Evaluating the effects of a multi-factorial quality improvement (QI) strategy targeted at primary care health care professionals on management of people with diabetes

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ABSTRACT

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Title of Thesis: Evaluating the effects of a multi-factorial quality improvement (QI) strategy targeted at primary care health care professionals on management of people with diabetes.

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Diabetes has now been recognised as an epidemic globally. The burden of the disease and its complications are outstripping health care systems all over the world. The rising prevalence coupled with the increasing life expectancy makes it impossible for specialist centres to cope with the demands of diabetes care, which was the case until 20-30 years ago, thus necessitating a “left shift” to primary care.

The aim of this research is to critically appraise the evidence on the effectiveness of interventions targeting primary care professionals on improvement of cardio-metabolic risk factors including glycated Haemoglobin (HbA1c), blood pressure and total or LDL-cholesterol. A further aim is to quantify the effect of intensive glucose lowering either alone or as part of a multifactorial intervention on non-fatal myocardial infarction (MI), non-fatal stroke, cardiovascular disease (CV) mortality and all-cause mortality in patients with type 2 diabetes. Finally, the impact of any interventions effective in controlling the cardio-metabolic risk factors will be considered in a real world restructured diabetes service on non-elective bed days, outpatient attendances and hospitalisation for diabetes and its complications will be assessed.

This thesis used 2 methodologies. In the first instance, a systematic review of interventions targeting primary care professionals on improvement of cardio-metabolic risk factors, and another systematic review and meta-

analysis of studies on intensive glucose lowering and multifactorial interventions on cardiovascular and mortality outcomes were conducted. Secondly, a before- and-after study of general practices on non-elective bed days, outpatient attendances and hospitalisation for diabetes and its complications was also conducted.

Main findings.

1. A systematic review of interventions targeting primary care professionals on improvement of cardio-metabolic risk factors showed that multifaceted professional interventions were more effective than single interventions targeting single primary or community care professionals in improving glycaemic control.
2. A meta-analysis of studies on intensive glucose lowering and multifactorial interventions on cardiovascular and mortality outcomes showed that apart from non-fatal myocardial infarctions, there was no evidence that intensive treatment reduced the risk of cardiovascular and mortality outcomes. Compared to standard care, intensive glucose lowering and multi-factorial intervention reduced the risk of non-fatal MI (RR 0.89, 95% CI 0.83 to 0.96) but not non-fatal stroke (RR 0.96, 95% CI 0.86 to 1.07), CV mortality (RR 1.01, 95% CI 0.91 to 1.13) or all-cause mortality (RR 1.01, 95% CI 0.94 to 1.08). The predictions indicated that, intensive glucose lowering is more likely to be beneficial in populations where the baseline incidence of CVD mortality is greater than 6.3 deaths per 1000 person-years.
3. A before-and-after analysis of a structured diabetes shared care service redesign, involving enhanced diabetes-skilled primary care physicians, nurses and health care assistants in primary care settings was conducted. Compared to an integrated specialist–community care core diabetes service, the new enhanced service did not show an increase hospitalisation (the difference between the non-elective bed days in core practices and that in enhanced practices was not significant, mean = 2.20 per 100 patients, p =

0.14)), first outpatients' attendances (the difference between the mean first outpatient attendance in the core practices and that in enhanced practices was 0.02 per 100 patients p=0.92) and admissions for diabetes related complications (the difference was 0.30 per 100 patients, p=0.55).

Conclusion

The rising demand of diabetes care requires a primary care well organised to deliver a diabetes services without compromising quality. A well-organised multidisciplinary diabetes-skilled primary care team, using multi-faceted interventions, can deliver a diabetes service without increasing diabetes related complications, out-patient attendances and hospitalisations. Cardio-metabolic risk factor control is an essential part of diabetes management. Intensive glucose lowering and multifactorial interventions can reduce non-fatal myocardial infarctions.

For Vicky, Boresi, Borenyi, David and Faith.

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Authorship

The contribution of a number of individuals to this thesis is formally acknowledged.

Professor Kamlesh Khunti contributed to study design and participated in the analysis of the before-and-after study of the impact of an enhanced primary care diabetes service on diabetes outcomes. He also acted as a third reviewer for the systematic reviews. Dr Danielle Bodicoat advised on the statistical aspects of the before-and-after study of the impact of an enhanced primary care diabetes service on diabetes outcomes. Dr Felix Achana helped with the statistical analysis in the meta-analysis.

I confirm that no part of the material offered has previously been submitted by me for a degree in this or any other university. If material has been generated through joint work, my independent contribution has been clearly indicated. In all other cases, material from the work of others has been acknowledged and citations and paraphrases suitably indicated.

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Chapter 1

1 INTRODUCTION

Diabetes has now been recognised as an epidemic globally. In 2013, the prevalence of diabetes was estimated to be 382 million worldwide and this is expected to rise to 592 million by 2035 (1). It is a complex chronic disease affecting multiple organ systems, often accompanied by other co-morbid conditions with an associated disease management burden for patients.

1.1 Types of diabetes

Diabetes mellitus broadly presents as the type 1 and type 2 diabetes; however, there are other variants such as the genetic types and secondary diabetes due to conditions pancreatitis, hemochromatosis, Cushions, acromegaly and cystic fibrosis (2). Gestational diabetes appears during pregnancy and can lead to serious health risks for both the mother and child. It associated with an increased risk of both mother and child developing type 2 diabetes later in life.

1.1a Type 2 diabetes

This accounts for over 90% of people with diabetes. The prevalence of Type 2 diabetes increases steadily after the age of 45 years (3). It is one of the most common long term condition in nearly all developed countries, and continues to increase in incidence and prevalence as a result of changing lifestyles, reduced physical activity, and increased obesity. Population growth, ageing of populations and urbanization with associated lifestyle change are the main drivers of the worldwide epidemic of diabetes.

Type 2 diabetes does not usually present with acute complications requiring urgent admission, for example ketoacidosis. As a result, some

people still regard it as a mild form of diabetes, even though it is a very complex and heterogeneous disease and its aetiology still poorly understood, apart from the fact that it has a genetic propensity and becomes overt due to lifestyle changes including decreased activity and poor diet. It is characterised by insulin resistance with inadequate pancreatic beta-cell insulin secretion to compensate for the insulin insensitivity (2). Insulin insensitivity is characterised by obesity generally and increased intra-abdominal fat. It is worsened by physical inactivity, energy dense high fat diet, early nutrition, increased alcohol intake, increased saturated fat, smoking and stress. Type 2 diabetes is commonly associated with raised blood pressure, hyperlipidaemia and a tendency to thrombosis. This combination is often described as Reaven's Syndrome.

The insulin deficiency is progressive over time, such that the high glucose levels usually worsen relentlessly over a timescale of years, requiring continued escalation of blood glucose lowering therapy (4). The worsening insulin deficiency with age means elderly people with thin phenotypes can be diagnosed with type 2 diabetes and indeed, in the middle aged population with a new diagnosis of diabetes, it can be difficult to differentiate type 1 and 2 (5).

In type 2 diabetes patients whose hyperglycaemia has yet to be treated or is being treated sub-optimally osmotic symptoms of diabetes, like polyuria, polydipsia, polyphagia, weight loss and fatigue can develop. Even though Diabetic coma (ketoacidosis) is uncommon in Type 2 diabetes, it can also present in rare situations, especially in advanced diabetes, when beta-cell function is almost non-existent and there is no endogenous insulin secretion. Ketosis-prone type 2 diabetes is an atypical diabetes (type 1B diabetes), also called Flatbush diabetes and is named after an area in New York where the first reported case in 1994 was done. The patients are usually type 2 with ketoacidosis but are misclassified as type 1. They are typically non-white Europeans (Afro-Caribbeans), middle aged, phenotype of T2DM and have negative antibodies (6). Commonly in the presence of

exacerbating factors (infection, drugs), insulin deficiency and high sugar intake can lead to a related state (hyperosmolar coma).

Increasingly type 2 diabetes is being seen in younger age groups even though most people diagnosed with it are usually older. The phenomenon of increasing type 2 diabetes among children and adolescents may be due to increasing obesity and, particularly, of increasing central obesity (7). There is a strong relationship between childhood obesity and the development of insulin resistance in early adulthood (8). There may be underestimation of the magnitude of type 2 diabetes in young people because these patients may be under diagnosed as they may present with no or just few symptoms. They may also be misclassified as type 1 diabetes if more severe hyperglycemia was noted at diagnosis. Also, case reporting mainly by paediatric endocrinologists could lead to few data in this age-group.

Certain ethnic groups show a particularly high prevalence of glycaemic abnormality among young persons, and diabetes prevalence appears to be increasing. In the USA, young type 2 diabetes occur mainly in African-American, Mexican-American, Native-American, and Asian-American children and young adults, and in the UK, it is the south Asian population. A U.S. study of 167 obese adolescents and children showed a 4% prevalence of type 2 diabetes, all occurring among Hispanic and black adolescents, suggesting environmental and/or genetic differences contributing to the more common occurrence of glycaemic abnormality in the U.S (9). In the U.K., the risk of type 2 diabetes is 13.5 times greater among Asian than white children (10). This review also noted that that other factors like a sedentary lifestyle, strong family history of T2DM, and less affluent socioeconomic status all predispose young people to type 2 diabetes. All these young type 2s invariably will have insulin resistance irrespective of their nationalities, socio-economic backgrounds and ethnicities. The differentiation of a young type 2 from monogenic genetic types of diabetes is therefore made a little easier by focusing on the

features of insulin resistance which will be absent in the presence of β cell dysfunction in Maturity Onset Diabetes of the Young.

