi IP, Sunter AB. A theory for record Linkage. *J Am Stat Assoc* 1969;40:1183–210.
19. Loh V, Harding J, Koshkina V, et al. The validity of self-reported cancer in an Australian population study. *Australian and New Zealand journal of public health*. 2014;38(1):35–8.
20. Wang J, Thornton JC, Bari S, et al. Comparisons of waist circumferences measured at 4 sites. *Am J Clin Nutr* 2003;77:379–84.
21. Krakauer NY, Krakauer JC. A new body shape index predicts mortality hazard independently of body mass index. *PloS One* 2012;7:e39504
22. Arnold M, Pandeya N, Byrnes G, et al. Global burden of cancer attributable to high body-mass index in 2010: a population-based study. *Lancet Oncol*. 2015;16:36–46.
23. Woodward M. Epidemiology: Study design and data analysis. 3rd ed. Boca Raton: CRC Press, 2014.
24. Selvin S. Statistical Analysis of Epidemiologic Data. New York: NY: Oxford University Press, 1996.
25. Newson RB. Comparing the predictive powers of survival models using harrell's C or somers' D. *Stata J* 2010;10:339–58.
26. Carlsson AC, Riserus U, Engstrom G, et al. Novel and established anthropometric measures and the prediction of incident cardiovascular disease: a cohort study. *Int J Obes* 2013;37:1579–85.
27. Song X, Jousilahti P, Stehouwer CD, et al. Comparison of various surrogate obesity indicators as predictors of cardiovascular mortality in four european populations. *Eur J Clin Nutr* 2013;67: 1298–302.
28. Schapira DV, Kumar NB, Lyman GH, et al. Abdominal obesity and breast cancer risk. *Ann Internal Med* 1990;112:182–6.
29. Huang Z, Willett WC, Colditz GA, et al. Waist circumference, waist:hip ratio, and risk of breast cancer in the nurses' health study. *Am J Epidemiol* 1999;150:1316–24.
30. Moghaddam AA, Woodward M, Huxley R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. *Cancer Epidemiol Biomarkers Prev* 2007;16:2533–47.
31. Steffen A, Schulze MB, Pischon T, et al. Anthropometry and esophageal cancer risk in the european prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev*. 2009;18:2079–89.
32. Friedenreich C, Cust A, Lahmann PH, et al. Anthropometric factors and risk of endometrial

cancer: the european prospective investigation into cancer and nutrition. *Cancer Causes Control* 2007;18:399–413.

33. Aune D, Greenwood DC, Chan DS, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. *Ann oncol*. 2012;23:843–52.
34. Hsing AW, Deng J, Sesterhenn IA, et al. Body size and prostate cancer: a population-based case-control study in China. *Cancer Epidemiol Biomarkers Prev* 2000;9(12):1335–41.
35. Prabhat P, Tewari R, Natu SM, et al. Is central obesity, hyperinsulinemia and dyslipidemia associated with high-grade prostate cancer? a descriptive cross-sectional study. *Indian J Urol* 2010;26:502–6.
36. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med* 2010;61:301–16.
37. Renehan AG, Zwahlen M, Minder C, et al. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* 2004;363:1346–53.
38. Kaaks R, Rinaldi S, Key TJ, et al. Postmenopausal serum androgens, oestrogens and breast cancer risk: the european prospective investigation into cancer and nutrition. *Endocrine-Relat Cancer* 2005;12:1071–82.
39. Derby CA, Zilber S, Brambilla D, et al. Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones: the massachusetts male ageing study. *Clin Endocrinol*. 2006;65:125–31.
40. Kelesidis I, Kelesidis T, Mantzoros CS. Adiponectin and cancer: a systematic review. *Br J Cancer*. 2006;94:1221–5.
41. Larsson SC, Wolk A. Obesity and Colon and Rectal Cancer Risk: a meta-Analysis of Prospective Studies. *Am J Clin Nutr* 2007;86:556–65.
42. Hou N, Hong S, Wang W, et al. Hormone Replacement Therapy and Breast Cancer: Heterogenous Risks by Race, Weight, and Breast Density. *J Natl Cancer Inst* 2013; 105:1365–72.
43. Hoffmeister M, Raum E, Winter J, et al. Hormone replacement therapy, body mass, and the risk of colorectal cancer among postmenopausal women from germany. *Br J Cancer* 2007;97:1486–1492.

Supplementary Data

Supplementary Table 1 Baseline characteristics and follow-up data by study in men

Study	N	Age (years)	BMI (kg/m2)	WC (cm)	HC (cm)	WHR	WtHR	ABSI ($m^{11/6}kg^{-2/3}$)	Median follow-up (years)	All cancer	Obesity-related cancer (N)
Australian National Blood Pressure Trial 2 (ANBP2)	2,633	72.2 (4.8)	27.2 (3.7)	100.4 (10.0)	105.3 (7.7)	0.95 (0.05)	0.59 (0.06)	0.0848 (0.0043)	10.9	764	146
Australian Longitudinal Study of Aging	373	78.6 (6.1)	26.0 (3.3)	97.3 (9.4)	102.7 (7.4)	0.95 (0.06)	0.57 (0.05)	0.0853 (0.0046)	6.5	179	14
Australian Diabetes Obesity and Lifestyle Study	4,621	51.1 (14.0)	27.3 (4.1)	97.6 (11.4)	104.4 (7.6)	0.93 (0.06)	0.56 (0.07)	0.0815 (0.0044)	8.7	423	63
Crossroads Undiagnosed Study	601	52.9 (15.6)	28.1 (4.3)	101.3 (11.6)	106.5 (8.1)	0.95 (0.06)	0.58 (0.07)	0.0830 (0.0045)	6.8	48	9
Fremantle Diabetes Study	618	61.7 (12.8)	29.3 (5.2)	99.0 (13.0)	109.4 (11.2)	0.90 (0.08)	0.60 (0.08)	0.0813 (0.0052)	13.2	178	33
Geelong Osteoporosis Study	1,313	53.9 (19.2)	27.0 (4.1)	97.2 (11.3)	100.7 (8.8)	0.96 (0.06)	0.56 (0.07)	0.0817 (0.0049)	4.7	118	19
Health in Men Study	10,482	71.4 (4.3)	26.9 (3.7)	100.7 (10.3)	103.2 (7.1)	0.97 (0.06)	0.59 (0.06)	0.0859 (0.0038)	10.6	3,135	601
Melbourne Collaborative Cohort Study	16,505	55.7 (8.8)	27.2 (3.6)	93.5 (10.0)	101.1 (7.1)	0.92 (0.06)	0.54 (0.06)	0.0789 (0.0045)	16.5	3,642	n/a
Northwest Adelaide Health Study	1,763	49.6 (16.2)	27.9 (4.7)	99.9 (12.8)	104.7 (9.2)	0.94 (0.06)	0.57 (0.08)	0.0823 (0.0044)	8.1	156	21
Perth Risk Factor Prevalence Cohort Study 1989	947	45.2 (13.5)	26.2 (3.4)	91.0 (10.2)	101.3 (6.5)	0.90 (0.06)	0.52 (0.06)	0.0782 (0.0041)	19.3	168	31
Perth Risk Factor Prevalence Cohort Study 1994	878	46.8 (13.5)	26.4 (3.8)	95.0 (11.2)	104.9 (7.0)	0.90 (0.07)	0.54 (0.07)	0.0811 (0.0057)	14.4	121	19
Total	40,734	59.8 (13.3)	27.2 (3.8)	96.9 (11.0)	102.8 (7.7)	0.94 (0.07)	0.56 (0.07)	0.0818 (0.0053)	11.1	8,872	956

Abbreviations: BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; WtHR: Weight-to-Height Ratio; ABSI: A body shape index. Data are means (SD) or as noted

Supplementary Table 2 Baseline characteristics and follow-up data by study in women

Study	N	Age (years)	BMI (kg/m2)	WC (cm)	HC (cm)	WHR	WtHR	ABSI ($m^{11/6}kg^{-2/3}$)	Median follow-up (years)	All cancer (N)	Obesity-related cancer (N)
Australian National Blood Pressure Trial 2 (ANBP2)	2,840	73.2 (5.0)	27.2 (4.5)	89.7 (11.0)	105.8 (10.2)	0.85 (0.06)	0.57 (0.07)	0.0792 (0.0057)	11.2	471	223
Australian Longitudinal Study of Aging	230	75.7 (6.3)	26.2 (4.8)	87.2 (11.2)	103.8 (9.8)	0.84 (0.06)	0.56 (0.07)	0.0792 (0.0061)	13.8	48	14
Australian Diabetes Obesity and Lifestyle Study	5,603	51.0 (14.3)	26.9 (5.5)	85.6 (13.3)	105.4 (11.5)	0.81 (0.07)	0.53 (0.08)	0.0752 (0.0052)	8.7	388	171
Crossroads Undiagnosed Study	749	52.0 (15.3)	27.8 (5.8)	89.4 (13.6)	107.9 (12.4)	0.83 (0.06)	0.55 (0.09)	0.0770 (0.0053)	6.9	46	22
Fremantle Diabetes Study	640	62.5 (13.0)	29.3 (5.4)	99.0 (13.1)	109.4 (11.5)	0.91 (0.08)	0.60 (0.08)	0.0815 (0.0054)	16.1	116	53
Geelong Osteoporosis Study	1,568	49.3 (20.1)	26.6 (5.3)	84.6 (12.8)	105.3 (11.5)	0.80 (0.07)	0.53 (0.08)	0.0751 (0.0054)	12.3	149	80
Melbourne Collaborative Cohort Study	23,388	51.9 (8.6)	26.8 (4.9)	80.1 (11.7)	101.8 (9.9)	0.79 (0.07)	0.50 (0.08)	0.0709 (0.0054)	17.0	3,319	n/a
North West Adelaide Health Study	1,918	49.4 (15.8)	27.8 (6.0)	89.9 (14.1)	107.5 (12.7)	0.83 (0.07)	0.56 (0.09)	0.0774 (0.0053)	8.2	91	45
Perth Risk Factor Prevalence Cohort Study 1989	941	45.2 (13.5)	25.3 (4.5)	77.4 (10.9)	101.6 (9.2)	0.76 (0.06)	0.48 (0.07)	0.0708 (0.0044)	19.3	117	59
Perth Risk Factor Prevalence Cohort Study 1994	847	46.7 (13.5)	26.1 (5.0)	82.0 (11.7)	105.6 (10.3)	0.77 (0.06)	0.51 (0.07)	0.0735 (0.0045)	14.4	87	55
Total	38,724	55.0 (12.5)	26.9 (5.1)	82.8 (12.8)	103.4(10.7)	0.80 (0.07)	0.52 (0.08)	0.0731 (0.0062)	16.0	4,832	701

Abbreviations: BMI: Body mass index; WC: Waist circumference; HC: Hip circumference; WHR: Waist-to-hip ratio; WtHR: Waist-to-Height Ratio; ABSI: A body shape index. Data are means (SD) or as noted

Supplementary Table 3 Coefficients and p-values for the difference in c-statistics between each anthropometric measures' discriminative ability for cancer outcomes, as compared to BMI

	Coefficients and p-values											
	Model 1^		Model 1+WC		Model 1+HC		Model 1+WHR		Model 1+WtHR		Model 1+ABSI	
Men	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value
All cancer	-0.0001	0.505	-0.0007	0.003	-0.0004	0.013	-0.0003	0.287	0.0000	0.834	-0.0002	0.397
Colorectal	-0.0037	0.021	-0.0042	0.001	-0.0001	0.949	-0.0026	0.140	-0.0005	0.541	0.0008	0.671
Prostate	-0.0001	0.823	0.0001	0.420	-4.20e-06	0.974	0.0001	0.230	-0.0002	0.503	-0.0003	0.292
Obesity-related cancer	-0.0034	0.170	-0.0011	0.498	-0.0023	0.179	0.0020	0.381	0.0080	0.544	0.0022	0.461
Women												
All cancer	0.0010	0.077	-0.0008	0.054	-0.0005	0.102	0.0004	0.544	0.0004	0.210	0.0007	0.235
Colorectal cancer	0.0028	0.765	-0.0017	0.049	-0.0001	0.847	-0.0019	0.118	-0.0008	0.174	-0.0015	0.250
PM breast cancer	0.0020	0.258	0.0001	0.907	-0.0017	0.115	0.0020	0.243	0.0016	0.173	0.0018	0.348
Obesity-related cancer	0.004	0.115	-0.0014	0.287	-0.004	0.680	0.0023	0.306	0.0005	0.681	0.0034	0.149

Abbreviations: BMI: Body Mass Index; WC: Waist Circumference; HC: Hip Circumference; WHR: Waist-to-Hip Ratio; WtHR: Weight-to-Height Ratio; ABSI: A Body Shape Index; PM: Post-menopause. ^Model 1: Age, education, smoking and study cohort. All models model adjusted for age, smoking status, education and study cohort using follow-up time as the time scale.

