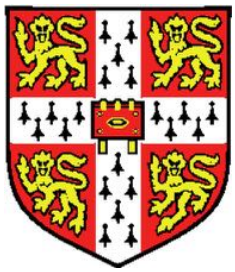
Optimising cardiovascular risk management early in the diabetes disease trajectory



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Optimising cardiovascular risk management early in the diabetes disease trajectory

Type 2 diabetes increases an individual's risk of Cardiovascular Disease (CVD). Trials have demonstrated the long term macro-vascular benefits of lowering glucose, as well as other CVD risk factors, in populations with established diabetes. As the diagnostic criterion for diabetes is a threshold on a continuous measure of glucose control, it has been hypothesised that targeting risk factors earlier in the disease trajectory may have even greater effects on rates of complications.

Many nations have introduced programmes to diagnose diabetes earlier, including the NHS in England, where the Health Checks programme offers individuals at '*high risk*' diabetes testing. This will lead to a greater number of individuals being diagnosed earlier in the course of the disease when treatment decisions are less informed by evidence. Some of the potential harms of intensive treatment are likely to manifest early, while benefits will likely appear years later. Much of the literature relates to lowering CVD risk factors years after diagnosis or arises from studies conducted more than 20 years ago, which may not represent the effects of managing risk factors intensively from diagnosis in contemporary care.

Firstly, I demonstrate that in a population with screen-detected diabetes there is a degree of pharmacotherapy burden at diagnosis, that then intensifies over the following five years.

Secondly, I show that there is a large variation in glycaemic control and CVD risk factors after diagnosis at the individual level, which I have characterised and described.

Thirdly, I have shown that promoting intensive treatment from the day of diagnosis leads to improvements in cardio-metabolic health, and that increases in medication can decrease the modelled risk of a CVD event.

Lastly, I show that the risk reduction associated with intensification of pharmacotherapy is not achieved at the expense of quality of life.

In conclusion, type 2 diabetes is a disease intertwined with cardio-metabolic health, and actively approaching diabetes care as a multifactorial intervention to improve a cluster of cardio-metabolic risk factors via encouragement of lifestyle change supported by pharmacotherapy is likely to improve health. However, guidelines do not represent diabetes care at the individual level, and further research that both improves our understanding of individual variation and how to communicate these complex relationships will benefit our attempts to further personalise medicine.

Acknowledgements

I am forever thankful to Dr Rebecca Simmons, who was my primary supervisor for the first year of my PhD. Her approach towards supervision was focused on supporting and enriching my transition from student to independent researcher, despite the fact that such an endeavour (possibly even more so in my case...) was well beyond the task she was charged with.

Professor Simon Griffin, my primary supervisor after Dr Simmon's departure to the Vice-Chancellor's office, continued to be supervisor that both mentored and inspired. Professor Griffin's incredible ability to see the important clinical questions added a great deal of clarity and clinical relevance to this thesis. His command of both the big picture in diabetes epidemiology, along with the dance floor at every conference we attended, has made it a pleasure to work with him.

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I would also like to thank my parents, for the enumerable things they've done over the last 28 years that led to me being in a position to write this thesis; the Middle Combination Room at Jesus College, for making Cambridge home; and Joe, Tom, Ben, Rob, Amanda and assorted other miscreants, for providing many entertaining distractions from this thesis.

And of course Tina, for being der größte Schatz seit geschnittenem Schwarzbrot.

Declaration

All analysis chapters have, or are in the process of being, published. Co-authors have commented on the ideas I present but the text is my own. I played no part in the conception or implementation of the ADDITION-*Europe* study. I participated in formulating research questions, primarily with Prof. Griffin and Dr. Simmons (my supervisor until her move to the Vice-Chancellor's office), and led on developing suitable analysis plans. Mr Stephen Sharp reviewed and commented on statistical analysis plans used in chapters involving ADDITION-*Europe* and ADDITION-*Cambridge*. I was responsible for all data analyses in this thesis.

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the preceding paragraph and specified in the text.

This thesis is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in this preface and specified in the text.

This dissertation does not exceed 60,000 words, excluding figures, photos, tables, appendices and bibliography.

Dedicated to Nana

Dissemination

Accepted publications resulting from this thesis

J. Black, G. Long, S. Sharp, *et al.*, "Change in cardio-protective medication and health-related quality of life after diagnosis of screen-detected diabetes: results from the ADDITION-Cambridge cohort", *Diabetes Research and Clinical Practice*, 2015, ISSN: 01688227. DOI: 10.1016/j.diabres.2015.04.013

J. A. Black, S. J. Sharp, N. J. Wareham, *et al.*, "Change in cardiovascular risk factors following early diagnosis of type 2 diabetes: a cohort analysis of a cluster-randomised trial.", *The British journal of general practice : the journal of the Royal College of General Practitioners*, vol. 64, no. 621, e208–16, Apr. 2014, ISSN: 1478-5242. DOI: 10.3399/bjgp14X677833

J. A. Black, S. J. Sharp, N. J. Wareham, *et al.*, "Does early intensive multifactorial therapy reduce modelled cardiovascular risk in individuals with screen-detected diabetes? Results from the ADDITION-Europe cluster randomized trial.", *Diabetic medicine : a journal of the British Diabetic Association*, vol. 31, no. 6, pp. 647–56, Jun. 2014, ISSN: 1464-5491. DOI: 10.1111/dme.12410

J. A. Black, R.K Simmons, C. Boothby, *et al.*, "Medication burden in the first five years following diagnosis of type 2 diabetes: findings from the ADDITION-*UK* trial cohort", *BMJ Open Diabetes Research and Care* (In press)

Submitted publications resulting from this thesis

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Conference presentations resulting from this thesis: Oral

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J. A. Black, "Screen detected type 2 diabetes: do we need intensive treatment?", in *Jesus College Graduate Conference*, Cambridge, 2013

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J. A. Black, "Intensive treatment of diabetes to avert coronary heart disease", in *Building Bridges in Medical Science*, Cambridge, 2012

Other external talks resulting from this thesis

J. A. Black. "Optimising cardiovascular risk management early in the diabetes disease trajectory", seminar at the *Primary Care Unit, Institute of Public Health*, Cambridge, 2015

J. A. Black. "Optimising cardiovascular risk management early in the diabetes disease trajectory", seminar at the *German Diabetes Center (DDZ)*, Düsseldorf, 2015

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Acronyms

4S Scandinavian Simvastatin Survival Study. 9, 17, 111

ABCD Appropriate Blood Pressure Control in Diabetes study. 10

ACCORD Action to Control Cardiovascular Risk in Diabetes study. 8, 10, 15, 20, 91, 129, 140

ACE Angiotensin-Converting-Enzyme. 10, 16, 28, 29, 91, 113

ACR Albumin Creatinine Ratio. 32, 83, 86

ADA American Diabetes Association. 1–3, 20, 50, 74, 108, 148

ADDITION-*Cambridge* Cambridge centre of ADDITION-*Europe*. 29, 30, 49, 73, 91, 112, 113, 117, 125–127, 130, 133, 134, 136–140, 147

ADDITION-*Denmark* Danish centre of ADDITION-*Europe*. 31, 32, 36, 37, 41, 42, 50–52, 58, 60–65, 67, 68, 71, 94, 117, 130, 144, 145, 148, 151, 226

ADDITION-*Europe* Anglo-Danish-Dutch Study of Intensive Treatment in People With screen-detected Diabetes in Primary Care *(pages not shown)*.

ADDITION-*Plus* A trial with a sample that overlaps ADDITION-*Cambridge* exploring the effect of an individually tailored theory based behaviour change intervention. 112, 127

ADDITION-*UK* Cambridge and Leicester centres of ADDITION-*Europe*. 30, 31, 36, 38, 39, 41, 43–53, 91, 112, 117, 126, 127

ADDQoL Audit of diabetes-dependent quality of life questionaire. 130–133, 135

ADDQoL-AWI Audit of diabetes-dependent quality of life average weighted index. 132, 136, 137, 139–141

ADVANCE Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation. 15, 20

AF Atrial Fibrillation. 32

ATC Anatomical Therapeutic Chemical Classification[11]. 29, 32, 36, 37, 52, 113, 131

BIC Bayesian information criterion. 59

BMI Body Mass Index. 11, 32, 44, 65, 78, 83–87, 97, 108, 117, 134, 145

BP Blood Pressure. 79, 86, 91

CARDS Collaborative Atorvastatin Diabetes Study. 9, 126

CHD Coronary Heart Disease. 3, 32, 33, 102

CVD Cardiovascular Disease (*pages not shown*).

DALYs Disability Adjusted Life-Years. 5

DCCT Diabetes Control and Complications Trial. 13

DESMOND Diabetes Education and Self Management for Ongoing and Newly Diagnosed programme. 30, 31, 87

DIN Doctor's Independent Network. 7

DSC Diabetes Symptoms Distress Checklist. 8

DTSQ World Health Organisation Diabetes Treatment Satisfaction Questionnaire. 8

EDIC Epidemiology of Diabetes Interventions and Complications. 13, 20

EPAQ2 EPIC-Norfolk Physical Activity Questionnaire. 132

EQ-5D European Quality of Life Questionnaire. 75, 78, 130–141, 147

ERFC Emerging Risk Factors Collaboration. 3, 148

FPG Fasting Plasma Glucose. 2, 14, 148

GBD Global Burden of Disease. 5

GBTM Group Based Trajectory Model. 57, 59, 61

GLINT Glucose Lowering In Non-diabetic hyperglycaemia Trial. 69

GP General Practitioner. 9, 22, 28–31, 38, 46, 50, 53, 58, 60, 73, 74, 88, 89, 111, 144, 147, 148, 150, 151

HbA_{1C} Glycosylated hemoglobin (*pages not shown*).

HES Hospital Episode Statistics. 8

HOPE Heart Outcomes Prevention Evaluation Trial. 10, 111

HOT Hypertension Optimum Treatment trial. 10

HPS Heart Protection Study. 9, 17, 28, 126

HR Hazard Ratio (*pages not shown*).

HRQoL Health Related Quality of Life. 8, 22, 128–132, 134, 136, 137, 139–143, 147, 150–152

HRS Health and Retirement Study. 11

IDF International Diabetes Federation. 5

IGT Impaired Glucose Tolerance. 4

IMD Index of multiple deprivation. 30, 31, 39, 46, 53, 127, 132, 133

IRR Incidence Rate Ratio (*pages not shown*).

LADA Latent Autoimmune Diabetes in Adults. 2, 4, 7

LDL Low-density Lipoprotein. 9, 17

Look-AHEAD Action for Health in Diabetes. 10, 11, 18

MCS SF-36 mental component score. 8, 129, 131, 133, 135–137, 141

MIM Missing Indicator Method. 94, 105

NHS National Health Service. 7, 23, 35

NICE National Institute of Health and Clinical Excellence. 18, 20, 50, 51

NNT Number Needed to Treat. 106

NSC National Screening Committee. 21, 23

OGTT Oral Glucose Tolerance Test. 2, 29, 30

OR Odds Ratio (*pages not shown*).

PACIC Patient Assessment Chronic Illness Care questionnaire. 130

PCS SF-36 physical component score. 8, 129, 131, 133, 135–137, 141

PHQ-9 9 item Patient Health Questionnaire. 8

PMM Pattern Mixture Model. 94, 102, 105

PROactive Prospective pioglitazone clinical trial in macro-vascular events. 15

QOF Quality and Outcomes Framework. 92

RCT Randomised Controlled Trial. 10, 12, 14, 16, 22, 25, 91, 126, 129, 141, 149

RR Relative Risk (*pages not shown*).

SCI-DC Scottish Care Information Diabetes Collaboration. 6

SF-36 The Short Form (36) Health Survey. 8, 129–132, 134, 136, 137, 139–141, 147

Steno-2 Steno centre type 2 diabetes study. 16, 17, 19, 20, 28, 55, 56, 58, 125–128, 147

THIN The Health Improvement Network. 7

UGDP University Group Diabetes Program. 13, 14

UKPDS United Kingdom Prospective Diabetes Study. 9, 10, 14, 15, 17–20, 22, 23, 32, 50–52, 55–57, 68–70, 73–75, 87, 92, 93, 103, 107, 111, 126, 140, 145–148, 150

USPSTF United States Preventive Services Task Force. 21, 148

VADT Veteran Affairs Diabetes Trial. 15, 20, 23

W-BQ12 12-item short form of the Well-Being Questionnaire. 147

WHO World Health Organization. 2, 3

Chapter 1

Introduction

"Extreme thirst, a better appetite than what is natural,...passes from 10 to 12 pints of water in the 24 hours....The urine is sweet, and two quarts yielded four ounces of an extract exactly resembling thick treacle, but not so sweet."
—Matthew Dobson, *Practice of Physick*, *1777*

1.1 Diabetes

The clustering of excessive thirst and sweet, honey-like, urine had been known throughout antiquity.[12] Yet it was Thomas Willis (1621-75), in his *Pharmaceutice rationalis*, who defined the modern condition of diabetes mellitus. In 1777, Matthew Dobson (1732-84) proved conclusively that people with diabetes had elevated levels of sugar in their urine and blood. The first appearance of diabetes as a condition in the *New England Journal of Medicine and Surgery* was not until 1812, and at the time the clinical definition was restricted to the then fatal condition we now call type 1 diabetes.[12] In 1889, it was discovered that removing the pancreas of dogs led to type 1 diabetes and death, and in 1910 it was first hypothesised that diabetes was related to a single chemical, newly named insulin, that was secreted from within the clusters of cells in the pancreas called the islets of Langerhorns.[12] A decade later, in 1922, bovine insulin was successfully administered to young Leonard Thompson and type 1 diabetes no longer meant a painful death before adulthood.[13] Banting and Macleod received the Nobel Prize for developing bovine insulin, and between their award in 1923 and 1992 a flurry of research resulted in ten scientists receiving Nobel Prizes for diabetes related research.

1.1.1 Subsets of diabetes

Diabetes is not a single condition, but a heterogenous clustering of clinical conditions with overlapping mechanisms and complications. The American Diabetes Association (ADA) divides diabetes into the following four clinical categories[14]:

Type 1 diabetes usually has an early onset, and is characterised by an autoimmune response which leads to destruction of the pancreatic β cells present in the islets of

Langerhorns. The lack of insulin leads to an absolute deficiency, and without an external source of insulin, eventually death. As the age of onset is not a definitive means to identify type 1 diabetes, differentiation can be improved by testing for antibodies specific to islet cells and insulin that would indicate an immune response has initiated.[15] Additionally, levels of C-peptide, a molecule produced in tandem with insulin, can indicate whether insulin secretion has been interrupted.[16]

Gestational diabetes which is transient and related to pregnancy.

Other types of diabetes *with specific causes* not contained within the other clusters. Examples are diabetes related to other conditions and/or their treatment (e.g. pancreatic diseases) or specific and established genetic defects in insulin production or function.

Type 2 diabetes, which is the focus of this thesis. It is the most common form of diabetes and relates to varying degrees of defect in insulin secretion and resistance. Throughout the remaining thesis, diabetes and type 2 diabetes will be used interchangeably.

While the ADA guidelines introduce diabetes as being able to be grouped into four '*types*', many diabetes researchers would include a fifth category for Latent Autoimmune Diabetes in Adults (LADA). Often known as type 1.5, LADA is characterised by an older onset than type 1 and the presence of islet antibodies but with a slow progression of β cell failure. While the mechanism with which LADA leads to variation in glycaemia is similar to type 1, the later onset means that around 10% of a population with clinically diagnosed type 2 diabetes may have LADA.[17]

Type 1, in addition to some rare genetic forms of diabetes, is unique in being a specific pathological condition where there is an absolute deficiency in insulin. Type 2 diabetes can more easily be identified as a disease of exclusion, because it can manifest as a varying combination of insulin deficiency and insulin insensitivity characterised by poor blood glucose control and the absence of features suggesting it is actually one of the other categories of diabetes.

1.1.2 Definition and diagnosis of type 2 diabetes

Type 2 diabetes is characterised by defects in insulin signalling and/or secretion that lead to metabolic imbalances.[18] Insulin, a hormone produced in the β cells of the pancreas, promotes the uptake and storage of glucose, and inhibits the release of glucagon, a peptide that promotes the release of glucose into the blood stream. In healthy individuals, insulin and glucagon form part of a feedback mechanism that regulates fat and carbohydrate metabolism, keeping blood glucose levels high enough to provide the necessary cellular fuel, but low enough to not be toxic.[19] In individuals with diabetes the body is unable to respond to glycaemic challenges appropriately, although how much of this is caused by insulin secretion or insulin function differs amongst individuals.[18]

The 2006 World Health Organization (WHO) diagnostic criteria for diabetes was a Fasting Plasma Glucose (FPG) of $\geq$7.0 mmomL^{-1} or a 2 hour 75g glucose load Oral Glucose Tolerance

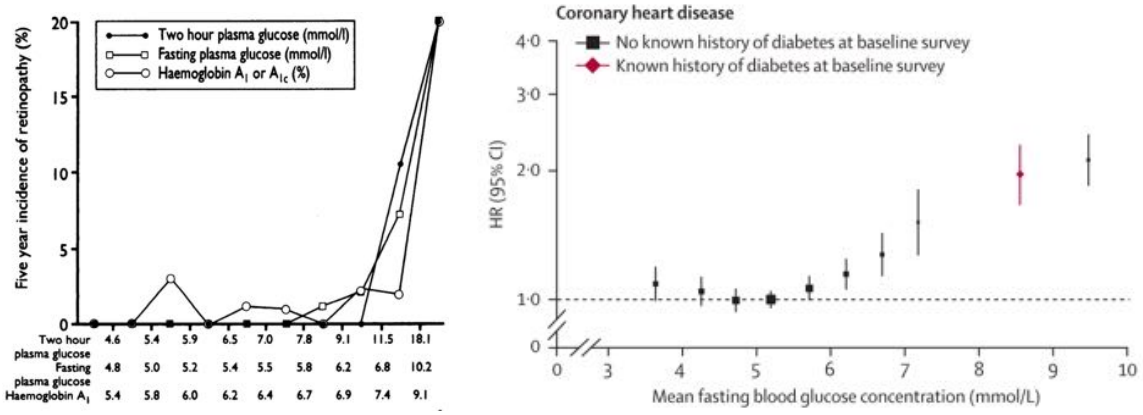
Test (OGTT) of $\geq$11.1 mmomL^{-1}.[20] In 2011 the WHO also recommended the use of HbA_{1C}, at a threshold of 48 mmol mol^{-1} ($\geq$6.5%).[21] The 2014 ADA guidelines include the WHO definition, and expand it to include a random plasma glucose of $\geq$11.1 mmomL^{-1} in the presence of the classic symptoms of hyperglyceamia.[14]

As a diagnosis of diabetes may lead to changes in the individuals lifestyle and mental state[22–24], that in the American context could extend as far dramatic increases in insurance premiums, epidemiological definitions of diabetes can allow for a higher rate of false positives than clinical definitions.[18] While a clinical diagnosis requires confirmation of testing (in the absence of symptoms that suggest hyperglycaemia)[14], epidemiological studies routinely use a single abnormal blood glucose level to define a case of diabetes.

The diagnostic threshold used in diabetes represents a significant level of poor glyceamic control that is likely to have microvascular and macrovascular implications.[14,20] The binary classification of diabetes as a clinical condition does not mean that there is an underlying threshold in risk, as glyceamia has a continuous relationship with both microvascular[25] and macrovascular disease.[26,27]

Figure 1.1a shows deciles of three glyceamic measures against the prevalence of retinopathy in a population of Pima Indians not receiving glucose lowering medication at baseline.[28] The figure, published in 1994, shows a marked increase in the five year incidence of retinopathy in individuals above the 80$^{\text{th}}$ centile. This finding was repeated in other populations[29], and provided a clinical justification to set the threshold for diabetes diagnosis at a point of hyperglycaemia that is associated with a subsequent increased risk of retinopathy. Replication of the methodology used in the Pima Indians, in a nationally representative American sample, found a slightly more linear association where retinopathy already began to become prevalent beyond an HbA_{1C} of 37 mmol mol^{-1} (5.5%).[30] This later study used two retinal photos of each eye rather than one, and this greater sensitivity in detecting retinopathy may explain why the relationship now appears more linear. The studies mentioned earlier, that helped establish the diabetes threshold[28,29], were also in a Pima Indian and Egyptian population, who have been documented as having a more severe diabetes burden than the general population.

Figure 1.1b shows data from an individual patient data meta-analysis of 102 studies by the Emerging Risk Factors Collaboration (ERFC).[31] In total 698,782 people experienced 26,505 incident cases of coronary heart disease over the follow up period. This large study provided evidence, shown in Figure 1.1b, of a gradual association between increasing fasting blood glucose and Coronary Heart Disease (CHD). The threshold for diabetes was originally set based on the risk of retinopathy and in the absence of evidence of an association with macrovascular disease. Yet diabetes is a complex condition and an increased risk of conditions like CHD[31] and all-cause mortality[32] can be present at levels of hyperglycaemia below the diagnostic threshold.



(a) Retinopathy and glycaemia.

(b) Coronary Heart Disease and glycaemia.

Figure 1.1: The left figure (a) is taken from *McCance et al(1994)BMJ,308(6940)1323-8* and shows an early study that suggested there was a threshold effect of glycaemia and microvascular disease. The right figure (b), taken from *Sarwar et al(2011)NEJM,364(9)829-41*, published 17 years later, shows a more contemporary observation of a linear relationship between glycaemia and macrovascular disease. The reference group is 5-5.5 mmolL^{-1}. Figures are reproduced with permission.

1.1.3 Risk factors and pathogenesis

Progression to diabetes is generally assumed to follow a multistage pathogenesis: this is marked by a long period of increased β cell function, which secretes insulin, to compensate for an increasing insulin resistance. When β can longer compensate for the insulin resistance, there is a progression to unstable glycaemia leading to a clinical diagnosis of type 2 diabetes.[33,34] This gradual decline in β cell function differentiates type 2 diabetes from type 1, as in type 1 diabetes an autoimmune response, in most cases, destroys β cell function completely.

While a brief summary of the pathogenesis of diabetes has been presented, it is important to note that the aetiology of the disease is neither simple or homogenous. The deterioration of glycaemia from mild insulin resistance to diabetes is not as concrete as a simple description suggests. Before reaching the clinical threshold of diabetes, individuals can have a condition called Impaired Glucose Tolerance (IGT), yet not all individuals with IGT continue on a path of glycaemic disfunction towards diabetes.[35] As mentioned in Section 1.1.1 on page 2, because type 2 diabetes is often diagnosed by eliminating other potential conditions, a routine clinical diagnosis cannot be guaranteed to exclude individuals with LADA, or in potentially even type 1 diabetes.

> *"I chalk up the fact that I got* [type 2] *diabetes to my body saying, 'Dude, you have been doing wrong for way too long!' "*
>
> — Randy Jackson, *Body with Soul (Memoir/diabetes self-help book), 2003*

Risk factors for complications of diabetes are the primary concern for this thesis, so I will only briefly touch on the the risk factors for type 2 diabetes. While genetic variants

increasing the risk of type 2 diabetes have been identified[36], known variants only account for around 10% of the heritability, and the presence of known genetic variants in an individual only increases risk by a similar percentage.[12] While current knowledge about genetic determinants is limited[37], much stronger associations are seen with modifiable risk factors like body weight.[12,38]

Modifiable risk factors for diabetes include diet, physical activity and smoking behaviour, and exposure to these risk factors can in in turn contribute to unfavourable increases in other risk factors like cardiometabolic health and obesity.[39] Overweight/obesity, central adiposity, elevated triglycerides, low HDL and high LDL cholesterol and elevated blood pressure are all associated with increased risk of type 2 diabetes, and the presence of these risk factors tend to cluster together in individuals.[39,40] Non-modifiable factors include increasing age, ethnicity and a family history of diabetes.[40]

Emerging risk factors include traffic and industrial environmental pollution[41], although teasing out causation is difficult as exposure is related to social inequalities, and can be assumed to have a long cumulative effect. Subclinical inflammation is increasingly being suggested as process of diabetes pathogenesis.[42–44] The mechanisms for inflammation are not well explained[43], but the excess adipose tissue present in obesity often leads to chronic inflammation[45]. This hypothesis over a role of inflammation is supported by evidence that the molecules associated with subclinical inflammation are further elevated in South Asians with obesity[46], who are known to be at a higher risk of type 2 diabetes.

1.2 Burden of type 2 diabetes

1.2.1 Increasing importance of type 2 diabetes

After the breakthrough in survivability of type 1 diabetes that followed the introduction of bovine insulin, in the 1930's doctors began to comment that diabetes was becoming *"a disease of middle life and old age* ..[and]..*complicating conditions involving the cardiovascular system have assumed a new important prominence which cannot be disregarded"*.[47] As Leonard Thompson, the first recipient of intravenous insulin, was only 25 at the time this comment was made (and would die two years later from pneumonia), we can be fairly certain that this observation about elevated cardiovascular disease is referring to a growing concern over the relationship between type 2 diabetes and early death from CVD.

1.2.2 Secular trends and predictions

Type 2 diabetes has emerged as a major threat to global health.[49,50] The global prevalence of all diabetes, among adults aged 20-79 years, was estimated to be 8.3% in 2011, and is expected to increase to 9.9% by 2030.[51] From 1990 to 2010, diabetes moved from the 21st to the 14th ranked cause of lost Disability Adjusted Life-Years (DALYs), and from 15th to 9th in terms of cause of death, according to a 2010 Global Burden of Disease (GBD) study.[52,53] Figure 1.2, a map reproduced from the International Diabetes Federation (IDF) Diabetes

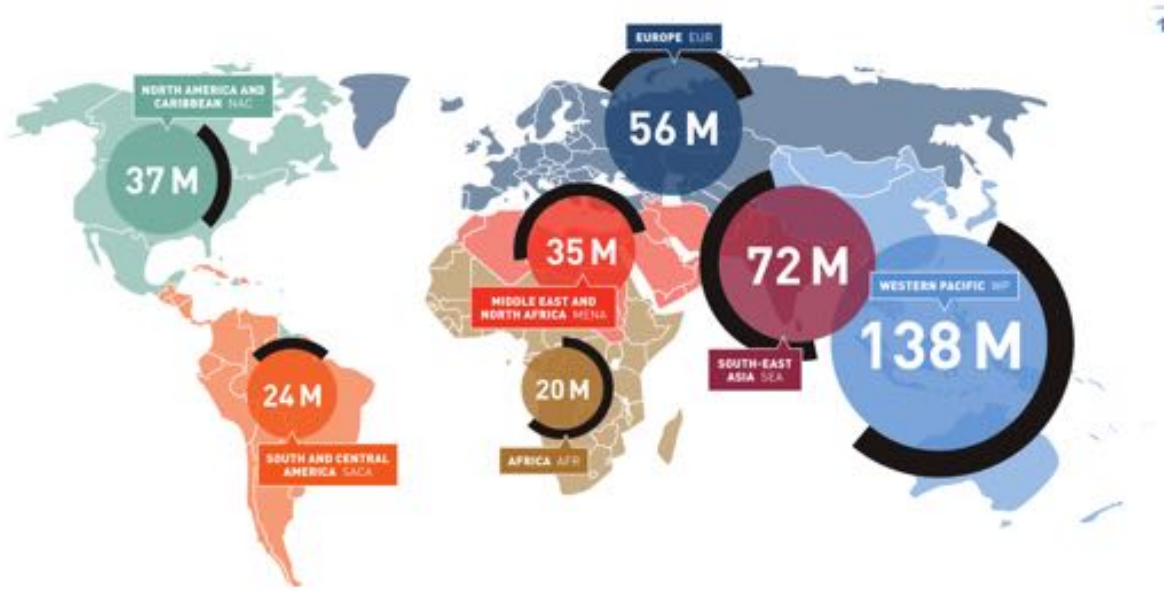


Figure 1.2: This figure, reproduced with permission from the sixth edition of the IDF Diabetes Atlas[48], shows the number estimated to have both diagnosed and undiagnosed diabetes globally in 2013. The black bars on the circumference of each circle represent the proportion of the estimate that is undiagnosed.

Atlas[48], shows the millions of people estimated to be living with diabetes in each world region. These estimates include individuals that are currently undiagnosed. The black lines, which represent the undiagnosed proportion, highlight that in some heavily populated regions of the world the majority of individuals with diabetes are not clinically diagnosed. There is a great variety of sources that contribute to these global burden estimates. In Scotland, accurate information on the prevalence and trends of diabetes prevalence is available from the Scottish Care Information Diabetes Collaboration (SCI-DC), a nation-wide network of diabetes care providers. In Tunisia, estimates of the prevalence of diabetes relies on identifying and testing a sample of the population, and then inferring from this sample what the national prevalence is.[54]

In 2013 the European prevalence of type 2 diabetes was estimated as 8.5%.[42] While variance in diabetes prevalence is seen across social gradients and ethnicities within countries, variance across European nations is also high, ranging from 2.4% in Moldova to 14.9% in Turkey.[42] An example of the complexities in diabetes prevalence is seen in Germany, where the less economically developed north-east is estimated to have both higher rates of diagnosed diabetes and undiagnosed diabetes than the more developed southern border regions.[55]

In one UK study, the prevalence of type 2 diabetes was estimated to have increased from 2.5% in 1996 to 3.9% in 2005.[56] The authors also noted that, in 2005, diabetes was more prevalent in men (29% higher) and increased linearly with age, from 0.4% in individuals aged 10-19 to 17% of individuals aged 70-79.[56] In a similar study, using a different sample of general practices, type 2 diabetes prevalence in England and Wales was estimated to have increased from 1.7% in 1994 to 2.5% in 2001.[57] These UK estimates came from two practice databases:

The Health Improvement Network (THIN)[56] and the Doctor's Independent Network (DIN).[57] As the practice records did not differentiate diabetes type, algorithms were used to define whether an individual had type 1 or 2, with the primary definition of type 1 in DIN being the initiation of insulin within 90 days, below an age threshold (which was not stated) or they had experienced a ketoacidosis event. In addition to expecting some individuals with type 2 being younger and potentially requiring insulin within 90 days, this coding scheme would likely result in LADA cases being classified as type 2. The ability to differentiate type 1 and 2 becomes even more difficult when using practice records if an individual transfers into the database, on insulin, after diagnosis. In the case of the THIN database[56], the authors assumed that if an individual was reported as being first diagnosed at younger than 35, and they redeemed an insulin prescription within 180 days of joining the practice, they had type 1 diabetes. This coding scheme for type 1 and 2 diabetes, when compared to blind retrospective review by a single clinician, was found to have a sensitivity of 94% and a specificity of 93%.[56] While the exact prevalence remains unknown, all studies suggest a general trend toward increasing prevalence.

1.2.3 Diabetes related morbidity and mortality

The associations between diabetes and micro-vascular complications are well documented in the literature, and include increased risk of nephropathy, neuropathy and retinopathy.[58–61] Diabetic retinopathy is exacerbated in the presence of hypertension, and is both the leading cause of adult-onset blindness in high-income countries and responsible for 4.8% of blindness globally.[62]

Diabetes is associated with an increased risk of macro-vascular complications. This is likely due to hyperglycaemia and diabetes specific risks in the presence of other traditional risk factors, such as dyslipidaemia and hypertension, interacting with arthrosclerosis.[49,58,63] While CVD mortality has decreased in the last decade[42], likely due to improvements in care, both all-cause and cardiovascular disease mortality rates are higher in people with diabetes than the general population.[49,50,64] Globally, 6.8% of all-cause mortality across all ages is associated with the presence of diabetes.[65] Conditions that, in addition to causing large amounts of morbidity, are often associated with diabetes related mortality include stroke, myocardial infarction, heart failure and end stage renal disease.[49]

1.2.4 Economic burden of diabetes

In 2010 the estimated direct cost to the National Health Service (NHS) of diabetes was £3,717 per patient per year.[66] This is close to a 2007 estimate of £3,104.[67] While the estimates appear to give accuracy to the pound, they rely on many extrapolations from a wide range of data sources. The second estimate, produced by the Economist Intelligence Unit, is presented on faith and without any methods.

The methods used were presented with more clarity in a 2010/11 (financial year) estimate of the costs to the NHS of treating type 2 diabetes and it's complications, which was estimated

at £8.8 billion.[68] Less than a quarter of this estimate was related to the treatment and management of diabetes, with the majority of diabetes related expenditure being on the complications that arise from diabetes.[68] The estimates were derived from Hospital Episode Statistics (HES), national level costs for expenditures like prescriptions and estimates on the prevalence of type 1 and type 2 diabetes. Several costs like foot care and primary care glucose testing were not included in this estimate, suggesting that despite the inaccuracy, the cost to the NHS is likely to be even higher. Complications of diabetes were also estimated, and for each complication inaccuracy will be present in estimating the proportion of incident cases that are attributable to diabetes. The authors further estimate that an additional £13.0 billion was lost through productivity costs. These costs include the effect of early mortality on loss in salary, and that individuals with diabetes are likely to be more absent from work due to sickness. The indirect costs are likely to be much higher if viewed in the context of the loss of ideal health attributed to diabetes.

1.2.5 Quality of life burden of diabetes

Within the Hoorn study, a comparison can be made between 116 individuals with screen-detected diabetes, and 49 with clinically diagnosed diabetes at ~2 weeks after diagnosis.[69] Screen detected individuals were more likely be overweight (BMI≥25; 89% vs 73%; p=0.01) but less likely to be hypertensive (75% vs. 59%; p=0.04), prescribed oral glucose lowering medication (24% vs. 78%; p<0.01) or anti-depressives (0 vs 6%; p=0.03).[69] Compared to the the clinically diagnosed arm, the screen detected sample had preferable Health Related Quality of Life (HRQoL) when measured by the SF-36 mental component score (MCS) (mean 54, SD 9; vs mean 49, SD 12; p=0.01) and the general well-being item of the W-BQ12 (mean 28, SD 7; mean 25, SD 7).[69] These estimates represent an unadjusted cross-sectional profile of screened vs. routinely diagnosed populations, which does not account for different characteristics. The measure was also only available ~2 weeks after diagnosis, so no information is given on the impact of being diagnosed via the two methods on HRQoL.

The Action to Control Cardiovascular Risk in Diabetes study (ACCORD) trial included aggressive glycaemic control targets of 42 $\mathrm{mmol\,mol^{-1}}$ (<6%) in the intensive arm, and 53-63 $\mathrm{mmol\,mol^{-1}}$ (7-7.9%) in the routine care arm, and individuals recruited had long standing diabetes and evidence of CVD. Change in HRQoL was measured by the The Short Form (36) Health Survey (SF-36), Diabetes Symptoms Distress Checklist (DSC), World Health Organisation Diabetes Treatment Satisfaction Questionnaire (DTSQ) and 9 item Patient Health Questionnaire (PHQ-9). After randomisation, individuals receiving intensive treatment reported a larger decrease in SF-36 physical component score (PCS) and perceived hypoglycaemia (DTSQ item), but greater treatment satisfaction (DTSQ scale) and less hyperglycaemia (DTSQ item). The ACCORD researchers believed that the statistically significant change in the PCS was '*trivial*', and that there was no clinically significant impact of intensive treatment on HRQoL.

Bohlin *et al* took a qualitative approach to assessing the impact of diabetes by reviewing the way in which individuals with diabetes, who were diagnosed >1 year earlier and hadn't

initiated insulin, discussed the topic of treatment burden.[70] They found that in 46 consultations, 83 topics relating to treatment burden were discussed. The burden of administrating treatments was discussed 28 (34%) times, the potential effects and consequences of treatments 24 (29%) times, patient concern over being able to attain medication 19 (23%) times, and trouble complying with the monitoring required for safe use 12 (14%) times. While the issues over purchasing and getting access to medications may only be prominent due to the study's American locale, it appears that the primary concern for patients when talking with their General Practitioner (GP)s is centred around how to incorporate the medication regime into their lives. Bohlin *et al* noted that two coders independently reviewed all 46 consultations, and there was an 85% agreement rate. The coders first calibrated their coding technique on similar consultations till the reached >90% agreement. While this suggests they attained good inter-rater reliability, there is no evidence that their method is a valid representation of a patient's concern over the burden treatment choices will have on their life.

1.3 Prevention of type 2 diabetes complications

Efforts to prevent diabetes have largely focused on tertiary prevention, which is the treatment of people with established diabetes in order to improve health and limit complications. People with type 2 diabetes are at an increased risk of macro and microvascular disease.[71,72] and studies have evaluated treatments to lower CVD risk factors in order to prevent these complications.

1.3.1 Cholesterol lowering in diabetes

The Scandinavian Simvastatin Survival Study (4S)[73] and the Heart Protection Study (HPS)[74] clinical trials demonstrated that, in sub-groups of individuals with diabetes, single risk factor therapy to lower cholesterol led to significant decreases in the risk of CVD. This was supported by the diabetes specific Collaborative Atorvastatin Diabetes Study (CARDS), of atorvastatin in patients without high levels of Low-density Lipoprotein (LDL) cholesterol, which was stopped early due to the efficacy of the drug in preventing CVD events.[75] A 2008 meta-analysis including 4S, HPS and 12 other studies found a significant reduction in the risk of a composite CVD event in people with type 2 diabetes (RR 0.79; 99%CI 0.72,0.87, per $\mathrm{mmol\,l^{-1}}$ reduction).[76] This meta-analysis highlighted that the proportional protective effect remained, despite pre-treatment LDL levels down to $2.6\,\mathrm{mmol\,l^{-1}}$. Suggesting that while the absolute risk may differ, the proportion by which statin treatment may decrease risk remains stable in cases of dyslipidemia.

1.3.2 Blood pressure lowering in diabetes

The United Kingdom Prospective Diabetes Study (UKPDS) included two groups randomised to different intensities of blood pressure control.[77] Eight years after randomisation there was a clinically important reduction in micro and macrovascular complications and diabetes

related deaths. This finding was supported by the Heart Outcomes Prevention Evaluation Trial (HOPE), which found that prescription of an Angiotensin-Converting-Enzyme (ACE) inhibitor in people with diabetes was associated with a reduction in the risk of a composite CVD outcome.[78] A 2012 meta-analysis summarised the findings of the Appropriate Blood Pressure Control in Diabetes study (ABCD), Hypertension Optimum Treatment trial (HOT) and ACCORD.[79] These contemporary trials had a more intensive treatment target than the UKPDS, and a statistically significant reduction in risk was present only for strokes (RR 0.65; 95%CI 0.48, 0.86). The ACCORD trial, which was the only trial in the meta-analysis to comprehensively report adverse events, noted that the intensively treated group had higher rates of adverse events that were life threatening, caused permanent disability or required hospitalisation (2.2% vs. 1.7%, p>0.05).[79]

1.3.3 Weight loss in diabetes

"I have high blood sugars, and Type 2 diabetes is not going to kill me. I just have to eat right, exercise, lose weight, and watch what I eat, and I will be fine for the rest of my life."
—Tom Hanks, *Late Night with Letterman (Interview), 2013*

Weight reduction in individuals with type 2 diabetes through changes in diet and exercise is universally promoted.[80,81] In a sample of 11 individuals, diagnosed with diabetes less than four years previously, and not receiving insulin, thiazolidinediones or β blockers, acute restriction to a <600 kcalday^{-1} resulted in a trend towards normal β cell function and insulin sensitivity.[82] In this study, hepatic insulin sensitivity returned to normal in the first seven days after diagnosis, and over the following eight weeks β cell function returned to a point at which insulin secretion matched a control group without diabetes.[82] The costs associated with the intensive nature of this study led to a small sample size. While this study suggests the pathogenesis is reversible, it is unknown whether this finding holds in populations with long standing diabetes or severe glycaemic dysfunction. Dixon *et al* noted a similar relationship in an Randomised Controlled Trial (RCT) of adjustable gastric banding, where the proportion of individuals below an HbA_{1C} of 44 mmol mol^{-1} (6.2%) and not on diabetes related medication improved in the surgery arm (mean weight loss of 20%, SD 9%), compared to the arm that received only a lifestyle intervention (mean weight loss 1.4%, SD 4.9%).[83]

A comprehensive literature review of studies in individuals with and without diabetes suggest that weight loss is associated with improvements in glycaemic control, although the greatest improvements are restricted to the population that are very overweight at diagnosis, and are able to achieve lifestyle changes (often with pharmacological support) that lead to weight loss.[84]

The Action for Health in Diabetes (Look-AHEAD) study of lifestyle changes in type 2 diabetes, which aimed to achieve weight loss in the intervention group, was stopped early at 9.6 years as they predicted that they would find no association between the promotion of lifestyle changes and incident CVD at the intended study end point of 11.5-13.5 years.[85]

However, reductions in the short term outcomes of sleep apnea, depression, poor quality of life and urinary incontinence were seen in the intensive lifestyle modification arm.[85] The lifestyle intervention arm were aiming for a weight loss of at least 7% by restricting their diet to 1,200-1,800 $\frac{kcal}{day}$ and undertaking 175 $\frac{mins}{week}$ of moderate intensity physical activity. At one year, mean weight loss in the intervention group was higher (8.6% vs 0.7%), although the difference had decreased by the study end (6.0% vs 3.5%). These difference resulted in a higher prevalence of partial or complete remission of diabetes at one (11.5%; 95%CI 10.1,12.8 vs. 2.0%; 95%CI 1.4,2.6) and four years (7.3%; 95%CI 6.2,8.4 vs. 2.0%; 95%CI 1.5,2.7) in the lifestyle intervention group.[86]

The promotion of weight loss in the general practice must acknowledge that there will be a large variation in what is achieved. Evidence of divergent Body Mass Index (BMI) trajectories was present in the Health and Retirement Study (HRS), where four distinct BMI trajectories were identified.[87] While the presence of clusters of BMI change is important, the shape and number of trajectories identified in the HRS is not representative of weight loss after diagnosis as this was a population with a median diabetes duration of 8.7 years, and the four trajectories were modelled with a shared latent class to values of a disability measure.

While the Look-AHEAD trial suggests pragmatic interventions will suffer from efficiency losses, there is compelling evidence of weight loss leading to improvements in cardiometabolic health in physiological, cohort and longitudinal studies.[80] As such, weight loss in those with excess body weight remains an important goal in diabetes management despite the difficulties in translating advice into action.

1.3.4 Glucose lowering in diabetes

1.3.4.1 Non-randomised cohorts

While trials represent the evidence with the least exposure to confounding and bias, the size of the effect explored is limited to what can be achieved through an intervention. Cohort analyses allow a much wider range of glycaemic control to be assessed, as long as the discrepancy between looking at individuals that change HbA_{1C} in the cohort studies and those that are randomised to interventions to lower HbA_{1C}, are addressed.

Currie *et al*[88], in a study of 47,970 British individuals with type 2 diabetes who recently intensified treatment, looked at the risk of CVD by decile of the mean HbA_{1C} of all recorded measurements during follow up. Figure 1.3, taken (with permission) from Currie *et al*'s paper, shows that, relative to the reference decile (median HbA_{1C} 7.6%; 95%CI 7.4,7.7), there was a U-shaped curve of increasing CVD risk as HbA_{1C} increased or decreased. The authors compared two treatment strategies in their analysis, and found similar results, which led them to suggest that in addition to there being upper targets for HbA_{1C}, there may also be a lower limit of healthy HbA_{1C} for individuals with a diagnosis of diabetes. I address this assumption in detail later in this discussion, as it is best discussed in tandem with the trial evidence presented below (see Section 1.3.4.5 on page 15). However, it is important to note that individuals in Currie *et al*'s study had either gone from mono to combination oral

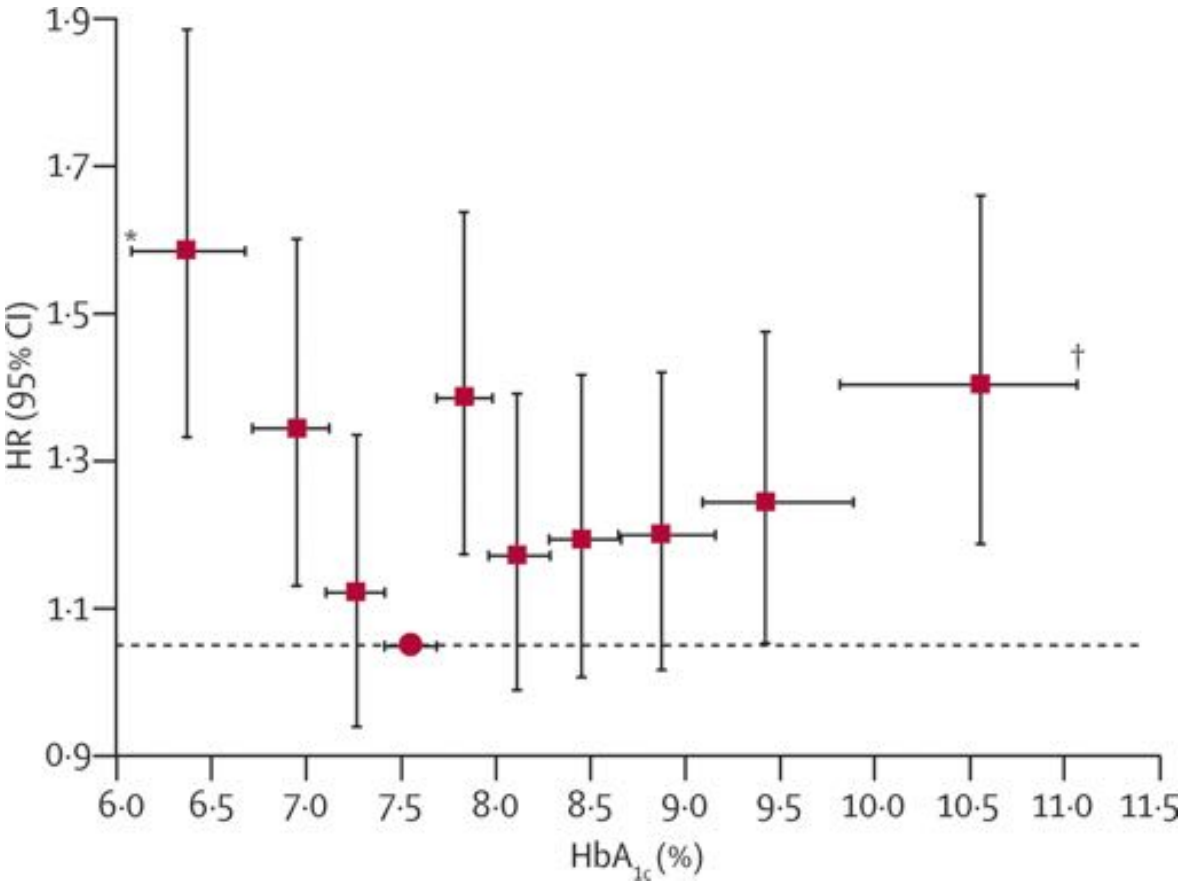


Figure 1.3: Hazard ratios for progression to first large-vessel disease event by HbA1c decile, with Cox proportional hazards model. Vertical error bars show 95% CIs, horizontal bars show HbA_{1C} range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Model specification, for people with no previous cardiovascular disease only: age, sex, Charlson index (age unadjusted), total cholesterol, smoking status history, and cohort membership. This figure was published in *Currie et al(2010)Lancet,375(9713):6-12*, and is reproduced with permission.

therapy, or had initiated insulin therapy. So the mortality effect within the those individuals with an HbA_{1C} $<48\,mmol\,mol^{-1}$ (<6.5%) represents individuals with long standing diabetes that is being treated by multiple medications to near normal levels. Within this context, it is difficult to understand how this finding applies to individuals much earlier in the disease trajectory who may be able to lower HbA_{1C} levels via only lifestyle changes or initiation of metformin.

1.3.4.2 Early trials in type 1 diabetes

In 1993 Wang *et al*[89] published a meta-analysis of the effect of intensive blood glucose control on type 1 diabetes that summarised the body of knowledge from 1966 to 1991. Across the sixteen RCTs meta-analysed, they found that intensive blood glucose control decreased the risk of retinopathy and nephropathy. While this was type 1 diabetes, and both the standard and intensive treatments were based around insulin at different intensities and frequencies,

this meta-analysis established the microvascular benefits of avoiding hyperglyceamia. Only six of the sixteen trials reported the frequency of severe hypoglyceamic events, and while there was a non significant trend to more events in the intensive treatment group, the trials were individually all underpowered to assess this less common event, and an association continued to be absent in the meta-analyses.[89]

The Diabetes Control and Complications Trial (DCCT) trial solidified that intensive glucose control using insulin prevents the development of microvascular disease in a young population (mean age 27) with type 1 diabetes.[90] The post trial follow up of the DCCT, called the Epidemiology of Diabetes Interventions and Complications (EDIC) study, found that the effect of intensive glucose control in the first 6.5 years led to a decrease in CVD risk at 17 years[91], leading to the hypothesis that treatment early in the disease trajectory may alter the disease course. While microvascular events were averted, in the intensive treatment arm there were 61.2 hypoglycaemic events per 100 patient-years vs. 18.7 per 100 patient-years in the routine care arm.[92] The DCCT and Wang *et al*'s meta-analysis of published studies helped identify the benefits of better glucose control in type 1 diabetes, albeit at an increased risk of hypoglycaemia, but the picture is less clear when looking at type 2 diabetes.

1.3.4.3 The UGDP

In 1960 the University Group Diabetes Program (UGDP) began recruiting patients to the first trial in people with type 2 diabetes. Individuals diagnosed less than one year earlier were randomised to five treatments: (i) variable insulin adjusted to maintain good glucose control, (ii) insulin on daily fixed dose (iii) tolbutamide, (iv) phenformin (added two years into the study when this biguanide became available) and (v) a lactose pill as a placebo for the oral medication. All arms of the trial received diet advice.

Ten years later the authors concluded that *"the findings of this study indicate that the combination of diet and tolbutamide therapy is no more effective than diet alone in prolonging life. Moreover, the findings suggest that tolbutamide and diet may be less effective than diet alone or than diet and insulin at least in so far as cardiovascular mortality is concerned."*[93] The UGDP study concluded that the sulphonylureas demonstrated no benefit over diet alone, and several years later the biguanide was also stopped under the same conclusions.[94] Much of the controversy that surrounds this study comes from the mortality rate, shown in Figure 1.4. This figure suggests that tolbutamide led to excess mortality. While the investigators took a cautious approach and concluded there was no benefit of treatment, rather than there was harm, the tolbutamide arm was stopped early.

The findings were heavily criticised for numerous methodological flaws. These flaws are the potential reason why two curious results were noted. Firstly, there was an excess of CVD risk factors in the tolbutamide arm suggesting an even distribution of confounders across arms at baseline was not achieved.[95,96] Secondly, the CVD mortality seen in females from the placebo arm, who made up 70% of this group, was an implausible 2%.[95,96] The controversy surrounding the use of sulphonylureas would continue to linger till the present day, despite a large body of evidence contradicting a harmful effect on CVD mortality[97,98], and the removal

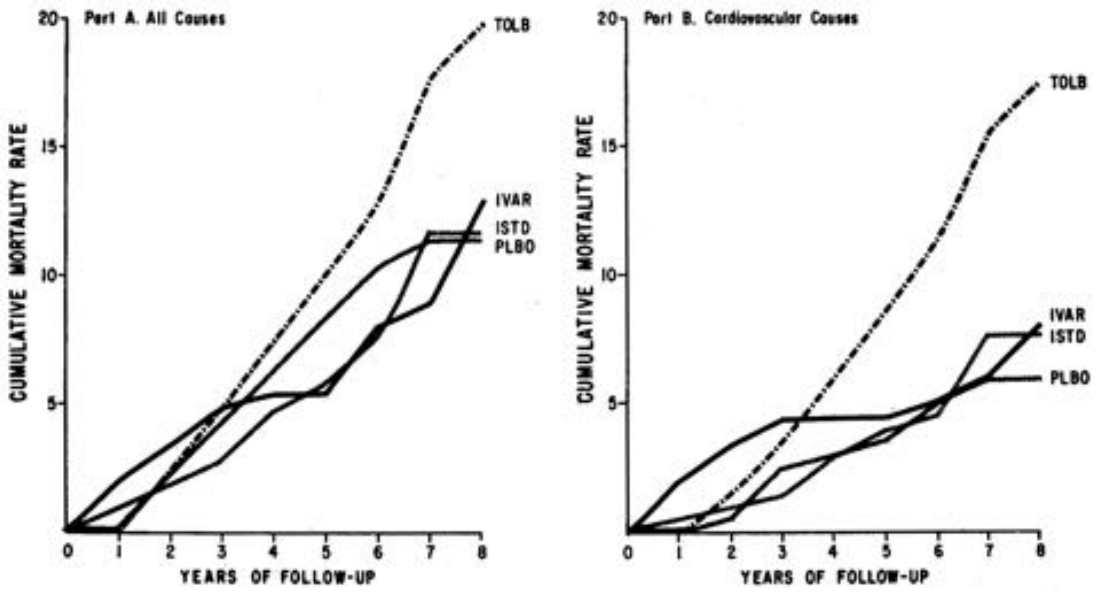


Figure 1.4: Excess mortality in the UGDP study. Cumulative mortality = rates per 100 population at risk by year of follow-up. TOLB = tolbutamide. IVAR = insulin variable. ISTD = insulin standard. PLBO = placebo. Reproduced with permission from *UGDP (1970) Diabetes 19(Sup2):474-830.*

of the the potential mechanism for excess CVD from later generations of sulphonylureas that was identified by laboratory based studies supporting the UGDP findings.[99]

1.3.4.4 The UKPDS

The UKPDS was 10-year RCT where the primary question was the to explore the micro- and macrovascular effects of randomisation to diet advice and routine care (target FPG $15\,\mathrm{mmol\,l^{-1}}$) or intensive management (target FPG $6\,\mathrm{mmol\,l^{-1}}$).[100] Numerous facets were added to this trial, to enable it to explore other questions like the role of blood pressure lowering and sulphonylureas vs. insulin and metformin (in obese individuals).

At ten-year follow up, HbA_{1C} in the intensive treatment group was significantly lower than the control group ($53\,\mathrm{mmol\,mol^{-1}}$, 95%CI 44,64; 7.0%, 95%CI 6.2, 8.2 and 63 , 95%CI 52,73; 7.9%, 6.9, 8.8, respectively). The risk of any-diabetes related end-point was lower in the intensive treatment group (RR 0.88; 95%CI 0.79, 0.99), which the authors postulated as primarily due to the lowered rate of microvascular disease.[100] In a metformin vs. routine care trial nested within the overweight participants, significant reductions in CVD and all-cause mortality were reported at ten year follow up.[101] In the post trial follow up, 30 years after randomisation and ten years after treatment ended (recruitment spanned 14 years), there was significant decrease in all-cause mortality for the insulin-sulphonylurea (RR 0.87; 95%CI 0.79,0.96) and metformin groups (RR 0.73; 95%CI 0.59,0.89).[102]

The UKPDS was a landmark trial in type 2 diabetes, that indicated that improvements in glycaemic control translate into a reduction in diabetes-related complications. The absolute differences though highlighted the importance in managing treatment, particularly in

the elderly and those with many comorbidities and/or complications were small reductions in distal risk may be less tangible. The UKPDS population were diagnosed from 1977 to 1991, when both diabetes care and awareness, which may influence the likelihood of clinical diagnosis, were very different. Prescribing patterns for both CVD reduction and diabetes have also changed, as routine care now involves metformin as first line therapy and more intensive management of CVD risk factors is common both before and after diabetes diagnosis.[14,103]

1.3.4.5 ACCORD, ADVANCE, VADT and intensifying glycaemic control

Three recent trials, comprising ACCORD, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veteran Affairs Diabetes Trial (VADT), attempted to establish if the protective effect of lowering HbA_{1C} on vascular disease was improved by targeting HbA_{1C} levels closer to levels found in people free of diabetes. ACCORD, the study with the lowest HbA_{1C} target ($42\,mmol\,mol^{-1}$; <6.0%), was stopped early, after an excess of deaths in the intensive treatment arm. This appeared to mirror the findings from Currie *et al*'s cohort analysis, where they concluded that having near-normal glyceamic control had a negative effect. Subsequent analyses suggest that the excess mortality in ACCORD was concentrated in individuals that were randomised to intensive care and tight glyceamic control, but were failing to attain the lower blood glucose.[104] This suggests that it is not low HbA_{1C} but the act of attempting to attain low HbA_{1C} values in patients failing to reach targets that raises the risk of mortality. In an analysis that combined the 3.7 years of the trial, with 1.2 years of follow up after randomisation was stopped, there was a significant benefit of intensive treatment for preventing myocardial infarctions (HR 0.84; 95%CI 0.72,0.97).[105]

Despite this, all three studies failed to establish a reduction in their primary outcome of CVD after five years of intensive goal setting[106,107], although in addition to the *post-hoc* analysis of ACCORD showing a benefit for myocardial infarction prevention, a *post-hoc* analysis of participants in the VADT with a duration of diabetes <12 years found a significant benefit of intensive treatment.[108] A 2009 meta-analysis, also including the UKPDS and Prospective pioglitazone clinical trial in macro-vascular events (PROactive) trials, suggested an overall protective effect of intensive treatment for non-fatal myocardial infarction (OR 0.83; 95%CI 0.75,0.93), but not stroke (OR 0.93; 95%CI 0.81, 1.06), and no increased risk of all cause mortality (OR 1.02; 95%CI 0.87,1.19).[109] Like the UKPDS, extended follow up of the VADT five years after the intervention ended (in total 10 years from randomisation) suggested a protective effect of intensive treatment on CVD (HR 0.83; 95%CI 0.70,0.99), but not CVD mortality (HR 0.88; 95%CI 0.64,1.20) or all-cause mortality (HR 1.05; 95%CI 0.89,1.25).[110]

Several key issues remain in applying the results of ACCORD, ADVANCE and the VADT to populations with screen-detected diabetes. As the trials were based in populations with long standing diabetes, low HbA_{1C} targets are likely to involve a higher degree of pharmacotherapy, and the effect on complications from lowering HbA_{1C} later in the disease trajectory might differ from arresting the gradual loss of glycaemic control in those much earlier in the diabetes disease trajectory.

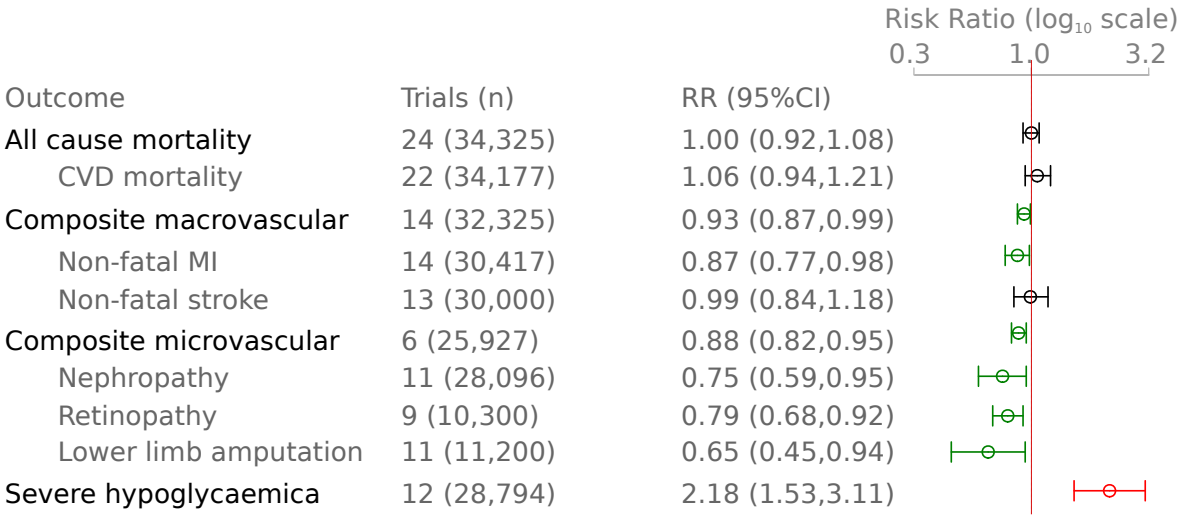


Figure 1.5: I have plotted the summary results from the Cochrane review on intensive glycaemic control vs. routine care in type 2 diabetes: *Sahuquillo* et al *(2013) Cochrane database of systematic reviews 11:CD008143.*[111]

1.3.4.6 Cochrane review on glycaemic control

Figure 1.5 is an illustrated table of the main results from a Cochrane review of intensive glycaemic control vs. routine care in type 2 diabetes. This review found a protective effect from intensive HbA_{1C} target setting for microvascular disease, with less certainty over the benefit for preventing macrovascular disease. There was a large amount of heterogeneity across the trials, with follow up ranging from three days to ten years, and the target of the routine care typically being between $53\,\mathrm{mmol\,mol^{-1}}$ and $64\,\mathrm{mmol\,mol^{-1}}$ (7% to 8%) while intensive control was often a target of $42\,\mathrm{mmol\,mol^{-1}}$ (6%), $48\,\mathrm{mmol\,mol^{-1}}$ (6.5%) or $53\,\mathrm{mmol\,mol^{-1}}$ (7%). This variation in what defines treatment, in addition to the variation in the underlying populations duration of diabetes, means that the ability to extrapolate these results to those diagnosed with diabetes earlier is difficult.

1.3.5 Steno-2 and multifactorial treatment

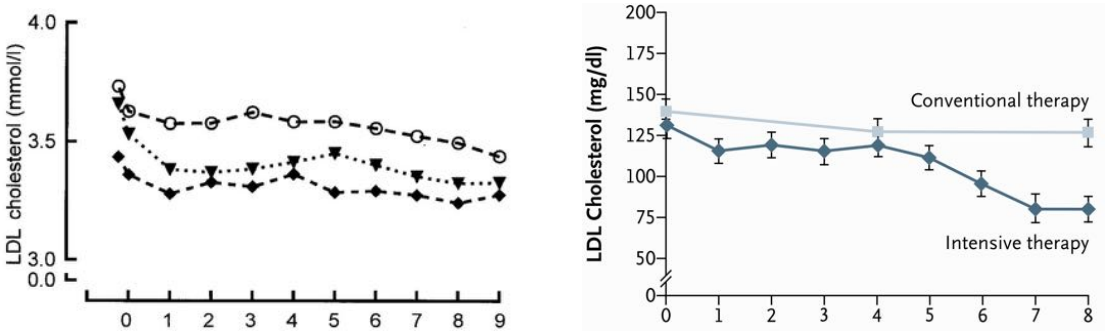
Steno centre type 2 diabetes study (Steno-2) was a small (n=160) RCT comparing routine care with behaviour modification and pharmacological therapy to lower both HbA_{1C} ($48\,\mathrm{mmol\,mol^{-1}}$; <6.5%) and CVD risk factors ($<\frac{130}{80}$ mmHg blood pressure, $<4.5\,\mathrm{mmol\,l^{-1}}$ total cholesterol and $<1.7\,\mathrm{mmol\,l^{-1}}$ triglycerides). Lifestyle changes included lowing fat intake, increasing exercise and smoking cessation promotion. Aspirin, vitamin supplements and an ACE inhibitor were also advised in the intervention group. At 7.8 years the trial found that the intensive treatment group had a 53% lower risk of CVD (HR 0.47; 95%CI 0.24,0.73).[112] The benefits of multifactorial treatment were long lasting and 5.5 years after randomisation ended, CVD risk (HR 0.41; 95%CI 0.25, 0.67) and all-cause mortality remained lower (HR 0.54; 95%CI 0.32,0.89).[113]

1.3.6 Changes in CVD risk factors

As ADDITION-*Europe* is a novel population with screen-detected diabetes, finding other sources of information on the expected patterning of CVD risk factor changes is difficult. Almost all studies have also presented mean changes, which are useful for exploring the population effect of a treatment or disease, but make it difficult to communicate how a particular individuals CVD risk factors are likely to change over time. Understanding these mean population level changes in risk factors will give a solid base for then exploring what drives the heterogeneity seen at the individual level.

1.3.6.1 Change in cholesterol after diabetes diagnosis

Figure 1.6a shows the decrease in LDL that occurred after diabetes diagnosis in the first 2,999 individuals recruited to the UKPDS. This change occurred despite the UKPDS study predating 4S and the HPS, which showed the benefits of cholesterol therapy within populations with type 2 diabetes. Whether the decrease after diagnosis is a product of lifestyle changes, tightened goal setting, or simply routine care of dyslipidemia that was picked up during the course of diabetes diagnosis, it highlights that CVD risk factor reduction has been part of diabetes care before it was formally incorporated into the guidelines.



(a) Change in LDL in the UKPDS

(b) Change in LDL in Steno-2

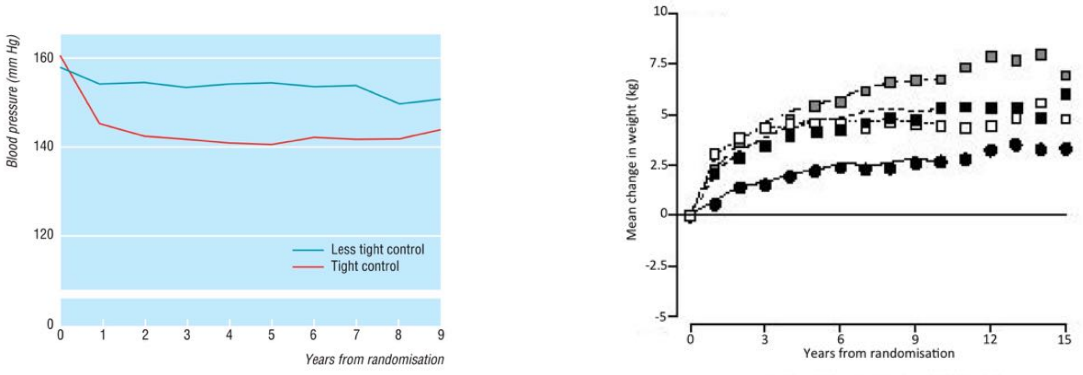
Figure 1.6: Figure 1.6a is the change in LDL cholesterol in the first 9 years after diagnosis in the UKPDS. ◯ = white. ▼ = Black. ♦ = South Asian. Reproduced from *Davis et al (2001) Diabetes Care 24(7):1167-74*[114] with permission. Figure 1.6b is the change in LDL in the 8 years after randomisation in Steno-2. Reproduced from *Gaede et al (2003) New England Journal of Medicine 348(5):383-93* with permission.[112]

Figure 1.6b shows a population with long standing diabetes from the Steno-2 trial randomised to a multifactorial intervention. The routine care arm had a total cholesterol target of $<13.9\,\mathrm{mmol\,l^{-1}}$ ($<250\,\mathrm{mgdl^{-1}}$) for the first six years, and then $<10.6\,\mathrm{mmol\,l^{-1}}$ ($<190\,\mathrm{mgdl^{-1}}$) for the remaining two years. The intensive care arm had a total cholesterol target of <10.6 ($<190\,\mathrm{mgdl^{-1}}$) for the first six years, and then $<9.7\,\mathrm{mmol\,l^{-1}}$ ($<175\,\mathrm{mgdl^{-1}}$) for the remaining two years. The changes seen in Figure 1.6b suggest that intensive goal setting is successful in attaining and then maintaing lower lipid levels when applied within a multifactorial intervention that also includes lifestyle promotion. In the absence of screen-detected populations to draw reference from, Figure 1.6 suggests that in a screen detected population we can expect

to see a decrease in lipids after diagnosis, that is successful maintained over the first decade after diagnosis.

1.3.6.2 Change in blood pressure after diabetes diagnosis

Within the UKPDS a sub-sample of hypertensive individuals with newly diagnosed diabetes were randomised to a tight ($<\frac{150}{85}$ mmHg) or less stringent ($<\frac{180}{105}$ mmHg) BP target. Figure 1.7a shows the changes in systolic BP in the that were seen in the two arms in the first nine years of the study. From the figure it is clear that the intervention was successful in lowering the average systolic blood pressure after diagnosis, and maintaining this over nine years. In 2002, National Institute of Health and Clinical Excellence (NICE) guidelines for the management of diabetes of type 2 diabetes were promoting a minimum of bi-annual monitoring and lifestyle advice for individuals with a BP $>\frac{160}{100}$ mmHg, and pharmacotherapy if the individual had microalbuminuria/proteinura or a modelled 10 year coronary event risk of >15%. Less certain is what the trajectories blood pressure control will look like in a contemporary screen-detected population.



(a) Change in systolic BP in the UKPDS

(b) Change in weight in the UKPDS

Figure 1.7: Figure 1.7a is the change in systolic BP in the first 9 years after diagnosis in the UKPDS. Reproduced from *UKPDS Group (1998) BMJ 317(7160):703-13*[77] with permission. Figure 1.7b is the change in weight in the first 9 years after diagnosis in the UKPDS. ◯ = white. ▼ = Black. ♦ = South Asian. Reproduced from *Davis et al (2001) Diabetes Care 24(7):1167-74*[114] with permission.

1.3.6.3 Change in weight after diabetes diagnosis

In the UKPDS individuals received diet advice soon after diagnosis, and there was a small decrease in weight, that gradually rebounded in the first few years before plateauing (Figure 1.7b). The Look-AHEAD study involved a more intensive lifestyle intervention in an overweight (>25 kgm^{-2}) diabetes population. While changes in weight were more dramatic[85], how these trajectories relate to a screen-detected population where not all individuals are initially overweight, and the lifestyle intervention is pragmatic, is uncertain.