Most guidelines broadly normally suggest that people with type 2 diabetes should start with lifestyle intervention approaches like diet and exercise; then to add monotherapy with metformin if tolerated; then to use combinations of two oral medications if glycaemic control is still not adequate, and then to add insulin if there is still no adequate control. For symptomatic patients with marked hyperglycaemia at diagnosis or when ketoacidosis is present, a reasonable approach is to start with insulin with subsequent efforts to taper this and substitute metformin (11).

From the above exposition on type 2 diabetes, it can be concluded that in order to avoid misclassification of misdiagnosis of type 2 diabetes, clinician have to consider it first, in adult Caucasian patients presenting with a new diagnosis of diabetes and have an obese phenotype. A diagnosis of type 2 diabetes should also be considered in young patients from ethnic minority groups and in those in whom oral hypoglycaemic agents were started at diagnosis (12).

1.1b Type 1 Diabetes

Type 1 diabetes is much less common than type 2 diabetes and typically affects younger individuals. Type 1 diabetes usually begins before age 40, although there are exceptions. It accounts for only about 5-10% of all cases of diabetes; even though this continues to rise worldwide (13). Even though environmental factors like exposure to various viruses (for example, Cocksackie virus), diet and vitamin D have been noted to trigger the onset and progression to overt diabetes there is a strong genetic component, inherited mainly through the HLA complex. It is associated with deficiency of insulin due to an autoimmune disorder in which antibodies are produced against the Islet cells of the pancreas. Other antibodies implicated are insulin autoantibodies (IAAs), and autoantibodies to the 65-kDa isoform of GAD and the tyrosine phosphatase-related IA-2 molecule (13, 14). It has been noted that both in family studies and in surveys based on general population, the number of

detectable autoantibodies is very closely related to progression to clinical type 1 diabetes with positivity for three to four autoantibodies being associated with a 5-10-year risk of developing clinical type 1 diabetes in the range of 60–100% (14). The onset of these first symptoms may be fairly abrupt or more gradual. The time interval from emergence of autoantibodies to frank diabetes type 1 can be a few months in infants and young children, but in some people it may take years - in some cases more than 10 years (14). Clinical type 1 diabetes represents end-stage immunological destruction of the pancreatic Islet cells. About 10-20% of beta cells are left by the time of diagnosis of type 1 diabetes.

About a quarter of people with new type 1 diabetes are usually diagnosed when they first present with Diabetic Ketoacidosis which usually can be misconstrued as something else, eg viral gastroenteritis. The rest of the type 1 diabetes patients are diagnosed during health screening and incidental detection of hyperglycemia during other medical investigations. Some are also diagnosed after presentation with typical symptoms like polyuria, polydipsia weight loss and fatigue. It is not uncommon to pick up type 1 diabetes for the first time after the patients have been admitted for complications like myocardial infarctions, strokes, retinopathies and nephropathies (13).

Latent Autoimmune Diabetes of Adults (LADA) also known as slow-onset Type 1 autoimmune diabetes in adults is genetically-linked and is hereditary. The patients are frequently initially misdiagnosed as having Type 2 diabetes based on age. Over 5-10% of T2DM could have LADA. These patients may not require insulin as diet / life style alone may be enough. It is usually not easy to differentiate this from type 2 diabetes but a normal BMI and positive auto-antibody tests (Islet, GAD, c-peptide) can help. It is usually important to advise the patient to lose weight prior diagnosis (5).

From diagnosis, the treatment of type1 diabetes is insulin replacement, even though newly diagnosed patients can sometimes experience a partial

remission phase (or 'honeymoon period') during which a reasonably well controlled HbA1c level of less than 7% can be maintained without insulin or with just a low dosage of insulin (0.5 units/kg body weight/day)(13). Diagnosis of type 1 diabetes should be suspected as being incorrect if there is a strong family history of diabetes with marked obesity. Acanthosis nigricans is not detected in type 1 diabetes. Also the presence of insulin resistance and a fasting c-peptide within a normal range should alert clinicians that the diagnosis of type 1 diabetes could possibly be wrong. The patient is unlikely to be a type 1 if there are no complications like diabetic ketoacidosis in the absence of insulin long after the "Honeymoon period", which will normally be about 3-5 years after diagnosis (13).

1.2 Burden of diabetes and its complications

Diabetes and its complications are major causes of early death in most countries. In 2015, approximately 5.0 million people aged between 20 and 79 years died from diabetes (15). This is equivalent to one death every six seconds. Diabetes accounted for 14.5% of global all-cause mortality among people in this age group (15). This is higher than the combined number of deaths from the infectious diseases (1.5 million deaths from HIV/AIDS, 1.5 million from tuberculosis and 0.6 million from malaria in 2013) (16) 46.6% of deaths due to diabetes are in people under the age of 60, the most productive age group.

Health care expenditures for people with diabetes have been found to be two- to three-fold higher than people without diabetes (17-19), mainly due increased use of health services, loss of productivity and disability. As a result, diabetes imposes a large economic burden on individuals and families, national health systems and countries (15).

A conservative estimate by the International Diabetes Federation suggests that health spending on diabetes accounted for 11.6% of total health expenditure worldwide in 2015 (15). Over 80% of the countries covered

in this report dedicated between 5% and 20% of their total health expenditure to diabetes.

Global health spending to treat diabetes and prevent complications was estimated to range from USD673 billion to USD1,197 billion in 2015 (15). By 2040, this number is projected to exceed USD802 billion to USD1,452 billion in today's dollars (15). The UK has 4 million people living with diabetes. It is currently estimated that about £10 billion is spent by the NHS on diabetes and this represents 10 per cent of the NHS budget is spent on diabetes (20). Cardiovascular diseases (CVD) are the leading cause of mortality both in men and women in the UK, accounting for one in three deaths for both sexes (21). CVD prevalence is similarly inequitable, with over 3 million Britons currently suffering from CVD. Annual UK costs exceed £30 billion and NHS costs alone exceed £14 billion and are still rising (22, 23). Cardiovascular disease is the most common cause of death and disability among people with diabetes.

1.3 Complications of diabetes

Generally, the long term harmful effects of hyperglycaemia are separated into macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy). A clear understanding of the relationship between diabetes and cardiovascular disease is needed because rising prevalence of diabetes and the therapeutic armamentarium for primary and secondary prevention of these complications.

The rising prevalence coupled with the increasing life expectancy makes it impossible for specialist centres to cope with the demands of diabetes care, which was the case until 20-30 years ago, thus necessitating a "left shift" to primary care (24). The community or primary care diabetes management is therefore a logical focal point for implementing strategies that improve the care of people with diabetes (25). The multidisciplinary approach to diabetes management is based on the premise that, on a background of a

common framework, decisions on the aims of treatment should be dictated by the insight of several professions. This normally requires team-building focusing on developing a common culture and giving priority to professional and social interaction. The purpose of this multidisciplinary approach is to ensure that the activities around the complexities of early and late management and treatment of cardiovascular risk factors, glycaemia and complications are coordinated; with the aim of ensuring an optimal individualised management plan for each patient.

1.3a Microvascular complications.

***Retinopathy*.**

The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycaemia. Development of diabetic retinopathy in patients with type 2 diabetes was found to be related to both severity of hyperglycaemia and presence of hypertension in the U.K. Prospective Diabetes Study (UKPDS), and most patients with type 1 diabetes develop evidence of retinopathy within 20 years of diagnosis (26, 27). Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes (28).

The pathway for the development of diabetes retinopathy has been attributed to various mechanisms. High glucose levels increase the utilization of sugar molecules in the polyol pathway, leading to sorbitol accumulation in cells. Osmotic stress from sorbitol accumulation has been postulated as an underlying mechanism in the development of diabetic microvascular complications, including diabetic retinopathy (28). Cells are also thought to be injured by glycoproteins. High glucose concentrations can promote the nonenzymatic formation of advanced glycosylated end products (AGEs) (28). Oxidative stress may also play an important role in cellular injury from hyperglycaemia. High glucose levels can stimulate free radical production and reactive oxygen species formation (28). Growth factors, including vascular endothelial growth factor (VEGF), growth hormone, and transforming growth factor β, have also been postulated to

play important roles in the development of diabetic retinopathy. VEGF production is increased in diabetic retinopathy, possibly in response to hypoxia (28).

Diabetes retinopathy spans through the trajectory of background retinopathy to proliferative retinopathy leading to blindness. Background retinopathy includes such features as small haemorrhages in the middle layers of the retina referred to as "dot haemorrhages." Hard exudates are caused by lipid deposition that typically occurs at the margins of haemorrhages. Microaneurysms are small vascular dilatations that occur in the retina, often as the first sign of retinopathy. They clinically appear as red dots during retinal examination. Retinal oedema may result from microvascular leakage and is indicative of compromise of the blood-retinal barrier. Proliferative retinopathy is characterized by the formation of new blood vessels on the surface of the retina and can lead to vitreous haemorrhage. White areas on the retina ("cotton wool spots") can be a sign of impending proliferative retinopathy. If proliferation continues, blindness can occur through vitreous haemorrhage and traction retinal detachment. With no intervention, visual loss may occur (29).