Declaration for Thesis – Chapter 6.2

Harding JL, Sooriyakumaran M, Anstey K, et al. Hypertension, anti-hypertensive treatment and cancer risk: a pooled collaborative analysis of 12 Australian and New Zealand cohorts. *Journal of Hypertension*. 2016; 34(1):149-55

In the case of Chapter 6.2, the nature and extent of my contribution to the work was the following:

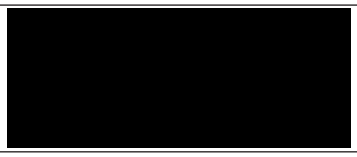
Nature of contribution	**Extent of contribution (%)**
Acquisition of data, data management, analysis and interpretation of data, conceptualisation and writing of manuscript, critical revision, corresponding author	70%

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

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Manoshyani Sooriyakumaran	Data analysis, writing of manuscript, critical revision	30%
Kaarin Anstey	Data provision and approval of final draft for publication	
Robert Adams	Data provision and approval of final draft for publication	
Beverley Balkau	Data provision and approval of final draft for publication	
Tom Briffa	Data provision and approval of final draft for publication	
Timothy Davis	Data provision and approval of final draft for publication	
Wendy Davis	Data provision and approval of final draft for publication	
Annette Dobson	Data provision and approval of final draft for publication	
Graham Giles	Data provision and approval of final draft for publication	
Janet Grant	Data provision and approval of final draft for publication	
Matthew Knuiman	Data provision and approval of final draft for publication	
Mary Luszcz	Data provision and approval of final draft for publication	
Paul Mitchell	Data provision and approval of final draft for publication	
Julie Pasco	Data provision and approval of final draft for publication	
Christopher Reid	Data provision and approval of final draft for publication	

David Simmons	Data provision and approval of final draft for publication	
Leon Simons	Data provision and approval of final draft for publication	
Andrew Tonkin	Data provision and approval of final draft for publication	
Mark Woodward	Data provision and approval of final draft for publication	
Jonathan Shaw	Conceptualisation, critical revision, approval of final draft for publication	
Dianna Magliano	Conceptualisation, data acquisition, critical revision, approval of final draft for publication	

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

Candidate's Signature		Date: 31/03/2016
Main Supervisor's Signature		Date: 31/03/2016

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

Original Article

Hypertension, antihypertensive treatment and cancer incidence and mortality: a pooled collaborative analysis of 12 Australian and New Zealand cohorts

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Background: Observational studies examining associations between hypertension and cancer are inconsistent. We explored the association of hypertension, graded hypertension and antihypertensive treatment with cancer incidence and mortality.

Method: Eighty-six thousand five hundred and ninety-three participants from the Australian and New Zealand Diabetes and Cancer Collaboration were linked to the National Death Index and Australian Cancer Database. Cox proportional hazards models estimated hazard ratios and 95% confidence intervals (95% CI) for the association of treated and untreated hypertension with cancer incidence and mortality.

Results: Over a median follow-up of 15.1 years, 12 070 incident and 4350 fatal cancers were identified. Untreated and treated hypertension, compared with normotension, were associated with an increased risk for cancer incidence [hazard ratio 1.06, 95% CI (1.00–1.11) and 1.09 (1.02–1.16) respectively], and cancer mortality (1.07, 0.98–1.18) and (1.15, 1.03–1.28), respectively. When compared with untreated hypertension, treated hypertension did not have a significantly greater risk for cancer incidence (1.03, 0.97–1.10) or mortality (1.07, 0.97–1.19). A significant dose–response relationship was observed between graded hypertension and cancer incidence and mortality; $P_{trend} = 0.053$ and $P_{trend} = 0.001$, respectively. When stratified by treatment status, these relationships remained significant in untreated, but not in treated, hypertension.

Conclusion: Hypertension, both treated and untreated, is associated with a modest increased risk for cancer incidence and mortality. Similar risks in treated and untreated hypertension suggest that the increased cancer risk is not explained by the use of antihypertensive treatment.

Keywords: antihypertensive treatment, cancer, cancer mortality, hypertension

Abbreviations: ACD, Australian Cancer Database; AIHW, Australian Institute of Health and Welfare; ANZDCC, Australian and New Zealand Diabetes and Cancer Collaboration; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; FDS, Fremantle Diabetes Study; HREC, Human Research and Ethics Committee; ICD, International Classification of Disease; MCCS, Melbourne Collaborative Cohort Study; NDI, National Death Index; NZ, New Zealand; SBP, systolic blood pressure

BACKGROUND

Metabolic abnormalities related to obesity, for example hyperglycemia and hypertriglyceridemia, have been linked to an increased risk for

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cancer [1,2]. Emerging evidence suggests that other metabolic abnormalities, such as hypertension, may also be associated with an increased risk for cancer [3–6]. Two main hypotheses have been proposed to explain this observation. First, medications used in the treatment of hypertension may cause cancer by directly promoting carcinogenesis, accelerating other carcinogens or impeding defense mechanisms [7]. Second, there may be a common mechanism linking blood pressure (BP) regulation and cancer development, independent of antihypertensive treatment [8]. In addition, it is also possible that cancer itself may lead to hypertension [9].

To date, observational studies on the association between hypertension and cancer show inconsistent results. A large Swedish cohort reported a 7% [95% confidence interval (CI): 4–9%)] increase in incident cancer risk per 10 mmHg increase in BP [10]. This association, however, did not account for antihypertensive treatment, and was observed only in men [10]. A second, smaller, Swedish cohort of men demonstrated a 41% increase in risk of cancer incidence when comparing the highest quintile of SBP with the lowest, even after adjustment for antihypertensive medication at baseline [8]. Other studies report that antihypertensive medication, in particular diuretics, may be associated with an increased cancer risk even in those who are normotensive [11,12]. However, a recent meta-analysis concluded that diuretics or any other single antihypertensive medication was not associated with an increased cancer risk, though it could not be ruled out that a combination of antihypertensive drugs may confer an increased risk for overall cancer [13].

For cancer mortality, evidence is less clear. Early work by Dyer *et al.* [3] showed a 50 and 80% increased risk in cancer mortality among hypertensive men compared with normotensive men for systolic and diastolic hypertension, respectively. A more recent meta-analysis reported a 23% increased risk in cancer mortality in those with hypertension compared with those without, though significant heterogeneity among studies was noted and the included studies did not adjust for BP treatment [4].

Using data from a large pool of prospective studies, we examine the association between treated and untreated hypertension, graded hypertension and cancer incidence and mortality.

METHODS

Study population

The Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC) is a pooled study composed of 18 prospective studies in Australia and New Zealand with data on 153 025 men and women. Details of sampling procedures, study designs and methods for each of the respective studies have been described elsewhere [14]. In brief, the chief investigators of epidemiological studies in Australia and New Zealand conducted from 1983 onwards with data on diabetes, obesity and the metabolic syndrome and with a minimum sample size of 1000 individuals were invited to participate in the ANZDCC study. For the current analysis, we included observational studies that had measured BP and information on antihypertensive treatment (12 cohorts; $n = 91\,781$). To prevent reverse causation, we excluded participants with a cancer diagnosis prior to baseline date ($n = 3022$) or who were underweight at baseline ($n = 843$). We further excluded participants with missing data on age, sex, smoking or BP ($n = 1323$). A total of 86 593 participants (40 965 men; 45 628 women) with complete data were included in the final data analysis.

Data linkage

Australian participants of the ANZDCC cohort were linked to the Australian Cancer Database, a register of all primary, malignant cancers diagnosed in Australia since 1982, and the National Death Index (NDI). Linkage was performed by the Australian Institute of Health and Welfare (AIHW) and the Western Australian Data Linkage Unit (for Fremantle Diabetes Study (FDS) only), using first name, second name, last name, sex and date of birth [15]. New Zealand participants of the ANZDCC cohort, those from the Fletcher Challenge Study, were linked to the New Zealand Cancer Registry and Mortality Database using National Health Index numbers; unique identifiers assigned to every person who uses health and disability support services in New Zealand. Cancer status of the cohort was determined until 31 December 2008 for 10 of the 12 cohorts and until 31 August 2010 for the Melbourne Collaborative Cohort Study (MCCS) and 31 October 2012 for FDS. Mortality status was determined until 31 March 2012 for nine of the 12 cohorts, and until 31 December 2009 for the Fletcher Challenge Study, 30 April 2011 for MCCS and 31 January 2013 for FDS. We set a match link rate of 97.70% (true matches/correct links) with link accuracy of 97.92% (1.08% expected to be false-positive links). Twenty-seven percent of links underwent clerical review, performed by AIHW.

Definition of covariates and outcomes

Details of baseline BP measurements, by study, are provided in Supplementary Table 1, http://links.lww.com/HJH/A541. Untreated hypertension was defined as elevated SBP or DBP of at least 140 or 90 mmHg, respectively, with no self-reported use of antihypertensive treatment, and treated hypertension was defined by self-reported use of antihypertensive treatment; no information on specific antihypertensive drugs was available. Those who did not have elevated SBP or DBP and who did not report using antihypertensives were defined as 'normotensive'. 'Any hypertension' was defined as untreated or treated hypertension. Graded hypertension was classified according to the European Society of Hypertension and the European Society of Cardiology guidelines as follows: normal: SBP <130 mmHg or DBP <85 mmHg; high normal: SBP 130–139 mmHg or DBP 85–89 mmHg; graded hypertension 1: SBP 140–159 mmHg or DBP 90–99 mmHg; graded hypertension 2: SBP 160–179 mmHg or DBP 100–109 mmHg; graded hypertension 3: SBP ≥180 mmHg or DBP≥110 mmHg [16].

Biomedical tests collected data on cholesterol (mmol/l); diabetes was defined by self-report, fasting plasma glucose of at least 126 mg/dl (7.0 mmol/l) or use of glucose-lowering medication; BMI was computed as weight (kg) divided by the square of height (m). Information on education, smoking status and alcohol status was collected by

questionnaires. These risk factors were harmonized across studies to reflect common categories as follows: smoking [current, ex-smoker and never-smoker (ex and current smokers were combined into a single category of 'ever' smokers)]; education (high school or lower, above high school); alcohol (meeting guidelines of ≤ two drinks on any occasion or not meeting guidelines) [17]. Total physical activity time was calculated as the sum of time spent walking (if continuous and for >10 min) or performing moderate-intensity activity, and double the time spent in vigorous-intensity activity. This double weighting has been used because of the need to reflect that participation in vigorous intensity physical activity confers greater health benefits than participation in moderate activity [18]. Participants were then categorized as meeting Australian physical activity guidelines (≥150 min/week) or not meeting guidelines (≥0 min/week and <150 min/week) [19]. Cancer was defined according to the International Classification of Disease 10th Revision (ICD-10); C00-C97, D45-D46 and D47.1-D47.3 with cancers coded according to ICD-9 recoded as appropriate. Incidence of cancer was defined as the first occurrence of cancer or death from cancer if that was the first time the cancer had been reported. Fatal cancer includes all those who died from cancer as reported by the NDI.

Statistical analysis

For outcomes of cancer incidence (fatal and nonfatal cancer), individuals were followed from baseline date to date of cancer diagnosis, date of death or date of linkage to cancer registries, whichever occurred first. For outcomes of cancer mortality, individuals were followed from baseline date to date of death or date of linkage to mortality registries, whichever came first.

Differences in baseline characteristics, by cancer outcome, were assessed using Pearson's chi-square test for proportions and Student's *t*-test for means as appropriate. Heterogeneity of studies was explored by conducting a meta-analysis using a random effects model and statistical heterogeneity was estimated by the I^2 statistic [20]. Cox proportional hazards models (with age as the time scale) were used to compute hazard rate ratios and 95% confidence intervals (95% CI) of cancer incidence and mortality associated with untreated and treated hypertension, any hypertension and graded hypertension, as defined above. Analyses of graded hypertension were performed on the total population, and then stratified by antihypertensive use. Proportional hazards assumptions were satisfied, as assessed with graphs of log–log plots of the relative hazards by time for discrete variables and by scaled Schoenfeld residuals. All models used age as the time scale and were adjusted for sex, smoking and study cohort whereby baseline hazards for each included study were adjusted for. Additional models were adjusted for education, diabetes status, BMI, physical activity, cholesterol and alcohol intake where data were available.

All analyses were done using STATA version 12.1 (StataCorp, College Station, Texas, USA). This study was approved by the Alfred Health Human Research and Ethics Committee (HREC), the AIHW HREC and the Western Australian Department of Health HREC.

RESULTS

Over a median follow-up of 15.1 years, 12 070 incident and 4350 fatal cancers were identified over 1 128 742 and 1 317 274 person-years, respectively. Baseline characteristics of the study population, by cancer outcome, are shown in Table 1. In brief, those who developed cancer were more likely to be men, older, less educated, ever smokers, hypertensive, diabetic, and have higher mean BMI, cholesterol, SBP and DBP values compared with those who did not develop cancer.

Baseline characteristics, by study, are shown in Supplementary Tables 2A and 2B, http://links.lww.com/HJH/A541. The proportion of participants with hypertension (treated or untreated) in each study cohort ranged from 27.4% in the Fletcher Challenge Study to 75.9% in the Dubbo Study of the Elderly. There was no significant heterogeneity across studies for the relationship between hypertension and cancer incidence: $I^2 = 24.1$ and 41.2% for untreated hypertension and treated hypertension, respectively.

TABLE 1. Baseline characteristics among the Australian and New Zealand Diabetes and Cancer Collaboration cohort which developed an incident cancer during follow-up compared with those that did not

	No cancer	Cancer	*P* value
N	74 523	12 070	
Men (%)	46.1	54.9	<0.001
Age (years)	51.5 (13.7)	59.9 (10.2)	<0.001
Education (above high school)	38.0	33.1	<0.001
Smoking (ever smoker)	45.7	52.2	<0.001
Physical activity (meeting guidelines)	54.1	53.5	0.241
Alcohol (meeting guidelines)	72.0	72.3	0.107
BMI (kg/m^2)	26.8 (4.6)	27.2 (4.4)	<0.001
Cholesterol (mmol/l)	5.5 (1.1)	5.7 (1.1)	<0.001
Diabetes (%)	6.0	9.1	<0.001
SBP (mmHg)	132.9 (20.0)	140.3 (20.6)	<0.001
DBP (mmHg)	76.3 (11.8)	78.5 (12.0)	<0.001
Untreated hypertension (%)	24.2	32.6	<0.001
Treated hypertension (%)	16.4	24.7	<0.001

Data shown as mean (SD) or proportions; meeting physical activity guidelines: ≥150 min/week; meeting alcohol guidelines: ≤ two drinks on any one occasion.