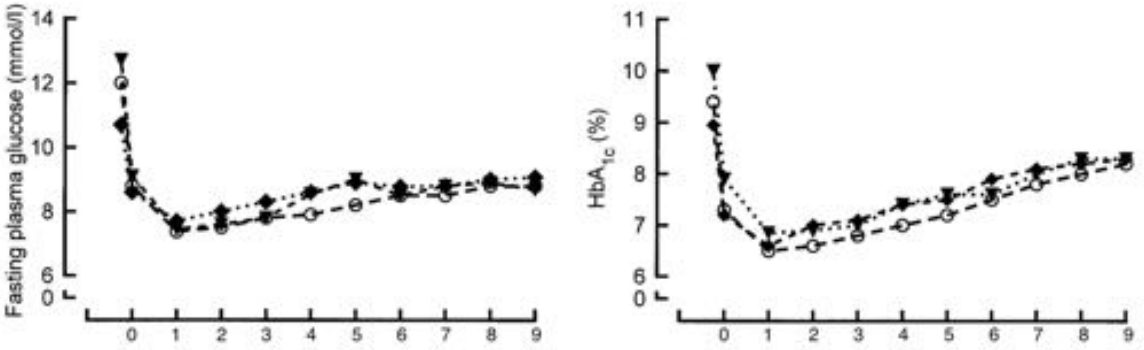


Figure 1.8: Change in FPG and HbA_{1C} in the first 9 years after diagnosis in the UKPDS, including the 3 month diet only run in period if FPG<15 mmol l^{-1}. ◯ = white. ▼ = Black. ♦ = South Asian. Reproduced from *Davis et al (2001) Diabetes Care 24(7):1167-74* with permission.[114]

1.3.6.4 Glycaemic control after diagnosis

Figure 1.8 shows the change in blood glucose in the first nine years after diagnosis, in a cohort analysis of the UKPDS. This figure represents one of the few times the UKPDS presented trajectories of blood glucose during the diet only run-in period (although individuals with an FPG>15 mmol l^{-1} were randomised immediately), and highlights the large improvement in blood glucose, which is then followed by a gradual loss of glycaemic control. Figure 1.8 represents only the first 15 of the 23 UKPDS centres[114], so it remains unclear how these trajectories from a sample diagnosed 20-38 years ago (in 2015) reflects modern therapies.

1.3.6.5 Medication burden of diabetes

Risk factors for CVD overlap with risk factors for diabetes, so it is not surprising that people diagnosed with diabetes tend to be on multiple cardioprotective medications.[115,116] Steno-2 has highlighted the importance of multifactorial treatment of cardio-metabolic health in populations with type 2 diabetes, which is seen in the adoption of lower thresholds for pharmacotherapy initiation in individuals with diabetes.[14,117,118]

In populations with established diabetes, four to ten medications a day is common.[119–122] These estimates though come from diverse populations, who by their older age alone can be expected to be taking more medication. Limited information on medication in a screen detected population is available from the Hoorn study, where 20% self-reported taking lipid lowering medication, and 45% blood pressure lowering medication. A screen detected diagnosis is likely to bring forward the initiation of pharmacotherapy of both glucose lowering medication, as well as lower the threshold for medications related to other CVD risk factors.[14,117,118] Yet there is little knowledge of what medication profile of a screen-diagnosed population looks like, and how it changes after diagnosis.

1.3.7 Managing diabetes: evolution of best practice

Observational studies show that uncontrolled glycaemia is associated with a higher risk of CVD events[32], which is supported by the UKPDS and EDIC demonstrating the long term macro-vascular benefits of lowering glucose in populations with diabetes.[91,102] This suggests pharmacotherapy is a reliable way to improve both short and long term outcomes in diabetes.[109,123] The ACCORD trial indicated that the lowering agents themselves may lead to unwanted events, if treatment targets are set too low and aggressively sought in non-responsive individuals.[124–126] ACCORD, VADT and ADVANCE, were set in older populations with a greater proportion already diagnosed with CVD. As the populations were further along the diabetes disease trajectory, these studies should be seen in the context that lowering blood glucose, and intensive lowering to near-normal targets using pharmaceutical agents, will likely have different positive and negative effects on health depending on whether someone is newly diagnosed with near normal glyceamic control, or has long standing poor glyceamic control that has been resistant to lifestyle and even oral medication. Steno-2 has demonstrated the benefit of conservative HbA_{1C} targets, as part of a multifactorial treatment targeting all CVD risk factors. There is some evidence from a trial that suggests short term ($\sim$14 day) very intensive insulin therapy may improve β function[123], potentially modifying the natural history of the disease. Behaviour modification has the potential to aid in lowering HbA_{1C} and CVD risk factors, alleviating some of the pharmacotherapy burden. Unfortunately, evidence suggests that the role of current diabetes management education and health promotion initiatives is likely to be small.[85,127]

Steno-2 solidified evidence that intensively treating multiple risk factors, via a multifactorial intervention, lowers CVD event rates and all cause mortality in people with diabetes. Although there is concern about adverse events when aggressive glucose and blood pressure targets are set that attempt to mirror a population without diabetes[79,106], management of CVD risk factors in individuals with diabetes is recommended in clinical practice.[117,118,128]

This body of evidence has influenced the American Standards of Medical Care in Diabetes and British NICE guidelines[14,117,118], which promote the use of metformin as well as diet and lifestyle advice in those with diabetes. HbA_{1C} targets of less than $\sim 53\,\mathrm{mmol\,mol^{-1}}$ ($\sim$7%) are generally suggested, but ultimately targets are set following a dialogue with the individual. While the extent to which patient centred multifactorial care influences the application of clinical guideline recommendations in practice is unknown, best practice for routine care across both guidelines involves target based CVD risk factor management with consideration of potential individualised health behaviours and preferences that may represent either barriers or opportunities for change.

Diabetes treatment guidelines continue to evolve. Contrasting ADA guidelines from 2000[103] and 2014[14], it becomes apparent that there has been a shift towards increased promotion of opportunistic screening in older and overweight individuals, and suggested treatment targets for CVD risk factors have been expanded to account for individual diversity, in particular by acknowledging multiple chronic illnesses might be present.

1.3.8 Early detection of diabetes

The research outlined so far has been conducted in people with clinically diagnosed diabetes. Typically, these are individuals who present with symptoms of diabetes and are subsequently tested and diagnosed. Recently, attention has focused on the early detection and treatment of diabetes.[129,130]

When an individual's glyceamic control deteriorates to the point that they meet the clinical threshold for diagnosis, they will often either have no symptoms, or they may be unable to recognise them.[130] Yet diabetes can be detected before symptoms appear in a routine practice setting.[20,129,131] Awareness of the risk of diabetes has increased both among clinicians and the general public, meaning opportunistic testing and earlier diagnosis has become more common in the last few decades. It is difficult to say with certainty how many individuals have un-diagnosed diabetes in a contemporary setting, as awareness (which would decrease the undiagnosed burden) has increased alongside increasing prevalence of modifiable risk factors like obesity (which would increase the absolute undiagnosed burden). The ratio of undiagnosed to diagnosed diabetes is higher in less developed countries[48], and older estimates suggest that individuals often have diabetes for 4-7 years before diagnosis.[131] Contemporary English studies suggest around a quarter of the people with diabetes are undiagnosed.[132,133]

1.3.9 Screening for diabetes

> *"Medical science has made such tremendous progress that there is hardly a healthy human left."*
>
> —Aldous Huxley, *Door of Perception, 1946*

Previous studies have suggested a benefit of intensive treatment early in the disease trajectory.[91,102] However, it remains unclear if there is sufficient evidence for systematic screening for diabetes[134] outside of targeting at risk groups or through opportunistic screening.[128,135,136]

In 2001 Wareham *et al*[135] evaluated the UK National Screening Committee (NSC) criteria against the evidence for diabetes screening, which was then updated by Simmons *et al*[130] in 2010. The United States Preventive Services Task Force (USPSTF) also completed a review of the literature on screening in 2015.[137] Below I have summarised Wareham, Simmon and the USPSTF's findings in a list. References are present where I have included outside sources, not present in these three papers.

Important condition with a known natural history: Diabetes is an important condition that increases the risk of CVD events, early mortality and represents an economic and quality of life burden. The stages of the disease are well documented, and there is a measurable progression from healthy to poor glyceamic control.

Has a known latent period: In 1992, Harris *et al* estimated individuals reach the threshold for diabetes 4-7 years before a clinical diagnosis.[131] This estimate was derived from extrapolating back from the known prevalence of retinopathy at diagnosis, to estimate

when retinopathy is likely to of begun. In the Ely study, were individuals were recruited between 1990-1992, the lead time appeared to be around 3.3 years.[129]

Cost-effective primary preventions should be in place first: Efforts to lower population levels of obesity and improve diet and exercise like Change4Life[138] are in place, but of limited effectiveness and not at the intensity of effective strategies identified in studies.

There should be a simple, safe and precise screening test: Diagnostic labels in diabetes are derived from the relationship between glyceamic control and future risk of microvascular complications. Whether individuals meet this criteria is measurable in general practice and separated sufficiently from those with 'healthy' blood glucose control. Individuals at risk can by identified by risk scores and capillary testing, and diabetes can be diagnosed in the general practice by taking venous samples. The introduction of diagnosis based on HbA_{1C} means a non-fasting sample, which minimises disruption to the individual being screened.

There should be an effective treatment: While the UKPDS demonstrated a benefit of tight glyceamic control, diagnosis of diabetes will also lead to tighter management of total cardio-vascular health, the long-term effects of which are promising.[3]

There should be RCTs of the effectiveness in lowering mortality or morbidity: While not published in 2010 when the criteria were last assessed, Simmons *et al* later found no association between cardiovascular or diabetes related mortality 10-years after one round of screening in high-risk individuals.[134]

The benefits of screening should out weigh the harm: The ADDITION-*Europe* trial suggests that the there is limited negative impact of diabetes on HRQoL, although it is unclear whether the label of early diagnosed diabetes is beneficial over just lowering CVD risk factors in those at risk of undiagnosed diabetes.

Screening should be cost-effective: While there is limited evidence of diabetes screening being cost-effective as an individual program, individuals at risk of diabetes are also at risk of CVD, and any programme is likely to span both conditions.

It should not put too much burden on staff and facilities: Modelling studies suggest that screening could result in savings to the NHS[139], and while these direct health service estimates are full of uncertainty in areas as simple as the cost of an HbA_{1C} test (it varies by time and place), quantifying the difference in indirect economic and societal burden is even more difficult. An important aspect is that a screening programme is not just a measurement, as the purpose of screening must be explained, individuals with a positive result will receive treatment, and individuals with a negative result are still likely to be at risk of future diabetes and CVD. A screening programme would likely need to take advantage of a range of providers and settings beyond just the GP consultation to prevent overburdening primary care consultations.

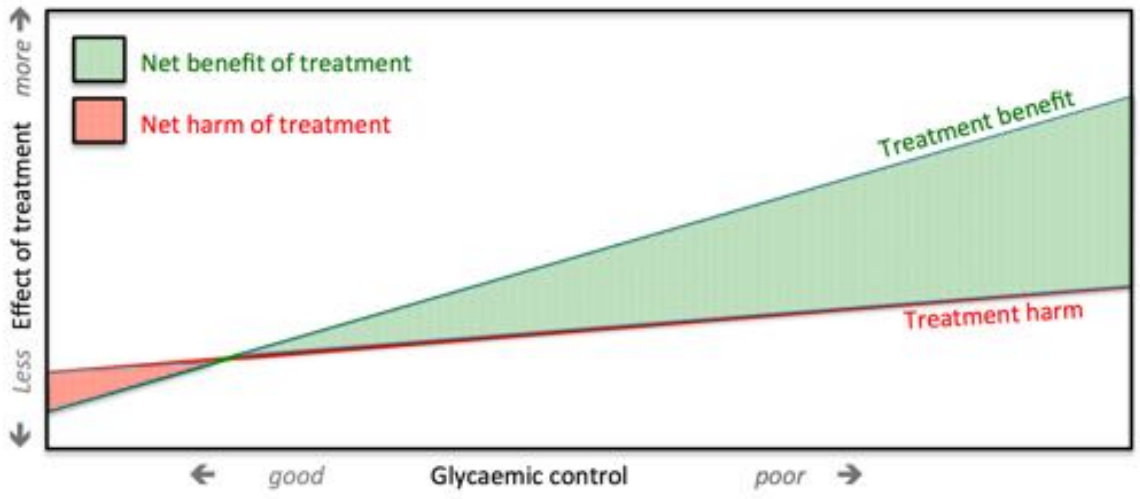


Figure 1.9: Hypothetical balance between treatment benefit and harm

The likely high proportion of undiagnosed cases of diabetes, the significant number of patients with complications at clinical diagnosis, the high potentially modifiable CVD risk at diagnosis[140], and the long latent phase of the condition[129,131] provides some evidence for screening and early treatment, particularly in older individuals or those already at risk of CVD.[130,136,141,142] While screening for diabetes does not meet the NSC criteria outright, many nations have introduced screening programmes for diabetes amongst a package of cardiovascular risk reduction, including the NHS in England, which tests for risk of diabetes within it's Health Checks programme.[128,143,144] This will lead to a greater number of individuals being diagnosed earlier.

There is little evidence to inform the treatment of these individuals. Results from the UKPDS[102], and a sub-group of analysis of the VADT[108], suggest a benefit from intensive treatment of glucose in those with shorter diabetes duration. However, there are a number of outstanding uncertainties that need to be resolved before intensive multifactorial treatment can be recommended in this group.[106]

Figure 1.9 shows a hypothetical balance between treatment harm and benefit. Individuals with poor glyceamic control, who would be to the right in Figure 1.9, are likely to experience large decreases in blood glucose and CVD risk factors after diagnosis (under the assumption high blood glucose and poor cardiometabolic health are clustered). While the treatments employed to achieve that change may come with a burden, it is outweighed by the improvements in quality of life from the intended purpose of the pharmacotherapy. In individuals with 'lower' blood glucose at diagnosis, who would be more to the left of Figure 1.9, they are likely to have smaller attainable improvements in glyceamic control and CVD risk factors as they aim to stay within targets. Even if the relative risk ratios for CVD stay constant in those with better cardio-metabolic health, their lower absolute risks may mean they reach the point where the burden of treatment may outweigh the risk. This is particularly relevant in the unexplored screen-detected population, where individuals are more likely to have no symptoms, and the assumed benefits of early detection may be a decade or more in the future.

1.4 Aims

My thesis will examine the treatment of type 2 diabetes early in the disease trajectory, with a particular focus on the benefits and harms of intensive glucose lowering. Using data from a unique cohort of individuals with screen-detected diabetes (ADDITION-*Europe*), I aim to address the following research questions:

- What is medication burden of a screen-detected diabetes population, and how does it change after diagnosis (Chapter 3)?
- Are there distinct groupings of HbA_{1C} trajectories following diagnosis (Chapter 4)?
- How do CVD risk factors change after early diagnosis (Chapter 5)?
- What are the potential long term benefits of intensive treatment in a screen-detected diabetes population (Chapter 6)?
- Are changes in CVD medication associated with incident CVD (Chapter 7)?
- Is intensification of medication associated with changes in HRQoL (Chapter 8)?

Chapter 2

Key data sources

2.1 ADDITION-Europe

In the following section I will present information on the ADDITION-*Europe* trial. I varied between analysing this trial as a complete trial, and by centre, depending on the availability of data to answer each research question.

2.1.0.1 Summary

The ADDITION-*Europe* study was a cluster RCT comparing intensive multifactorial treatment with routine care among people with screen-detected diabetes in primary care. The primary endpoint (composite CVD event) at five years was available for 99.9% ($\frac{3055}{3057}$) of the screen-detected participants. After a median follow up of 5.9 years, there were significant improvements in CVD risk factors (HbA_{1C}, cholesterol and blood pressure) in both groups. The incidence of first cardiovascular event was 7.2% (135 per 1000 person-years) in the intensive treatment group and 8.5% (159 per 1000 person-years) in the routine care group. A small non-significant reduction in both CVD events (HR 0.83, 95% CI 0.651.05) and all-cause mortality (HR 0.91; 0.69, 1.21) was observed.[145]

2.1.0.2 ADDITION-Europe aims

The aims of ADDITION-*Europe* were to evaluate the feasibility of screening for undiagnosed diabetes, and whether pragmatic multifactorial treatment of hyperglyceamia and CVD risk factors from diagnosis was cost-effective.[146]

2.1.0.3 Methods used in ADDITION-Europe

The ADDITION-*Europe* trial protocol[146] and primary outcome paper[145] have been published (Clinical Trials.Gov registration `NCT00237549`). ADDITION-*Europe* was a primary-care based study of screening for type 2 diabetes followed by a pragmatic cluster RCT comparing intensive multifactorial treatment with routine care in four centres (Cambridge, UK; Denmark; Leicester, UK; the Netherlands; Figure 2.1). Of 1312 general practices invited to

Figure 2.1: Map showing the location of ADDITION-*Europe* centres and the collaborating institutes within each centre.

participate, 379 (29%) agreed and 343 (26%) were independently randomised to screening plus routine care of diabetes or screening followed by intensive multifactorial treatment. Between April 2001 and December 2006, practices undertook stepwise screening of patients. Within ADDITION-*Europe*, median prevalence of known diabetes was 3.5% (excluding Denmark, where it was unknown). Screening and treatment protocols differed by centre (Table 2.1). Specific explanations of centre level variation from the ADDITION-*Europe* methods is given in Table 2.1 and in later sections for for the Danish (Section 2.1.3), UK (Cambridge & Leicester, Section 2.1.2) and Cambridge studies (Section 2.1.1). Due to an increase in missing data for smoking status, in all primary analyses smoking status at baseline was carried forward if missing at follow up.

2.1.0.4 Screening in ADDITION-Europe

In all centres, except Leicester, risk stratification was completed using locally relevant diabetes risk questionnaires (Table 2.1).

2.1.0.5 Exclusion criteria

Individuals were not invited for screening if they were pregnant or lactating, housebound, terminally ill with a prognosis of less than twelve months, or had a psychiatric illness likely to invalidate consent. Individuals were diagnosed with diabetes according to WHO criteria.[18] Of the 3233 patients identified with diabetes by screening, 3057 (95%) consented to participate in the trial. The study was approved by local ethics committees in each centre. All participants provided written informed consent.

Table 2.1: Characteristics of screening and intervention design by centre, reproduced from *Griffin et al(2011)Lancet,378:156-67*[145]

Centre	Screening program	Intensive care protocol
Cambridge	Electronic medical records of patients aged 40-69 years were used to calculate the Cambridge diabetes risk score[147] for each individual. Individuals with a score $\geq$0.17 (those in the top 25% of the risk distribution) were invited to a stepwise screening programme, including capillary random blood glucose, fasting blood glucose and HbA_{1C} tests.	Practice-based educational meetings held with family physicians and nurses to discuss treatment targets, algorithms, and lifestyle advice. Audit and feedback via follow-up practice-based meetings up to twice per year Practice staff provided with educational materials for patients. Small financial incentives given to family physicians equivalent of three 10 min consultations with a family physician and three 15 min consultations wit a nurse, per patient, per year, for 3 years.
Leicester	All patients aged 40-69 years were invited to undergo an oral glucose tolerance test.	Patients referred to structured education programme. Follow up every 2 months in the first year offered, and every four months after. Clinic staff chased up missed appointments, and financial incentives given for participating equivalent of three 10 min consultations with a family physician and three 15 min consultations wit a nurse, per patient, per year, for 3 years.
Denmark	All patients aged 40-69 years were either sent or opportunistically asked to complete a questionnaire containing the Danish Diabetes Risk Score.[148] Patients with a score $\geq$5 were then invited for stepwise diabetes screening.	Practice based meetings to discuss treatment targets. Follow up and feedback up to twice a year. Educational materials provided to patients. Financial incentives given to practices for participating equivalent of three 10 min consultations with a family physician and three 15 min consultations wit a nurse, per patient, per year, for 3 years.
Netherlands	Participants aged 60-69 years were sent the symptom risk questionnaire from the Hoorn study.[149] Individuals that scored $\geq$4 (in the 41 practices near the study centre) or $\geq$6 (38 practices further away from the study centre) were invited to attend their practice for a diabetes screening assessment.	Practice based meetings to discuss treatment targets. Follow up and feedback up to twice a year. Patient sent reminders if overdue for assessment. Financial incentives given to practices for participating equivalent of three 10 min consultations with a family physician and three 15 min consultations wit a nurse, per patient, per year, for 3 years.

2.1.0.6 Treatment allocation

Practices were randomised to provide routine care or intensive multifactorial treatment in a 1:1 ratio. Statisticians in each centre, independent of measurement teams, conducted randomisation. In Cambridge, randomisation included minimisation for local hospital and the number of patients per practice with diabetes. In Leicester, minimisation included deprivation status and prevalence of diabetes. In Denmark, randomisation included stratification by county and number of full time family physicians. In the Netherlands, practices were stratified before randomisation by solo or group practice.

All eligible patients identified as having diabetes in the screening phase were managed according to the treatment group to which their practice was allocated to. In the routine care group, family physicians continued to provide conventional care, which was governed by national best practice guidelines in all centres. In the intensive treatment group, routine care was supplemented by the addition of several features (Table 2.1). This included financial support to facilitate increased frequency of contact between the patient and practitioner as well as dietician referrals for all participants. A minimum of three practice based, in person, meetings to set and monitor targets were delivered by local experts.

2.1.0.7 Intensive care treatment regime

A treatment protocol, based on the stepwise regime of the Steno-2 study[112], aimed to use personal targets to manage blood glucose, blood pressure and lipid levels. The treatment targets were based on previous trial data, and were reviewed and updated three times during follow up. Broadly, within the intensive treatment group, diet advice was given if HbA_{1C} levels were $>48\,\mathrm{mmol\,mol^{-1}}$ (>6.5%), and a target of $<53\,\mathrm{mmol\,mol^{-1}}$ (<7.0%) was sought. Treatment aimed to lower blood pressure below $\frac{135}{85}$ mmHg. If CVD was present and blood pressure was $\geq \frac{120}{80}$ mmHg, ACE inhibitors titrated to maximum dose were prescribed. A target of $<5.0\,\mathrm{mmol\,l^{-1}}$ total cholesterol was set in those free of ischemic heart disease, and $<4.5\,\mathrm{mmol\,l^{-1}}$ in individuals with ischemic heart disease. After the HPS demonstrated the proportional risk reduction from statin therapy in diabetes was present in those without high cholesterol[74], the algorithm was amended to recommend statin therapy in all individuals in the intensive treatment group with total cholesterol $>3.5\,\mathrm{mmol\,l^{-1}}$. All individuals on blood pressure lowering medication and without specific contraindications were recommended to be on daily aspirin (75-80 mg). Subsequent changes at each review were made according to a defined protocol, but the ultimate decision on whether to prescribe remained with the GP.

2.1.0.8 Data collection

Clinical measures were collected at diagnosis, one and five years. Outcomes were collected using standard operating procedures, or collected directly from practice records. All staff collecting data were unaware of treatment allocations. The primary outcome was a composite CVD endpoint of cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, revascularisation or non-traumatic amputation. Events were independently adjudicated.

The trial was originally powered to detect a 30% reduction in the primary outcome at 5% significance and with 90% power at five years. Across centres, deprivation was available as employment status and age left full-time education.

2.1.0.9 Assessment of medication

Medication use in the main trial analysis was from self-report using a standardised questionnaire. It was then coded into Anatomical Therapeutic Chemical Classification[11] (ATC) codes by staff unaware of group allocation. ATC codes where then grouped into the following thirteen classes: metformin, sulphonylurea, thiazolidinedione, insulin, any other glucose lowering medication, ACE inhibitor, β blocker, calcium channel blocker, diuretic, other blood pressure lowering medication, statin, other lipid lowering medication, low dose aspirin. These thirteen classes were then further collapsed into two types of summary variables for three classes of medication: glucose lowering, blood pressure lowering and lipid lowering medication. One type was a binary 'at least one' of that class, while the other type of summary variable derived was a count of how many types of that one class an individual was on (e.g., an individual on metformin and a sulphonylurea would be coded as 'on' for the binary variable of 'on glucose lowering medication', but would have a value of two for the count of glucose lowering medications). Both these summary categories and the thirteen classes are then reported.

2.1.1 ADDITION-Cambridge

In the Cambridge centre of ADDITION-*Europe* (ADDITION-*Cambridge*) electronic medical records of patients aged 40-69 years were used to calculate each individual's Cambridge diabetes risk score.[147] If their score was ≥ 0.17 they were invited by mail to attend an initial random capillary glucose test as part of a stepwise screening programme including capillary random blood glucose, fasting blood glucose and confirmatory OGTT. ADDITION-*Cambridge* was the only centre in ADDITION-*Europe* to also include a control arm of practices that did not screen for diabetes. The screening procedure in ADDITION-*Cambridge* has been published in detail[150], allowing for insight into how the number of individuals identified at risk and invited for screening translated into the number diagnosed. Figure 2.2 shows that of the 35,297 individuals invited for screening, 2.5% were identified with undiagnosed diabetes. As 25% of individuals with elevated risk of diabetes did not attend screening, and 5% were deemed unfit for screening by their GP, the true number of undiagnosed diabetes is likely higher.

The Cambridge arm received ethics approval from the Eastern Multi-Centre Research Ethics Committee (ref:02/5/54)[150] and all participants provided written informed consent.

867 individuals received care from their practice, where GPs and/or nurses discussed treatment options, set targets and discussed positive lifestyle changes. Progress was audited and feedback given via follow-up practice-based meetings up to twice per year. GPs recieved payment for up to nine 10 minute consultations with a GP, and nine 15 minute consultations with a nurse, in the first three years after diagnosis.

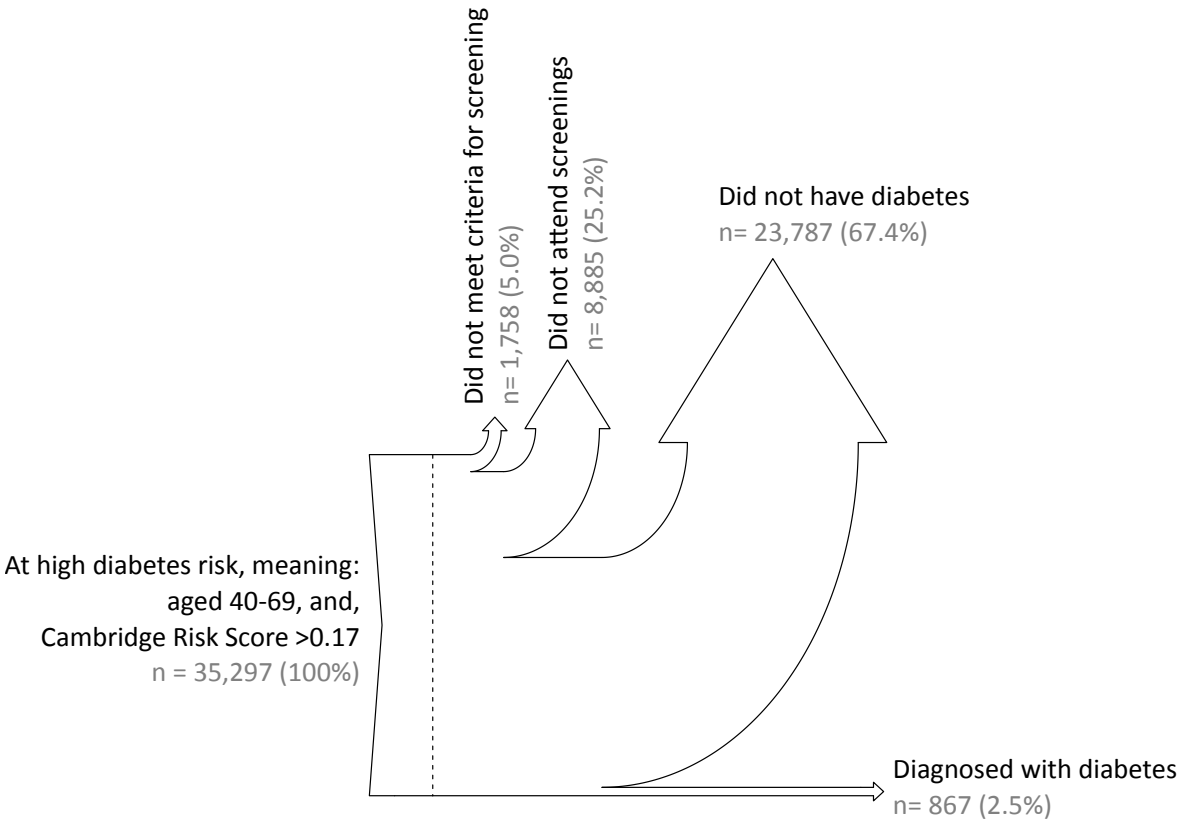


Figure 2.2: Sankey plot showing the flow of individuals from those identified at risk of diabetes, through to those diagnosed, within ADDITION-*Cambridge*. Width of arrows is to scale. Figure created in *R* from numbers present in the following paper: *Echouffo-Tcheugui et al(2009)BMC Public Health,9:136*

2.1.1.1 Assessment of medication

Within ADDITION-*Cambridge*, only the self-reported medication measure used in ADDITION-*Europe* was available (see Section 2.1.0.9, page 29).

2.1.2 ADDITION-UK

Differences between the Cambridge and Leicester centres of ADDITION-*Europe* (ADDITION-*UK*) are discussed here, as ADDITION-*Cambridge* was discussed in Section 2.1.1. Unlike the stepwise screening programme in Cambridge (Section 2.1.1), in Leicester all individuals aged 40-69 years, were invited directly to an initial diagnostic OGTT. Following diagnosis, patients were referred to the Diabetes Education and Self Management for Ongoing and Newly Diagnosed programme (DESMOND) structured education programme[151] in a peripatetic rather than general practice setting. Patients in the intensive treatment arm were offered appointments with a diabetes nurse or GP, at a peripatetic clinic, for every two months in the first year, and every four months thereafter. Staff were also prompted to follow up with patients that missed appointments.

The Leicester centre recruited 20 general practices, and contained less participants than Cambridge (159 vs 867). The mean practice Index of multiple deprivation (IMD) for the

Leicester centre matched the national reference quintiles for deprivation in an urban UK population[152], while the median IMD in the Cambridge centre was close to that of the wider Cambridgeshire region. Individual level IMD scores were not available for the Leicester centre. The Leicester centre also had greater ethnic diversity, with 40% of the newly diagnosed non-white, compared to 3.5% in Cambridge, and 5.7% across all of ADDITION-*Europe*.

2.1.2.1 Assessment of medication

Data for ADDITION-*UK* came from merging the individual centre datasets, rather than the official ADDITION-*Europe* data release. As such, within the Leicester arm, medication was available from a database of prescribed medications that was used within DESMOND, which is assumed to be a complete record of prescribed medication. Medication from the Cambridge arm remained the self-report data available across ADDITION-*Europe*. Both the self-report and database derived medication were coded into medication counts in an analogous procedure.

2.1.3 ADDITION-Denmark

In the Danish centre of ADDITION-*Europe* (ADDITION-*Denmark*), individuals aged 40-69 years were sent letters that included questions from the Danish Diabetes Risk Score Questionnaire.[148] Participants completed the risk score themselves, and if they calculated a score ≥ 5 (representing high risk) they were advised to contact their GP to arrange an appointment for diagnostic testing. Opportunistic screening was also completed by asking eligible patients attending their general practice to complete the risk score questionnaire before their consultation, and those with scores ≥ 5 underwent further testing. Self-report questionnaires were used to collect information on socio-demographic information and lifestyle habits. The study was approved by the Committee on Biomedical Research Ethics and the Danish Data Protection Agency and all participants provided written informed consent.

1,385 individuals with screen-detected diabetes were recruited in ADDITION-*Denmark*. More individuals with undiagnosed diabetes were found in the intensive treatment arm (910 vs 623), and the prevalence of previous CVD at diagnosis was higher (8.8% vs. 5.6%). This suggests that practices in the intensive treatment arm may have been more likely to offer opportunistic screening to people with poor cardio-metabolic health.

2.1.3.1 Frequent measurement of HbA_{1C}

In ADDITION-*Denmark* GPs collected HbA_{1C} measurements every three months in the first year, and every six months thereafter. These values were able to be be accessed by both the lab, and those collected from the case report forms used in the trial. The lab records were taken as the preferred source of HbA_{1C}, but as they were not complete case report forms were used as well. The discrepancy between the two sources was small and while I was unable to find the reason a small proportion of the lab records were not in the registry, but present in

the case report forms, contact with collaborators in Denmark and the low number led to the conclusion that this would have no effect on any conclusions drawn from the data.

2.1.3.2 Assessment of medication

Redeemed prescriptions were collected via linkage to the Danish National Prescription Registry, which has complete coverage of all redeemed prescriptions in Denmark since 1994.[153] For each individual medication was available from at least one year before diagnosis till approximately eight years after diagnosis. Full data on the redeemed ATC coded medication was available. As my analysis plan was restricted to medications related to diabetes and CVD I first broke down medication into the same coding scheme used in ADDITION-*Europe* (Section 2.1.0.9, page 29). Each ATC code also had the redemption date, but no information on dose. To calculate a measure of whether individuals were on medication I constructed a matrix for each individual that had 365 days before diagnosis until 2000 days after diagnosis on the x axis, and each of the ADDITION-*Europe* medication classes on the y axis. Then, at a daily resolution, I calculated whether an individual had redeemed a medication from that class in the last 90 days. These matrices were used in Chapter 3 and Chapter 4 were I present medication use specific to ADDITION-*Denmark*.

As I did not have dose and quantity of medications redeemed, I made the assumption that each prescription would last for a maximum period of 90 days. While an algorithm exists for assessing medication use based on prescription histories, it requires information on both the dose and medication redeemed.[154]

2.2 UKPDS CVD risk engine

I used ten-year modelled CVD risk, calculated from the UKPDS model (version 3 β)[155], in several analyses within this thesis (Sections 5.2 and 6.2). This is a diabetes-specific risk assessment tool that estimates the absolute risk of fatal or non-fatal CVD within a defined time frame up to 20 years.

The variables used in the model include age, gender, ethnicity, smoking status, HbA_{1C}, systolic blood pressure, total:HDL cholesterol ratio, Atrial Fibrillation (AF), previous myocardial infarction or stroke, microalbuminuria (Albumin Creatinine Ratio (ACR) $\geq 2.5\,\mathrm{mg\,mmol^{-1}}$ in men, or $\geq 3.5\,\mathrm{mg\,mmol^{-1}}$ in women), macroalbuminuria (ACR $\geq 30\,\mathrm{mg\,mmol^{-1}}$), duration of diagnosed diabetes & BMI (Figure 2.3). AF can be omitted from the UKPDS model. As AF was not available in ADDITION-*Europe* it was not used in Sections 5.2 and 6.2. Due to a large amount of missing data in one centre of ADDITION-*Europe* (29%), smoking status at follow up was carried forward for all primary analyses.

Derived from over 40,000 patient-years of data and 1,115 CVD events[155], the latest refinement of the UKPDS risk score is the most appropriate tool for predicting ten-year modelled CVD risk in a UK population with diabetes.[156,157] To date, only the UKPDS stroke[158] and CHD[159] modelled risk engines have been published in full. This is the primary reason why no external evaluations of the CVD engine have been completed. The UKPDS CHD engine

has been shown to overestimate both CHD and CVD risk in populations with established diabetes[156]. In a contemporary population with screen-detected diabetes, who are likely to have their CVD risk managed to a tighter degree both before and after diagnosis, this overestimation will likely be higher.

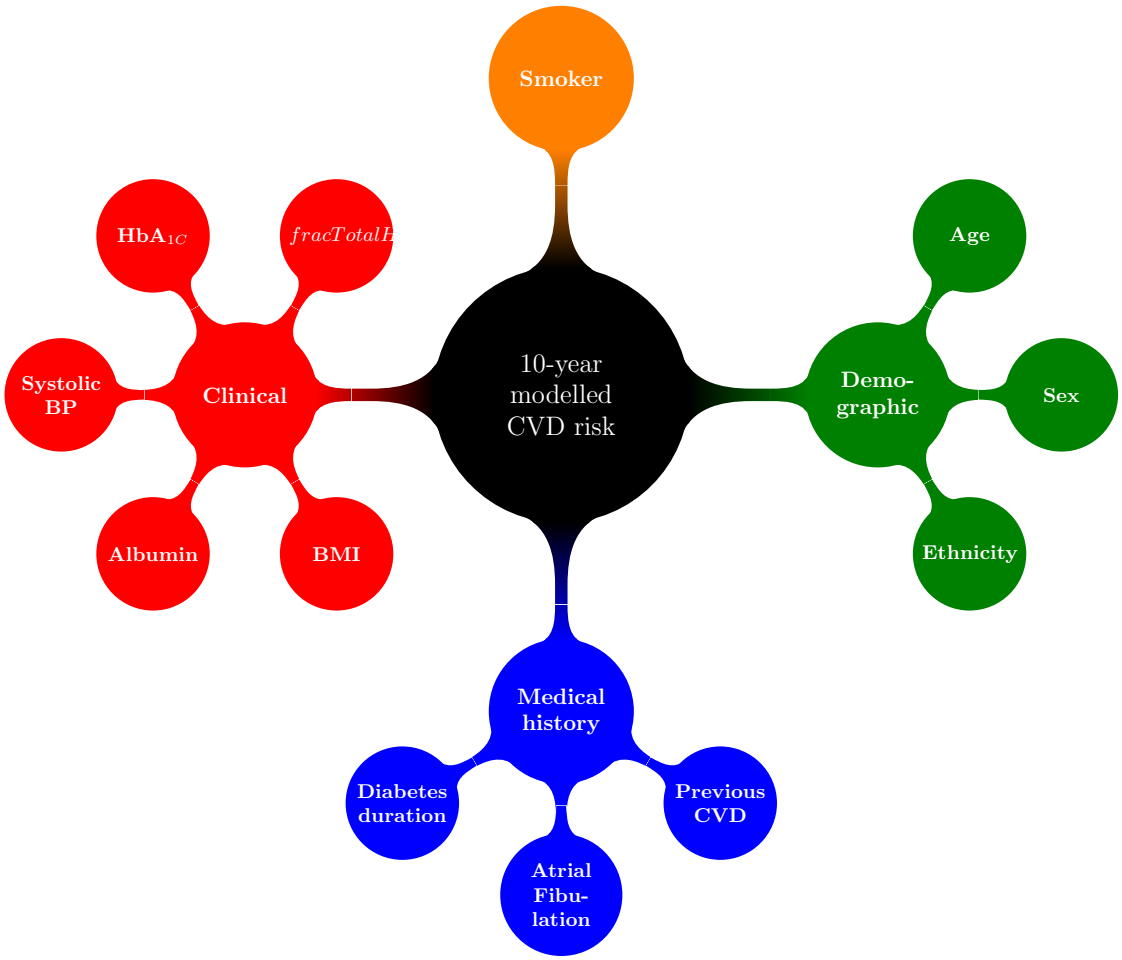


Figure 2.3: Variables used by the UKPDS (version 3 β) CVD risk score organised in demographic, clinical, medical history and health behaviour (smoking status) domains. Created using the Tikzpicture package in LaTeX.

Chapter 3

Medication burden in the first five years following diagnosis of type 2 diabetes

3.1 Introduction and aims

Medication burden is high among individuals with established type 2 diabetes.[115,116] I will restrict the term medication burden in this chapter to define the quantity of pharmacotherapies applied, and in later chapters I will discuss how this medication burden influences both cardiometabolic health (Chapters 6 and 7) and quality of life (Chapter 8).

Results from a systematic review indicate that diabetes patients take in the range of four to ten medications a day.[119] In an American study of 875 individuals with diabetes, 50% reported taking seven or more prescription medications a day.[120] Estimates from English patients with diabetes suggest an average of six medications a day[121], while in one Scottish study 6% of the population with type 2 diabetes were taking more than 4 pills a day from oral glucose lowering medication alone.[122] Individuals with diabetes are prescribed a number of cardio-protective drugs, but there is also evidence to suggest high levels of prescription of other drug classes for treatment of neuropathy[160], depression[161], gastric and rheumatologic complaints.[162] In 2012-13 in England, 9.3% of the total cost of prescriptions in the NHS was related to diabetes.[163] As treatment regimens become more complex, patients are more likely to experience adverse side-effects[164] and less likely to remain adherent to all prescribed medications.[122,165]

The pharmacological treatment burden among individuals with screen-detected or recently diagnosed diabetes is unknown. Given that population screening for diabetes has been recommended by several national organisations and the NHS currently includes assessment of risk of diabetes in its Health Checks programme[144], more individuals will be found earlier in the disease trajectory. Further, there is growing evidence for the benefit of intensive treatment of risk factors early in the course of the disease[102,145], which suggests that screen-detected patients may be prescribed a larger number of cardio-protective drugs earlier than

they might previously have been. Although there is some evidence that improved medication adherence may improve health-related quality of life in symptomatic diabetic patients[166,167], individuals earlier in the disease trajectory are unlikely to have symptoms and may be less likely to adhere to complex medication regimes.[168,169] Guidelines promote a multifactorial approach to diabetes care from diagnosis that includes pharmacotherapy for multiple CVD related conditions.[117,170] Despite the increasing number of individuals with screen-detected diabetes, many of whom have comorbidities, there is an absence of knowledge about what the pharmacotherapy burden is at diagnosis in this population, and how it changes in the first five years. It is important that this is described so that patients and practitioners are informed about the likely course and burden of treatment.

3.1.1 Aims

I aimed to (i) describe medication burden at diagnosis, one and five-years in individuals with screen-detected diabetes using available data from ADDITION-*Europe*, ADDITION-*Denmark* and ADDITION-*UK* and (ii), using data from ADDITION-*UK*, examine in detail if age, sex, intensive treatment, or modelled 10-year CVD risk was associated with the change in the number of medications that individuals were prescribed in the five years after diagnosis.

3.2 Methods

In this analysis I use data from ADDITION-*Europe*, ADDITION-*Denmark* & ADDITION-*UK*. Each study has been described in detail; ADDITION-*Europe* in Section 2.1.0.3, on page 25; ADDITION-*Denmark* in Section 2.1.3, on page 31 and ADDITION-*UK* in Section 2.1.2, on page 30. Methods specific to this analysis are described below.

Three combinations of the ADDITION-*Europe* trial sample have been used in this analysis to enable me to describe changes in medication after diagnosis with the most efficient use of the data.

1. **Change in cardio-protective medication** Within the main trial analysis of ADDITION-*Europe*, cardio-protective medication was derived from ATC codes at diagnosis and five years. This meant that data from all four ADDITION-*Europe* centres could be used when discussing changes in cardio-protective medication after diagnosis. Medication at the ADDITION-*Europe* level was self-reported, as detailed in Section 2.1.0.9 on page 29.

2. **Daily estimates of cardio-protective medication** In ADDITION-*Denmark* the ATC code and date of redemption was available for every prescribed medication, meaning a daily picture of cardio-protective medication use in the year before, and five years after, diagnosis could be explored. How I coded the registry data from ADDITION-*Denmark* is detailed in Section 2.1.3.2 on page 32.

3. **Total medication burden** Within ADDITION-*UK*, raw ATC codes were available at diagnosis, one and five years. This allowed a detailed breakdown of prescription

patterns including non cardioprotective medication. Raw ATC codes were coded from self-reported medication in Cambridge, and peripatetic database records in Leicester.

To reflect the differing samples used to describe medication after diabetes diagnosis, the methods and results are nested within each of the three categories listed above.

3.2.1 Change in cardio-protective medication in ADDITION-Europe

At diagnosis and five years self-reported ATC coded medication were used to determine if an individual reported any anti-hypertensive, any diabetes medication or any lipid lowering medication. The proportion taking each combination of the three drugs at diagnosis and five years is reported. Change in medication after diagnosis was also stratified by baseline quartiles of 10-year UKPDS modelled CVD risk (see Section 2.2 on page 32), and presented at diagnosis and five years, to reflect treatment targets being set in the context of cardio-metabolic health at diagnosis.

3.2.2 Daily estimates of cardio-protective medication for ADDITION-Denmark

Redeemed prescriptions were collected via linkage to the Danish National Prescription Registry, which has complete coverage of all redeemed prescriptions in Denmark since 1994.[153] In order to estimate the proportion of individuals on any anti-hypertensive, any diabetes medication, any lipid lowering medication or aspirin day to day for every day one year before diagnosis, and 2000 days after, I coded each individual as being on that medication if they had redeemed a prescription in the last 90 days. While I had access to complete medication histories of participants, my analysis plan was restricted to presenting only medications related to diabetes, which is why only information on cardio-protective medication was extracted from the ATC codes. The proportion estimated to be taking each group of cardio-protective medication on a daily basis from one year before to five years after diagnosis is graphically presented. The full methodology on how I coded medication use in ADDITION-*Denmark* is given in Section 2.1.3.2 (page 32).

3.2.3 Total medication burden in ADDITION-UK

3.2.3.1 Assessment of complete medication use

Participants were encouraged to bring their repeat prescription summaries to each health assessment. In Cambridge, self-reported medication, collected via a health economics questionnaire which records information on all prescribed medication was completed by the participants using the prescription summaries as a reference where possible.[171] A database of prescribed medications from the peripatetic clinics was available in Leicester. ATC codes were used to derive counts for each participant within the following 23 classes of medication: insulin, metformin, sulphonylurea, thiazolidinediones, other glucose lowering medication, ace-inhibitors, β blockers, calcium channel blockers, diuretics, other blood pressure lowering medications, lipid lowering, antithrombotic, gastrointestinal related, skin related, hormone

Table 3.1: ATC medications coded as *'other diabetes'*

General class	Specific medication
Alpha-glucosidase inhibitors	Acarbose
	Migilitol
	Voglibose
Guar gum	
GLP-1 agonists	Exenatide
	Liraglutide
	Lixisenatide
Meglitinides	Repaglinide
	Mitiglinide
	Nateglinide
SGLT-2 inhibitors	Dapagliflozon
	Empagliflozin
	Canagliflozin
Benflourex[†]	
Pramlintide	

[†] European Medicines Agency called for withdrawal across the European Union in 2009.

replacement therapy or urogenital, systemic steroids, thyroid related, anti-inflammatory, analgesic, anti-epileptic, psychiatric, respiratory and eye related. Medication counts in this analysis refer to the number of the 23 classes prescribed (not overall pill count), while medication agent refers to one of the 23 explored classes of medication. For several analyses, these 23 categories were also collapsed into diabetes-related (insulin, metformin, sulphonylurea, thiazolidinediones, other glucose lowering medication), cardio-protective (ace-inhibitors, β blockers, calcium channel blockers, diuretics, other hypertension-related medications, lipid lowering, antithrombotic) and other (the remaining 11 non-CVD or diabetes categories). The medications listed as '*other diabetes medication*' are given in Table 3.1. Medication types that were not within these categories, for example acute medications like antibiotics, were not included in these analyses.

3.2.3.2 Co-morbidity at diagnosis

Individuals at diagnosis were asked if they have been told by their GP that they have high blood pressure, high cholesterol, or had experienced a myocardial infarction or stroke. These values are presented as raw counts and proportions as an indicator of cardio-metabolic health of the sample at the time of detection by screening.

3.2.3.3 Statistical analysis

As the primary analysis concerned the total medication burden in ADDITION-*UK*, baseline and five year descriptive characteristics of the cohort were summarised in detail for ADDITION-*UK* using means, medians and proportions. As pre-existing cardiovascular disease would imply prior knowledge and treatment of elevated CVD risk factors, the proportion reporting being told that they had high blood pressure or high cholesterol, or had experienced a previous CVD event is presented. I described the medication profile of the ADDITION-

UK cohort at diagnosis and one and five years following diagnosis. Using complete case linear regression, I explored the mutually adjusted associations between age, baseline 10-year UKPDS CVD risk, sex, treatment group, baseline number of medications on (i) change in total number of medications, (ii) change in cardio-protective medications and (iii) change in other medications between diagnosis and five years. Change in diabetes-related medications from diagnosis to five years was not normally distributed (; distribution of change in diabetes medication from one to five years, ranging from no change to four additional medications), and instead was distributed in a manner common to count data. To enable an appropriate model to be fit, an analogous Poisson regression model was used to explore the association between baseline predictors and change in diabetes-related medication over five years. Standard errors were adjusted for clustering by the patients general practice in the models.

In order to characterise missing data, I used logistic regression models to derive the odds of being included in the complete-case analysis, individually adjusted for age, sex, baseline 10-year UKPDS CVD risk, treatment group and 2004 IMD. IMD scores were only available for the 867 individuals (86% of the sample) from the Cambridge centre, so the association between missing data and socio-economic status is described using a smaller dataset for this sensitivity analysis.

3.2.3.4 Pooling treatment arms

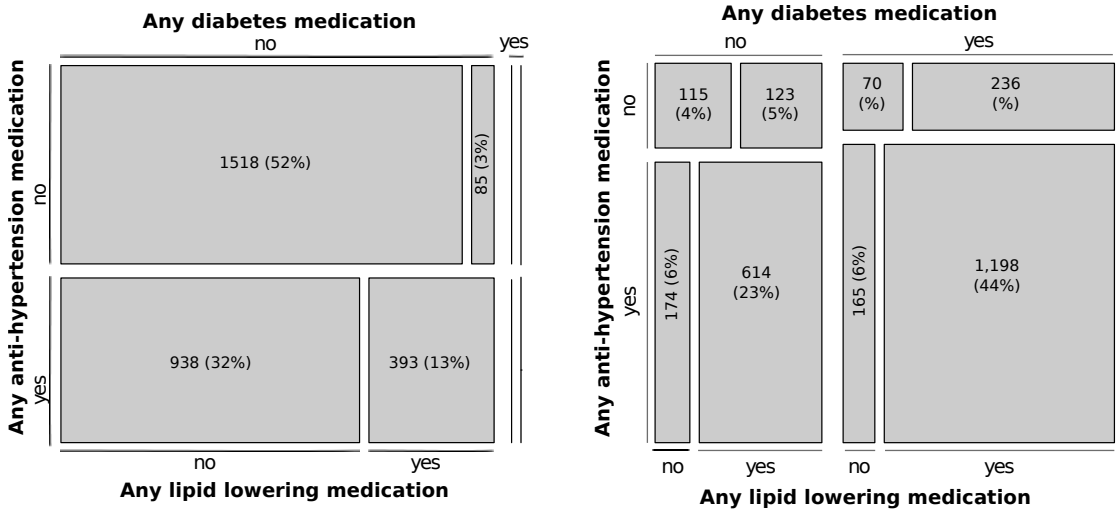
Small differences in both the outcome and treatment between routine care and intensive treatment in ADDITION-*Europe* have been previously reported.[145] The absolute difference between treatment arms was small, which is likely linked to the continual improvement of routine care, most likely accelerated through the introduction of the Diabetes National Service Framework in 2001[172], clinical guidelines for targeting blood pressure and lipids in people with diabetes in 2002[170], and the Quality and Outcomes Framework in 2004.[145,172] Current guidelines for the treatment of type 2 diabetes are similar to the protocol used in the intensive treatment arm of ADDITION-*UK*.[118,145] As such, treatment arms are pooled in the main analysis and the difference between arms is presented as a sensitivity analysis.

3.3 Results

3.3.1 Change in cardio-protective medication

Figure 3.1a shows that at diagnosis many participants in ADDITION-*Europe* reported taking blood pressure lowering (32%) or blood pressure and lipid lowering medication (13%). At diagnosis, 52% of individuals were on no glucose, lipid or blood pressure lowering. Five years later 4% of the sample were on no glucose, blood pressure or lipid lowering medication, and 44% were on all three types of medication (Figure 3.1b).

Figure 3.2 gives an indication of proportions of ADDITION-*Europe* participants prescribed each cardio-metabolic drug stratifying by baseline cardio-metabolic health. While



(a) At diagnosis (n=2,949)

(b) 5 years after diagnosis (n=2,695)

Figure 3.1: Visual representation of the relative number of participants prescribed diabetes, blood pressure and lipid controlling drug types in ADDITION-*Europe* at baseline and diagnosis. Size of box represents proportion. 15 individuals reported taking diabetes medication at diagnosis.

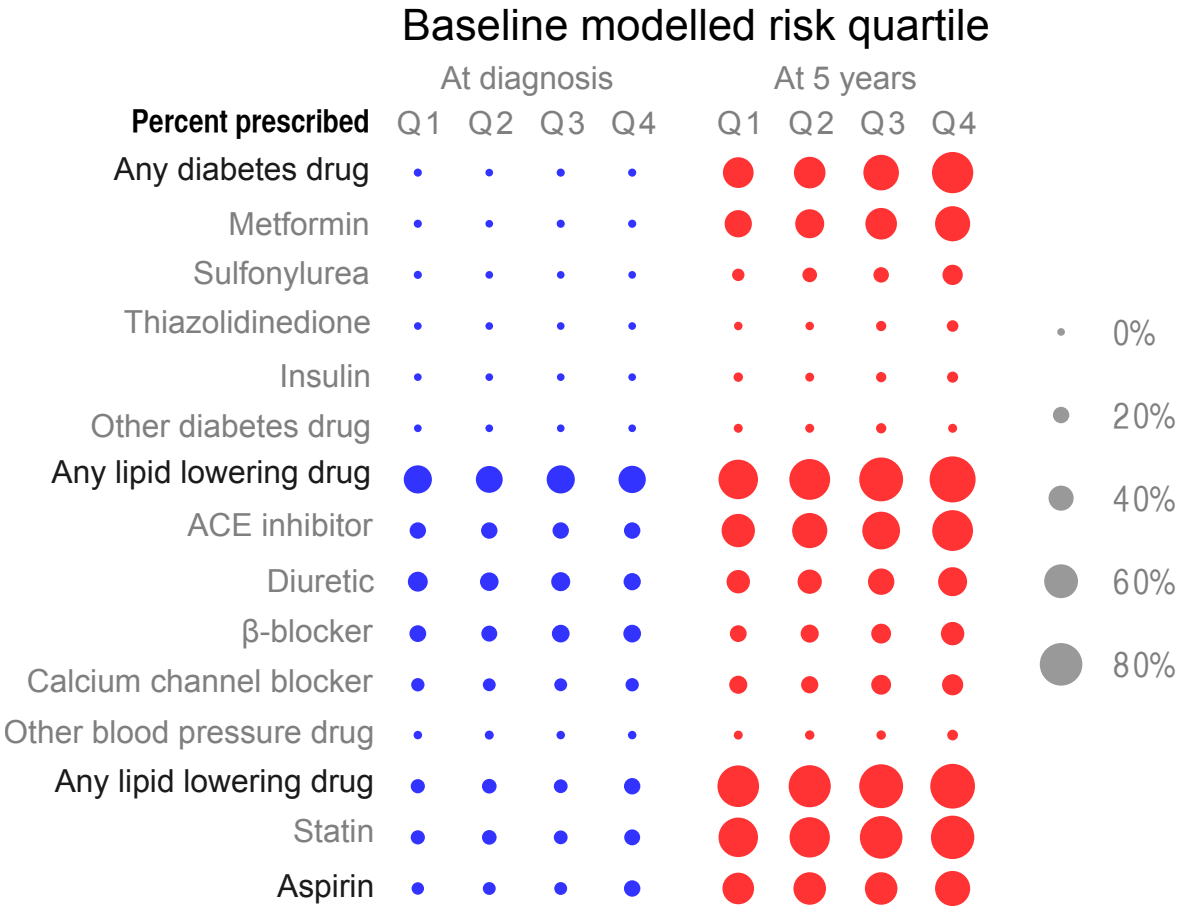


Figure 3.2: Quick reference plot showing the number of CVD medications, by agent, in ADDITION-*Europe* participants at diagnosis and 5 years. Size of circle is relative to proportion prescribed medication. Q1 is the lowest quartile of 10-year modelled UKPDS CVD risk at diagnosis, Q4 is the highest.

there appears to be a slight trend of greater prescription rates in those at higher baseline CVD risk, these differences are small relative to the large increases in medication seen when looking at changes over time between diagnosis and five years.

3.3.2 Daily estimates of cardio-protective medication

Follow up for medication data in the 910 individuals in ADDITION-*Denmark* is assumed to be 100%, with losses to follow up present only on death or emigration. Figure 3.3 shows the proportion of individuals that are estimated to be currently have a supply of each medication (redeemed that medication in the last 90 days), on a daily basis, from one year before diagnosis, to five years after. A large increase in glucose lowering medication was seen in the six months after diabetes diagnosis, with a gradual increase in the proportion taking glucose lowering medication to five years (Figure 3.3a). Blood pressure lowering medication was redeemed by more than a quarter of the population before diagnosis, and after an initial increase remained fairly static through to five years (Figure 3.3b). The proportion that reedemed lipid lowering medication (Figure 3.3c) and aspirin (Figure 3.3d) was lower at diagnosis, and both medication types saw a large increase after diagnosis followed by a plateau with around half the sample reedeming each medication through to five years.

3.3.3 Total medication burden

3.3.3.1 Cohort characteristics

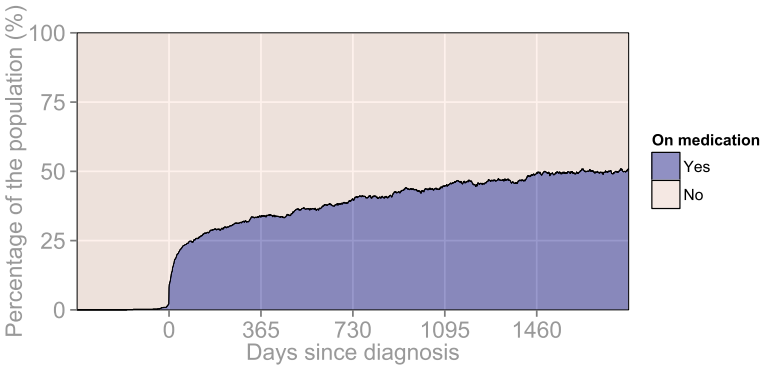
At diagnosis, the ADDITION-*UK* cohort had a mean age of 61 years (SD 7), a median 10-year UKPDS modelled CVD risk of 19% (IQR 13, 27) and 61% were male (Table 3.2). Of the 1,026 individuals in the ADDITION-*UK* cohort, 1,024 (99.8%) had medication data at diagnosis, 1,008 (99%) at one year, and 930 (96%) at five years. Ten people died before one year follow up, and 59 before five year follow up.

3.3.3.2 Total medication burden

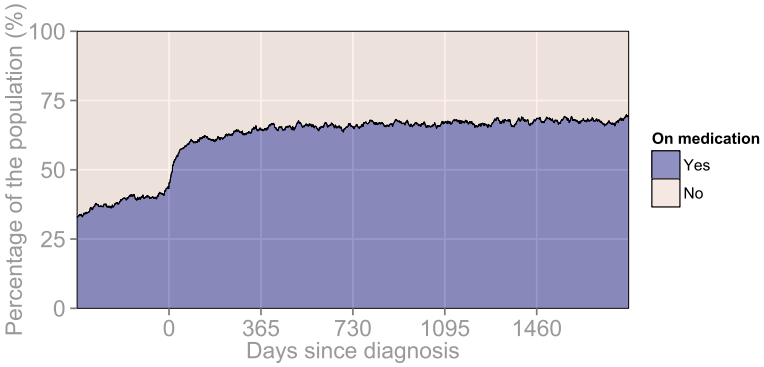
At diagnosis, individuals tended to report taking two medications (median 2; IQR 0, 4). This was most commonly a cardio-protective medication (median 1; IQR 0, 3), although some individuals were on more than one non-cardio-protective medication at diagnosis (Figure 3.4). One year after diagnosis a median of 3 medications (IQR 0,6) were recorded. At five years, individuals were typically prescribed six medications (median 6; IQR 5, 8), which included one diabetes-related medication (median 1; IQR 0, 1), four cardio-protective medications (median 4; IQR 3, 5) and one other medication (median 1; IQR 0, 2).

3.3.3.3 Diabetes-related and cardio-protective medication

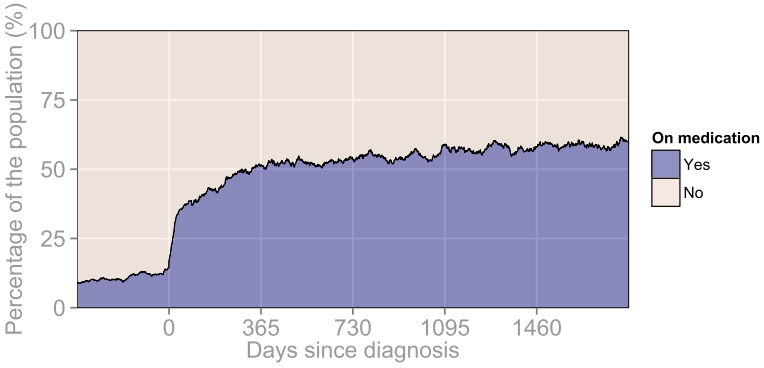
After diagnosis, both the variety and number of cardio-protective and diabetes medications increased (Figure 3.4 & Figure 3.5). At one year, 23% of individuals were prescribed any type of diabetes medication, which increased to 62% at five years. Between diagnosis, one and



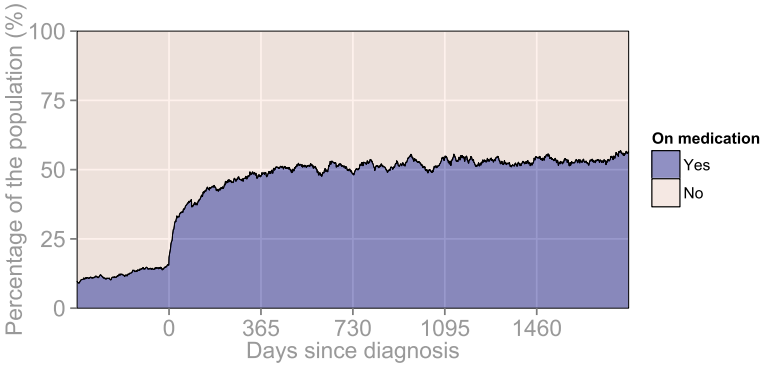
(a) Proportion of individuals '*on*'† glucose lowering medication.



(b) Proportion of individuals '*on*'† blood pressure lowering medication.



(c) Proportion of individuals '*on*'† lipid lowering medication.



(d) Proportion of individuals '*on*'† aspirin.

Figure 3.3: Medication use from one year before, until five years after, screen-detected diagnosis of diabetes in ADDITION-*Denmark*. †*'On'*, coded on a daily basis for the entire time span, is 'yes' if the individual redeemed the medication in the previous 90 days.

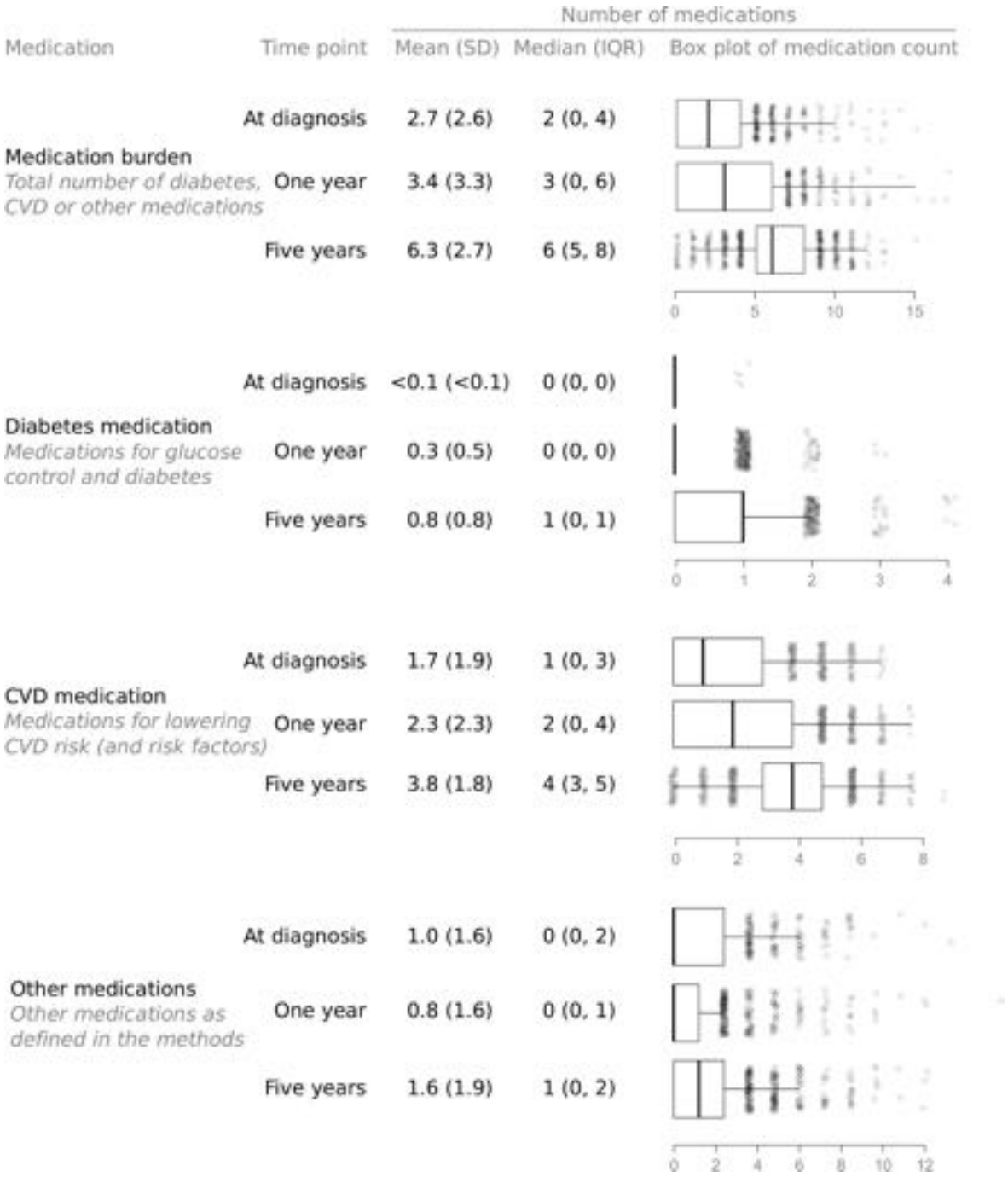


Figure 3.4: Count of medication types reported in the ADDITION-*UK* cohort at diagnosis, one and five years. Box-plots represent number of agents, points represent values outside inter-quartile range.

Table 3.2: Baseline characteristics of the ADDITION-UK cohort, overall and by previous CVD status and CVD risk quartile

	10-year UKPDS CVD risk: Lowest quartile 5,17	10-year UKPDS CVD risk: Highest quartile 36,92	No CVD	Previous CVD	**Total**
N[†]	244	244	858	106	**1026**
Age in years (SD)	56 (8)	64 (5)	60 (8)	63 (5)	**61 (7)**
% Male	40%	83%	60%	74%	**61%**
% White	80%	98%	93%	96%	**91%**
10-year CVD risk (IQR)	14 (11,15)	47 (40,56)	24 (17,33)	45 (35,56)	**25 (17,36)**
BMI kgm^2 (SD)	33 (6)	33 (6)	33 (6)	33 (6)	**31 (5)**
% HbA_{1C}	6.6 (1.1)	8.3 (2.2)	7.4 (1.7)	7.1 (1.6)	**7.3 (1.7)**
HbA_{1C} $mmolmol^{-1}$	49 (12)	68 (24)	57 (19)	53 (17)	**57 (18)**
Systolic BP mmHg	133 (16)	153 (23)	143 (19)	139 (22)	**146 (17)**
Total cholesterol $mmolL^{-1}$	5.2 (1.0)	5.5 (1.3)	5.5 (1.1)	4.6 (1.0)	**5.6 (1.2)**

[†] Number of participants recruited at diagnosis.

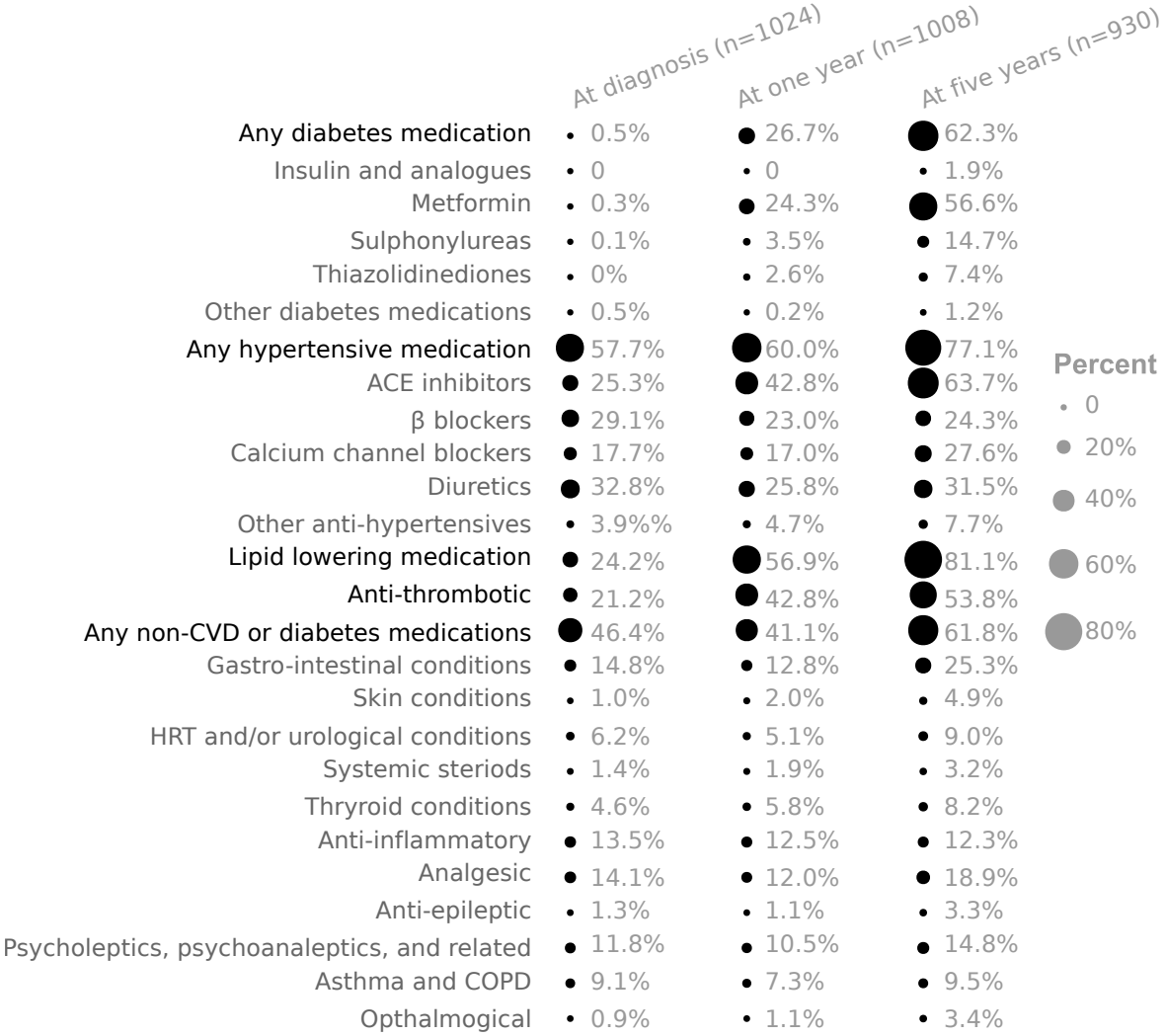


Figure 3.5: Proportion of participants prescribed medication, by agent, in ADDITION-*UK* from diagnosis to 5 years.