The implementation of a diabetes retinopathy service should comprise of a multidisciplinary team of clinicians who understand the natural history of the condition and options for early detection and treatment. These will normally be permanent staffs at a fixed or mobile retinal screening unit who are engaged in regular professional development updates. The aims of the service should to be to improve access to retinopathy screening, particularly for those for whom access has traditionally been limited; the housebound, patients who are disabled, elderly, indigenous or from non-English speaking backgrounds. In the paediatric and adolescent populations, it is essential to have an ophthalmologist with expertise in diabetic retinopathy, and an understanding of the risk for retinopathy in the paediatric population backed up with team that has an experience in counselling the young persons and their families on the importance of early prevention and intervention (30). The co-ordination and supervision

of such a service requires proper leadership to identify clinical incidents, safety assessments and drawing up proper interventions to tackle these deficiencies. The General Practitioner keeps an updated register for diabetes patients for a call-recall system for retinopathy screening. This is co-ordinated through appropriate liaison between the hospital eye service and screening programme.

Successful multidisciplinary co-ordinated retinal screening services should have the necessary components not just for screening but for investigations and management. There has to be immediate access to facilities for fluorescein angiography and OCT (optical coherence tomography) to allow patients with maculopathy to be treated within 10 weeks (31) those with new proliferative retinopathy to be treated with laser within 2 weeks (31-33). Patients needing urgent photocoagulation should be able to have it carried out immediately. For patient convenience it is better to have the laser treatment carried out on the day of diagnosis of the problem is made; therefore, there should be sufficient laser clinics or staff available to undertake the treatment outside laser clinics. Intravitreal drug delivery facilities will be needed at any treating centre [(32), but vitreo-retinal surgery if not available locally can be referred to a tertiary referral centre. For patients with visual impairment, appropriate counselling services should be available.

Diabetes Nephropathy

With rising prevalence of type 2 diabetes, its effects on the kidneys have become the leading cause of end stage renal failure (ESRF) in most Western countries. The presence of Chronic Kidney Disease (CKD) increases the risk of cardiovascular morbidity and mortality and increases the risk of progression to ESRF (34). Approximately 20 –30% of all diabetic subjects will develop evidence of diabetic nephropathy. The classical pathway to this is the trajectory from microalbuminuria, to overt nephropathy or macroalbuminuria, and finally ESRF.

The renin angiotensin system has been known and been pivotal in the progression of patients with diabetes and renal impairment in end stage renal failure. The reno-protective effect of angiotensin-II receptor blockers independently of blood pressure reduction was demonstrated strongly in the Irbesartan Diabetic Nephropathy Trial and RENAAL study. Both ACE inhibitors and ARBs have been shown to decrease the risk of progression to macroalbuminuria in patients with microalbuminuria by as much as 60–70%. These drugs are recommended as the first-line pharmacological treatment of microalbuminuria, even in patients without hypertension (35). In recent times, with the rising therapeutic armamentarium in diabetes other antidiabetic drugs have shown impressive reductions rates of progressions of proteinuria and end renal end points (36, 37).

Diabetic nephropathy is a progressive disease and as such requires the input of a number of health care professions at various stages of the disease trajectory. The primary care teams after initial diagnosis of early disease can reduce the progression of renal disease with the use of angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blockers (ARB) (38, 39). Specialist assessment should be available to patients with, or at high risk of renal disease for referrals by the primary care teams as the disease progresses. The late management and treatment of complications should be well co-ordinated with the diabetes renal service working closely with nephrology services. Diabetes nephrology services should have appropriately trained staff and systems in place not just to organise the service effectively in a timely manner during disease deterioration but to manage acute complications like hypoglycaemia during episodes of dialysis. Multicomponent structured patient educational interventions which have been shown to be effective in predialysis and dialysis care (40). The role of the dietician is invaluable in this group of patients to not only maintain adequate nutrition but to prevent abnormal electrolyte excursions (41).

Diabetic neuropathy

Diabetic neuropathy is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes (42).

The precise nature of injury to the peripheral nerves from hyperglycaemia is not known but likely is related to mechanisms such as polyol accumulation, injury from AGEs, and oxidative stress. Peripheral neuropathy in diabetes can present in several different forms, including sensory, focal/multifocal, and autonomic neuropathies.

Chronic sensorimotor distal symmetric polyneuropathy is the most common form of neuropathy in diabetes. Typically, patients experience burning, tingling, and "electrical" pain, but sometimes they may experience simple numbness. In patients who experience pain, it may be worse at night. Patients with simple numbness, loss of sensation to vibration and temperature can present with a painless foot ulceration (42). Patients who have lost 10-g monofilament sensation are at considerably elevated risk for developing foot ulceration (43).

Pure sensory neuropathy is relatively rare and associated with periods of poor glycemic control or considerable fluctuation in diabetes control. It is characterized by isolated sensory findings without signs of motor neuropathy. Symptoms are typically most prominent at night (42). Mononeuropathies typically have a more sudden onset and involve virtually any nerve, but most commonly the median, ulnar, and radial nerves are affected... Diabetic amyotrophy may be a manifestation of diabetic mononeuropathy and is characterized by severe pain and muscle weakness and atrophy, usually in large thigh muscles (42). Several other forms of neuropathy may mimic the findings in diabetic sensory neuropathy and mononeuropathy. Diabetic autonomic neuropathy also causes significant morbidity and even mortality in patients with diabetes. Neurological dysfunction may occur in most organ systems and can by manifest by gastroparesis, constipation, diarrhoea, anhidrosis, bladder dysfunction, erectile dysfunction, exercise intolerance, resting tachycardia,

silent ischemia, and even sudden cardiac death (42). Cardiovascular autonomic dysfunction is associated with increased risk of silent myocardial ischemia and mortality (44). Amitriptyline, imiprimine, paroxetine, citalopram, gabapentin, pregabalin, carbamazepine, topiramate, duloxetine, tramadol, and oxycodone have all been used to treat painful symptoms, but only duloxetine and pregabalin possess official indications for the treatment of painful peripheral diabetic neuropathy (42).

Foot ulceration has been reported as the leading cause of hospital admission and amputation in individuals with diabetes (45). Acute diabetes-related foot ulcers require multidisciplinary management and best practice care, including debridement, offloading, dressings, management of infection, modified footwear and management of extrinsic factors (46). Treatment of diabetic foot ulcers vary widely, depending upon the skills of the attending clinicians. Best practice is deemed to be a multi-disciplinary approach, where the holistic view of the patient is sought, and a care plan developed around this person's individual needs. However, these MDTs are not always available. The multidisciplinary teams ideally should include appropriately trained staff to include: orthotists, podiatrists/ podiatric surgeons or both, vascular surgeons, orthopaedic surgeons, diabetologists, microbiologists, radiologists, diabetes specialist nurses (including a diabetes specialist inpatient nurse), ward link nurses and consultants in pain management (with an interest in diabetic neuropathy) (46).

For patients at no added risk, foot care education is usually all that is required, but as they become at risk, twice annual review including foot inspection, footwear assessment, and foot care education become necessary. Patients at high risk (i.e. those with more than 2 risk factors), need reviewing every 3-6 months including foot inspection, footwear assessment, and potential need for vascular assessment or referral. Referral to multidisciplinary foot care team within 24 hrs for management of ulcers and infection is mandatory (47). To ensure a seamless package of

care for people with foot care problems, it is important that they are put at the centre of the decision-making process, and have access to accurate information and support. The organisation of care has to involve appropriate health care professionals including community podiatrist who have a clear referral pathway to specialist services. The multidisciplinary specialist teams must endeavour to hold joint clinics in order for service to be more effective and to reduce duplication of visits (48). For the in-patient with diabetes, close observations for risk factors and prevention of foot ulceration is crucial as this can be a vulnerable situation with increase in pressure related ulcers.

For the seamless organisation of care around the diabetes foot patient, there needs to be ready availability of services to support the management. Facilities for pressure area offloading, like orthotic services, foot casting and prosthetic services. Also imaging, including X-ray, CT, MRI and microbiological support services need to be available.

1.3b Macro-vascular complications of diabetes

Multifactorial intervention in the management of type 2 diabetes is known to lead to the reductions in cardiovascular mortality (49). In order for primary care professionals to provide an effective service for people with diabetes, there needs to be clear evidence-based messages around the various the cardiovascular risk factor control domains.

As discussed above, the relationship between diabetes and its control and the reduction of microvascular complications has been proven repeatedly in large scale randomised controlled trials (27, 50, 51), however the same cannot be said of macrovascular complications. The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from LDL particles accumulate in the endothelial wall of arteries. In addition to

atheroma formation, there is strong evidence of increased platelet adhesion and hypercoagulability in type 2 diabetes (52).

Diabetes increases the risk that an individual will develop cardiovascular disease (CVD). Although the precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined, the association between the two is profound. CVD is the primary cause of death in people with either type 1 or type 2 diabetes (50, 53). In fact, CVD accounts for the greatest component of health care expenditures in people with diabetes (50, 54). Despite these strong associations, intensively controlling glycaemia has not always led to a reduction in macrovascular complications (55-57). In trials where macrovascular benefits have been shown, this normally occurs after decades (27). In trials that did not show macrovascular benefits or indeed showed and increase risk of macrovascular complications, the cause of the increased risk or the blunting of any minor macrovascular benefits, could be due to the pleiotropic effects of the medications used in the treatment of diabetes. In recent years, there have been a proliferation of newer agents for the treatment of diabetes and all these have to demonstrate cardiovascular safety as required by licensing bodies. The wide therapeutic armamentarium, with the potential of adverse pleiotropic macrovascular complications, creates a significant layer of complexity for primary care teams, who may not be specialised enough in the area of diabetes. On the background of these complexities, any model of diabetes care which relies on primary care teams as the focus of service delivery will need to explore and critically appraise all the evidence around cardiovascular risk reduction by primary care teams in diabetes patients. Coronary heart disease and stroke prevention in diabetes patients is therefore the focus of the initial aspects of this project and the findings of the review will hopefully feed into the design of a primary care based integrated diabetes service.