TABLE 2. Hazard ratios and 95% confidence intervals for the association between hypertension and cancer incidence and mortality

	Mean (SD)		HR (95% CI)				
	Systolic blood pressure	Diastolic blood pressure	Model 1	Model 2	Model 3	Model 4	Model 5
Cancer incidence							
N (total)			86 593	86 593	86 122	68 703	48 552
No. of events			12 070	12 070	11 977	10 257	7 818
Person (years)			1 128 742	1 128 742	1 123 734	966 633	757 104
Analysis 1							
Normotensive	121.2 (10.7)	71.4 (9.0)	ref	ref	ref	ref	*ref*
Untreated HT	151.8 (14.1)	84.8 (10.7)	1.06 (1.01–1.11)	1.01 (0.97–1.06)	1.02 (0.97–1.06)	1.03 (0.98–1.08)	1.06 (1.00–1.11)
Treated HT	149.6 (21.1)	81.8 (12.6)	1.07 (1.02–1.12)	1.06 (1.01–1.12)	1.07 (1.02–1.13)	1.06 (1.01–1.12)	1.09 (1.02–1.16)
Analysis 2							
Untreated HT	151.8 (14.1)	84.8 (10.7)	ref	ref	ref	ref	*ref*
Treated HT	149.6 (21.1)	81.8 (12.6)	1.00 (0.96–1.06)	1.05 (1.00–1.10)	1.05 (1.00–1.11)	1.03 (0.98–1.09)	1.03 (0.97–1.10)
Analysis 3							
Normotensive	121.2 (10.7)	71.4 (9.0)	ref	ref	ref	ref	*ref*
Any HT	150.9 (17.4)	83.6 (11.6)	1.07 (1.03–1.11)	1.04 (1.00–1.08)	1.04 (1.00–1.08)	1.04 (1.00–1.09)	1.06 (1.02–1.12)
Cancer mortality							
N (total)			86 593	86 593	86 122	68 703	48 552
No. of events			4350	4350	4312	3643	2577
Person (years)			1 317 274	1 317 274	1 311 126	1 101 688	820 305
Analysis 1							
Normotensive	121.2 (10.7)	71.4 (9.0)	ref	ref	ref	ref	*ref*
Untreated HT	151.8 (14.1)	84.8 (10.7)	1.09 (1.02–1.18)	1.05 (0.98–1.13)	1.05 (0.97–1.13)	1.04 (0.96–1.12)	1.07 (0.98–1.18)
Treated HT	149.6 (21.1)	81.8 (12.6)	1.10 (1.01–1.18)	1.13 (1.05–1.23)	1.13 (1.04–1.22)	1.10 (1.01–1.21)	1.15 (1.03–1.28)
Analysis 2							
Untreated HT	151.8 (14.1)	84.8 (10.7)	ref	ref	ref	ref	*ref*
Treated HT	149.6 (21.1)	81.8 (12.6)	1.00 (0.93–1.08)	1.08 (1.00–1.16)	1.08 (1.00–1.03)	1.07 (0.98–1.16)	1.07 (0.97–1.19)
Analysis 3							
Normotensive	121.2 (10.7)	71.4 (9.0)	ref	ref	ref	ref	*ref*
Any HT	150.9 (17.4)	83.6 (11.6)	1.09 (1.03–1.17)	1.08 (1.02–1.16)	1.08 (1.01–1.15)	1.06 (0.99–1.14)	1.10 (1.01–1.20)

Model 1 = Unadjusted; Model 2 = Adjusted for sex, study name, smoking; Model 3 = Model 2 + education; Model 4 = Model 3 + BMI, diabetes status, physical activity; Model 5 = Model 4 + alcohol and cholesterol. Age is the time scale in all models. Any HT = untreated + treated HT. HT, hypertension.

Those with untreated and treated hypertension at baseline were more likely to develop cancer during follow-up compared with those who were normotensive in fully adjusted models: hazard ratio: 1.09, 95% CI (1.02–1.16) and 1.06 (1.00–1.11), respectively (Table 2). There was no difference in risk for cancer among those with treated hypertension compared with untreated hypertension in fully adjusted models (1.03, 0.97–1.10). Compared with normotensive, any hypertension had a 1.06 (1.02–1.12) increased risk for cancer incidence (Table 2).

Treated hypertension and untreated hypertension had an increased risk for cancer mortality compared with those who were normotensive in fully adjusted models (1.07, 0.98–1.18) and (1.15, 1.03–1.28), respectively, though this reached statistical significance only in those with treated hypertension (Table 2). When compared with untreated hypertension, treated hypertension had similar risks for cancer mortality (1.07, 0.97–1.19) in fully adjusted models. Compared with normotensive, any hypertension had a 1.10 (1.01–1.20) increased risk for cancer mortality.

A dose–response relationship was observed between graded hypertension and cancer incidence in fully adjusted models, $P_{trend} = 0.053$ (Table 3). The highest risk estimates were seen in those with SBP 160–179 mmHg or DBP 100–109 mmHg: 1.08 (1.00–1.17). When stratified by antihypertensive status, this relationship remained significant in those with untreated hypertension, $P_{trend} = 0.015$, but was attenuated in treated hypertension, $P_{trend} = 0.258$. A dose–

TABLE 3. Hazard ratios (95% confidence interval) for the association between graded hypertension and cancer incidence and mortality

				Cancer incidence			Cancer mortality		
Graded HT	*N*	No. of incident cancers	No. of fatal cancers	Total population (*N* = 86 593)	No treatment (*N* = 71 364)	Treatment (*N* = 15 229)	Total population (*N* = 86 593)	No treatment (N = 71 364)	Treatment (N = 15 229)
Normal	37 287	3596	1050	ref	ref	ref	ref	*ref*	*ref*
High normal	16 674	2368	877	1.00 (0.94–1.07)	1.00 (0.94–1.07)	0.98 (0.80–1.21)	1.11 (0.99–1.25)	1.13 (0.99–1.28)	1.05 (0.73–1.51)
Graded HT1	22 091	3901	1467	1.05 (0.99–1.11)	1.05 (0.99–1.12)	0.98 (0.82–1.17)	1.12 (1.00–1.24)	1.08 (0.96–1.22)	1.22 (0.90–1.66)
Graded HT2	7797	1629	691	1.08 (1.00–1.17)	1.12 (1.02–1.23)	0.93 (0.77–1.13)	1.25 (1.10–1.43)	1.36 (1.16–1.59)	1.06 (0.76–1.48)
Graded HT3	2744	576	265	1.03 (0.91–1.17)	1.08 (0.91–1.28)	0.90 (0.72–1.13)	1.23 (1.01–1.50)	1.20 (0.90–1.60)	1.19 (0.82–1.74)
P_{trend}				0.053	0.015	0.258	0.001	0.002	0.543

Models adjusted for sex, smoking, study cohort, education, BMI, cholesterol, diabetes, physical activity and alcohol with age as the timescale. Graded HT: normal: SBP<130 g or DBP<85; high normal: SBP 130–139 or DBP 85–89; graded HT1: SBP 140–159 or DBP 90–99; graded HT2: SBP 160–179 or DBP 100–109; graded HT3: SBP ≥180 or DBP ≥110. HT, hypertension.

response relationship was also observed between graded hypertension and cancer mortality, $P_{trend} = 0.001$ with highest risk estimates seen in those with SBP 160–179 mmHg or DBP 100–109 mmHg, 1.36 (1.16–1.59). When stratified by treatment status, this dose–response relationship remained significant in untreated hypertension ($P_{trend} = 0.002$), but not in treated hypertension ($P_{trend} = 0.543$).

DISCUSSION

In this large prospective pooled cohort, we found a significant but modest increased risk for cancer incidence among those with treated and untreated hypertension compared with those who were normotensive. For cancer mortality, untreated and treated hypertension had similar risk estimates, but this reached statistical significance in those with treated hypertension only. We found no difference in risk for cancer incidence or mortality in treated hypertension as compared with untreated hypertension. For graded hypertension, we found that those with SBP 160–179 mmHg or DBP 100–10 mmHg had an 8 and 36% increased risk for cancer incidence and mortality, respectively, compared with the lowest grade of hypertension. This association was independent of treatment status with elevated risks observed in both untreated and treated hypertension, though these were significant only in untreated hypertension.

Comparison to literature

Our findings are consistent with other observational data that have found a positive association between hypertension and cancer incidence. Stock *et al.* [10] found a 29% increased risk for cancer among men and women in the highest quartile of BP compared with the lowest quartile, though this study did not account for antihypertensive treatment which may explain the higher effect size relative to our study. Our analyses of graded hypertension showed that those with SBP 160–179 mmHg or DBP 100–109 mmHg had an 8% increased risk for cancer relative to those in the lowest category. These estimates are, however, lower than those reported by a Swedish study of over 7000 men which found a 41% increased risk for cancer incidence among men in the highest quintile of BP compared with those in the lower quintile, even after adjustment for antihypertensive treatment [8]. However, this study recruited men referred to a specialist hypertension clinic and therefore it is expected that this population would have a higher risk estimate than a general population sample. For cancer mortality, our finding of a 7–15% increased risk for untreated and treated hypertension is similar to that by Goldbourt *et al.* [21] of a 10% increased risk for men with than without hypertension. We also noted a 23% increased risk for mortality in those with the highest grade of hypertension as compared with the lowest, similar to the overall estimate of 23% found in the 2002 meta-analysis by Grossman *et al.* [4]. This meta-analysis, however, was unable to account for the role of antihypertensive medication and the authors could not rule out publication bias.

The underlying mechanisms between hypertension and increased cancer risk are not clear. In animal models, dysregulation of apoptosis, induced by high BP, has been shown to promote the growth of cancer cells [22]. In addition, hormones, which play a role in the development of hypertension, possess mitogenic effects [23,24] and it is also possible that the association between hypertension and cancer is because of shared risk factors such as genetics, obesity, smoking and poor diet [8]. In our study, we adjusted for potential confounding effects of BMI, smoking, physical activity, cholesterol, alcohol and diabetes, but we were unable to explore further the roles of poor diet and/or genetics. Alternatively, antihypertensive medication may increase cancer risk, though findings are conflicting. A 2001 meta-analysis found an independent association between thiazide diuretics and an increased risk for cancer (hazard ratio 2.00, 95% CI 1.55–2.59), though this finding was not supported in a second meta-analysis which concluded that no single antihypertensive class has sufficient or consistent evidence for a significant increase in malignancy risk, including thiazide diuretics [13,25]. Our results are consistent with the latter finding insofar as cancer risk was similar in both treated and untreated hypertension groups.

Strengths and weaknesses

Our study combined data from 12 large population-based studies from Australia and New Zealand, with sufficient power to investigate the association between hypertension and risk of cancer incidence and mortality, by hypertension treatment status. There are several limitations to this study that should also be acknowledged. First, it is possible that the relationship between hypertension and cancer differs by cancer site with studies showing increased risks specifically for renal cancers among those with hypertension [26]. Examining site-specific cancers was beyond the scope of the pooled cohort. Second, we did not have information about the type or dose of antihypertensive medications that participants were taking and therefore could not explore the role of specific antihypertensive treatments on the development of cancer and subsequent mortality. Further, we only had data on hypertension and antihypertensive use at baseline. It is possible that the results in untreated patients might be because of unmeasured confounding by antihypertensive drug intake during follow-up and lack of compliance to therapy. Third, it is possible that our results of graded hypertension, when stratified by antihypertensive status, may be the result of a type II error whereby we were underpowered to detect true associations among those with treated hypertension in the highest categories of graded hypertension. Last, the advantage of pooled cohort studies is the increase in study power which allows meaningful analyses of outcomes such as cancer. However, limitations of pooled cohorts include the heterogeneity of included studies and the loss of discrimination of covariates during harmonization across studies. In the current study, covariates of physical activity and education were each collapsed into binary categories to provide consistency across studies. All other covariates were objectively measured (e.g. cholesterol BP, height and weight) and therefore more easily combined across studies. In addition, the level of heterogeneity was low ($I^2 = 24.1$–41.2%) and the magnitude of associations between hypertension and cancer was similar between studies. Therefore,

we believe that it is unlikely that this harmonization process had a significant impact on our results.

In conclusion, this large pooled collaborative study suggests that treated and untreated hypertension are modestly associated with a higher risk for the development of cancer and subsequent cancer mortality in men and women in Australia and New Zealand. For men and women in the highest grade of hypertension, we additionally show that there is an increased cancer risk that is not explained by the use of antihypertensive treatment. Our findings are of public health importance insofar as both hypertension and cancer are common and potentially preventable conditions.