Table 3.3: Association between baseline characteristics at diagnosis and change in medication count between diagnosis and five years in the ADDITION-*UK* cohort.

	Change in total medication count β (95%CI)	Change in diabetes medication IRR[†](95%CI)	Change in CVD medication β (95%CI)	Change in other medication β (95%CI)
Number of medications at diagnosis[‡]	-0.49 (-0.56,-0.42)	-	-0.50 (-0.56,-0.44)	-0.30 (-0.37,-0.22)
Male gender	-0.25 (-0.57,0.06)	0.86 (0.75,0.99)	-0.11 (-0.33,0.10)	0.12 (-0.10,0.34)
Intensive treatment arm	0.44 (0.10,0.78)	1.14 (1.01,1.30)	0.39 (0.09,0.69)	-0.08 (-0.30,0.13)
Age at diagnosis (years)	-0.03 (-0.05,-0.01)	0.96 (0.95,0.97)	-0.02 (-0.03,0.002)	0.02 (0.01,0.04)
Modelled 10-year UKPDS CVD risk (%)	0.04 (0.02,0.05)	1.02 (1.01,1.03)	0.02 (0.01,0.03)	0.00 (-0.01,0.01)

[†] IRR = Incidence Rate Ratio
[‡] Number of medications of the medication type that is the dependent variable in that columns regression.

five years, the prescription of anti-hypertensive (55% to 51% to 77%), lipid lowering (24% to 48% to 81%) and anti-thrombotic (20% to 36% to 54%) medication increased. In this screen-detected population, many individuals reported using no glucose lowering medication at one and five years (78% and 38%, respectively, Figure 3.4 & Figure 3.5).

3.3.3.4 Other medications

At diagnosis, 42% of individuals were prescribed other types of medication, which increased to 62% at five years after diabetes diagnosis (Figure 3.5). The most common type of agent was for gastro-intestinal conditions (13% at diagnosis, and 25% at five years). Many individuals also reported anti-inflammatory (12% at diagnosis, and 12% at five years), analgesic (12% at diagnosis, and 19% at five years) and psychotherapy (11% at diagnosis, and 15% at five years) related prescriptions.

3.3.3.5 Predictors of prescribed medication at five years

The baseline characteristics associated with an increase in the total number of prescribed drugs between diagnosis and five years (see Table 3.3) were a younger age (β -0.03, 95%CI -0.05, -0.01), a higher baseline modelled 10-year UKPDS CVD risk score (β 0.04, 95%CI 0.04, 95%CI 0.02, 0.05), randomisation to the intensive treatment arm of the trial (β 0.44, 95%CI 0.01, 0.78), and being prescribed less medications at diagnosis (β -0.49, 95%CI -0.56, -0.42). Sex was not associated with change in total number of medications. Similarly, the baseline characteristics associated with an increase in cardio-protective medication were a higher 10-year CVD risk (β 0.02, 95%CI 0.01, 0.02), randomisation to the intensive treatment arm (β 0.39, 95%CI 0.09, 0.69) and being prescribed less medication at baseline (β -0.50, 95%CI -0.56, -0.44). An increase in diabetes-related medication was associated with female sex (IRR 0.86, 95%CI 0.75, 0.99), younger age (years; IRR 0.96, 95%CI 0.95, 0.97), having a higher baseline 10-year CVD risk (IRR 1.02, 95%CI 1.01, 1.02) and randomisation to the intensive treatment arm (IRR 1.15, 95%CI 0.01, 1.30).

3.3.3.6 Presence of comorbidities at diagnosis

Figure 3.6 shows the proportions reporting having been told by their GP that they had high blood pressure or high cholesterol before diagnosis, stratified by whether they had previously experienced a CVD event, in the 841 individuals from ADDITION-*UK* that responded to these questions. Approximately a third of the sample had either high blood pressure (35%) and normal cholesterol, or reported having elevated blood pressure and cholesterol (37%). While the remaining third had previously been told they had high cholesterol with (21%) or without (7%) high blood pressure (Figure 3.6).

While 34% reported having normal blood pressure and cholesterol and were free of previous CVD, 6% had been previously told they have elevated blood pressure, cholesterol and had experienced a CVD event (Figure 3.6).

3.3.3.7 Sensitivity analysis

Compared to individuals with medication data at five years, those without medication data were more likely to be female (OR 0.56; 95%CI 0.35, 0.89), older (one year; OR 0.97; 0.94, 0.999), to have had a previous CVD event (OR 0.49; 95%CI 0.29, 0.90) and to be in the intensive arm of the trial (OR 2.04; 95%CI 1.32, 3.20). There was no association between loss to follow up and ethnicity (White vs. other; OR 0.77; 95%CI 0.31, 1.60) or socio-economic deprivation (1 point IMD change; OR 0.99; 95%CI 0.97, 1.02).

3.3.3.8 Intensive treatment effect

Figure 3.7 shows the difference in proportion prescribed each agent between the routine care and intensive treatment arms of ADDITION-*UK*. A higher proportion of individuals were prescribed blood pressure lowering agents ACE inhibitors (12%; 95%CI 6,8) and β blockers (7%; 95%CI 2,13), as well as lipid lowering medication (6%; 95%CI 0.4,11) and aspirin (12%; 95%CI 6,19) (Figure 3.7). No evidence for differences in non-CVD or non-diabetes medications was identified between treatment arms.

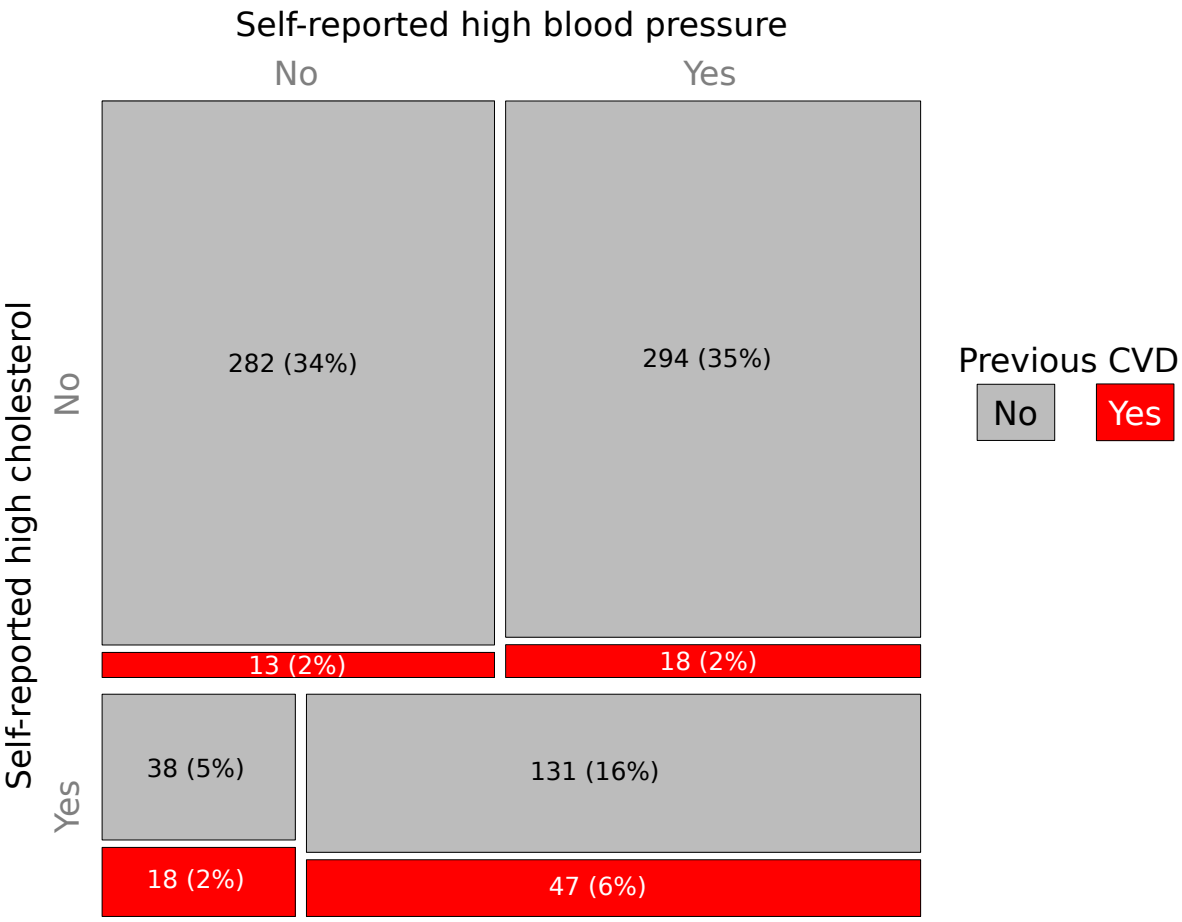


Figure 3.6: Mosaic plot showing the relative proportions that self-reported having been told by a doctor they had high cholesterol or blood pressure at diagnosis in ADDITION-*UK*. Further divided by colour is self-reported myocardial infarction or stroke before diagnosis vs. no previous CVD. Only individuals with complete data (n=841) are included in this plot.

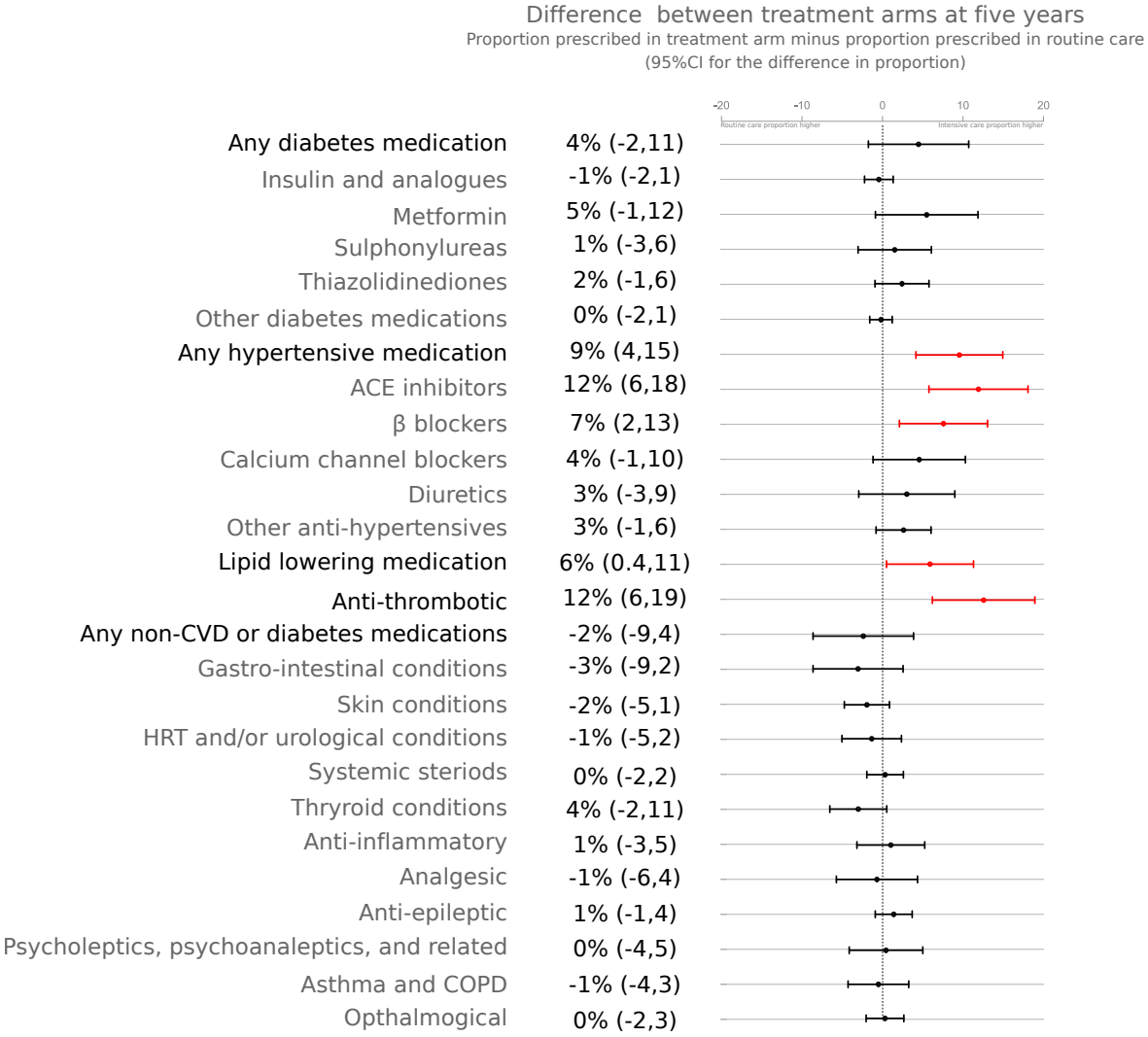


Figure 3.7: Difference in medication at 5 years by treatment arm in ADDITION-*UK*. Formula for difference in proportion: $p_{intervention} - p_{routinecare}$. 95%CI for the difference in proportion were calculated as recommended in *Newcombe et al (1998) Statistics in Medicine 17:857-72* using the `prop.test` command in *R*.

3.4 Discussion

In a population of individuals with screen-detected type 2 diabetes, I described the prevalence of diabetes-related, cardio-protective and other medications from diagnosis to five years. The majority of cardio-protective medication changes happened immediately after diagnosis, although there was a gradual increase in glucose lowering medication after the initial increase for the full five years of follow up. At diagnosis, 45% of individuals reported being prescribed blood pressure lowering, lipid lowering, or both types of medication in ADDITION-*Europe*. Many individuals in ADDITION-*UK* reported medications not related to cardio-protection before diagnosis (42%), and this increased along with a rise in the number of diabetes-related and cardio-protective drugs. The screen-detected diabetes population had a degree of poor cardio-metabolic health, with only 34% of the sample free of high blood pressure, high cholesterol and CVD at diagnosis. At five years, individuals were typically prescribed six medications, including one diabetes-related medication, four cardio-protective medications, and one other medication. This suggests that there is a significant degree of multi-morbidity and polypharmacy present in individuals with screen-detected diabetes. Following diagnosis, individuals were more likely to be prescribed diabetes-related medication if they were younger, female, had a high modelled CVD and if they were randomised to the intensive treatment arm of the trial (Table 3.3). Higher modelled CVD risk at baseline was associated with a greater increase in cardio-protective medication, but not a increase in other medications. As recommended in national guidelines, these results suggest that the treatment of diabetes was influenced by the underlying risk of CVD.

3.4.1 Context within the literature

This is the first description of daily changes in cardio-protective medication, and total medication burden at diagnosis, one and five years in a large cohort of individuals with screen-detected diabetes. In a subset of the Dutch Hoorn Study, among 195 individuals with screen-detected diabetes, 45% were taking blood-pressure lowering medication, and 20% were taking lipid lowering medication at diagnosis.[173] In ADDITION-*UK* at diagnosis, 55% of individuals were taking blood pressure lowering medication, and 24% lipid lowering medication, in agreement with the results of the Hoorn screening sub-sample. In a separate publication from the Hoorn study, two weeks after diagnosis 24% of the screen-detected and 78% of the clinically detected individuals were prescribed oral glucose lowering medication.[69]

The step-wise screening programme carried out in ADDITION-*Cambridge* used the Cambridge Risk Score to identify those at the highest risk of undiagnosed diabetes.[147] This score includes blood pressure medication as a variable, which may have led to an overestimate in the number of individuals taking anti-hypertensive medication in this sample. Similar screening strategies were used in all ADDITION-*Europe* centres except Leicester. In 2005-2006, in an American population with long-standing diabetes, 90% of the population were taking glucose lowering medications, 78% were taking anti-hypertensives and 26% were on statins.[174] This contrasts with ADDITION-*UK*, where glucose lowering medications were less common

(62%, at five years), and statins were more common (54%, at five years). Statin use was the pharmacotherapy that differed by the greatest margin between arms of the ADDITION-*UK* trial (47% for routine care vs. 60% after the promotion of intensive care, at five years). These results suggest that the promotion of statin use is the most readily adopted treatment after diagnosis in a screen-detected population.

Previous literature has noted that the prescription of cardio-protective medication often lags behind glucose lowering medication, suggesting a disproportionate emphasis on controlling glucose rather than overall CVD risk reduction.[174,175] Khunti *et al*, in a clinical database based retrospective cohort of 50,476 individuals with diabetes on one oral glucose lowering medication, found that the median time between a person exceeding an HbA_{1C} of $64\,mmol\,mol^{-1}$ (8%) and intensification of treatment was 1.6 years, while the clinical inertia for individuals with uncontrolled glycaemia warranting insulin was longer than the seven year follow up.[176] In both arms of ADDITION-*UK*, use of anti-hypertensive and lipid lowering medication was reported by around four-fifths of the participants (77% and 81%, respectively), and glucose lowering and aspirin use was reported for three-fifths of the population (62% and 54%, respectively). While it is important to note that pharmacotherapy was not required in the first five years after diagnosis for all individuals (for example if the individual finds lifestyle changes are sufficient to manage CVD risk factors), results from this analysis suggest that the prescription of cardio-protective medication did not lag behind that of glucose-lowering. This also highlights the differences between a screen-detected population, and the degenerative nature of diabetes identified in the clinically diagnosed, and older, UKPDS.[102] Overall, 20% of individuals were on metformin at one year, and 57% at five years, despite metformin being recommended as a first line glucose lowering medication, and immediate initiation being recommended by NICE if overweight or non-responsive to lifestyle interventions.[170] I cannot clearly separate lack of suitable care from sufficient in this analysis. Variation in individual care from written guidelines was also seen in ADDITION-*Denmark*, where half of the individuals that met the clinical threshold for blood pressure lowering medication were actually prescribed medication.[153] Variation in treatment could be a positive indicator of patient centred care or a deficit between patient need and prescribed medication. This is because individuals and their GP, as part of an informed and collaborative management approach that is recommended in the latest NICE and ADA guidelines[14,117], may decide to set less intensive risk factor goals. More detailed knowledge on the circumstances around treatment choices in screen-detected populations would help inform whether the prescription of cardio-protective and glucose lowering medication should be higher in this population, or that the proportions prescribed medications in this study represent adequate care in relation to GP and patient needs and priorities.

In this analysis, 6% had experienced a CVD event and been told by their doctor they had high blood pressure and high cholesterol, indicating their was a degree of poor cardio-metabolic health present at diagnosis. While information on non-CVD comorbidities was not available, prescription rates of non-CVD or diabetes medications suggests there is also a degree of other comorbidities present in a sample of individuals with early diagnosed diabetes

(Figure 3.5). When looking at prescription patterns by quartile of baseline 10-year modelled CVD risk, the differences in prescription rates by cardio-metabolic health at diagnosis are small compared to the large increase in medication that occurs between diagnosis and five years. An increase in diabetes medication from diagnosis to five years was associated with being female, younger, having a GP who was in the trial arm promoted to treat intensively, and having a higher baseline risk of a CVD event. In the Hoorn study, two weeks after screen-detected diabetes diagnosis, 24% of the population were taking glucose-lowering medication.[69] While previous literature suggests there is no association between the prescription of diabetes related medication and gender.[177,178]

The UKPDS, NHANES II & NHANES III demonstrated that diabetes, in the two decades before ADDITION-*UK* began recruitment, was a degenerative disorder, requiring continued treatment intensification as insulin sensitivity and secretion became increasingly disfunctional.[179,180] I have shown that this pattern remains present in ADDITION-*Denmark* (at daily resolution), and in ADDITION-*UK* (one to five years), despite the improvements in treatment and the earlier diagnosis on the diabetes disease trajectory. The extension of this pattern earlier along the disease trajectory provides evidence for calls for investigations into whether earlier intervention aimed at improving glyceamic control before the clinical threshold of diabetes is reached would be more effective at arresting the gradual deterioration of glyceamic control and maintaining β-cell function.[116]

Current evidence in long standing type 2 diabetes suggests self-reported adherence to glucose lowering medication is high.[154] Redeemed prescription data from Scotland contradicts this, as Donnan *et al* reported that 34% of individuals on metformin redeemed enough medication over one year to reach greater than 90% adherence, with the median amount of medication collected in one year covering 302 days.[122] Danish data suggests that many individuals are non-persistant (∼1-5%) or never redeem (∼5-10%) their metformin prescriptions.[154] More information is needed on the relationship between prescribed, redeemed and applied medication, if intensification and greater polypharmacy is to take place in asymptomatic populations where the motivation for good adherence might be less.

Current NICE guidelines[117] suggest the prescription of four medications in nearly all individuals with type 2 diabetes, and 19 other medications for specific combinations of conditions or failure to attain targets.[181] Drumbeck *et al*[181], looking at potential interactions with metformin, sulphonylureas, ACE inhibitors and simvastatin, found five potentially dangerous interactions with medications promoted in treating chronic kidney disease. I have identified that there is a large proportion of individuals prescribed medications not related diabetes, where there is little information on how the multitude of drug combinations could effect adherence and treatment effectiveness.

Recommendations on what constitutes best practice in pharmacotherapy also changed during the follow up of this study. In 2002, during recruitment (which spanned from 2001 to 2006), NICE released guidelines highlighting the importance of blood pressure and lipid targets in individuals with type 2 diabetes.[170] By 2010, around five year follow up, NICE guidelines emphasised CVD risk factor target setting as an informed joint decision, with at

least annual review.[117] The rate at which guideline amendments filtered through to changes in treatment is less certain. González *et al*[56] tracked longitudinal trends in diabetes treatments in the UK from 1996 to 2005, and they found that in both incident cases, and in individuals with long standing diabetes, there was a shift away from the use of sulphonylureas, which are linked to increased body weight and higher rate of hypoglyceamia[116], towards metformin and thiazolidinediones.

3.4.2 Strengths and limitations

The large number of individuals with medication data at diagnosis and five years (n=2,604; 85% of randomised sample) in ADDITION-*Europe* allows a robust exploration of the proportions prescribed different combinations of medication before and after diabetes diagnosis. In ADDITION-*Denmark*, the complete information on when each medication was redeemed allows novel estimation of daily numbers for each medication. The presentation of medication data at this resolution is unique to this analysis.

While all individuals aged 40-69 years were invited to screening in Leicester, in Cambridge only those in the top quartile of modelled risk of diabetes were invited (see Table 2.1 on page 27 for the screening strategies by trial centre). As the risk score used does not have perfect sensitivity[147], and includes CVD risk factors as predictors, individuals not invited are likely to have better cardiometabolic health. This would unfairly skew my results to suggesting cardiometabolic health is worse in a screen detected population. In the Cambridge centre, 55% reported blood pressure lowering medication and 24% lipid lowering medication. In Leicester 34% and 13% were prescribed blood pressure lowering and lipid lowering medication, respectively. Whether the bias present is towards over or under representing a screen-detected population depends on how screen-detection is applied. As an example, it is very unlikely screening for diabetes will be undertaken on all individuals like it was in the Leicester centre of ADDITION-*Europe*, while high risk strategies like the NHS health checks are already underway in England.[144]

The primary analysis in ADDITION-*UK* is using a large cohort (n=1,026) with consistency in outcome measurement and little loss to follow up in individuals prescription histories (4% at five years). ADDITION-*UK* (91% white ethnicity) was less diverse than the UKPDS (81% white ethnicity)[77], which may limit generalisability. However, ADDITION-*UK* remains the only study able to characterise medication changes after screen-detected diabetes diagnosis while receiving contemporary diabetes care. This analysis uses prescribed medications, which is likely to be an over count of the redeemed and consumed prevalence. Some medications may also be available without a prescription. Accuracy of medication data was improved by encouraging participants to bring repeat prescriptions to the health assessment, the use of a health economics questionnaire[171] and accessing a peripatetic database. For the secondary analysis of change in medications, my analysis assumes that a change from zero to one medication is directly comparable to a change from four to five, or two to one. Medication was coded into 23 classes, but antiinfectives, antiparasitics and antineoplastic medications (as defined by the ATC) were not included as they were acute (e.g. infections) or rare (e.g.

cancer). As the primary analysis in ADDITION-*UK* collected snapshots of medication use at baseline, one and five years after diagnosis, I was not able to give accurate prevalences for acutely prescribed medications. The number of medical agents was chosen over the raw pill count as some medications can be taken as combination pills, or can be split across multiple doses. This could unduly increase the impact of some medications that are taken multiple times a day on the final medication count. There is also likely to be less agreement between the doctor prescribed treatments and daily pill count, compared to reported types of medical agent, as pill count includes both agent and information on frequency and method of dose. This analysis is unable to describe the pharmacotherapy of individuals that died during follow up, and it is likely that if medication at the time of death was available, it would introduce greater heterogeneity to this analysis. There was no association between loss to follow up and change in medication, although this analysis was limited to the sub-sample of Cambridge participants (86% of the sample) due to individual patient level IMD scores not being available for Leicester.

3.4.3 Implications for practice

Individuals with screen-detected diabetes are often taking multiple medications before diagnosis, despite being identified early in the diabetes disease trajectory. This includes both cardio-protective medications, and other medications including; gastro-intestinal, anti-inflammatories, analgesics and psychiatric/neurological medications. After diagnosis, family physicians and patients appear to adopt pharmacological strategies that target both CVD risk reduction and glycaemia, providing evidence against concerns of over-prioritising glycaemic target. The increased prescription of cardio-protective medication was associated with higher baseline CVD risk, indicating an association between need and care. While this result is promising, it remains unclear if the prescription rates of glycaemic and cardio-protective medication in this population with elevated cardio-vascular risk reflect individualised treatment based on patient led priorities or a deficit in the application of pharmacological intervention.

As goal setting and treatment choice in diabetes care is a shared decision between GP and patient[14,117], understanding that treatment intensification over time is likely, and does not represent a failure by the patient, will also aid in clinical practice.

3.4.4 In the context of optimising CVD risk management

As I have now established the medication burden in a screen-detected diabetes population, in the remaining chapters I will explore how CVD risk factors change (Chapters 4 and 5), whether the promotion of intensive care from screen diagnosis results in less CVD events (Chapters 6 and 7), and if there is a relationship between medication burden and quality of life (Chapter 8).

Chapter 4

Glycaemic control trajectories among people with diabetes diagnosed by screening from the ADDITION-Denmark cohort

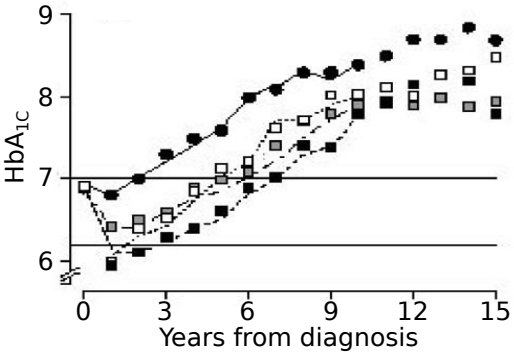
4.1 Introduction

In Chapter 3 I presented information on the large increase in glucose lowering medication after screen-detected diagnosis, and the continued gradual intensification over time. Good glycaemic control in combination with management of other CVD risk factors is promoted after diagnosis of diabetes to reduce the risk of micro- and macrovascular disease[117,145], yet little is known about who glycaemic control is patterned over time in an early detected population.

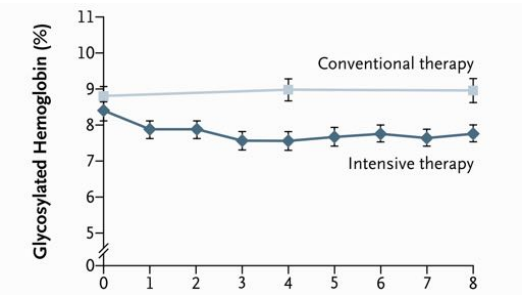
4.1.1 Glycaemic control after diagnosis

The UKPDS suggests HbA_{1C} levels usually decline in the first year, before gradually increasing over the following 15 years (Figure 4.1a).[77] Figure 4.1b shows the glycaemic control trajectories for both arms of the Steno-2 trial, which was a population with long standing diabetes. Most national recommendations promote individualised patient care[125], and this leads to patient-centred variation in both practitioner and patient behaviour.[182] Known factors such as co-morbidities, and unknown factors, such as pharmacogenomics, also lead to heterogeneity in both the treatment strategies employed as well as their effectiveness in maintaining good glycaemic control.[183] This implies that the baseline level of a CVD risk factor like HbA_{1C}, which represents a single snapshot in time, may not be representative of the likely change in both that risk factor, and overall CVD risk a person will experience in subsequent years. In a general population, Chamnan et al[184] found a significant association between change in HbA_{1C} over three years and incident CVD when adjusting for baseline HbA_{1C}.

This association was attenuated to no effect when also adjusted for multiple variables including systolic BP, total cholesterol, use of statin therapy, gender and age. The method used was crude, as it reduced complex continuous changes in HbA_{1C} to a single change statistic, and the model used was not able to account for potential clustering of different trajectories by unspecified variables. Many questions remain over how glycaemic control evolves after diagnosis.



(a) Glycaemic control in the UKPDS



(b) Glycaemic control in Steno-2

Figure 4.1: Figure 4.1a shows glycaemic control in the UKPDS trial. Reproduced with permission from *UKPDS Group. (1998) Lancet, 352(9131):837-853.*[100] Figure 4.1b shows glycaemic control in the Steno-2 trial. Reproduced with permission from *Gaede et al. (2003) New England journal of medicine, 348(5):383-93.*[112]

Type 2 diabetes itself is an exclusionary disease, in that it encompasses individuals with poor glucose control that do not meet specific criteria for alternative categories of diabetes like type 1 or gestational diabetes (as described in detail in Section 1.1.1 on page 1).[14] There is increasing evidence of multiple underlying physiopathologies present within this category of type 2 diabetes. The primary manifestation of this heterogeneity is in the varying contribution of insulin sensitivity and secretion to an individual's poor glycaemic control.[185] There is increasing evidence that some of this variation may be explained by sub-groups of individuals with immunological abnormalities that could drive pathological differences that lead to heterogeneity in the secretion vs sensitivity balance.[186] Regardless of the lack of clarity in our understanding of what drives these differences, it is reasonable to expect that clusters of glyceamic control exist in a population with screen-detected diabetes.

Traditional methods assign individuals to a single latent process, and use explanatory variables and random error to describe variation from that trajectory. Diabetes is a complex disease, with a diverse range of applied treatments, and this suggests that there will be heterogeneity in glycaemic control after diagnosis which can be grouped into distinct trajectories. Both the shape and characteristics of different trajectories may help in both describing the diversity in effective glycaemic control, as well as identify which individuals may need closer monitoring and intensified treatment. This is particularly important immediately after diagnosis of diabetes, as treatment often lags behind changes in need, and lowering CVD risk factors earlier in the disease trajectory may have long term benefits in the prevention of

complications.[102,145]

The UKPDS demonstrated that after diabetes diagnosis an individuals glucose levels typically reduce as a result of changes in lifestyle behaviour and/or treatment with hypoglycaemic medication.[102,187] Maintaining good glycaemic levels (HbA_{1C} <7%) over the longer-term is a more challenging goal and many patients saw increases in their HbA_{1C} following an initial reduction. Previous research examining multimodal changes in HbA_{1C} following diagnosis typically stratify patients into those with 'good' or 'poor' adherence to glycaemic targets[188], but these crude categories may mask a more complex pattern of HbA_{1C} change.

4.1.2 Defining glycaemic trajectories

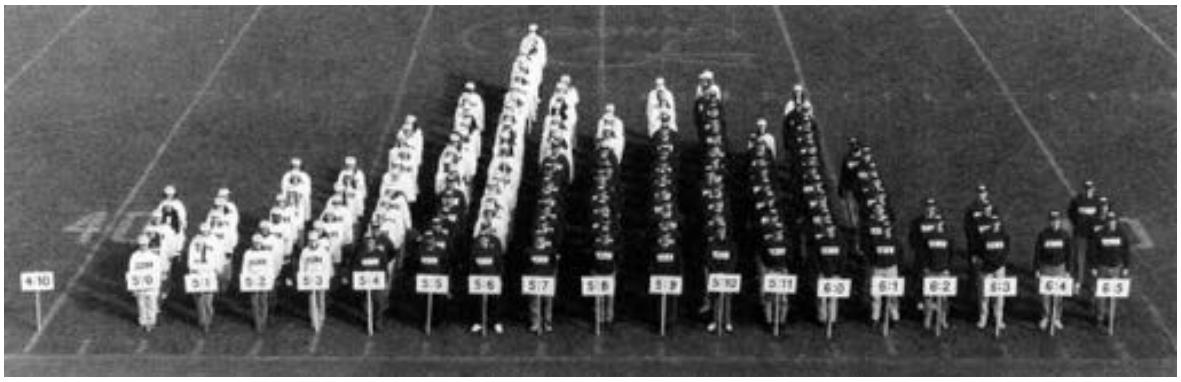


Figure 4.2: A 'living histogram' of the bimodel nature of 143 student's heights from the University of Connecticut, with females in white and males in black. *Published in The Hartford Courant newspaper article 'Reaching New Heights', November 23, 1996*

Figure 4.2 is a histograph, with males in black jerseys, and females in white. In Figure 4.2, the overall distribution of student heights looks vaguely Gaussian (▁▃▆▇▅▃▂▁). As the students are wearing different colour jerseys, we can also look at the distribution by gender. When separated by gender, the kurtosis of the gender-specific distributions increases, and the left skewed female (▁▃▆▇▅▂▁) and right shifted male heights (▁▂▃▅▆▇▅▃▁) take on a more recognisable (peaked) Gaussian structure. Without knowledge of gender, we would say that student heights are distributed around a mean of approximately 5 feet 8 inches. The information on gender though suggests that a better description of height is to say there is a bimodal distribution, with a large degree of overlap, where males tend to be taller. While the definition of just how different the two distributions need to be in order to be bimodel is debated[189], it is not debated that being able to separate heights by gender, in the sample presented in Figure 4.2, improves our ability to guess an individuals height. In diabetes, the question I wished to explore was how varied is glyceamic control after diagnosis, and if there are distinct sub-distributions of glyceamic control that might have clinical significance. Glyceamic control though is not a fixed descriptor like sex or age, and must first be defined.

When looking cross-sectionally, methods like K-means analysis allows us to separate out multimodal distributions of multiple variables into statistically sound and clinically informative groups. A longitudinal extension of this concept, the Group Based Trajectory Model

(GBTM), allows us to extend this idea of clustering data to look at how a variable changes over time, by defining distinct distributions of an observed variable over a time period, and empirically group the individuals based on the probability of membership to each of the identified clusters of trajectories.[190,191] These empirically defined trajectories often map directly to subjective conceptualisations of how clinicians believe different clusters of individuals disease progress over time.[190] The number and the shape of the trajectories are derived from individual HbA_{1C} measurements taken over a series of years in the same group of patients.[190,192] After teasing out such groupings from the individual level trajectories present, describing the characteristics of clusters of divergent trajectories at baseline can provide a statistical snapshot of the characteristics of the individuals from each longitudinal cluster.[190]

4.1.3 Aims

Among 910 Danish participants with screen-detected diabetes I aimed to identify (i) trajectories of HbA_{1C} change over five-years of follow-up, (ii) describe and compare baseline characteristics of each of the identified trajectory groups and (iii) describe changes in medication within trajectory groups.

4.2 Methods

4.2.1 Data collection

This analysis was a *post-hoc* cohort analysis of the intensive treatment arm of ADDITION-*Denmark*. The methods used in ADDITION-*Denmark* are presented in Section 2.1.3 (Page 31). Methods specific to this analysis are presented here.

Only the intensive treatment arm was included in this analysis. GPs in the intensive treatment arm of ADDITION-*Denmark* were encouraged to regularly test HbA_{1C}, providing a a large number of measurements to explore trajectories within. The intensive treatment group family physicians were encouraged through guidelines, educational meetings, and audits with feedback to introduce a stepwise target-led drug treatment regime to reduce hyperglycaemia, hypertension and hyperlipidaemia[150,152] based on the Steno-2 study.[112] Targets included HbA_{1C} $<53\,\mathrm{mmol\,mol^{-1}}$ (<7.0%), blood pressure $\leq\frac{135}{85}$ mmHg, cholesterol $<5\,\mathrm{mmol\,l^{-1}}$ without ischaemic heart disease or $<4.5\,\mathrm{mmol\,l^{-1}}$ with ischaemic heart disease, prescription of aspirin to those treated with anti-hypertensive medication and prescription of a statin to all patients with a cholesterol level $\geq 3.5\,\mathrm{mmol\,l^{-1}}$ within four weeks of the diagnosis of diabetes.

Redeemed prescriptions were collected via linkage to the Danish National Prescription Registry, which has complete coverage of all redeemed prescriptions in Denmark since 1994 (see Section 2.1.3.2 on page 32 for details).[153] Information on HbA_{1C} data collection is in Section 2.1.3.1 on page 31.

Baseline characteristics of the population are presented for the entire cohort and for each of the identified trajectory groups. Patients saw their family physicians every three months

for the first year, and then every six months. I also report the percentage of individuals that redeemed a prescription for any glucose lowering, lipid lowering, anti-hypertensive or anti-thrombotic medication in the previous 90 days at each measurement time point

4.2.2 Trajectory analysis

A GBTM was used to identify distinct trajectories in HbA_{1C} levels during the five years following diagnosis. The model was fit in a two stage process: first the number of trajectories present in the cohort (range 2-6) was evaluated by minimising the Bayesian information criterion (BIC).[190] As goodness of fit increases at the expense of complexity when a higher order polynomial is specified for each trajectory, all trajectories were modelled as cubic for the purposes of defining the number of groups. Secondly, after identifying the number of trajectories, addition and elimination was used to identify which polynomial function of time since diagnosis was appropriate. An un-adjusted model was fit, so that the identified trajectories reflect the differing demographics of the individuals that constitute each trajectory group.

4.2.3 Assessing model fit

Subject-specific and marginal residuals were checked against predictions, and the fit of the terms in the final cubic trajectory model were checked. Participants were assigned to a specific trajectory based on the highest posterior probability of membership. A mean posterior probability of trajectory membership of >0.85 was *a priori* set as an indicator of adequate separation of identified trajectories While mean posterior probabilities >0.7 have been seen as adequate in the literature[193], I believed a more conservative approach was more defensible.

4.2.4 Comparing baseline characteristics of trajectory groups

Finally, I compared the baseline characteristics and medication during follow-up of the trajectory groups, reporting mean differences with 95%CI for continuous variables and the difference in proportions for binary variables. Trajectories were subjectively named according to relative start and end HbA_{1C} values (*high-low* and *low-low*). An additional post-hoc comparison was included of two of the identified groups (*med-low* and *med-high*).

4.3 Results

At diagnosis of diabetes the participants had a mean age of 60 (SD 7) years and 57% were male (Table 4.1). Between diagnosis and five years, 71 (7.8%) participants had a CVD event and 51 (5.6%) died from a non-CVD related cause. Five individuals did not have follow up HbA_{1C} measurements, and were excluded from the analysis. Few individuals were prescribed glucose lowering medication before diabetes diagnosis (n=8, 1%) (Figure 6.2 , although many individuals were prescribed lipid lowering (14%), anti-hypertensive (43%) and anti-thrombotic medication (17%). Three months after diagnosis, 27% of individuals

Table 4.1: Baseline characteristics of the ADDITION-*Denmark* intensive treatment trial cohort: overall and by trajectory

		HbA_{1C} trajectory group[†]			
Mean (SD), unless specified	Whole cohort	Low-low	Med-low	Med-high	High-med
N	905	792	74	21	19
Male %	57%	55%	73%	71%	68%
Age	60 (7)	60 (7)	57 (6)	56 (8)	54 (6)
BMI	30.8 (5.4)	30.7 (5.3)	31.0 (5.0)	34.2 (6.3)	32.9 (9.0)
Current smoker %	26%	26%	20%	37%	29%
HbA_{1C} %	6.8 (1.5)	6.4 (0.9)	9.4 (1.9)	8.5 (2.5)	11.0 (1.6)
HbA_{1C} $mmolmol^{-1}$	51 (16)	46 (9)	79 (20)	69 (27)	97 (18)
Total cholesterol $mmolL^{-1}$	5.6 (1.1)	5.5 (1.1)	5.9 (1.2)	6.0 (1.2)	5.9 (1.4)
LDL cholesterol $mmolL^{-1}$	3.4 (1.0)	3.3 (1.0)	3.5 (0.9)	3.5 (1.0)	3.4 (1.5)
HDL cholesterol $mmolL^{-1}$	1.4(0.4)	1.4 (0.4)	1.3 (0.3)	1.2 (0.2)	1.3 (0.3)
Triglycerides $mmolL^{-1}$	1.9 (1.3)	1.8 (1.2)	2.4 (1.5)	3.3 (2.4)	2.5 (1.2)
Non CVD death	5.6%	5.8%	4.1%	9.5%	0
Any CVD event[‡]	7.8%	7.4%	6.8%	14.3%	21.0%

[†] Trajectories are arbitrarily named based on subjective assessment of the shape of the mean trajectory of the group.
[‡] CVD event is a composite cardiovascular endpoint of cardiovascular mortality, non-fatal myocardial infarction or stroke, revascularisation and non-traumatic amputation.

had redeemed any glucose lowering drug in the last three months, 14% metformin and 7% a sulphonylurea. At five years 56% had redeemed any glucose lowering drug, 39% metformin and 18% a sulphonylurea.

4.3.1 Post-hoc analysis plan amendments

4.3.1.1 Change in HbA_{1C} by baseline decile of HbA_{1C}

Baseline HbA_{1C} was identified as a defining feature of two of the four identified trajectories. To help explain the relationship between HbA_{1C} at diagnosis and how it predicted change at five years, I have produced Figure 4.3, which shows the change in glyceamic control by HbA_{1C} at diagnosis in the wider ADDITION-*Europe* study. In the 50-60% with the lowest HbA_{1C} at diagnosis, glyceamic control has a central tendency to stay the same (with a large amount of variation), and in the 40-50% of individuals with the highest HbA_{1C} at diagnosis, there is a central tendency towards improvements in glyceamic control at five years, most dramatically in the decile with the highest baseline HbA_{1C} (Figure 4.3).

4.3.1.2 Follow up truncation

While lab reported HbA_{1C} was the primary source (as explained in Section 2.1.3.1 on page 31), for some measurements only HbA_{1C} variables collected by the practice were available (Figure 4.4). I was unable to identify why some measurements were entered by GPs, but not submitted by the laboratory. As the values should theoretically be identical, when laboratory

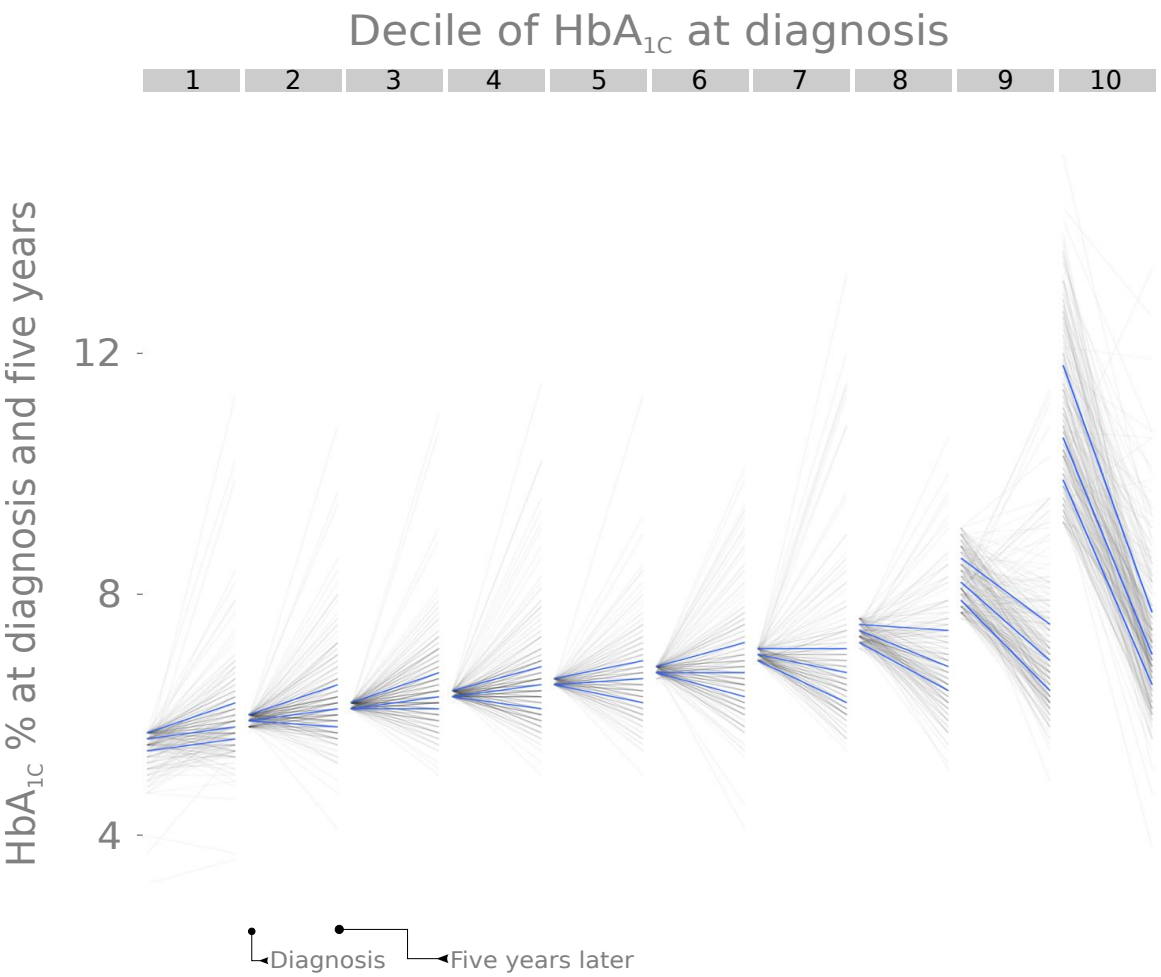


Figure 4.3: Change in HbA_{1C} from diagnosis to five years, by decile of baseline HbA_{1C}, in ADDITION-*Europe*. Grey lines represent an individual, and blue lines represent the median and inter-quartile range.

measurements were missing values were collected from the study case report form completed in the practice. Figure 4.4 shows the number of measurements that came from either source, or were missing, at each time point.

Additionally, due in part to the rolling recruitment of ADDITION-*Denmark*, the number of measurements available recorded decreased dramatically after five years (Figure 4.4). A *post-hoc* decision was made when reviewing this loss to follow up, before running the models, to truncate the dataset at five years; the truncation was made at exactly 2,000 days to capture the five year consultation, as consultations tended to be slightly more than three months apart and there was a lag present by five years. This decision was made as GBTMs are sensitive to bias from loss to follow up. In the truncated five year dataset there was a median of 11 (IQR 8,13) HbA_{1C} measurements available.

Figure 4.5 is a histogram showing when individuals contributed their last HbA_{1C} value to

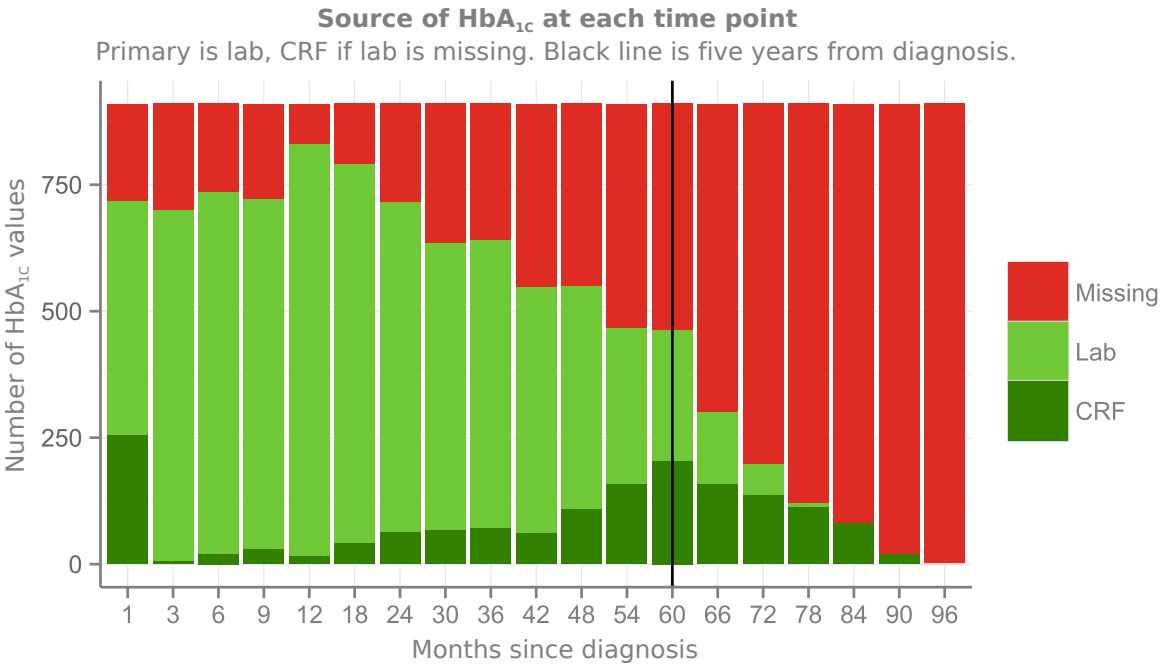


Figure 4.4: Source of HbA_{1C} values from ADDITION-*Denmark* used in this analysis. If available, lab reported HbA_{1C} was used. CRF = Case Report Form completed by doctors, lab results collected from database.

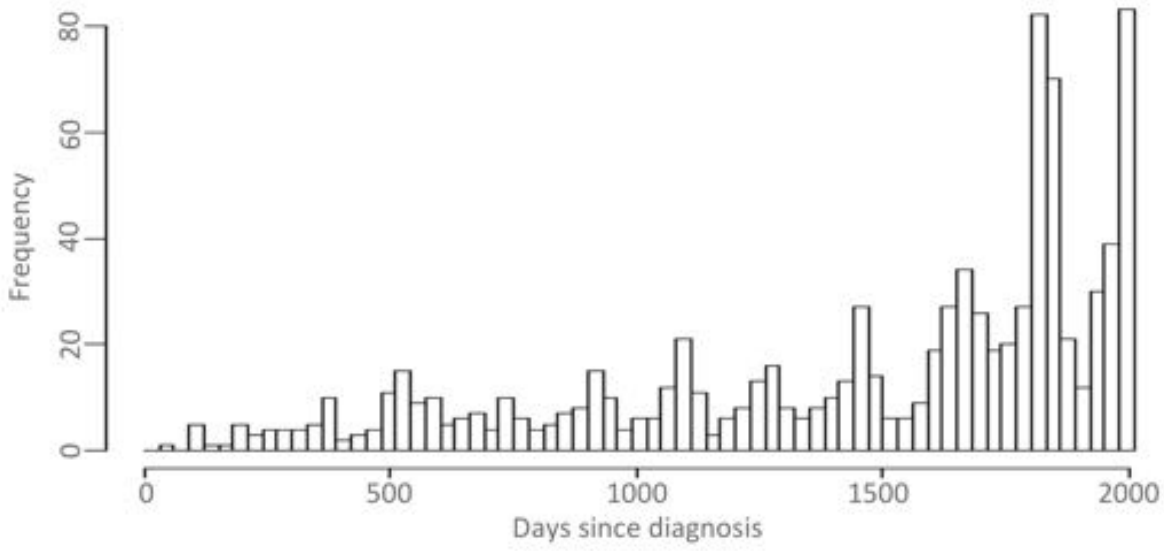


Figure 4.5: Histograph showing when individuals provided their last HbA_{1C} measurement, truncated at the 2,000 day cut off.

the analysis. The twin peaks approaching five years represent the arbitrary nature of choosing a truncation point that suitably captured data at five years. The 2,000 day cut off can be reasonably assumed to capture all observations that were made at 'five years' accounting for the variation in how often follow ups were scheduled, although some individuals measurements will be from participants five year and six month consultations.

4.3.2 Median change in HbA_{1C}

For the entire analysis sample, mean HbA_{1C} at diagnosis was 6.5% (SD 1.5). Variance in HbA_{1C} measurements decreased from diagnosis to the three month consultation (Figure 4.6), and remained fairly static over the following 5 years. Figure 4.6 shows that the population median HbA_{1C} decreased slightly after diagnosis, then remained around 6.5% for the first five years.

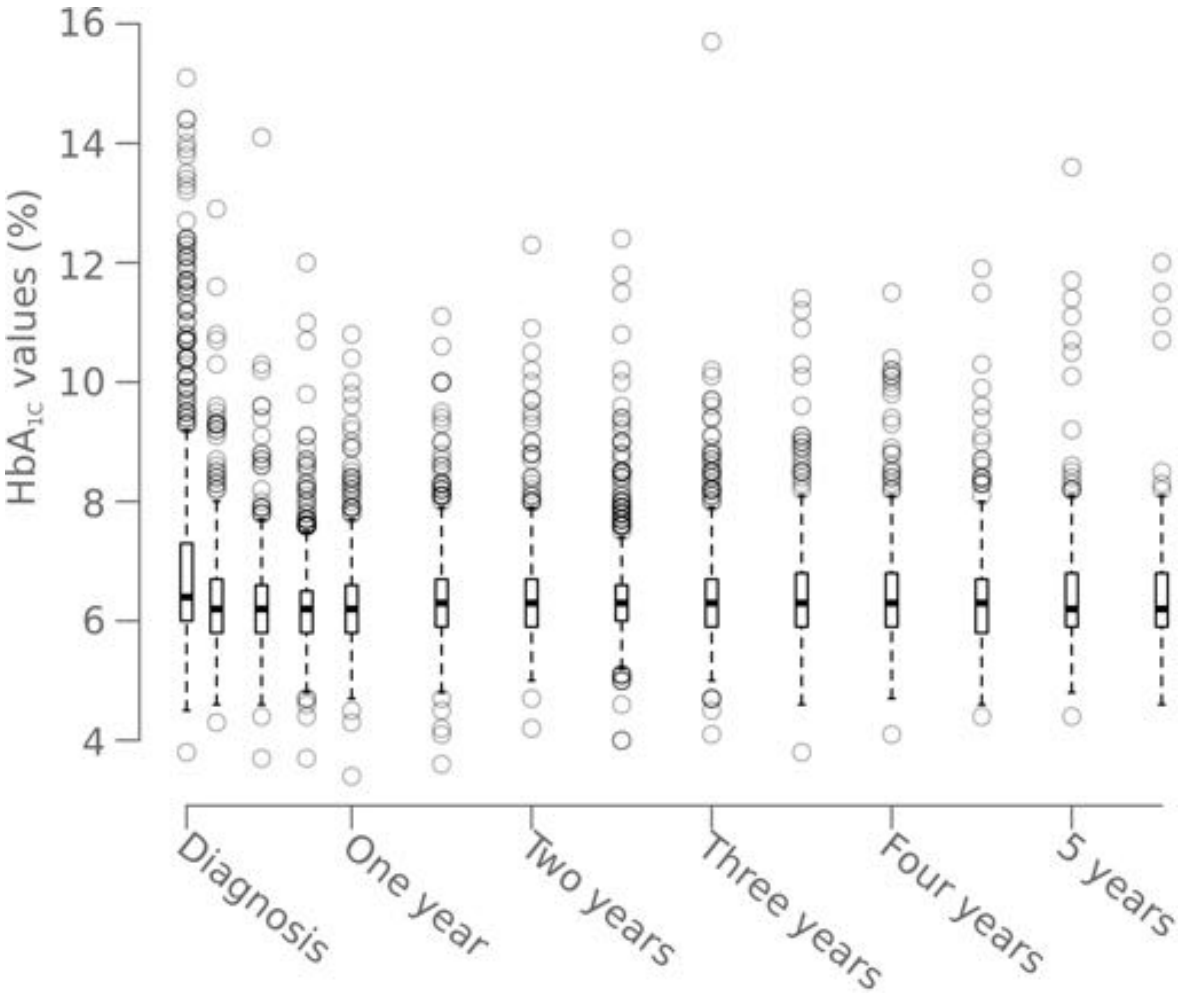


Figure 4.6: Box-plot showing median change in HbA_{1C}, inter-quartile range, and measurements outside the inter-quartile range in the intensive treatment group of the ADDITION-*Denmark* trial.

4.3.3 Identified trajectory groups

Four trajectories of glycaemic control were identified in the cohort (Figure 4.7). The majority of individuals (n=792, 87.5%) can be grouped into a trajectory that started low (mean HbA_{1C}; 6.4%, SD 0.9) and remained low over the five years of follow-up, which I named low-low (Table 4.1; —, the adjacent sparkline is a visual reminder of the low-low trajectory. The green rectangle represents an HbA_{1C} of less than 7.5%). Two trajectories, called medium-low (—) and medium-high (—), were identified for individuals who had an elevated HbA_{1C} at diagnosis (mean HbA_{1C}; 9.4%, SD 1.9 and 8.5%, SD 2.5). The medium-low (—) group improved glycaemic control over follow-up (n=74, 8.2%), while the medium-high (—) group deteriorated over follow-up (n=21, 2.3%) (Figure 4.7). A fourth group, high-medium (—; n=19, 2.1%), had very high glucose values at diagnosis (mean HbA_{1C}; 11%, SD 1.6) which improved over follow up (Figure 4.7).

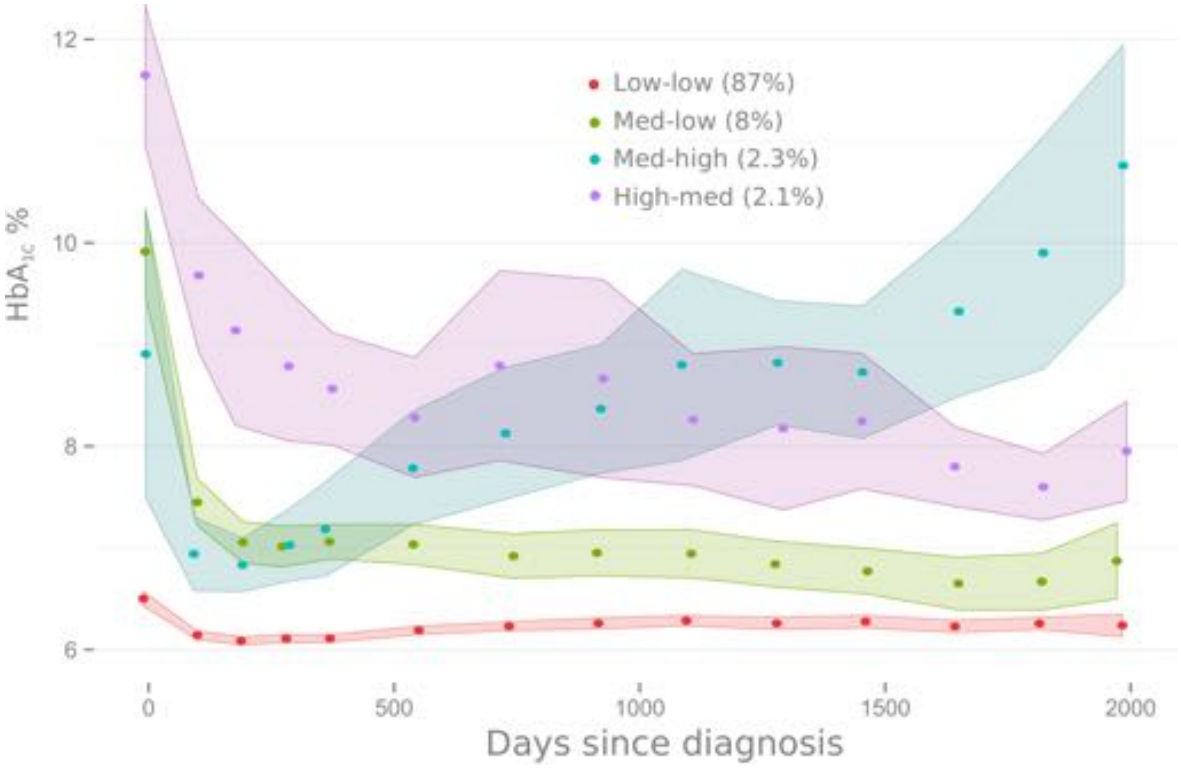


Figure 4.7: Mean (95%CI) HbA_{1C} values at each time point for the four HbA_{1C} trajectory groups identified in ADDITION-*Denmark*, from diagnosis to five years.

4.3.4 Model fit

The mean predicted probability of group membership was lowest for the medium-low (—) group (p=0.86), which suggests adequate differentiation between trajectories. Plots of the residuals suggest a good fit, although predicted values for the medium-high group lagged behind observed values due to the abrupt change in glycaemic control in the first three months. Removing individuals that had an event or died during follow up did not change the

Table 4.2: Comparison baseline characteristics of each identified HbA_{1C} trajectory in ADDITION-*Denmark* to the preferred low-low and med-low trajectories

	Reference low-low mean difference[†]or difference in proportions[‡](95%CI)			Reference med-low; mean difference[†]or difference in proportions[‡](95%CI)
	Med-low (—)	Med-high (—)	High-med (—)	Med-high (—)
Male	18% (6,29)	16% (-6,39)	13% (-11,37)	-2% (-25,22)
Age (1 year)	-2.9 (-4. 5,-1.3)	-3.7 (-7.2,-0.2)	-6.1 (-9.1,-3.1)	-0.8 (-4.6,2.9)
BMI (1 kgm^{-2})	0.3 (-0.97,1.56)	3.6 (0.6, 6.5)	2.2 (-2.8,7.2)	3.3 (0.08,6.4)
Current smoker	-6% (-16,5)	11% (-14,36)	4% (-21,29)	17% (-10,44)
HbA_{1C} % (1 unit)	3.0 (2.5,3.4)	2.1 (0.9,3.3)	4.6 (3.8,5.4)	-0.9 (-2.2,0.4)
HbA_{1C} (1 $mmolmol^{-1}$)[*]	32 (28,37)	23 (9,35)	50 (42,59)	-10 (-24,4)
Total cholesterol (1 $mmolL^{-1}$)	0.3 (0.03,0.6)	0.5 (-0.09,1.01)	-0.35 (-1,0.31)	0.1 (-0.5,0.7)
LDL cholesterol (1 $mmolL^{-1}$)	0.1 (-0.1,0.4)	0.2 (-0.4,0.7)	0.1 (-0.7,0.9)	0.04 (-0.5,0.6)
HDL cholesterol (1 $mmolL^{-1}$)	-0.1 (-0.2,-0.03)	-0.2 (-0.3,0.08)	-0.1 (-0.3,0.03)	-0.1 (-0.2,0.04)
HDL cholesterol (1 $mmolL^{-1}$)	0.6 (0.2,0.9)	1.5 (-0.31,2.58)	0.6 (0.03,-1.3)	1.0 (-0.3,2.1)

Trajectories are arbitrarily named based on subjective assessment of the shape of the mean trajectory of the group.
[†] Mean difference for continuous variables.
[‡] Difference in proportions for binary variables.
[*] International Federation of Clinical Chemistry units.

shape of the trajectories substantially.

4.3.5 Trajectory characteristics

The low-low (—) trajectory group, with good glycaemic control over five years, was selected as the primary comparison group. Individuals in the low-low (—) group were older and had lower baseline HbA_{1C} levels than individuals in the remaining three trajectories (Table 4.2). Comparing the medium-low (—) to low-low (—) trajectories, medium-low (—) had higher total cholesterol (0.3 $mmol\,l^{-1}$; 95%CI 0.03,0.6) and triglycerides at baseline (0.6 $mmol\,l^{-1}$; 95%CI 0.2,0.9). The medium-high (—) group had a higher BMI then the low-low group (—; 3.6 kgm^{-2}; 95%CI 0.6,6.5). The high-medium (—) group, which contained only 19 individuals, differed only in being younger and having a higher baseline HbA_{1C} than the low-low (—) group (Table 4.2).

4.3.5.1 Medication by trajectory

Formal statistical comparisons of medication patterns during follow-up were not undertaken due to the uneven distribution of individuals across groups limiting power, although raw values are reported (Figure 4.8). Individuals in the low-low (—) trajectory redeemed the lowest number of prescriptions for glucose lowering medication. Individuals in the low-low (—) and medium-low (—) trajectories were less likely to be prescribed sulphonylureas than individuals in the less favourable medium-high (—) and high-medium (—) trajectory groups. In general, metformin then sulphonylureas were the most commonly prescribed glucose lowering medications across the four trajectory groups. Insulin use remained rare in the low-low (—)

group, but by three years, 50% of the 19 individuals in the high-medium () group had redeemed a prescription for insulin in the last three months.

Figure 4.8: Medication use by trajectory group within ADDITION-*Denmark* (proportions in circles). Prescription medication redemption data is assumed to have 100% coverage. Individuals that died have been excluded from this figure, although patterns of agent redemption are similar including individuals that died during following up (see Figure C.1, on page 226).

4.4 Discussion

In this prospective cohort of individuals with screen-detected diabetes, I identified four clinically distinct trajectories of glycaemic control. The majority of individuals (87.5%) had slightly elevated HbA_{1C} at diagnosis and were able to maintain good glycaemic control over the following five years (the low-low trajectory,). A small proportion had high levels of blood glucose at diagnosis that improved over five years (high-med , 2.1%). The final two sub-sets of the sample had similar high levels of glycaemia at diagnosis. One group was able to attain and maintain glycaemic targets (med-low , 8.2%), while the other initially attained good control, but then deteriorated over five years (med-high , 2.3%). The majority of individuals (96%) experienced a glucose trajectory that was predominately below an HbA_{1C} threshold of 8% from three months after diagnosis. While power was limited due to the small size of divergent trajectories, traditional risk factors and medication choices at diagnosis did not explain why some individuals diverge into less ideal glycaemic trajectories.

4.4.1 Context within the literature

The majority of studies exploring changes in glycaemia in diabetes assume a single latent process, variations from which can be adjusted for using collected covariates. This analysis does not rely on a single underlying trajectory, and instead allows the observed trajectories to be clustered into similar groups. This novel approach prevents direct comparisons with the literature to date.

Soon after diabetes diagnosis, an individuals glucose levels typically reduce as a result of changes in lifestyle behaviour and/or treatment with hypoglycaemic medication.[102,187] In the UKPDS, after an initial decrease, HbA_{1C} values increased gradually over the next 15 years.[101] This contrasts with the maintenance of good glycaemic control experienced by the majority of individuals in ADDITION-*Denmark*, and is likely related to both the earlier diagnosis and temporal shifts in what constitutes best practice in diabetes care. The UKPDS recruited between 1977 and 1991, while the ADDITION-*Denmark* recruited from 2001 to 2004. In addition to ADDITION-*Denmark* participants being screen-detected, rather than recently diagnosed individuals, the treatment protocol applied (Table 2.1, page 27) suggests that participants in this analysis experienced a level of close to contemporary guidelines.[194] Long term post trial follow up of the UKPDS showed that the gradual deterioration in glyceamic control had begun to plateau in the first five years after the trial intervention ended for both treatment groups (1997 to 2002).[102]

4.4.2 Medication and glycaemic control

Elevated values of CVD risk factors have been associated with both a higher probability of being prescribed glucose-lowering medicine as well as greater decreases in HbA_{1C} after diagnosis in ADDITION-*Europe*.[2] In all four identified trajectories HbA_{1C} values decreased immediately after diagnosis, with larger decreases present in those with a higher baseline

HbA_{1C}. Of particular concern were the small subset (n=21) of individuals that had gradually increasing HbA_{1C} levels after an initial decrease after diagnosis. Differentiating the characteristics of individuals that had a poor long term HbA_{1C} from those that had similar baseline HbA_{1C} measurements at diagnosis but stable trajectories was difficult due to the low number of individuals. Individuals with a suboptimal trajectory appeared to be more likely to receive sulphonylureas, but otherwise their prescription redemption history was very similar to individuals with a preferred trajectory. Khunti et al, in a sample of 81,573 individuals with diabetes, demonstrated that increases in the prescription of glucose lowering drugs can lag more than seven years behind changes in HbA_{1C} values.[176] While information on potential external reasons for not intensifying treatment is unavailable for this analysis, this clinical inertia appears to be present in the trajectory that experienced the worse glycaemic trajectory after diagnosis (med-high, ).