Coronary Heart Disease

Among macrovascular diabetes complications, coronary heart disease has been associated with diabetes in numerous studies beginning with the Framingham study.24 More recent studies using Mendelian randomization analyses support a causal role for diabetes and its associated high glucose levels on CAD, and suggest that long-term glucose lowering may reduce CAD events (58). Type 2 diabetes typically occurs in the setting of the metabolic syndrome, which also includes abdominal obesity, hypertension, hyperlipidaemia, and increased coagulability. These other factors can also act to promote CVD. Even in this setting of multiple risk factors, type 2 diabetes acts as an independent risk factor for the development of ischemic disease and death (59).

Diabetes and Stroke

Patients with type 2 diabetes have a much higher risk of stroke, with an increased risk of 2.5- to 3.5-fold compared to nondiabetic subjects (59-61). Diabetes is also a strong independent predictor of risk of stroke and cerebrovascular disease as in coronary artery disease (38). Risk of stroke-related dementia and recurrence, as well as stroke-related mortality, is elevated in patients with diabetes (52).

Although HbA1c has been clearly demonstrated to be a marker and a strong predictor of diabetic vascular damage and complications in diabetic patients (62), its prognostic significance in the acute cerebrovascular disease still represents an intriguing issue deserving further investigations

Cardiovascular risk factor control

Given this public health burden, prevention of cardiovascular disease has become a priority in recent years. In 2009, the Department of Health introduced the NHS Health Checks programme in England, which aims to assess people aged 40-74 years for their CVD risk (http://www.healthcheck.nhs.uk/). Assessing risk of CVD has emerged as a simplistic way of targeting intervention strategies at those who are

asymptomatic but at high risk of developing CVD (individuals scoring >20% risk).

The majority of CVD can be prevented by addressing risk factors that can be controlled, treated or modified such as lack of physical activity, unhealthy diet, overweight/obesity, high blood pressure, cholesterol, tobacco use and diabetes. Furthermore, the mainstay therapies for high risk individuals are long-term statins and anti-hypertension medication. However, research has shown that only half of individuals continue to take prescribed statins at six months, with further declines in adherence at one year (63). This finding is especially prominent in asymptomatic individuals, where such treatment is preventive (64, 65).

Therefore, reducing the above risk factors along with improving medication adherence can rapidly reduce the likelihood of developing CVD and interventions targeting these areas are essential for individuals identified as having a high risk of CVD.

The National Health Service health checks programme introduced in England in April 2009 for adults aged 40 to 74 years is purposed to assess the risk of developing vascular or metabolic disease and manage the risk factors of those identified as high risk to prevent disease progression and improve outcomes. The programme therefore serves as good opportunity to identify people with type 2 diabetes and those at risk of diabetes (66)

There are varying reports of uptake of the NHS health checks in different populations. Even though the Department of Health assumes a 75% uptake in their cost effectiveness modelling (67), low uptakes rates of 29% have been reported in some areas (68). Lower rates of uptake of screening programmes are reported among ethnic minorities and in areas of socioeconomic deprivation (69). Possible reasons of the low uptake in minority groups could be cultural, economic and fatalistic acceptance of the cause and course of the diabetes. Whatever the reasons, racial/ethnic disparities can be worsened if high risk or selective screening in these groups is not considered seriously. A more aggressive call and recall of

these population groups for the NHS health checks coupled with strategies to prevent the onset of diabetes through diet and lifestyle changes that are culturally sensitive and population specific is therefore essential (70).

On the contrary, other studies have reported significantly higher attendance for the NHS health checks programmes among patients from south Asian (53.0%) or mixed (57.8%) ethnic backgrounds (71). This finding makes the programme a welcome intervention for reducing the disparities of diabetes prevalence between the different populations.

For all patients aged between 40-74 years without a diagnosed existing vascular disease, if they have a blood pressure of ≥140/90, BMI ≥30 Kg/m^2 (27.5 Kg/m2 in minority ethnic groups), a test for diabetes either with fasting plasma glucose or glycated haemoglobin (HbA1c) is suggested. Recent observational studies have reported a 33.3% failure rate of identifying patients of known ethnicities at risk of developing or having diabetes when this approach is followed (72). Hence, a generic application of the programme to all populations could potentially lead to further widening of inequalities. Fine tuning the programme to reflect various population needs is therefore a better option.

The recent National Institute of Clinical Excellence (NICE) guidance on preventing type 2 diabetes: risk identification and interventions for individuals at high risk, recommends a two-step process of strategically targeting screening at those with highest risk. In this process a patient's risk of developing diabetes would be quantified initially using a suitable risk evaluation (by self- assessment scores or computerized scores) which does not require biochemical measurements. Risk above an agreed threshold would prompt blood sampling for HbA1c along with other tests required for cardiovascular risk assessment (73). Better still; a one-step approach with measurement of HbA1c in all may be the better option to adopt in areas of high prevalence, especially where there is relatively socio-economically deprived population with a high proportion of residents from ethnic minorities (74). A blood sample would be taken for

HbA1c analysis and lipid profiling for cardiovascular risk screening. Patients are then classified as being at risk of diabetes if they have elevated HbA1c levels below the diabetes threshold (6.0-6.4%) and would be invited back for repeat screening at 12 monthly regular intervals. Those at low risk (HbA1<6% or 42 mmol/mol) will be followed up 5 yearly and those with HbA1c ≥ 6.5% will be labelled as diabetes after repeat test for confirmation if asymptomatic. These people will then be removed from the call and recall NHS health check programme and managed through existing diabetes care pathways.

The uptake of the NHS health checks modelled around 75% by the department of health is no doubt going to create a major impact on workload for health care assistants, nurses, laboratories and general practitioners. If 2.2 million people are screened at this level of uptake, it is estimated that between 84,038 to 89,231 people will diagnosed with type 2 diabetes. Even if the uptake was around 45% (1.35 million people screened), between 51567 to 54,755 people will be diagnosed (75). Given that in the UK, people of South Asian backgrounds are at a higher risk of developing type 2 diabetes and do so at about 5 years earlier than the white population (76), an earlier screening age for these high risk groups would be appropriate, however the department of health does not recommend starting screening at an earlier age for people in these high risk groups probably because of the anticipated impact these huge numbers is going to have. Using marginal analysis and profit maximisation however, it might still be prudent to consider earlier screening age for high risk groups. The £332m per year cost of the programme from the economic modelling by the Department of Health will adequately fund the screening but once these screen detected cases are found, management of the disease and subsequent complications is going to stretch the already overburdened health system. It is hoped that a proportion of the suggested average annual benefit of £3.8bn will be used to tackle the issue of inequalities (67).

The control of the multiple strands of cardiovascular risk factors in diabetes care requires multi-disciplinary teams. The organisation of the

teams needs clinicians not just to have the expertise in their chosen fields but also to be skilled in an inter-professional approach. Coronary heart disease (CHD) is a frequent complication and a major cause of mortality in people with diabetes. Therefore, its presence can create added complexity for an already burdensome regimen. The presence of a complex health and illness profile is found to be associated with worse control of cardio-metabolic risk factors independent of regimen intensity and history of CHD (77). This is compounded by the fact that management of the major cardiovascular risk factors in diabetes have all raised questions on the benefits of high risk factor control. In glycaemic control for example, although early intensive treatment in diabetes results in lasting benefit, including for CVD risk reduction (78), intensive glycaemic control in late diagnosis and in patients if background cardiovascular disease does not reduce major cardiovascular events and indeed may increase mortality (56). Similarly, even though major reductions in cardiovascular outcomes is seen in patients receiving tight control of blood pressure compared with those receiving conventional control if the base line blood pressure was high (79, 80) tight control of systolic BP among patients with diabetes and coronary artery disease has not been shown to improve cardiovascular outcomes (81). Indeed, an increased mortality in intensively treated newly diagnosed diabetes patients has also been noted and therefore caution in lowering blood pressure too aggressively is recommended in these patients (82). Regarding cholesterol, a reduction in 1 mmol/l LDL leads to 20-25% reduction in CVD events (major coronary events, coronary revascularisation and ischaemic stroke) (83). However, among patients at increased diabetes risk, (those with baseline evidence of impaired fasting glucose, metabolic syndrome, severe obesity, and elevated HbA1c) the risk of development of diabetes among statin-treated patients appears to be raised. However, the overall cardiovascular and mortality benefits of statin therapy exceed the risk for developing diabetes (84). Nevertheless, this finding introduces another complexity in cardiovascular risk management in diabetes. Thus the control of the various risk factors could potentially require the inputs of other team members with expertise on those areas.

The treatment of the complications and co-morbidities requires co-ordination across a number of specialists. System management is therefore essential, including the flexibility to deliver personalised care and identifying and meeting the individual needs of people with complex needs. In dealing with these complexities, integration of care around the patient is pivotal to deliver seamless, optimal and effective care. In developing a diabetes service, it is important to know what the components and of the service ought to be and the mode of implementation required. Even though the models of care delivery in diabetes vary from country to country, the components required are broadly similar. The implementation is what varies from place to place. The choice of implementation strategy depends on the local needs and the availability of various component resources. In many developed countries, there is usually a national strategy in delivering diabetes care.

In a generic service model, there must be integration across all levels of the service in order to provide a seamless transition for patients and ensure appropriate referrals take place, with clear and agreed referral criteria and clinical protocols for chronic and emergency management. Good communication links and joint working between the practice diabetes leads and specialist care teams is essential for the planning of services and to provide a framework for audit, quality assurance and performance monitoring.