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Authors' contributions: J.L.H. (Baker IDI Heart and Diabetes Institute, Monash University) wrote the article, had full access to all the data and conducted the analyses. M.S. (Baker IDI Heart and Diabetes Institute, Monash University) contributed to data analysis and reviewed/edited the article. J.E.S. (Baker IDI Heart and Diabetes Institute, Monash University) and D.J.M. (Baker IDI Heart and Diabetes Institute, Monash University) contributed to conceptualization, discussion and reviewed/edited article. D.J.M. 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. All authors contributed to the collaboration and reviewed the article and approved the final version.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005; 293:194–202.
2. Borena W, Stocks T, Jonsson H, Strohmaier S, Nagel G, Bjorge T, *et al.* Serum triglycerides and cancer risk in the metabolic syndrome and cancer (Me-Can) collaborative study. *Cancer Causes Control* 2011; 22:291–299.
3. Dyer AR, Stamler J, Berkson DM, Lindberg HA, Stevens E. High blood-pressure: a risk factor for cancer mortality? *Lancet* 1975; 1:1051–1056.
4. Grossman E, Messerli FH, Boyko V, Goldbourt U. Is there an association between hypertension and cancer mortality? *Am J Med* 2002; 112:479–486.
5. Kato S, Takamoto N, Matsumoto K, Kudo M, Hanaoka K. Malignant neoplasm related mortality and morbidity of hypertensive outpatients in Japanese men and women. *J Insurance Medicine* 2013; 43:233–243.
6. Goon PK, Stonelake PS, Lip GY. Hypertension, antihypertensive therapy and neoplasia. *Curr Pharm Des* 2007; 13:2539–2544.
7. Grossman E, Messerli FH, Goldbourt U. Antihypertensive therapy and the risk of malignancies. *Eur Heart J* 2001; 22:1343–1352.
8. Rosengren A, Himmelmann A, Wilhelmsen L, Branehog I, Wedel H. Hypertension and long-term cancer incidence and mortality among Swedish men. *J Hypertens* 1998; 16:933–940.
9. Buck C, Donner A. Cancer incidence in hypertensives. *Cancer* 1987; 59:1386–1390.
10. Stocks T, Van Hemelrijck M, Manjer J, Bjorge T, Ulmer H, Hallmans G, *et al.* Blood pressure and risk of cancer incidence and mortality in the Metabolic Syndrome and Cancer Project. *Hypertension* 2012; 59:802–810.
11. Corrao G, Scotti L, Bagnardi V, Sega R. Hypertension, antihypertensive therapy and renal-cell cancer: a meta-analysis. *Curr Drug Saf* 2007; 2:125–133.
12. Schmieder RE, Delles C, Messerli FH. Diuretic therapy and the risk for renal cell carcinoma. *J Nephrol* 2000; 13:343–346.
13. Bangalore S, Kumar S, Kjeldsen SE, Makani H, Grossman E, Wetterslev J, *et al.* Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324 168 participants from randomised trials. *Lancet Oncol* 2011; 12:65–82.
14. Harding JL, Shaw JE, Koshkina V, Magliano DJ. Cohort profile: the Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC). *Australiasian Epidemiologist* 2014; 21:51–57.
15. Fellegi IP, Sunter AB. A theory for record linkage. *J Am Stat Assoc* 1969; 64:1183–1210.
16. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, *et al.* 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31:1281–1357.
17. National Health and Medical Research Council. Australian Guidelines to Reduce Health Risks from Drinking Alcohol Canberra: NHMRC; 2009. http://www.nhmrc.gov.au/health-topics/alcohol-guidelines. [Accessed 11 June 2015]
18. Armstrong T, Bauman ADJ. *Physical Activity Patterns of Australian Adults. Results of the 1999 National Physical Activity Survey. AIHW Catalogue no. CVD10.* Canberra: Australian Institute of Health and Welfare, 2000.
19. Australian Institute of Health and Welfare. *The active Australia survey: a guide and manual for implementation, analysis and reporting.* Canberra: Australian Institute of Health and Welfare, 2003.
20. Woodward M. *Epidemiology: study design and data analysis*, 2nd ed. Boca Raton: Chapman and Hall/CRC; 2004.
21. Goldbourt U, Holtzman E, Yaari S, Cohen L, Katz L, Neufeld HN. Elevated systolic blood pressure as a predictor of long-term cancer mortality: analysis by site and histologic subtype in 10 000 middle-aged and elderly men. *J Natl Cancer Inst* 1986; 77:63–70.
22. Hamet P, Richard L, Dam TV, Teiger E, Orlov SN, Gaboury L, *et al.* Apoptosis in target organs of hypertension. *Hypertension* 1995; 26:642–648.
23. Stumpe KO. Hypertension and the risk of cancer: is there new evidence? *J Hypertens* 2002; 20:565–567.
24. Meyer P. Increased intracellular calcium: from hypertension to cancer. *J Hypertens - Supplement* 1987; 5:S3–S4.
25. Ioannidis JP, Zhou Y, Chang CQ, Schully SD, Khoury MJ, Freedman AN. Potential increased risk of cancer from commonly used medications: an umbrella review of meta-analyses. *Ann Oncol* 2014; 25:16–23.
26. Weikert S, Boeing H, Pischon T, Weikert C, Olsen A, Tjonneland A, *et al.* Blood pressure and risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. *Am J Epidemiol* 2008; 167:438–446.

Reviewers' Summary Evaluations

Reviewer 1

This paper investigates the relations between hypertension and cancer in a very large group of patients issuing from various cohorts. The authors demonstrate that hypertension and cancer are associated with a dose/response curve, and this relation is not influenced by concomitant treatment. The paper has a high power, the association is significant statistically, but relatively weak. The dilution due to the merging of numerous databases is compensated by the very large numbers and the restricted number of outcomes.

Reviewer 2

The authors have pooled the data from 12 major cohorts on 86 593 participants from the Australian and New Zealand Diabetes and Cancer Collaboration and had been followed for a median of 15.1 years. They found that treated and untreated hypertensive individuals had increased risk of cancer incidence compared to normotensive individuals, with no difference in risk between the treated and untreated individuals. They also found an apparent dose–response relationship between graded hypertension and cancer incidence risk. The authors have used appropriate methodology in this complicated process. The results that treatment of hypertension is not associated with increased risk of cancer if reassuring.

Supplementary Data

Supplementary Table 1 Baseline measurement of blood pressure, by study cohort

Study	Number of measurements taken	Rest before measurement (min)	Position	Instrument
Australian Diabetes Obesity and Lifestyle Study	2	5	Seated	Mercury sphygmomanometer
Blue Mountains Eye Study	2	10	Seated	Mercury sphygmomanometer
Crossroads Undiagnosed Disease Study	2	5	Seated	Mercury sphygmomanometer
Dubbo Study of the Elderly	2	10	Seated	Mercury sphygmomanometer
Fletcher Challenge Study	2	5	Seated	Mercury sphygmomanometer
Fremantle Diabetes Study	1	5	Supine	Automated Monitor (Dinamap 1846sX)
Geelong Osteoporosis Study	2	5	Seated	Automated Monitor (UA-751)
Melbourne Collaborative Cohort Study	3	5	Seated	Automated Monitor (Dinamap 1846sX)
North West Adelaide Health Study	2	5-10	Seated	Mercury sphygmomanometer
Path Through Life Project	2	3	Seated	Automated monitor (Omron M4 722C1)
Risk Factor Prevalence Cohort Studies 1989 and 1994	2	5	Seated	Mercury sphygmomanometer

Supplementary Table 2A Baseline characteristics and follow-up data by individual cohort

	Australian Diabetes, Obesity, and Lifestyle Study	The Blue Mountains Eye Study	Crossroads Undiagnosed Disease Study	Dubbo Study of the Elderly	Fletcher Challenge Study	Fremantle Diabetes Study
N	10,435	4,280	1,362	2,632	10,336	1,284
Year of baseline examination	1999-2000	1992-1993	2001-2002	1988-1989	1992-1993	1993-1996
Median follow-up time	8.7	11.7	6.8	16.1	15.7	15.0
% Men	45.0	43.5	44.3	44.1	72.2	49.2
Age (years)	51.0 (14.2)	64.5 (9.6)	52.3 (15.5)	69.0 (6.9)	43.5 (15.1)	62.2 (13.0)
Education (above high school)	37.1	61.5	25.3	27.5	37.4	12.0
Smoking (ever smoker)	44.9	51.3	48.9	46.0	55.2	55.5
Alcohol (meeting guidelines)	63.4	n/a	n/a	n/a	56.7	n/a
Body Mass Index (kg/m^2)	27.1 (4.9)	26.8 (4.6)	27.9 (5.2)	26.1 (4.1)	26.5 (4.1)	29.3 (5.3)
Cholesterol (mmol/L)	5.7 (1.1)	5.9 (1.1)	5.3 (1.0)	6.5 (1.2)	5.4 (1.2)	5.4 (1.1)
Systolic blood pressure (mmHg)	129.1 (18.7)	144.6 (21.3)	131.8 (22.3)	147.6 (24.2)	125.9 (16.9)	149.4 (24.1)
Diastolic blood pressure (mmHg)	70.1 (11.8)	83.8 (10.4)	72.2 (10.1)	79.3 (12.0)	76.9 (11.1)	80.1 (11.2)
Physical activity (meeting guidelines)	n/a	33.7	51.2	48.8	73.1	n/a
Untreated hypertension	16.6	39.6	19.8	27.9	19.3	18.0
Treated hypertension	15.1	31.6	23.6	48.0	8.1	26.9
Diabetes	5.8	7.3	7.1	6.2	2.1	100.0
No. of non-fatal cancer events	825	832	96	663	1057	299
No. of fatal cancer events	282	427	39	339	380	126

Data shown as N, mean (SD) or proportions; n/a indicates data was not available; Meeting physical activity guidelines: ≥150 min/week; Meeting alcohol guidelines: ≤2 drinks on any one occasion

Supplementary Table 2B Baseline characteristics and follow-up data by individual cohort

	Geelong Osteoporosis Study	Melbourne Collaborative Cohort Study	Northwest Adelaide Health Study	Path Through Life Project	Risk Factor Prevalence Cohort Studies 1	Risk Factor Prevalence Cohort Studies 2	Total population
N	2,660	39,828	3,775	6,384	1,890	1,727	86,593
Year of baseline examination	1993-1997; 2001-2006	1991-1994	1999-2000; 2002-2003	1999-2002	1989	1994	1989-2003
Median follow-up time	6.7	16.9	8.1	8.3	19.3	14.4	15.5
% Men	48.4	41.4	47.7	49.5	50.1	50.8	47.3
Age (years)	53.0 (19.2)	55.2 (8.7)	49.4 (16.1)	43.6 (15.9)	45.2 (13.5)	46.8 (13.5)	52.7 (13.6)
Education (above high school)	28.4	32.5	55.5	67.0	19.8	19.1	37.3
Smoking (ever smoker)	48.4	42.5	55.2	46.7	53.6	51.2	56.6
Alcohol (meeting guidelines)	n/a	78.4	n/a	n/a	n/a	n/a	n/a
Body Mass Index (kg/m^2)	26.8 (4.7)	27.0 (4.4)	27.9 (5.4)	25.8 (5.0)	25.7 (4.0)	26.3 (4.4)	26.9 (4.6)
Cholesterol (mmol/L)	n/a	5.5 (1.1)	5.2 (1.1)	.	5.7 (1.2)	5.4(1.0)	5.6 (1.1)
Systolic blood pressure (mmHg)	128.7 (20.7)	137.0 (19.2)	127.4 (18.3)	128.9 (19.1)	128.6 (20.9)	129.9 (21.3)	134 (20.3)
Diastolic blood pressure (mmHg)	78.1 (12.2)	76.3 (11.6)	80.5 (10.2)	79.4 (10.9)	76.1 (11.5)	80.5 (12.2)	76.6 (11.9)
Physical activity (meeting guidelines)	.	55.0	35.3	60.0	21.6	20.7	54.0
Untreated hypertension	18.0	29.4	16.8	22.8	20.6	27.8	25.3
Treated hypertension	25.9	16.6	19.5	13.2	10.1	10.7	17.6
Diabetes	5.3	5.7	4.1	3.3	2.3	4.5	6.5
No. of non-fatal cancer events	267	6,942	253	341	286	209	12,070
No. of fatal cancer events	115	2,274	94	93	112	69	4,350

Data shown as N, mean (SD) or proportions; n/a indicates data was not available; Meeting physical activity guidelines: ≥150 min/week; Meeting alcohol guidelines: ≤2 drinks on any one occasion

CHAPTER 7

Discussion

7.1 Key Findings

The primary focus of this thesis was to investigate associations between metabolic disease and cancer while addressing methodological challenges in previous research such as detection bias and reverse causation. The key findings from each chapter are summarised below.

In Chapter 3.1, trends in all-cause and cause-specific mortality in people with type 1 and type 2 diabetes were reported. Findings from this work were three-fold. First, we demonstrated significant declines in excess all-cause mortality in both type 1 and type 2 diabetes between 1997 and 2010. However, it was noted that there is still a 3 and 1.2 times excess risk in people with type 1 and type 2 diabetes, respectively, as compared with the general population. Continued efforts to rectify this disparity are needed. Second, we observed a decline in the proportion of deaths attributed to cardiovascular disease (CVD) among people with type 1 and type 2 diabetes over time. Coinciding with this decline in mortality from CVD, we highlight the emergence of cancer as a leading cause of death among diabetes. This finding is of significant importance in light of the rising prevalence of diabetes, the decline in CVD mortality among diabetes and an ageing population. These factors suggest that cancer is likely to become the leading cause of death among people with diabetes if current trends continue. Third, one of the most important and novel findings from this work is that a substantial and increasing proportion of CVD deaths among people with diabetes are attributed to diabetes on death certificates, leading to underestimates in the CVD mortality burden among people with diabetes. If confirmed in other data populations, this has important ramifications for the understanding of mortality patterns.