Within the low-low () group, participants who had a low HbA_{1C} at diagnosis and maintained good glyceamic over the five years, the prescription of glucose lowering medication increased from 24% at six months, to 50% at five years. This provides evidence that, despite intervening to arrest glyceamic disfunction earlier, diabetes continues to progress requiring greater uptake of pharmacotherapy over time in a pattern seen in long standing[180] diabetes. The UKPDS provides further insight on this deterioration of glyceamic function, as in a subset of patients that were adherent to sulphonylureas for the first six years, they found that β-cell function improved in the first year after diagnosis, but gradually deteriorated over the next five years to around the point it was at diagnosis.[179] The ongoing Glucose Lowering In Non-diabetic hyperglycaemia Trial (GLINT) (Trial registration: ISRCTN34875079), which in 2024 will report on the effect of glucose lowering via metformin vs. placebo in those with elevated blood glucose below the diabetes threshold, should provide interesting evidence on whether intervening even earlier in the disease trajectory will prevent the gradual disfunction in glyceamic control.

4.4.3 Is there clinical inertia in pharmacotherapy?

Individuals in the low-low () trajectory appeared to redeem less glucose lowering medication than the other trajectories three months after diagnosis. Suggesting if clinical inertia is present, treatment choices at diagnosis remain driven by glucose levels at diagnosis. Less certain is the relationship between trajectory and medication over time. In this study, sulphonylurea redemption appeared to show a similar pattern of low uptake between the low-low () and med-low () groups, while the proportion redeeming in med-high () increased after two years, and was constant after diagnosis in high-med (). The patterns seen in high-med () and med-high () may reflect the underlying changes in glycaemic control being experienced, while the low-low () and med-low () group were less likely to need the addition of a sulphonylurea to their treatment strategy due to maintaining good control.

4.4.4 Reasons for cautious interpretation

Previous research examining changes in HbA_{1C} following diagnosis either take a simple single change value[184], or stratify patients into those with 'good' or 'poor' adherence to glycaemic targets[140,195], but these crude categories are either overly simplistic (change statistics) or rely on subjective groupings (such as 'good' and 'poor'), and may mask a more complex pattern of HbA_{1C} change. This study is a novel description of the heterogeneity present in glycaemic trajectories, using a population with an unparalleled number of repeated glycaemic measurements and linkage to a national prescription redemption database that can be assumed to have full coverage.[153] The model used is sensitive to bias if the glyceamic control of individuals that were lost to follow up diverts from the pattern of individuals not lost to follow up who were following a similar pattern of HbA_{1C} values. As follow up was fairly frequent (median of eleven follow ups in five years), most individuals contributed a large number of observations to the analysis.

Removing individuals without five years of data did not have substantial effects on the trajectories produced. The identified trajectories remain dependent on the data being modelled, and a different number of trajectories, as well as different shapes, would likely be identified if looking at a different time frame in the same population. Individuals were assigned to trajectories based on their predicted probability of group membership. While the model appeared to differentiate the trajectories well, the four groups are a statistical device, and no individual can be categorically defined as following their assigned trajectory. Rather, an individual assigned to a category merely followed a trajectory that matched that particular trajectory better than the other three. Figure 4.9 shows the variation present within each trajectory, and highlights the importance of acknowledging that the identified trajectories represent a mean trajectory over many time points, and that at each snapshot of time there is a lot of variation present at an individual level. So while the identified trajectories provide a more granular view of changes in glycaemic control after diagnosis than the classical 'initial decrease followed by gradual increase' noted in the UKPDS, these clusters still represent mean processes from which there is individual variation.

In the comparisons between trajectories present, I do not account for the uncertainty in each individuals' group membership. Choi et al, in a paper exploring trajectories of caregiver psychological distress, addressed the uncertainty of individuals membership by weighting each person's contribution to the multinomial model comparing trajectories by the probability of group membership.[196] While instinctively this method seems promising, the statistical merits have not been explored and this technique was not employed. As with any repeated analysis, the possibility exists for regression to the mean. This is unlikely to have much effect in this analysis, as HbA_{1C} trajectories span many repeated measurements.

4.4.5 Implications for practice

I identified four distinct trajectories of HbA_{1C} after detection of diabetes by screening that have not been previously described in the literature. The majority of individuals follow

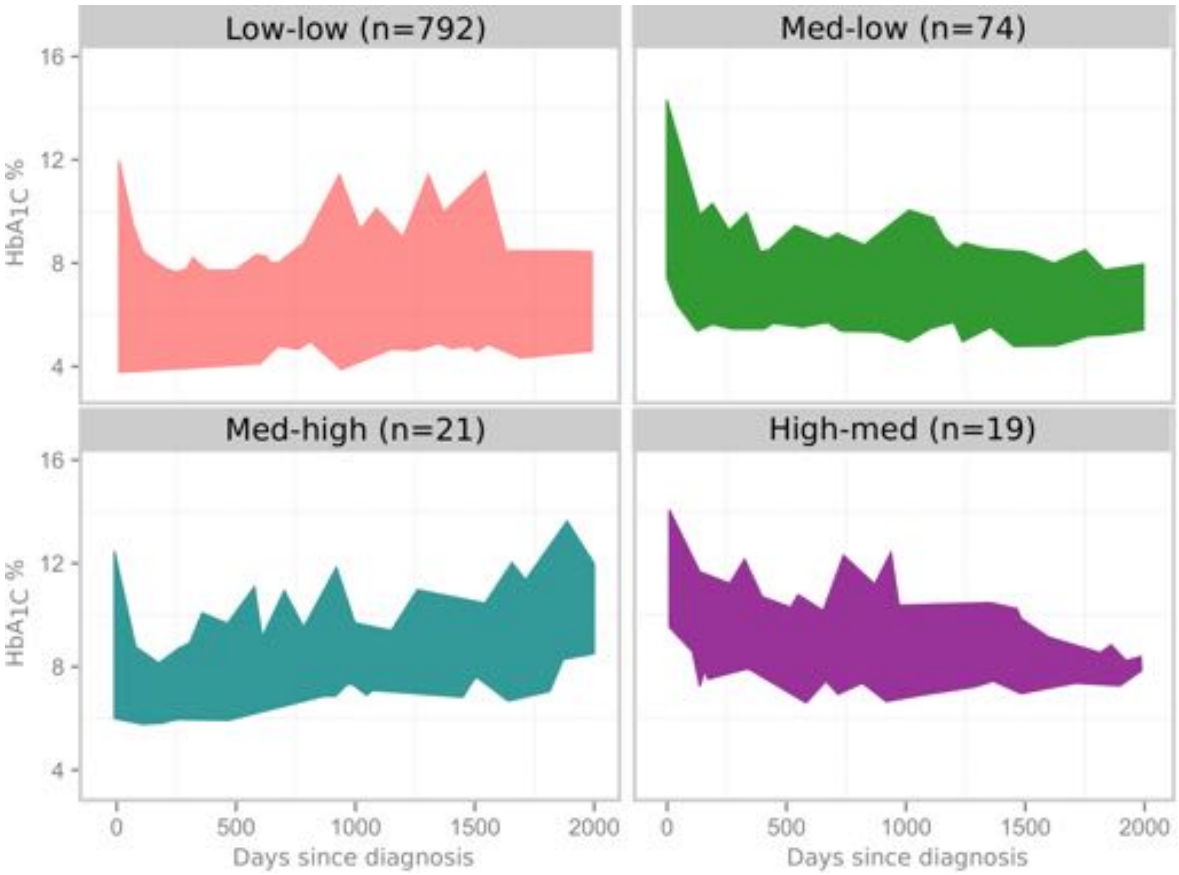


Figure 4.9: Range of individual HbA_{1C} values within the four trajectory clusters identified in ADDITION-*Denmark*. The coloured polygon within each plot represents the range of values present within that group at each day of the 2000 day follow up. The observation with the lowest probability of belonging to each assigned group (i.e. the observation with the worst fit) has been excluded to prevent the potential of an edge of the polygon representing one individual.

a stable trajectory after diagnosis, with a greater decrease immediately after diagnosis for individuals with elevated initial HbA_{1C} values. A small proportion though experience a gradual deterioration in glycaemic control after an initial decrease, although more research is needed to confirm whether this is likely to be a product of clinical inertia in responding to changes in HbA_{1C}, differing pathophysiology or pharmacogenetic interactions.[197] The results suggest that while good glycaemic control was maintained in a large proportion of this Danish population, subsets of the population experience divergent trajectories that are difficult to differentiate at diagnosis. Researchers, policy makers and patients should be aware of this heterogeneity, and that there is a distinct minority of individuals that are not well described in the literature.

4.4.6 In the context of optimising CVD risk management

Having previously established the medication burden of diabetes (Chapter 3), I have now shown that glycaemic control tends to be adequate, although there are divergent sub-groups.

Diabetes care though is about total cardiometabolic health, and so in the next chapter (Chapter 5) I will explore changes in CVD risk factors after diagnosis.

Chapter 5

Change in cardiovascular disease risk factors following diagnosis of type 2 diabetes by screening

5.1 Introduction and aims

People with screen-detected diabetes are often on multiple medications and that pharmacotherapy burden then increases after diagnosis (Chapter 3), and the majority of individuals in an intervention promoting tighter glycaemic control are able to arrest any degradation in glycaemic control over the first five years after diagnosis (Chapter 4). At screen diagnosis, individuals exhibit an adverse CVD risk profile.[140] This variation in cardiometabolic health has been reported in ADDITION-*Cambridge*, where we also know that the modelled risk of CVD decreased 5.3% on average over the 14 months after diagnosis.[198] The mean shifts in a population are an important observation in order to understand the societal and health system burden of a condition, or in the case of randomised studies the effectiveness of a treatment in a population. For GPs who wish to discuss CVD risk factor reduction targets, population means obscure the fact that potential changes in CVD risk factors at the individual level can be expected to be directly related to how far from recommended targets for each risk factor a person is at diagnosis. Associated factors that lead to individual level departures from population level averages can be modelled, but understanding how multiple risk factors may influence an individual trajectory is difficult.

Figure 5.1 shows three modelled trajectories derived using the UKPDS outcomes model for changes in HbA_{1C} and Total:HDL cholesterol in the first 15 years after clinical (non-screened) diagnosis. These estimates are shown alongside the actual observed mean seen in the UKPDS trial. These two risk factors provide an example of the variation in trajectories that is expected based on initial values of a risk factor. Individuals with low HbA_{1C} or Total:HDL cholesterol at diagnosis tend to see increases by five years, while those with high values are predicted to decrease. It is only individuals near the mean at diagnosis that experience a change in the risk factors that mirrors the sample mean. The curves shown in

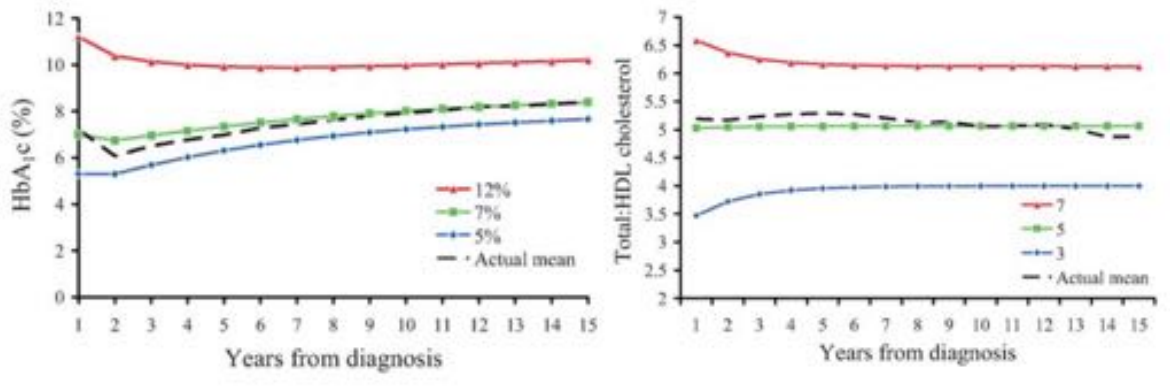


Figure 5.1: Simulated vs mean actual change in HbA_{1C} and Total:HDL cholesterol using the UKPDS outcomes model. Figure reproduced with permission from *Clarke et al(2004)Diabetologia,47(10)1747-59.*

Figure 5.1, while illustrative of the variation that is not represented by a single mean for the sample, are not applicable in a contemporary setting as they show simulated change in a model that was only validated to predict outcomes, the UKPDS population were diagnosed decades ago when diagnosis in a clinical setting was likely later, and treatments like statin therapy were not yet established.[74]

In addition to the variation in changes in risk factors, evidence suggests that primary care teams may be reluctant to prescribe intensive treatment to asymptomatic individuals with screen-detected diabetes and there are also examples of inequity in provision of healthcare for patients with diabetes.[199,200] An analysis that stratified change in risk factors by underlying risk at diagnosis and included a measure of deprivation would be able to provide some evidence towards the relationship between need and achieved change.

The ADA *Standards of Medical Care in Diabetes* state that *'...individuals must also assume an active role in their care'*, and that *'the management plan should be formulated as a collaborative therapeutic alliance'*.[14] In England, contemporary guidelines encourage GPs to *'involve the person in decisions about their individual HbA_{1C} target level...'* and that blood pressure therapy should be based around *'...individually agreed targets'*.[118] While GPs may from prior clinical experience be able to approximate how an individual's CVD risk factors will change, there are no empirical estimates with which they can frame a discussion over how a recently diagnosed patients CVD risk factors may change over time.

Earlier in this introduction I hypothesised that changes in cardiometabolic health are strongly associated with health at diagnosis. English guidelines state that *'if the person is considered not to be at high cardiovascular risk, estimate cardiovascular risk annually using the UKPDS risk engine'* and to *'consider using cardiovascular risk estimates from the UKPDS risk engine'* when discussing care.[118] This suggests that the UKPDS risk score has been identified as a suitable, and simple, method to differentiate different levels of cardiometabolic health that should already be utilised in practices throughout the UK.

In diabetes care CVD risk factor targets are routinely set[14,117], yet as I have shown with HbA_{1C} in Chapter 4, the absolute achievable change differs dramatically based on where

an individual is at diagnosis, and the traditional stance taken from the UKPDS that blood glucose drops then increases after diagnosis obscures this diversity. I hoped that by taking 10-year modelled CVD risk, as a proxy of cardiometabolic health, to stratify the population at diagnosis, I could then provide information on the expected trajectories of CVD risk factors that are more applicable to the individual in a clinical setting.

5.1.1 Aims

Using ADDITION-*Europe*, this chapter examines (i) baseline CVD risk profiles and medication patterns, (ii) change in treatment and CVD risk factors stratified by UKPDS modelled CVD risk and (iii), and how these changes are patterned by socio-economic status.

5.2 Methods

This cohort analysis uses data from the ADDITION-*Europe* trial, details of which are given in Section 2.1.0.3 on page 25. For this analysis, self-reported age left full time education was first grouped into tertiles, and then dichotomised into 1st vs. 2nd and 3rd tertile. I varied the education cut point by country due to a marked difference in age left education in Denmark (Figure 5.2). Tertile breakpoints fell on 16 years in the United Kingdom and the Netherlands and 21 years in Denmark, which were also the mode for each country. As the cut points fell on duplicated values, individuals were assigned to the *'higher'* education category. A second deprivation measure, employment status, was self-reported and coded as *'in employment'* vs. *'retired/unemployed/other'*.

5.2.1 Statistical analysis

Ten-year modelled CVD risk was calculated from the UKPDS model (version 3 β)[155] at baseline and five years post-diagnosis. The risk score and how values were calculated in ADDITION-*Europe* is documented in Section 2.2 (page 32).

To describe changes in general cardiometabolic health, the population was first divided into deciles of 10 year UKPDS modelled risk. Change in modelled CVD risk, by decile, was then presented graphically. For the main analysis the deciles of modelled CVD risk were collapsed into quartiles. Socio-demographic (age, sex, ethnicity, education), health behaviour (smoking status), health utility assessed by the summary index score of the European Quality of Life Questionnaire (EQ-5D)[201] and clinical characteristics were summarised by risk quartile and in the cohort as a whole.

Within each modelled CVD risk quartile, the mean absolute change in each CVD risk factor was calculated. To adjust for the differing demographic characteristics of each quartile, linear regression was used to estimate the mean absolute change in each CVD risk factor by baseline CVD risk quartile, adjusted for age at diagnosis, gender, ethnicity, age left full-time education and randomisation group. The mean values specified in Equation (5.1) of each regression coefficient where then applied to the regression equation to estimate the

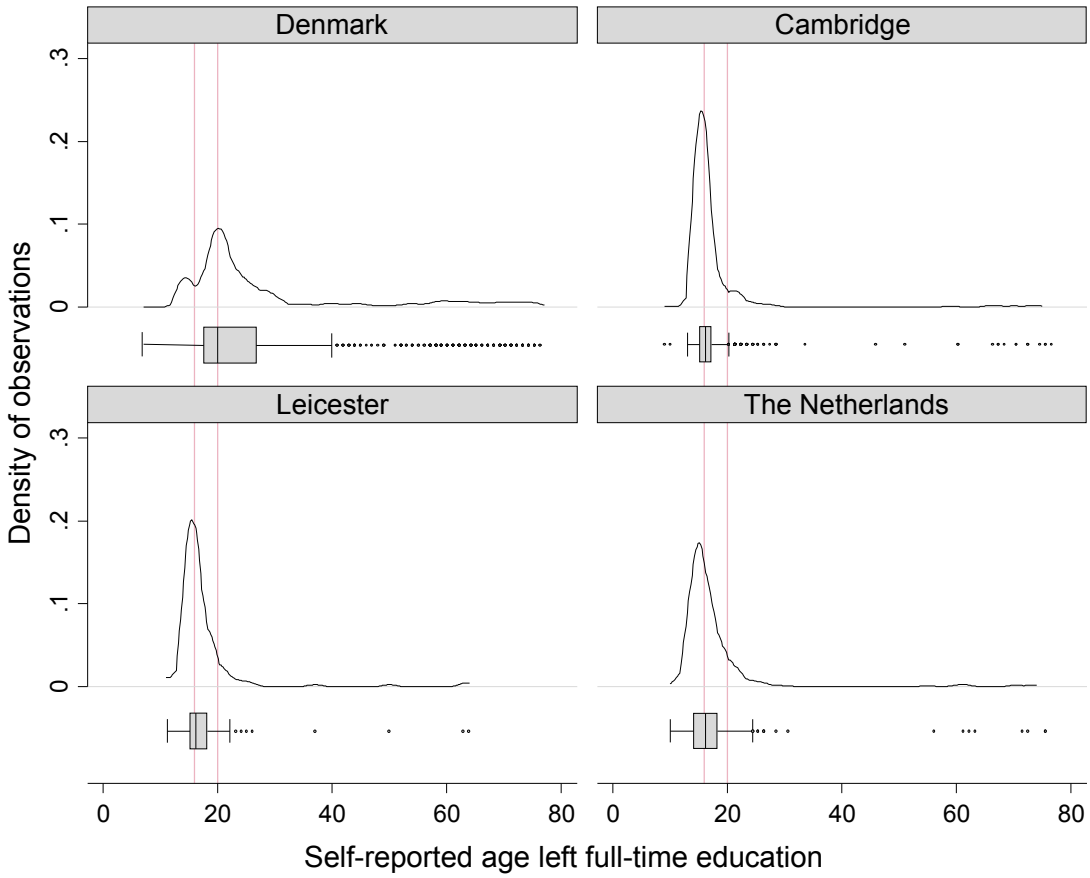


Figure 5.2: Differing distributions of age left education by centre in ADDITION-*Europe*, expressed as kernel density estimates and box plots. Red line indicates 16 and 20 years, which are the two cut points used in the analysis.

adjusted mean change (where ϵ, the estimator of variance, accounts for non-independence within practices).

$$\ln \frac{p}{1-p} = \alpha + \beta_{Age} 60.1 + \beta_{LowEducation} 0.44 + \beta_{Female} 0.42 + \beta_{White} 0.94 + \beta_{IntensiveArm} 0.55 + \epsilon \tag{5.1}$$

Linear regression analyses were undertaken separately within each centre, incorporating a robust variance estimate to allow for practice level clustering. Adjusted means for each centre were then combined via fixed effects meta-analysis, with an I^2 of <75% set as an *a priori* threshold before the level of heterogeneity would prevent the use of fixed effects meta-analysis.[202]

The predicted probability of being prescribed any blood pressure lowering, lipid lowering or glucose lowering medication between diagnosis and five years adjusting for demographic variables (within quartiles of baseline CVD risk) was calculated using a logistic model analogous to the primary analysis model. The adjusted linear predictor (y) of the log odds of reporting initiation of medication use was expressed as predicted probabilities (p) using Equation (5.2).

$$p = \frac{e^y}{1 + e^y} \tag{5.2}$$

5.2.2 Sensitivity analysis

The primary analysis was repeated in only the routine care arm, and results that conflicted are reported in the results (Section 5.3.8, page 84). Fixed effects meta-analyses of centre level regressions was used selected as a parsimonious primary model as I did not expect the true effects to vary across centres. The primary analysis was also repeated using a multilevel model of practices within centres. These multilevel models allowed for the possibility of the four ADDITION-*Europe* centres representing a distribution of true effects.

Potential interactions between baseline modelled CVD risk and education were explored in a a multilevel model analogous to the primary analysis, except applied to the entire sample rather than stratified by quartile of modelled risk at diagnosis. Only significant interactions are reported (Section 5.3.7, page 83).

To explore the possibility that the observed associations were dependent on how modelled CVD risk was stratified, I produced scatter plots of change in each risk factor by baseline modelled CVD risk. Using quartiles appeared to accurately summarise the continuous relationship between risk factors and baseline risk. Results were similar within randomisation groups, and they were combined into a single cohort with adjustment for trial group. A multilevel logistic model (practices within centres) was used to explore socio-demographic information that predicted loss to follow up. Regression to the mean within quartiles was explored by plotting baseline values against change scores.[203]

5.3 Results

5.3.1 Participant characteristics at diagnosis

196 people died before five-year follow up, 48 of which were CVD related deaths. Complete data to calculate the UKPDS risk score at diagnosis was missing for 443 individuals. Baseline socio-demographic characteristics were similar between individuals who were included in the analysis (n=2,418) and those who were excluded due to missing clinical data at baseline or follow up (n=443), except for sex, where women were more likely to have missing data than men (OR 1.3; 95%CI 1.04, 1.6).

5.3.2 Risk factors at diagnosis by modelled CVD risk

As expected, the level of baseline CVD risk factors increased from the lowest to the highest quartile of baseline modelled CVD risk (Table 5.1). Compared to the highest risk quartile, people in the lowest risk quartile were more likely to be female (67% vs. 19%), younger (56 years, SD 7.2 vs. 63 years, SD 5.5) and to be more highly educated (54% vs. 33%). Individuals at low risk were also more likely to be non-smokers (86% vs. 62%), free of cardiovascular disease and have more favourable clinical characteristics (Table 5.1). The proportion of the

Table 5.1: UKPDS (version 3) modelled CVD risk score in the ADDITION-*Europe* trial cohort at baseline by centile and combined

		10-year modelled CVD risk by quartile and overall at diagnosis				
	N(%)[†]	<25th centile	25th-49th centile	50th-75th centile	>75th centile	Combined
Self-reported						
% Female	2418 (85%)	67%	47%	33%	19%	42%
Mean (SD) age in years at diagnosis	2418 (85%)	56 (7)	60 (7)	62 (6)	63 (5.5)	60 (7)
White ethnicity	2418 (85%)	91%	94%	95%	98%	94%
Low education	1853 (65%)	39%	40%	47%	53%	45%
Current smoker	2389 (84%)	14%	23%	30%	38%	26%
Median (IQR[‡]) units of alcohol per week	2141 (75%)	4 (1,10)	4 (1,13)	5 (1,14)	5 (1,14)	4 (1,12)
Mean (SD) EQ-5D score	2312 (81%)	0.82 (0.22)	0.84 (0.20)	0.85 (0.20)	0.82 (0.22)	0.83 (0.21)
Any glucose lowering drug	2378 (83%)	0.7%	0.3%	0.8%	0.5%	0.6%
Any hypertensive drug	2378 (83%)	47%	44%	47%	45%	46%
Any lipid lowering drug	2378 (83%)	15%	16%	14%	20%	16%
History of myocardial infarction	2292 (80%)	0.2%	1.6%	4.5%	17.8%	6.0%
History of stroke	2254 (79%)	0.2%	0.7%	1.5%	6.1%	2.1%
Clinical						
Mean (SD) BMI in kgm^{-2}	2418 (85%)	31 (6)	32 (6)	32 (6)	32 (5)	32 (6)
Median (IQR[‡]) HbA_{1C} %	2418 (85%)	6.2 (5.9,6.7)	6.5 (6.1,7.0)	6.7 (6.2,7.6)	7.2 (6.6,9.2)	6.6 (6.1,7.4)
Median (IQR[‡]) HbA_{1C} $mmol\,mol^{-1}$	2418 (85%)	44 (41,50)	48 (43,53)	50 (44,60)	60 (49,77)	49 (43,57)
Mean (SD) systolic blood pressure in mmHg	2418 (85%)	137 (17)	146 (18)	153 (20)	161 (24)	149 (22)
Mean (SD) total:HDL cholesterol ratio	2418 (85%)	3.8 (1.1)	4.4 (1.2)	4.9 (1.3)	5.7 (1.6)	4.7 (1.5)
Median (IQR[‡]) trigylcerides in $mmolL^{-1}$	2417 (85%)	1.4 (1.0,1.9)	1.5 (1.1,2.1)	1.7 (1.3,2.4)	2.1 (1.5,3.0)	1.6 (1.2,2.4)
Median albumin creatinine ratio (IQR[‡])	2259 (79%)	0.7 (0.3,1.4)	0.8 (0.4,1.5)	0.9 (0.4,2.0)	1.4 (0.6,3.5)	0.9 (0.4,2.0)
Range 10-year modelled CVD risk at baseline	2418 (85%)	4,17	17,25	25,35	35,93	-
Had CVD event during followup	2418 (85%)	2.1%	4.3%	6.8%	11.3%	6.1%

[†] Total with risk score available at baseline and follow up.
[‡] IQR = inter-quartile range.

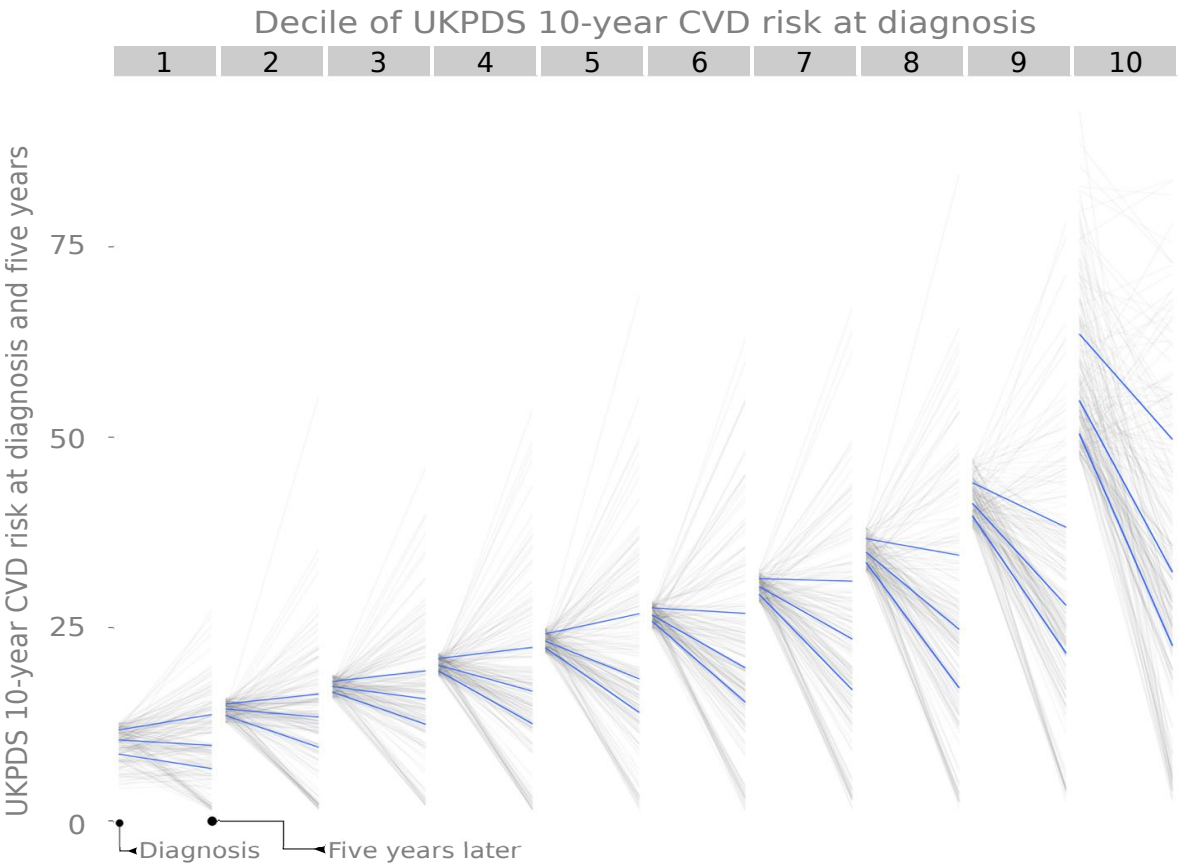


Figure 5.3: Change in 10-year modelled UKPDS CVD risk from diagnosis to five years, by decile of baseline risk, in ADDITION-*Europe*. Grey lines represent an individual, and blue lines represent the median and inter-quartile range.

population prescribed cardio-protective medication (lipid, glucose or blood pressure lowering medication) at baseline varied by at most 5% (absolute percentage points) across the four quartiles (Table 5.1), although prescription rates were also low (<50% for Blood Pressure (BP) lowering medication and <21% for lipid lowering medication).

5.3.3 Variation in change in modelled CVD risk by decile

Figure 5.3 shows change in 10 year modelled CVD risk from diagnosis to five years, by decile of modelled CVD risk at diagnosis. Individuals in the lower deciles tended to maintain similar levels of modelled CVD risk from diagnosis to five years after diagnosis. As the baseline decile increased, the achieved reduction in modelled CVD risk also increased (Figure 5.3). There was a large amount of variation at the individual level, which increased with decile of modelled risk.

5.3.4 Variation in change in modelled CVD risk by quartile

Figure 5.4 shows the distribution of change in modelled CVD risk from baseline to five-year follow-up by quartile of modelled risk at diagnosis. On average there was a reduction in modelled CVD risk across the whole trial cohort. Participants in the highest quartile of

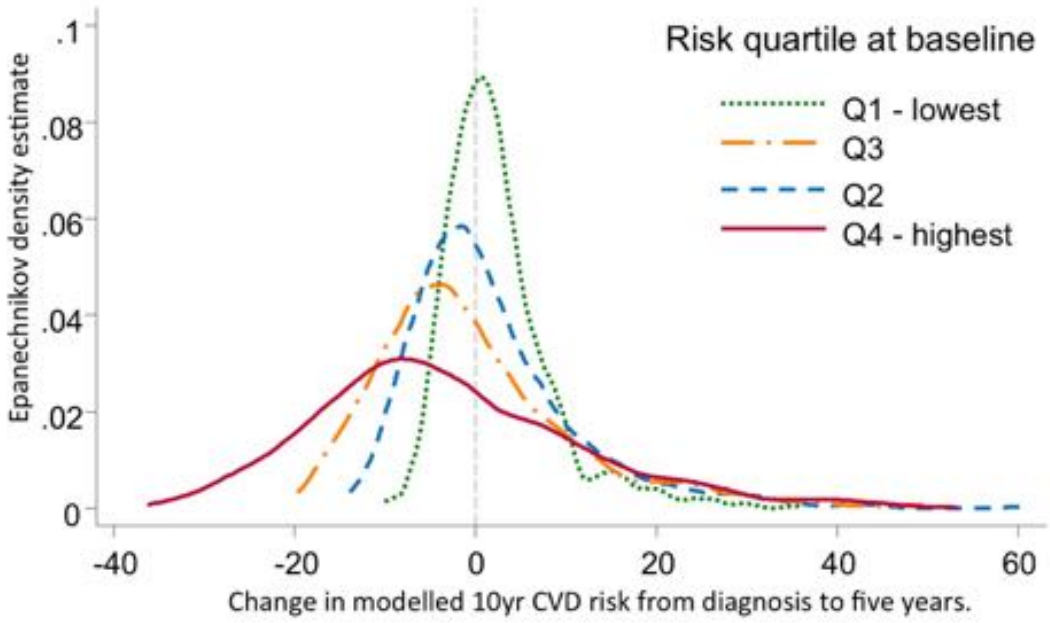


Figure 5.4: Distribution of change in modelled CVD risk in ADDITION-*Europe* from diagnosis to 5 years, by quartile of modelled CVD risk at diagnosis.

modelled CVD risk at baseline showed the largest reduction in CVD risk, and the largest variation in change. Participants in the lowest quartile of modelled risk at baseline had very similar levels of CVD risk at five-year follow-up and showed the least variation in risk change.

5.3.5 Change in CVD risk factors at 5 years

5.3.5.1 BMI

There was a small mean reduction in BMI in the whole cohort between baseline and follow-up ($-0.5\,\mathrm{kgm^{-2}}$). Reductions were largest among participants in the second quartile for modelled CVD risk (Q2; $-0.7\,\mathrm{kgm^{-2}}$; 95%CI -0.9, -0.5) and Q3 ($-0.7\,\mathrm{kgm^{-2}}$; 95%CI -0.1, -0.5). No significant reductions were observed in Q1 and Q4 (Table 5.2 and Figure 5.5).

5.3.5.2 HbA_{1C}

Median HbA_{1C} at diagnosis ranged from $44\,\mathrm{mmol\,mol^{-1}}$ (6.2%) in Q1 to $55\,\mathrm{mmol\,mol^{-1}}$ (7.2%) in Q4 (Table 5.1). A significant mean increase in HbA_{1C} was observed in the lowest quartile of baseline risk ($+2\,\mathrm{mmol\,mol^{-1}}$, 95%CI 1,3; 0.1%, 95%CI 0.05, 0.2) over five-years of follow-up. There was no statistically significant change in HbA_{1C} levels in Q2, while large reductions were seen in Q3 (-7 $\mathrm{mmol\,mol^{-1}}$, 95%CI -8,-5; -1.5%; 95%CI -1.7, -1.2) and Q4 (-16 $\mathrm{mmol\,mol^{-1}}$, 95%CI -19,-14; -2.3%, 95%CO -2.5,-2.2).

5.3.5.3 Systolic blood pressure

Mean systolic blood pressure at diagnosis ranged from 137 mmHg (SD 17) in Q1 to 161 mmHg (SD 24) in Q4. In all four quartiles, mean systolic blood pressure reduced (-12.0

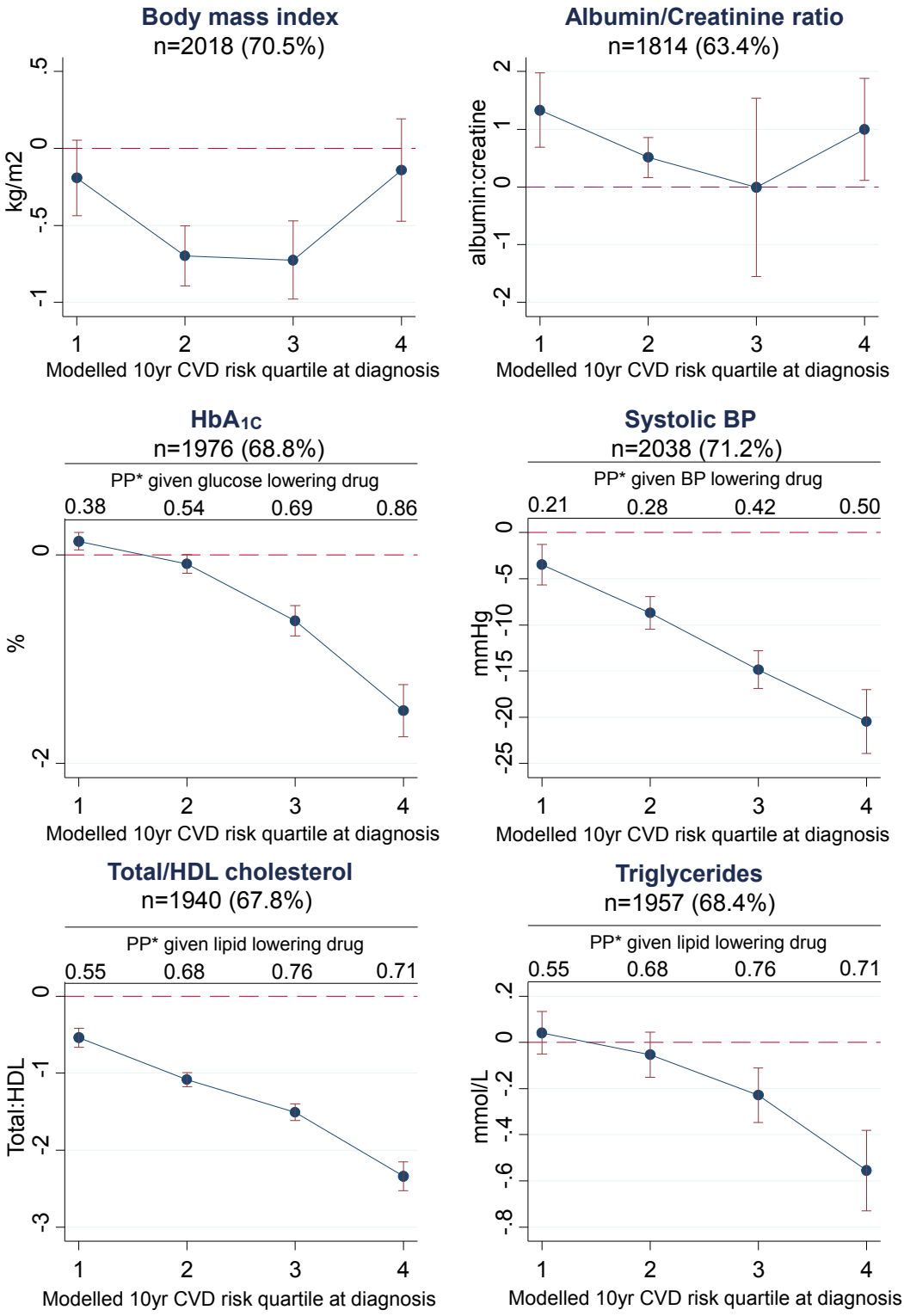


Figure 5.5: Adjusted change in CVD risk factors from baseline to 5 years in ADDITION-*Europe*, stratified by UKPDS V3 modelled CVD risk. PP=predicted proportion. See Section 5.2.1 on page 75 for details on how estimates within quartiles were conditioned to the entire sample.

Table 5.2: Adjusted and unadjusted change between diagnosis and five years in CVD risk factors, by modelled CVD risk quartile at diagnosis

	Baseline modelled CVD risk				
	$<25^{th}$ centile	25^{th}-49^{th} centile	50^{th}-75^{th} centile	$>75^{th}$ centile	Combined
Mean (SD) unadjusted change					
BMI in kgm^{-2}	-0.3 (2.4)	-0.6 (2.4)	-0.8 (2.6)	-0.4 (2.7)	-0.5 (2.6)
Mean (SD) systolic blood pressure in mmHg	-6 (18)	-10 (21)	-16 (22)	-20 (25)	-13 (22)
Mean HbA_{1C} % (SD)	0.17 (0.97)	-0.10 (1.13)	-0.42 (1.54)	-1.19 (1.91)	-0.38 (1.52)
Mean HbA_{1C} $mmol\,mol^{-1}$ (SD)	2 (11)	-1 (12)	-5 (17)	-13 (21)	-4 (16)
Mean (SD) total cholesterol:HDL ratio	-0.67 (1.06)	-1.07 (1.21)	-1.42 (1.30)	-1.92 (1.62)	-1.26 (1.39)
Mean triglycerides (SD) in $mmolL^{-1}$	-0.03 (0.91)	-0.11 (1.45)	-0.24 (1.18)	-0.58 (1.62)	-0.24 (1.33)
Mean albumin creatinine ratio (SD)	1.1 (6.9)	1.8 (17.4)	0.2 (24.9)	3.0 (29.5)	1.5 (21.3)
Percent change in proportion reporting glucose lowering drug	53%	56%	63%	76%	61%
Percent change in proportion reporting blood pressure lowering drug	25%	32%	35%	43%	34%
Percent change in proportion reporting lipid lowering drug	62%	63%	69%	65%	64%
Mean (SD) adjusted[†]change					
BMI in kgm^{-2}	-0.2 (-0.4,0.05)	-0.7 (-0.9,-0.5)	-0.7 (-0.1,-0.5)	-0.1 (-0.5,0.2)	-0.5 (-0.6,-0.4)
Mean (SD) systolic blood pressure in mmHg	-4 (-6,-1)	-9 (-11,-7)	-15 (-17,-13)	-21 (-24,-17)	-12 (-13,-11)
Mean HbA_{1C} % (SD)	0.1 (0.05,0.2)	-0.1 (-0.2,0.01)	-1.5 (-1.7,-1.2)	-2.3 (-2.5,-2.2)	-1.3 (-1.4,-1.2)
Mean HbA_{1C} $mmol\,mol^{-1}$ (SD)	2 (1,3)	-1 (-2,0)	-7 (-8,-5)	-16 (-19,-14)	-4 (-5,-3)
Mean (SD) total cholesterol:HDL ratio	-0.5 (-0.7,-0.4)	-1.1 (-1.2,-1.0)	-1.5 (-1.6,-1.4)	-2.3 (-2.5,-2.2)	-1.3 (-1.4,-1.2)
Mean triglycerides (SD) in $mmolL^{-1}$	0.0 (-0.05,0.1)	-0.1 (-0.2,0.04)	-0.2 (-0.4,-0.1)	-0.6 (-0.7,-0.4)	-0.2 (-0.3,-0.2)
Mean albumin creatinine ratio (SD)	1.3 (0.7,2.0)	0.5 (0.2,0.9)	0.0 (-1.6,1.5)	1.0 (0.1,1.9)	1.0 (0.3,1.8)
Adjusted[†]predicted probability of being prescribed medication at five years (if not prescribed at baseline)					
Glucose lowering drug	0.38 (0.31,0.44)	0.54 (0.50,0.59)	0.69 (0.64,0.74)	0.86 (0.81,0.90)	0.62 (0.60,0.65)
Blood pressure lowering drug	0.21 (0.16,0.25)	0.28 (0.24,0.33)	0.42 (0.36,0.48)	0.50 (0.44,0.57)	0.36 (0.33,0.39)
Lipid lowering drug	0.55 (0.48,0.62)	0.68 (0.63,0.73)	0.76 (0.70,0.81)	0.71 (0.65,0.78)	0.69 (0.66,0.71)

[†] Adjusted for age, gender, white ethnicity, randomisation group, age left education.

mmHg; 95%CI -13.1, -10.8). The smallest reduction was observed in Q1 (-3.5 mmHg; 95%CI -5.7, -1.3) and the largest reduction in Q4 (-20.5 mmHg; 95%CI -23.9, -17.0)

5.3.5.4 Total:HDL cholesterol ratio

The mean (SD) total:HDL cholesterol ratio was 3.8 (1.1) in Q1 at baseline and 5.7 (1.6) in Q4. From diagnosis to 5 year follow-up the total:HDL cholesterol ratio decreased in all four quartiles, with the smallest reduction in Q1 (-0.5; 95%CI -0.7, -0.4) and the largest in Q4 (-2.3; 95%CI -2.5, -2.2) .

5.3.5.5 Albumin:Creatinine ratio (ACR)

Median ACR at baseline ranged from 0.7 in Q1 to 1.4 in Q4. Significant increases were observed in Q1 ($1.3\,\mathrm{mg\,mmol^{-1}}$; 95%CI 0.7, 2.0), Q2 $0.5\,\mathrm{mg\,mmol^{-1}}$; 95%CI 0.2, 0.9) and Q4 ($1.0\,\mathrm{mg\,mmol^{-1}}$; 95%CI 0.1, 1.9). No change was noted in Q3.

5.3.5.6 Triglycerides

At diagnosis, median triglyceride levels ranged from $1.4\,\mathrm{mmol\,l^{-1}}$ in Q1 to $2.1\,\mathrm{mmol\,l^{-1}}$ in Q4. At five years, triglyceride levels had decreased in Q3 ($-0.2\,\mathrm{mmol\,l^{-1}}$; 95%CI -0.4, -0.1) and Q4 ($-0.6\,\mathrm{mmol\,l^{-1}}$; 95%CI -0.7, -0.4), with no change observed in Q1 and Q2.

5.3.6 Pharmacotherapy

There was a large increase in the prescription of cardio-protective medication from baseline to five years across quartiles and in the overall cohort (Table 5.2 and Figure 3.1). Those at the highest baseline modelled CVD risk were most likely to report taking cardio-protective treatment at five years (Table 5.2).

5.3.7 Socio-economic patterning

Within the centre and quartile specific regression models, there was a consistent non-statistically significant tendency towards an association between low education and an increase in CVD risk factors, particularly for change in BMI in those in the highest quartile of modelled CVD risk at diagnosis. Low power within each stratum, and the quantity of models (6 risk factors x 4 quartiles = 24 models) meant that the primary analysis was not an efficient mechanism to explore relationships between adjusting variables and the change in each risk factor.

In a multilevel model, which assessed individuals within practices within centres and without stratifying by modelled CVD risk, underlying characteristics of the associations could be explored in more detail. Low education was not associated with change in any risk factor independently at a $p = 0.05$ threshold, but when included as a potential interaction term with underlying CVD risk, there was a statistically significant interaction present for change in BMI (Figure 5.6). This interaction suggested that low education was associated with an increase in BMI in participants with a modelled CVD risk >40% at diagnosis (Figure 5.6).

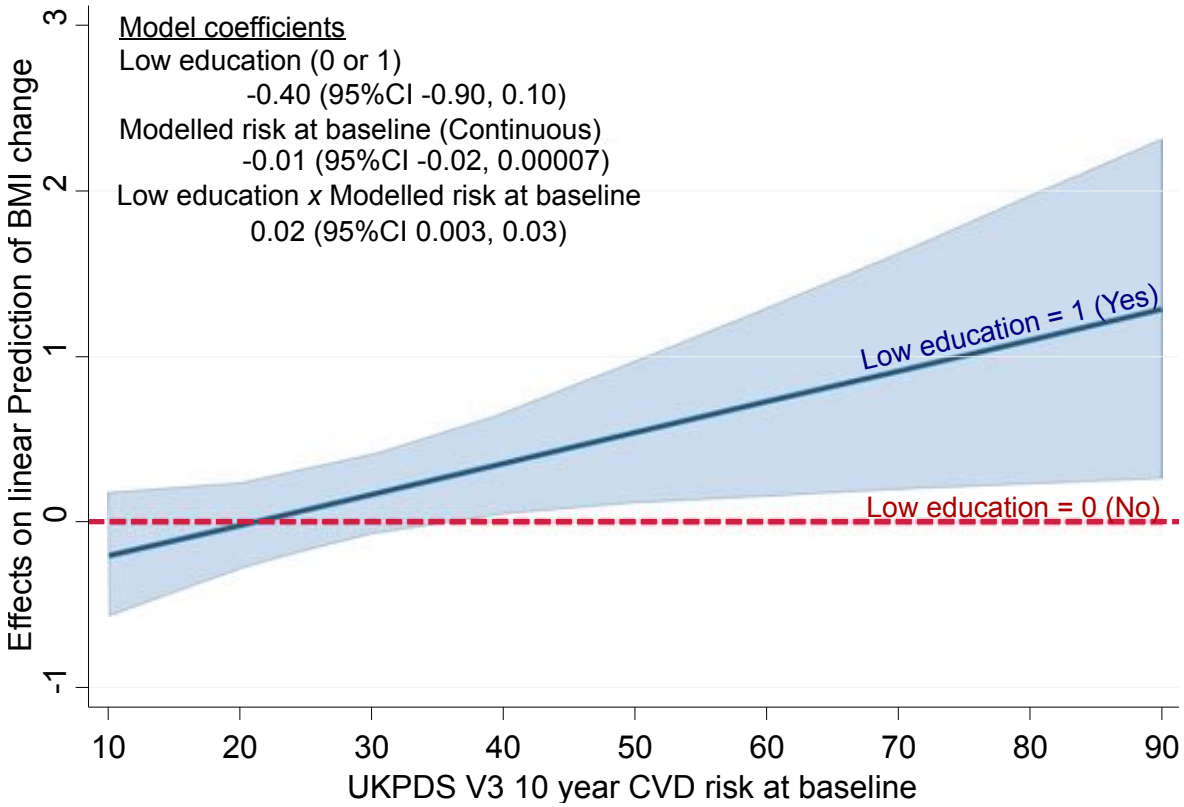


Figure 5.6: How predicted change in BMI (y-axis) is influenced by low education and different levels of baseline modelled CVD risk in ADDITION-*Europe*, demonstrating the interaction between low education and baseline modelled CVD risk, with 95%CI

Figure 5.7 shows the concentration of the available data that underpins the identified interaction between education and baseline CVD risk. While model residuals were homoscedastic over baseline modelled CVD risk, Figure 5.7 demonstrates a sparsity of observations with modelled CVD at diagnosis of over 40%.

5.3.8 Sensitivity analyses

A sensitivity analysis excluding practices that received the intervention (promotion of intensive multifactorial diabetes care) demonstrated a non-significant decrease in systolic blood pressure in Q1 (-2.9 mmHg; 95%CI -6.2, 0.5), and an increase in triglycerides in Q1 ($0.2\,\mathrm{mmol\,l^{-1}}$; 95%CI 0.04, 0.3). Results were otherwise similar which suggested that the treatment groups could be pooled. In all multilevel model results except BMI, a linear fit for all variables was acceptable.

When an interaction term for education and modelled CVD risk was included in a model estimating change in BMI, a plot of the residuals for continuous change in modelled CVD risk suggested a good linear fit. This contrasted with the u-shaped relationship found in the primary analysis for change in BMI. While variation was present between centres, I^2 values $<75\%$ in the primary analysis and intraclass coefficients <0.05 for each level of the multilevel models provided evidence that the heterogeneity did not violate the assumption that change

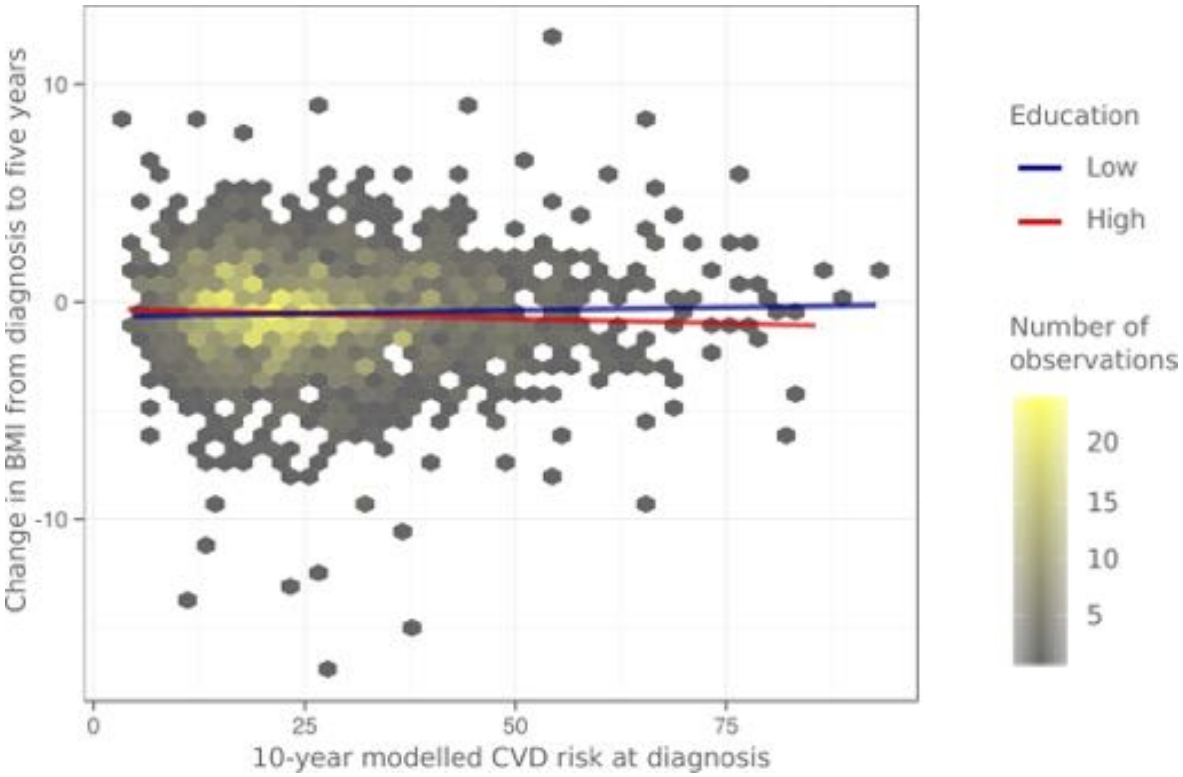


Figure 5.7: Hex-binned scatter plot of modelled CVD at diagnosis against change in BMI from diagnosis to five years. Bins are coloured based on the count of observations they contain, with dark indicating few point, and yellow areas of high datapoint concentration. Line of best fit ($y = \alpha + \beta_{RS}x_{RS} + \epsilon$, RS = 10-year modelled risk score) for each education status is overlaid.

in each CVD risk factors was a common process across centres. Visual inspection of change scores against baseline values suggested that regression to the mean was minimal (although assumed to be present to some degree). Employment status was explored as an alternative proxy for socio-economic status to education, and no associations were detected.

5.4 Discussion

There was large variation in modelled CVD risk at diagnosis among this group of individuals with screen-detected diabetes. Compared to those at lowest risk, people in the highest modelled CVD risk quartile were more likely to be older, male, smokers and to have a low education status. There was little difference in the proportion of participants prescribed cardio-protective drugs across the CVD risk quartiles at baseline. After five years of follow-up there was a reduction in modelled CVD risk across the whole cohort. The pattern across quartiles suggested that increasing modelled CVD risk at diagnosis led to larger decreases in risk on average, but also greater variation in the change an individual would be likely to experience. As the largest reductions in modelled risk were seen in participants who were in the highest quartile of CVD risk at diagnosis, it appeared that treatment was offered appropriately.

For lipid, glucose and blood pressure lowering medication, those at highest CVD risk at baseline were most likely to be prescribed cardio-protective therapy at five years. Participants in the lowest quartile of risk at baseline had very similar levels of modelled CVD risk at five-year follow-up and showed the least variation in change in modelled risk.

5.4.1 Socioeconomic status and change in CVD risk factors

No associations were detected between age left education and change in; ACR, HbA_{1C}, systolic BP, total:HDL cholesterol or triglycerides. An interaction was present for change in BMI that suggested individuals with a UKPDS risk score at diagnosis of more than 40% and had less education were more likely to increase their BMI in the five years after diabetes diagnosis. Figure 5.7 highlights the potential limitations of this finding. It shows that most individuals have a UKPDS risk score that is centred around 20%, so conclusions about the effect of this interaction at high levels of CVD risk at diagnosis (where there are very few observations) are could be at risk of being artefacts from where the data points are denser. As the relationship between education and change in BMI was strongest in the highest quartile of baseline modelled CVD risk, and there was no strong evidence of a poor fit at high values of modelled CVD risk, the varied effect of education on change in BMI based on a person's cardiometabolic health at diagnosis is likely robust.

Of the six CVD risk factors presented, BMI was the only risk factor that appeared to not have a linear relationship with increasing modelled CVD risk. When testing for hypothesised interactions between modelled risk and education, there appeared to be a constant variance of the errors along modelled CVD risk at diagnosis. This suggests that the u-shaped relationship present in change in BMI for the primary analysis, where individuals with high CVD risk at diagnosis do not decrease their BMI, may be due to the influence of low education. The true effect of low education is likely inadequately adjusted for in the primary analysis due to the partitioning of the dataset into four groups by modelled CVD risk and it's absence from the model despite modelled risk in Q4 ranging from 35% to 93%.

Employment status was explored as an alternative measure of deprivation, but no associations were found. I used two measures of deprivation in this analysis to try and capture the differing role of where an individual started from (education level) and what their state is at the time of diagnosis (employment). During the analysis I realised employment status was of limited use as most individuals were either working or retired, meaning currently not in employment was not a strong indicator of an individuals access to resources. Townsend defined deprivation (technically he was defining 'poverty') as: *'People are deprived of the conditions of life which ordinarily define membership of society. If they lack or are denied resources to obtain these conditions of life and so fulfil membership of society, they are in poverty'.*[204] This construct is unlikely to be addressed by a single measure, and ideally multifactorial measures should be used to capture the level of deprivation an individual experiences.[205] In older individuals though, education is commonly used and has been shown to be correlated with health outcomes.[206] The possibility exists that there is a relationship with deprivation that was not identified due to limited proxies available in this study.

5.4.2 Comparison with other studies

The adverse CVD risk profile at baseline in the ADDITION-*Europe* cohort has been observed in other cohorts of individuals with newly diagnosed diabetes. Compared to the UKPDS sample, ADDITION-*Europe* participants were older (60 vs. 53 years), had a higher BMI (32 vs. 28 kgm^{-2}), were less ethnically heterogeneous (white 94% vs. 81%), and were less likely to be a current smoker (26% vs. 31%).[100] By contrast, UKPDS participants were prescribed lower rates of cardio-protective medication and had higher values of cardiovascular risk factors.[100] UKPDS participants were also recruited from a clinical setting between 1977 and 1991[100], and many of the differences seen are likely related to both changes in routine care and diagnosis being later along the disease trajectory than was achieved in the screen-detected ADDITION-*Europe* study.

Individuals with the highest modelled CVD risk at diagnosis in the ADDITION-*Europe* cohort were prescribed similar numbers of cardio-protective drugs to those at lowest risk. After five years of follow-up, the largest reductions in modelled CVD risk were seen in participants who were in the highest quartile of risk at baseline. This supports one-year results from the ADDITION-*Cambridge* study, where those at highest baseline risk experienced the largest reduction in risk.[198] Our findings also support data from the UKPDS, which suggest that the greatest improvements in cardiovascular risk factors were seen among individuals with the highest initial values after diagnosis of diabetes.[207] In the UKPDS, after an initial reduction in HbA_{1C} of ~3%, HbA_{1C} slowly increased over the first six years after diagnosis by ~1% in both intervention arms[114], and an overweight sub-cohort[208],while a more gradual decline in systolic blood pressure values was observed in the nine years after diagnosis.[100] In the more recent DESMOND study[209], in which baseline information was collected up to six weeks after diagnosis[127], a similar pattern of a very large reduction in HbA_{1C} was followed by a gradual increase over the first year.[209] In DESMOND, the UKPDS and ADDITION-*Europe*, HbA_{1C} values at the final follow up point were lower than values at diagnosis.[114,209]

5.4.3 Strengths and limitations

The strengths of the ADDITION-*Europe* study design have been previously highlighted in Section 2.1.0.3. This analysis was limited to those who were alive at five years. As 48 CVD related deaths occurred across the four quartiles, between diagnosis and five years, the results will likely be slightly biased towards a healthier cohort than if all individuals with screen-detected diabetes had been included.

A measured CVD risk factor represents a sampled measurement from a distribution of measurements centred around the true measurement. This variation could come from measurement errors, mistakes in the protocol for taking the measurement, or general fluctuations relating to the environment (e.g. white coat hypertension, especially hot or cool day, stress, etc). The fact that we can only measure a risk factor as a sample from the true value of that risk factor is what underlies the problem called regression to the mean.[203,210] The variation that leads to regression to the mean should be random[210], but in this analysis if the mea-

surement was inflated at diagnosis due to a systematic error that was not present at follow up (or the other way around), a similar effect will be seen.

As an example, regression to the mean can occur if there is no real change in the risk factor, but at diagnosis the measurement was from the tail of the distribution of possible measurements, which means we are more likely to see a value towards the true mean at five years (i.e. a change). This effect was likely to be inflated in this analysis because I divided the sample into quartiles based on baseline measurements of a variable that is correlated to the CVD risk factors. If an individual's true mean was actually in a different quartile of baseline risk, then they are more likely to have a value that suggests change when measured at five years.

To explore this effect the baseline value of each risk factor against the change at five years was plotted within quartiles and overall. As these plots did not suggest that individuals with extremely low values at diagnosis tended to increase, and those with high values did not tend to decrease, relative to the shape of the scattered data across the rest of the range of values, there was no evidence of regression to the mean. While this is a crude test[210], several features of the study design also helped limit regression to the mean. Modelled CVD risk is by design correlated to CVD risk factors, but the effect of partitioning is likely to be less than if the actual risk factors were used to divide the population at baseline. Some clinical variables, such as blood pressure, were collected three times, which may have helped reduce the regression to the mean. Other risk factors like HbA_{1C} are likely to be more robust to random fluctuations. While there is likely to still be some regression to the mean present in this analysis, it is also likely to introduce a small amount of imprecision relative to the large and consistent changes seen in this analysis.

The change in each risk factor appeared to be normally distributed within each quartile, and sensitivity analyses treating modelled CVD risk as a continuous measure suggested that the quartiles represented the underlying patterns in an easily interpretable manner.

5.4.4 Implications for practice

Calculation of modelled CVD risk might be a useful tool for guiding treatment decisions in newly diagnosed diabetes patients. It is also recommended for use during diabetes consultations in England.[118] Identifying who is at highest risk will help target treatment to those who need it the most and is likely to lead to a reduction in treatment inequity.[81] This analysis provides a reference point for patients and their GPs when considering what are achievable goals for changes in risk factors early in the course of the disease, accounting for the diverse cardiometabolic profile present in newly diagnosed patients. This is important as primary care is striving towards diabetes care that is ever more tailored to the patient[14,118], and the results presented provide can provide realistic expectations for how risk factors will change in the first five years after diagnosis.

5.5 Conclusion

After five-years of follow-up, ADDITION-*Europe* participants at highest baseline risk were more likely to be prescribed lipid, glucose or blood pressure lowering drugs after adjusting for several demographic covariates that varied by quartile, including age, that may influence pharmacotherapy decisions by practitioners.[128] This suggests that within ADDITION-*Europe* GP's were effective at reducing inequity in treatment provision and that treatment was offered appropriately in relation to underlying CVD risk. Despite a higher proportion of individuals in the highest risk quartile having left education at a younger age, no association between education or employment status with change in modelled CVD risk was observed. There was no evidence for socio-economic inequity in changes in risk factors in the overall trial cohort or when the population was stratified by baseline CVD risk. This suggests that despite the inequity in risk at diagnosis identified in ADDITION-*Europe* and in other cohorts with diabetes[211–213], there was no social inequity in the delivery of treatment.

A large variation in modelled CVD risk at the point of diagnosis among individuals with screen-detected diabetes was identified. There were significant reductions in CVD risk factors from baseline to five-year follow-up, with the largest reductions observed in those at highest baseline CVD risk. Individuals with highest modelled CVD risk at diagnosis were most likely to be prescribed cardio-protective therapy at five years. Furthermore, there was limited variation in change in modelled CVD risk or prescription of cardio-protective treatment by socio-economic status, suggesting that treatment was equitable. Further analysis characterising CVD risk factor trajectories could aid in both refining realistic goals for patients and identifying patterns that would allow a more nuanced approached to CVD risk prevention initiatives.

5.5.1 In the context of optimising CVD risk management

In a screen diagnosed population with diabetes, I have demonstrated that there is a heterogeneity in cardiometabolic health at diagnosis (including HbA_{1C}; Chapter 4). This leads to diversity in the achievable change in each risk factor, and quantifying these changes will help inform patients and GPs when coming to shared decisions on treatment plans. In the remaining chapters I will explore the relationship between early treatment and events (Chapters 6 and 7), and whether these changes in medication are associated with an adverse burden in quality of life (Chapter 8).

Chapter 6

Effect of intensive treatment on modelled CVD risk at five years

6.1 Introduction and aims

I have demonstrated that a screen diagnosis of diabetes leads to an intensification of medication (Chapter 3), and improvements in blood glucose and other CVD risk factors (Chapters 4 and 5. Despite calls for opportunistic screening and testing of high risk individuals[14,143,144], we know little about what the effects of intensive treatment are earlier in the diabetes disease trajectory.

Among individuals with established diabetes, risk of CVD and mortality can be reduced by intensive treatment of multiple risk factors including blood pressure and cholesterol.[112,113] The merits of tight glycaemic control in a recently diagnosed population[102], and across multiple populations with established diabetes[109], has been identified in RCTs. Although there is evidence from ACCORD that the process of attempting to attain low glycaemic targets in resistant individuals may lead to excess deaths[104,106], individuals in ACCORD had a median duration of diabetes of 10 years and current CVD or at least two elevated CVD risk factors.[214] As ADDITION-*Europe* intervened much earlier in the disease trajectory, and the application of the intervention was pragmatic and the intervention itself was less aggressive, excess mortality was not expected.

In the ADDITION-*Cambridge* centre of ADDITION-*Europe*, a downward shift in modelled CVD risk was observed at one year.[198] In Section 3.3.3.8 (page 46) I showed that individuals in the intensive treatment arm of ADDITION-*UK* were more likely to be prescribed BP lowering ACE inhibitors and β blockers, lipid lowering medication and aspirin. The main ADDITION-*Europe* 5-year trial analysis paper mirrored my findings for pharmacotherapy, and also demonstrated that there were greater reductions in the intensive treatment arm for glycaemia (HbA_{1C} -0.08%; 95%CI -0.14,-0.02; $mmol\,mol^{-1}$ not reported), BP (systolic BP -2.9mmHg; 95%CI -4.5,-1.2) and lipids (total cholesterol $-0.27\,mmol\,l^{-1}$; 95%CI -0.34,-0.19).[145]

Figure 6.1 shows the cumulative incidence of CVD events in ADDITION-*Europe*. At five

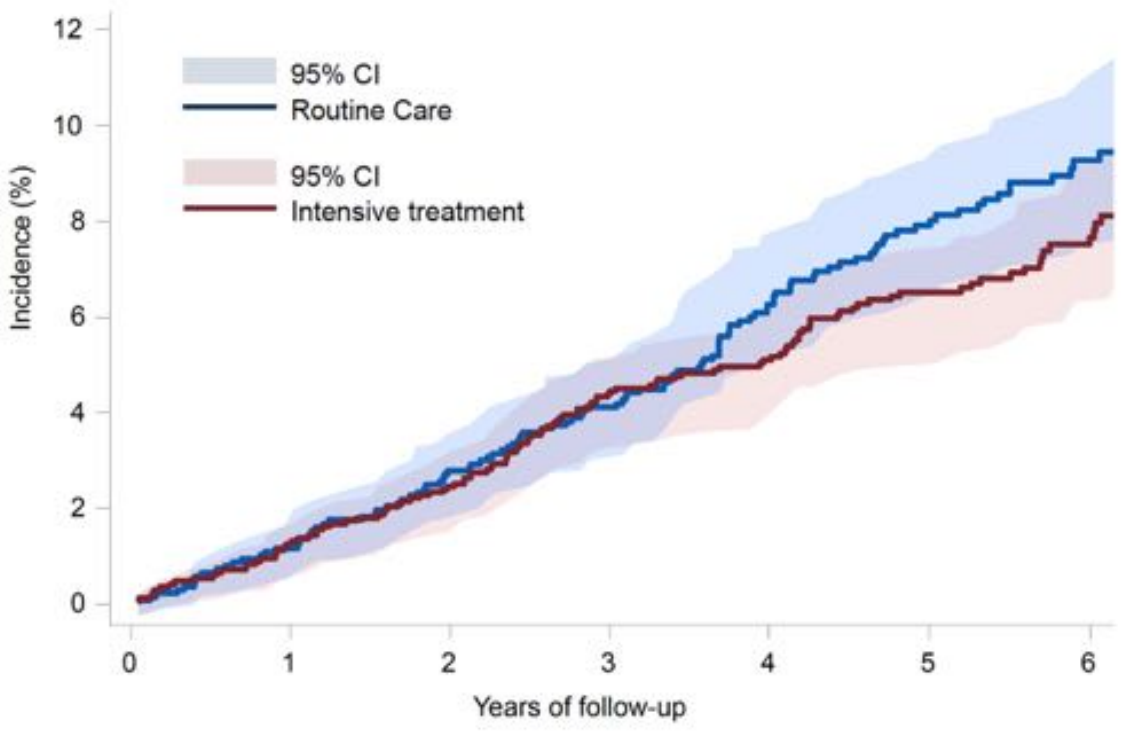


Figure 6.1: Cumulative incidence of CVD events in the intensive treatment vs. routine care groups of the ADDITION-*Europe* trial, *Stata* graphic originally presented in *Griffin et al(2011)Lancet,378:156-67.*[145] I received the original *Stata* code from Mr Stephen Sharp and replicated the figure in the *R* language using a later release of the ADDITION-*Europe* dataset.

years there was a non-significant 17% reduction in cardiovascular events.[145] The ambiguity of this finding is assumed to be due to a lowered event rate in both arms due to increases in routine care like statin therapy coupled with the slow pathogenesis of CVD in an early detected population leading to a low number of events in the five years after screen diagnosis. A similar finding was found for microvascular disease, where there was a non-significant lower risk of retinopathy and neuropathy, and the event rate was lower than expected in both arms.[215] An improvement in routine care was noted between 2000 and 2004 when measured by both process and outcome markers.[172] Khunti *et al*[172] tied this directly to the introduction of financial incentives to meet care targets within the Quality and Outcomes Framework (QOF) of the newly introduced General Practice Contract. Although Khunti *et al*'s et al conclusion over the effectiveness of QOFs is open to potential ecological fallacy, and the introduction of new guidelines highlighting the importance of total cardiometabolic health between 2000 and 2002 will also have had an effect[103,170,216,217], improvements in routine care accelerated soon after ADDITION-*Europe* began recruiting.