Care provision in the community settings (that is, other than within GP practices) requires a collaborative approach from diabetes specialists support teams. These teams are constructed based on the needs of the local population and can comprise a collaborative team of diabetes specialist nurses, diabetes consultants, dieticians, diabetic retinopathy screening teams and podiatrists. They can offer clinic based care, outreach support to practices and nursing homes, rapid access community clinics, development of agreed clinical care pathways for various aspects of diabetes care and referrals, and telephone and web based support for complex cases, again depending on the needs of the locality. This support

needs to be flexible in approach and multi-stranded to reflect the varying gaps in knowledge of the health care professionals. The fundamentals of any such programme should be applicable and transferable to other diabetes care providers.

These components require a co-ordinated approach between multiple healthcare professionals in different sectors of health and social care. For local populations, a local model of care is required, which can be developed in more detail, with roles and responsibilities clearly identified. Ideally, care should be provided within each locality to agreed care pathways, and each care provider should be clear of their role and relationship with other providers. The delivery of integrated diabetes care in any locality requires leadership and teams working through co-operation, co-ordination and collaboration, working to a shared vision of healthcare, and drawing together the skills and relationships across the healthcare community. This integrated collaborative approach has been shown to be effective not only in mental illness but also in the management of people with mental disease and other chronic physical multi-morbidities (85). Specialist diabetes teams, often with extended roles, working in primary care through community consultants, form a central 'hub' of expertise to support the delivery of high-quality and effective delivery of diabetes care.

1.4 Exemplary models of diabetes care

Overview of current models of care

In the USA, there is a drive to incorporate elements of the chronic care model into diabetes care. Systems' redesigns, self-management and decision support and organisation of diabetes care in the community could collective improve outcomes in diabetes and reduce cost (86). An organisation like Kaiser Permanente are using these components in diabetes care and showing improvements in admission rates and outpatients clinic attendances, born out of the challenge of providing medical care to industrial workers during the Great Depression and World

War II, when most people could not afford to go to the doctor, is using these components in diabetes care and showing improvements in admission rates and outpatients clinic attendances (87). It provides affordable, high quality health care services and improves the health of its members and the communities served. It defines the integrated model of health care financing and delivery through its unique partnerships. The ethos of the service is to have a social purpose, quality-driven, shared accountability, integration along multiple dimensions, prevention and management of complications. In this organisation, the primary care physician is at the centre, but may be helped by nurses (sometimes specializing in diabetes or other conditions), medical assistants (sometimes dedicated population management assistants), health educators, pharmacists, social workers, psychologists and specialists. It is however unclear whether a similar model focusing on just primary care or community care professions could lead to cardiovascular risk factor control in people with diabetes in the UK. If this was proven to be the case, it could lead to the same benefits as the chronic care model being delivered at a lower cost closer to the patients' homes with the guarantee of continuity from the usual primary care physicians. In the next chapter a review of all interventions targeting primary care or community based professionals on glycaemic and cardiovascular risk factor control in people with diabetes will be considered in detail.

Some current UK models of care and their shortcomings.

In the UK, the changes occurring in the NHS present an opportunity for clinicians in primary and specialist care to collaborate to bring about quality improvement in diabetes care. In recent times, two exemplary models have been rolled out in England that are reaping some early successes; the Portsmouth Super Six Model (88) and the Derby Integrated diabetes care model (89). In the Portsmouth Super Six model, the collaboration between primary care and secondary care clinicians has resulted in ring-fenced specialist areas in diabetes, left to be managed in

secondary care, where expert input from diabetologists and multidisciplinary care teams are. These six specialist diabetes areas are: antenatal diabetes, renal (estimated glomerular filtration rate <30), diabetic foot care, insulin pumps, type 1/adolescent diabetes (unstable control) and inpatient diabetes. Hospital diabetes clinics developed historically from the need for supervision of insulin treatment. Inevitably they also recruited large numbers of patients not managed by insulin, and the problem has been compounded by increases in life expectancy. The work load has thus increased over the decades and the specialist's role in insulin management has now been limited to the acutely ill diabetic patients including patients with diabetic ketoacidosis, those with acute myocardial infarctions, intensive care patients and those on renal wards who need meticulous insulin management to foster early recovery. Patients requiring very complex insulin regimes for the control of their diabetes, like those needing very large doses and those needing insulin in combination with GLP-1 analogues are best dealt with by the specialist. All other diabetes care should be delivered in primary care, with specialist providing educational support and advice for primary care clinicians in the management complex diabetes. Despite the success of this model as an exemplar model of diabetes care in the UK, it is limited by the lack of recognition of a complex group of patients with diabetes who need to be under specialist multidisciplinary settings in secondary care. These patients may not necessary fall in the "super six" category, but are too complex to be managed in primary care settings by generalists. Examples of such complex patients are young poorly controlled type 2 diabetes patients, very obese poorly controlled type 2 patients and poorly controlled type 2 patients with either micro-vascular or macro-vascular complications. Another limitation of the Portsmouth "super six" model is the complexities around the contractual arrangements of the supporting secondary care consultants. Due to the difficulty in arranging their contracts, the supporting consultants had to form a limited liability company, independent of either their primary care or secondary care

trusts. This arrangement creates uncertainties on the longevity of the service.

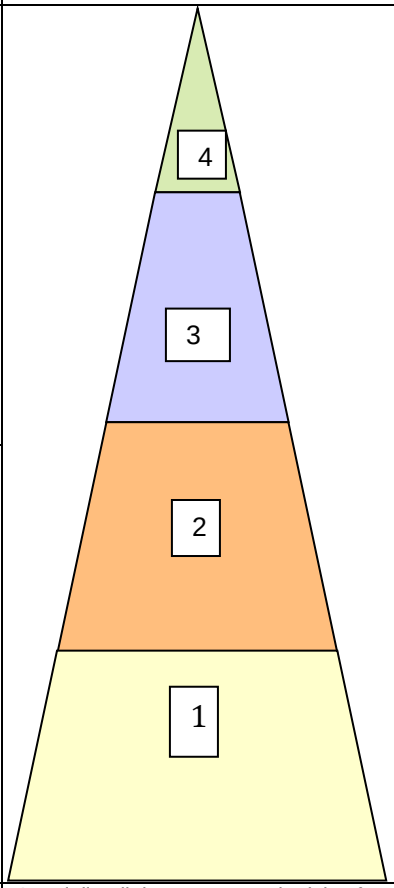
In the Derby Integrated diabetes care model on the other hand, innovative collaboration between primary care and specialists resulted in the creation of a new NHS organisation, which provides integrated diabetes care for their local population. The new NHS organisations are jointly and equally owned by an acute hospital trust and local GPs. With the patient in the "hub", delivery of care revolved around them, with the organisational structure, clinical pathways and financial planning all aligning seamlessly (89). This arrangement sounds more secured than the Portsmouth "super six" model, however, the contractual negotiations probably needed protracted legal negotiations in order to reach and consensus. Despite this long drawn out process, it is still unclear even if this model can stand the test of time.

Another established model is The NHS Westminster Model of Care for Diabetes Services (90). In this model integration of care is fostered by an emphasis on the primary, intermediate and secondary care of type 2 diabetes largely using common locally agreed pathways. The integration also stretches to social services, giving patients a seamless pathway of care irrespective of their health and social requirements. Through these pathways, patients are triaged either to secondary care or intermediate care and no patients are referred directly to secondary care (level 4) without first going through the community-based specialist diabetes services (level 3). (Figure 1). The limitation of this model, like most other integrated models of care, is that continuity of care can be lost due to the multiplicity of professionals involved in different settings, all of them with only a prime concern of the diabetes, and probably not so much of an involvement of other bio-psycho-social factors.

Due to the limitations of all these models, there is a need to configure and appraise a new model based on the ideals of the aforementioned models, but with particular attention to primary care teams. Every patient in the

UK, has a registered general practitioner who is responsible of co-ordinating the health and social needs of individual patients. It therefore makes sense to configure a primary care based integrated diabetes service where continuity of care for the patient can be guaranteed closer to the patient's home. Various interventions targeting primary care teams need to be explored in the context of not just diabetes, but other multi-morbid conditions.

Figure 1: Westminster Diabetes Service Model

<table>
<tr><th>Lead Clinical Responsibility</th><th>Level of care</th><th>Setting</th><th>Providers</th><th>Contracting mechanism</th></tr>
<tr><td>Consultant Diabetologist</td><td rowspan="4"> 
</td><td>Hospital setting</td><td>Acute trust</td><td>Payment by Results</td></tr>
<tr><td rowspan="2">General Practitioner</td><td>Community Setting</td><td>Provider of community services +
Provider of acute services
+
Provider of retinopathy screening service</td><td>Service level agreement (SLA) / contract with community service provider
+
Separate SLA/contract with acute provider to cover services provided within intermediate care service and interventions provided to support GPs to provide high quality care
+
Contract with provider of retinopathy screening service</td></tr>
<tr><td>GP Surgery / residential setting / patient's home</td><td>GP(s) + practice nurses + other staff employed by practice</td><td>General Medical Services (GMS) contract, including Quality and Outcomes Framework (QOF)
+/-
Local Enhanced Service (LES)</td></tr>
<tr><td>Level 4</td><td colspan="4">Specialist diabetes care and advice for patients provided within a hospital-based setting</td></tr>
<tr><td>Level 3</td><td colspan="4">Specialist diabetes care and advice for patients provided within a community-based setting (eg community-based diabetes centre, health centre, Polyclinic)
- including insulin starts</td></tr>
<tr><td>Level 2</td><td colspan="4">Elements of primary care services for people with diabetes that are provided in community settings (ie other than within GP surgeries)
- including patient education programmes, dietetics, podiatry and diabetic retinopathy screening.</td></tr>
<tr><td>Level 1</td><td colspan="4">Care provided by GP(s) + practice nurses + other staff employed by GP practices
The introduction of a local enhanced service (LES) can enable PCTs to set standards for the quality of diabetes care provided by GPs and their staff (eg training to be undertaken, adherence to agreed care pathways and referral protocols, etc..); and can also provide a mechanism for PCTs to reward practices for providing ongoing diabetes care for a higher proportion of patients, as well as for providing services that are nor usually provided by GP practices (eg insulin initiation).</td></tr>
</table>

1.5 Interventions on Health care professional

Patients with type 2 diabetes are very heterogeneous and there is no single universal pathway or guideline the can be applied to all of them. The emergence of new therapies for diabetes, in addition to metformin, sulphonylureas and insulin, gives clinicians a wide range of options to address the needs of their patients. The issue however is; clinicians will need in-depth knowledge of these new therapies in order to use them. Complex decision making like deciding which agents can be used in elderly frail patients, those with multi-morbidities, renal failure and those with long standing diabetes can be contribute to clinical inertia in optimising glycaemic control.