Chapter 3.2 extended this work by exploring recent trends in all-cause, CVD, diabetes and cancer-specific mortality rates in both type 1 and type 2 diabetes, by age. To our knowledge, this is the first time that trends in absolute cause-specific mortality rates in diabetes have been explored by age group and are important data to inform public health to prioritise where prevention and treatment efforts may have the greatest impact. Chapter 3.2 reports significant declines in age-standardised mortality rates (ASMRs) for all-cause, CVD and diabetes in both type 1 and type 2 diabetes, while cancer ASMRs remain unchanged. These trends suggest continued success in the treatment of diabetes and its complications, consistent with conclusions from Chapter 3.1. However, these improvements were not seen across the entire age spectrum, with younger ages (<40 years) not experiencing the same declines in mortality as older populations and even more concerning, for type 2 diabetes, increases in all-cause and cancer mortality were noted in age group 0–40. In addition, the absence of a decline in cancer ASMRs among people with diabetes warrants urgent attention.

After demonstrating the emergence of cancer as a leading cause of death among people with diabetes in Chapter 3.1, Chapter 4 aimed to quantify associations between type 1 and type 2 diabetes and a number of site-specific cancers. This is one of the first studies worldwide with adequate power to specifically investigate

associations by diabetes type and rarer cancers. The main finding from this work is that both type 1 and type 2 diabetes have an increased risk for a number of site-specific cancers, as compared with the general population, and that risk estimates in type 1 and type 2 diabetes are similar. This is an important finding as type 1 and type 2 diabetes have different disease aetiologies with respect to insulin resistance and hyperinsulinaemia, yet similar risk estimates for cancer and therefore, this knowledge may help disentangle underlying causal pathways. For example, data presented in this paper suggest that hyperglycaemia (common to both type 1 and type 2 diabetes) may be the causal pathway linking diabetes and cancer and not endogenous hyperinsulinemia (found only in type 2 diabetes) as has previously been hypothesised. These findings should, of course, be taken in light of the inability of the NDSS dataset to adjust for important confounders such as smoking and obesity (discussed in detail in section 7.2). In addition, by comparing incidence and mortality risk in time segments within two years of diabetes diagnosis, we show that detection bias and reverse causation explain some, but not all, of the cancer risk among newly diagnosed type 2 diabetes.

Chapter 5 reports the risks for overall cancer and the three most common site-specific cancers (colorectal, prostate and breast cancer) associated with the components of the metabolic syndrome (MetS), both separately and jointly. Findings from this paper suggest that those with five positive components of the MetS are at increased risks for overall and colorectal cancers and these associations appear to be driven largely by central obesity and elevated blood pressure (BP). This paper also demonstrates that the MetS is only a moderate predictor of cancer risk and thus does not present strong evidence for the use of the MetS in a clinical setting as a useful means for assessing an individual's risk for overall, colorectal, breast or prostate cancers. The MetS may be useful in assessing risk for other site-specific cancers, however we were unable to explore other site-specific cancers in this chapter due to the small numbers of rare cancers.

Chapter 5 suggested that observed associations between the MetS and cancer are largely driven by central obesity and BP. Chapters 6.1 and 6.2, therefore, explored associations of obesity with cancer and BP with cancer, respectively, in more detail. Chapter 6.1 reports, for the first time, comparisons between a large range of anthropometric markers in terms of magnitude and discriminative ability for various cancer outcomes. We report that all anthropometric measures, including measures of central and general obesity, are associated with overall, colorectal, post-menopausal breast and obesity-related cancers in men and women, but not prostate cancer. In addition, while all anthropometric measures were similarly moderately predictive of cancer risk, waist circumference (WC) discriminated significantly better than body mass index (BMI). This work suggests that central obesity, which is more strongly associated with metabolic and inflammatory cytokines as well as insulin resistance, may be more strongly related to cancer than general adiposity. However, given all anthropometric measures were only moderately predictive of cancer risk, evidence in Chapter 6.1 does not support a recommendation for one anthropometric marker over another for assessing an individual's risk of cancer in a clinical setting.

The final key finding reported in this thesis comes from an analysis of the association of hypertension, graded hypertension and anti-hypertensive treatment with cancer incidence and mortality. Specifically, we addressed inconsistencies in the current evidence-base as to whether hypertension or anti-hypertensive treatment is associated with cancer. We report that hypertension, treated and untreated, is associated with a modest (6–9%)

increased risk for cancer incidence and mortality. Similar risks in treated and untreated hypertension suggest that the increased cancer risk is explained by underlying mechanisms of the hypertensive state, and not the use of anti-hypertensive treatment.

7.2 Strengths and Limitations

This thesis has several strengths, predominantly in the novelty of several published manuscripts, backed by robust methods and comprehensive datasets. Strengths and limitations pertaining to each study have been summarised in the respective strengths and limitations section of each publication. Here, I will discuss in detail the key strengths and limitations of the data sources used to quantify associations between metabolic disease and cancer.

Chapters 3 and 4 report mortality and cancer outcomes among an Australian diabetes population, registrants of the National Diabetes Service Scheme (NDSS). The main strength of this data source is that it is population-based with a large sample size, a long follow-up time and the ability to distinguish between type 1 and type 2 diabetes. There are several limitations, however, that should be acknowledged. First, the NDSS is an administrative database, and there are inherent limitations with using administrative databases for research purposes.[1] Namely, for our study, the lack of precise information about the type of diabetes for all registrants was not available. The classification of diabetes, particularly in young patients, is challenging and misclassification can occur. However, the proportions of type 1 and type 2 diabetes in this study (~8% vs. ~92%) are similar in other Australian data.[2] Further, the proportion of type 2 diabetic patients who were also on insulin is consistent with other studies.[3] Given these well-known demographics and our very large sample size, we believe that any misclassification in this study will not change overall conclusions from this work.

The NDSS is considered the best available national data source for estimating overall prevalence of diagnosed diabetes in Australia.[4] However, to date, there is no published data on the completeness of the NDSS, i.e. what proportion of people with diagnosed diabetes are in fact registered on the NDSS. However, data from the Fremantle Diabetes Study (FDS), a cohort study of people with diabetes, showed that 88% and 87% of type 1 and type 2 diabetes, respectively, were registered on the NDSS, including 81% of diet-treated participants (W Davis, personal communication). In addition, a pilot study conducted by Magliano and Shaw using the national Australian Diabetes Obesity and Lifestyle Study (AusDiab) reported that 80%, 90% and 100% of people with known diabetes on diet, oral medication and insulin therapy reported being on the NDSS, respectively (unpublished data). Taken together, thesedata confirm very high capture rates in all groups, while indicating that there is a small, but definite bias towards more advanced diabetes. In particular, capture of type 1 diabetes is almost 100% while for type 2 diabetes, it is likely that the NDSS underestimates those with diet-controlled diabetes as the diabetes-related products provided through the scheme may not be needed.

Last, the NDSS provides one of the largest datasets for people with diagnosed diabetes in the world. The data reported in Chapters 3 and 4 would not be possible without population datasets of this magnitude. However, our findings are limited by a lack of covariates in the dataset. Therefore, we were unable to explore the extent to which obesity, smoking, socioeconomic position, family history of cancer, pharmaceutical treatments

and/or quality of care contributed to the observed trends in mortality among people with diabetes, or associations between diabetes and cancer. However, studies of type 2 diabetes that have been able to account for obesity, lifestyle-related factors and diabetes treatments have still observed elevated risks for a number of cancers.[5,6] Therefore, it is unlikely that these factors explain the entire association between diabetes and cancer.

Chapters 5 and 6 use data obtained from the Australian and New Zealand Diabetes and Cancer Collaboration (ANZDCC), a pooled cohort comprised of all longitudinal cohorts in Australia and New Zealand (ANZ) from 1983 onwards with information on diabetes, hypertension, anthropometry and the MetS, and with a sample size ≥1000. The purpose of ANZDCC, the study sample and strengths and weaknesses of this pooled cohort have been detailed in Chapter 2.2. The key strength of the ANZDCC that distinguishes it from previous work is that it is the largest study to ever examine the relationship between diabetes, obesity, the MetS, hypertension and cancer. Specifically, the large sample size of ANZDCC allowed us to explore site-specific cancers. The 18 included cohort studies have breadth in the range of variables collected not seen in any other pooled cancer studies, thus allowing adjustment for important confounding factors such as physical activity, socioeconomic position and smoking.

On the other hand, pooled analyses are often limited by the heterogeneity of included studies and risk loss of discrimination during harmonisation of covariates across studies. However, pooled cohorts are often the only way of obtaining large enough study numbers to undertake meaningful analyses of outcomes such as cancer, and other pooled cohort studies have made major contributions to our understanding of disease risk factors by employing this method. In this thesis covariates of physical activity and education were each collapsed into binary categories to provide consistency across studies. All other covariates were objectively measured (e.g. cholesterol, BP, height and weight) and therefore more easily combined across studies. Further, the level of heterogeneity reported between studies in publications presented in Chapters 5, 6.1 and 6.2 are relatively low, in the magnitude of $I2$ = 12–42%. Therefore, it is unlikely that this harmonisation process has a significant impact on the results. In addition, prospective cohort studies with long follow-up periods such as those included in the ANZDCC have inherent biases related to sampling and response rates. The average response rates of cohort studies in ANZDCC is 60.5% ranging from 35.5% in the Australian Longitudinal Study of Women's Health (ALSWH) to 82.4% in the Blue Mountains Eye Study (BMES). These low to moderate response rates may, of course, introduce selection bias and therefore, limit the generalisability of our results.

Finally, obtaining mortality and cancer information in Australia can be difficult for large-scale studies such as those reported here as unique health identifiers are not available. Therefore, linkage is based on probabilistic algorithms that a given name, date of birth and State of residence will correctly link records belonging to the same individual. Again, this may introduce misclassification. However, for all primary analyses in each chapter, cut-offs with a high positive match rate (>97.0%) were applied. Further, several sensitivity analyses were performed where the positive match rate was increased and decreased and conclusions were unchanged.

7.3 Implications and Future Directions

From the outset, this thesis identified knowledge gaps in the field of metabolic disease and cancer and proceeded

to advance that knowledge. The importance of understanding these associations is underpinned by the fact that diabetes, obesity and cancer represent global health priority areas. Evidence provided in this thesis not only quantifies the cancer risk among people with diabetes and the MetS, but also informs us where prevention strategies should be targeted and where resources would be best allocated. There are several clinical and public health implications from this work, along with implications for researchers. These are discussed in detail below.

7.3.1 Clinical implications

This thesis has provided substantive evidence to suggest that people with diabetes, both type 1 and type 2, have significant increased risks for a number of cancers including rarer cancers such as chronic myeloid leukaemia and thyroid cancers. The data provides evidence to suggest that diabetes clinicians should be vigilant in ensuring that diabetes patients adhere to routine cancer screening, according to standard protocols for the general population. The ability to identify cancers at an early stage will be an important step forward in preventing premature mortality from cancer among people with diabetes. In addition, this thesis suggests a role for hyperglycaemia as the likely mechanism underpinning associations between diabetes and cancer. This suggests that diabetes management of hyperglycaemia will also be an important step forward in cancer prevention.

The potential role of obesity and the MetS as predictors of future cancer risk was explored. While people with obesity and the MetS are at increased risks for cancer, these markers are only moderate predictors of cancer risk and therefore not a useful way of deciding who is or is not likely to get cancer. Perhaps this is because cancer is so heterogeneous it is unlikely that one single underlying mechanism underpins these associations, with different sex and cancer site-specific biological mechanisms more likely to play a role. Therefore, this data does not suggest that the use of either of these measures should be introduced as a routine screening tool for cancer. Rather, obesity and the MetS should be considered in combination with other traditional risk factors for cancer such as smoking.

Last, the study on hypertension and cancer risk has important implications in relation to the pharmacological management of hypertension. Previous studies have suggested thatanti-hypertensive medication may result in an increased risk for cancer. This may lead to changes in the way anti-hypertensive medication is prescribed due to concerns among patients and clinicians alike. However in this study hypertension, not anti-hypertensive medication, was associated with an increased cancer risk. Therefore, consideration of cancer as a consequence of anti-hypertensive medication is not necessary, particularly in light of their effective management of CVD risk. Further data from large cohort studies with detailed information on anti-hypertensive medication is warranted to confirm findings presented here.

7.3.2 Public health implications

Data on mortality trends among diabetes can be used to inform where prevention strategies should be targeted and where resources are best allocated. Diabetes is now prominent on the global health agenda, with specific targets for access to essential medicines in the treatment of diabetes and its complications and for prevention of

obesity and diabetes.[8] It is essential that health professionals, government and policy-makers alike understand the full range of consequences of diabetes. Our data show that, with improvements in prevention and treatment of CVD, cancer is likely to become the leading cause of death among people with diabetes if current trends continue. This suggests that we need to adapt our health care systems to meet the changing needs of diabetes patients in the future and adds further weight to the need for lifestyle modification programs to prevent both type 2 diabetes and cancer.

In addition, the number of young-onset type 2 diabetes is increasing.[7] Emerging evidence suggests that young-onset type 2 diabetes is associated with a greater mortality, more diabetes complications and unfavourable cardiovascular disease risk factors, even compared with type 1 diabetes.[8,9] In the most recent International Diabetes Federation (IDF) Diabetes Atlas, the rapid and largely unexplained rise in young-onset type 2 diabetes was described as a global health crisis and an urgent call was made for more information on this aspect of the diabetes epidemic.[7] This thesis reports that while mortality rates from all-cause, CVD, diabetes and cancer is, in general, decreasing among type 1 and type 2 diabetes, in young-onset type 2 diabetes (0–40 years) mortality from CVD or diabetes has not decreased since 2000, and even worse, mortality from all-cause and cancer has increased. This data highlights the severity of young-onset type 2 diabetes and the urgent need for diabetes prevention efforts to be targeted toward youth. Current guidelines for diabetes management in young people needs to be reassessed to incorporate more aggressive management of risk factors to prevent unnecessary and untimely deaths in this group of people.