While Figure 6.1 suggests that the incidence may have been attenuated in the intensive arm from four years, this is speculative as there are not enough events to support this as a firm conclusion. In the UKPDS, a comparison of tight blood pressure control vs less tight control suggested a similar divergence in the incidence of CVD and renal failure where a small

difference in the event rate at one year began to diverge to a greater degree from six years after diagnosis.[77] The UKPDS also demonstrated that the benefits of tighter glucose control become apparent across the whole trial only during post trial monitoring (a continued benefit was noted in the overweight/metformin sub-study).[102] As the UKPDS finding comes from after the intervention ended, it gives evidence that there is a potential legacy effect in which the benefits of changes to risk factor exposure early in the disease persist and continue to show a treatment benefit years later. Although skeptics could attribute this legacy effect to continued application of the intensive protocol in the intensive arm, and a failure of routine care to match new evidence provided by the UKPDS.

These findings suggest that longer term follow up maybe needed in order to establish whether early intensive treatment reduces cardiovascular risk. In the absence of long term data on hard outcomes, the difference in 10-year modelled CVD risk at five years in ADDITION-*Europe* can shed light on the early CVD experience of screen-detected individuals.

6.1.0.1 Aims

I aimed to (i) describe the change in 10-year modelled cardiovascular risk in the five years following diagnosis by screening, and (ii) quantify the impact of the intervention on 10-year modelled cardiovascular risk at five years.

6.2 Methods

This cohort analysis used data from the ADDITION-*Europe* trial, details of which are given in Section 2.1.0.3, on page 25. Methods specific to the analysis presented in this chapter are given here.

6.2.1 Design

Individuals were followed for a mean of 5.7 years (median 5.9 years, histogram ▁▃▆▃▁). The primary endpoint for this analysis was ten-year modelled CVD risk, calculated from the UKPDS model[155] (for details see Section 2.2, page 32), at five years post-diagnosis.

6.2.2 Statistical analysis

All analyses were by intention to treat. Individuals who had died before five-year follow up were excluded from all analyses. I summarised characteristics of ADDITION-*Europe* participants by trial group at baseline and five-year follow-up. Intervention effect on descriptive variables was calculated from a centre level linear or logistic models, adjusted for baseline value and allowing for clustering by practice, which were then combined using fixed effects meta-analysis.

I estimated the intervention effect on 10-year modelled CVD risk at five years within each centre using linear regression, with adjustment for modelled CVD at diagnosis. A robust

variance estimate based on practice level clustering was specified in the model. Centre-specific estimates of the difference between treatment groups were combined using fixed-effects meta-analysis. The I^2 statistic was used to estimate heterogeneity between study centres, where I pre-specified 75% as a threshold to indicate substantial heterogeneity that violates the assumption that observed differences between centres were due to chance.[202]

The decision to adjust for baseline values of the variable of interest in each model was made as there was some evidence of bias being introduced to the trial by a protocol amendment in one centre. ADDITION-*Denmark* allowed opportunistic recruitment to accelerate recruitment, and exposure of practices to the intervention may have influenced who was recruited and partly explain why 5% ($\frac{30}{579}$) in the routine care arm had previous CVD at diagnosis, compared with 8% ($\frac{68}{837}$) in the intensive treatment arm. While there was insufficient evidence of bias in recruitment to warrant changes to the main trial analysis[145], I believed that this analysis was more sensitive to bias as the analysis was focused on a measure of the same cardiometabolic risk factors that may have introduced bias into the trial.

6.2.3 Sensitivity analysis

In order to characterise missing data, I used logistic regression to model the odds of having a missing modelled risk score value at follow up adjusting for demographic and risk factor measurements as well as clustering at baseline.

The following sensitivity analyses were explored:

Excluding missing smoking information: Data on smoking status at five years were missing disproportionally to the other variables, so was carried forward in ADDITION-*Europe* (see page 26). As a sensitivity analysis the primary analysis was repeated excluding those with no smoking data at five years.

Excluding individuals who experience CVD during follow up: The primary analysis was repeated excluding those individuals that experienced a non-fatal CVD event between diagnosis and five year follow up.

Missing Indicator Method (MIM): Modelled UKPDS values missing at baseline were replaced with the mean for the whole sample and a missing indicator to the model.[218]

MIM and Pattern Mixture Model (PMM): The effect of non-random loss to follow up was tested using a PMM under the assumption that mean modelled risk was 10% higher in those lost to follow up.[219,220]

Multilevel model: Rather than meta-analysing centre level models as in the primary analysis, I accounted for centre and practice level variance using a multilevel model.

To explore the effects of losses to follow up not being random, I also produced a plot of how the mean difference between trial arms would change over a variety of different scenarios. In a model in which missing values at baseline were imputed using MIM, I imputed missing values

of modelled CVD risk at follow up with the assumption that the distribution was between 10% lower to 10% higher than individuals present at follow up (i.e. $\delta = [-10, -9, ..., 9, 10]$). The potential also exists for this non-random missingness to be restricted to one arm, so I also plotted the effect of changing δ in only the intensive treatment or routine care arm.

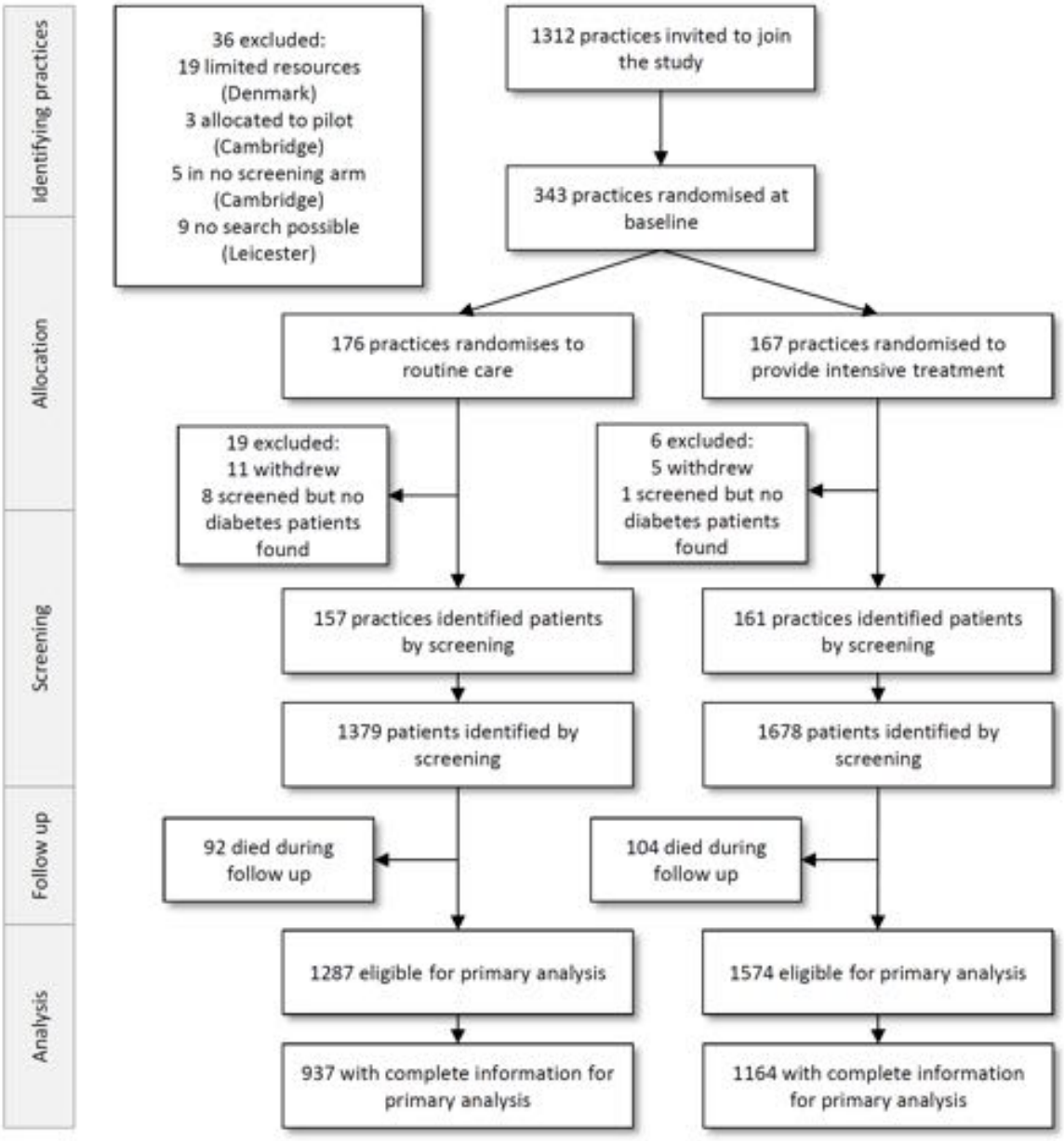


Figure 6.2: CONSORT diagram of the ADDITION-*Europe* trial participant flow.

6.3 Results

6.3.1 Participant characteristics

196 people were excluded as they died before five-year follow-up (Figure 6.2). A further 760 individuals were excluded as they did not have complete data to calculate the UKPDS risk score at baseline and follow-up, leaving 2101 (73%) participants with complete data for analysis. Participants who did not have data for modelled risk at follow up were more likely to smoke at baseline (OR 1.6; 95%CI 1.2, 2.4) and to be obese (BMI >30, OR 1.6; 1.1, 2.3) than those with complete data. No other differences between those lost to follow up and the complete case analysis sample were found. Practices were well matched at baseline.[145] Participants were well matched for socio-demographic, anthropometric, biochemical and treatment characteristics between treatment groups at baseline (Table 6.1). There were minor differences between groups in some centres. Use of hypertensive and lipid lowering drugs was higher in the intensive treatment group in Leicester. In Denmark, the intensive treatment group had a larger number of participants who reported previous myocardial infarction (6.2% vs. 4.5%) and stroke (2.6% vs. 1.3%) at baseline compared to the routine care group. Further, there were more patients with diabetes in the intensive treatment compared to routine the care group (837 and 579, respectively). Between centres, a lower prevalence of previous myocardial infarction or stroke at baseline was present in Denmark and in the Netherlands compared to the UK centres. All other values were similar between centres.

Prescription of cardio-protective drugs increased in both groups, with glucose lowering, anti-hypertensive and lipid lowering drugs more commonly prescribed in the intensive treatment than the routine care group at follow up (Table 6.1). At five years, there were improvements in CVD risk factors in both groups (Table 6.1). There were small but significant differences between groups for change in HbA_{1C} ($-0.9\,\mathrm{mmol\,mol^{-1}}$, 95%CI -1.7,-0.1; -0.1%, -0.2,-0.01), systolic blood pressure (-3 mmHg; 95%CI -5,-1) and Total:HDL ratio (-0.1; 95%CI -0.2, -0.06) and LDL cholesterol ($-0.2\,\mathrm{mmol\,l^{-1}}$; 95%CI -0.3,-0.1), in favour of the intensive treatment group.

6.3.2 Change in ten-year modelled CVD risk at five years

Ten-year modelled CVD risk was 27.3 (SD 13.9, histogram ▮▂▁) at baseline in the ADDITION-*Europe* trial cohort and 21.3 (SD 13.8, histogram ▮▂▁) at five years. Table 6.2 shows that the central estimate of mean modelled risk decreased in both treatment groups in all four centres. Figure 6.3 shows that there was a large variation in absolute change in modelled risk, with no clear pattern in the association between risk at the two time points. This variation was also apparent when looking at change relative to other individuals, by plotting movement between modelled risk quintiles at baseline and five years (Figure 6.4). When looking at movement between quintiles of modelled risk at diagnosis and five years there was a large amount of movement into both quintiles of greater and less modelled CVD risk, suggesting that there was also a large variation in the ranking of individuals modelled CVD risk between the two time points (Figure 6.4). Figure 6.5 shows the distribution of CVD risk at baseline

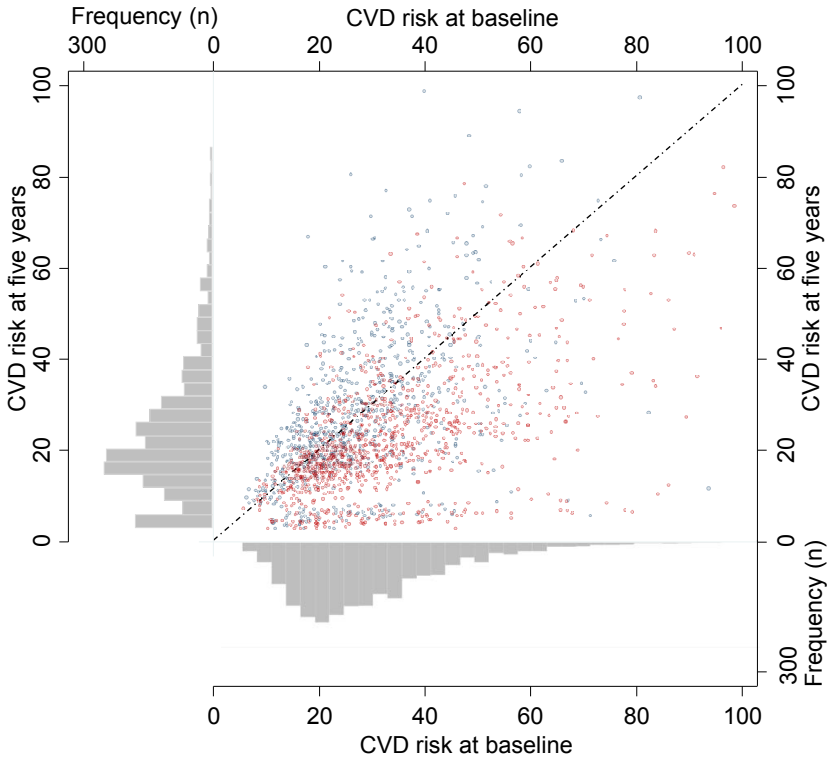


Figure 6.3: Scatter graph of ADDITION-*Europe* participants 10-year modelled risk centiles at baseline and five years after diagnosis, with histograms superimposed under each axis. Red=intensive treatment group, blue=routine care group

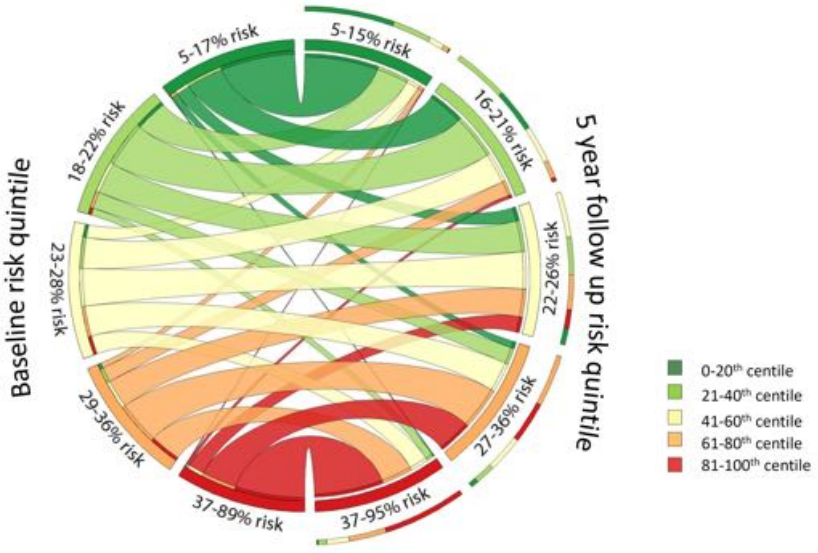


Figure 6.4: Movement of individuals from modelled CVD risk quintile at baseline to quintile at five years after diagnosis ADDITION-*Europe*

Table 6.1: Characteristics of the ADDITION-*Europe* trial cohort with complete data for UKPDS risk score at baseline and follow up (mean 5.7 years).

Measure	Routine care (n=937)			Intensive treatment (n=1164)			
	Baseline	Followup	Mean change baseline to followup (SD) Measure	Baseline	Followup	Mean change baseline to followup (SD)	Intervention effect β/OR[†] (95%CI)
Female sex	42%	-	-	41%	-	-	-
Mean (SD) age in years at diagnosis	60 (7)	-	-	60 (7)	-	-	-
White ethnicity	93%	-	-	96%	-	-	-
Employed	46%	-	-	42%	-	-	-
Any glucose lowering drug	0.4%	57%	56%	0.6%	67%	67%	1.6 (1.3,2.0)
Any hypertensive drug	44%	74%	30%	46%	84%	37%	1.8 (1.3,2.3)
Any lipid lowering drug	15%	78%	63%	18%	85%	67%	1.5 (1.1,1.9)
History of myocardial infarction	4.9%	-	-	6.5%	-	-	
History of stroke	1.6%	-	-	2.6%	-	-	
Current smoker	25%	20%	-4.6%	25%	20%	-4.9%	0.7 (0.4,1,1)
Median (IQR) units of alcohol per week	5 (1,12)	4 (0,11)	-1.3 (8.7)	5 (1,13)	3 (0,10)	-1.3 (7.8)	-0.2 (-0.8,0.3)
Mean (SD) BMI in kgm^{-2}	31 (5)	31 (6)	-0.5 (2.4)	32 (5)	31 (6)	-0.5 (2.6)	-0.03 (-0.2,0.2)
Median (IQR) HbA_{1C} %	6.6 (6.1,7.3)	6.5 (6.1,7.1)	-0.3 (1.6)	6.5 (6.1,7.3)	6.4 (6.0,6.9)	-0.4 (1.4)	-0.1 (-0.2,-0.01)
Median (IQR) HbA_{1C} $mmolmol^{-1}$	49 (43,56)	48 (43,54)	-3 (17)	48 (34,56)	46 (42,52)	-5 (16)	-0.9 (-1.7,-0.1)
Mean (SD) systolic blood pressure in mmHg	150 (21)	138 (18)	-12 (22)	148 (22)	135 (17)	-13 (22)	-3 (-5,-1)
Mean (SD) total:HDL cholesterol	4.7 (1.5)	3.5 (1.0)	-1.2 (1.4)	4.7 (1.5)	3.3 (1.1)	-1.3 (1.4)	-0.1 (-0.2, -0.06)
Mean (SD) LDL cholesterol in $mmolL^{-1}$	3.5 (1.0)	2.3 (0.8)	-1.2 (1.1)	3.4 (1.0)	2.0 (0.8)	-1.4 (1.1)	-0.2 (-0.3,-0.1)
Median (IQR) triglycerides in $mmolL^{-1}$	1.7 (1.2,2.4)	1.6 (1.1,2.3)	-0.3 (1.4)	1.6 (1.2,2.3)	1.5 (1.0,2.1)	-0.2 (1.3)	-0.04 (-0.1,0.03)
Mean (SD) albumin creatine ration cholesterol in $mmolL^{-1}$	0.9 (0.4,1.9)	1.1 (0.6,2.7)	1.7 (19.7)	0.8 (0.4,2.0)	1.2 (0.7,2.6)	1.5 (23.2)	-0.7 (-1.8,0.4)

[†] OR=Odds ratio. Intervention effect is estimated from a meta-analysis of centre level linear or logistic regression model, with the measure as the outcome, adjusted for baseline value with robust errors to allow for clustering by general practice.

and follow-up separately by treatment group. For both groups, the distribution of modelled CVD risk shifted slightly to the left.

6.3.3 Difference in modelled risk at 5 years

Within all four centres modelled CVD risk was lower in the intensive treatment group compared to the routine care group at five years (Figure 6.6). The difference between groups ranged from -0.9 (95%CI -3.6, 1.7) in Cambridge to -4.8 (95%CI -8.4, -1.3) in the Netherlands. There was moderate variation between centres (I^2= 53.6%). When results from each centre were combined, ten-year modelled CVD risk was significantly lower in the intensive treatment group (-2.0; 95%CI -3.1, -0.9), while adjusting for baseline CVD risk and practice level clustering.

Table 6.2: UKPDS (version 3) modelled CVD risk score in the ADDITION-*Europe* trial cohort at baseline and 5.7 years by centre and combined

Centre	Routine care (n=937)				Intensive treatment (n=1164)			
	Total with data[1](% of randomised)	Mean at baseline (SD)	Mean at follow up (SD)	Mean change baseline to follow up	Total with data[†](% of randomised)	Mean at baseline (SD)	Mean at follow up (SD)	Mean change baseline to follow up
Cambridge	285 (75%)	28 (14)	23 (14)	-5 (14)	334 (77%)	29 (15)	22 (14)	-6 (14)
Leicester	77 (81%)	24 (11)	20 (14)	-2 (10)	56 (93%)	28 (14)	19 (12)	-9 (11)
Denmark	423 (73%)	25 (12)	22 (14)	-5 (14)	594 (71%)	25 (13)	20 (14)	-5 (12)
Netherlands	152 (66%)	34 (14)	23 (15)	-10 (16)	180 (73%)	36 (16)	21 (14)	-15 (11)
Combined	937 (73%)	27 (13)	22 (14)	-5 (12)	1164 (74%)	28 (15)	21 (14)	-7 (9)

[†] Total with risk score available at baseline and follow up.

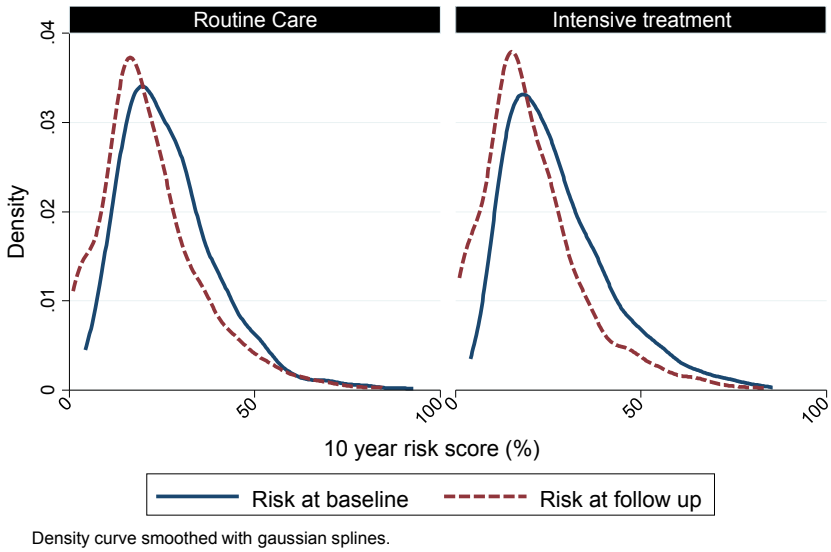


Figure 6.5: Distribution of UKPDS v3 modelled CVD risk in ADDITION-*Europe* participants at diagnosis & 5 year follow up

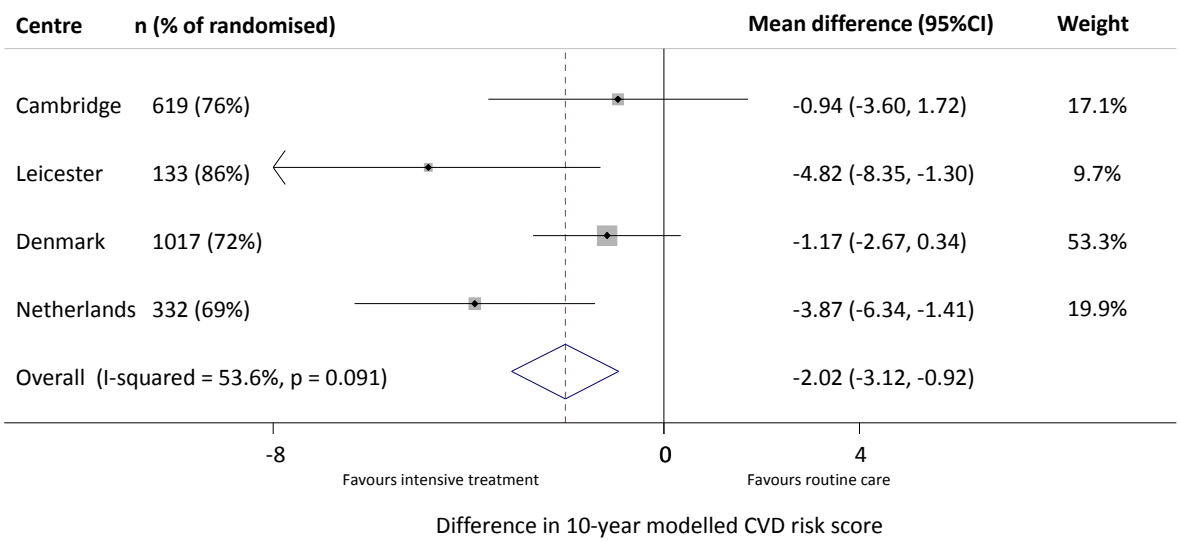


Figure 6.6: Difference in UKPDS CVD modelled risk between ADDITION-*Europe* treatment groups at five year follow up. Adjusted for clustering and baseline modelled risk.

6.3.4 Sensitivity analyses

A multilevel model of practices inside centres was explored. Intraclass correlation at the centre (0.02; 95%CI <0.01,0.08), and practices within centres (0.04; 95% 0.01,0.09) was low. Estimates of the mean difference between treatment arm from the multilevel model paralleled those from the primary analysis (Figure 6.7).

Using the missing indicator method to include individuals with missing CVD risk at baseline, and assuming that missing UKPDS risk scores at five years were 10% higher than the observed mean risk, produced an overall effect estimate that was very similar to the primary analysis result (Figure 6.7). Similarly, results remained the same when individuals with incident CVD were excluded, and when individuals with missing data for smoking at five years were excluded (Figure 6.7).

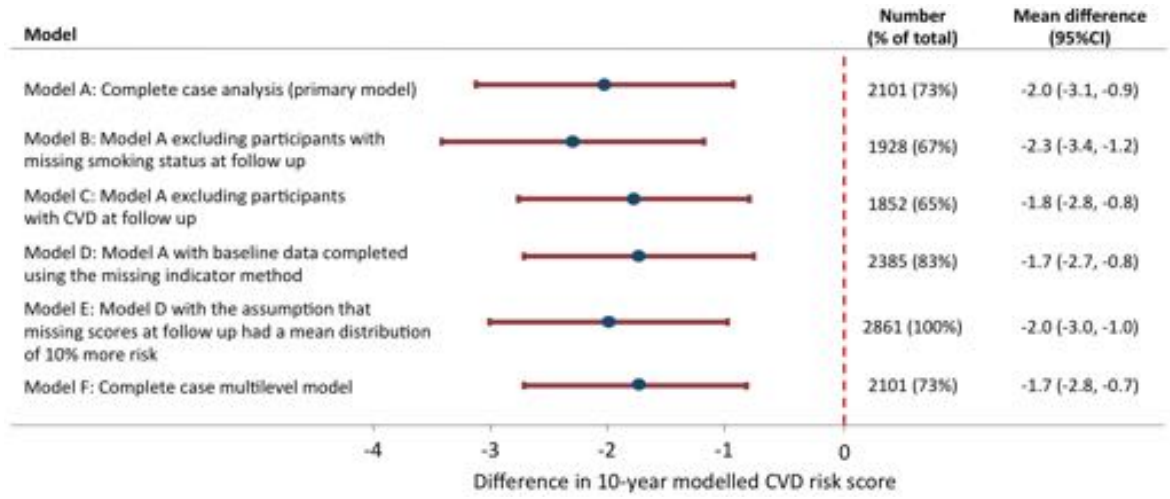


Figure 6.7: Sensitivity analysis of the difference in modelled CVD risk scores at five year follow up

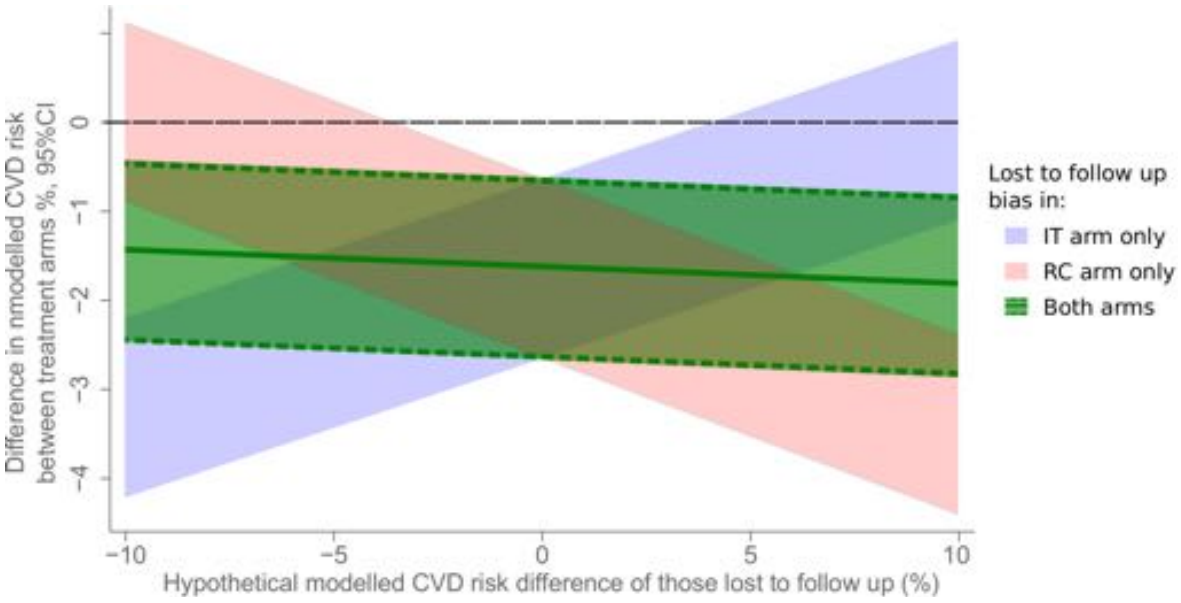


Figure 6.8: Range of treatment effects, derived from a PMM, expected under a range of biases that may be present in why individuals do not provide modelled CVD at five years.

Model E, presented in Figure 6.7, assumes that bias in loss to follow up is constant across trial arms. Figure 6.8 extends this sensitivity analysis to look at a range of different scenarios of bias present in those lost to follow up. The main analysis findings are likely to remain robust if individuals that were lost to follow up have a mean modelled risk score at diagnosis of 10% higher to 10% lower (the range explored in Figure 6.8). If only the individuals in the intensive treatment arm had a modelled CVD risk at diagnosis ~5% or *more*, or only those in the routine care arm had a mean modelled CVD risk ~5% or *lower*, this analysis is at risk of falsely identifying a difference between treatment arms.

6.4 Discussion

Despite increasing age and duration of diabetes there was no increase in modelled 10-year CVD risk in patients with diabetes in the five years following detection by screening. Further, compared with routine care, modest increases in intensity of treatment in the first five years after diagnosis were associated with improvements in CVD risk factors and with a small but significantly lower modelled 10-year CVD risk value at five years (-2.0; 95%CI -3.1,-0.9). This result highlights the importance for practitioners of targeting cardiovascular risk factors early in the diabetes disease trajectory, when the rate of CVD risk progression may be slowed.

6.4.1 Comparison with other studies

One-year results from ADDITION-*Cambridge* showed a reduction in modelled ten-year risk from 31% to 26% in the entire trial cohort.[198] Data from ADDITION-*Leicester* showed that five-year CHD risk decreased from 8.5% at baseline to 5.1% at 13 months, with an additional reduction of -1.49% (95%CI -2.20, -0.77) in the intensive treatment compared to the routine

care group.[221] These findings were supported by a small but non-significant reduction in the relative hazard of the composite CVD endpoint (HR 0.83; 95%CI 0.65, 1.05) in the ADDITION-*Europe* trial at five years.[145] There are no other trial data from screen-detected diabetes populations with which to compare my results. However, similar improvements in CVD risk factors from baseline to five years and the absolute values for risk factors at five years, were seen in the clinically diagnosed diabetes patients in the UKPDS trial at six years of follow up.[179] Similar decreases in CVD risk factor values in the 12 months following diagnosis have been reported among newly diagnosed patients enrolled in lifestyle interventions for CVD risk reduction.[209,222]

In ADDITION-*Europe*, 5.3% of individuals in the routine care group experienced a myocardial infarction or stroke in the first five years. This was less than expected, as 9.3% of the routine care group experienced a myocardial infarction or stroke in the first six years of follow up in the younger UKPDS cohort (mean age 53 vs 60 years).[179] While the length of follow up differs, it is likely that the extent of the difference is due to underlying changes in best practice for routine care. At baseline in the UKPDS, which began recruitment two decades before ADDITION-*Europe*, 12% of patients were prescribed blood pressure lowering medication and 0.3% of individuals were prescribed lipid lowering medication.[73] In ADDITION-*Europe*, at baseline, 45% were prescribed anti-hypertensive medication and 16% were prescribed lipid lowering medication. While some of this difference may be due to the use of risk scores used in all centres except Leicester identifying those with poor cardiometabolic health, the difference is large enough to still provide evidence that cardiovascular disease prevention in populations at risk of diabetes has improved between the recruitment phases of the two studies. Furthermore, the delivery of diabetes care in the general practice setting continued to improve throughout the trial. The introduction of the Quality and Outcomes Framework in the UK and evidence-based guidelines in the Netherlands and Denmark, as well as general promotion of CVD risk management in people with diabetes[172,223,224], may have decreased the potential to achieve a difference in treatment and thus a larger difference in CVD risk between groups.[223]

Even if all risk factors were to stay constant over time, increasing age and duration of diabetes would lead to an increase in CVD risk.[155] In ADDITION-*Europe* there was no increase in modelled CVD risk from baseline to five years in both the intensive treatment and routine care group. It is important to acknowledge that changes in the UKPDS risk score from baseline to five years were primarily correlated with changes in the modifiable CVD risk factors lipids, glucose and blood pressure in the ADDITION-*Europe* cohort (see Figure 6.9 on page 104 for a *post hoc* correlation plot of change in modelled CVD risk score components against change in modelled risk). This shows that within this analysis, the change in 10-year modelled CVD risk was primarily associated with changes in the modifiable risk factors HbA_{1C}, systolic BP, and cholesterol (simple two variable associations are presented and these variables are all correlated).

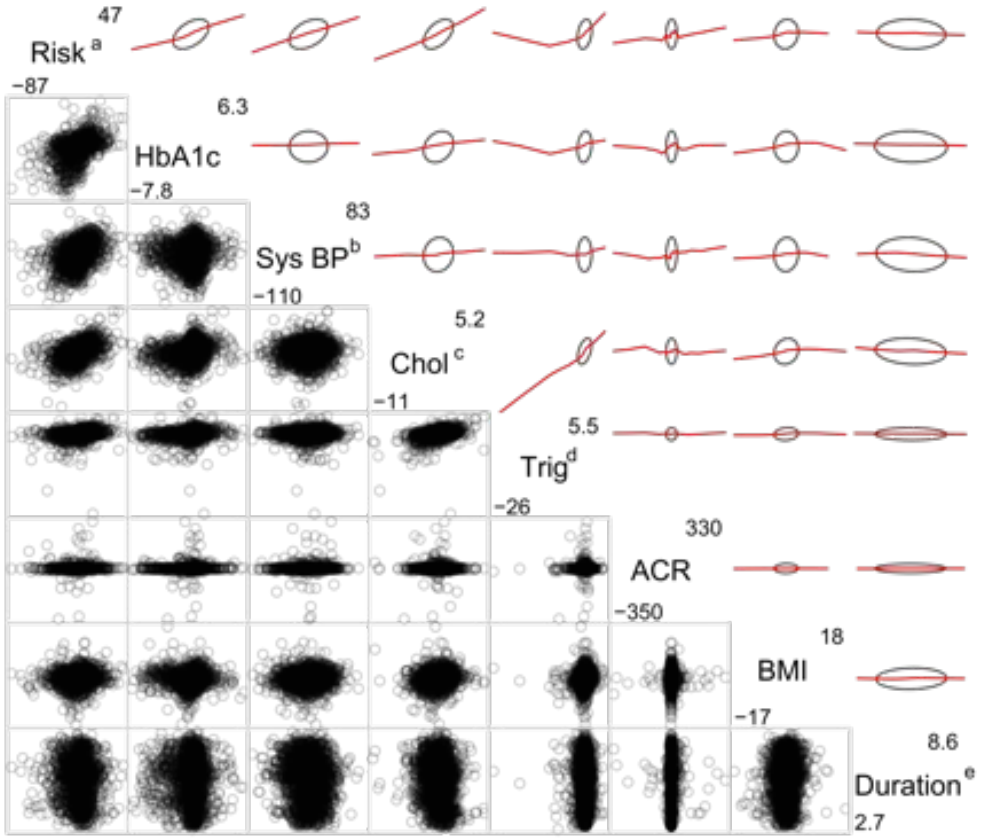


Figure 6.9: *Post-hoc* correlation between change values of clinical risk factors and modelled risk from diagnosis to 5 years in ADDITION-*Europe*, pooling treatment groups. Scatter graphs (lower diagonal) and Loess smoothed curves with bivariate 68% concentration ellipses (upper diagonal) of the absolute change of each variable are plotted. Maximum and minimum change are listed beside each label. [a]*UKPDS modelled 10-year CVD risk.* [b]*Systolic blood pressure.* [c]*Cholesterol ratio.* [d]*Triglycerides.* [e]*Time between diagnosis and 5 year follow up. NOTE: ACR is collapsed into two binary variables in the UKPDS model*

6.4.2 Strengths and limitations

ADDITION-*Europe* participants were recruited from a large population based sample in three European countries. Participants were diagnosed according to WHO criteria. Randomising general practices reduced the risk of intervention contamination. Treatment guidelines across the centres at baseline were similar[172,223–225], but centres were encouraged to use screening programmes and implement treatment algorithms in a manner that best suited their local environment. There was high participant retention at five-year follow-up. Clinically important outcomes were assessed using standard operating procedures and staff were blind to treatment allocation. There were few differences between individuals with and without follow-up data. Overall, 27% of data was missing from the primary analysis. After accounting for missing data at baseline using MIM, and those lost to follow up by assuming that they had 10% higher risk than those available at five years via a PMM model, there was minimal shift in the central estimate and the results remained statistically significant (Figure 6.7).

People that died between baseline and follow-up were excluded from this analysis (n=196). While 24% (n=48) of these deaths were attributed to CVD, 1.6% ($\frac{22}{1377}$) of the routine care group randomised at baseline, and 1.5% ($\frac{26}{1678}$) of the intensive treatment group experienced a CVD related death before follow up. By excluding the 196 incident deaths before follow up it is likely that I have underestimated the total effect of intensive treatment. Participants were predominantly of white ethnic origin (93%), potentially limiting the extrapolation of these findings to more ethnically diverse centres. However, as prevention of diabetes related complications in ethnic minorities is also effective[226], it is likely that the finding in favour of the intervention would remain. The most notable difference in the application of the treatment algorithm was in Leicester, where the education components of the intervention were delivered through the DESMOND structured education programme. Further differences were seen in Denmark, where practices completed opportunistic screening, potentially leading to over-selection of those at increased risk at baseline. It is likely these influences, in combination with differences in national characteristics across centres, accounted for most of the 54% of heterogeneity not due to chance identified in the analysis (I^2 statistic 53.6%).

The UKPDS risk model was derived in a population diagnosed with diabetes up to three decades before ADDITION-*Europe* participants. While it is likely that risk was overestimated in a contemporary cohort like ADDITION-*Europe*, where a high level of routine care was evident, this should not influence the effect size estimate differentially by randomisation group or in ranking risk between individuals. As I have real events at five years, and modelled CVD at diagnosis, a comparison of 5-year modelled CVD risk and true events could be done. However, this was not undertaken as it was outside of the remit of the agreement made with Oxford University to access the latest β of the UKPDS risk model, and CVD risk factors are likely to have changed immediately after diagnosis, which would increase the overestimation of the model and prevent a fair evaluation being made.

Table 6.3: Combining observed events at 5 years[145] with the expected events 5-15 years based off 10-year UKPDS modelled risk at 5 years in ADDITION-*Europe*.

		Routine care	Intensive treatment
Recruited		1379	1678
At 5 year follow up	*Had a CVD event*	117	121
	Died from other cause	70	78
	Free of CVD and alive	1192	1479
10-year CVD risk at 5 years		20[†]	18.2 (17.2,12.2)[‡]
Predicted number of events		276	269 (255,284)[‡]
Proportion predicted to experience a CVD		28.5%	26.4% (25.4,27.4)

Predictions given are crude estimates, subject to limitations presented in Section 6.4.3.
[†] Median 10-year UKPDS risk score in the routine care group.
[‡] Estimates derived from the secondary analysis excluding individuals experiencing CVD events before 5 years (-1.78; 95%CI -2.76,-0.79).

6.4.3 A back of the envelope prediction of 15 year results

In this analysis I have provided robust evidence of a benefit of intensive treatment in preventing CVD events based on cardiometabolic health at five years. The possibility exists to informally extend this finding to provide a rough estimate of the benefit in terms more relatable than differences in a risk score. This additional analysis has been presented in the discussion as the crucial caveats that underlie it make the conclusions less robust, and more representative of my own interpretation of the results. Table 6.3 shows the steps required to combine the true number of events that occurred before five years, with the expected number of events in those alive at five years based on the results of this analysis. Following the logic laid out in Table 6.3, I can estimate that by 15 year follow up 28.5% ($\frac{276}{1379}$) of the routine care arm will experience a CVD event, and 26.4% ($\frac{269}{1678}$) of the intensive treatment arm.

Figure 6.10 graphically presents the values derived in Table 6.3. There are 1,000 circles in the figure representing a hypothetical population of 1,000 individuals. The 264 red circles are people who are likely to experience a CVD event in the first 15 years even if intensive treatment is recommended at diagnosis. The 11 green circles represent the number of individuals that are likely to be protected by the intervention, while the 20 blue circles represent the range of the 95%CI interval. So taking the 11 green as a base, I am 95% certain that between 12 to 32 CVD events in the first 15 years could be averted per 1000 people diagnosed.

Table 6.3 can also be presented as a Number Needed to Treat (NNT). Under the assumptions specified in Equation (6.1), I am 95% certain the interval from 32 to 91 contains the number needed to treat to prevent a CVD event occurring in the first 15 years after diagnosis.

$$\begin{aligned} RCE &= \text{Proportion expected to experience an event in RC arm} \\ ITE &= \text{Proportion expected to experience event in IT arm} \\ NNT &= \frac{1}{RCE - ITE} \end{aligned} \tag{6.1}$$

Figure 6.10 highlights that even with screen-detection, and intensive treatment, over a

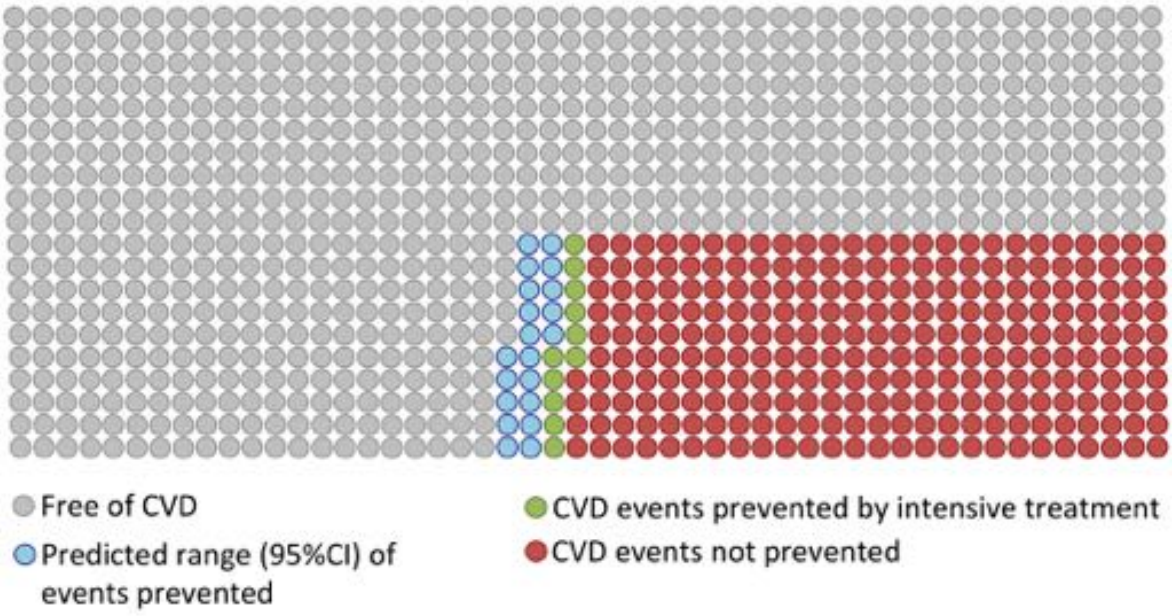


Figure 6.10: Crude estimate of intensive treatment benefit at 15 years. There is a 95% chance that the range of 11 to 31 contains the number of people who will not have CVD events due to intensive treatment at 15 years after diagnosis.

quarter of individuals are likely to experience a CVD event. The 2015 Global Burden of Disease study ranked ischaemic heart disease as the leading cause of years lost to early death and disability globally, and second in Western Europe.[52] In ADDITION-*Europe* we hoped to see whether intensive treatment soon after diagnosis could arrest the gradual deterioration of glyceamic control seen in the UKPDS.[100] The benefit of treatment seen here likely does not address the excess CVD risk seen in individuals with diabetes[227,228]

These numbers help interpret the results of my analysis, but there are large number of caveats that made me feel this analysis was more appropriately seen as a data led discussion. Following are the main limitations for Table 6.3 and Figure 6.10:

The modelled risk is an overestimate, as detailed in Section 2.2 (page 33), the UKPDS model was derived from a population that was diagnosed from 1977 to 1991, and improvements in routine care mean that the model is likely to overestimate the event rate, which will decrease the number of events and thus the power, in the real 15 year results.

Variance in the routine care arm was ignored, and a more realistic number would need to account for the uncertainty in the number of events the routine care arm are expected to see. This was a limitation of a succinct summary combining my results with previously published results from ADDITION-*Europe*.

Losses to follow up were excluded from the estimate used, but sensitivity analyses (Figures 6.7 and 6.8, page 101) suggest the estimates are robust to non-random missingness.

6.4.4 Implications for practice

The fundamental question that arises is whether a difference in 10-year CVD risk of 2% at five years, is likely to lead to clinically meaningful change in event rates. I have produced a rough estimate combining this result with the observed events that suggests 12 to 32 CVD events could be averted for 1,000 individuals screened and intensively treated from diagnosis. Routine care though has improved, and I have likely overestimated the number of CVD events that will occur. While a modelling study based on ADDITION-*Europe* suggests that the majority of the benefit comes from early detection, rather than the promotion of intensive treatment beyond routine care after diagnosis.[229] While a cost-effectiveness study suggests that intensive treatment at screen diagnosis is not cost-effective[230], this study took the assumption that all individuals received the full cost of the intervention. Work is ongoing (as of July 2015) to reassess the cost-effectiveness of ADDITION-*Europe* using actual incurred costs.

Previous literature has indicated that the benefits of intensive treatment are not restricted to those at highest risk.[221] In the ADDITION-*Europe* trial cohort, there was no increase in modelled CVD risk from baseline to five year follow-up. This has important implications for diabetes treatment. The ADA recommends that diabetes testing should be considered in adults of any age with a BMI>25 kgm^{-2} and one or more known risk factors for diabetes.[128] Screening guidelines or programmes have also been introduced in the UK[144], Canada[141], and Australia.[231] These recommendations are likely to result in an increased number of individuals detected earlier in the disease trajectory. If early detection followed by intensive treatment, or even followed by the high standard of routine care now offered by primary care providers, leads to a population level shift in CVD risk, it is likely that a large number of CVD events might be averted. Small increases in treatment were not associated with a significant reduction in risk of events within five years[145], but were associated with a significant reduction in modelled events from 5 to 15 years. This suggests long term follow up of ADDITION-*Europe* beyond five years may mirror post-trial findings from the UKPDS study.[102] It is still unclear (i) whether this slowing of CVD risk progression in the first five years after diagnosis leads to a sustained reduction in actual CVD events over a longer follow up time, and (ii) which individuals achieved more risk reduction than others in order to inform the development and targeting of future interventions.

6.5 Conclusion

When compared to routine care, a modest increase in the treatment of risk factors among patients with type 2 diabetes in the first five years after detection by screening, was associated with a small but significant reduction in modelled CVD risk at five years. Furthermore, modelled CVD risk estimates were the same at baseline and follow up, in spite of increases in age and diabetes duration. General practitioners are therefore encouraged to treat multiple cardiovascular risk factors early and intensively in the diabetes disease trajectory, where the rate of CVD risk progression may be slowed. Longer term follow-up of the ADDITION-

Europe trial cohort, alongside examination of microvascular, quality of life and cost data, is needed to establish the cost-effectiveness of early intensive treatment among screen-detected patients.

6.5.1 In the context of optimising CVD risk management

I have shown that individuals diagnosed with diabetes detected by screening are on multiple medications (Chapter 3), and in this chapter I have shown that this increased burden leads to a statistically significant decrease in the expected number of CVD events. In the remaining chapters I will address the uncertainty around what the role of intensification of medication is outside of a pragmatic intervention where the difference between treatment arms is small (Chapter 7), and whether there is evidence for or against concern of the burden of treatment intensification on quality of life (Chapter 8).

Chapter 7

Change in cardio-protective medication and incident CVD after diagnosis of screen-detected diabetes

7.1 Introduction

In Chapter 3 (page 35) I demonstrated that 41% of individuals with screen-detected diabetes are already taking medications un-related to CVD prevention at the point of diagnosis, and that the number of medications prescribed, particularly those that are cardio-protective, increases in the subsequent five years. Then in Chapters 4 and 5 (page 55, and 73, respectively) I presented the improvements that occur in CVD risk factors after diagnosis. In Chapter 6 (page 91), I provide evidence that encouraging GPs to more intensively manage risk factors leads to improvements in cardio-metabolic health, and is likely to be beneficial in terms of CVD events in the long term. However, questions remain over what the direct effect of changes in medication are on a screen-detected population, outside of the pragmatic multi-factorial intensification seen in ADDITION-*Europe*.

The UKPDS, HOPE, and 4S studies have shown us that treatment of individual CVD risk factors like blood pressure[77,232], cholesterol[73] and glucose[109] lowers the risk of CVD events in populations with diabetes. However, these study populations had either long standing diabetes, or in the case of the UKPDS, clinically diagnosed diabetes from as early as 1977. Several studies also restricted their sample to individuals with excess CVD risk, or early signs of CVD.[73,109] Intensive intervention in these populations with elevated CVD risk factors would potentially allow a greater change, and subsequently treatment benefit, than what maybe seen in a screen-detected population. Conversely, the UKPDS also provides evidence that intensified glucose control after clinical diagnosis led to a long term decrease in the risk of CVD events in the main study population (and a persisting benefit in the overweight sub-sample), despite the convergence in glycaemic control between the intervention and routine care within one year of randomisation ending.[102] Extrapolating from this finding in the UKPDS to even earlier in the disease trajectory, for example a screen-detected population, it is possible that

there could be additional benefits in the prevention of CVD.

Within ADDITION-*Cambridge*, Charles *et al*[198] found that an increase in medication as a continuous variable led to a statistically significant decrease in the 10-year modelled risk of a CVD event (using an older version of the UKPDS model than is presented in Section 2.2 on page 32), while changes in physical activity and serum vitamin C were not associated changes in modelled CVD risk.[198] These findings were limited to concurrent changes, and so lacked temporal spacing, and the outcome was the intermediate of cardiometabolic health.

Long *et al*, also within ADDITION-*Cambridge*, expanded on the intermediate outcomes explored by Charles *et al* by looking at change in a composite healthy behaviour score and the risk of CVD events. Long *et al* found that a positive change in the health score was associated with a lower risk of a CVD event.[233] The health score used gave one point for each of the following: increasing physical activity, decreasing alcohol consumption, increasing fibre and vitamin C and decreasing total energy and fat intake. As this study was conducted in an older population, the possibility exists that change in lifestyle behaviours was undertaken at a higher proportion by those that were less frail, and who also had a higher risk of a CVD event. While the components used for the risk score are supported in the literature, they were selected for this analysis based on stepwise forward regression within the same data source, meaning the results are open to chance findings specific to this analysis. Age starting at diagnosis was used as the underlying timescale in the cox model, yet individuals must have attended one year follow up to be included, meaning that individuals were '*immortal*' for the first year of follow up. This would also likely lead to non-proportionality of hazards, although the effect would be constant for all individuals. A trial with a sample that overlaps ADDITION-*Cambridge* exploring the effect of an individually tailored theory based behaviour change intervention (ADDITION-*Plus*)[234] found that there was no statistically significant benefit, further weakening a potential causal relationship that was identified in the observational evidence from Long *et al*.

ADDITION-*Europe* explored the role of early intensification of treatment, but the achieved difference in the pharmacological treatment component of the pragmatic intervention was small.[145] In Figure 3.7 (page 48), in Chapter 3, I presented a detailed summary of differences in medication use between treatment groups of ADDITION-*UK* at five years. Significant differences included: higher prevalence of blood pressure lowering medication (9% higher; 95%CI 4,15), lipid lowering medication (6% higher; 95%CI 0.4,11) and aspirin (12% higher; 95%CI 6,19). By analysing ADDITION as a cohort study, while carefully adjusting for potential confounding, a greater gradient of change in total cardio-protective medication can be explored as a potential predictor of the incidence of CVD.

7.1.1 Aims

To investigate whether changes in cardio-protective medication from diagnosis to one year were associated with incidence of CVD over the following four years.

7.2 Methods

7.2.1 Cohort description

This cohort analysis uses data from the ADDITION-*Cambridge* trial, details of which are given in Section 2.1.1 on page 29. Of particular relevance to this analysis is that medication in ADDITION-*Cambridge* was based on self-report, augmented where possible with repeat prescription slips. Details on how medication data were collected is given in Section 2.1.1.1. The primary end point was incident CVD, which was a composite measure of CVD death, non-fatal myocardial infarction, stroke, revascularisation or non-traumatic amputation.

7.2.1.1 Change in medication

ATC codes were collapsed into 13 agent types. Five types were for glucose lowering medication: metformin, insulin, sulphonylurea, thiazolidinediones, or other diabetes medication. Eight types referred to medication related to CVD: ACE-inhibitors, β blockers, calcium channel blockers, diuretics, other blood pressure medications, statins, other lipid lowering medication and aspirin. Medication count at each time point was the count of whether the individual was taking these 13 agent types. Change in CVD medication was calculated by subtracting self-reported medication count at diagnosis, from the count at one year. At all points in this analysis, medication refers to only these 13 types, as non-CVD or diabetes related medication has been not included.

7.2.1.2 Outcome ascertainment

The outcome was an independently adjudicated composite measure of CVD events, as detailed in Section 2.1.0.8, page 28.

7.2.2 Statistical analysis

A Kaplan-Meier plot was used to visualise the relationship between the nominal categories of *decrease*, *no change* or *increase* in medication. This plot was also used to give evidence towards the suitability of taking change in medication as continuous, without accounting for a potential different effect in individuals who decreased medication vs. those that increased. The model with the highest number of individuals lost to follow up was used to code a binary variable of *in analysis* or *lost to follow up*. Sex, age at diagnosis, membership of the randomisation group and 10-year modelled CVD risk were explored in a logistic regression model as predictors of being *in analysis* or *lost to follow up*.

7.2.2.1 Follow up period

In the primary analysis, follow up time was *a priori* stated to start the day after one year follow up. As noted in Section 7.3.6, as part of the model fitting process the follow up period was adjusted where stated in the results. Figure 7.1 visualises the timeframe for data

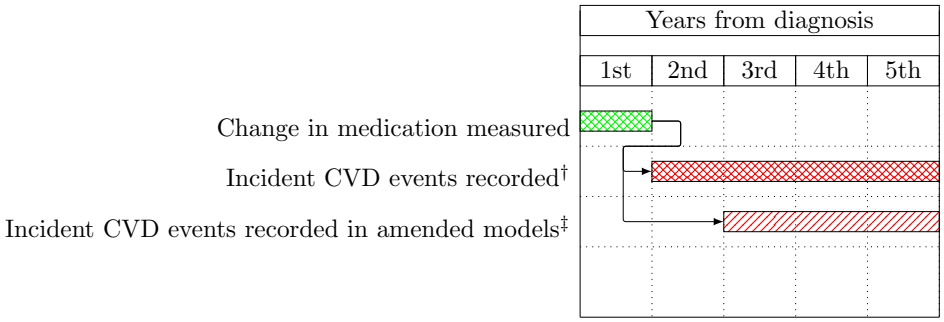


Figure 7.1: Timeframes for collecting the exposure (change in medication) and event (CVD event) data in this analysis. † The primary model. ‡ Where the effect of change in medication varied over time, the analysis was amended to model the period with proportional hazards.

collection, showing the collection of change in medication data from diagnosis to one year, followed by the collection of event data starting at one year follow up for the majority of models, and 12 months later for models that were modified to ensure proportional hazards were maintained.

7.2.2.2 Fitting the Cox proportional hazard models

Cox proportional hazard models were used to explore how changes in medication were associated with the risk of CVD events. The primary model was continuous change in the count of diabetes and CVD medication. All models were adjusted for gender, membership of the intensive treatment arm, 10-year modelled CVD risk, age at diagnosis, HbA_{1C} at diagnosis and self-reported high blood pressure or high cholesterol at diagnosis. In the complete sample model, previous cardiovascular disease was also adjusted for.

The proportional hazards assumption was tested by taking the Pearson product-moment correlation between scaled Schoenfeld residuals and ranked time. A $p<0.05$ was seen as evidence of a lack in proportionality.[235] Although, as p values here are strongly linked to sample size and this test is insensitive to non-zero slopes that have a zero'ed summary linear fit (e.g. quadratic relationships like ⌒), the interaction of time and scaled Schoenfeld residuals was also plotted. Violations of the proportional hazards assumption for the primary analysis were accounted for by two methods: (*i*) partitioning follow up into periods of proportional time based on plotted residuals, and (*ii*) in a separate model which accounted for the interaction of parameters with time. In sensitivity analyses, due to the complexity of interpreting models with interaction terms, only the simpler partitioned models were used when proportional hazards were violated.

7.2.2.3 Relative hazards

Relative hazards were used to represent the change in the hazard as change in medication varied using Equation (7.1). The relative hazard, as a special case of the hazards ratio where $x_j = 0$, allowed me to calculate the hazard relative of x_i compared to no change, rather than

a single step in a coefficients unit. To prevent extrapolation beyond the observed events, I limited the range of x_i values explored to values between the 5th and 95th centile of the observed change in medication values.

$$\frac{h_i(t)}{h_j(t)} = e^{x_i(\beta_1+\beta_2 ln(t))} \tag{7.1}$$

7.2.2.4 Post-estimation of effect of medication change on events

Post-estimation simulations were used to describe uncertainty in the relationship between change in medication and risk of a CVD event.

To create the simulated relative hazards, a sample of 1,000 coefficient and intercept point estimates were drawn from a multivariate normal distribution centred on each parameters mean and variance, derived from the model parameter and parameter-covariance estimates.[236] The distribution of coefficient combinations identified summarises all knowledge on potential variation in the model I have identified across all of its parameters.[236,237] I then produced the simulated HR based on each of the 1,000 draws of the model over a range of values for change in the variable of interest (CVD medication for one analysis, and days from diagnosis for another) that I specified (the 5th to 95th centile was always used to prevent out of sample extrapolation), allowing a relative hazard adjusted for; sex, age at diagnosis, 10-year CVD risk at diagnosis, HbA_{1C} at diagnosis, being in the routine care arm, and self-reported previous CVD, high BP and high cholesterol to be calculated. Simulated relative hazards were also used as they enablied me to visualise interaction terms in a way that is easy to interpret.[236]

Use of simulated relative hazards also allows density measures like medians and IQR's to be reported, rather than estimates of the HR derived from a normal distribution. This can be beneficial, particularly in estimates that approach zero, where the lower bound leads to bias in central intervals.[238]

7.2.2.5 Sensitivity analyses

The primary model was a full sample analysis including individuals who reported being told by their doctor that they had previously experienced a myocardial infarction or stroke. Every model was repeated in only individuals that were free of self-reported myocardial infarction or stroke, and both results have been presented.

Defining change in medication with the available data is also open to variation, and the following methods were also explored:

Change in CVD and diabetes medication was separated into change in diabetes medication, and change in CVD medication, and entered as unique terms in a model that was otherwise analogous to the primary analysis.

Increase, same, or decrease in CVD or diabetes medication were explored as a binary changes relative to no change in a model that was otherwise analogous to the primary analysis.

Each component of cardio-protective medication (glucose, blood pressure and lipid lowering, as well as aspirin) were modelled as a unique binary predictor of increase or same/decrease in a model that was otherwise analogous to the primary analysis.

In a subset without people who decreased medication the primary analysis was repeated, under the assumption that a decision to decrease medication may be due to causes that invalidate the requirement that going from 0 to -1 medication is the same as 0 to 1.

All cause mortality was also modelled as the event , in a model otherwise analogous to the primary analysis.

7.3 Results

Of 867 individuals recruited at diagnosis, two individuals withdrew consent and seven had a CVD event before one year follow up, leaving 858 eligible participants. Of those alive and free of CVD at one year followup, 104 decreased their CVD or diabetes medication count, 191 had the same number, 431 increased and 132 did not have complete medication data. Forty-five events occurred between one year follow up and the censoring date, at a median of 2.4 years (Range 66,1826 days; histogram ), or 3.4 years if counting from diagnosis. Individuals were censored at 31/12/2009, and at censoring there was a median of 5.0 years follow up (IQR 4.9,5.8; histogram ).

7.3.1 Losses to follow up

A complete case analysis resulted in 80% ($\frac{687}{858}$) of individuals eligible at baseline being available for analysis, with missing individuals primarily being due to missing medication or variables used in adjusting the cox model. Included individuals contributed 2,972 person-years of follow up. In a logistic model comparing those lost to follow up against those available to the analyses, no associations were found with sex, age, 10-year modelled CVD risk at diagnosis or membership of the intervention group.

7.3.2 Cohort characteristics

Table 7.1 presents the characteristics of the cohort at diagnosis, stratified by whether their medication decreased, stayed the same or increased. Individuals that decreased their CVD or diabetes related medication after diagnosis tended to be prescribed more medication (median 4; IQR 3,5) at diagnosis than those who stayed the same (median 1; IQR 0,3) or increased (median 1; IQR 0,2). People who decreased medication had lower HbA_{1C}, total cholesterol and blood pressure than those that remained the same or increased, but were older and had a higher 10-year modelled CVD risk. Individuals that decreased medication tended to report having been diagnosed with high BP, high cholesterol and previous CVD more commonly (Table 7.1).

Table 7.1: Baseline characteristics and number of CVD related deaths by change in medication in ADDITION-*Cambridge*.

	How medication changed from diagnosis to one year		
	Decrease (n=104)	Same (n=191)	Increase (n=431)
Male sex	65%	66%	58%
Median age at diagnosis (IQR)	64 (59,67)	63 (56,67)	62 (56,67)
Mean BMI (SD)	33 (6)	34 (6)	33 (5)
HbA_{1C} % (IQR)	6.6 (6.2,7.2)	6.7 (6.1,7.2)	7.0 (6.3,8.4)
HbA_{1C} mmol mol^{-1} (IQR)	49 (44,55)	50 (43,55)	53 (45,68)
Total cholesterol mmol l^{-1} (SD)	4.8 (1.2)	5.3 (1.1)	5.5 (1.1)
Systolic BP (SD)	137 (20	141 (18)	144 (20)
Median 10-year CVD risk score at diagnosis (IQR)	27 (20,37)	24 (17,34)	26 (18,37)
Median CVD medications at diagnosis (IQR)	4 (3,5)	1 (0,3)	1 (0,2)
Diagnosed with high BP	73%	54%	58%
Diagnosed with high cholesterol	73%	29%	15%
Diagnosed with previous CVD	35%	10%	5%
Had CVD death	5	4	1
Had myocardial infarction	4	4	3
Had stroke	3	1	5
Had revascularisation	3	5	7
Had non-traumatic amputation	0	0	0
Had any CVD event	15 (14%)	14 (7%)	16 (4%)

7.3.3 Change in medication after diagnosis

In Section 3.3.1 (page 39) I presented a detailed analysis of how medication changes after screen-detected diagnosis of diabetes in ADDITION-*Europe*, ADDITION-*UK* and ADDITION-*Denmark*. Briefly, in ADDITION-*Cambridge* between diagnosis and one year follow up there was a median increase of one medication (IQR 0,2; range -5,7; histogram). Looking by medication type, there was no median change in diabetes medication (IQR 0,1; range 0,3; histogram ) and a median increase of one CVD medication (IQR 0,2; range -5,5; histogram). Despite the central tendency of no change, 31% of the sample initiated a diabetes medication from diagnosis to one year.

7.3.4 Number of events

Between one and five year follow up 6% ($\frac{45}{726}$) of individuals had a CVD event. The number of individuals that experienced each component of the composite CVD event measure was low (Table 7.1), with 10 CVD deaths, 11 myocardial infarctions, 9 strokes and 15 revascularisations.

7.3.5 Change in medication and incident events

Figure 7.2 is a Kaplan-Meier plot showing the unadjusted survival curves from diagnosis (unlike the primary analysis this includes individuals that experienced a CVD event before one year follow up, but still provided medication data at one year follow up). There was a statistically significant difference in survival times between those that increased, decreased or didn't change the total number of CVD medications (log rank test $p<0.01$). The Kaplan-Meier survival probability estimates at five years after diagnosis were 0.95 for individuals that increased their medication, 0.93 for those with no change and 0.84 for individuals that decreased their diabetes or CVD medication.

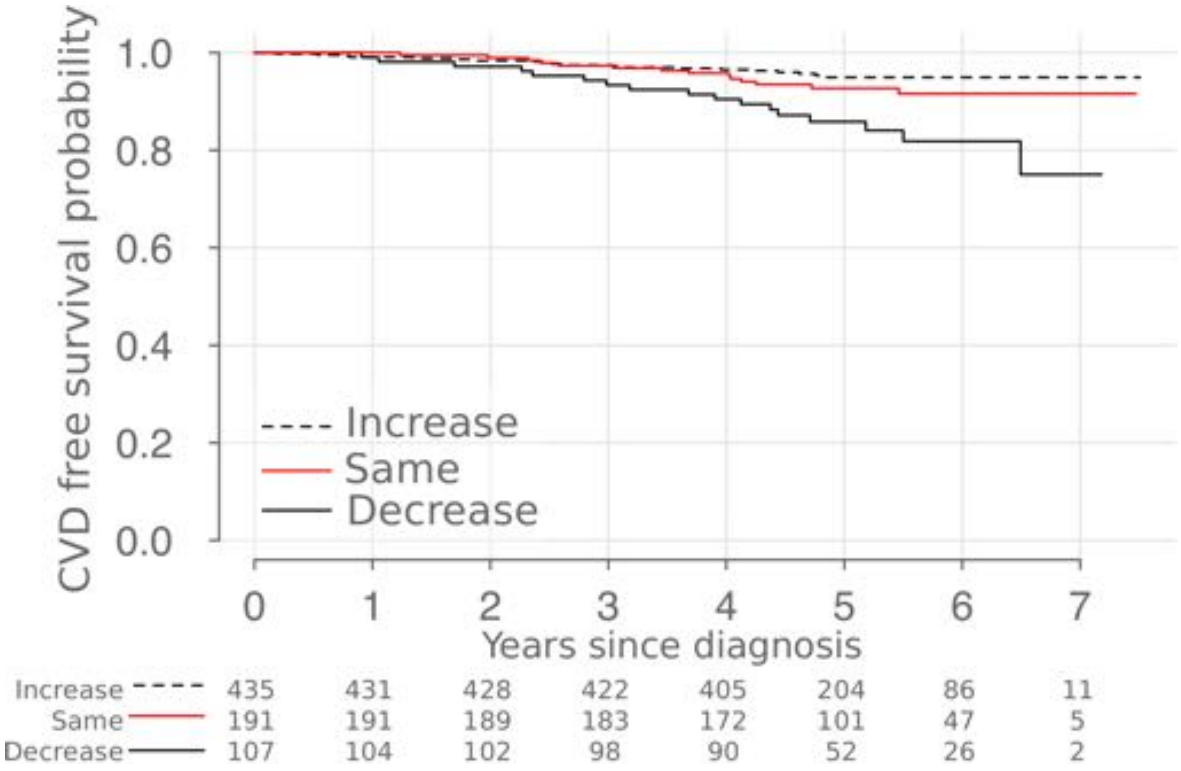
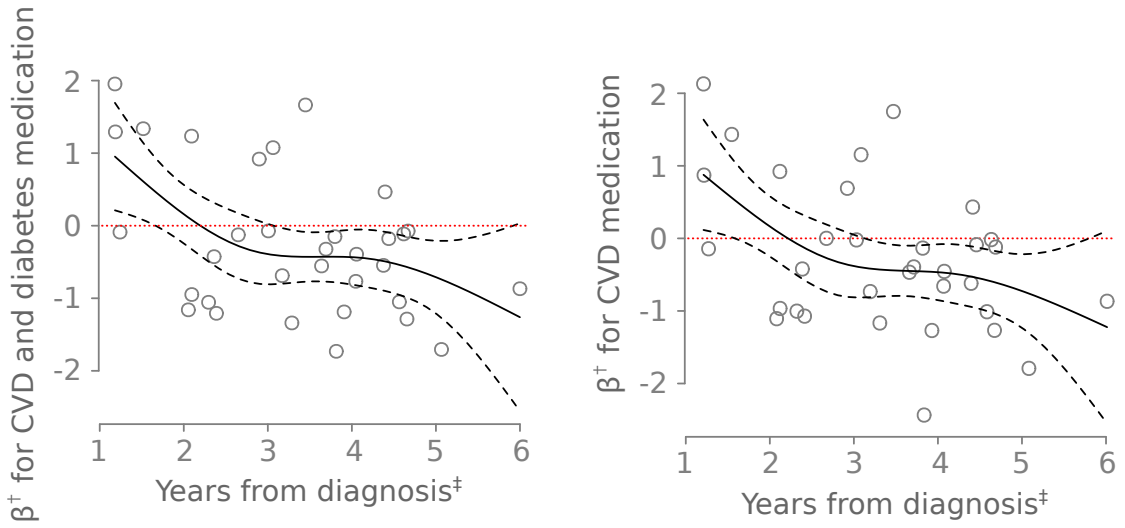


Figure 7.2: Kaplan-Meier plot estimating the crude survivor function for individuals that decreased, increased or kept their CVD or diabetes related medication the same. The table under the plot represents the number still being followed up at each time point, and survival rather than cumulative incidence is presented to more intuitively mirror this table.