Improving quality in diabetes care has always focused on the education of patients and the organisation of the teams providing the service and less so on the health care provider. Variations of care in the management of cardiovascular risk in diabetes still exists (91) even though we now have good quality evidence showing that patients can achieve good outcomes when various quality improvement strategies around prevention and management of diabetes are implemented (92). As a result, innovative evidenced-based approaches, focusing on educating the primary care physicians, are needed to increase awareness of the risks and access to integrated diabetes care services. A systematic review focusing on glycaemic control over a median follow up of thirteen months showed a reduction in HbA1c of 0.42% (95% CI 0.29-0.54) when QI strategies were employed. This review identified team changes and case managements as the only two strategies to significantly reduce HbA1c if combined with other strategies. These 2 strategies were associated with improvements in in HbA1c of at least 0.5% (93).

A more recent systematic review looked at the role of QI strategies more broadly across the clinical spectrum of diabetes care; from glycaemic control to vascular risk management, micro-vascular complications and smoking cessation (94). The quality indicators that seemed to have a

marked effect on glycaemic control and vascular risk management were team changes, case management, patient education, facilitated relay of information and promotion of self-management. In terms of glycaemic control alone, all QI strategies are associated with a significant lowering of glycaemic control when baseline HbA1c when sample size are corrected for, with the exception of clinician education (94). There was however no differentiation of which clinicians were being educated. Even though educating the Diabetes Specialist Nurses and specialists is important, it is unlikely to result in HbA1c reduction, as they most likely will have those skills already, but educating general practitioners could potentially lead to improvement in glycaemic control. A recent observational study concluded that that primary care physicians were less likely to follow prescribed guidelines for diabetes care than their secondary care colleagues (95). Poor infrastructure in primary care to deal with the increasing work load related to diabetes care has also been sited (96). Despite these, most patients with type 2 diabetes in many European countries are now being treated in primary (97). GP education in the complex areas of diabetes care like insulin initiation and intensification is therefore desirable. Changes in various national guidelines have resulted in General Practitioners taking over the responsibility of initiating insulin, which was previously the sole responsibility of the secondary care teams. In 2006, the Dutch recommended insulin initiation by all primary care physicians if it is indicated (98). The guidelines in the Netherlands, provided detailed information on appropriate therapeutic regimes and also recommended that anybody on two or more oral hypoglycaemic drugs but with HbA1c of more than 7.5% should be initiated on a long acting basal insulin. This simple and straightforward guide resulted in 67% of primary care physicians initiating and monitoring insulin rather than referring to the hospitals, and another 17% monitored insulin regimes initiated in secondary care (98).

With the proliferation of newer anti-diabetic agents in recent years, GP education is therefore crucial in keeping pace with the changes.

GLP 1 agonist have the advantage of weight reduction and are therefore attractive to obese type 2 diabetes patients, but the side effect of nausea and vomiting is a potential draw back, clinician education on the frequency of these side effects and injection technique is therefore necessary.

DPP-4 inhibitors are also proving attractive albeit the modest HbA1c reduction associated with them, simply because they are taken orally and are weight neutral and on their own will not cause any hypoglycaemia. The fixed dosing of linagliptin without need for dose reduction in renal patients is particularly exciting for GPs.

Pioglitazone is particularly useful in severe insulin resistant patients, and can possibly improve serum HDL and decrease triglyceride. The problem however is the possibility of weight gain due to fluid retention and heart failures, bone fractures and possible increase in bladder cancer.

Even in the case of metformin with a huge amount experience in its use, GP education on what cut-off renal threshold to avoid it, effects on vitamin B12 absorption, its GI side effects and when to consider slow release versions will all be desirable.

Sulphonylureas are proving less popular with clinicians because of the weight gains and hypoglycaemia associated with them but they still have a place in a lot of patients and GP education on when to consider them could be financially prudent as they are relatively inexpensive.

Clinician education on the new and advanced therapies in diabetes has to keep pace with this fast rate of development of new drugs in order to improve outcomes. This however comes at a cost which might serve as a barrier for clinicians. The pharmaceutical companies are a necessary evil in this regard. Sponsorship for doctors and nurses for educational events has come under enormous criticism lately because of concerns around the ethics of providing fair and neutral information about drugs and products (99). Delivering medical education on new and advance therapies of diabetes in the form of lectures and presentations sponsored by pharmaceutical companies is not ideal as these companies get to choose to

topic, content and speakers. So the clinicians really have no choice but to just learn what is taught them, which may not necessarily be what will improve the outcomes for their patients. Emphasis is now being put on helping healthcare professionals to measure and improve what they do in their practices (competence and performance). GPs who want to improve their knowledge on new and advanced therapies in diabetes could achieve this by completing practice quality improvement modules in which they review the care they deliver to their patients through an audit process of comparing their outcomes with standards of excellence, identifying their own learning needs and creating a plan for improvement. This plan could then be aided by pharmaceutical companies not just through didactic lecture room power point presentations, but through mentorship, case-based discussions, reminders and feedback.

With the reconfiguration of CCGs across the country, models of diabetes care that involves collaboration of between primary and secondary are springing up with early successes. In this collaboration, in addition to patients getting a seamless pathway of care, through the different strata of the models, primary care physician can get advice, educational support and mentorship from their secondary care colleagues on specific patient management issues at no extra cost (88).

1.5 Primary care management of the multi-morbid diabetes patient

As the population lives longer, we are faced with an epidemic of multi-morbidity and rising complexity of health needs (100). It is estimated that 25% of people live with a long-term condition; the majority with more than one (101, 102), thus resulting in excess health service spending on dealing with these conditions. Multi-morbidity tends to be more prevalent in populations with increased deprivation (102). Nearly all our research is based on single diseases and tends to exclude patients with complex morbidity.

Currently integration of care is considered as the ultimate goal for the management of long-term conditions and multi-morbidities (103). The methods adopted for dealing with this wield the technique of intervention provision characterised by evidence-based condition-specific protocols of best practice, together with developing multiple professional teams to deal with the complexities of multi-morbidities (104).

Despite this current practice, even though critical review of the current evidence of the effects of integrated care demonstrated improvements in processes like adherence to protocols, there was little impact on patient outcomes or costs to health services (105).

Expert generalist practice involving practitioners trained in the principles and practice of interpretive medicine, dealing with the first contact care of wide ranging complex undifferentiated problems, has been suggested as an alternative strategy for dealing with the problem of multi-morbidity (106).

However, there is paucity of practice-based evidence demonstrating the benefits of multi-morbidity care packages by generalists.

Chapter 2

A systematic review of Interventions targeting primary care or community based professionals on glycaemic and cardiovascular risk factor control in people with diabetes.

2.1 Synopsis of chapter 2

The objective was to review the interventions targeting primary care or community based professionals on glycaemic and cardiovascular risk factor control in people with diabetes.

A systematic review of randomised controlled trials evaluating the effectiveness of interventions targeting primary care or community based professionals on diabetes and cardiovascular risk factor control was conducted. Searches were conducted in MEDLINE database from inception up to 27TH September 2015. Articles related to diabetes were also retrieved from the Cochrane EPOC database and EMBASE and scanned bibliographies for key articles.

The results showed heterogeneity in terms of interventions and participants amongst the 30 studies (39,439 patients) that met the inclusion criteria. Nine of the studies focused on general or family practitioners, five on pharmacists, three on nurses and one each on dieticians and community workers. Twelve studies targeted multi-disciplinary teams.

Educational interventions did not seem to have a positive impact on HbA1c, systolic blood pressure or lipid profiles. The use of telemedicine, clinician reminders and feedback showed mixed results but there was a level of consistency in improvement in HbA1c when multifaceted interventions on multidisciplinary teams were implemented. Targeting general or family physicians was largely ineffective in improving the

cardiovascular risk factors considered, except when using a computer application on insulin handling of type 2 diabetes or customised simulated cases with feedbacks. Similarly, interventions targeting nurses did not improve outcomes compared to standard care.

It was therefore concluded that multifaceted professional interventions were more effective than single interventions targeting single primary or community care professionals in improving glycaemic control.

2.2 Literature review

In the primary care setting, the care of people with diabetes does not solely lie on the primary care physician. On the contrary, various other professionals play key roles around the various facets of the care of people with diabetes. Different interventions will probably work better for different professional roles to improve outcomes. A consideration is herein given to the various professional roles and interventions in the primary care setting around the care of people with diabetes.