7.3.3 Methodological concerns of epidemiological analyses for consideration

International Classification of Disease (ICD) codes for mortality are widely used in epidemiological research to assess the health of populations, direct the allocation of funds and inform appropriate health care policy. But this thesis shows that misclassification of cause of death (COD) can have major implications for the conclusions drawn from epidemiological research.[10,11] The proportion of CVD deaths potentially underestimated by using underlying COD was 39% and 26% for type 1 and type 2 diabetes, respectively. And this proportion has increased over time most likely due to an increasing awareness among doctors that diabetes is a key etiological factor in the development of CVD. This data shows that when death from CVD is attributed to diabetes (often correctly) on the death certificate, it can significantly obscure patterns of CVD mortality if only underlying COD is used to attribute COD. Similar issues may also apply to other chronic diseases and their complications. When considering mortality data, particularly for diabetes populations, reliance on underlying COD may be misleading.

Last, detection bias and reverse causation explain some, but not all, of the association between type 2 diabetes and some cancers. For type 1 diabetes, the number of cancer outcomes was too low to split by follow-up time. It is not expected that detection bias and/or reverse causation would largely contribute to associations between type 1 diabetes and cancer as people with type 1 diabetes are interacting with the healthcare system at a much younger age. By exploring associations between type 2 diabetes and cancer in different time segments following a new diabetes diagnosis, detection bias and reverse causation can be dissected from true associations. This should be a consideration of future research analysing similar associations.

7.4 Conclusion

This body of work has added to the current evidence-base in the association between metabolic disease and cancer. This work has been published in several key papers. These papers have quantified the excess risk of a number of site-specific cancers among people with metabolic disease and addressed methodological challenges not considered in previous research. This work has wide ranging clinical and public health implications.

These include insights into the potential cancer mechanisms; assessment of the burden and consequences of metabolic disease; recommendations to clinicians to be vigilant in ensuring diabetes patients are up to date with cancer screening according to screening guidelines for the general population; aggressive management of risk factors among young-onset type 2 diabetes to prevent premature mortality; the need to adapt our health care systems to meet the changing needs of diabetes patients in the future and the need for lifestyle modification programs to prevent both type 2 diabetes and cancer. It is imperative that we use this data to inform policies that will improve the health and care of people living with metabolic disease.

References

1. Hoover KW, Guoyu T, Kent CK, SO. A. Epidemiologic research using administrative databases: Garbage in, garbage out. *Obstetrics and Gynecology*. 2011;117(3):729-730.
2. Australian Institute of Health and Welfare. *Diabetes prevalence in Australia: detailed estimates for 2007-08*. Canberra, Australia: AIHW 2011.
3. Koro CE, Bowlin SJ, Bourgeois N, DO. F. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. *Diabetes Care*. 2004;27:17-20.
4. Australian Institute of Health and Welfare. *Diabetes prevalence in Australia. An assessment of national data sources*. Australian Institute of Health and Welfare, Canberra2009.
5. Joh HK, Willett WC, Cho E. Type 2 diabetes and the risk of renal cell cancer in women. *Diabetes Care*. 2011;34(7):1552-1556.
6. Luo J, Beresford S, Chen C, et al. Association between diabetes, diabetes treatment and risk of developing endometrial cancer. *British Journal of Cancer*. 2014;111(7):1432-1439.
7. International Diabetes Federation. *Diabetes Atlas Seventh Edition*. International Diabetes Federation. 2015.
8. Constantino MI, Molyneaux L, Limacher-Gisler F, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes Care*. 2013;36(12):3863-3869.
9. Rhodes ET, Prosser LA, Hoerger TJ, Lieu T, Ludwig DS, Laffel LM. Estimated morbidity and mortality in adolescents and young adults diagnosed with Type 2 diabetes mellitus. *Diabetic Medicine*. 2012;29(4):453-463.
10. Pekkanen J, Sunyer J, Chinn S. Nondifferential disease misclassification may bias incidence risk ratios away from the null. *Journal of Clininical Epidemiology*. 2006;59(3):281-289.
11. Harriss LR, Ajani A. E, Hunt D, et al. Accuracy of national mortality codes in identifying adjudicated cardiovascular deaths. *Australian and New Zealand Journal of Public Health*. 2011;35(5):466-476.

APPENDICES

Pancreatic cancer and diabetes – what is the link?

Pancreatic cancer is an aggressive malignancy which is invariably fatal. It is the 12th most prevalent cancer worldwide, and is the 9th most frequent cause of cancer death in Western countries, including Australia. The 5-year overall survival is less than 1%, a figure which has not changed in 20 years.[1] Like many cancers, smoking is a key risk factor, estimated to be responsible for approximately 30% of all pancreatic cancers. Data on other key risk factors for pancreatic cancer are rare, however obesity, family history of pancreatic cancer, and diabetes have been shown to be independent risk factors. Pancreatic cancer has few symptoms in the early stages, and most people are diagnosed in metastatic stages of the disease. Notable symptoms of pancreatic cancer include weight loss, abdominal pain and obstructive jaundice. Treatment failure is common, with few patients with metastatic disease surviving beyond 4-6 months. Currently there is no screening test for pancreatic cancer and this has contributed to the lack of the improvement in survival rates. However, although progress is slow, evidence is accumulating to suggest that new onset diabetes may be an early marker of this disease and that this could be utilised with other factors in the screening of those at high risk of pancreatic cancer.

The relationship between diabetes and pancreatic cancer is complex. Despite the significant investment by scientists exploring the link between diabetes and cancer, the temporal relationship between diabetes and pancreatic cancer is still not resolved, and the question remains: is diabetes an independent risk factor for pancreatic cancer or does pancreatic cancer cause diabetes?

DOES DIABETES CAUSE CANCER?

Diabetes was first linked to pancreatic cancer in 1974 in a case series from Olmsted, Minnesota. Among this case series of pancreatic cancers, 17% had diabetes and almost half of these diabetes cases had been diagnosed at least 2 years before diagnosis of pancreatic cancer. In contrast, two decades later, results from a case-control study of pancreatic cancer and diabetes showed that most diabetes diagnoses in patients with pancreatic cancer occurred at the same time or after pancreatic cancer diagnosis, suggesting that cancer was causing the diabetes.[2] Since then several meta-analyses have been published, which estimate the relative risk (RR) of pancreatic cancer among people with established diabetes (mostly type 2, T2D) to be approximately 2, in comparison to people without diabetes. One of these meta-analyses explored the issue of reverse causation and showed that among those with a long history of diabetes (of approximately 5 years), the excess risk of pancreatic cancer was about 50% lower than in individuals for whom the duration of diabetes was shorter. This suggests that at least some of the excess risk of pancreatic cancer among diabetes patients was due to reverse causation. In other words, in some cases, although the clinical diagnosis of diabetes preceded that of pancreatic cancer, the cancer probably developed first, and may well have actually caused diabetes. This issue has also been explored by our group[3] and we showed that the RR for pancreatic cancer among diabetes patients in different time periods following diabetes diagnosis decreased from around 10 in the first 3 months post-diabetes diagnosis, to approximately 1.5 in the first 24 months post-diabetes diagnosis. This gives support to the notion that reverse causation explains some, but certainly not all, of the association between diabetes and pancreatic cancer.[3]

> ***…is diabetes an independent risk factor for pancreatic cancer or does pancreatic cancer cause diabetes?***

A more recent meta-analysis combined data from 88 studies and reported that diabetes was associated with a RR for pancreatic cancer of 1.97 (95% CI 1.78 - 2.18). Once again, the risk of pancreatic cancer was greatest early after the diagnosis of diabetes, starting from a RR of 6.69 and decreasing to 1.36 at 10 years post-diabetes diagnosis.[1] Importantly, just like the other analyses, some increased risk of pancreatic cancer persists many years after diagnosis of diabetes. Interestingly, pre-diabetes has also been associated with pancreatic cancer, with a recent study demonstrating that every 0.56 mmol/L increase in fasting blood glucose was associated with a 14% increase in the risk of pancreatic cancer. This raises the possibility that pre-diabetes may represent a good opportunity for prevention of pancreatic cancer.[4]

For type 1 diabetes (T1D), data linking diabetes with pancreatic cancer are scarce. A meta-analysis of 9 studies comprising young onset diabetes reported a RR of around 2, similar to the RR reported by our group in those with T1D using data from a national Australian diabetes register.[3] Although neither of these studies can rule out reverse causality completely, it provides fairly robust evidence in this regard. Given the extreme infrequency of pancreatic cancer in people under 25, it is more likely that T1D precedes pancreatic cancer than the other way around.

Overall, the data support the concept that diabetes (T1D and T2D) is an independent risk factor for pancreatic cancer.

THE BIOLOGICAL MECHANISMS LINKING DIABETES AND CANCER

There are several possible mechanisms linking diabetes to cancer, particularly pancreatic cancer. These include insulin resistance, hyperinsulinaemia and increased levels of insulin-like growth factor 1 (IGF-1), and the glucose supply hypothesis. But among these, controversy exists about which mechanism holds the most weight. The insulin/IGF-1 link is attractive as the mechanistic link between these two diseases for several reasons. There is good evidence to suggest that reduced insulin sensitivity, with compensatory hyperinsulinaemia and elevated IGF-1 seen in T2D, results in the stimulation of cell proliferation. This is consistent with the fact that both IGF-1 and insulin are mitogenic hormones which are in high concentrations in diabetes. Animal and cell experiments have shown that receptors for both hormones are highly expressed on cancer cells in those with diabetes and therefore these hormones could act as tumour growth factors.

The glucose supply hypothesis states that since cancer cells are highly metabolic and have high glucose requirements, tumour growth may be regulated by the availability of glucose. This is particularly relevant to pancreatic cancer as these cells depend heavily on glucose for growth. In fact, pancreatic cancer cells are described as having a 'glucose addiction', exhibiting increased glucose uptake relative to other cancer cells. Hyperglycaemia may therefore increase the risk of pancreatic cancer by providing more fuel for tumour growth. This is supported by studies that show that cancer risk is positively related to higher glycosylated haemoglobin (HbA1c). If the glucose supply hypothesis is true and glucose is the real culprit (rather than insulin), we would expect people with good control of diabetes would reduce their risk of developing cancer. However, this has not been borne out in trial data. Recent large-scale randomised controlled trials of intensified glycaemic control for T2D observed no difference between intensified and conventional treatment arms in terms of secondary outcomes of cancer incidence or mortality. The caveats here though are that these trials were short in duration, and not powered to observe differences in cancer rates between intensive treatment of glycaemia and standard care.

DOES PANCREATIC CANCER CAUSE DIABETES?

Pancreatic cancer undoubtedly causes diabetes, although direct

SUMMARY OF RED FLAGS TO DIAGNOSE PANCREATIC CANCER:

While there are few specific symptoms of pancreatic cancer, weight loss, abdominal pain and obstructive jaundice are considered red flags for this malignancy. In addition, smoking and family history of pancreatric cancer increase the index of suspicion for this cancer. Whenever any of the three cardinal symptoms are observed in combination with recent onset of diabetes, pancreatic cancer should be strongly considered.

DIABETES AND PANCREATIC CANCER

destruction of pancreatic tissue may not be the only mechanism, with paracrine effects probably playing a role as well. Thus, there is a higher prevalence of diabetes in pancreatic cancer populations than in other cancers or non-cancer groups.[2] Diabetes in pancreatic cancer is often new onset, arising only a short time before the cancer is diagnosed and suggesting that cancer is causing the condition. Several studies show that most cases of diabetes occurring in association with pancreatic cancer are either diagnosed concomitantly with the cancer (approximately 40% of cases) or within 2 years before the diagnosis of cancer (16%). In other studies, diabetes was new onset in relation to the cancer diagnosis, appearing <24 months before the cancer in around 80% of pancreatic cancer patients.[2] Several studies have also shown that diabetes improves following resection of tumours despite surgical removal of variable amounts of pancreas.[2]

> ***...in some cases, although the clinical diagnosis of diabetes preceded that of pancreatic cancer, the cancer probably developed first, and may well have actually caused diabetes.***

Interest in the association of new onset diabetes with pancreatic cancer is driven by the hope that new onset diabetes may be or become an important marker of pancreatic cancer. Although new onset diabetes on its own could never be useful as an early marker of pancreatic cancer for the general population, it could possibly identify a group that could be scrutinised more closely for other indications of pancreatic cancer. For example, there is emerging data to suggest that modest weight loss during or around the time of new onset diabetes may also be a feature of pancreatic cancer. Weight loss occurring with new onset diabetes, combined with traditional risk factors of cancer such as age and smoking, could be assessed with a screening protocol and lead to the diagnosis of asymptomatic, early-stage pancreatic cancer in those with a high hereditary risk of pancreatic cancer. In addition, studies have also shown that pancreatic tumour-secreted products such as vanin-1, matrix metalloproteinase 9, S100 calcium binding protein and islet amyloid polypeptide (amylin) might have a role to play as tumour markers and predictors of early disease.

Diabetes has become a pandemic and continues to increase in many parts of the world. Taken as a whole, the literature supports the concept that long-standing diabetes is an aetiological factor for pancreatic cancer. In addition, new onset diabetes may be an early sign of pancreatic cancer and could be used in conjunction with other risk factors (such as weight loss, smoking, and age >50) to identify those at high risk of this disease. Given that treatment for this malignancy is not promising and death is imminent in these patients, there appears a very strong impetus to invest in research in the area of early identification of pancreatic cancer.