(a) Primary analysis

(b) Sensitivity analysis

Figure 7.3: Plot suggesting hazard from change in cvd and diabetes medication (Figure 7.3a) is non-proportional. In a sensitivity analysis seperating CVD and diabetes medication, the effect only remained for change in CVD medication (Figure 7.3b). † Schoenfeld residuals have been scaled to obtain estimates of the time-varying coefficient. ‡ Within the model $time = 0$ was date of one year follow up.

7.3.6 Violation of proportional hazards

In a Cox proportional hazards model we assume that the hazards from two observations are proportional, and that proportionality remains constant over time. If this is not true than the parameter estimates are likely to be biased and underpowered.[239]

The Pearson product-moment correlation (r) between scaled Schoenfeld residuals and ranked time suggests that the proportional hazards assumption for change in medication in the primary analysis was violated (r=-0.31, χ^2=5.81, p=0.02). When separating CVD and diabetes medication into unique parameters, non-proportionality over time remained present for change in CVD medication only (r=-0.42, χ^2=10.81, p<0.01).

Figure 7.3 shows the variation in fit over time for the primary analysis (Figure 7.3a), and the change in CVD medication variable (Figure 7.3b) from a model where CVD medication and diabetes medication were separate parameters. If the proportional hazards assumption held, I would expect to see line with a slope close to zero. I found that in both Figures 7.3a and 7.3b it appeared that an additional medication was associated with an higher risk in the first year of follow up, but the hazard appeared to stabilise from the second year of follow up. To address the violation of the non-proportional hazards, two strategies were employed:

Amended model 1) Splitting the model into periods of proportional hazards. A subjective interpretation of Figure 7.3 suggests that dividing the model into before and after 12 months after one year follow up would lead to hazards that are proportional over time. As this leaves inadequate power for the model investigating the first 12 months, I only present the second model looking from 12 months after one year follow

up (effectively 2 years after diagnosis) in Section 7.3.7.

Amended model 2) Modelling the effect of time within the primary model by including an interaction term was also completed, which is presented in Section 7.3.8. This method is recommended as it enables a model that reflects the fact that the influence of pharmacotherapies may differ over time - for example the effect could be cumulative or alternatively the individual or the disease pathogenesis may only be temporarily disrupted by the medication, and thus the effect on events becomes a function of time.[240]

7.3.7 Primary analysis - removing early events (Amended model 1)

In a model looking at CVD events from 12 months after one year follow up (i.e. following for events from ~2 years after diagnosis), an additional medication was associated with a lower risk of a CVD event (HR 0.64; 95%CI 0.50,0.81), when adjusting for sex, 10-year modelled CVD risk at diagnosis, age, previous CVD, high BP or cholesterol and intensive treatment allocation. When looking at a subsample of only those free of CVD at diagnosis, a protective effect from an additional CVD or diabetes medication remained present (HR 0.64; 95%CI 0.49,0.84).

Figure 7.4 shows the relative hazard of a CVD event based on a change in CVD or diabetes medication between -1 and +4 in the model excluding individuals with previous CVD. These simulated results combine the uncertainty of each component of the regression model, and how this effects the predicted hazards for an individual (methods detailed in Section 7.2.2.4, page 115). From these simulated hazards, it is clear that individuals who decreased their medication were at increased risk of a CVD event, while those that increased saw a protective effect. In the section below I look more closely at three potential changes in the number of CVD and diabetes medications from diagnosis to one year and how these influence the relative hazard of an event for an individual by using post-estimation to calculate the change in hazard beyond a simple increase from zero to one (that accounts for the variance and bounding limit of zero in the model):

Decreased CVD or diabetes medication by one: Predicted to result in a 56% higher risk of a CVD event (simulated median relative hazard compared to no change 1.56; IQR 1.14,1.71; histogram ).

Increased CVD or diabetes medication by one: Predicted to result in a 36% lower risk (simulated median relative hazard compared to no change 0.64; IQR 0.58,0.71; histogram ).

Increased CVD or diabetes medication by three: Predicted to result in a 73% lower risk (simulated median relative hazard compared to no change 0.27; IQR 0.19,0.35; histogram ).

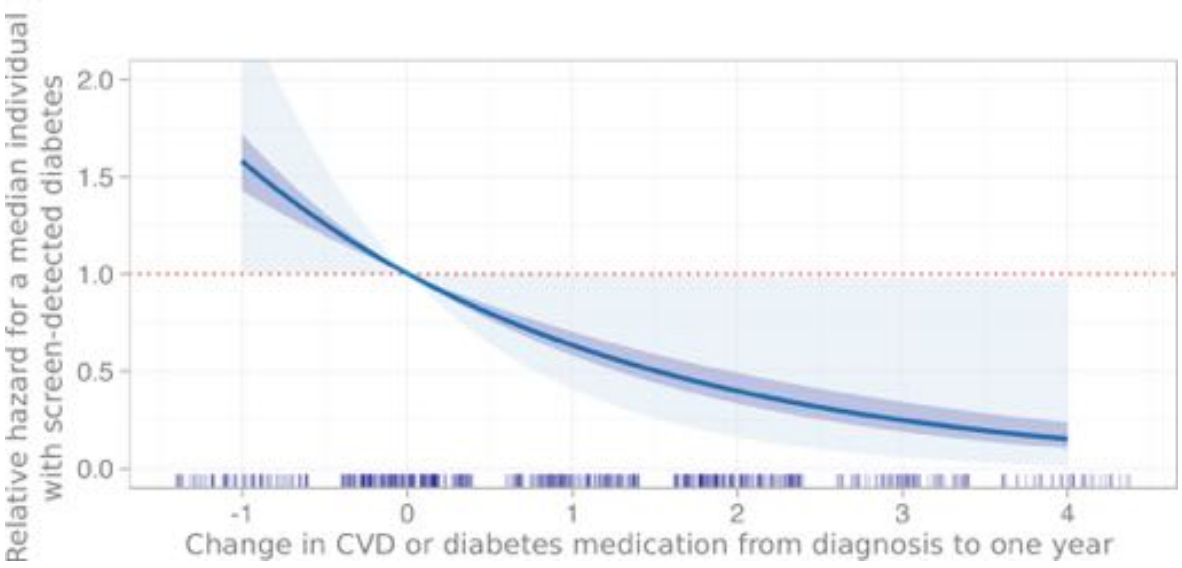


Figure 7.4: Plot of 1,000 simulated predictions of the relative hazard of a CVD event from two to five years after diagnosis based on change in diabetes and CVD related medication between diagnosis and one year. Predictions adjusted (methods detailed in Section 7.2.2.4, page 115). Change in medication range is 5^{th} to 95^{th} centile of the simulated hazards. Light blue is range of predicted relative hazards, darker blue is IQR, and the dark blue line is the median estimates. Rug plot shows number of individuals that changed medication by that value.

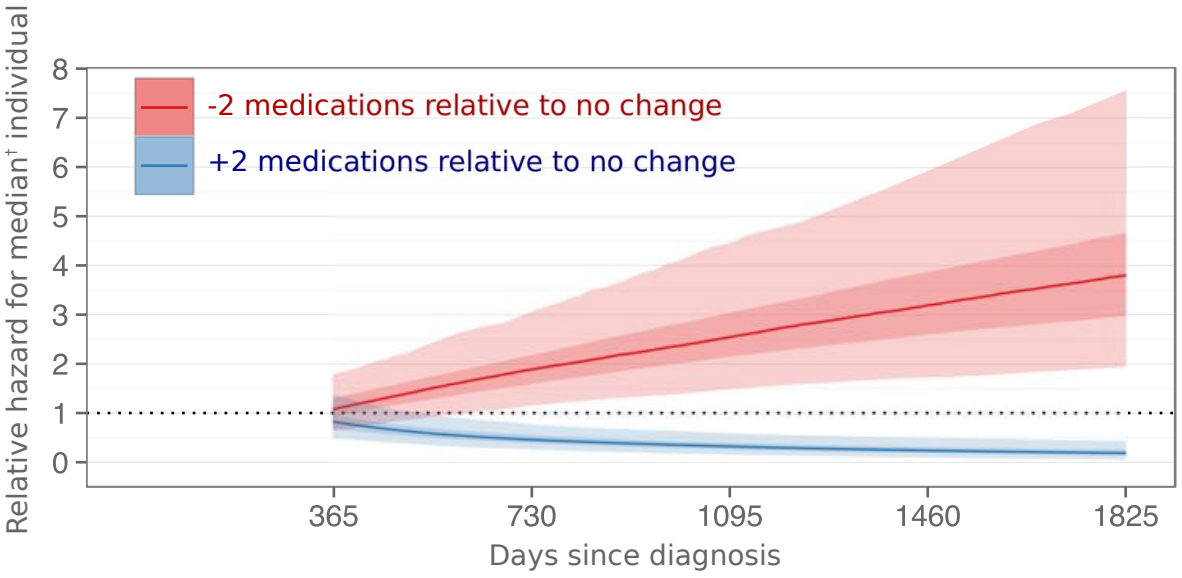


Figure 7.5: Simulated effect of time on varying the proportionality of the medication change hazard. 1,000 draws were taken form a distribution of possible regression parameters. Outer ribbon represents range of predicted relative hazards, inner the IQR, and the median estimate is overlaid as a line. † Predictions adjusted (methods detailed in Section 7.2.2.4, page 115).

7.3.8 Primary analysis accounting for varying effect (Amended model 2)

When allowing for a time interaction in a model adjusted for sex, 10-year modelled CVD risk at diagnosis, age, previous CVD, high BP or cholesterol and intensive treatment allocation, the association with medication is described by two variables: change in CVD or diabetes medication, HR 9.2; 95%CI 2.1,39.9 and log time against change in CVD or diabetes medication, HR 0.68 (95%CI 0.54,0.85). For the model including only those free of CVD at diagnosis, the coefficients were; change in CVD or diabetes medication, HR 8.5 (95%CI 2.0,35.7) and log time against change in CVD or diabetes medication, HR 0.69 (95%CI 0.55,0.86).

While the two coefficients required by the interaction enable the varying effect of change in medication on CVD risk to be modelled, interpretation of this value is difficult. Figure 7.5 represents two sets of relative hazards based on an increase of two medications, or a decrease of two medications (compared to no change in medication) in a model with an interaction term between change in CVD and diabetes medication and time. After around one year there is a clear divergence, where an increase in medication appears to have a protective benefit, while a decrease in medication increases the hazard for a CVD event. It appears that the effect diverges further over time, but the large amount of variance present in the simulated relative hazards is likely to be the reason why the partitioned time model presented in Section 7.3.7 did not find evidence of a violation of the proportional hazards assumption between 730 days and the censor date.

7.3.9 Sensitivity analyses

All sensitivity analyses were adjusted for sex, 10-year modelled CVD risk at diagnosis, age, previous CVD, high BP or cholesterol and intensive treatment allocation.

As discussed in Section 7.3.6, the proportional hazards assumption was violated for the primary analysis. When separating diabetes and CVD medication into two measures, this violation remained present for change in CVD medication (as plotted in Figure 7.3b). While two techniques were used to address this in the primary analysis, for this sensitivity analysis I only modelled events from 12 months after one year follow up as that was when the hazards appeared to become proportional (Figure 7.3b). For the other sensitivity analyses the proportional hazards assumption was robust, and they still follow the original analysis plan of starting follow up on the day after one year follow up. While CVD medication and not diabetes medication was associated with a protective effect in a model excluding previous CVD, a non statistically significant protective effect appeared to be present for increasing diabetes or CVD medication in a model in which the two were unique parameters (Figure 7.6).

In a model in which change in medication was a binary increased or decreased, there was no statistically significant association in the full sample (Figure 7.6) but the direction of effect was in line with the primary analysis finding of an increase in medications being protective and a decrease having the opposite association. Within the model excluding individuals with previous CVD, a decrease in medication was associated with a 154% increase in the risk of a CVD event (HR 2.54; 95%CI 1.02,6.31).

Change in medication was also separated into four parameters: glucose lowering, BP lowering, lipid lowering and aspirin. No statistically significant associations were detected, although precision was low in these analyses (Figure 7.6) due to the low sample size and event rate.

No associations were detected when repeating the analysis in only individuals that increased their medication, and when the primary analysis was repeated changing the outcome to all-cause mortality, the full sample model found a protective effect from increasing medication (HR 0.76; 95%CI 0.64,0.92) that was not present in the sample excluding individuals with previous CVD (Figure 7.6).

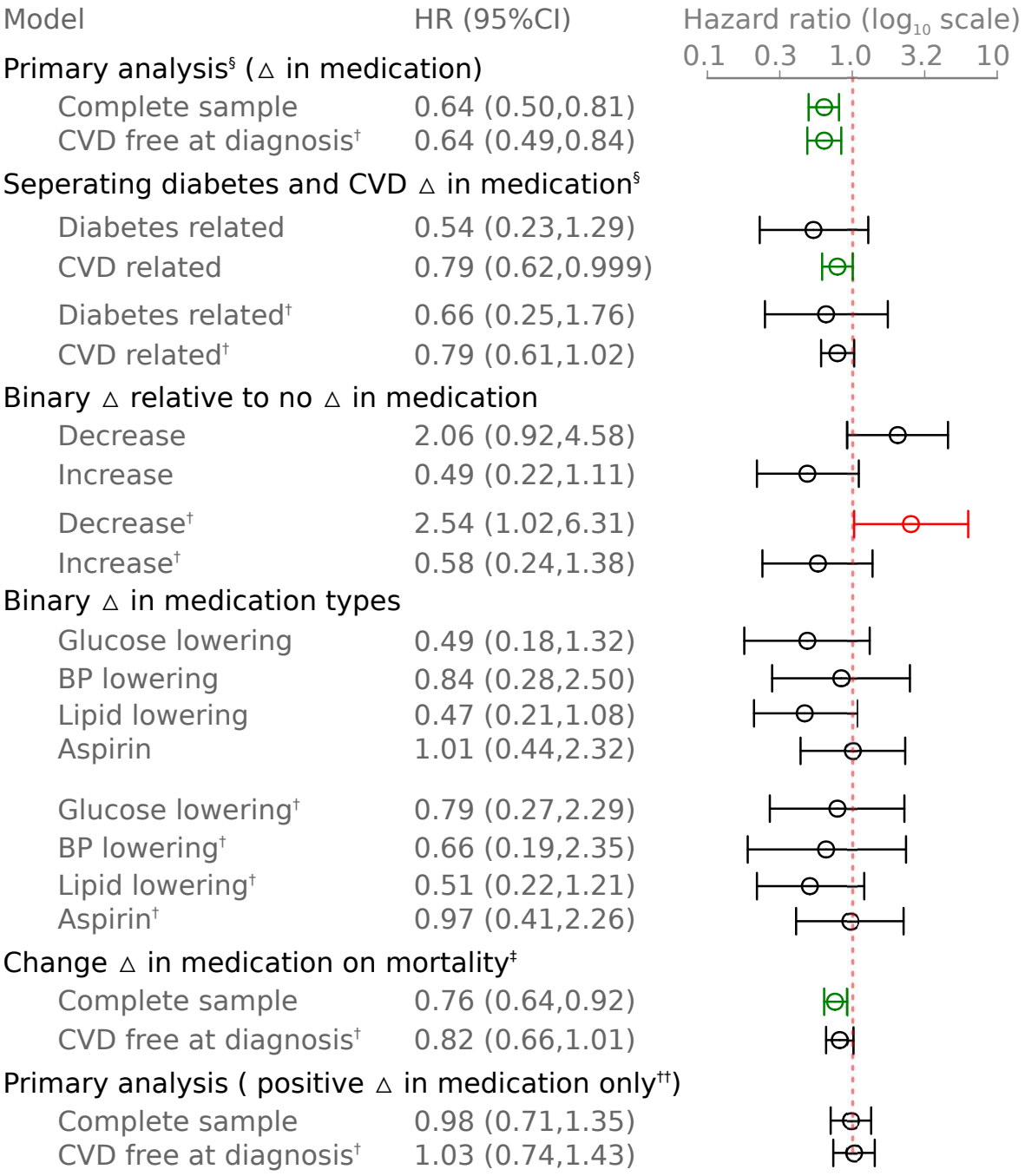


Figure 7.6: Results of the primary and sensitivity analyses modelling the association between change in medication from diagnosis to one year on the hazard of CVD. All results are adjusted for sex, modelled CVD risk at diagnosis, age and randomisation to the intensive treatment group. △ = change. § Model of events from 12 months after one year follow up (~2 years after diagnosis). † Sample restricted to individuals free of CVD at diagnosis. ‡ All-cause mortality rather than CVD events was the event for this sensitivity analysis. †† Excluding individuals that decreased their CVD or diabetes medication from diagnosis to one year.

7.4 Discussion

In ADDITION-*Cambridge*, I have shown that change in medication from diagnosis to one year is associated with incidence of CVD events from two to five years after diagnosis. In a model adjusted for demographics and cardio-metabolic health, an additional medication was associated with a 36% decreased risk of a CVD event (HR 0.64; 95%CI 0.50,0.81). In real terms, for an individual representative of the average person screen-detected person with diabetes (based on the ADDITION-*Cambridge* sample), the model suggested that a decrease in CVD or diabetes medication was associated with a 27% higher risk of a CVD event (simulated median relative hazard compared to no change 1.27; IQR 1.18,1.38), while an increase in one medication was associated with a 21% lower risk (simulated median relative hazard compared to no change 0.79; IQR 0.73,0.85).

While I identified that an overall increase in CVD or diabetes medication was associated with a protective effect, non-significant protective effects were present in the majority of sensitivity analyses that used different methods to describe how cardio-protective medication changed after diagnosis. I may not have been able to confidently detect an effect of change in the components of cardio-protective medication as there will be concordance present between the changes in each type of medication. This is likely as the prevalence of high CVD risk factors tends to cluster in individuals[45], which would lead to changes in medication to manage these risk factors being correlated, and an attempt to independently explore effects being attenuated. This is not problematic though, as the benefits of mono-therapy is established through studies using randomisation to avoid confounding[77,109,208,232], and in this thesis I am more interested in medication changes as a whole, rather than the merits of particular agents. This allows me to reflect the fact that diabetes care is not about treating an individual component like glucose control, but a wider spectrum of cardio-protective intervention for multiple risk factors to prevent CVD.[14,117]

Individuals that decreased their medication count after diagnosis experienced a higher rate of CVD events (14% vs. 7% in those that did not change the number of medications, and 4% in those that increased). Despite these divergent event rates, individuals that decreased their medication did not appear to have poorer cardio-metabolic health based on their CVD risk factors at diagnosis. This highlights the fact that those at the highest risk of a CVD event (or another CVD event) are also the most likely to already be monitoring and treating CVD risk factors at diagnosis, so are less likely to be initiating treatment due to the recent diabetes diagnosis. This reinforces the role of this analysis in providing evidence of the outcomes in individuals that do change their medication, rather than individuals randomised to interventions to promote more intensive CVD risk factor targets.

7.4.1 Context within the literature

In Steno-2 160 individuals with type 2 diabetes and microalbuminuria were randomised to intensive treatment of CVD risk factors through a step-wise application of lifestyle advice and pharmacotherapy to attain CVD risk factor targets.[112] At 7.8 year follow up, individuals

in the intensive treatment arm were 55% (HR 0.45; 95%CI 0.23,0.91) less likely to experience a composite CVD event.[112] Steno-2 recruited a sample with long standing diabetes who were randomised to treatment strategies, while in ADDITION-*Cambridge* I have explored the relationship within screen-diagnosed individuals that changed medication, which means comparisons must be approached with caution. Under this caveat, in my analysis I found that an increase of three medications was associated with a predicted 51% lower (relative hazard to no change 0.49; 95%CI 0.39,0.61) risk of a composite CVD event. While Steno-2 did not report change in medication information in a comparable way, intensification of CVD risk factor control in a population with long standing diabetes can be assumed to involve pharmacotherapy intensification, and it suggests that my results suggest the effectiveness of pharmacotherapy within a multifactorial approach to diabetes care.

While this analysis uses a novel screen-detected diabetes population who received multifactorial diabetes care, my findings are in keeping with previous research from RCTs of interventions that led to treatment intensification for individual CVD risk factors. The UKPDS demonstrated the benefit of improving both glucose control, particularly with metformin in overweight individuals, and lowering blood pressure levels.[77,102] The HPS and CARDS trials demonstrated the benefit of statin use in people with diabetes.[74,75] While there is less consensus on the benefit of aspirin outside of individuals with previous CVD[14,117], in Chapter 3 (page 35) I demonstrated that in ADDITION-*UK* 21% reported aspirin at diagnosis, and this doubled (42%) at one year. While a screen-detected population may have a lower event rate than many of the populations were mono-therapies and individual risk factor control were evaluated, there is evidence that the percentage risk reductions remain constant regardless of absolute risk.[74]

7.4.2 Strengths and limitations

I have presented a novel analysis of a well defined population with type 2 diabetes that was detected by screening. As routine care continues to evolve[14,117,170,241], these results give a unique insight into a population that received care that is similar to contemporary practice. ADDITION-*Cambridge* was suitably powered to detect a 'clinically meaningful' effect of the intervention in five years[150], although the power available was attenuated as the event rate in both arms was lower than expected. As this analysis is a cohort analysis it is able to leverage the full variation in treatment changes, so the improvements in routine care that limited the potential to detect an effect in the trial analysis are less intrusive.

As this analysis is non-randomised, the possibility remains that confounding variables have not been suitably adjusted for. Of primary concern in this regard is the potential that adjusting for medication count at diagnosis, and CVD health, did not capture the full spectrum of cardio-metabolic health that may drive treatment decisions at diagnosis. Although, my results are in keeping with the findings of the randomised Steno-2, and the statistically non-significant protective effect in ADDITION-*Europe*[145], where multifactorial interventions included comprehensive management of cardiovascular health.

While the majority of studies focus on the both individual[109,208] and multifactorial di-

abetes care[113] with an emphasis on pharmacotherapy, in ADDITION-*Cambridge*, Long *et al* have also identified that individuals who make positive changes to their lifestyle in the year after diabetes diagnosis have a reduced risk of experiencing a CVD event.[233] While a link between health behaviour change was found in a observational analysis of ADDITION-*Cambridge*, and in preventing the onset of diabetes[242], a large randomised trial of intensive lifestyle intervention in type 2 diabetes did not reduce the rate of CVD events at 9.6 years in an overweight population[85], who potentially had a greater potential treatment benefit than a less overweight screen-detected population. Likewise, ADDITION-*Plus* found no effect on health behaviours or CVD risk factors from individualised theory based lifestyle intervention over the first year after diagnosis.[234] This suggests that a causal link between health behaviour and CVD events is possible, but it is not established that achievable change in lifestyle is connected to risk of CVD events. While the potential of pharmacotherapy intensification leading to behaviour changes in diabetes is also not established. As such, while adjustment for health behaviour would be ideal, the lack of precision and increased proportion of missing data led to the decision not to adjust for health behaviours. Socio-economic status was also not adjusted for, and while I did not find an association between IMD and medication change in ADDITION-*UK* (Chapter 3), or an association between age left full time education and change CVD risk factors (except for obesity) in ADDITION-*Europe*, associations have been found in the literature.[200,212]

Repeating the analysis without individuals that decreased their medication after diagnosis leads to estimates of an association centred on no effect. The binary inclusion of up or down into the model, and the raw survival rates from the Kaplan Meier plot, suggests that there is a broadly linear effect of change in medication, so available evidence suggests that the primary model is appropriate in treating change in medication as continuous. However, when the primary analysis is repeated in only those who increased medication, the result becomes insignificant (not presented is that the relationship is also non-significant in only those that decreased). While I hypothesise that the centred estimate is due to low power, I cannot rule out that the associations seen are primarily driven by individuals that decrease medication in the first year being more frail[125], which in turn leads to an increased incidence of CVD events.

This analysis aims to expand on our knowledge of single risk factor therapy, and multi-factorial interventions like Steno-2, to the effect of changes in multiple medication types for multiple risk factors centred around the prevention of micro- and macro-vascular disease. I have used self-reported medication, which for repeat medication for chronic conditions like hypertension can closely mirror pharmacy redemptions.[243] However, it should be noted that there is uncertainty on how redeemed medication translates into actual use by the individual.[244]

7.4.3 Implications for practice

The ADDITION-*Europe* trial was evaluating the effect of promotion of intensive treatment, and manipulated a small difference between arms through the pragmatic way in which the

intervention was applied, and improvements in the routine care early in the trial.[103,170,172,216] This analysis uses a cohort approach to assess the difference in treatment over a larger gradient than what was achieved in the trial.

Individuals that increase their medication burden from diagnosis to one year have a reduced risk of a CVD event in the first five years after diagnosis. This finding, alongside existing evidence from Steno-2[112,113], suggests that the increase in total medication that comes with treating multiple risk factors for CVD in individuals with type 2 diabetes is beneficial in terms of reducing future events.

7.4.4 In the context of optimising CVD risk management

The remaining question, which I will address in Chapter 8 (page 129), is whether this intensification of treatment is indeed a burden by exploring associations between medication change and HRQoL.

Chapter 8

Change in cardio-protective medication and HRQoL after diagnosis of screen-detected diabetes

8.1 Introduction and aims

Type 2 diabetes is associated with increased risk of morbidity, early mortality[50] and reduced HRQoL.[245] Pharmacological management of individuals with established diabetes reduces cardiovascular risk,[102] which I have shown in Chapters 6 and 7. However, treatment regimens may impact on a patients illness experience and their HRQoL and interventions that improve cardiovascular risk factor levels do not necessarily improve HRQoL.[246] Establishing a balance between the benefits and harms of pharmacological treatment is particularly important among individuals with screen-detected diabetes, for whom the disease is asymptomatic, but the burden of being diagnosed and treated tangible.[168,246] The advent of national screening programmes, such as the NHS Health Checks, means that more people with clinically asymptomatic diabetes will be diagnosed. There is limited research examining how the burden of treatment might affect HRQoL for individuals identified earlier in the diabetes disease trajectory.

Among patients with established diabetes, a systematic review of 33 studies found that pharmacotherapy to improve glucose control and lifestyle interventions improved quality of life as measured by the SF-36.[247] Study design in this meta-analysis varied greatly, from RCTs to pre-post and cohort studies, and the review did not satisfactorily attempt to test the robustness of the finding in homogenous interventions with methodologically strong analyses. Interestingly, the ACCORD study, which was stopped early due to excess mortality in the treatment arm, found no evidence of a negative impact of the SF-36 component scores (MCS and PCS) or treatment satisfaction in either changes from diagnosis to four years, or between treatment arms.[124] While this is promising, ACCORD's early conclusion is a reminder that HRQoL is a population measure and rare hypoglycaemic events that cause a severe burden to a minority of individuals may be masked within the wider population HRQoL.

In a cross-sectional analysis, five years after diagnosis in ADDITION-*Europe*, individuals with poorer glycaemic control were more likely to report a negative impact on diabetes specific QoL.[248] In ADDITION-*Cambridge*, Kuznetsov *et al* looked at changes in HbA_{1C} from one to five years after diagnosis, and HRQoL at five years.[249] While they found that individuals whose HbA_{1C} increased were more likely to report a negative impact on the their HRQoL, these cross-sectional and cohort analyses describe the association between HRQoL and actual change in glycaemic control. For concern over medicalisation to be addressed, the effect of treatment regardless of underlying changes in glycaemic control must be assessed. In ADDITION-*Denmark*, no evidence was found at six years of a difference in how individuals in the intensive multifactorial treatment and routine care arm viewed the process of managing chronic disease, as assessed by the Patient Assessment Chronic Illness Care questionnaire (PACIC).[250]

However, further research is needed to elucidate the relationship between cardio-protective medication and HRQoL. This information would help inform diabetes management strategies early in the diabetes disease trajectory, and address concerns over excess treatment early in the diabetes trajectory.[124,251]

8.1.1 Aims

Among 867 participants with screen-detected diabetes (the ADDITION-*Cambridge* trial cohort), I described the association between (i) change in cardio-protective medication from diagnosis to one year and change in general HRQoL (EQ-5D) and (ii) change in cardio-protective medication from one to five years and change in general (EQ-5D, SF-36) and diabetes-specific HRQoL (Audit of diabetes-dependent quality of life questionaire (ADDQoL)). My secondary aim was to establish whether change in cardio-protective medication in the first year after diagnosis was associated with changes in HRQoL from one to five years.

8.2 Methods

8.2.1 Cohort description

I used data from the Cambridge centre of the ADDITION-*Europe* trial. ADDITION-*Cambridge* methods are presented in Section 2.1.1 on page 29. Briefly, Individuals aged 40 to 69 years from 49 practices in Eastern England, not known to have diabetes, and with a diabetes risk score derived from practice records[147] corresponding to the top 25% of the population distribution were invited for stepwise screening. Exclusion criteria were pregnancy, lactation, an illness with a likely prognosis of less than one year or a psychiatric illness likely to limit study involvement or invalidate informed consent. 867 patients were found to have diabetes according to 1999 WHO diagnostic criteria[252] and agreed to take part in the treatment trial.

8.2.2 Measuring HRQoL

Trained staff assessed patients health at baseline, one year and five years and collected biochemical and anthropometric data according to standard operating procedures. Self-report questionnaires were used to collect information on socio-demographic characteristics, lifestyle habits and medication use. Changes in biochemical measures and medication from baseline to five-year follow-up have been reported previously.[253]

The EQ-5D was administered at diagnosis, one and five years. The EQ-5D assesses health utility over five domains of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with three levels of functioning, which results in 243 health states with scores ranging from -0.594 to +1.00 (full health).[254] The SF-36 measures health status and consists of 36 items over eight health domains; it can be summarised into PCS and MCS scores that range from 0 to 100, with higher scores indicating better health.[255] The ADDQoL, measures an individuals perception of the impact of diabetes on various aspects of their HRQoL, and can be summarised as an average weighted index score that ranges from -9 (negative impact) to +3 (positive impact).[256] The SF-36 and ADDQoL were collected at one and five years only. For the purposes of brevity, health status, diabetes-related QoL and HRQoL are treated as synonymous in this thesis.

Participants were encouraged to bring their repeat prescription summaries to each health assessment. They also filled in a health economics questionnaire[171], which asks for information on all prescribed medication. Self-reported medication was ATC coded[11] and grouped into 13 types of cardio-protective agent: aspirin; any statin; any other lipid lowering medication; any ACE inhibitor; any β-blocker; any calcium channel blocker; any diuretic; any other blood pressure lowering medication; any thiazolidinedione; any sulphonylurea; metformin; insulin; or any other glucose lowering medication. Cardio-protective medication count was defined as the total number of the 13 cardio-protective agents each participant reported taking at each time point: diagnosis, one and five years.

8.2.3 Statistical analysis

Individuals that died between diagnosis and one year (n=8), and one year and five years (n=47), were excluded from the analysis sample. Only cases with complete data were included. Participant characteristics were described at baseline, one year and five years using means, medians and proportions. Differences in characteristics between participants with and without complete data were examined using logistic regression.

To describe change in cardio-protective medication, data were collapsed into three groups: (i) no change or a reduction in the number of cardio-protective agents; (ii) an increase of one cardio-protective agent; and (iii) an increase of 2 cardio-protective agents. The baseline EQ-5D score was subtracted from one year to calculate the change in EQ-5D from diagnosis to one year. One-year HRQoL measures were subtracted from five-year measures to calculate change in HRQoL from one to five years. Multivariable linear regression was used to quantify the association between change in cardio-protective medication and change in EQ-5D from

baseline to one year with standard errors adjusted for clustering by practice.[257] A multilevel model accounting for individuals within practices was considered, but due to a lack of heterogeneity explained by practice in the primary analyses, it was rejected for a parsimonious model. All models were adjusted for age at diagnosis, gender, 2004 English IMD score[258], self-reported CVD at baseline, ethnicity, baseline value of the HRQoL measure, baseline HbA_{1C} level, randomisation group and practice level clustering. In a second series of linear regression models, I examined the association between change in cardio-protective medication from one to five years and (i) change in EQ-5D; (ii) change in SF-36 (physical and mental score) and (iii) change in Audit of diabetes-dependent quality of life average weighted index (ADDQoL-AWI) from one year to five years. I adjusted the model for the same factors outlined above, as well as self-reported CVD at one year.

In a secondary analysis, the association between change in cardio-protective medication in the first year after diagnosis and changes in HRQoL (EQ-5D, SF-36 and ADDQoL-AWI) from one to five years was assessed in a linear model analogous to the primary analysis.

Different versions of the ADDQoL were used (ADDQoL-18 and ADDQoL-19) at one and five years. The authors of the ADDQoL state that the measure remains robust if up to six items are removed.[259] I removed the following items from the summary score as they differed between questionnaires: 'holidays/leisure activities', 'travel/journeys', 'society/people reaction', 'dependence', 'enjoyment of food', and 'closest personal relationship'. The Cronbach's α for the ADDQoL-AWI un-weighted items that were constant across both questionnaires at one- and five-year follow-up was 0.90 and 0.94, respectively. In addition, I included a sensitivity analysis using a Paretian model[260] of the complete ADDQoL questionnaires, which ignored the relative importance of change, instead focusing on the four possible directions of change. Four categories were derived; (A) increase in any ADDQoL domain, (B) no change across domains, (C) decrease in any domain, (D) mixed change, and regressed in a multinomial model that was analogous to the primary analysis.

Four additional sensitivity analyses were undertaken. Firstly, change in the number of medications was fitted as a continuous variable, rather than a categorical variable. Secondly, data points missing for ethnicity, IMD, change in agents, baseline of HRQoL measure and change in the HRQoL measure in the primary analysis were imputed 100 times using chained equations to account for missing-ness. Thirdly, change in energy intake (food frequency questionnaire derived $\frac{kcal}{day}$) or physical activity (EPIC-Norfolk Physical Activity Questionnaire (EPAQ2)[261]) after diagnosis might have confounded the observations and were added to the model as covariates. Lastly, interactions between randomisation group and change in medication were explored and the main analysis was also repeated in only the routine care group.

Table 8.1: Participant characteristics of ADDITION-*Cambridge* cohort at baseline, one and five years.

	Baseline		One year		Five years	
Measure	N (%)	Value	N (%)	Value	N (%)	Value
Median age at diagnosis in years (IQR)	867 (100%)	63 (56,67)	-	-	-	-
% Male	867 (100%)	61%	-	-	-	-
Median IMD score[†](IQR)	750 (87%)	11 (7,18)	-	-	-	-
% White ethnicity	859 (99%)	96%	-	-	-	-
% Any lipid medication (IQR)	865 (100%)	24%	849 (99%)	66%	782 (96%)	82%
% Any BP medication (IQR)	865 (100%)	58%	849 (99%)	69%	782 (96%)	79%
% Any diabetes medication	865 (100%)	0.5%	849 (99%)	31%	782 (96%)	62%
% Aspirin medication	865 (100%)	20%	849 (99%)	35%	782 (96%)	44%
Median number of lipid medications (IQR)	865 (100%)	0 (0,0)	849 (99%)	0 (1,0)	782 (96%)	1 (1,1)
Median number of BP medications (IQR)	865 (100%)	1 (0,2)	849 (99%)	1 (0,2)	782 (96%)	1 (1,2)
Median number of diabetes medications (IQR)	865 (100%)	0 (0,0)	849 (99%)	0 (0,1)	782 (96%)	1(0,1)
HbA_{1C}>53mmolmol^{-1} (7%) and not on any diabetes medication	791 (91%)	39%	726 (85%)	1%	683 (84%)	8%
Median HbA_{1C} % (IQR)	846 (98%)	6.8 (6.3,7.7)	692 (81%)	6.4 (6.0,6.8)	765 (88%)	6.9 (6.4,7.4)
Median HbA_{1C} mmolmol^{-1} (IQR)	846 (98%)	51 (45,61)	692 (81%)	46 (42,51)	765 (88%)	52 (46,57)
Median number reported cardio-protective medications (IQR)	867 (100%)	1 (0,2)	849 (99%)	2 (1,3)	782 (96%)	3 (2,4)
Median EQ-5D index score (IQR)	852 (98%)	0.85 (0.73,1)	739 (86%)	0.85 (0.73,1)	663 (82%)	0.85 (0.73,1)
Median MCS (IQR)	-	-	709 (83%)	56 (48,59)	660 (81%)	57 (51,60)
Median PCS (IQR)	-	-	709 (83%)	48 (39,54)	660 (81%)	48 (36,54)
Median ADDQoL (IQR)	-	-	721 (84%)	-0.39 (-1,-0.06)	669 (82%)	-0.37 (-0.11,-0.86)
% had CVD event	-	-	-	-	866 (100%)	7%
% Alive	867 (100%)	100%	866 (100%)	99%	866 (100%)	94%

- = Data unavailable; BP=blood-pressure; HbA_{1C}= glycosylated haemoglobin; EQ-5D=European Quality of Life Questionnaire; MCS=Mental component score; PCS=Physical component score; ADDQoL=Audit of diabetes-dependent quality of life average weighted index; IQR=inter-quartile range.

[†] Cambridgeshire county had a mean IMD score of 11.7 in 2004 (http://data.gov.uk/dataset/imd_2004).

8.3 Results

8.3.1 Cohort characteristics

867 patients agreed to participate in ADDITION-*Cambridge* and attended baseline measurement. Two participants withdrew from the study, while seven participants had a CVD event before one year follow up, and 55 (6%) before five year follow up. The median (IQR) value of the EQ-5D score at baseline for participants that were included in the analysis was 0.85 (0.73, 1). This was higher than the score for those who died and were excluded from the analysis (0.73; 0.62, 1). Participants who did not have complete data at five year follow-up reported lower levels of physical activity (at baseline) than those who attended. There were no other

significant differences between those with complete data at five years and those with missing data for baseline age, sex, BMI, current smoker, self-reported previous CVD, health status (EQ-5D) or number of cardio-protective agents. The greatest amount of missing data at one and five years was for the SF-36 (18%, $\frac{151}{860}$ and 19%, $\frac{151}{805}$, respectively). Missing medication and HRQoL data at one and five years was not clustered in the same individuals, leading to an increased level of missing data in the complete case analysis models (Table 8.2).

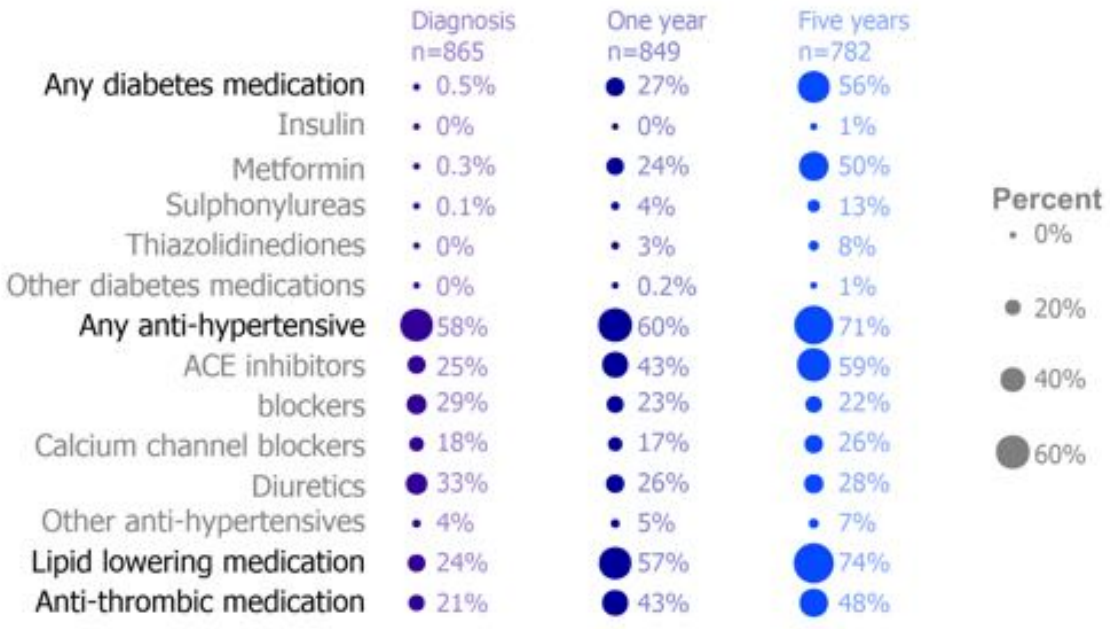


Figure 8.1: The proportion of ADDITION-*Cambridge* participants reporting cardio-protective medication at diagnosis, one and five years.

8.3.2 Change from baseline to one year

Four individuals (0.5%) reported being prescribed a glucose-lowering agent before diagnosis (Table 8.2) (three metformin, one a sulphonylurea). 24% of participants were taking a lipid-lowering agent, 58% a blood pressure-lowering agent and 19% aspirin at baseline (Figure 8.1). From diagnosis to one year there was an increase in the median number of prescribed agents, from 2 (IQR 1, 3) to 3 (IQR 2, 4). At one year follow-up, 251 (34%) individuals reported the same or a reduced number of prescribed cardio-protective agents, 185 (25%) one additional agent and 295 (40%) two or more agents. From baseline to one year, median EQ-5D scores remained constant at 0.85 (IQR 0.73, 1) and a large proportion of individuals (45%, $\frac{327}{729}$) reported no change in health utility (Figure 8.2). There was no evidence of an association between change in the number of cardio-protective medications and change in the EQ-5D score from baseline to one year (Figure 8.1).

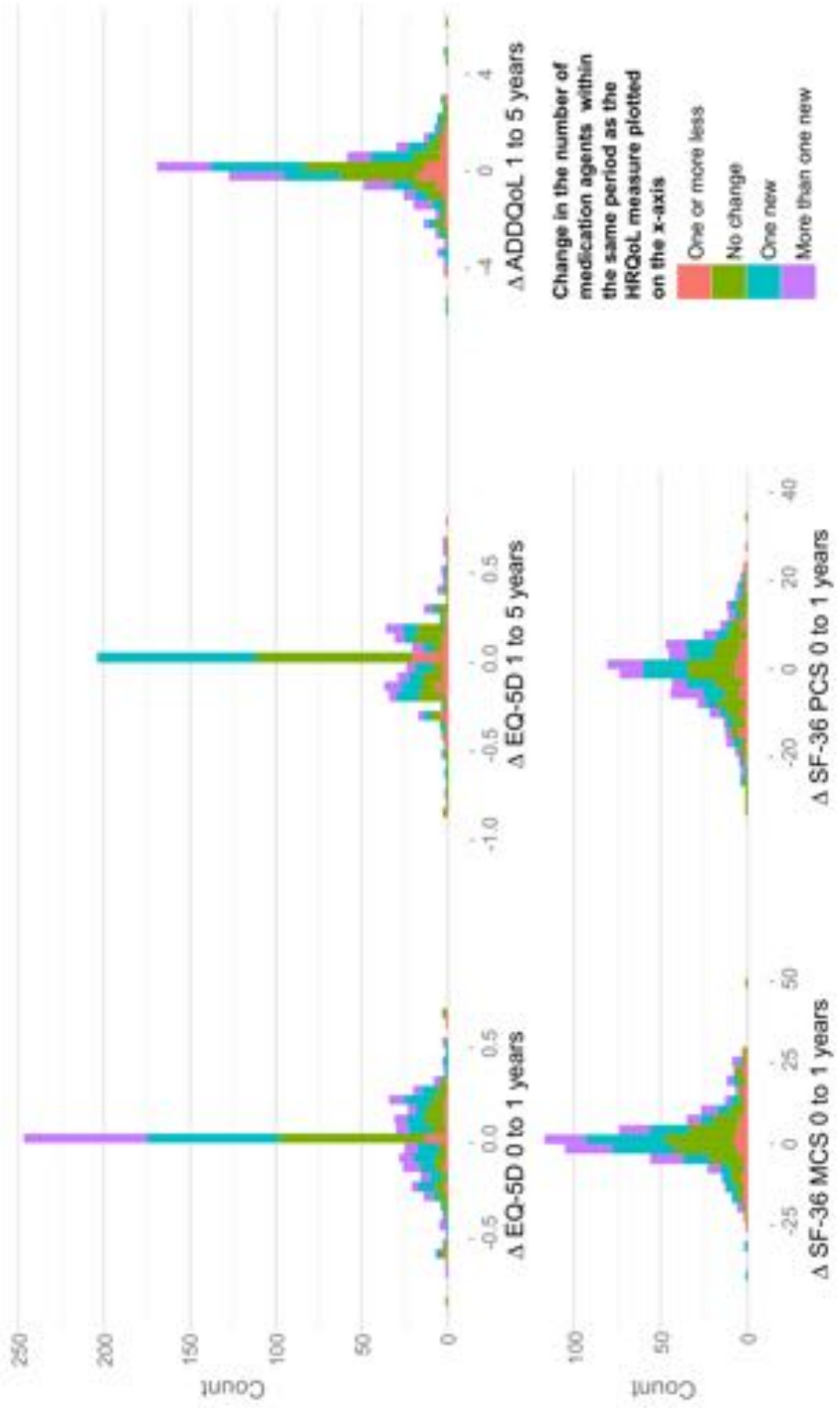


Figure 8.2: Distribution of change in HRQoL (EQ-5D, ADDQoL MCS, and PCS) from 0-1 and 1-5 years, colour coded by change in medication.

Table 8.2: Associations between change in number of cardio-protective agents and HRQoL in ADDITION-*Cambridge* cohort.

		Change in agents, relative to no change/decrease in agents			
		One more agent		More than one agent	
Outcome measure	n (%)	β (95%CI)	p-value	β (95%CI)	p-value
Complete case analysis (primary analysis)					
△ EQ-5D, 0-1 year	601 (70%)	-0.02 (-0.05,0.01)	0.21	-0.02 (-0.05,0.01)	0.25
△ EQ-5D, 1-5 years	513 (63%)	0.02 (-0.02,0.05)	0.32	0.05 (0.02,0.08)	<0.01
△ MCS, 1-5 years	488 (60%)	-0.5 (-2.2,1.2)	0.55	-0.4 (-1.9,1.0)	0.54
△ PCS, 1-5 years	488 (60%)	2.1 (0.3,4.0)	0.02	0.5 (-1.4,2.3)	0.63
△ ADDQoL-AWI, 1-5 years	510 (63%)	-0.11 (-0.36,0.14)	0.38	-0.20 (-0.38,-0.02)	0.03
Imputed					
△ EQ-5D, 0-1 year	859 (100%)	-0.03 (-0.06, 0.05)	0.10	-0.02 (-0.06, 0.01)	0.10
△ EQ-5D, 1-5 years	811 (100%)	-0.01 (-0.05, 0.03)	0.59	0.06 (0.02, 0.10)	0.01
△ SF-36 MCS, 1-5 years	811 (100%)	-0.1 (-1.5, 1.3)	0.86	-0.5 (-2.0, 1.1)	0.83
△ SF-36 PCS, 1-5 years	811 (100%)	2.1 (0.4, 3.8)	0.02	0.2 (-1.6, 1.9)	0.83
△ ADDQoL-AWI, 1-5 years	811 (100%)	-0.20 (-0.44, 0.05)	0.12	-0.32 (-0.51,-0.13)	<0.01
Including △PA and △Energy					
△ EQ-5D, 0-1 year	539 (69%)	-0.02 (-0.05,0.02)	0.28	-0.02 (-0.05, 0.01)	0.03
Routine care arm only					
△ EQ-5D, 0-1 year	301 (73%)	-0.05 (-0.10,0.00)	0.07	0.00 (-0.05, 0.05)	0.98
△ EQ-5D, 1-5 years	252 (66%)	-0.02 (-0.04,0.08)	0.46	0.03 (-0.02, 0.08)	0.46
△ SF-36 MCS, 1-5 years	242 (64%)	0.5 (-1.6, 2.6)	0.64	-0.2 (-2.2, 1.8)	0.83
△ SF-36 PCS, 1-5 years	242 (64%)	0.8 (-3.0, 4.7)	0.76	-0.2 (-3.4, 3.1)	0.91
△ ADDQoL-AWI, 1-5 years	245 (64%)	-0.18 (-0.50, 0.15)	0.28	-0.26 (-0.49, -0.03)	0.03

β coefficients (95% confidence interval) from a linear regression model adjusted for age at diagnosis, gender, 2004 IMD, self-reported CVD at baseline, ethnicity, baseline value of the HRQoL measure, randomisation group and practice level clustering. △=Change; BP=blood-pressure; EQ-5D=European Quality of Life questionnaire MCS=Mental component score; PCS=Physical component score; ADDQoL-AWI=Audit of diabetes-dependent quality of life average weighted index.

8.3.3 Change from one to five years

From one to five years after diagnosis, use of any anti-hypertensive agent increased from 69% to 79%; larger increases were seen in the reporting of any lipid-lowering agents (66% to 82%) and any glucose-lowering agents (31% to 62%). Aspirin use increased from 35% at one year, to 44% at five years. At one and five years, a median total of 3 (IQR 2, 4) and 4 (IQR 3, 5) cardio-protective agents were reported, respectively. Over the same time period, 219 (36%) reported no increase in cardio-protective medication, 192 (32%) one more agent and 193 (32%) two or more additional cardio-protective agents. At one year, the median ADDQoL-AWI score was -0.39 (IQR -1, -0.06), suggesting that the majority of individuals

reported a negative impact of diabetes on their HRQoL. Consistent with the baseline to one year results, change in EQ-5D, SF-36 and ADDQoL-AWI measures between one and five years were distributed evenly around no change (Figure 8.2). There was no association between increases in cardio-protective medication and change in the SF-36 MCS (Table 8.2). Increasing cardio-protective medication was associated with an increase in the change in the SF-36 PCS, but the association was only statistically significant for an increase of one agent (2.1; 95%CI 0.3, 4.0). Conversely, while an increase in one, or more than one, agents was associated with an increase in the EQ-5D index score, the relationship was only statistically significant for one or more additional agents (0.05; 95%CI 0.02, 0.08). The ADDQoL-AWI score contradicted the EQ-5D and SF-36 PCS, with more than one additional agent associated with a statistically significant decrease in change in ADDQoL-AWI score (-0.20; 95%CI -0.38, -0.02) (Table 8.2).

8.3.4 Change in general health status

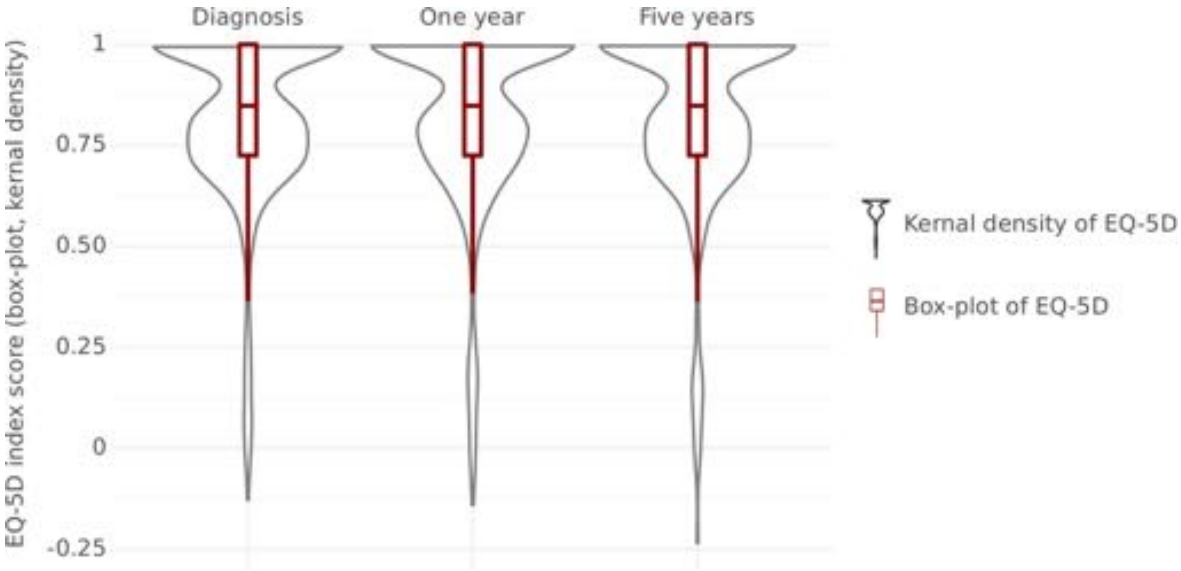
The EQ-5D was available at all three time points. The median and IQR EQ-5D index score remained constant at all three time points (Figure 8.3a). At diagnosis 42% of the sample reported no problems in all five domains of health. This proportion was stable at one (46%) and five (44%) years (Figure 8.3b).

8.3.5 Secondary analyses

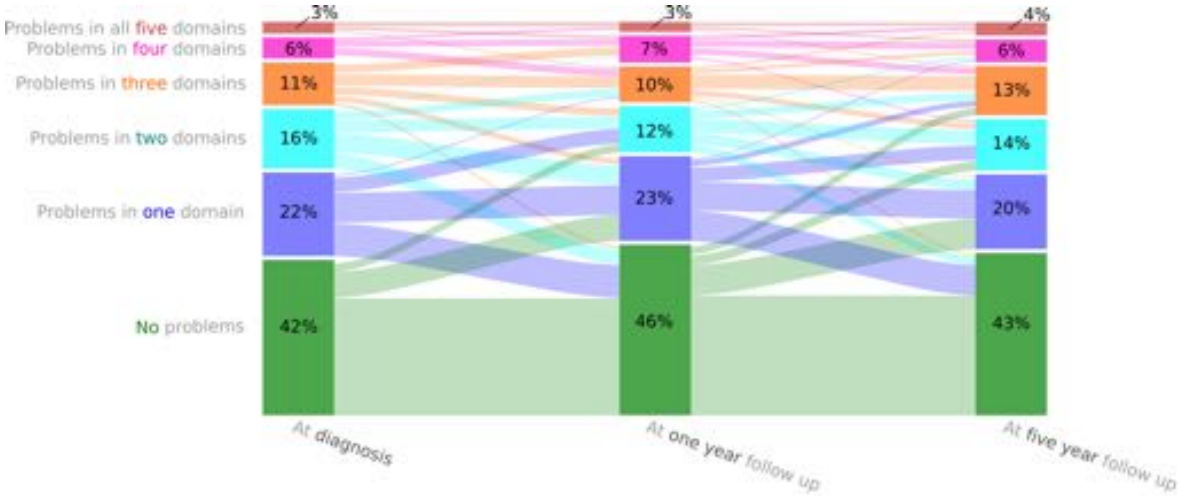
I found no associations between change in medication in the first year after diagnosis, and subsequent change in EQ-5D, SF-36 PCS and SF-36 MCS, or ADDQoL-AWI from one to five years in models that were adjusted for potential confounders and HRQoL at one year (Table 8.2).

8.3.6 Sensitivity analyses

When modelling cardio-protective medication as a continuous variable, similar statistically non-significant associations were identified, replicating findings from the main analysis. Similarly, coefficients from models based on imputed data replicated findings from the complete case analysis. There was no evidence of an association between change in the ADDQoL-AWI and cardio-protective medication in a multinomial analysis of no change against an increase, decrease or mixed change across ADDQoL domain scores. Changes in physical activity and energy intake in the year after diagnosis did not influence the associations between change in HRQoL and change in cardio-protective medication. Models analogous to the primary analysis run in the routine care arm of ADDITION-*Cambridge* suggested that treatment arms could be merged. Likewise, no interactions between the randomisation group and change in agents were detected.



(a) Distribution of EQ-5D index scores.



(b) Alluvial plot showing shifts in the number of domains from the EQ-5D participants in reported at diagnosis, one and five years.

Figure 8.3: Distribution of the EQ-5D index score (Figure 8.3a) and and an alluvial plot (Figure 8.3b) showing the variation in number of domains reported as being impaired in the EQ-5D among participants in ADDITION-*Cambridge* at diagnosis, one and five years.

8.4 Discussion

Increases in the number of cardio-protective medications from diabetes diagnosis to one and five-year follow-up were not consistently associated with change in HRQoL, and whether the magnitude of observed changes is clinically significant remains uncertain across all associations.

For the EQ-5D, the smallest change associated with a clinically meaningful change in health status amongst individuals with diabetes is between 0.058 and 0.158[262], while in the general population a change in the EQ-5D of <0.07 can indicate a potential clinically relevant change.[263] This suggests the increase in change in EQ-5D associated with more than one additional agent (0.05; 95%CI 0.02, 0.08), while statistically significant, is unlikely to be clinically meaningful. More complex is an apparent decrease in change in diabetes-specific ADDQoL-AWI (lowered diabetes-specific quality of life) associated with more than one additional agent (-0.20; 95%CI -0.38, -0.02). In an Australian population of 14,439 people with diabetes the mean difference in ADDQoL-AWI between those with and without complications was 0.69.[264] The narrow confidence intervals around the estimated associations suggest no clinically meaningful association between treatment intensification after diagnosis and HRQoL for the EQ-5D, but it remains unclear whether a decrease of up to 0.38 in the ADDQoL, which ranges from -9 to positive 3, is clinically relevant.

8.4.1 Context within the literature

As ADDITION-*Cambridge* is a novel cohort of individuals with screen-detected diabetes, few direct comparisons with published literature are possible. Shortly after diagnosis, 43% of individuals with screen-detected diabetes from the Hoorn Study were prescribed anti-hypertensive medication, 17% lipid lowering medication and 24% oral diabetes medication.[69] Among middle aged populations with established diabetes, the average number of prescribed cardio-protective medications is between four and five.[265,266] Despite a significant treatment burden, many individuals with established diabetes remained untreated for CVD risk factors such as blood pressure and cholesterol.[265] In ADDITION-*Cambridge*, individuals reported a median of two (IQR 3, 4) cardio-protective medication at diagnosis and four (IQR 3, 5) by five year follow-up. This is likely due to the population being diagnosed earlier in the disease trajectory. However, as I presented in Section 3.4.1 (page 50) and Section 4.4.3 (page 69), there was still evidence of under-treatment in this cohort.

While populations with diabetes tend to have a lower HRQoL than the general population[267,268], individuals with screen-detected diabetes have better HRQoL than those with clinically diagnosed diabetes at diagnosis.[69] There is limited literature with which to compare my findings on change in HRQoL among individuals with screen-detected diabetes as most published research has been conducted in populations with long-standing diabetes. Seppälä *et al*, in a Finnish population, found that SF-36 assessed HRQoL was lower in the 91 individuals with undiagnosed diabetes than in those with normal glucose tolerance.[267] Grandy *et al*[269] demonstrated a small decrease in mean EQ-5D index score (-0.031, SD 0.158) over a five year

time period in people with an average diabetes duration of nine years (SD 7.8).[269]

In terms of the association between medication and HRQoL, Wexler *et al* reported an inverse association between HRQoL and longer diabetes duration, prescription of more than 7 medications, older age and being female.[245] There are few data from trials concerning the relationship between intensifying treatment and HRQoL.[270] The UKPDS trial, which enrolled recently diagnosed individuals more than a decade before ADDITION-*Europe*, found no difference between individuals with a conventional or intensified treatment protocol.[271] The ACCORD trial, which included individuals with established diabetes and early CVD, concluded that there was no HRQoL benefit from very intensive (HbA_{1C} <42 mmol mol^{-1}; 6%) over moderate glycaemic control (HbA_{1C} 53-63 mmol mol^{-1}; 7.0-7.9%).[124] In a trial analysis of the ADDITION-*Europe* cohort, in which relatively small differences in treatment intensity were achieved, there were no differences between EQ-5D, SF-36 or ADDQoL-AWI scores for individuals in the routine care and intensive treatment groups.[253]

8.4.2 Strengths and limitations

ADDITION-*Cambridge* is a large cohort of individuals with screen-detected diabetes and long-term follow-up. Standardised measurements and high response rates at diagnosis, one year and five years allowed the examination of changes in treatment burden and HRQoL measures. In addition to disease specific and general HRQoL measures after diagnosis, a unique strength of this study is the collection of general HRQoL before a screen diagnosis of diabetes. Participants were encouraged to bring repeat prescription scripts, and self-report medication data were collected using an adaption of a validated questionnaire[171] in order to compute the total number of cardio-protective agents to describe treatment burden. This method applies equal weight to each cardio-protective medication. I did not examine the potential differing effect of individual drugs on HRQoL. Nor did I conduct pill counts or account for differing doses of prescribed treatments. In the sensitivity analysis, cardio-protective medication was explored as a continuous variable and results did not differ; this suggests that collapsing medication change into an ordered categorical variable did not obscure a small change. The use of fewer questions from the original ADDQoL questionnaire might have affected the instruments sensitivity. However, the Cronbachs α indicated high reliability in the shortened ADDQoL-AWI version at both time points (0.90 and 0.94). This analysis was conducted in the first five years after detection by screening. This population was younger and closer to ideal health than cohorts with established diabetes. The association between treatment intensity and HRQoL could change as duration of diabetes and age increases.

Only a general HRQoL measure (the EQ-5D) was administered before individuals were diagnosed with diabetes. At baseline, the population had a mean EQ-5D index score of 0.81 (SD 0.21; median 0.85; IQR 0.73, 1). The average value for a general British population aged 55-64 years is 0.80 (SD 0.26).[254] This suggests that individuals with screen-detected diabetes have a comparable HRQoL to the general public, which potentially limits the ability of the EQ-5D to detect small changes in HRQoL when many individuals may remain at ideal health (score of 1). However, the EQ-5D has demonstrated an ability to distinguish between

populations with and without different complications of diabetes[272], although this study like most validation studies is assessing the EQ-5D as a population measure of HRQoL, rather than its ability classify individuals in a clinical setting. The difference in these population estimates for the EQ-5D, and SF-36 PCS, compared to the ADDQoL-AWI and MCS, provide weak evidence that the association between cardio-protective medication and psychological HRQoL differ from changes in functional HRQoL. This finding is surprising as qualitative interviews suggest that the initial process of being screened and labelled with the condition of early detected diabetes is more often seen as a positive 'wake up call' than a negative experience.[22]

I compared concurrent changes in cardio-protective medication and HRQoL between two time points, which were one and four years apart. This may hide short term changes in the prescription of medications and HRQoL within these time points. Understanding such changes would inform the temporality of the association, but would require a much finer resolution of prescription patterns and HRQoL over the five year period.

I found little evidence that increases in cardio-protective medication had an adverse impact HRQoL in people with screen-detected diabetes. There was no association between change in cardio-protective medication and the EQ-5D from diagnosis to one year. While statistically significant positive associations were present between change in medication and both the EQ-5D and PCS, and a negative association was present with change in the ADDQoL-AWI, no association was consistently present for both change in one agent, and change in more than one agent.

There are potential long term effects of treatment that may not manifest in suitable numbers by five years for detection, or are limited to only a small sample of the population. For instance, thiazolidinediones have been linked to an increased risk of heart failure in a meta-analysis of 29 RCTs[273], while there some disputed evidence of the medication class also being associated with increased fracture risk.[274]

8.4.3 Implications for practice

In this observational analysis, I found no consistent association between an increase in medication and reduced HRQoL, yet targeted management of CVD risk factors in diabetes improves cardiovascular health.[102] These results suggest that clinicians should not be concerned that increasing the number of cardio-protective medications will impact negatively on quality of life among individuals with screen-detected diabetes. While this association provides additional evidence that increasing the number of prescribed cardio-protective medications does not impact negatively on quality of life among individuals with screen-detected diabetes, the lack of clarity over when a small change is clinically relevant highlights the failings of existing measures and the importance of more research in how to assess burden and HRQoL in this population. As such this study in concurrence with the literature suggests that intensification of treatment early in the diabetes trajectory does not negatively impact HRQoL. Although, that statement must continue to be viewed in the context of literature on rare and serious hypoglycaemic related events and the lack of resolution available in our quantitive measures

of HRQoL to measure the construct itself.

8.4.4 In the context of optimising CVD risk management

I have shown that individuals diagnosed with diabetes are on multiple medications (Chapter 3), and as a population are successful at attaining and maintaining CVD targets (Chapters 4 and 5). In this chapter I have given evidence that this medication burden is not at the expense of HRQoL.

Chapter 9

Discussion

The benefits of tight glycaemic control and CVD risk factor lowering have been established in long standing and clinically diagnosed diabetes. Diagnosis with diabetes represents crossing a threshold of glycaemic control, yet there is increasing evidence that rather than a threshold effect, micro- and macrovascular damage has a more linear relationship with glycaemic control. This has led to the assumption that earlier treatment would be beneficial, and the initiation of early detection schemes like the NHS Health Checks in England. The balance between the positive and negative aspects of treatment was unknown in this population.

9.1 Discussion of analyses

In this thesis I have described the treatment profile of a population following diagnosis of diabetes by screening, how CVD risk factors and modelled CVD risk changes, whether intensification of treatment in this screen-detected population lowers the risk of incident CVD, and if that intensification leads to a HRQoL burden.

First I will briefly summarise the purpose and conclusions from each of my analyses (Section 9.1). I will then conclude (Section 9.2), discuss limitations that spanned the analyses (Section 9.3), discuss areas for future research (Section 9.4) and implications of the findings and recommendations potentially arising from the work (Section 9.5).

9.1.1 Medication burden after screening based diagnosis

In Chapter 3 (page 35) I presented the medication profile of a population at diagnosis of diabetes by screening, and described how their medication burden changed in the five years after diagnosis. At diagnosis, 45% of individuals were prescribed either lipid or blood pressure lowering medication, or both (although in three centres this was influenced by the use of diabetes risk scores in the screening program). Medications not related to diabetes and CVD were also common, with 42% reporting taking another medication class at diagnosis.

The majority of changes to medication happened in the months after diagnosis, although for glucose lowering medication in particular there was a gradual increase in prescriptions after the initial uptake at diagnosis. Metformin tended to be the first-line therapy for glycaemic control, while there was variation in the use of medications for lowering BP. Prescription re-

demption was available at a daily resolution in ADDITION-*Denmark* and, in the arm where intensive treatment was promoted, it became apparent that intensification of pharmacotherapy primarily occurs in the six months after diagnosis. However, for glucose medication in particular there was a continued increase in the prevalence of medication use over time, suggesting treatment intensification continues at gradual rate for glucose lowering medication in the five years after early diagnosis.

Many individuals with screen diagnosed diabetes have been told they have diabetes years before symptoms and complications that would lead to concern and clinician led diagnosis are likely to be manifest.[129,131] While it appears logical to assume that a population with screen-detected diabetes is 'healthier', this is a statement that remains relevant only in comparison to a clinically diagnosed population.[69] At screen diagnosis a population with diabetes is often already on cardio-protective medication, as well as medication for other conditions, such as; gastro-intestinal medications, anti-inflammatories, analgesics and psychiatric/neurological medications.

9.1.2 Trajectories of glycaemic control after diagnosis

> *"No disease suffered by a live man can be known, for every living person has his own peculiarities and always has his own peculiar, personal, novel, complicated disease, unknown to medicine."*
>
> —Leo Tolstoy, *War and Peace*, *1869*

If treatment intensifies, we would also be expecting to see changes in cardiometabolic health. Traditionally we explore associations by taking a single latent process and describing what measured coefficients are associated with deviations from that process. This method is robust, but complicated relationships make it difficult to understand how these coefficients interact within an individual, and there may be unmeasured factors further expanding the heterogeneity present. In Chapter 4 (page 55) I took the reverse approach, and instead first looked for clusters in how HbA_{1C} changes over time.

I hypothesised that there would be distinct clusters of individuals based on their glycaemic control as; there is diversity in the degree of blood glucose control at diagnosis[198], GP level treatment variation[275], and a concern in the literature and clinical settings about over-treatment[276] which may influence patient and GP decisions, and individuals vary in their uptake[164,188,277] and response[164,197] to diabetes medication.

I identified that, in the intensive arm of ADDITION-*Denmark*, there were four distinct trajectories of glycaemic control. The majority of individuals (87.5%) had slightly elevated HbA_{1C} at diagnosis and were able to maintain good glycaemic control over the following five years (the low-low trajectory, ⎯). There were two other distinct clusters of trajectories that had poorer glycaemic control, but also started with much higher levels of blood glucose at diagnosis (med-low ⎽╲, 8.2% and high-med ╲⎽, 2.1%). These first three trajectories, which all showed a decrease in blood glucose and a maintenance of glycaemic control, represent over 97% of the sample. A fourth divergent trajectory of individuals with poor glycaemic control

was identified (med-high , 2.3%). As very few people followed this trajectory, there were not sufficient numbers to look closely at what characterises this group at diagnosis.