2.2a Community Pharmacists

A sustainable collaborative care approach for people with diabetes should make use of the community pharmacists, a local and accessible resource that is increasingly regarded as the first port of call for patients to seek help with the management of chronic disease. By offering programmes for monitoring therapeutic interventions, improving compliance with medication, and by educating patients about their lifestyle to improving their quality of life, community pharmacists play a vital role in managing diabetes and its complications (107, 108). On the average, the community pharmacist consults with the diabetes patient three to eight times more frequently than other patients (109). As a result of this, in addition to bringing 'medicines expertise' to the team-based care of people with diabetes and performing root-cause analysis of adverse events with diabetes medicines to contribute to the patient/medicine safety agenda, the community pharmacist can lead the collaborative care approach of

managing diabetes and reducing associated cardiovascular risk factors. The use of the collaboration can bridge the gap between successful pharmacy screening programme for diabetes and practitioner follow up of these patients (110). This role can be extended to patients in residential care and housebound patients.

2.2b Practice Nurses

In primary care setting, chronic disease management is increasingly being carried out by practice nurses with general practitioners intervening only in complex cases (111). In the case of diabetes this has become even more necessary because of the increasing prevalence and the burden of caring for people with the disease. It is known that despite the worsening of health related quality of life and an increase in diabetes related symptoms, practice nurses are able to achieve results, which are comparable to those achieved by a general practitioner in terms of cardio-metabolic risk factor reduction (111). Patients treated by practice nurses also reported being more satisfied with their treatment than those treated by a general practitioner (111). Practices nurses, using clinical guidelines, can therefore safely deliver the care of people with type 2 diabetes. This makes the nursing team in primary an important resource in a multidisciplinary primary care team. The extension of the practice nurse's role to include the initiation and titration of medications complements their other roles like supporting, educating and enabling patients to manage diabetes care thus ensuring a holistic delivery of care closer to home. However, they can potentially over utilise insulin inappropriately. The close collaborative working between the nurses and the doctors can limit any potential over utilisation of insulin management if it were to occur.

2.2c General or Family Practitioners

The use of primary care physicians (General or Family practitioners) can be as good if not better than hospital outpatient if regular review of patients is guaranteed (25). The enhancement of the generalist's care for diabetes patients with the use of quality improvement strategies like audit and feedback is an effective tool for reducing patient cardiovascular risk profile (112). The generalist's role often includes active case management

of patients with multiple conditions. In these patient groups, continuity of care is of paramount importance. Multidisciplinary primary care teams, led by the generalist, therefore have a fundamental role in the prevention and identification of diabetes as well as in routine care at a level that fits with their competencies. They will ensure an accurate disease register is maintained to enable a call-recall system for annual reviews. They work co-operatively with other members of the team, seeking their views, acknowledging their contribution and using their skills appropriately. Patients with poor cardiovascular risk factor controls and those with early signs of micro-vascular complications can be identified and referred onto more specialist centres. The generalist has a more longitudinal relationship with patients with chronic conditions like diabetes. They have the responsibility of coordinating the management of the patient's acute and chronic complications of diabetes over time. They have an understanding of the patient in relation to their socio-economic and cultural background and additionally, recognise the impact of the problem on the patient's family and carers. They will therefore use appropriate support agencies including primary health care team members targeted to the needs of the patient of with diabetes.

The pay-for-performance initiative started in the UK in 2004 is probably the most ambitious quality improvement strategy and initially yielded some obvious improvements in the care of people with diabetes (113) but these benefits reached a plateau across the population (114) and did not lead to reduction in the variations in care(115, 116). The organisation of general practitioner specialist clinics in primary care has limited evidence in terms of reduction of cardiovascular risk factors. The provision of primary care services for patients with diabetes, whether traditional general practitioner clinics or diabetes clinics run by general practitioners with special interests, is effective in reducing HbA1c, cholesterol and blood pressure (117).

2.2d Diabetes Specialists

Hospital diabetes clinics developed historically from the need for supervision of insulin treatment. Inevitably they also recruited large numbers of patients not managed with insulin. The workload has thus increased over the decades. With the majority of diabetes patients now being managed in primary care, the specialist's role in insulin management has now been limited to the acutely ill patients with diabetes including patients with diabetic ketoacidosis, those with acute myocardial infarctions, intensive care patients and those on renal wards who need meticulous insulin management to foster early recovery. Type 1 or type 2 diabetes patients who require very complex insulin regimes for the control of their diabetes, like those needing very large doses and those needing insulin in combination with newer therapies are best dealt with by the specialist. Most consultants with a specialist interest in diabetes are based in acute hospitals where they also deliver general medicine, alongside training roles, general management and research. As a result of these multiple roles they are very well placed to provide multidisciplinary diabetes specialist teams with leadership though providing support and education to community diabetes services. In some areas the integration of services has made necessary the employment of an increasing number of community diabetes consultants who deliver and co-ordinate services in a community setting only.

2.2e Dieticians

The use of dietary education has been found to improve anthropometric measures and glycaemic control and use of less prescribed medication (118). By using improvements in diabetes patient's knowledge of how to self-manage his or her illness, dietician–led diabetes management programmes can be an effective strategy for glycaemic control and improving dietary habits for patients with poorly controlled type 2 diabetes (119). Registered dieticians therefore can contribute greatly to the comprehensive care plans for diabetic patients. They work as members of multidisciplinary teams across a variety of healthcare settings, including primary and specialist care. Their caseload might encompass working with

children, adults, young people and individuals with mental health problems. They also have an important role in the management of diabetes patients with severe obesity. The dietician can also offer support for patients with type 1 diabetes in areas around carbohydrate counting. In primary care, their role could be in advising those at risk of diabetes and those who are newly diagnosed on the appropriate dietary requirements. In the case of complex diabetes patients needing initialisation or augmentation of insulin therapy the dietician support is normally needed. Within a specialist care setting they support antenatal and postnatal care of diabetes patients. In the obese diabetes patients needing bariatric surgery, they can provide dietary support before and after the procedure. For patients with mental health issues like eating disorders, dietician support to maintain weight and glycaemic control can be sought. On the dialysis units and inpatient wards, diabetes patients will normally need complex nutritional care such as enteral feeding. The dietician supports people with complex problems such as gastroparesis and pancreatitis.

2.2f Community Health workers

Diabetes programmes can include community health workers in the multidisciplinary teams in a variety of roles. They usually reside in the target community and are given special training to help bring health services and health education as well as health promotion to their local communities. They also mobilise members of the community to adopt behaviours that improve their overall health and living conditions [(120-122). This important resource has can lead to improvements in patients' knowledge and behaviour and in some cases even improve biochemical outcomes in diabetes and promote health (123). The optimal role of peer support of community lay educators is particularly crucial in the low-income underserved populations, particularly for racial and ethnic minority communities (121, 124-126). Their knowledge of the language, culture and the geographic communities can be used to co-ordinate care in partnership with health care systems (127). Their functions include activities such as home visits, health education, and outreach activities for ambulatory care sites (122).

2.2g Interventions

Case management is said to occur when individuals or teams acting in an additional role to the primary care physicians, coordinate the diagnosis, treatment, or routine management of patients, for example arrangement for referrals, follow-up of test results(128)

Health professional educations programmes seek to increase their understanding in the evidence-based recommendations around the management of people with diabetes. Diabetes educational interventions can be delivered in conferences or workshops, distribution of educational materials (written, video, or other), and educational outreach visits.

Financial incentives directed at primary care providers are usually linked the achievements of some process or clinical outcomes.

Clinician reminders can be paper-based or electronic systems and are normally intended to aid the call and recall system for regular reviews of biochemical and clinical markers of poor control of diabetes. In some situations, a decision support in the form of a suggestion of appropriate action, through the use of telemedicine in cases suboptimal control of the illness is couple with the clinician reminders (128).

Another common intervention used is the auditing and feeding back of the performance of primary care professionals on their clinical performance over a specified period.

Sometimes health care professional interventions include the expansion of the roles of other non-physician professionals like nurses or pharmacists to carry out routine clinical checks and prescribing. In some cases, adding another physician or, pharmacist, dietician, podiatrists or diabetes specialist nurse to the primary care teams creates a multi-disciplinary team intervention for the care of people with diabetes.

A review of all these interventions showed that in studies on patients who had poor baseline achievement of quality indicators, there were larger effects on HbA1c, systolic and diastolic blood pressure, and LDL

cholesterol. Team changes, case management, patients' education, were associated with decreases in HbA1c of more than 0·5% in trials with baseline HbA1c greater than 8·0% (128). However, larger reductions in HbA1c are noted irrespective of the baseline HbA1C when interventions were directed at whole system of chronic disease management (128). Interventions involving team changes and case management reduced HbA1c values by 0.33% and more (95% CI, 0.12% to 0.54%; P=.004) and 0.22% more (95% CI, 0.00% to 0.44%; P=.04) (129). However, case management that included revision of roles like independent medication changes was associated with a reduction in HbA1c values of 0.80% (95% CI, 0.51% to 1.10%), compared with only 0.32% (95% CI, 0.14% to 0.49%) for all other interventions (P=.002 for this comparison)(129). In this review however, the remaining interventions in diabetes care produced only small to modest improvements in glycaemic control.

2.3 Background to the systematic review of interventions targeting primary care or community based professionals on glycaemic and cardiovascular risk factor control in people with diabetes

Despite the ready availability of evidence-based diabetes guidelines and continuing professional development programmes, the gap between evidence-based best practice and quality of care is widely recognized (130). Effective strategies (131-134) that promote the adoption of the best practice clinical guidelines for primary care management of diabetes therefore need examination. Continuing medical education is a commonly employed mechanism to improve primary care physicians' clinical practice (133).