PRACTICE POINTS:

- **There is evidence that diabetes can lead to pancreatic cancer, and that pancreatic cancer can cause diabetes.**
- **Pancreatic cancer has a very high mortality, and it is currently difficult to diagnose early.**
- **New onset diabetes, together with other risk factors such as weight loss, smoking and age >50, may be prove to be a useful early warning sign of the development of pancreatic cancer.**

REFERENCES

1. Batabyal P, Vander Hoorn S, Christophi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. Ann Surg Oncol. 2014 Jul;21(7):2453-62.
2. Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. Lancet Oncol. 2009 Jan;10(1):88-95.
3. Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation. Diabetes Care 2015;38:264-270. Diabetes Care. 2015 Apr;38(4):734-5.
4. Liao WC, Tu YK, Wu MS, Lin JT, Wang HP, Chien KL.Blood glucose concentration and risk of pancreatic cancer: systematic review and dose-response meta-analysis. BMJ. 2015 Jan 2;349:g7371

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CORRESPONDENCE

Glycemic Control and Excess Mortality in Type 1 Diabetes

TO THE EDITOR: Lind et al. (Nov. 20 issue)[1] found that patients with type 1 diabetes and a glycated hemoglobin level of 6.9% or lower had a risk of death that was twice as high as the risk among matched controls. The hazard ratio for death from cardiovascular disease was 3.64 among patients with diabetes who had normoalbuminuria (albumin:creatinine ratio, <3 mg per millimole), as compared with controls. However, a reduced threshold to define microalbuminuria has been suggested already.[2] A very low level of urinary albumin clearance, exceeding just 4.8 μg per minute (corresponding to an albumin:creatinine ratio of >0.7 mg per millimole), is a strong predictor of coronary heart disease and death in apparently healthy persons.[2] In a study involving adolescents with type 1 diabetes, participants in the highest tertile of urinary albumin excretion had more evidence of early renal and cardiovascular disease than those in the lower tertiles.[3]

We believe that it would have been wise to use this low cutoff point in analyses to assess the true increased risk of death among patients with diabetes. Furthermore, it may be reasonable to use angiotensin-converting–enzyme inhibitors to modify low-grade microalbuminuria in an effort to reduce the incidence of cardiovascular events.[4]

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1. Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2014;371:1972-82.
2. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation 2004;110:32-5.
3. Marcovecchio ML, Woodside J, Jones T, et al. Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT): urinary screening and baseline biochemical and cardiovascular assessments. Diabetes Care 2014;37:805-13.
4. Schmieder RE, Schrader J, Zidek W, et al. Low-grade albuminuria and cardiovascular risk: what is the evidence? Clin Res Cardiol 2007;96:247-57.

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TO THE EDITOR: Lind et al. report valuable data regarding the relationship between the glycated hemoglobin level and the risk of death among adults with type 1 diabetes. Their conclusion that a glycated hemoglobin level of 6.9% or lower is associated with a risk of death that is twice as high as that in the general population implies that the risk is uniform among patients with this low level of glycated hemoglobin. It would not be surprising if the risk was not uniform, since the degree of hyperglycemia varies according to the glycated hemoglobin level. For instance, in a study that used continuous glucose monitoring,

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glucose levels were above 180 mg per deciliter for approximately 1 hour longer per day and above 250 mg per deciliter for approximately half an hour longer per day in patients with a mean glycated hemoglobin level of 6.8%, as compared with those with a mean glycated hemoglobin level of 6.4%.[1] It would be extremely valuable in the counseling of patients with type 1 diabetes to know the risk of death that is associated with categories of glycated hemoglobin levels that are less than 6.9%. The sample of 6142 participants with a glycated hemoglobin level of 6.9% or lower is sufficiently large for a meaningful analysis.

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No potential conflict of interest relevant to this letter was reported.

1. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care 2009;32:1378-83.

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TO THE EDITOR: Lind et al. appear to have based the categorization of deaths in their study on the underlying cause of death. However, this approach may not adequately capture the burden of deaths due to cardiovascular disease. When a death certificate indicates that a terminal cardiovascular event was due to diabetes, the underlying cause of death is a diabetes code, not a cardiovascular code. We recently found that deaths due to cardiovascular causes were underestimated by 38% among patients with type 1 diabetes and by 26% among those with type 2 diabetes.[1] In the study by Lind et al., among all the deaths that occurred in the group of patients with diabetes, 15% were categorized as unspecified diabetes-related deaths and 3% as due to diabetes with vascular complications. Inspection of the full series of codes on the death certificates is likely to indicate that most of the latter group and some of the former should be added to the 34% of deaths that were attributed to cardiovascular disease. The inclusion of these deaths as deaths due to cardiovascular disease reflects the true cardiovascular mortality of these patients and should be a routine part of analyses of mortality in diabetes.

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1. Harding JL, Shaw JE, Peeters A, Guiver T, Davidson S, Magliano DJ. Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997-2010. Diabetes Care 2014;37:2579-86.

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THE AUTHORS REPLY: Tornese et al. suggest that we should have considered using a lower cutoff for microalbuminuria. Although low-grade albuminuria may be associated with an increased risk of adverse cardiovascular events, to our knowledge this new, lower threshold has not yet been endorsed in practice guidelines or adopted in routine clinical use.[1] Therefore, we felt that in a population-based epidemiologic analysis, such as our study, it was most prudent to use the thresholds for albuminuria that are recommended by professional societies in contemporary guidelines and that are used routinely by clinicians. We agree that further large-scale population-based investigations should be pursued to understand better the relationship between a lower cutoff for albuminuria and cardiovascular and renal outcomes in patients with type 1 diabetes, which may ultimately influence whether this lower cutoff should be adopted in clinical practice. However, such analyses may be difficult to perform in current population-based registries (e.g., the National Diabetes Register), since the current values for the albumin:creatinine ratio are not always reported in such registries (rather, they report whether microalbuminuria exists, according to current guideline-recommended thresholds).

Regarding the recommendation by Beck to use a threshold lower than 6.9% for the glycated hemoglobin level: we carefully considered this in our analyses. However, our intent was to examine the relationship between various categories of glycemic control and adverse outcomes using the cutoffs that are currently endorsed by the guidelines and adopted by clinicians in routine practice; hence we defined a glycated hemoglobin level of 6.9% or lower (≤52 mmol per mole) as the on-target control category.[1] Although the proposed analyses examining the relationship

between lower thresholds for glycated hemoglobin (as well as albuminuria and possibly other variables of interest) and adverse cardiovascular events were beyond the scope of our study, we agree that such investigations would be valuable and should be pursued in future studies.

In response to Magliano et al.: we agree that the proportion of deaths due to cardiovascular disease in our study is likely to be an underestimation and that cardiovascular disease probably contributed to a fair share of the deaths categorized as having diabetes as the underlying cause. However, because many of the deaths due to diabetes had multiple or unspecified complications (including cardiovascular disease), and furthermore, because we were not able to validate the final chain of events leading to death from the data in the register, we used a conservative approach.

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Since publication of his article, Dr. Lind reports receiving consulting fees from Eli Lilly. No further potential conflict of interest was reported.

1. American Diabetes Association. Standards of medical care in diabetes — 2014. Diabetes Care 2014;37:Suppl 1:S14-S80.

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Mutations in *NPC1L1* and Coronary Heart Disease

TO THE EDITOR: The Myocardial Infarction Genetics Consortium Investigators (Nov. 27 issue)[1] reported an association between reduced frequency of coronary artery disease and modestly lower levels of total cholesterol and low-density lipoprotein (LDL) cholesterol in carriers of inactivating variants of *NPC1L1* as compared with noncarriers. In the Geisinger MyCode cohort, we found seven heterozygous carriers of an inactivating variant in *NPC1L1* (R406X) in persons of European ancestry. Using a validated definition for coronary artery disease from the database of Genotypes and Phenotypes (dbGaP), we found no carrier of an inactivating variant of *NPC1L1* with coronary artery disease as compared with 1001 cases of disease in 15,886 noncarriers. In persons for whom data on lipid levels were available before or without lipid-lowering therapy, there was no significant difference in mean plasma levels of LDL cholesterol between *NPC1L1* inactivating carriers and noncarriers (126 mg per deciliter vs. 125 mg per deciliter), and mean total cholesterol was lower in *NPC1L1* inactivating carriers than in noncarriers (206 mg per deciliter vs. 210 mg per deciliter). Our data are consistent with the suggestion of the Consortium that the modest change in plasma lipid levels alone does not explain the apparent protective effect of the *NPC1L1* stop variants against coronary artery disease.

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No potential conflict of interest relevant to this letter was reported.

1. The Myocardial Infarction Genetics Consortium Investigators. Inactivating mutations in *NPC1L1* and protection from coronary heart disease. N Engl J Med 2014;371:2072-82.

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TO THE EDITOR: The Myocardial Infarction Genetics Consortium Investigators tested the association between inactivating mutations in *NPC1L1* and the risk of coronary heart disease. Heterozygous carriers of *NPC1L1* inactivating mutations had a mean LDL cholesterol level that was only 12 mg per deciliter lower than in noncarriers, but resulted in a dramatic relative risk reduction of 53%. This finding validates the concept that lifelong LDL cholesterol reduction has a greater impact on risk[1] than pharmacologic interventions, such as statin therapy, initiated later in life.[2]

We have previously hypothesized that increased dietary sterol (cholesterol and xenosterol) absorption via NPC1L1 is associated with increased cardiovascular risk.[3,4] We further posit that there are sterol species in our diets (such as oxysterols, oxyphytosterols, etc.) that may be mechanistically linked to atherosclerosis development. We

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Eye injuries and tasers

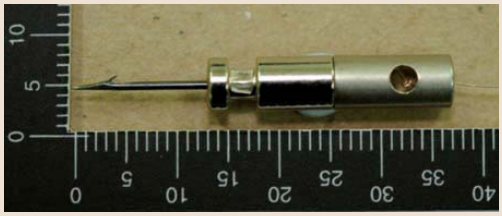
To the Editor: Taser (TASER International) injuries have been topical in the news media. This provides an important reminder of the possible traumatic sequelae associated with the use of electronic control devices.

A taser is a battery-powered unit that uses a nitrogen cartridge to propel two darts on a 7 m copper wire.[1] Each dart consists of a 4 mm harpoon-like barbed electrode on a 13 mm × 1 mm shaft (Box), deployed at 18 m/s from a distance of 3–6 m. Increasingly, tasers are being used by police in every state of Australia to subdue violent people.

When the deployed darts attach to a target individual's skin or clothing, a current of up to 50 000 volts is released for a period of up to 5 s, depending on the skin's resistance (which varies based on fat content, thickness, cleanliness and body chemistry).[2] The mechanical impact of the barbs, combined with the subsequent voltage released, represents a considerable hazard to eyes, genitalia and large blood vessels in the neck.[2]

Essentially, the eyeball is a liquid-filled globe with a wall thickness < 1 mm, making it particularly susceptible to electrical damage. TASER International states that "serious injury, including permanent vision loss" can result from barb contact with the eye.[3] Our literature search found seven case reports and one review of ocular damage relating to taser use.[1,2,4–8] In five cases, penetration of the globe was reported;[1,4,5,7,8] in three cases, entry through the lids made this difficult to determine without ophthalmic surgical examination.[1,2,7] Ocular damage associated with taser use includes mydriasis, iritis, macular cysts, lid lacerations, cataracts, retinal detachment, optic neuritis, vitreous haemorrhage and globe penetration.[6] Damage may be thermal or mechanical,[6] with visual outcome ranging from final visual acuity of 6/9 to total vision loss and enucleation.[1,2,4,5,7,8]

Taser dart, showing dimensions (mm)



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As taser use increases, medical staff need to be aware of the implications of both the impact energy and the electrical damage associated with taser deployment. As in the management of a barbed fishhook penetrating the eye or ocular area, a taser barb should not be removed at the scene but should be immobilised (eg, by covering it with a foam or paper cup) until appropriate ophthalmic surgical removal is possible.[1]

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1 Ng W, Chehade M. Taser penetrating ocular injury. *Am J Ophthalmol* 2005; 139: 713-715.
2 Sayegh RR, Madsen KA, Adler JD, et al. Diffuse retinal injury from a non-penetrating TASER dart. *Doc Ophthalmol* 2011; 123: 135-159.
3 TASER International. Volunteer: warnings, risks, release and indemnification agreement. http://www.taser.com/images/training/training-resources/downloads/Volunteer_Exposure_Release_030113.pdf (accessed Jan 2014).
4 Chen SL, Richard CK, Murthy RC, Lauer AK. Perforating ocular injury by Taser. *Clin Experiment Ophthalmol* 2006; 34: 378-380.
5 Teymoorian S, San Filippo AN, Poulose AK, Lyon DB. Perforating globe injury from Taser trauma. *Ophthal Plast Reconstr Surg* 2010; 26: 306-308.
6 Robb M, Close B, Furyk J, Aitken P. Review article: emergency department implications of the TASER. *Emerg Med Australas* 2009; 21: 250-258.
7 Han JS, Chopra A, Carr D. Ophthalmic injuries from a TASER. *CJEM* 2009; 11: 90-93.
8 Li JY, Hamill MB. Catastrophic globe disruption as a result of a TASER injury. *J Emerg Med* 2013; 44: 65-67. ❑

Severe alkali burns from beer line cleaners warrant mandatory safety guidelines

To the Editor: Two patients at our tertiary referral eye hospital had received severe alkali burns to the face and eyes while cleaning beer lines. In hotels, pubs and clubs, beer lines are cleaned weekly using strong alkaline solutions at high pressure. In an accident, alkali released under high pressure can produce blinding damage.