A hypothesis could be made that these divergent trajectories may reflect the role of pharmacogenetics[197], yet a larger sample would be needed to explore any associations in the rare med-high () group in a robust manner. Overall though, the majority of individuals in a group randomised to promotion of intensive treatment similar to current guidelines were able to attain and then maintain stable glycaemic control in the first five years after a diagnosis with diabetes after screening. This finding contradicts that seen in the UKPDS, where HbA_{1C} was seen to deteriorate over time.[179]

9.1.3 Change in risk factors after diagnosis

In Chapter 4 (page 55) I showed that more than 97% of the intensive treatment arm of ADDITION-*Denmark* were able to improve their glycaemic control over the five years after diagnosis. Glycaemic control alone does not drive excess CVD risk, and management of cardiometabolic health has been shown to be very effective in type 2 diabetes.[113] In Chapter 5 (page 73) I documented how BMI, the albumin:creatinine ratio, HbA_{1C}, systolic BP, total:HDL cholesterol and triglycerides changed after diagnosis. I explored this change by first stratifying the population by 10-year UKPDS modelled CVD risk, as achievable change in CVD risk factors is strongly related to where values are at diagnosis. In this analysis I demonstrated that changes in glycaemic control, blood pressure and lipids are strongly correlated with the individuals cardiometabolic health at diagnosis. This results in CVD risk factor control for the quarter of the population with the best cardiometabolic health at diagnosis being about maintenance over the next five years, while those in the quarter with the highest risk of a CVD event at diagnosis are able to lower their CVD risk factors over the next five years.

9.1.4 Modelled long term effects of intensive treatment

"Those who have knowledge, don't predict.
Those who predict, don't have knowledge."
—Lao Tzu, *Attributed without source, c.550 BCE*

ADDITION-*Europe* found a non-statistically significant benefit of intensive treatment at five years after screen diagnosis on micro- and macrovascular disease.[145,215] In Chapter 6 (page 91) I extended this finding by modelling the 10-year CVD risk in the two trial arms at five years. I found that there was a significantly lower 10-year modelled CVD risk in the intensive treatment arm at five years (-2%; 95%CI -3.1,-0.9). This suggests that targeting CVD risk factors early is beneficial, and that long term follow up is likely to lead to statistically significant differences in the incidence of CVD like that seen in the UKPDS, even though the achieved difference in CVD risk factors in ADDITION-*Europe* was small.[145]

While statistically significant, the difference in modelled risk I identified was small, and the clinical and economic impact of treatment is uncertain. This is particularly of concern

as the UKPDS risk score is known to overestimate the risk of events (as I discussed in Section 2.2 on page 33), meaning there will be less events and thus the absolute difference between treatment arms at 15 years may in fact be smaller. Regardless, longer term follow-up of ADDITION-*Europe* is likely to be required before an accurate picture on the cost-effectiveness of the trial can be determined. In the UKPDS, there appeared to be a legacy effect where the CVD event rate remained attenuated long after the intervention ended, despite the convergence of glycaemic control, supporting the hypothesis that longer follow up will be needed in ADDITION-*Europe*.[102]

9.1.5 Change in medication and CVD

"It is medicine, not scenery, for which a sick man must go searching."
—Seneca, *Epistulae ad Lucilium*, *c.65 AD*

In Chapter 6 I showed that a multifactorial promotion of intensive treatment in a population with diabetes diagnosed by screening led to reduction in modelled risk of CVD events from 5-15 years. ADDITION-*Europe* was a multifactorial intervention, which was associated with small but statistically significant differences in treatment between the trial arms. To explore the association between change in medication and incident CVD events, I looked at change in medication from diagnosis to one year, and the incidence of events from one to five years (Chapter 7 on page 111).

I found that an increase in cardioprotective medication between diagnosis and one year was associated with a lower risk of a CVD event (HR 0.64; 95%CI 0.50,0.81). The possibility exists that a third factor like general health status or quality of life influences both prescription of medication and CVD risk. No suitable measures of frailty beyond age were collected in ADDITION-*Europe*. Available measures of lifestyle change were imprecise, and their use would have greatly increased the number of missing observations in the analysis sample. The association between lifestyle change and both change in medication and CVD events is also not robust. With these caveats in mind, my results suggest that amongst individuals that intensify medication after diagnosis there is a reduced risk of an event, and this result supports the modelled trial analysis (Chapter 6) in suggesting intensive treatment from diagnosis reduces the risk of CVD events.

9.1.6 Change in medication and HRQoL after diagnosis

Having identified that the promotion of intensive treatment from diagnosis improves cardiometabolic health (Chapter 6), and that increases in medication are associated with a protective effect for CVD (Chapter 7), the key question is whether this additional treatment burden adversely impacts quality of life.

"I am dying from the treatment of too many physicians."
—Alexander the Great, *Attributed without source*, *c.535 BCE*

In the trial analysis of ADDITION-*Europe*, no difference was found between intensive treatment and routine care for the SF-36, EQ-5D or the 12-item short form of the Well-Being Questionnaire (W-BQ12). This mirrors the findings of the UKPDS, although participants in the UKPDS were diagnosed decades earlier and did not receive multifactorial treatment (HRQoL in the UKPDS was explored by randomisation to glucose and blood pressure lowering separately[271]).

The difference in pharmacotherapy between arms in ADDITION-*Europe* was small, so in Chapter 8 (page 129) I analysed ADDITION-*Cambridge* as a cohort study to see whether change in medication from diagnosis to one year was associated with changes in HRQoL. There were small and inconsistent associations present, and while there are some suggested values for defining clinically meaningful thresholds of HRQoL measures[262,263], the statistically significant changes were most likely not clinically meaningful when dealing with clinical populations.

I detected no consistent positive or negative association between medication change and HRQoL, yet there is a demonstrated benefit from the promotion of intensive treatment, as well as an association between actual medication change and improvements in cardiometabolic health. This analysis, in the context of the existing literature, gives further evidence that GPs should not be concerned that treating patients more intensively from the day of diagnosis necessitates a direct trade off between reductions in the risk of CVD and HRQoL.

9.2 Conclusions

The overarching question addressed by this thesis is: *within a population with type 2 diabetes that has been detected early by screening, does achievement and maintenance of tight control of blood glucose and other CVD risk factors from diagnosis prove beneficial over the more reactive approach seen in routine care?* Intensive glucose lowering in newly diagnosed individuals led to a lowered risk of myocardial infarctions in the UKPDS, and the relationship between fasting glucose and CVD death appears to extend below the diagnostic threshold for diabetes.[32] My findings support the assumption that early treatment of cardiovascular risk results in a lowered risk of CVD events, and this is not achieved at the expense of lowered HRQoL.

9.2.1 Early intensive treatment

In populations with diabetes, there is a well established excess risk of CVD.[71,126,227] When an individual is diagnosed with type 2 diabetes, they have reached a threshold of glucose control that has been tested for, which may or may not of been due to the manifestation of symptoms related to hyperglycaemia. Yet we have increasing evidence that the effect of poor glycaemic control on micro- and macrovascular disease does not have a threshold, and there is increasing interest in the potential to intervene even earlier in the continuum of glycaemic function, or even before insulin resistance and β cell dysfunction result in noticeable changes in blood glucose.[278] My results suggest that the protective effect of multifactorial interventions established by Steno-2[113] appears to continue through to earlier in the disease

trajectory, although this finding is extrapolated from improvements in CVD risk factors, rather than events. To date the strongest evidence of the potential benefits of extending treatment to pre-diabetes comes from an ERFC meta-analysis of 102 studies[279], which found an excess risk of CVD in individuals within the range of FPG considered a sign of 'pre-diabetes' (FPG>5.6 mmol l^{-1} and <6.9 mmol l^{-1} under ADA guidelines[14]). Pre-diabetes is distinct from diabetes though, and while screening does not appear to provide a reduced risk of mortality in the first 10-years[134], a recent (2015) report on screening for diabetes by the USPSTF acknowledged that intervention before the diabetes threshold has the added effect of preventing some of the population's glucose control deteriorating which in turn averts the progression of those individuals to diabetes.[137] However, a skeptic would potentially question how many individuals with pre-diabetes would in fact transition to diabetes if they did remain diagnosed.

9.2.2 Individual variation

Guidelines promote individualised care, yet setting treatment goals as a collaboration between GP and patient requires the succinct translation of the relationship between the potential harm and benefit of medications and individual patient characteristics, which can contribute to a large variation in target attainment. I demonstrated that individuals with cardiometabolic risk factors close to guideline recommended values are usually able to maintain low values, while those with poor cardiometabolic health have a larger achievable change, and a larger variation in the subsequent change in their CVD risk factors over the five years after diagnosis. I identified four clusters of HbA_{1C} trajectories in ADDITION-*Denmark*, and 87% of individuals were allocated to a trajectory group that had an HbA_{1C} centred on 46 mmol mol^{-1} (SD 9; 6.8%, SD 1.5) at diagnosis, and remained low for the following five years (—). Two of the remaining trajectories were predominately patterned by their initial HbA_{1C} levels being higher (—and —). The remaining cluster followed a divergent trajectory (—), that was not able to be well characterised due to its rarity. This is a direct contradiction to the UKPDS, where the divergent trajectory was the norm.[179]

The term 'shared decision making' has entered current guidelines[14,117], and embodies the aim of general practice to empower patients to be able to make informed decisions. Conflicting with this aspiration of how care should be delivered - a recent survey commissioned by the British Medical Association found that 54% of GPs felt their current workload was "*unmanageable or unsustainable*"[280] and the average consultation in 2006/07 was 11.7 minutes for GPs and 15.5 minutes for practice nurses and nurse practitioners.[281] While peripatetic clinics incorporating lay educators are able to defer some of the care burden from the practice[151], communicating the complex relationship between the benefits and potential harms of intensifying medication at diagnosis and subsequent visits as the individual ages and the disease progresses is a difficult task. The simplified descriptions of how medication (Chapter 3), glycaemic control (Chapter 8) and CVD risk factors (Chapter 5) change, as well as what the potential impact of intensification is (Chapters 6 to 8) I present, will aid in describing the expected prognosis and relative benefits of different treatment strategies.

9.3 Limitations

Within each chapter I have discussed the limitations relevant to each analysis. In the following section, I will discuss general themes that were constant across this thesis.

Modelling work using ADDITION-*Europe* suggests that the combination of screening and early intervention is beneficial over routine diagnosis and delayed treatment initiation.[229] While this finding supports my conclusions, a more granular breakdown of the benefits of early detection vs. intensive treatment after detection suggests that the majority of this finding is driven by the early diagnosis, and not the intensity to which CVD risk factors are lowered after diagnosis.[229] This thesis supports a small protective effect of intensive treatment from early diagnosis, but the possibility exists that simply the knowledge that an individual has the diagnosis is sufficient to enable routine care to successfully manage CVD risk. This potential is strong in ADDITION-*Europe*, as the difference between routine care and the intensive treatment protocol decreased while the study recruitment was ongoing.[103,170,216,217]

The effect of 'treatment intensification ' is a reoccurring exposure in this thesis that attempts to capture the total pharmacotherapy burden of cardioprotective medication that spans multiple medication classes. In Chapters 3, 7 and 8 I used the number of classes as the primary measure of 'treatment intensification '. This method does not account for the different adverse effects that are specific to each type of medication. The role of individual medications has been addressed by seminal RCTs[75,77,78,100,101,126], but a diagnosis of diabetes leads to an uptake in multiple medications (Chapter 3). Alternatively, a count of pills rather than agents would reflect what the individual with diabetes experiences, but then there is less connection between the medication and underlying burden of active ingredients as doses can vary and a medication split across two pills or multiple doses a day. Where possible, I also conducted multiple sensitivity analyses, which included looking at associations by medication class. There was often a degree of concordance when uptake in one medication class (e.g. β blockers) was correlated with uptake of another (e.g. statins) which led to increased variance and attenuation in mutually adjusted models making it difficult to detect independent effects. This though is not necessary a limitation, as my analysis remains focused on the total 'treatment intensification' experienced after diabetes diagnosis.

A more technical limitation is that a feedback mechanism exists in pharmacotherapy for CVD risk factors, particularly for glucose lowering medication.[282] This is because pharmacotherapy will be reviewed at each consultation. Within ADDITION-*Europe* medication change was primarily intensification of medication as diabetes progresses, but the possibility exists for medication to be decreased due to external factors like frailty, or improvements in lifestyle allowing medication to be discontinued.[125] I have attempted to address this by taking changes from diagnosis to one year to represent the period in which treatment strategies are tested and refined. The one year time frame, while conveniently reflecting a patients one year review, was dictated by the available data in ADDITION-*Europe*. More detailed information on continuous medication changes, and whether stability of medication regimes or time spent on different regimes influenced outcomes, alongside information on diet, physical activity,

and general frailty would provide a much greater level of detail on the role of medication as part of a multifactorial therapy.

ADDITION-*Europe* participants were predominantly of white ethnic origin.[145] While the Leicester centre was expected to recruit 30% of it's sample from the British South Asian[152], it remains difficult to generalise the results of ADDITION-*Europe* to minorities. Beyond ethnicity, ADDITION-*Europe* participants were drawn from a large population-based sample, and biological data and self-reported characteristics were collected using standardised protocols and questionnaires.

9.4 Areas for future research

In Chapter 4 I found that glycaemic control in the five years after diagnosis in an intensively managed Danish population was beneficial for the majority of the population. This is at odds with the gradual deterioration seen in the first six years of the UKPDS[179], and research highlighting that a lag exists between loss of glycaemic control and intensification of treatment.[176] In my analysis, I could not tease out whether the promotion of tighter CVD risk factor goals was primarily associated with the improved level of glycaemic control, or whether it was largely being driven by the 3-6 monthly consultations being applied to the entire sample. While a Cochrane meta-analysis suggests that self-monitoring of blood glucose is of minimal benefit[283], the possibility exists that clinical inertia in responding to loss of glycaemic control is reduced with frequent contact. This leads on to the even more fundamental question concerning whether the shape of these glycaemic trajectories over time are related to CVD events and HRQoL. Models to link these HbA_{1C} trajectories to CVD event data or trajectories of HRQoL exist[284], but larger sample sizes would be needed as the majority of individuals experience good glycaemic control.

GPs already practice personalised medicine to a greater or lesser degree. Knowledge of the patient's characteristics is an essential input when translating a guideline into a treatment strategy, to the point where some commentators have called for a rebranding of the term to 'precision medicine'.[285] It would be impractical to attempt to incorporate the huge diversity of treatment options into static guidelines, yet the encroachment of technology suggests that in the future dynamically generated treatment decision aids will become common place. This is applicable to Chapters 4 and 5, where I described clusters of glycaemic control and how much of the heterogeneity in CVD risk factor reduction is merely dependent on baseline cardiometabolic health. Statisticians working in prostate cancer are building the next generation of risk scores by incorporating the shape of risk factor trajectories over time[286,287], which could be replicated using glycaemic control trajectories. The possibility exists to enhance discussions about pharmacotherapy through visual aids that adjust to the individuals characteristics, so patients with a large achievable change can see how they are progressing compared to a modelled summary. Conversely, those with good cardiometabolic health can be reassured that intensification of treatment to maintain goals is for some an unfortunate eventuality and not a failure on their behalf. Such advances are of course dependent on

the continued uptake and accrual of information into practice databases and will be greatly strengthened by the future potential of easily (and cheaply) measured biomarkers and genetic determinants of both CVD risk and treatment effect variation.[285] The question over whether such advances that may empower patients and simplify shared discussion making will result in changes that avert CVD events is a separate and less certain question.[288]

Whether intensive treatment is beneficial to screen-detected populations is likely to be a trade off from a small protective effect with an added economic burden. While a recent paper suggests ADDITION-*Europe* was not cost-effective[230], it relied on assumed costs if there was complete uptake of treatment recommendations. This inflated the costs of the intervention, and work is currently underway to use the actual health records to quantify real costs.

Questions also remain over the interaction between the patient and GP that led to treatment decisions. While I did not explore GP level variation in prescribing patterns, in ADDITION-*Denmark* variation in lipid lowering rates at the GP level has been linked to differing risk of all-cause mortality. Further, decisions to not set aggressive CVD risk factor goals, regardless of potential increases in risk of CVD events, may in fact of been informed and valid decisions made as part of a shared decision with the GP. The ongoing *Introdia* (`introdia.com`) is an example of a study attempting to understand the complex relationship interaction that leads to treatment decisions, and will provide more information on how much of the clinical inertia and apparent lack of intensity in prescribing is in fact a deficiency in care.

Stand along screening and management of diabetes does not reflect the shared risk factors diabetes has with CVD and other conditions like kidney disease. Future studies of the effectiveness of combined programs like the NHS Health Checks are likely to create a more accurate picture of the cost of both screening and intensive treatment than standalone tests of each of these related conditions.

9.5 Implications

The benefits of intensive therapy will not only be limited to macrovascular disease, which is what I have focused on. The relative contribution of glycaemic control compared to other CVD risk factors in preventing microvascular disease is stronger[58], which is reflected in the literature supporting intensive glucose control to prevent microvascular disease. As such, the case for intensive treatment is likely to be stronger when the entire burden of complications is addressed.

The implications for this thesis are derived from a pragmatic promotion of intensive care filtered through GPs, and associations derived from individuals that did increase their medication count. This is an important distinction, as the GP helps ensure that treatment decisions are appropriate to the individual (e.g. if they are frail[125]), potentially ensuring a HRQoL burden is averted.

Type 2 diabetes is being diagnosed earlier in the disease trajectory, while most of our information on how to treat it is based on populations much further along the disease trajec-

tory. My research suggests that intensification of treatment in an early diagnosed population is protective for CVD, and does not lead to an excess HRQoL burden.

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Appendix A

Other publications published during the PhD

Other publications 1st authored during this thesis

J. A. Black, M. Park, J. Gregson, *et al.*, "Child obesity cut-offs as derived from parental perceptions: cross-sectional questionnaire", *British Journal of General Practice*, vol. 65, no. 633, e234–e239, 2015, ISSN: 0960-1643. DOI: 10.3399/bjgp15X684385

J. A. Black, B. White, R. M. Viner, and R. K. Simmons, "Bariatric surgery for obese children and adolescents: a systematic review and meta-analysis.", *Obesity reviews : an official journal of the International Association for the Study of Obesity*, vol. 14, no. 8, pp. 634–44, Aug. 2013, ISSN: 1467-789X. DOI: 10.1111/obr.12037

Other publications co-authored during this thesis

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C. L. Falconer, A. Skow, J. A. Black, *et al.*, "The majority of parents of overweight and very overweight children underestimate their child's weight status and weight-related health risk", *Archives of Disease in Childhood*, vol. 97, no. Suppl 1, A181–A181, May 2012, ISSN: 0003-9888. DOI: 10.1136/archdischild-2012-301885.424

C. L. Falconer, M. Park, A. Skow, *et al.*, "Scoping the impact of the national child measurement programme feedback on the child obesity pathway: study protocol.", *BMC public*

health, vol. 12, no. 1, p. 783, Sep. 2012, ISSN: 1471-2458. DOI: 10.1186/1471-2458-12-783

C. J. L. Murray, T. Vos, R. Lozano, *et al.*, "Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.", *Lancet*, vol. 380, no. 9859, pp. 2197–223, Jan. 2013, ISSN: 1474-547X. DOI: 10.1016/S0140-6736(12)61689-4

T. Vos, A. D. Flaxman, M. Naghavi, *et al.*, "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010.", *Lancet*, vol. 380, no. 9859, pp. 2163–96, Jan. 2013, ISSN: 1474-547X. DOI: 10.1016/S0140-6736(12)61729-2

Appendix B

Published papers

B.1 Publication derived from Chapter 3

BMJ Open Diabetes Research & Care

Medication burden in the first five years following diagnosis of type 2 diabetes: findings from the ADDITION-UK trial cohort

Journal:	*BMJ Open Diabetes Research & Care*
Manuscript ID:	bmjdrc-2014-000075.R2
Article Type:	Research
Date Submitted by the Author:	n/a
Complete List of Authors:	Black, James; University of Cambridge, MRC Epidemiology Unit Simmons, Rebecca; University of Cambridge, MRC Epidemiology Unit Boothby, Clare; University of Cambridge, MRC Epidemiology Unit Davies, Melanie; Department of Cardiovascular Sciences, Leicester Royal Infirmary Webb, David; Department of Cardiovascular Sciences, Leicester Royal Infirmary Khunti, Kamlesh; Department of Cardiovascular Sciences, Leicester Royal Infirmary Long, Grianne; University of Cambridge, MRC Epidemiology Unit Griffin, Simon; University of Cambridge, MRC Epidemiology Unit; University of Cambridge, Institute for Public Health
Keywords:	Medication, Screening

Medication burden in the first five years following diagnosis of type 2 diabetes: findings from the *ADDITION-UK* trial cohort

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Bullet points

- Screen-detected diabetes is usually asymptomatic, but individuals often have multi-morbidity
- Just under half of individuals with screen detected diabetes are on drugs not related to CVD at diagnosis
- Many individuals did not start glucose lowering medication in the five years after diagnosis

Abstract (247 words)

Individuals with screen-detected diabetes are likely to receive intensified pharmacotherapy to improve glycaemic control and general cardio-metabolic health. Individuals are often asymptomatic, and little is known about the degree to which polypharmacy is present both before, and after diagnosis. We aimed to describe and characterise the pharmacotherapy burden of individuals with screen-detected diabetes at diagnosis, one and five years post-diagnosis.

The prescription histories of 1026 individuals with screen-detected diabetes enrolled in the *ADDITION-UK* trial of the promotion of intensive treatment were coded into general medication types at diagnosis, one and five years post-diagnosis. The association between change in the count of several medication types and age, baseline 10-year UKPDS CVD risk, sex, intensive treatment group and number of medications was explored.

Just under half of individuals were on drugs unrelated to cardio-protection before diagnosis (42%), and this increased along with a rise in the number of prescribed diabetes-related and cardio-protective drugs. The medication profile over the first five years suggests multi-morbidity and polypharmacy is present in individuals with screen-detected diabetes. Higher modelled CVD risk at baseline was associated with a greater increase in cardio-protective and diabetes-related medication, but not an increase in other medications. As recommended in national guidelines, our results suggest that treatment of diabetes was influenced by the underlying risk of CVD. While many individuals did not start glucose lowering and cardio-protective therapies in the first five years after diagnosis, more information is required to understand whether this represents unmet need, or patient centred care.

Introduction

Medication burden is high among individuals with established type 2 diabetes. Results from a systematic review indicate that diabetes patients take in the range of four to ten medications a day.[1] In an American study of 875 individuals with diabetes, 50% reported taking seven or more prescription medications a day[2]. Estimates from English patients with diabetes suggest an average of six medications a day.[3] Individuals with diabetes are prescribed a number of cardio-protective drugs, but there is also evidence to suggest high levels of prescription of other drug classes e.g. treatment for neuropathy[4], depression[5], and gastric and rheumatologic complaints[6]. In 2012-13 in England, 9.3% of the total cost of prescriptions in the NHS was related to diabetes.[7] As treatment regimens become more complex, patients are more likely to experience adverse side-effects[8] and less likely to remain adherent to all prescribed medications.[9,10]

Less is known about treatment burden among individuals with screen-detected or recently diagnosed diabetes. Given that population screening for diabetes has been recommended by several national organisations and the NHS currently includes assessment of risk of diabetes in its Health Checks programme[11], more individuals will be found earlier in the disease trajectory. Further, there is growing evidence for the benefit of intensive treatment of risk factors early in the course of the disease[12,13], which suggests that screen-detected patients may be prescribed a larger number of cardio-protective drugs earlier than they might previously have been. Although there is some evidence that improved medication adherence may improve health-related quality of life in symptomatic diabetic patients[14,15], individuals earlier in the disease trajectory are unlikely to have symptoms and may be less likely to adhere to complex medication regimes.[16,17] There is currently little knowledge of medication burden in people with screen-detected diabetes, many of whom will have few or no symptoms. Guidelines promote a multifactorial approach to diabetes care from diagnosis that includes pharmacotherapy for multiple CVD related conditions.[18,19] Despite the increasing number of individuals with screen-detected diabetes, many of whom have comorbidities, there is an absence of knowledge about what the pharmacotherapy burden is at diagnosis in this population, and how it changes in the first five years. It is important that this is described so that patients and practitioners are informed about the likely course and burden of treatment. We aimed to (i) describe medication burden at diagnosis, one and five-years in individuals with screen-detected diabetes and (ii) examine if age, sex, intensive treatment, or modelled 10-year CVD risk was associated with the number of drugs individuals were prescribed at five years after diagnosis.

Methods

The *ADDITION* study is a primary care based screening and intervention study for type 2 diabetes (ClinicalTrials.gov, CNT00237549). It was carried out in Denmark, the Netherlands and two UK centres (Leicester and Cambridge). The study has been described in detail elsewhere.[13,20,21] In this paper we describe data from the two UK centres. Briefly, individuals aged 40-69 years in Leicester were invited to attend an Oral Glucose Tolerance Test (OGTT). Individuals in Cambridge aged 40-69 years with a high risk of diabetes

in Cambridge (Cambridge Risk Score[22] ≥ 0.17) were invited to a stepwise screening programme including a random capillary glucose test and $HbA_{1C,}$ followed by a fasting capillary glucose test and a confirmatory OGTT. Individuals were diagnosed using the WHO 1999 definition of diabetes.[23] Exclusion criteria included pregnancy, lactation, an illness with a likely prognosis of less than one year or a psychiatric illness likely to limit study involvement or invalidate informed consent. Individuals found to have diabetes were treated according to the group to which their practice was allocated: routine care using national guidelines[19] or the promotion of intensive multifactorial treatment. In the intensive treatment group, GPs were encouraged through guidelines, educational meetings, and audits with feedback to introduce a stepwise target-led drug treatment regime to reduce hyperglycaemia, hypertension and hyperlipidaemia[20,21] similar to the STENO-2 study.[24] Trained staff assessed patients' health at baseline, one year and five years and collected biochemical and anthropometric data according to standard operating procedures. Self-report questionnaires were used to collect information on socio-demographic information, lifestyle habits and medication use. The study was approved by the relevant ethics committees[13,20,21] and all participants provided written informed consent.

Assessment of medication

In Cambridge, participants were encouraged to bring their repeat prescription summaries to each health assessment and self-reported medication was collected via a health economics questionnaire which asks for information on all prescribed medication.[25] In Leicester, prescription information could also be sourced directly from the records of a peripatetic clinic. Medication data were coded using the Anatomical Therapeutic Chemical Classification System (ATC).[26] ATC codes were used to derive counts for each participant within the following 23 classes of medication: insulin, metformin, sulphonylurea, thiazolidinediones, other glucose lowering medication, ace-inhibitors, beta-blockers, calcium channel blockers, diuretics, other blood pressure lowering medications, lipid lowering, antithrombotic, gastrointestinal related, skin related, hormone replacement therapy or urogenital, systemic steroids, thyroid related, anti-inflammatory, analgesic, anti-epileptic, psychiatric, respiratory and eye related. Medication counts in this analysis refer to the number of the 23 classes prescribed (not overall pill count), while medication agent refers to one of the 23 explored classes of medication. For several analyses, these 23 categories were also collapsed into diabetes-related (insulin, metformin, sulphonylurea, thiazolidinediones, other glucose lowering medication), cardio-protective (ace-inhibitors, beta-blockers, calcium channel blockers, diuretics, other hypertension-related medications, lipid lowering, antithrombotic) and other (remaining 11 classes). Medication types that were not within these categories, for example acute medications like antibiotics, were not included in these analyses.

Statistical analysis

Baseline and five year descriptive characteristics of the cohort were summarised using means, medians and proportions. We described the medication profile of the *ADDITION-UK* cohort at diagnosis, one and five years following diagnosis. Using complete case linear regression, we explored the mutually adjusted associations between age, baseline 10-year UKPDS CVD risk[27], sex, treatment group and baseline number of medications on (i) change in total number of medications, (ii) change in cardio-protective medications and (iii) change in

other medications between diagnosis and five years. Due to the distribution of change in diabetes-related medication being left-censored at zero an analogous Poisson regression model was used to explore the association between baseline predictors and change in diabetes-related medication over five years. Standard errors were used to adjust for clustering by GP practice in the models. As current guidelines for the treatment of type 2 diabetes are very similar to the protocol used in the intensive treatment arm of *ADDITION-UK,* and the achieved difference in treatment was small, treatment arms were pooled for the primary analysis.[13,28] A sensitivity analyse by randomisation arm showed little differences relative to overall changes.

In order to characterise missing data, we used logistic regression models to derive the odds of being included in the complete-case analysis, individually adjusted for age, sex, baseline UKPDS 10-year CVD risk, treatment group and 2004 indices of multiple deprivation (IMD). IMD scores were only available for the 867 individuals (86% of the sample) from the Cambridge area, so the association between missing data and socio-economic status is described using a smaller dataset for this sensitivity analysis.

The small differences in both the outcome and treatment between routine care and intensive treatment in *ADDITION-Europe* has been linked to the continual improvement of routine care, most likely accelerated through the introduction of the Diabetes National Service Framework in 2001[29], clinical guidelines for targeting blood pressure and lipids in people with diabetes in 2002[19], and the Quality and Outcomes Framework in 2004.[13,29] Current guidelines for the treatment of type 2 diabetes are similar to the protocol used in the intensive treatment arm of *ADDITION-UK*.[13,28] As such, while a statistically significant difference in cardio-protective and glucose lowering drugs is present, absolute differences in the prevalence of medications being reported are small, which is why treatment arms were pooled in this analysis.
Statistical analyses were performed using R 3.0.2 (checkpoint 2014-09-18).

Results

At diagnosis, the *ADDITION-UK* cohort had a mean age of 61 years (SD 7), a median UKPDS 10-year CVD risk of 19% (IQR 13, 27) and 61% were male (Table 1). Of the 1,026 individuals in the *ADDITION-UK* cohort, 1,024 (99.8%) had medication data at diagnosis, 1,008 (99% of living) at one year, and 930 (96% of living) at five years. Ten people died before one year follow up, and 59 before five year follow up.

Total medication burden

At diagnosis, most individuals reported taking two medications (median 2; IQR 0, 4). This was most commonly a cardio-protective medication (median 1; IQR 0, 3), although some individuals were on more than one non-cardio-protective medication at diagnosis (Figure 1). One year after diagnosis a median of 3 medications (IQR 0,6) were recorded. At five years, individuals were typically prescribed six medications (median 6; IQR 5, 8), which included one diabetes-related medication (median 1; IQR 0, 1), four cardio-protective medications (median 4; IQR 3, 5) and one other medication (median 1; IQR 0, 2).

Diabetes-related and cardio-protective medication

After diagnosis, both the variety and number of cardio-protective and diabetes medications increased (Figure 2). At one year, 23% of individuals were prescribed any type of diabetes medication, which increased to 62% at five years. Between diagnosis, one and five years, the prescription of anti-hypertensive (55% to 51% to 77%), lipid lowering (24% to 48% to 81%) and anti-thrombotic (20% to 36% to 54%) medication increased. In this screen-detected population, many individuals reported using no glucose lowering medication at one and five years (78% and 38%, respectively, Figure 1 and 2).

Other medications

At diagnosis, 42% of individuals were prescribed other types of medication, which increased to 62% at five years after diabetes diagnosis (Figure 2). The most common was for gastro-intestinal conditions (13% at diagnosis, and 25% at five years). Many individuals also reported anti-inflammatory (12% at diagnosis, and 12% at five years), analgesic (12% at diagnosis, and 19% at five years) and psychotherapy (11% at diagnosis, and 15% at five years) related prescriptions.

Association between baseline characteristics and number of prescribed drugs at five years

The baseline characteristics associated with an increase in the total number of prescribed drugs between diagnosis and five years were a younger age (β -0.03, 95%CI -0.05, -0.01), a higher baseline modelled 10-year UKPDS CVD risk score (β 0.04, 95%CI 0.04, 95%CI 0.02, 0.05), randomisation to the intensive treatment arm of the trial (β 0.44, 95%CI 0.01, 0.78), and being prescribed less medications at diagnosis (β -0.49, 95%CI -0.56, -0.42). Sex was not associated with change in total number of medications. Similarly, the baseline characteristics associated with an increase in cardio-protective medication were a higher 10-year CVD risk (β 0.02, 95%CI 0.01, 0.02), randomisation to the intensive treatment arm (β 0.39, 95%CI 0.09, 0.69) and being prescribed less medication at baseline (β -0.50, 95%CI -0.56, -0.44). An increase in diabetes-related medication was associated with female sex (IRR 0.86, 95%CI 0.75, 0.99), younger age (years; IRR 0.96, 95%CI 0.95, 0.97), having a higher baseline 10-year CVD risk (IRR 1.02, 95%CI 1.01, 1.02) and randomisation to the intensive treatment arm (IRR 1.15, 95%CI 0.01, 1.30).

Compared to individuals with medication data at five years, those without medication data were more likely to be female (OR 0.56; 95%CI 0.35, 0.89), older (one year; OR 0.97; 0.94, 0.999), to have had a previous CVD event (OR 0.49; 95%CI 0.29, 0.90) and to be in the intensive arm of the trial (OR 2.04; 95%CI 1.32, 3.20). There was no association between loss to follow up and ethnicity (White vs. other; OR 0.77; 95%CI 0.31, 1.60) or socio-economic deprivation (1 point IMD 2004 change; OR 0.99; 95%CI 0.97, 1.02).

Discussion

In a population of individuals with screen-detected type 2 diabetes, we described the prevalence of diabetes-related, cardio-protective and other medications at diagnosis, one and five years post-diagnosis. Many individuals were on medications not related to cardio-protection before diagnosis (42%), and this increased along with a rise in the number of diabetes-related and cardio-protective drugs. At five years, individuals were typically prescribed six medications, including one diabetes-related medication, four cardio-protective medications, and one other medication. This suggests that there is a significant degree of multi-morbidity and polypharmacy present in individuals with screen-detected diabetes. Following diagnosis, individuals were more likely to be prescribed diabetes-related medication if they were younger, female, had a high modelled CVD and if they were randomised to the intensive treatment arm of the trial. Younger individuals being prescribed more total and diabetes medication in the five years after diagnosis is in line with previous literature that identified those with early diabetes as having worse glycaemic control elevated and CVD risk factors.[30] In older individuals, the balance between treatment benefits and harm may also become less clear, which could also lead to the identified association. Higher modelled CVD risk at baseline was associated with a greater increase in cardio-protective medication, but not an increase in other medications. As recommended in national guidelines, our results suggest that the treatment of diabetes was influenced by the underlying risk of CVD.

This is the first description of total medication burden in a large cohort of individuals with screen-detected diabetes over five years of follow-up. In a subset of the Dutch Hoorn Study, among 195 individuals with screen-detected diabetes, 45% were taking blood-pressure lowering medication, and 20% were taking lipid lowering medication at diagnosis.[31] In *ADDITION-UK* at diagnosis, 55% of individuals were taking blood pressure lowering medication, and 24% lipid lowering medication, in agreement with the results of the Hoorn screening sub-sample. In a separate publication from the Hoorn study, two weeks after diagnosis 24% of the screen-detected and 78% of the clinically detected individuals were prescribed oral glucose lowering medication.[32] The step-wise screening programme carried out in *ADDITION-Cambridge* used the Cambridge Risk Score to identify those at the highest risk of undiagnosed diabetes.[22] This score includes blood pressure medication as a variable, which may have led to an overestimate in the number of individuals taking anti-hypertensive medication in this sample. In 2005-2006, in an American population with long-standing diabetes, 90% of the population were taking glucose lowering medications, 78% were taking anti-hypertensives and 26% were on statins.[33] This contrasts with *ADDITION-UK*, where glucose lowering medications were less common (62%, at five years), and statins were more common (54%, at five years). Statin use was the pharmacotherapy that differed by the greatest margin between arms of the *ADDITION-UK* trial (47% for routine care vs. 60% after the promotion of intensive care, at five years). Our results suggest that the promotion of statin use is the most readily accepted treatment after diagnosis compared to the introduction of glucose-lowering treatment. In ADDITION-Europe, we have previously demonstrated that individuals with the worst cardio-metabolic health at diagnosis were the most likely to be prescribed glucose, blood pressure and lipid lowering medication, and also were likely to achieve the greatest reductions in individual CVD risk factors over the five years immediately after diagnosis.[34]

Previous literature has noted that the prescription of cardio-protective medication often lags behind glucose lowering medication, suggesting a disproportionate emphasis on controlling glucose over CVD risk reduction.[33,35] In both arms of *ADDITION-UK, use of* anti-hypertensive and lipid lowering medication was reported by around four-fifths of the participants (77% and 81%, respectively), and glucose lowering and aspirin use was reported for three-fifths of the population (62% and 54%, respectively). Our results suggest that the prescription of cardio-protective medication did not lag behind that of glucose-lowering. Conversely, 20% of individuals were on metformin at one year, and 57% at five years, despite metformin being recommended as a first line glucose lowering medication, and immediate initiation being recommended by NICE if overweight or non-responsive to lifestyle interventions.[19] Variation in treatment could be a positive indicator of patient centred care or a deficit between patient need and prescribed medication. More detailed knowledge on the circumstances around treatment choices in screen-detected populations would help inform whether the prescription of cardio-protective and glucose lowering medication should be higher in this population, or that the proportions prescribed medications in this study represent adequate care in relation to GP and patient needs and priorities. An increase in diabetes medication from diagnosis to five years was associated with being female, younger, having a GP who was in the trial arm promoted to treat intensively, and having a higher baseline risk of a CVD event. In the Hoorn study, two weeks after screen-detected diabetes diagnosis, 24% of the population were taking glucose-lowering medication.[32] While previous literature suggests there is no association between the prescription of diabetes related medication and gender.[36,37]

Strengths and limitations

ADDITION-UK is a large cohort (n=1,026) with consistency in outcome measurement and little loss to follow up in individuals prescription histories (4% at five years). ADDITION-UK (91% white ethnicity) was less diverse than the UKPDS (81% white ethnicity)[38], which may limit generalisability. However, ADDITION-UK remains the only study able to characterise medication changes after screen-detected diabetes diagnosis while receiving contemporary diabetes care. This analysis uses prescribed medications, which is likely to be an over count of the redeemed and consumed prevalence. Some medications may also be available without a prescription. Accuracy of medication data was improved by encouraging participants to bring repeat prescriptions to the health assessment, the use of a health economics questionnaire[25] and cross-referencing GP records to collect medication data. For the secondary analysis of change in medications, our analysis assumes that a change from zero to one medication is directly comparable to a change from four to five, or two to one. Medication was coded into 23 classes, but antiinfectives, antiparasitics and antineoplastic medications (as defined by the ATC) were not included as they were acute (e.g. infections) or rare (e.g. cancer). As this study collected snapshots of medication use at baseline, one and five years after diagnosis, we are not able to give accurate prevalences for acutely prescribed medications. The number of medical agents was chosen over the raw pill count as some medications can be taken as 'combination' pills, or can be split across multiple doses. This could unduly increase the impact of some medications that are taken multiple times a day on the final medication count. There is also likely to be less agreement between the doctor prescribed treatments and daily pill count, compared to reported types of medical agent, as pill count includes both agent and information on frequency

and method of dose. Information on non-CVD related comorbidities that may influence medication was not collected. This analysis remains primarily descriptive, and does not directly assess the relationship between changes in cardio-metabolic health and pharmacotherapy. This analysis is unable to describe the pharmacotherapy of individuals that died during follow up, and it is likely that if medication at the time of death was available, it would introduce greater heterogeneity to this analysis. There was no association between loss to follow up and change in medication, although this analysis was limited to the sub-sample of Cambridge participants (86% of the sample) due to the IMD scores not being available for all centres.

Individuals with screen-detected diabetes are often taking multiple medications before diagnosis, despite being identified early in the diabetes disease trajectory. This includes both cardio-protective medications, and other medications including; gastro-intestinal, anti-inflammatories, analgesics and psychiatric/neurological medications. After diagnosis, GPs and patients appear to adopt pharmacological strategies that target both CVD risk reduction and glycaemia, providing evidence against concerns of over-prioritising glycaemic targets. The increased prescription of cardio-protective medication was associated with higher baseline CVD risk, indicating an association between need and care. While this result is promising, it remains unclear if the prescription rates of glycaemic and cardio-protective medication in this population with elevated cardio-vascular risk reflect individualised treatment based on patient led priorities or a deficit in the application of pharmacological intervention.

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Table 1: Baseline characteristics of the ADDITION-UK cohort, overall and by previous CVD status and CVD risk quartile

	10-year UKPDS CVD risk: Lowest quartile 5,17	10-year UKPDS CVD risk: Highest quartile 36,92	No CVD	Previous CVD**	**Total**
N*	244	244	858	106	**1026**
Mean age in years (SD)	55.6 (7.5)	64.2 (5.3)	60.3 (7.5)	63.1 (5.3)	**60.6 (7.4)**
Male %	40%	83%	60%	74%	**61%**
White %	80%	98%	93%	96%	**91%**
Median 10-year CVD risk (IQR)	14 (11, 15)	47 (40, 56)	24 (17, 33)	45 (35, 56)	**25 (17, 36)**
Mean BMI kg/m^2 (SD)	32.8 (5.8)	33.0 (5.8)	33.3 (5.7)	32.9 (6.1)	**30.8 (5.4)**
Mean HbA_{1c} %	6.6 (1.1)	8.3 (2.2)	7.4 (1.7)	7.1 (1.6)	**7.3 (1.7)**
Mean HbA_{1c} mmol/mol	49 (12)	68 (24)	57 (19)	53 (17)	**57 (18)**
Mean systolic BP mmHg (SD)	133 (16)	153 (23)	143 (19)	139 (22)	**146 (17)**
Mean total Cholesterol mmol/L (SD)	5.2 (1.0)	5.5 (1.3)	5.5 (1.1)	4.6 (1.0)	**5.6 (1.2)**
Self-reported CVD** %	1%	30%	0%	100%	**11%**
Self-reported high blood pressure %	60%	55%	57%	68%	**59%**
Self-reported high cholesterol %	27%	31%	23%	68%	**28%**

*Number of participants recruited at diagnosis **Previous myocardial infarction or stroke

Table 2: Association between baseline characteristics at diagnosis and change in medication count between diagnosis and five years in the ADDITION-UK cohort

	Change in total medication count		Change in diabetes medication		Change in CVD medication		Change in other medication	
	β**	95% CI	IRR**	95% CI	β**	95% CI	β**	95% CI
Number of medications at diagnosis*	-0.49	-0.56, -0.42	-	-	-0.50	-0.56, -0.44	-0.30	-0.37, -0.22
Male gender	-0.25	-0.57, 0.06	0.86	0.75, 0.99	-0.11	-0.33, 0.10	0.12	-0.10, 0.34
Intensive treatment arm	0.44	0.10, 0.78	1.14	1.01, 1.30	0.39	0.09, 0.69	-0.08	-0.30, 0.13
Age at diagnosis (years)	-0.03	-0.05, -0.01	0.96	0.95, 0.97	-0.02	-0.03, 0.002	0.02	0.01, 0.04
Modelling 10-year UKPDS CVD risk (%)	0.04	0.02, 0.05	1.02	1.01, 1.03	0.02	0.01, 0.03	0.00	-0.01, 0.01

*Number of medications of the medication type that is the dependent variable in that columns regression

** IRR = Incidence Rate Ratio from a Poisson regression model, β = Regression coefficient from a linear regression model

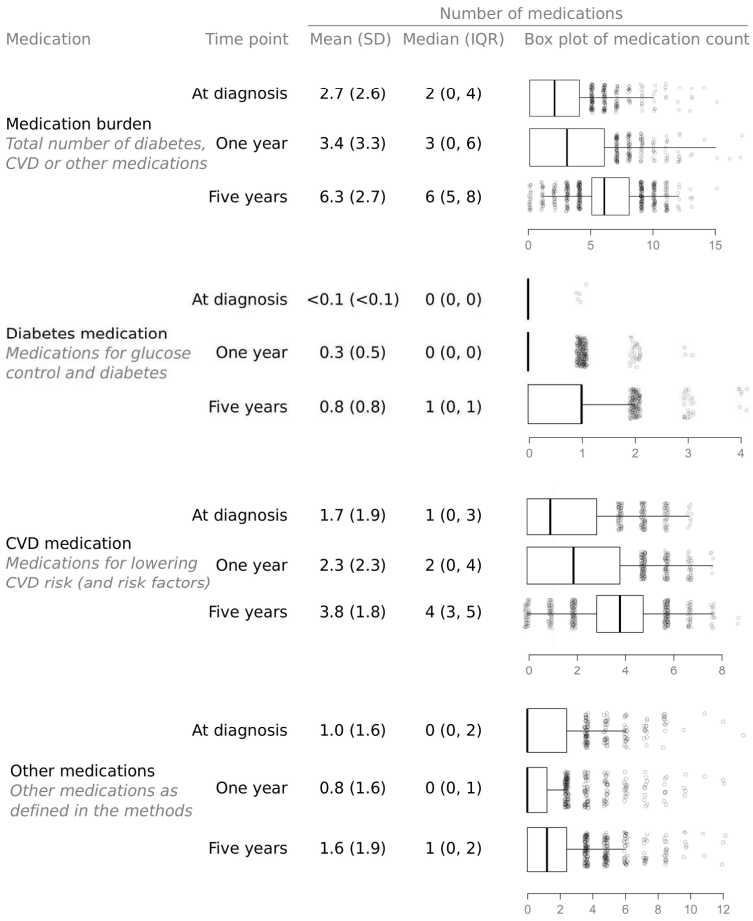

Figure 2 Count of medication types reported in the ADDITION-UK cohort at diagnosis, one and five years. Box-plots represent number of medications, points represent values outside inter-quartile range.
229x267mm (300 x 300 DPI)

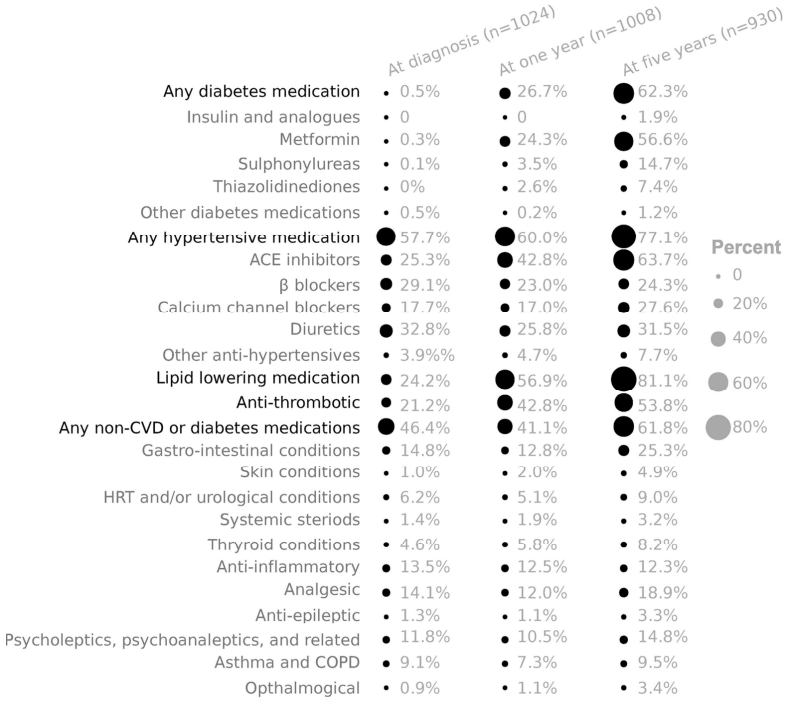

Figure 1: Proportions of self-reported medication use in the ADDITION-UK cohort at diagnosis, one and five years. Radius of circle is proportional to the percentage value.
123x110mm (300 x 300 DPI)

B.2 Publication derived from Chapter 5

Research

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Change in cardiovascular risk factors following early diagnosis of type 2 diabetes:

a cohort analysis of a cluster-randomised trial

Abstract

Background
There is little evidence to inform the targeted treatment of individuals found early in the diabetes disease trajectory.

Aim
To describe cardiovascular disease (CVD) risk profiles and treatment of individual CVD risk factors by modelled CVD risk at diagnosis; changes in treatment, modelled CVD risk, and CVD risk factors in the 5 years following diagnosis; and how these are patterned by socioeconomic status.

Design and setting
Cohort analysis of a cluster-randomised trial (ADDITION-Europe) in general practices in Denmark, England, and the Netherlands.

Method
A total of 2418 individuals with screen-detected diabetes were divided into quartiles of modelled 10-year CVD risk at diagnosis. Changes in treatment, modelled CVD risk, and CVD risk factors were assessed at 5 years.

Results
The largest reductions in risk factors and modelled CVD risk were seen in participants who were in the highest quartile of modelled risk at baseline, suggesting that treatment was offered appropriately. Participants in the lowest quartile of risk at baseline had very similar levels of modelled CVD risk at 5 years and showed the least variation in change in modelled risk. No association was found between socioeconomic status and changes in CVD risk factors, suggesting that treatment was equitable.

Conclusion
Diabetes management requires setting of individualised attainable targets. This analysis provides a reference point for patients, clinicians, and policymakers when considering goals for changes in risk factors early in the course of the disease that account for the diverse cardiometabolic profile present in individuals who are newly diagnosed with type 2 diabetes.

Keywords
cardiovascular diseases; diabetes mellitus, type 2; prevention and control; primary health care; risk assessment; risk factors; treatment heterogeneity.

INTRODUCTION

The promotion of opportunistic screening for diabetes,[1] coupled with the assessment of diabetes risk in national health checks programmes,[2] will lead to a greater number of individuals being diagnosed early in the disease trajectory. Among those with established diabetes, the risk of cardiovascular disease (CVD) and mortality can be reduced by intensive treatment of single risk factors, including blood pressure, cholesterol, and glucose.[3–6] Further, a small (*n* = 160) trial of multifactorial treatment found a protective effect at 13 years.[7] Screen-detected populations have a CVD risk profile that is distinct from that of individuals with clinically diagnosed or established diabetes,[8,9] and evidence to inform the treatment of individuals found earlier in the course of the disease, where CVD risk varies greatly,[8] is lacking. Results from ADDITION-Europe, a 5-year cluster randomised trial of intensive multifactorial treatment among screen-detected patients, show that it is possible to intensify treatment and reduce levels of many CVD risk factors in this high-risk group.[9] While the reduction in risk of cardiovascular events associated with the intervention was not statistically significant (hazard ratio = 0.83, 95% confidence interval [CI] = 0.65 to 1.05), there was no increase in modelled CVD risk in the 5 years following diagnosis, despite increasing age and diabetes duration. However, many patients were not prescribed recommended treatments.[8,9] In a screen-detected population that is free of symptoms, primary care teams may be reluctant to prescribe intensive treatment,[10] and patients may be reluctant to adhere, particularly if they only experience complications related to medications in the short term.[11] Further, there are examples of inequity in provision of health care for patients with diabetes.[12,13] To inform the development and implementation of treatment policies in this high-risk group, this study aimed to examine baseline CVD risk profiles and treatment of CVD risk factors; change in treatment, modelled CVD risk, and CVD risk factors; and (iii) how these are patterned by socioeconomic status.

METHOD

This cohort analysis used data from the

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How this fits in

Greater numbers of individuals are being diagnosed early in the diabetes disease trajectory, where there is little evidence to inform treatment. This study shows that the calculation of modelled cardiovascular disease risk is a useful tool for guiding treatment decisions in newly-diagnosed patients with diabetes. Identifying who is at highest risk will help target treatment to those who need it the most and is likely to lead to a reduction in treatment inequity.

ADDITION-Europe trial, details of which have been reported previously.[9] Briefly, ADDITION-Europe is a pragmatic primary care-based trial of intensive multifactorial treatment compared with routine care in those with screen-detected diabetes, in England, Denmark, and the Netherlands. Of 1312 general practices invited to participate, 379 (29%) agreed and 343 (26%) were independently randomised to screening plus routine care of diabetes, or screening followed by intensive multifactorial treatment of CVD risk factors. Screening took place between 2001 and 2006, and out of 3233 individuals found to have undiagnosed prevalent diabetes, 3057 (95%) agreed to take part in the treatment phase of the study.

Participants underwent a health assessment at baseline, and after a mean of 5.7 years (standard deviation [SD] = 1.3 years) post-diagnosis. Trained staff collected biochemical and anthropometric measurements, according to standard operating procedures.[14–16] Self-report questionnaires were used to collect information on sociodemographic information, lifestyle habits, and medication use. Education was first grouped into tertiles, depending on the age at which participants left full-time education, and then dichotomised into two groups; first versus second and third tertile (low education equals <16 years in the UK and the Netherlands; <21 years in Denmark). Employment status was self-reported.

The characteristics of the interventions to promote intensive treatment in each centre have been described previously and are outlined in Table 1.[14–17] Family doctors, practice nurses, and participants were educated in target-driven management (using medication and promotion of healthy lifestyles) of hyperglycaemia, blood pressure, and cholesterol, based on the stepwise regimen used in the Steno-2 study.[26]

Table 1. Treatment protocol for the routine care and intervention groups in ADDITION-Europe

Setting	Routine care	Intervention
Practice (except in Leicester, where patients had access to community-based clinics every 2 months)	Individuals in the routine care group received standard diabetes care according to national guidelines in each country.[18–21] During the course of the study, national guidelines incorporated some elements of the intervention.[22–24]	Treatment targets and algorithms were based on trial data.[3–6,14] Targets included: • keeping HbA1c below 53 mmol/l (7.0%) • blood pressure to ≤135/85 mm Hg • cholesterol to <5 mmol/l without ischaemic heart disease or <4.5 mmol/l with ischaemic heart disease • prescription of aspirin to those treated with antihypertensive medication. The treatment algorithm was amended to include a recommendation to prescribe a statin to all patients with a cholesterol level ≥3.5 mmol/l, following publication of the Heart Protection Study.[25]

Box 1. The UKPDS cardiovascular disease risk model

Background
A diabetes-specific risk-assessment tool that estimates the absolute risk of fatal or non-fatal CVD within a defined time frame up to 20 years. Participants with complete data on the UKPDS score variables at baseline were assessed.

Input variables
Age, sex, ethnicity, smoking status, glycated haemoglobin (HbA1c), systolic blood pressure, total:HDL (high density lipoprotein) cholesterol ratio, atrial fibrillation (AF), previous myocardial infarction or stroke, microalbuminuria (albumin:creatinine ratio ≥2.5 mg/mmol in males, or ≥3.5 mg/mmol in females), macroalbuminuria (albumin:creatinine ratio ≥30 mg/mmol), duration of diagnosed diabetes, and body mass index.

Notes on use
There were no data available on AF in ADDITION-Europe participants, so all individuals were coded as zero (no AF). There was a high proportion of missing data for smoking at 5-year follow-up in the Netherlands (29%). Baseline smoking status was used in the calculation of 5-year modelled CVD risk when follow-up values were missing.

Statistical analysis

Ten-year modelled CVD risk was calculated from the model of the UK Prospective Diabetes Study (UKPDS); version 3 beta),[27] at baseline and 5-years post-diagnosis. This is a diabetes-specific risk-assessment tool that estimates the absolute risk of fatal or non-fatal CVD within a defined time frame up to 20 years. Participants with complete data on the baseline UKPDS score variables, which are outlined in Box 1, were included in the analyses. The population was divided into quartiles of baseline-modelled CVD risk. Sociodemographic (age, sex, ethnicity, and education), health behaviour (smoking status), health utility (EQ-5D),[28] and clinical characteristics were summarised by risk quartile and in the cohort as a whole.

Within each modelled CVD risk quartile, the mean absolute change in each CVD

Table 2. Participant characteristics at diagnosis by modelled CVD risk quartile

Characteristic	*n* (%)[a]	10-year modelled CVD risk by quartile and overall at diagnosis: <25th centile (Q1)	25th to 49th centile (Q2)	50th to 75th centile (Q3)	>75th centile (Q4)	Combined
Self-reported						
% Female	2418 (84.5)	67.4	47.0	32.7	18.7	41.5
Mean (SD) age at diagnosis, years	2418 (84.5)	56.4 (7.2)	59.9 (6.6)	61.5 (6.1)	62.9 (5.5)	60.2 (6.8)
White ethnicity, %	2418 (84.5)	90.6	94.0	94.7	97.5	94.2
Low education, %	1853 (64.8)	39.2	39.7	46.8	52.7	44.5
Current smoker, %	2389	13.6	23.0	30.0	37.8	26.0
Median (IQR) units of alcohol per week	2141 (74.8)	4 (1 to 10)	4 (1 to 13)	5 (1 to 14)	5 (1 to 14)	4 (1 to 12)
Mean (SD) EQ-5D score	2312 (80.8)	0.82 (0.22)	0.84 (0.20)	0.85 (0.20)	0.82 (0.22)	0.83 (0.21)
% Prescribed any glucose-lowering drug[b]	2378 (83.1)	0.7	0.3	0.8	0.5	0.6
% Prescribed any lipid-lowering drug	2378 (83.1)	15.1	16.1	14.4	19.9	16.4
% History of myocardial infarction	2292 (80.1)	0.2	1.6	4.5	17.8	6.0
% History of stroke	2254 (78.8)	0.2	0.7	1.5	6.1	2.1
Clinical						
Mean (SD) BMI, kg/m^2	2418 (84.5)	31.0 (5.7)	31.5 (5.6)	32.0 (5.6)	32.0 (5.1)	31.6 (5.5)
Median (p25 to p75) HbA1c, %	2418 (84.5)	6.2 (5.9 to 6.7)	6.5 (6.1 to 7.0)	6.7 (6.2 to 7.6)	7.2 (6.6 to 9.2)	6.6 (6.1 to 7.4)
Mean (SD) systolic BP, mmHg	2418 (84.5)	137 (17)	146 (18)	153 (20)	161 (24)	149 (22)
Mean (SD) total:HDL cholesterol ratio	2418 (84.5)	3.8 (1.1)	4.4 (1.2)	4.9 (1.3)	5.7 (1.6)	4.7 (1.5)
Median (p25 to p75) triglycerides, mmol/l	2417 (84.5)	1.4 (1.0 to 1.9)	1.5 (1.1 to 2.1)	1.7 (1.3 to 2.4)	2.1 (1.5 to 3.0)	1.6 (1.2 to 2.4)
Median albumin creatinine ratio (p25 to p75), mg/mmol	2259 (79.0)	0.7 (0.3 to 1.4)	0.8 (0.4 to 1.5)	0.9 (0.4 to 2.0)	1.4 (0.6 to 3.5)	0.9 (0.4 to 2.0)
Minimum – maximum 10-year modelled CVD risk at baseline	2418 (84.5)	4.0–17.4	17.4–24.9	24.9–34.9	34.9–92.7	—
Experienced CVD event during follow-up, %	2418 (84.5)	2.1	4.3	6.8	11.3	6.1

BMI = body mass index. BP = blood pressure. CVD = cardiovascular disease. HbA1c = glycated haemoglobin. HDL = high-density lipoprotein. IQR = interquartile range. SD = standard deviation. UKPDS = UK Prospective Diabetes Study. [a]Number with variable and complete baseline UKPDS risk score (% included in the study). [b]A few participants were offered glucose-lowering medication before confirmatory diabetes diagnosis, owing to high blood glucose values at screening.

risk factor was calculated. To adjust for the differing demographic characteristics of each quartile, centre-specific linear regression models were used to estimate the change in each CVD risk factor within baseline CVD risk quartile, adjusted for age at diagnosis, sex, ethnicity, age of leaving full-time education, randomisation group, and clustering (robust standard errors). Adjusted means for each centre were combined via fixed-effects meta-analysis. The predicted probability of being prescribed any blood pressure-lowering, lipid-lowering, or glucose-lowering medication between diagnosis and 5 years, adjusting for demographic variables (within quartiles of baseline CVD risk), was calculated using a logistic model analogous to the primary analysis model.

Both the overall effect of education and potential interactions between low education and baseline cardiovascular risk were explored using centre-specific regression models as described above. The effect of employment status on change in each CVD risk factor was also examined.

The possibility that observed associations were dependent on the number of quartiles was explored by producing scatter plots of change in each risk factor by baseline modelled CVD risk. The study also explored whether the relationship between baseline risk quartile and risk factor change differed by trial group. Results were similar and trial groups were combined into a single cohort with adjustment for trial group. A multilevel logistic model (practices within centres) was used to explore sociodemographic

information that predicted loss to follow-up. Regression to the mean within quartiles was explored by plotting baseline values against change scores.[29] Data were analysed using Stata (version 12.1).

RESULTS

Participant characteristics

At 5 years, 196 people had died, 48 had independently adjudicated cardiovascular-related deaths before 5-year follow-up, and 443 individuals did not have complete data to calculate the UKPDS risk score at baseline. Baseline sociodemographic characteristics were similar between individuals who were included in the analysis (n = 2418) and those who were excluded because of missing clinical data at baseline or follow-up (n = 443), except for sex (females were more likely to have missing data than males [odds ratio = 1.3; 95% CI = 1.04 to 1.6]). Modelled risk at baseline was missing for 15.5% of the population, while missing data at 5 years ranged from 29% for systolic blood pressure to 37% for albumin:creatinine ratio (ACR).

Modelled 10-year CVD risk

Compared to the highest-risk quartile, people in the lowest-risk quartile were more likely to be female (67% versus 19%) and younger (56 years, SD = 7.2 years versus 63 years, SD = 5.5 years) and to be more highly educated (54% versus 33%). Individuals at low risk were also more likely to be non-smokers (86% versus 62%), to be free of CVD, and to have more favourable clinical characteristics (Table 2). The proportion of the population prescribed cardioprotective medication (lipid-, glucose- or blood pressure-lowering medication) at baseline was similar across the four quartiles (Table 2).

Figure 1 shows the distribution of change in modelled CVD risk from baseline to 5-year follow-up. Participants in the highest quartile of CVD risk at baseline showed the largest reduction in CVD risk, and the largest variation in change. Participants in the lowest quartile of modelled risk at baseline had very similar levels of CVD risk at 5-year follow-up and showed the least variation in risk change.

Body mass index

Adjusted reductions in body mass index (BMI) were largest among participants in the second (Q2) and third quartile (Q3) for modelled CVD risk (Q2: –0.7 kg/m^2; 95% CI = –0.9 kg/m^2 to –0.5 kg/m^2; Q3: –0.7 kg/m^2; 95% CI = –0.1 kg/m^2 to –0.5 kg/m^2; Figure 2). No significant reductions were observed in Q1 and Q4 (Table 3).

Glycated haemoglobin (HbA1c)

Baseline median HbA1c ranged from 6.2% in Q1 to 7.2% in Q4 (Table 2). A significant increase in HbA1c was observed in Q1 (+0.1%; 95% CI = 0.05 to 0.2) over 5 years of follow-up (Table 3). There was no change in HbA1c levels in Q2, while large reductions were seen in Q3 (–0.6%; 95% CI = –0.8% to

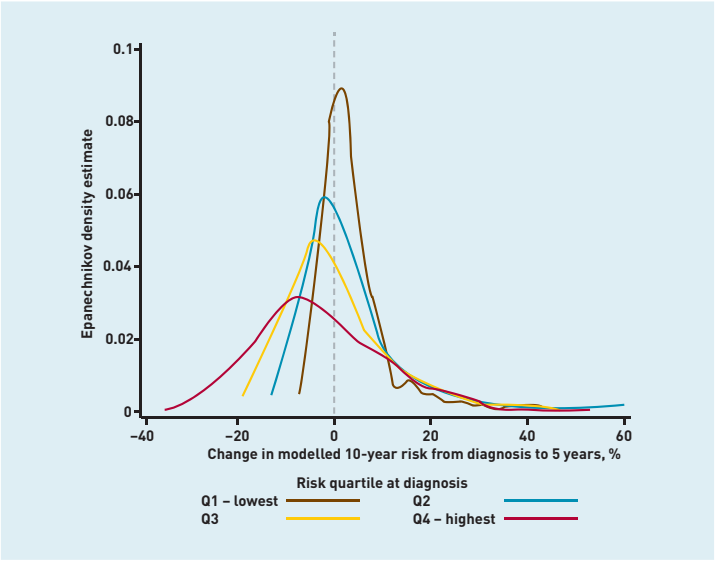
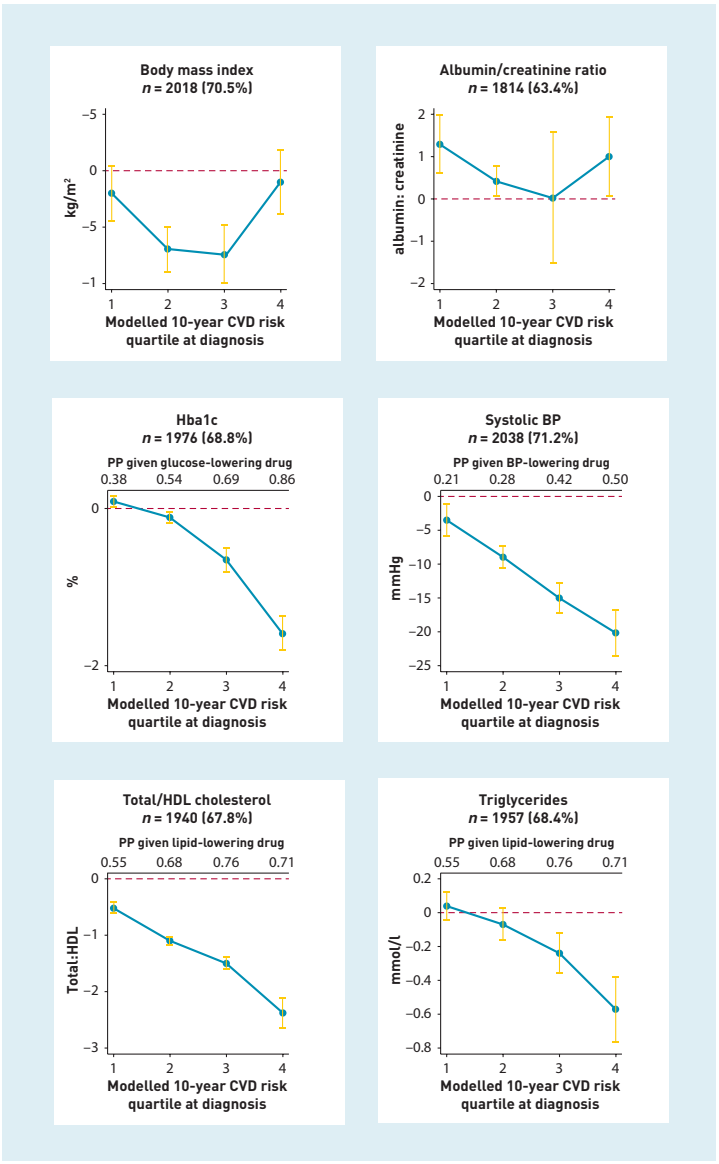


Figure 1. Distribution of change in modelled CVD risk from diagnosis to 5 years, by quartile of modelled CVD risk at diagnosis.

Figure 2. Absolute change from diagnosis to 5 years (with 95% CI), by modelled CVD risk quartile at diagnosis, adjusted for age, ethnicity, age of leaving full-time education, sex, randomisation group, and practice and centre clustering. Q1, 0–24th centile; Q4, 75–100th centile. BP = blood pressure. PP = predicted probability of being prescribed the medication at 5 years (if not on the drug at baseline), in an adjusted model analogous to the primary analysis.



–0.5%) and Q4 (–1.5%; 95% CI = –1.7% to –1.2%) (Table 3).

Systolic blood pressure

Baseline systolic blood pressure ranged from 137 mmHg (SD = 17) in Q1 to 161 mmHg (SD = 24 mmHg) in Q4 (Table 2). Over 5 years follow-up the smallest reduction was observed in Q1 (–3.5 mmHg; 95% CI = –5.7 mmHg to –1.3 mmHg) and the largest reduction in Q4 (–20.5 mmHg; 95% CI = –23.9 mmHg to –17.0 mmHg) (Table 3).