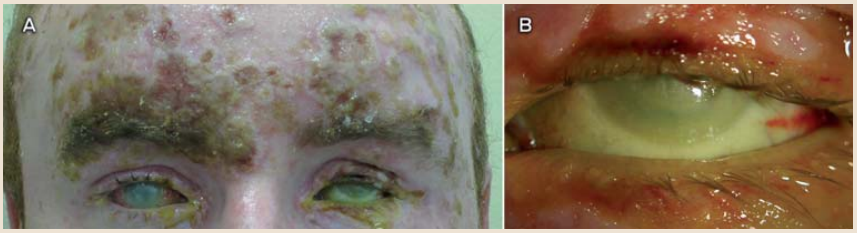
Our patients were young, typical of workers at these venues, and their injuries have had major impacts on their lives. One incident involved the face (60%–80% of facial skin) and both eyes (grade IV[1]) of a 23-year-old man (Box) using a commercially available beer line cleaner (potassium hydroxide; pH, 14). His eyes were immediately irrigated with water. His initial visual acuity was hand movements in the right eye and light perception in the left eye. He had bilateral corneal opacification and ocular ischaemia with hypotony in the left eye. He was treated according to burns protocol,[1] but a non-healing right corneal ulcer developed, requiring multiple operations. Bilateral reconstructive eyelid surgery was also needed.[2] His vision is currently light perception and no light perception with hypotony, respectively, in his right and left eyes. He requires further surgery to preserve his remaining vision, as well as ongoing psychological and social support.

The second patient received a grade IV injury to her left eye in 2006. Multiple operations were needed to heal the ocular surface, along with psychological and social support. After 4 years of treatment, her final visual acuity was light perception. She returned to limited work late in 2010.

Alkali injuries to the eye are devastating as they cause liquefactive necrosis and pass rapidly through the cornea to the eye's internal structures.[3] Damage to the stem cells of the ocular surface and intraocular structures produces permanent, difficult-to-treat and often blinding ocular disease. First aid should include copious ocular irrigation with water before referral to an emergency department.

Neither patient was wearing safety glasses. We found there are no mandatory safety guidelines in Australia (http://www.safeworkaustralia.gov.au), the United Kingdom (http://www.hse.gov.uk) or the United States (http://www.osha.gov), and perhaps worldwide, for beer line cleaning. Although the product information recommends use of safety equipment, this is not enforced and the equipment is usually not sufficient. Most workplaces provide safety glasses, but these offer suboptimal protection from a splash injury. Non-vented safety goggles are needed for adequate protection and should be worn throughout the cleaning procedure, from set-up to clean-up. We suggest that mandatory guidelines are indicated, as although such injuries are uncommon, they are severe and debilitating in the working-age group, with significant costs to the individual, health system and society.

Severe facial and ocular burns soon after injury



A: *Image shows the limbal and scleral ischaemia of the left eye and bilateral opaque corneas. The sunken appearance of the left eye, indicative of hypotony, is a very poor prognostic sign.* ***B:*** *A close-up view of the left eye, showing the cloudy cornea and limbal ischaemia.* ◆

> “Alkali injuries to the eye are devastating as they cause liquefactive necrosis”
>
> Samarawickrama et al

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Competing interests: No relevant disclosures.

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1 Roper-Hall MJ. Thermal and chemical burns. *Trans Ophthalmol Soc U K* 1965; 85: 631-653.
2 Tuft SJ, Shortt AJ. Surgical rehabilitation following severe ocular burns. *Eye (Lond)* 2009; 23: 1966-1971.
3 Cotsarelis G, Cheng SZ, Dong G, et al. Existence of slow-cycling limbal epithelial basal cells that can be preferentially stimulated to proliferate: implications on epithelial stem cells. *Cell* 1989; 57: 201-209. ❑

Linking data to improve health outcomes

To the Editor: Olver raises important issues concerning data linkage and the future of public health research in Australia.[1] We agree, but want to highlight several other impediments to research opportunities in Australia.

First, ethics applications to link multiple health databases are complex and inefficient. Each state has a different process — some require only a letter, others require full applications to ethics committees and data custodians. Multiple applications to multiple states should be unnecessary when a centralised data source is being used. Further, some ethics committees only meet quarterly, and meetings do not align between states. The process can take up to 2 years before approval is achieved. While the introduction of the National Ethics Application Form in 2006 heralded the streamlining of applications, this has not occurred, as the uptake of the form has been uneven across states.[2]

As a nation, we should learn from other models. Scandinavian countries lead the way in health linkage research[3,4] owing to their well thought out systems of unique health identifiers and administrative processes, which are not held up by bureaucracy. In Australia, linkage is conducted using probabilistic matching. This requires thorough understanding of the component databases and expertise in statistics and programming. This process is arduous and prone to errors and could be simplified by the use of unique health identifiers. Despite years of lobbying from researchers and some parliamentary members, we do not seem any closer to this becoming a reality.

Data linkage projects are where future public health research is headed. We need to minimise administration and long lag times between project approval and receiving data and to upskill staff in management and linkage of large datasets. This will facilitate productive research in Australia with more competitive outputs and, ultimately, better health outcomes for all Australians.

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[redacted]

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1 Olver IN. Linking data to improve health outcomes [editorial]. *Med J Aust* 2014; 200: 368-369.
2 Iedema RA, Allen S, Britton K, Hor S. Out of the frying pan? Streamlining the ethics review process of multisite qualitative research projects. *Aust Health Rev* 2013; 37: 137-139.
3 Lunde AS. The birth number concept and record linkage. *Am J Public Health* 1975; 65: 1165-1169.
4 Lunde AS, Lundeborg S, Lettenstrom GS, et al. Person-number systems of Sweden, Norway, Denmark, and Israel. *Vital Health Stat 2* 1980; (84): 1-59. ❑

To the Editor: The editorial by Olver[1] is a reminder of the usefulness of linking health datasets for research and evaluation. While data linkage is not a foreign concept to many health services researchers, such work with regard to Australian primary care is very limited. The recent review of Medicare Locals noted that the few linkages created "only occur in pockets and are often constrained by administrative, collaborative and/or legislative factors".[2] The public interest is not served by these barriers.

The unavailability of and lack of access to general practice data have hindered our ability to build a comprehensive picture of the interface between general practice and other health care services.[3] The benefits of linking anonymised, individual-level general practice data with other routinely collected health data are enormous; it enables us to map the entire patient journey both retrospectively and prospectively, gives us an insight into patients' use of health services, and provides us with the opportunity to assess whether the organisation of care for patients is effective and whether health services can be accessed by patients at the "right time". Such capabilities are very relevant for addressing issues such as the increasing demand for emergency department services and access to after-hours medical care.

Further attention to and investment in securing general practice data is urgently required. Until this is achieved, we will be unable to fully realise the benefits of data linkage for informing health policy and practice in primary care.

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> "The [ethics application] process can take up to 2 years before approval is achieved"
>
> Harding et al

Competing interests: The Melbourne East Monash General Practice Database (MAGNET) research platform is a collaboration between Inner East Melbourne Medicare Local and Monash University. Danielle Mazza is Scientific Director of MAGNET, Christopher Pearce is Deputy Director and Lyle Turner is the biostatistician.

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1 Olver IN. Linking data to improve health outcomes [editorial]. *Med J Aust* 2014; 200: 368-369.
2 Horvath J. Review of Medicare Locals. Canberra: Department of Health, 2014. http://www.health.gov.au/internet/main/publishing.nsf/Content/A69978FAABB1225ECA257CD3001810B7/$File/Review-of-Medicare-Locals-may-2014.pdf (accessed May 2014).
3 Australian Institute of Health and Welfare. Review and evaluation of Australian information about primary health care: a focus on general practice. Canberra: AIHW, 2008. (AIHW Cat. No. HWI 103.) http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442458110 (accessed May 2011). ❑

Newborn bloodspot screening: setting the Australian national policy agenda

To the Editor: The recent article by Maxwell and O'Leary[1] is timely in outlining the obstacles to introducing newborn screening tests in Australia, and the need for a nationally consistent approach, where the benefits of screening are proven. These obstacles exist despite clear policy developed by the professional newborn screening community.[2]

The absence of newborn screening for congenital adrenal hyperplasia (CAH) is the clearest example of the impact from the absence of any national mechanism, where initiatives to introduce such testing have bounced between state and

Correction

Incorrect statement: In "*Aboriginal community controlled health services: leading the way in primary care*" in the 16 June 2014 issue of the Journal (*Med J Aust* 2014; 200: 649-652), there was an error in the "Workforce and training" section on page 651. The sentence "The Leaders in Indigenous Medical Education (LIME) Network has recently signed an agreement with the National Aboriginal Community Controlled Health Organisation seeking to increase Aboriginal medical student placements in Indigenous primary health care settings with a view to increasing participation in and enhancing the effectiveness of the medical workforce" should have stated that the agreement was made with Medical Deans Australia New Zealand, not the LIME Network. The LIME Network is a project of Medical Deans that orchestrates many of their Indigenous health initiatives, but the partnerships between organisations are made at the Medical Deans level. ❑

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federal bodies for many years, despite clear evidence of benefit.[3] It is likely that a number of Australian children have died as a result of missed diagnoses while these initiatives have floundered.[4] In addition, the incidence of CAH in Aboriginal children is about 2.5 times that in non-Aboriginal children, suggesting an even greater need for national screening.[4]

CAH newborn screening has benefits additional to reduced mortality. There is a great difference for families in taking onboard the complexities of managing a child with CAH who is well, having been diagnosed through newborn screening, rather than a critically unwell neonate unnecessarily in adrenal crisis in the intensive care unit. Those of us who manage children with CAH in New Zealand, where screening exists, have observed this crucial difference.

Working groups and governmental announcements supporting screening for CAH are welcome; however, action is required now to introduce newborn screening for CAH Australia-wide. All that is required is political will, without which more Australian children will die unnecessarily.

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Competing interests: We are representatives of the Australasian Paediatric Endocrine Group, the key professional body for paediatric endocrinologists in Australasia.

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1 Maxwell SJ, O'Leary P. Newborn bloodspot screening: setting the Australian national policy agenda. *Med J Aust* 2014; 200: 142-143.
2 Royal Australasian College of Physicians, Human Genetics Society of Australasia. Policy: newborn bloodspot testing. http://hgsa.org.au/documents/item/29 (accessed Jul 2014).
3 Warne GL, Armstrong KL, Faunce TA, et al. The case for newborn screening for congenital adrenal hyperplasia in Australia. *Med J Aust* 2010; 192: 107.
4 Shetty VB, Bower C, Jones TW, et al. Ethnic and gender differences in rates of congenital adrenal hyperplasia in Western Australia over a 21 year period. *J Paediatr Child Health* 2012; 48: 1029-1032. ❑

Increasing incidence of *Clostridium difficile* infection, Australia, 2011–2012

To the Editor: Slimings and colleagues suggest that strain typing of *Clostridium difficile* would give greater insight into the epidemiology of this infection in Australia,[1] as it has in the United Kingdom,[2] demonstrating less inhospital transmission than suspected in the past. We believe this to be the case.

In a 2-year study of symptomatic *C. difficile* infection at our 350-bed tertiary hospital,[3] we identified 262 cases between October 2011 and October 2013. Of these, 150 (57%) were hospital-onset cases after 48 hours of admission. Ribotyping of 147 of these strains showed 44 different types. There appeared to be no secondary cases of diarrhoea from symptomatic patients in our hospital, where patients with *C. difficile* infection are isolated immediately after being identified.

We identified only one possible cluster of seven cases of ribotype QX076 on a rehabilitation ward between March and September 2013. This ward has only two rooms with ensuite toilet facilities, with most toilets being shared by four patients. When a toilet is flushed without the lid closed, aerosol production may lead to surface contamination within the toilet environment, increasing the risk of case-to-case transmission of *C. difficile*.[4] Apart from this cluster, most cases were singletons. As we found many different ribotypes, it could be hypothesised that cross-transmission is generally rare, with clustering being the exception rather than the rule.

The greatest numbers of cases were found on haematology/oncology and geriatric wards. No cases involving ribotype UK 027 were identified. The most common ribotypes in hospital- and community-onset cases belonged to the UK 014/020 group. There were 53 cases (20%) of community-onset infections without evidence of health care system contact. Fifteen of these had ribotypes not found in the hospital-onset cases.

Further investigations are required to assess the role of asymptomatic carriers in hospital infection and to define the relationship to toilet facilities and cleaning efficacy.

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Competing interests: No relevant disclosures.

doi: 10.5694/mja14.00547

1 Slimings C, Armstrong P, Beckingham WD, et al. Increasing incidence of *Clostridium difficile* infection, Australia, 2011–2012. *Med J Aust* 2014; 200: 272-276.
2 Eyre DW, Cule ML, Wilson DJ, et al. Diverse sources of *C. difficile* infection identified on whole-genome sequencing. *N Engl J Med* 2013; 369: 1195-1205.
3 Engelhardt NEP, Hong HE, Foster NF, et al. A two year study of symptomatic *Clostridium difficile* infection (CDI): rapid diagnosis and early isolation prevents case to case transmission [poster presentation]. Proceedings of Antimicrobials 2014: 15th Annual Scientific Meeting of the Australian Society for Antimicrobials; 2014 Feb 20-22; Melbourne, Australia.
4 Best EL, Sandoe JAT, Wilcox MH. Potential for aerosolization of *Clostridium difficile* after flushing toilets: the role of toilet lids in reducing environmental contamination risk. *J Hosp Infect* 2012; 80: 1-5. ❑