Total:HDL (high-density lipoprotein) cholesterol ratio

The mean (SD) total:HDL cholesterol ratio was 3.8 (1.1) in Q1 at baseline and 5.7 (1.6) in Q4 (Table 2). From diagnosis to 5-year

Table 3. Adjusted and unadjusted change between diagnosis and 5 years in CVD risk factors, by modelled CVD risk quartile at diagnosis

	Baseline modelled CVD risk				
Characteristic	**<25th centile (Q1)**	**25th to 49th centile (Q2)**	**50th to 75th centile (Q3)**	**>75th centile (Q4)**	**Combined**
Unadjusted change					
BMI, kg/m² (SD)	–0.3 (2.42)	–0.6 (2.40)	–0.84 (2.62)	–0.4 (2.74)	–0.53 (2.56)
Mean (SD) systolic BP, mmHg	–6.12 (18.4)	–9.61 (21.33)	–15.69 (21.51)	–19.92 (25.35)	–12.76 (22.38)
Mean HbA1c, % (SD)	0.17 (0.97)	–0.1 (1.13)	–0.42 (1.54)	–1.19 (1.91)	–0.38 (1.52)
Mean (SD) total cholesterol:HDL ratio	–0.67 (1.06)	–1.07 (1.21)	–1.42 (1.30)	–1.92 (1.62)	–1.26 (1.39)
Mean (SD) triglycerides, mmol/l	–0.03 (0.91)	–0.11 (1.45)	–0.24 (1.18)	–0.58 (1.62)	–0.24 (1.33)
Mean (SD) albumin:creatinine ratio	1.08 (6.87)	1.79 (17.38)	0.16 (24.86)	2.95 (29.53)	1.49 (21.30)
% Change in proportion prescribed glucose-lowering drug	53	56	63	76	61
% Change in proportion prescribed BP-lowering drug	25	32	35	43	34
% Change in proportion prescribed lipid-lowering drug	62	63	69	65	64
Change adjusted for age, sex, ethnicity, randomisation group, and low education, (95% CIs)					
BMI in kg/m²	–0.2 (–0.4 to 0.05)	–0.7 (–0.9 to –0.5)	–0.7 (–0.1 to –0.5)	–0.1 (–0.5 to 0.2)	–0.5 (–0.6 to –0.4)
Mean (SD) systolic BP, mmHg	–3.5 (–5.7 to –1.3)	–8.7 (–10.5 to –7.0)	–14.8 (–16.9 to –12.8)	–20.5 (–23.9 to –17.0)	–12.0 (–13.1 to –10.8)
Mean HbA1c, %	0.1 (0.05 to 0.2)	–0.1 (–0.2 to 0.01)	–0.6 (–0.8 to –0.5)	–1.5 (–1.7 to –1.2)	–0.4 (–0.44 to –0.3)
Mean (SD) total cholesterol:HDL ratio	–0.5 (–0.7 to –0.4)	–1.1 (–1.2 to –1.0)	–1.5 (–1.6 to –1.4)	–2.3 (–2.5 to –2.2)	–1.3 (–1.4 to –1.2)
Mean triglycerides in mmol/l	0.04 (–0.05 to 0.1)	–0.1 (–0.2 to 0.04)	–0.2 (–0.4 to –0.1)	–0.6 (–0.7 to –0.4)	–0.2 (–0.3 to –0.2)
Mean albumin:creatinine ratio	1.3 (0.7 to 2.0)	0.5 (0.2 to 0.9)	0.0 (–1.6 to 1.5)	1.0 (0.1 to 1.9)	1.0 (0.3 to 1.8)
Predicted probability of being prescribed medication at 5 years (if not prescribed at baseline)[a] (95% CIs)					
Prescribed any glucose-lowering drug	0.38 (0.31 to 0.44)	0.54 (0.50 to 0.59)	0.69 (0.64 to 0.74)	0.86 (0.81 to 0.90)	0.62 (0.60 to 0.65)
Prescribed any BP-lowering drug	0.21 (0.16 to 0.25)	0.28 (0.24 to 0.33)	0.42 (0.36 to 0.48)	0.50 (0.44 to 57)	0.36 (0.33 to 0.39)
Prescribed any lipid-lowering drug	0.55 (0.48 to 0.62)	0.68 (0.63 to 0.73)	0.76 (0.70 to 0.81)	0.71 (0.65 to 0.78)	0.69 (0.66 to 0.71)

[a]Adjusted for age, sex, ethnicity, randomisation group, and age of leaving full-time education, BMI = body mass index. BP = blood pressure. CVD = cardiovascular disease. HbA1c = glycated haemoglobin. HDL = high-density lipoprotein. SD = standard deviation.

follow-up, the total:HDL cholesterol ratio decreased in all four quartiles, with the smallest reduction in Q1 (–0.5; 95% CI –0.7 to –0.4) and the largest in Q4 (–2.3; 95% CI = –2.5 to –2.2) (Table 3).

Triglycerides

At diagnosis, median triglyceride levels ranged from 1.4 mmol/l in Q1 to 2.1 mmol/l in Q4 (Table 2). At 5 years, triglyceride levels had decreased in Q3 (–0.2 mmol/l; 95% CI = –0.4 mmol/l to –0. mmol/l) and Q4 (–0.6 mmol/l; 95% CI = –0.7 mmol/l to –0.4 mmol/l), with no change observed in Q1 and Q2 (Table 3).

Albumin:creatinine ratio

Median albumin:creatinine ratio at baseline ranged from 0.7 mg/mmol in Q1 to 1.4 mg/ mmol in Q4 (Table 2). At 5-year follow-up significant increases were observed in Q1 (+1.3 mg/mmol; 95% CI = 0.7 mg/mmol to 2.0 mg/mmol), Q2 (+0.5 mg/mmol; 95% CI = 0.2 mg/mmol to 0.9 mg/mmol), and Q4 (+1.0 mg/mmol; 95% CI = 0.1 mg/mmol to 1.9 mg/mmol). No change was noted in Q3 (Table 3).

Predicted probability of being allocated pharmacotherapy

The predicted probability of being prescribed cardioprotective medication at 5 years was higher in all four quartiles (Table 3). Those at the highest baseline modelled CVD risk were most likely to be prescribed cardioprotective treatment at 5 years (Table 3).

Socioeconomic patterning

No association between low education or employment status and change in CVD risk factors was present within any of the quartiles of baseline-modelled CVD risk.

Intervention effect

A sensitivity analysis excluding practices that received the intervention (promotion of intensive multifactorial diabetes care) demonstrated a non-significant decrease in systolic blood pressure in Q1 (–2.9 mmHg; 95% CI = –6.2 mmHg to 0.5 mmHg), and an increase in triglycerides in Q1 (0.2 mmol/l; 95% CI = 0.04 mmol/l to 0.3 mmol/l). Results otherwise suggested that the treatment groups could be pooled.

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DISCUSSION

Summary

There was large variation in modelled CVD risk at diagnosis among this group of individuals with screen-detected diabetes. Compared to those at lowest risk, individuals in the highest modelled CVD risk quartile were more likely to be older, male, and smokers and to have a low education status. There was no difference in the proportion of participants prescribed cardioprotective drugs across the CVD risk quartiles at baseline. The largest reductions in modelled risk were seen in participants who were in the highest quartile of CVD risk at baseline, suggesting that treatment was offered to those at highest risk. For lipid-, glucose-, and blood pressure-lowering medication, those at highest CVD risk at baseline were most likely to be prescribed cardioprotective therapy at 5 years. Participants in the lowest quartile of risk at baseline had very similar levels of modelled CVD risk at 5-year follow-up and showed the least variation in change in modelled risk. There was no variation in change in modelled CVD risk or prescription of cardioprotective treatment by socioeconomic status, suggesting that treatment was equitable.

Strengths and limitations

Data were collected from a large, representative population-based sample in three different European countries. There was high participant retention and little difference between individuals with and without follow-up data. Centrally trained staff collected data according to standard operating procedures. Recruitment of practices to the study was by self-selection, which may limit the generalisability of the study findings, but the baseline characteristics of the sample were nationally representative.[9] The study population was largely white, and so it was not possible to assess treatment inequity in relation to ethnicity. As only 48 CVD-related deaths occurred between diagnosis and 5 years, they probably introduced a minimal amount of bias. The UKPDS risk model is one of the most extensively validated risk scores for use in European populations with diabetes.[30,31] While it has been shown to overestimate risk in some contemporary populations with diabetes,[31] it is effective at ranking individuals (discrimination) and is therefore suitable for examination of characteristics by risk quartile and resource prioritisation.

Presenting the data by quartiles of baseline CVD risk could potentially lead to regression toward the mean.[29] To explore this effect, the baseline value of each risk factor was plotted against the change at 5 years. The lack of reduction in change in the tails suggests that the change values in Q1 and Q4 were not falsely attenuated. Clinical measurements were collected in triplicate, which may have helped reduce the potential for regression to the mean. The change in each risk factor was normally distributed within each quartile, and sensitivity analyses suggested that the quartiles represented the underlying patterns in an easily interpretable manner.

Comparison with existing literature

The adverse CVD risk profile at baseline in the ADDITION-Europe cohort has been observed in cohorts of individuals with newly-diagnosed diabetes.

After 5 years of follow-up in ADDITION-Europe, the largest reductions in modelled CVD risk were seen in participants who were in the highest quartile of risk at baseline. These findings support data from the UKPDS[32] and the Swedish National Diabetes register,[33] which suggest that the greatest improvements in cardiovascular risk factors were seen among individuals with the highest initial values after diagnosis of diabetes. In the UKPDS, after an initial very large reduction in HbA1c levels, HbA1c slowly increased over the first 6 years in both intervention arms,[34] and a sub-cohort of overweight individuals,[35] while a more gradual decline in systolic blood pressure values was observed in the 9 years after diagnosis.[4] In the more recent DESMOND (Diabetes Education and Self-Management for Ongoing and Newly Diagnosed) study,[36] in which baseline information was collected up to 6 weeks after diagnosis,[37] a similar pattern of a reduction in HbA1c, followed by a gradual increase, was observed.[36]

After 5 years of follow-up, ADDITION participants at highest baseline risk were more likely to be prescribed lipid-, glucose- or blood pressure-lowering drugs, after adjusting for several demographic covariates, including age, that may influence pharmacotherapy decisions by practitioners.[38] This is in line with the finding that those at highest risk at baseline in the Danish ADDITION cohort had near-normal all-cause mortality after 7 years of follow-up, while those at lower risk had an all-cause mortality that was approximately twice as high.[10] While the overall proportion of participants receiving cardioprotective medication could have been higher, the findings of the present study suggest that the ADDITION intervention was effective at reducing social inequity in treatment

provision and that treatment overall was offered in relation to underlying CVD risk. Despite a higher proportion of individuals in the highest-risk quartile having left education at a younger age, no association was observed between education or employment status and change in modelled CVD risk. There was no evidence for socioeconomic inequity in changes in risk factors in the overall trial cohort, or when the population was stratified by baseline CVD risk. This suggests that, despite the inequity in risk at diagnosis identified in ADDITION-Europe and in other cohorts with diabetes,[39–41] there was no social inequity in the delivery of treatment.

Implications for research and practice

The findings of this study suggest that the calculation of modelled CVD risk is a useful tool for guiding treatment decisions in newly-diagnosed patients with diabetes. Identifying who is at highest risk will help target treatment to those who need it the most, and is likely to lead to a reduction in treatment inequity.[42] The group identified at high risk in the study cohort had the highest prevalence of stroke and myocardial infarction at baseline and therefore had the greatest capacity to change. Intensive treatment by lifestyle intervention and prescription of cardioprotective medication is likely to lead to clinically important reductions in CVD risk factors and modelled CVD risk, particularly in individuals with a high CVD risk at diagnosis.

Among individuals with low CVD risk at diagnosis, an early-treatment approach is likely to offset the expected age and/or diabetes duration-related increase in modelled CVD risk. However, there is some evidence from the ADDITION-Denmark cohort to suggest that individuals at low risk are not being treated appropriately, leading to higher all-cause mortality compared to that for those at higher risk.[10] Calculation of modelled CVD risk can also aid individualised patient goal setting and empowerment of self-care.[18,38] This analysis provides a reference point for patients, clinicians, and policymakers when considering goals for changes in risk factors early in the course of the disease that account for the diverse cardiometabolic profile present in newly-diagnosed patients. Further analysis characterising CVD risk-factor trajectories could aid in both refining realistic goals for patients and identifying patterns that would allow a more nuanced approach to CVD risk-prevention initiatives.

Ethical approval

The study was approved by the ethics committee local to each study centre. All participating patients provided informed consent.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

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B.3 Publication derived from Chapter 6

DIABETICMedicine

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Research: Treatment

Does early intensive multifactorial therapy reduce modelled cardiovascular risk in individuals with screen-detected diabetes? Results from the ADDITION-Europe cluster randomized trial

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Abstract

Aims Little is known about the long-term effects of intensive multifactorial treatment early in the diabetes disease trajectory. In the absence of long-term data on hard outcomes, we described change in 10-year modelled cardiovascular risk in the 5 years following diagnosis, and quantified the impact of intensive treatment on 10-year modelled cardiovascular risk at 5 years.

Methods In a pragmatic, cluster-randomized, parallel-group trial in Denmark, the Netherlands and the UK, 3057 people with screen-detected Type 2 diabetes were randomized by general practice to receive (1) routine care of diabetes according to national guidelines (1379 patients) or (2) intensive multifactorial target-driven management (1678 patients). Ten-year modelled cardiovascular disease risk was calculated at baseline and 5 years using the UK Prospective Diabetes Study Risk Engine (version 3β).

Results Among 2101 individuals with complete data at follow up (73.4%), 10-year modelled cardiovascular disease risk was 27.3% (SD 13.9) at baseline and 21.3% (SD 13.8) at 5-year follow-up (intensive treatment group difference –6.9, SD 9.0; routine care group difference –5.0, SD 12.2). Modelled 10-year cardiovascular disease risk was lower in the intensive treatment group compared with the routine care group at 5 years, after adjustment for baseline cardiovascular disease risk and clustering (–2.0; 95% CI –3.1 to –0.9).

Conclusions Despite increasing age and diabetes duration, there was a decline in modelled cardiovascular disease risk in the 5 years following diagnosis. Compared with routine care, 10-year modelled cardiovascular disease risk was lower in the intensive treatment group at 5 years. Our results suggest that patients benefit from intensive treatment early in the diabetes disease trajectory, where the rate of cardiovascular disease risk progression may be slowed.

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Introduction

Type 2 diabetes is associated with significantly elevated all-cause and cardiovascular disease-related mortality, as well as a higher incidence of micro- and macrovascular disease. Among individuals with established diabetes, risk of cardiovascular disease and mortality can be reduced by intensive treatment of multiple risk factors, including blood pressure, cholesterol and glucose, although there remains some uncertainty about the merits of tight glycaemic control. Treatment of individual cardiovascular disease risk factors is also effective [1] but we know less about intensive treatment earlier in the disease trajectory. Long-term results from the UK Prospective Diabetes Study (UKPDS) suggest a beneficial effect of intensive treatment of glucose in those with shorter diabetes duration [2]. Promotion of opportunistic screening [3] and testing for diabetes in at-risk asymptomatic patients [4,5] will lead to a greater number of individuals being diagnosed early. However, there are a number of outstanding uncertainties that

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What's new?

- Little is known about intensive treatment of Type 2 diabetes early in the disease trajectory.
- In ADDITION-Europe, a cluster-randomized trial of multifactorial treatment vs. routine care among individuals with screen-detected diabetes, there was a decline in 10-year modelled cardiovascular disease risk in both trial groups in the 5 years following diagnosis.
- Compared with routine care, modest increases in intensity of treatment were associated with a small but significantly lower modelled cardiovascular disease risk value at 5 years.
- Practitioners should be encouraged to treat multiple risk factors intensively from diagnosis to reduce the cardiovascular burden of Type 2 diabetes.

need to be resolved before intensive multifactorial treatment can be recommended in this patient group.

ADDITION-Europe is a parallel-group randomized controlled trial exploring the effect of an intervention to promote intensive multifactorial treatment in a population with screen-detected Type 2 diabetes. Five-year results from the ADDITION-Europe trial show small but significant increases in treatment and reductions in many cardiovascular disease risk factors, but a non-significant 17% reduction in cardiovascular events [6]. Longer-term follow-up may be needed in order to establish whether early intensive treatment reduces cardiovascular risk [2].

In the absence of long-term data on hard outcomes, the difference in 10-year modelled cardiovascular disease risk at 5 years in ADDITION-Europe can shed light on the early cardiovascular disease experience of screen-detected individuals. We aimed to (1) describe the change in 10-year modelled cardiovascular risk in the 5 years following diagnosis with this screen-detected population and (2) quantify the impact of the intervention on 10-year modelled cardiovascular risk at 5 years.

Methods

The design and rationale for the ADDITION-Europe trial have been previously reported (Clinical Trials Registry No; NCT 00237549) [6]. In brief, ADDITION-Europe is a primary-care-based study of a pragmatic cluster randomized controlled trial in a screen-detected diabetes population, comparing intensive multifactorial treatment with routine care in four centres (Cambridge, UK; Denmark; Leicester, UK; the Netherlands). Of 1312 general practices invited to participate, 379 (29%) agreed and 343 (26%) were independently randomized into routine care or intensive multifactorial treatment. Between April 2001 and December 2006, practices undertook stepwise screening of patients aged 40–69 years (50–69 years in the Netherlands), without known diabetes. Individuals were not invited for screening if they were pregnant or lactating, housebound, terminally ill with a prognosis of less than 12 months or had a psychiatric illness likely to invalidate consent. Individuals were diagnosed with diabetes according to World Health Organization (WHO) criteria [7]. Of the 3233 patients identified with diabetes by screening, 3057 (95%) consented to participate in the trial. The study was approved by local ethics committees in each centre. All participants provided written informed consent.

Intervention

The characteristics of the interventions to promote intensive treatment in each centre have been described previously (http://www.addition.au.dk/) [6,8–11]. Family doctors, practice nurses and participants were educated in target-driven management (using medication and promotion of healthy lifestyles) of hyperglycaemia, blood pressure and cholesterol, based on the stepwise regimen used in the Steno-2 study [12]. The intervention delivered was practice based, except in Leicester, where patients also had access to individualized community clinics every 2 months [6,10]. Treatment targets and algorithms were based on trial data [6,8,13]. Targets included HbA_{1c} < 53 mmol/mol (7.0%) if HbA_{1C} > 47.5 mmol/mol (6.5%), blood pressure ≤ 135/85 mmHg if ≥ 120/80 mmHg, cholesterol < 5 mmol/l without ischaemic heart disease or < 4.5 mmol/l with ischaemic heart disease, and prescription of aspirin to those treated with anti-hypertensive medication. Statins were recommended to all patients with a cholesterol level ≥ 3.5 mmol/l following results from the Heart Protection Study [14]. Individuals in the routine care group received the standard pattern of diabetes care according to current recommendations in each centre.

Measurement and outcomes

Trained staff independently assessed patients' health at baseline and after 5 years of follow-up by collecting biochemical and anthropometric data according to standard operating procedures. Self-report questionnaires were used to collect information on socio-demographic information, lifestyle habits and medication use. All staff collecting measurements were unaware of treatment group allocation. Changes in biochemical measures and medication from baseline to 5-year follow-up have been reported previously [6].

Individuals were followed for a mean of 5.7 years. The primary endpoint for this analysis was 10-year modelled cardiovascular disease risk, calculated from the UKPDS model (version 3β) [15], at 5 years post-diagnosis. This is a diabetes-specific risk assessment tool that estimates the absolute risk of fatal or non-fatal cardiovascular disease within a defined time frame up to 20 years. Participants with complete data on the UKPDS score variables at baseline and

5-year follow-up were assessed. The variables include age, gender, ethnicity, smoking status, HbA_{1c}, systolic blood pressure, total-to-HDL cholesterol ratio, atrial fibrillation, previous myocardial infarction or stroke, microalbuminuria (albumin:creatine ratio ≥ 2.5 mg/mmol in men or ≥ 3.5 mg/mmol in women), macroalbuminuria (albumin:creatine ratio ≥ 30 mg/mmol), duration of diagnosed diabetes and BMI. We did not have data on atrial fibrillation in ADDITION-Europe participants, so all individuals were coded as zero (no atrial fibrillation). There was a large proportion of missing data for smoking at 5-year follow-up in the Netherlands (29%), so values from baseline were carried forward if missing at follow-up for all centres.

Statistical analysis

Individuals who had died before 5-year follow up were excluded from all analyses. We summarized characteristics of ADDITION-Europe participants by trial group at baseline and 5-year follow-up. We report change from baseline to follow-up in each treatment group. Intermediate endpoints and modelled cardiovascular disease risk at 5 years were analysed within each centre using linear or logistic regression, with adjustment for the endpoint baseline values. A robust variance estimate based on practice level clustering was specified in the model. Centre-specific estimates of the difference between treatment groups were combined using fixed-effects meta-analysis. The I^2 statistic was used to estimate heterogeneity between study centres [16].

In order to characterize missing data, we used logistic regression to model the odds of having a missing modelled risk score value at follow-up, adjusting for demographic and risk factor measurements as well as clustering at baseline. We also explored the impact of missing data at baseline and follow-up. First, individuals with missing modelled risk score at baseline were included in the analysis using the missing indicator method [17]. Then we extended the this analysis further with a pattern-mixture model [18], with the assumption that mean cardiovascular disease risk was, on average, 10% higher in individuals lost to follow-up.

We performed sensitivity analyses by (1) excluding individuals with prevalent or incident cardiovascular disease and (2) excluding those individuals with missing data for smoking at 5 years.

In all analyses, individuals were assigned to the groups to which they were originally randomized. Data were analysed using Stata version 12.1 (StataCorp., College Station, TX, USA).

Results

Participant characteristics

One hundred and ninety-six people were excluded as they died before 5-year follow-up (see Supporting Information, Fig. S1). A further 760 individuals were excluded as they did not have complete data to calculate the UKPDS risk score at baseline and follow-up, leaving 2101 (73%) participants with complete data for analysis. Participants who did not have data for modelled risk at follow-up were more likely to smoke at baseline (odds ratio 1.6; 95% CI 1.2–2.4) and be obese (BMI > 30 kg/m^2, odds ratio 1.6; 95% CI 1.1–2.3) than those with complete data. No other differences between those lost to follow-up and the complete case analysis sample were found. Practices were well matched at baseline [6]. Overall, participants were well matched at baseline (Table 1). There were minor differences between groups at the centre level. Use of hypertensive and lipid-lowering drugs was higher in the intensive treatment group in Leicester. In Denmark, the intensive treatment group had a larger number of participants who reported previous myocardial infarction (6.2% vs. 4.5%) and stroke (2.6% vs. 1.3%) at baseline compared with the routine care group. Further, there were more patients with diabetes in the intensive treatment compared with the routine care group (837 and 579, respectively). Between centres, a lower prevalence of previous myocardial infarction or stroke at baseline was present in Denmark and in the Netherlands compared with the UK centres. All other values were similar between centres.

Prescription of cardio-protective drugs increased in both groups, with glucose-lowering, anti-hypertensive and lipid-lowering drugs more commonly prescribed in the intervention group at follow-up (Table 1). There were small but significant differences between groups for change in systolic blood pressure and total:HDL ratio and LDL cholesterol, in favour of the intensive treatment group (Table 1).

Change in 10-year modelled cardiovascular disease risk

Ten-year modelled cardiovascular disease risk was 27.3% (SD 13.9) at baseline in the ADDITION-Europe trial cohort and 21.3% (SD 13.8) at 5 years (Table 2). Across all four centres there was a decline in modelled risk from baseline to follow-up in both the routine care (–5.0%; SD 12.2) and intensive care group (–6.9%; SD 9.0). Figure 1 shows the distribution of cardiovascular disease risk at baseline and follow-up separately by treatment group. For both groups, the distribution of modelled cardiovascular disease risk shifted to the left. Declines in modelled risk from diagnosis to 5 years were correlated with decreases in lipid, glucose and blood pressure values (see Supporting Information, Fig. S2).

Difference in 10-year modelled cardiovascular disease risk between groups at 5-year follow-up

Within all four centres, cardiovascular disease risk was lower in the intensive treatment group compared with the routine care group at 5 years (Fig. 2). The difference between

Table 1 Characteristics of the ADDITION-Europe trial cohort with complete data for the UK Prospective Diabetes Study Risk Engine (version 3β) at baseline and follow-up (mean 5.7 years)

	Routine care (n = 937)			Intensive treatment (n = 1164)			
Self reported	Baseline	Follow-up	Mean change from baseline to follow-up (SD)	Baseline	Follow-up	Mean change from baseline to follow-up (SD)	Intervention effect† β/odds ratio (95% CI)
Female sex	42%	—	—	41%	—	—	—
Mean (SD) age in years at diagnosis	59.9 (6.7)	—	—	60.1 (6.7)	—	—	—
White ethnicity	93%	—	—	96%	—	—	—
Employed	46%	—	—	42%	—	—	—
Any glucose-lowering drug	0.4%	57%	56%	0.6%	67%	67%	1.6 (1.3–2.0)
Any hypertensive drug	44%	74%	30%	46%	84%	37%	1.8 (1.3–2.3)
Any lipid-lowering drug	15%	78%	63%	18%	85%	67%	1.5 (1.1–1.9)
History of myocardial infarction	4.9%	—	—	7%	—	—	—
History of stroke	1.6%	—	—	2.6%	—	—	—
Current smoker	25%	20%	–4.6%	25%	20%	–4.9%	0.7 (0.4–1.1)
Median (p25, p75*) units of alcohol per week	5 (1–12)	4 (0–11)	–1.3 (8.7)	5 (1–13)	3 (0–10)	–1.3 (7.8)	–0.2 (–0.8 to 0.3)
Clinical							
Mean (SD) BMI in kg/m^2	31.4 (5.4)	30.9 (5.5)	–0.5 (2.4)	31.6 (5.4)	31.1 (5.5)	–0.5 (2.6)	–0.03 (–0.2 to 0.2)
Median (p25, p75*) HbA_{1c} in mmol/mol and%	49 (43–56); 6.6 (6.1–7.3)	48 (43–54); 6.5 (6.1–7.1)	–3.3 (17.0); –0.3 (1.6)	48 (43–56); 6.5 (6.1–7.3)	46 (42–52); 6.4 (6.0–6.9)	–4.7 (15.8); –0.4 (1.4)	–0.9 (–1.7 to –0.1); –0.1 (–0.2 to –0.01)
Mean (SD) systolic blood pressure in mmHg	149.9 (21.4)	138.0 (17.6)	–11.8 (22.3)	148.1 (21.9)	135.0 (16.6)	–13.3 (21.9)	–3.0 (–4.9 to –1.1)
Mean (SD) total cholesterol:HDL in mmol/l	4.7 (1.5)	3.5 (1.0)	–1.2 (1.4)	4.7 (1.5)	3.3 (1.1)	–1.3 (1.4)	–0.1 (–0.2 to –0.06)
Mean (SD) LDL cholesterol in mmol/l	3.5 (1.0)	2.3 (0.8)	–1.2 (1.1)	3.4 (1.0)	2.0 (0.8)	–1.4 (1.1)	–0.2 (–0.3 to –0.1)
Median (p25, p75*) triglycerides in mmol/l	1.7 (1.2–2.4)	1.6 (1.1–2.3)	–0.3 (1.4)	1.6 (1.2–2.3)	1.5 (1.0–2.1)	–0.2 (1.3)	–0.04 (–0.1 to 0.03)
Median albumincreatine ratio (p25, p75*)	0.86 (0.4–1.9)	1.1 (0.6–2.7)	1.7 (19.7)	0.8 (0.4–2.0)	1.2 (0.7–2.6)	1.5 (23.2)	–0.7 (–1.8 to 0.4)

*25th and 75th percentile. All change values were normally distributed, so mean change and standard deviation (SD) are presented.
†Intervention effect is estimated from a meta-analysis of centre level linear or logistic regression model, with the characteristic at follow-up as the outcome, adjusted for baseline value and with robust standard errors allowing for clustering by general practice.

Table 2 10-year modelled cardiovascular disease risk (UK Prospective Diabetes Risk Engine version 3β) in the ADDITION-Europe trial cohort at baseline and 5.7 years by centre and combined

	Routine care				Intensive treatment			
Centre	Total with data* (% of randomized)	Mean at baseline (SD)	Mean at follow-up (SD)	Mean change baseline to follow-up (SD)	Total with data* (% of randomized)	Mean at baseline (SD)	Mean at follow-up (SD)	Mean change baseline to follow-up (SD)
Cambridge	285 (75%)	27.7 (13.8)	22.8 (14.1)	–5.1 (14.4)	334 (77%)	29.3 (15.1)	22.1 (14.4)	–6.4 (14.0)
Leicester	77 (81%)	23.9 (11.4)	19.9 (13.9)	–2.3 (9.5)	56 (93%)	27.5 (13.9)	19.0 (12.0)	–8.5 (11.2)
Denmark	423 (73%)	25.4 (12.2)	21.5 (13.7)	–3.7 (12.8)	594 (71%)	25.0 (13.2)	20.2 (13.7)	–4.7 (12.1)
The Netherlands	152 (66%)	33.6 (14.3)	23.3 (14.7)	–9.8 (16.3)	180 (73%)	35.8 (15.7)	20.7 (13.8)	–14.7 (11.4)
Combined	937 (73%)	27.4 (13.3)	22.1 (14.0)	–5.0 (12.2)	1164 (74%)	28.1 (14.7)	20.7 (13.8)	–6.9 (9.0)

*Total with risk score available at baseline and follow-up.

groups ranged from –0.9% (95% CI –3.6 to 1.7) in Cambridge to –4.8% (95% CI –8.4 to –1.3) in the Netherlands. There was moderate variation between centres (I^2 = 53.6%). When results from each centre were combined, 10-year modelled cardiovascular disease risk was significantly lower: –2.0%; 95% CI –3.1 to –0.9 in the intensive treatment group, after adjustment for baseline cardiovascular disease risk and clustering. Sensitivity analyses suggest that this result was robust to data missing not at random (see Supporting Information, Fig. S3). Similarly, results remained the same when individuals with prevalent or incident cardiovascular disease were excluded, and when individuals with missing data for smoking at 5 years were excluded (see Supporting Information, Fig. S3).

Discussion

In spite of increasing age and duration of diabetes, there was a decline in modelled cardiovascular disease risk in patients with diabetes in the 5 years following detection by screening. Further, compared with routine care, modest increases in intensity of treatment in the first 5 years after diagnosis were associated with improvements in cardiovascular disease risk factors, and with a small but significantly lower modelled cardiovascular disease risk value at 5 years (–2.0%; 95% CI –3.1 to –0.9). Our results highlight the importance for practitioners of intensively targeting cardiovascular risk factors early in the diabetes disease trajectory, where the rate of cardiovascular disease risk progression may be slowed.

Comparison with other studies

A small but non-significant reduction in the relative hazard of the composite cardiovascular disease endpoint (hazard ratio 0.83; 95% CI 0.65–1.05) was present in the ADDITION-Europe trial at 5 years [6]. There are no other trial data from screen-detected diabetes populations with which to compare our results. However, similar improvements in the cardiovascular disease risk factors that drive modelled cardiovascular disease risk were seen in the patients with clinically diagnosed diabetes in the UKPDS trial at 6 years of follow-up [19]. Similar decreases in cardiovascular disease risk factor values in the 12 months following diagnosis have been reported among newly diagnosed patients enrolled in cardiovascular disease risk reduction lifestyle interventions [20,21]. While there is a lack of studies intervening early in the diabetes disease trajectory, our results are supported by studies of individuals with established diabetes, for example, in the multifactorial Steno-2 study[12,22], as well as similar 1-year modelled risk improvements in two trials of pharmacist-led behavioural advice compared to routine care [23,24].

In ADDITION-Europe, 5.3% of individuals in the routine care group experienced a myocardial infarction or stroke in the first 5 years, compared with 9.3% of the routine care

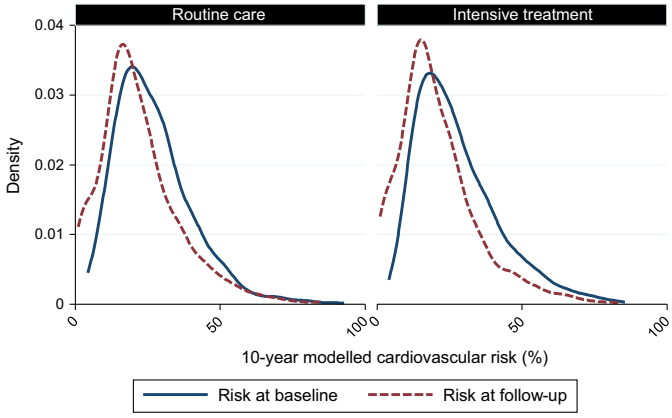

FIGURE 1 Distribution of 10-year modelled cardiovascular risk at baseline and 5.7-year follow-up in the ADDITION-Europe trial cohort by treatment group.

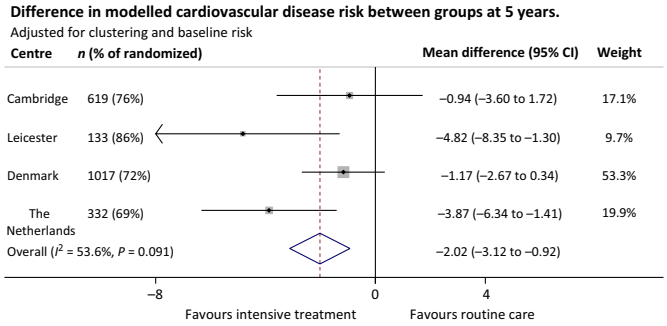

FIGURE 2 Difference in modelled cardiovascular disease risk between treatment groups at 5.7-year follow up in the ADDITION-Europe trial cohort, adjusted for baseline risk and accounting for clustering by general practice.

group in the first 6 years of follow-up in the younger UKPDS cohort (mean age 53 vs. 60 years) [19]. While the length of follow-up differs, it is likely that the extent of the difference is attributable to underlying changes in routine care. At baseline in the UKPDS, which began recruitment two decades before ADDITION-Europe, 12% of patients were prescribed blood pressure-lowering medication and 0.3% of individuals were prescribed lipid-lowering medication [13]. In ADDITION-Europe, at baseline, 45% were prescribed anti-hypertensive medication and 16% were prescribed lipid-lowering medication. This suggests that cardiovascular disease prevention in populations at risk of diabetes has improved between the recruitment phases of the two studies. Furthermore, the delivery of diabetes care in the general practice setting continued to improve throughout the trial. The introduction of the Quality and Outcomes Framework in the UK and evidence-based guidelines in the Netherlands and Denmark, as well as general promotion of cardiovascular disease risk management in people with diabetes [25–27], may have decreased the potential to achieve a difference in treatment and thus a larger difference in cardiovascular disease risk between groups [25].

Strengths and limitations

ADDITION-Europe participants were recruited from a large population-based sample in three European countries. Participants were diagnosed according to WHO criteria. Randomizing general practices reduced the risk of intervention contamination. Treatment guidelines across the centres at baseline were similar [25–28], but centres were encouraged to implement screening and treatment algorithms to suit their local environment. Participant retention was high at follow-up. We assessed clinically important outcomes using

standard operating procedures and staff were blind to treatment allocation. Overall, 27% of data were missing from the primary analysis. The effect of missing data at baseline and follow-up was explored using methods appropriate for a trial, and results suggested that the primary analysis likely represented an accurate intent-to-treat analysis. Derived from over 40 000 patient-years of data and 1115 cardiovascular disease events [15], the latest refinement of the UKPDS risk score is the most appropriate tool for predicting 10-year modelled cardiovascular disease risk in this population [29]. Modelled cardiovascular risk may have been overestimated in our contemporary cohort as routine care after diagnosis is more intensive than that experienced by the UKPDS population. This would not have altered our effect size estimates differentially by group. Clinically diagnosed atrial fibrillation was unavailable, and this variable was set to 0 in the UKPDS model. As there was no difference in self-reported atrial fibrillation at 5 years between routine care (13.3%) and intensive treatment groups (14.0%), it is unlikely that inclusion of this variable in the UKPDS model would affect our main findings.

People that died between baseline and follow-up were excluded from this analysis (n = 196). While 24% (n = 48) of these deaths were attributed to cardiovascular disease, 1.6% (22/1377) of the routine care group and 1.5% (26/1678) of the intensive treatment group experienced a cardiovascular disease-related death. By excluding the 196 incident deaths before follow-up, it is likely that we have slightly underestimated the effect of intensive treatment on modelled cardiovascular disease risk. Participants were predominantly of white ethnic origin (93%), potentially limiting the extrapolation of these findings to more ethnically diverse centres. However, as prevention of diabetes-related complications in ethnic minorities is also effective [30], it is likely that the finding in favour of the intervention would remain. The most notable difference in the application of the treatment algorithm was in Leicester, where the education components of the intervention were delivered through the DESMOND structured education programme (http://www.desmond-project.org.uk/). Further differences were seen in Denmark, where practices completed opportunistic screening, potentially leading to over-selection of those at increased risk at baseline. It is likely these influences, in combination with differences in national characteristics across centres, accounted for most of the 54% of heterogeneity not attributable to chance identified in the analysis (I^2 statistic 53.6%).

Implications for practice

Previous literature has indicated that the benefits of intensive treatment are not restricted to those at highest risk [31]. After receiving the diagnostic label of diabetes, many ADDITION-Europe participants were prescribed treatment for multiple cardiovascular disease risk factors [6] and there was a decline in modelled cardiovascular disease risk across the whole risk distribution from baseline to 5-year follow-up. This has important implications for diabetes treatment. The American Diabetes Association recommends that diabetes testing should be considered in adults of any age with a BMI $\geq$ 25 kg/m^2 and one or more known risk factors for diabetes [5]. Screening guidelines or programmes have also been introduced in the UK [4], Canada [32] and Australia [33]. These recommendations are likely to result in an increased number of individuals detected earlier in the disease trajectory. If early detection followed by intensive treatment, or even followed by the high standard of routine care now offered by primary care providers, leads to a population level shift in cardiovascular disease risk, it is likely that a large number of cardiovascular disease events might be averted. Small increases in treatment were not associated with a significant reduction in risk of events within 5 years [6], but were associated with a significant reduction in modelled events from 5 to 15 years. This suggests long-term follow-up of ADDITION-Europe beyond 5 years may mirror post-trial findings from the UKPDS study [2]. Future research should examine (1) whether this slowing of cardiovascular disease risk progression in the first 5 years after diagnosis leads to a sustained reduction in actual cardiovascular disease events over a longer follow-up time and (2) which individuals achieved more risk reduction than others to inform the development and targeting of future interventions.

Conclusion

When compared with routine care, a modest increase in the treatment of risk factors among patients with Type 2 diabetes in the first 5 years after detection by screening was associated with a small but significant reduction in 10-year modelled cardiovascular disease risk at 5 years. Furthermore, cardiovascular disease risk estimates declined across the whole cohort from baseline to follow-up, in spite of increases in age and diabetes duration. Health practitioners are therefore encouraged to treat multiple cardiovascular risk factors early and intensively in the diabetes disease trajectory, where the rate of cardiovascular disease risk progression may be slowed. Longer-term follow-up of outcomes in the ADDITION-Europe trial cohort, alongside examination of microvascular, quality of life and cost data, is planned to establish the cost-effectiveness of early intensive treatment among screen-detected patients.

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Competing interests

SJG and NJW have received an honorarium and travel expenses from Eli Lilly associated with membership of a data monitoring committee, and payment for preparing and delivering educational material from Novo Nordisk and the NHS; KB-J was director of the Steno Diabetes Centre, which is owned by Novo Nordisk, and holds stock in Novo Nordisk; MJD has served on advisory boards for Novo Nordisk, Eli Lilly, MSD, Bristol-Myers Squibb and Roche, and has received honoraria for speaking from Novo Nordisk, Eli Lilly, Sanofi-Aventis, Novartis and MSD; KK has participated in advisory boards for Novo Nordisk, Eli Lilly, MSD, Boehringer Ingelheim and Roche, and has received honoraria for speaking from Novo Nordisk, Eli Lilly, Sanofi-Aventis, Novartis and MSD; GEHMR has served as a consultant and participated in advisory boards for Novo Nordisk and MSD, and has received honoraria for speaking from Novo Nordisk; SJS, AS, JAB and RKS declare that they have no competing interests.

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ADDITION-Leicester

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. CONSORT diagram of the ADDITION-Europe trial.
Figure S2. Correlation between change values of clinical risk factors and modelled risk from diagnosis to 5 years in ADDITION-Europe.
Figure S3. Sensitivity analysis of smoking and cardiovascular disease assumptions and effect of missing data at baseline and follow-up on the difference in the UKPDS Risk Engine (version 3β) modelled cardiovascular disease risk score between treatment groups at 5.7-year follow-up in the ADDITION-Europe trial cohort.

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Change in cardio-protective medication and health-related quality of life after diagnosis of screen-detected diabetes: Results from the ADDITION-Cambridge cohort

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ABSTRACT

Aims: Establishing a balance between the benefits and harms of treatment is important among individuals with screen-detected diabetes, for whom the burden of treatment might be higher than the burden of the disease. We described the association between cardio-protective medication and health-related quality of life (HRQoL) among individuals with screen-detected diabetes.
Methods: 867 participants with screen-detected diabetes underwent clinical measurements at diagnosis, one and five years. General HRQoL (EQ5D) was measured at baseline, one- and five-years, and diabetes-specific HRQoL (ADDQoL-AWI) and health status (SF-36) at one and five years. Multivariable linear regression was used to quantify the association between change in HRQoL and change in cardio-protective medication.
Results: The median (IQR) number of prescribed cardio-protective agents was 2 (1 to 3) at diagnosis, 3 (2 to 4) at one year and 4 (3 to 5) at five years. Change in cardio-protective medication was not associated with change in HRQoL from diagnosis to one year. From one year to five years, change in cardio-protective agents was not associated with change in the SF-36 mental health score. One additional agent was associated with an increase in the SF-36 physical health score (2.1; 95%CI 0.4, 3.8) and an increase in the EQ-5D (0.05; 95%CI 0.02, 0.08). Conversely, one additional agent was associated with a decrease in the ADDQoL-AWI (−0.32; 95%CI −0.51, −0.13), compared to no change.
Conclusions: We found little evidence that increases in the number of cardio-protective medications impacted negatively on HRQoL among individuals with screen-detected diabetes over five years.

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1. Introduction

Type 2 diabetes is associated with increased risk of morbidity and early mortality [1] and a reduced health related quality of life (HRQoL) [2]. Pharmacological management of individuals with established diabetes reduces cardiovascular risk [3]. However, treatment regimens may impact on a patient's illness experience and their HRQoL and interventions that improve cardiovascular risk factor levels do not necessarily improve HRQoL [4]. Establishing a balance between the benefits and harms of pharmacological treatment is particularly important among individuals with screen-detected diabetes, for whom the burden of treatment might be higher than the burden of the disease [5,6]. The advent of national screening programmes, such as the NHS Health Checks, means that more people with clinically asymptomatic diabetes will be diagnosed. There is limited research examining how the burden of treatment might affect HRQoL for individuals identified earlier in the diabetes disease trajectory.

Among patients with established diabetes, most research supports an inverse association between glycosylated haemoglobin (HbA_{1C}) and diabetes-related QoL [7,8]. In a cohort of individuals with screen-detected diabetes, we recently showed that people whose HbA_{1C} decreased from one to five years post-diagnosis were less likely to report a negative impact of diabetes on their HRQoL [9]. However, further research is needed to elucidate the relationship between cardio-protective medication and HRQoL. This information would help inform diabetes management strategies early in the diabetes disease trajectory.

Among 867 participants with screen-detected diabetes (the ADDITION-Cambridge trial cohort), we described the association between (i) change in cardio-protective medication from diagnosis to one year and change in general HRQoL (EQ-5D) and (ii) change in cardio-protective medication from one to five years and change in general (EQ-5D, SF-36) and diabetes-specific HRQoL (ADDQoL-AWI). Our secondary aim was to establish whether change in cardio-protective medication in the first year after diagnosis was associated with changes in HRQoL from one to five years.

2. Methods

We used data from the Cambridge centre of the ADDITION-Europe trial [10], a pragmatic cluster randomised controlled trial comparing intensive multifactorial treatment with routine care in a screen-detected diabetes population in primary care [11]. The study protocol has been published [10]. Individuals aged 40 to 69 years from 49 practices in Eastern England, not known to have diabetes, and with a diabetes risk score derived from practice records [12] corresponding to the top 25% of the population distribution were invited for stepwise screening. Exclusion criteria were pregnancy, lactation, an illness with a likely prognosis of less than one year or a psychiatric illness likely to limit study involvement or invalidate informed consent. 867 patients were found to have diabetes according to 1999 WHO diagnostic criteria [13] and agreed to take part in the treatment trial. The study was approved by the Eastern Multi-Centre Research Ethics Committee (ref: 02/5/54) [10] and all participants provided written informed consent.

2.1. Intervention

Individuals were treated according to the group to which their practice was allocated: routine care according to national guidelines [14] ($n = 23$) or intensive multifactorial treatment ($n = 26$). In the intensive treatment arm, GPs were encouraged through guidelines, educational meetings, and audits with feedback to introduce a stepwise target-led drug treatment regime to reduce hyperglycaemia, hypertension and hyperlipidaemia [10] based on the STENO-2 study [15]. The intervention also included funding for practices to facilitate more frequent contact, a recommendation to refer all participants to a dietician, and theory based diabetes education materials for participants.

2.2. Measurement and outcomes

Trained staff assessed patients' health at baseline, one year and five years and collected biochemical and anthropometric data according to standard operating procedures. Self-report questionnaires were used to collect information on socio-demographic information, lifestyle habits and medication use. Changes in biochemical measures and medication from baseline to five-year follow-up have been reported previously [11].

The EuroQol three level index score (EQ-5D) was administered at diagnosis, one and five years. The EQ-5D assesses health utility over five domains of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with three levels of functioning, which results in 243 health states with scores ranging from −0.594 to +1.00 (full health) [16]. The Short Form Health Survey (SF-36) measures health status and consists of 36 items over eight health domains; it can be summarised into physical (PCS) and mental health summary (MCS) scores that range from 0 to 100, with higher scores indicating better health [17]. The Diabetes-specific Audit of Diabetes Dependent Quality of Life (ADDQoL), measures an individual's perception of the impact of diabetes on various aspects of their QoL, and can be summarised as an average weighted index score (ADDQoL-AWI) that ranges from -9 (negative impact) to +3 (positive impact) [18]. The SF-36 and ADDQoL-AWI were collected at one and five years only. For the purposes of brevity, health status, diabetes-related QoL and HRQoL are treated as synonymous in the text.

Participants were encouraged to bring their repeat prescription summaries to each health assessment to aid with the completion of a health economics questionnaire [19], which asks for information on all prescribed medication. Self-reported medication was ATC coded [20] and grouped into 13 types of cardio-protective agent: aspirin; any statin; any other lipid lowering medication; any ACE inhibitor; any β-blocker; any calcium channel blocker; any diuretic; any other blood pressure lowering medication; any thiazolidinedione; any sulphonylurea; metformin; insulin; or any other glucose lowering medication. Cardio-protective medication count was defined as the total number of the 13 cardio-protective agents

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each participant reported taking at each time point: diagnosis, one and five years.

2.3. Statistical analysis

Individuals that died between diagnosis and one year ($n = 8$), and one year and five years ($n = 47$), were excluded from the analysis sample. Only cases with complete data were included. Descriptive characteristics were described at baseline, one year and five years using means, medians and proportions. Differences in characteristics between participants with and without complete data were examined using logistic regression.

To describe change in cardio-protective medication, data were collapsed into three groups: (i) no change or a reduction in the number of cardio-protective agents (0); (ii) an increase of one cardio-protective agent (1); and (iii) an increase of $\geq$2 cardio-protective agents (2). The baseline EQ-5D score was subtracted from one year to calculate the change in EQ-5D from diagnosis to one year. One-year HRQoL measures were subtracted from five-year measures to calculate change in HRQoL from one to five years. Multivariable linear regression was used to quantify the association between change in cardio-protective medication and change in EQ-5D from baseline to one year with standard errors adjusted for clustering by practice. A multilevel model accounting for individuals within practices was considered, but due to a lack of heterogeneity explained by practice in the primary analyses, it was rejected for a parsimonious model. All models were adjusted for age at diagnosis, gender, 2004 English Index of Multiple Deprivation (IMD) score [21], self-reported CVD at baseline, ethnicity, baseline value of the HRQoL measure, baseline HbA_{1C} level, randomisation group and practice level clustering. In a second series of linear regression models, we examined the association between change in cardio-protective medication from one to five years and (i) change in EQ-5D; (ii) change in SF-36 (physical and mental score) and (iii) change in ADDQoL-AWI from one year to five years. We adjusted the model for the same factors outlined above, as well as self-reported CVD at one year.

In a secondary analysis, the association between change in cardio-protective medication in the first year after diagnosis and changes in HRQoL (EQ-5D, SF-36 and ADDQoL-AWI) from one to five years was assessed in a linear model analogous to the primary analysis.

Different versions of the ADDQoL were used (ADDQoL-18 and ADDQoL-19) at one and five years. The authors of the ADDQoL state that the measure remains robust if up to six items are removed [22]. We removed the following items from the summary score as they differed between questionnaires: 'holidays/leisure activities', 'travel/journeys', 'society/people reaction', 'dependence', 'enjoyment of food', and 'closest personal relationship'. The Cronbach's alpha for the ADDQoL-AWI un-weighted items that were constant across both questionnaires at one- and five-year follow-up was 0.90 and 0.94, respectively. In addition, we included a sensitivity analysis using a Paretian model [23] of the complete ADDQoL questionnaires, which ignored the relative importance of change, instead focusing on the four possible directions of change. Four categories were derived; (A) increase in any ADDQoL domain, (B) no change across domains, (C) decrease in any domain, (D) mixed change, and regressed in a multinomial model that was analogous to the primary analysis.

Four additional sensitivity analyses were undertaken. Firstly, change in the number of medications was fitted as a continuous variable, rather than a categorical variable. Secondly, data points missing for ethnicity, IMD, change in agents, baseline of HRQoL measure and change in the HRQoL measure in the primary analysis were imputed 100 times using chained equations to account for missingness. Thirdly, change in energy intake (food frequency questionnaire derived kcal/day) or physical activity (EPAQ2 [24]) after diagnosis might have confounded the observations and were added to the model as covariates. Lastly, interactions between randomisation group and change in medication were explored and the main analysis was also repeated in only the routine care group.

The ADDITION-Cambridge trial was powered to detect a 20% relative effect of intensive treatment on modelled CVD risk, with 90% power at the 5% level of significance assuming 30% of participants were lost to follow up [10]. Statistical analyses were completed in Stata 13 and figures using R 3.0.2.

3. Results

Eight hundred and sixty seven patients agreed to participate in ADDITION-Cambridge and attended baseline measurement. Eight (0.9%) participants died before one year follow up, and 55 (6%) before five year follow up (Table 1). The median (IQR) value of the EQ-5D score at baseline for participants that were included in the analysis was (0.85; 0.73, 1). This was higher than the score for those who died and were excluded from the analysis (0.73; 0.62, 1). Participants who did not have complete data at five year follow-up reported lower levels of physical activity (at baseline) than those who attended. There were no other significant differences between those with complete data at five years and those with missing data for baseline age, sex, BMI, current smoker, self-reported previous CVD, health status (EQ5-D) or number of cardio-protective agents. The greatest amount of missing data at one and five years was for the SF-36 (18%, 151/860 and 19%, 151/805, respectively). Missing medication and HRQoL data at one and five years was not clustered in the same individuals, leading to an increased level of missing data in the complete case analysis models (Table 2).

3.1. Change from baseline to one year

Four individuals (0.5%) reported being prescribed a glucose-lowering agent before diagnosis (Table 1) (three metformin, one a sulphonylurea). 24% of participants were taking a lipid-lowering agent, 58% a blood pressure-lowering agent and 19% aspirin at baseline. From diagnosis to one year there was an increase in the median number of prescribed agents, from 2 (IQR 1, 3) to 3 (2, 4). At one year follow-up, 251 (34%) individuals reported the same or a reduced number of prescribed cardio-protective agents, 185 (25%) one additional agent and 295 (40%) two or more agents. From baseline to one year, median EQ-5D

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Table 1 – Participant characteristics of ADDITION-Cambridge cohort at baseline, one and five years.

	Baseline		One year		Five Years	
	N (%)	Value	N (%)	Value	N (%)	Value
Median age at diagnosis in years (IQR)	867 (100%)	63 (56, 67)	–	–	–	–
% Male	867 (100%)	61%	–	–	–	–
Median IMD score* (IQR)	750 (87%)	11 (7, 18)	–	–	–	–
% White ethnicity	859 (99%)	96%	–	–	–	–
% Any lipid medication	865 (100%)	24%	849 (99%)	66%	782 (96%)	82%
% Any BP medication	865 (100%)	58%	849 (99%)	69%	782 (96%)	79%
% Any diabetes medication	865 (100%)	0.5%	849 (99%)	31%	782 (96%)	62%
% Aspirin medication	865 (100%)	20%	849 (99%)	35%	782 (96%)	44%
Median number of lipid medications (IQR)	865 (100%)	0 (0, 0)	849 (99%)	0 (1, 0)	782 (96%)	1 (1, 1)
Median number of BP medications (IQR)	865 (100%)	1 (0, 2)	849 (99%)	1 (0, 2)	782 (96%)	1.5 (1, 2)
Median number of diabetes medications (IQR)	865 (100%)	0 (0, 0)	849 (99%)	0 (0, 1)	782 (96%)	1 (0, 1)
$HbA_{1C} > 53$ mmol mol^{-1} (7%) and not on any diabetes medication	791 (91%)	39%	726 (85%)	1%	683 (84%)	8%
Median HbA_{1C} % (IQR)	846 (98%)	6.8 (6.3, 7.7)	692 (81%)	6.4 (6, 6.8)	765 (88%)	6.9 (6.4, 7.4)
Median HbA_{1C} % (IQR)	846 (98%)	51 (45, 61)	692 (81%)	46 (42,51)	765 (88%)	52 (46, 57)
Median number reported cardio-protective medications (IQR)	867 (100%)	1 (0, 2)	849 (99%)	2 (1, 3)	782 (96%)	3 (2, 4)
Median EQ-5D index score (IQR)	852 (98%)	0.85 (0.73, 1)	739 (86%)	0.85 (0.73, 1)	663 (82%)	0.85 (0.73, 1)
Median SF-36 MCS (IQR)	–	–	709 (83%)	56 (48, 59)	660 (81%)	57 (51, 60)
Median SF-36 PCS (IQR)	–	–	709 (83%)	48 (39, 54)	660 (81%)	48 (36, 54)
Median ADDQoL-AWI (IQR)	–	–	721 (84%)	−0.39 (−1, −0.06)	669 (82%)	−0.37 (−0.11, −0.86)
% Had CVD event	–	–	–	–	866 (100%)	7%
% Alive	867 (100%)	100%	866 (100%)	99%	866 (100%)	94%

– = Data unavailable; BP = blood-pressure; HBA_{1c} = glycosylated haemoglobin; EQ-5D = European Quality of Life Questionnaire; MCS = Mental component score; PCS = Physical component score; ADDQoL-AWI = Audit of diabetes-dependent quality of life average weighted index; IQR = interquartile range.

* Cambridgeshire county had a mean IMD score of 11.7 in 2004 (http://data.gov.uk/dataset/imd_2004).

scores remained constant at 0.85 (IQR 0.73, 1) and a large proportion of individuals (45%, 327/729) reported no change in health utility (Fig. 1). There was no evidence for an association between change in the number of cardio-protective medications and change in the EQ-5D score from baseline to one year (Table 2).

3.2. *Change from one to five years*

From one to five years after diagnosis, use of any anti-hypertensive agent increased from 69% to 79%; larger increases were seen in the reporting of any lipid-lowering agents (66% to 82%) and any glucose-lowering agents (31% to 62%). Aspirin use increased from 35% at one year, to 44% at five years. At one and five years, a median total of 3 (IQR 2, 4) and 4 (IQR 3, 5) cardio-protective agents were reported, respectively. Over the same time period, 219 (36%) individuals reported no increase in cardio-protective medication, 192 (32%) one more agent and 193 (32%) two or more additional cardio-protective agents. At one year, the median ADDQoL-AWI score was −0.39 (IQR −1, −0.06), suggesting that the majority of individuals reported a negative impact of diabetes on their HRQoL. Consistent with the baseline to one year results, change in EQ-5D, SF-36 and ADDQoL-AWI measures between one and five years were distributed evenly around no change (Fig. 1). There was no association between increases in cardio-protective medication and change in the SF-36 MCS score (Table 2). Increasing cardio-protective medication was associated with an increase in the SF36-PCS score, but the association was only statistically significant for an increase of one agent (2.1; 95%CI 0.3, 4.0). Conversely, while an increase in one, or more than one, agents was associated with an increase in the EQ-5D index score, the relationship was only statistically significant for one or more additional agents (0.05; 95%CI 0.02, 0.08). An association in the opposite direction was observed between change in cardio-protective medication and the ADDQoL-AWI score: more than one additional agent was associated with a statistically significant decrease in the ADDQoL-AWI score (−0.20; 95%CI −0.38, −0.02) (Table 2).

3.3. *Secondary analyses*

We found no associations between change in medication in the first year after diagnosis, and subsequent change in EQ-5D, SF-36 PCS and MCS, or ADDQoL-AWI from one to five years in models that were adjusted for potential confounders and HRQoL at one year.

3.4. *Sensitivity analyses*

When modelling cardio-protective medication as a continuous variable, similar statistically non-significant associations

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Table 2 – Associations between change in number of cardio-protective agents and HRQoL in ADDITION-Cambridge cohort.

Outcome measure	*n* (%)	Change in agents, relative to no change/decrease in agents			
		One more agent		More than one additional agent	
		β (95%CI)	*p*-Value	*β* (95%CI)	*p*-Value
Complete case analysis (Primary)					
ΔEQ-5D, 0 to 1 year	601 (70%)	−0.02 (−0.05, 0.01)	0.210	−0.02 (−0.05, 0.01)	0.253
ΔEQ-5D, 1 to 5 year	513 (63%)	0.02 (−0.02, 0.05)	0.317	0.05 (0.02, 0.08)	0.004
ΔSF-36 MCS, 1 to 5 years	488 (60%)	−0.5 (−2.2, 1.2)	0.552	−0.4 (−1.9, 1.0)	0.536
ΔSF-36 PCS, 1 to 5 years	488 (60%)	2.1 (0.3, 4.0)	0.024	0.5 (−1.4, 2.3)	0.632
ΔADDQoL-AWI, 1 to 5 years	510 (63%)	−0.11 (−0.36, 0.14)	0.380	−0.20 (−0.38, −0.02)	0.030
Imputed					
ΔEQ-5D, 0 to 1 year	859 (100%)	−0.03 (−0.06, 0.05)	0.102	−0.02 (−0.06, 0.01)	0.102
ΔEQ-5D, 1 to 5 years	811 (100%)	−0.01 (−0.05, 0.03)	0.594	0.06 (0.02, 0.10)	0.007
ΔSF-36 MCS, 1 to 5 years	811 (100%)	−0.1 (−1.5, 1.3)	0.862	−0.5 (−2.0, 1.1)	0.541
ΔSF-36 PCS, 1 to 5 years	811 (100%)	2.1 (0.4, 3.8)	0.019	0.2 (−1.6, 1.9)	0.832
ΔADDQoL-AWI, 1 to 5 years	811 (100%)	−0.20 (−0.44, 0.05)	0.116	−0.32 (−0.51,−0.13)	0.002
Including ΔPA and ΔEnergy					
ΔEQ-5D, 0 to 1 year	593 (69%)	−0.02 (−0.05,0.02)	0.277	−0.02 (−0.05, 0.01)	0.232
Routine care arm only					
ΔEQ-5D, 0 to 1 years	301 (73%)	−0.05 (−0.10,0.00)	0.073	0.00 (−0.05, 0.05)	0.976
ΔEQ-5D, 1 to 5 years	252 (66%)	−0.02 (−0.04,0.08)	0.458	0.03 (−0.02, 0.08)	0.458
ΔSF-36 MCS, 1 to 5 years	242 (64%)	0.5 (−1.6, 2.6)	0.636	−0.2 (−2.2, 1.8)	0.825
ΔSF-36 PCS, 1 to 5 years	242 (64%)	0.8 (−3.0, 4.7)	0.759	−0.2 (−3.4, 3.1)	0.909
ΔADDQoL-AWI, 1 to 5 years	245 (64%)	−0.18 (−0.50, 0.15)	0.275	−0.26 (−0.49, −0.03)	0.028

β coefficients (95% confidence interval) from a linear regression model adjusted for age at diagnosis, gender, 2004 IMD, self-reported CVD at baseline, ethnicity, baseline value of the HRQoL measure, randomisation group and practice level clustering.
Δ = Change; BP = blood-pressure; EQ-5D = European Quality of Life questionnaire MCS = Mental component score; PCS = Physical component score; ADDQoL-AWI = Audit of diabetes-dependent quality of life average weighted index.

were identified, replicating findings from the main analysis. Similarly, coefficients from models based on imputed data replicated findings from the complete case analysis. There was no evidence of an association between change in the ADDQoL-AWI and cardio-protective medication in a multinomial analysis of no change against an increase, decrease or mixed change across ADDQoL domain scores. Changes in physical activity and energy intake in the year after diagnosis did not influence the associations between change in HRQoL and change in cardio-protective medication. Models analogous to the primary analysis run in the routine care arm of ADDITION-Cambridge suggested that treatment arms could be merged. Likewise, no interactions between the randomisation group and change in agents were detected.

4. Discussion

We found little evidence that increases in the number of cardio-protective medications impacted negatively on HRQoL among individuals with screen-detected diabetes over five years. The few significant associations that we did observe were linked to clinically negligible changes in HRQoL measures.

For the EQ-5D, the smallest change associated with a clinically meaningful improvement in health status amongst individuals with diabetes is between 0.058 and 0.158 [25], while in the general population a change in the EQ-5D of >0.07 can indicate a potential clinically relevant change [26]. This suggests that the increase in EQ-5D associated with change in medication in our analysis, while statistically significant, is not likely to be clinically meaningful. More complex is an apparent decrease in diabetes-specific QoL associated with more than one additional agent (−0.20; 95%CI −0.38, −0.02). In an Australian population of 14,439 people with diabetes the mean difference in ADDQoL between those with and without complications was 0.69 [27]. It remains unclear whether a decrease of up to 0.38 in the ADDQoL, which ranges from −9 to +3, is clinically relevant.

As ADDITION-Cambridge is a novel cohort of individuals with screen-detected diabetes, few direct comparisons with published literature are possible. Shortly after diagnosis, 43% of individuals with screen-detected diabetes from the Hoorn Study were prescribed anti-hypertensive medication, 17% lipid lowering medication and 24% oral diabetes medication [28]. Among middle aged populations with established diabetes, the average number of prescribed cardio-protective medications is between four and five [5,29]. Despite a significant treatment burden, many individuals with established diabetes remained untreated for CVD risk factors such as blood pressure and cholesterol [29]. In ADDITION-Cambridge, individuals reported a median of two (IQR 3, 4) cardio-protective medication at diagnosis and four (IQR 3, 5) by five year follow-up. This is likely due to the population being diagnosed earlier in the disease trajectory. However, there was still evidence of under-treatment in our cohort [30].

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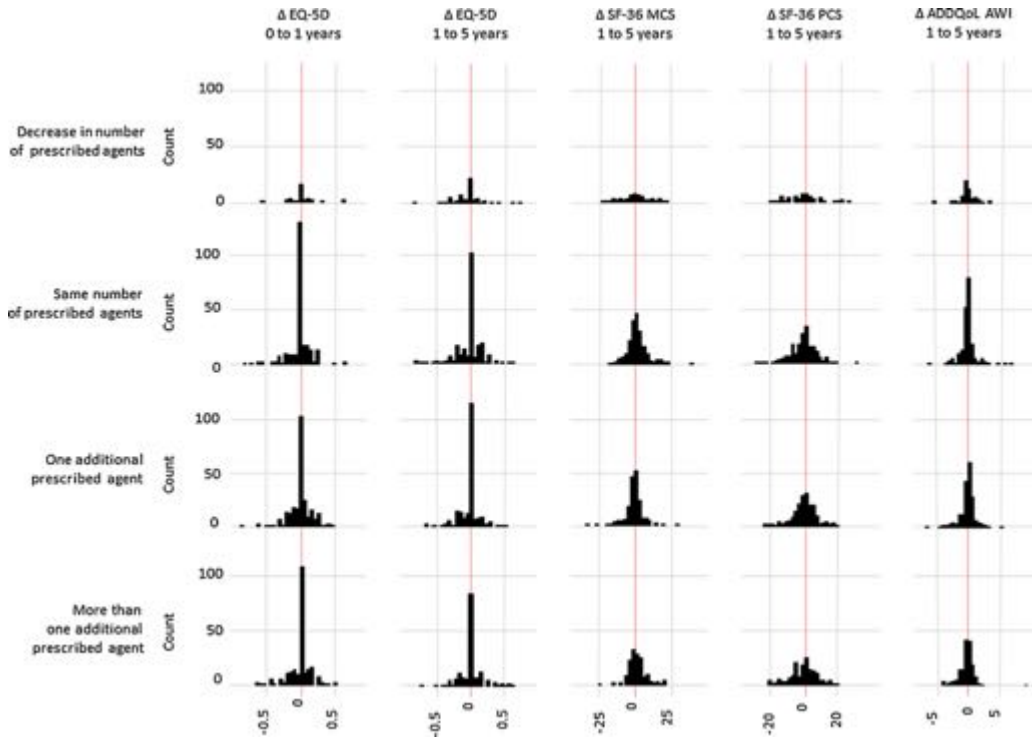

Fig. 1 – Distribution of change in quality of life measures by change in cardio-protective agents in ADDITION-Cambridge cohort. Δ = Change; SF-36 MCS = SF36 mental health summary score; SF-36 PCS = SF36 physical health summary score; ADDQoL-AWI = Audit of diabetes-dependent quality of life average weighted index.

While populations with diabetes tend to have a lower HRQoL than the general population [31,32], individuals with screen-detected diabetes have better HRQoL than those with clinically diagnosed diabetes at diagnosis [28]. There is limited literature with which to compare our findings on change in HRQoL among individuals with screen-detected diabetes as most published research has been conducted in populations with long-standing diabetes. Seppälä et al, in a Finnish population, found that SF-36 assessed HRQoL was lower in the 91 individuals with undiagnosed diabetes than in those with normal glucose tolerance [32]. Grandy et al. [33] demonstrated a small decrease in mean EQ-5D index score (−0.031 SD 0.158) over a five year time period in people with an average diabetes duration of nine years (SD 7.8) [33].

In terms of the association between medication and HRQoL, Wexler et al reported an inverse association between HRQoL and longer diabetes duration, prescription of more than 7 medications, older age and being female [2]. Trial evidence on the relationship between intensifying treatment and HRQoL is generally under-reported [34]. The UKPDS trial, which enrolled recently diagnosed individuals more than a decade before addition, found no difference between individuals with a conventional or intensified treatment protocol [35]. The ACCORD trial, which included individuals with established diabetes and early CVD, concluded that there was no HRQoL benefit from very intensive (HbA_{1C} < 42 mmol mol^{-1} [6%]) over moderate glycaemic control (HbA_{1C} 53–63 mmol mol^{-1} [7.0–7.9%]) [7]. In a trial analysis of the ADDITION-Europe cohort, in which relatively small differences in treatment intensity were achieved, there were no differences between EQ-5D or SF-36 scores for individuals in the routine care and intensive treatment groups [11]. In our observational analysis, we found no consistent association between an increase in medication and reduced HRQoL. While this suggests that increasing the number of prescribed cardio-protective medications does not impact negatively on quality of life among individuals with screen-detected diabetes, more research in populations with diabetes detected early in the disease trajectory is needed to confirm this finding.

4.1. *Strengths and limitations*

ADDITION-Cambridge is a large cohort of individuals with screen-detected diabetes and long-term follow-up. Standardised measurements and high response rates at diagnosis, one year and five years allowed the examination of changes in treatment burden and HRQoL measures. In addition to disease specific and general HRQoL measures after diagnosis, a unique

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strength of this study is the measurement of general HRQoL before a screen diagnosis of diabetes. Participants were encouraged to bring repeat prescription summaries, and we collected self-report medication data using an adaption of a validated questionnaire [19]. We computed the total number of cardio-protective agents to describe treatment burden, a method which applies equal weight to each agent. We did not examine the potential differing effect of individual drugs on HRQoL. Nor did we conduct pill counts or account for differing doses of prescribed treatments. In the sensitivity analysis, cardio-protective medication was explored as a continuous variable and results did not differ; this suggests that collapsing medication change into an ordered categorical variable did not obscure a small change. The use of fewer questions from the original ADDQoL questionnaire might have affected the instrument's sensitivity. However, the Cronbach's alpha indicated high reliability in the shortened ADDQoL-AWI version at both time points (0.90 and 0.94). Our analysis was conducted in the first five years after detection by screening. This population was younger and closer to ideal health than cohorts with established diabetes. The association between treatment intensity and HRQoL could change as duration of diabetes and age increases.

Only a general HRQoL measure (the EQ-5D) was measured before individuals were diagnosed with diabetes. At baseline, our population had a mean EQ-5D index score of 0.81 (SD 0.21; median 0.85; IQR 0.73, 1). The average value for a general British population aged 55–64 is 0.80 (SD 0.26) [36]. This suggests individuals with screen detected diabetes have a comparable HRQoL to the general public, which potentially limits the ability of the EQ-5D to detect small changes in HRQoL when many individuals may remain at 'ideal health (score of 1)'. However, the EQ-5D has demonstrated an ability to distinguish between populations with and without different complications of diabetes [37]. The difference in our estimates for the EQ-5D, and SF-36 PCS, compared to the ADDQoL-AWI and SF36 MCS, provide weak evidence that the association between cardio-protective medication and mental HRQoL differs from physical HRQoL. This finding is surprising as qualitative interviews suggest that the initial process of being screened and labelled with the condition of early detected diabetes is more often seen as a positive ''wake up call'' than a negative experience [38]. Further research is needed to establish if there is a clinically or economically relevant association.

We compared concurrent changes in cardio-protective medication and HRQoL between two time points, which were one and four years apart. This may hide short term changes in the prescription of medications and HRQoL within these time points. Understanding such changes would inform the temporality of the association, but would require a much finer resolution of prescription patterns and HRQoL over the five year period.

5. Conclusion

We found little evidence that increases in cardio-protective medication had an adverse impact on HRQoL in people with screen detected diabetes. There was no association between change in cardio-protective medication and the EQ-5D from diagnosis to one year. The few observations we observed from one to four years were small, in different directions, and the changes in HRQoL were clinically negligible. Targeted management of CVD risk factors in diabetes improves cardiovascular health [3]. Our results suggest that clinicians should not be concerned that increasing the number of cardio-protective medications will impact negatively on quality of life among individuals with screen-detected diabetes.

Conflicts of interest statement

SJG received an honorarium and reimbursement of travel expenses from Eli Lilly associated with membership of an independent data monitoring committee for a randomised trial of a medication to lower glucose. The remaining authors declare that they have no conflicts of interest.

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Appendix C

Supporting documents

Figure C.1: Medication use by trajectory group within ADDITION-*Denmark* including individuals that died during follow up.