Even though several publications and reviews have been published on interventions targeted at primary care professionals to improve outcomes, not many have been published in the field of diabetes. The only systematic review looking at just primary care professionals in the community

settings was published in 2001 (135). It is therefore important to update and critically evaluate the evidence for these interventions in view of the global burden of the disease. If they are found to be ineffective, payers will need to explore the reasons and perhaps invest the limited resources elsewhere. On the other hand, if some interventions are found to be effective, best practice could be shared for implementation in various countries to equip primary care and community based staff with the skill and capacity to deal with this "left shift".

2.4 Aims and objectives

The aim of this systematic review was to evaluate randomised controlled trials on this topic. The studies outcomes evaluated were glycated haemoglobin (HbA1c), systolic blood pressure (SBP) and total and LDL-cholesterol.

2.5 Methods

2.5a Search strategies

A combination of text words and quality improvement Medical Subject Headings related to diabetes and the stated outcomes were used to search the MEDLINE database from inception up to 27th September 2015. All articles related to diabetes care from the Cochrane EPOC database and EMBASE, and scanned bibliographies from key articles were also retrieved. The detailed search terms are shown in Appendix 2.1. The review was registered on PROSPERO (registration number 2014013448) and is within the scope of the Centre for Reviews and Dissemination.

2.5b Study selection

The titles and abstracts of all retrieved articles were screened first. Two reviewers then screened the full text of papers selected. Any study on patients with type 1 or type 2 diabetes in primary care or community settings in which the intervention was either Clinician Education, Clinician

Reminders, Team Changes, Case Management, Electronic Patient Registry, telemedicine, Audit and Feedback was included. Interventions targeting only patients (for example, structured patient education, self-management or patient reminders) were excluded as there is now good evidence on the effectiveness of these interventions on various health outcomes (136-140). These studies were however included if the interventions involved at least one component directed at clinician behaviour or organizational change. Multiple interventions or interventions that involved using the multidisciplinary team members, expansion of their roles or addition of other professionals such as pharmacists and nutritionists to the primary health care teams, were classified as multi-component interventions. Only studies looking at the cardiovascular risk factors HbA1c, SBP and total or LDL-cholesterol were included. Disagreements were resolved by consensus.

2.5c Data extraction

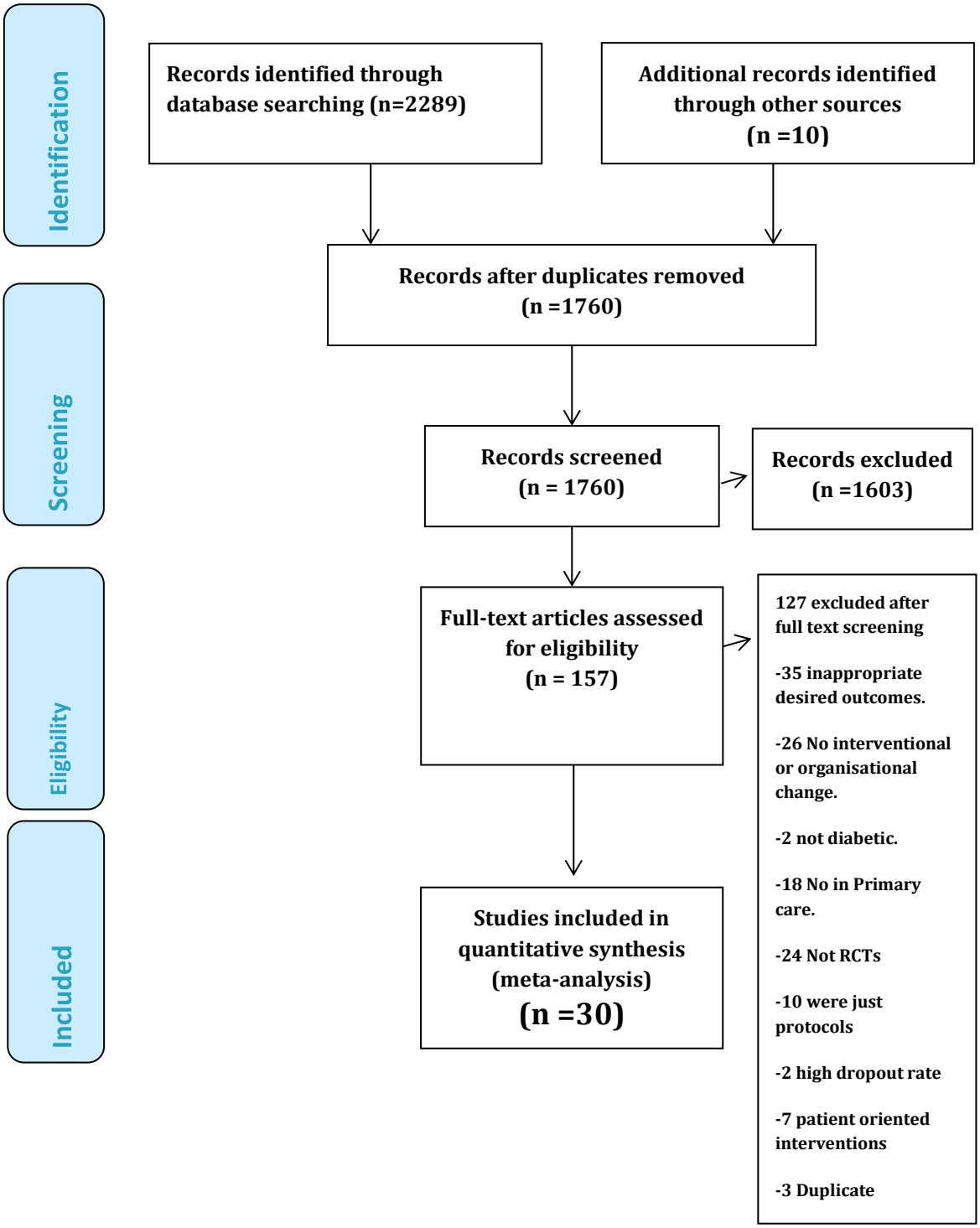
Data extraction was conducted using the Cochrane Group Data collection form for intervention reviews: RCTs only (version 3, April 2014), modified to meet the selection criteria by reducing the risk of bias. The information on the data collection forms included: author, year of publication, participants, location/setting, study design, interventions, outcomes reported and description of any other important sources of bias. The effects of the various interventions on the selected outcomes were considered in relation to the various health care professionals. Study results on HbA1c, cholesterol and blood pressure were classified as 'positive' if they were statistically significant or if the authors reported it so in the absence of inferential statistics. Because of heterogeneity due to large differences in clinical or methodological nature between the studies, it was decided a priori not to pool the data from the studies in a meta-analysis. Instead, a qualitative assessment of the effects was based on the quality of the studies using the Cochrane risk of bias tool. Important sources of bias were considered around the following domains: random sequence generation (selection bias), blinding of outcome assessment

(detection bias), incomplete outcome data (attrition bias) and selective outcome reporting (reporting bias).

2.6 Results

A summary of the literature search results is shown in Fig. 2. The search of the computerized databases identified 2289 citations and another 10 citations after scanning bibliographies for key articles on the subject. After excluding duplicates and studies clearly not related to the objective of our review, 1760 articles were considered for screening and 157 articles were eligible for full-text review. Overall a total of 30 articles met the inclusion criteria for this review

Figure 2: Flow chart for literature search for the systematic review of interventions targeting primary care or community based professionals on the glycaemic and cardiovascular risk factor control in people with diabetes.



2.6a Study characteristics and participants

Tables 1 and 2 show a summary of all the studies included. The studies included 13 randomized controlled trials (141-152)and 17 cluster randomized controlled trials (153-169). In five studies the interventions were carried out on the whole diabetes population; in the remaining 25 studies only people with type 2 diabetes were included. Ten studies were conducted in the USA (142, 144, 146, 150, 154, 157, 159, 160, 164, 166), four in the UK (147, 149, 153, 162), four in Australia, (141, 155, 167, 169), three in Denmark (145, 161, 163), two in the Netherlands (111, 143) and one each in Spain (156), Ireland (158), Belgium (170), American Samoa (143), Taiwan (152) and Israel (165). All the studies were published between 2003 and 2014.

Across all the studies a total of 39,439 patients were randomised and followed up for a mean duration of 16.7 months, ranging from 6 to 72 months. Nine of the studies focused on general practitioners or family practitioners (154-158, 160-162, 170). Of these, 3 studies considered some form of feedback as an intervention; either as electronic feedback (161), feedback benchmarked against other centres (170) and customised simulated patient with feedbacks (159). A further four of the studies targeting general practitioners considered education (154, 155, 158, 162) and the remaining 2 studies included telemedicine interventions (156, 157).

Three studies focused on interventions aimed at practice nurses; one of which was face to face review of glucose levels, blood pressure and lipid profile according to a specified protocol (111)another used telephone reminders (167) and in the third, practice nurses were offered a Self-determination theory – based course including communication training (145). Five studies included interventions aimed at pharmacists (141, 144, 146, 149, 169) who provided enhanced care to patients such counselling, advising, diabetes education, using applied algorithms for managing glucose control and decreasing cardiovascular risk factors, and addressing barriers to care. Only one study examined the role of dietician on diabetes

self-management education (152). Another considered the community health worker's role in providing culturally tailored assistance with self-management and education (151). One study (154) had two intervention arms; a chronic care model intervention which fits our definition of a multi-faceted intervention, and healthcare professional education intervention.

Twelve studies satisfied the definition of multicomponent interventions or targeted multi-disciplinary teams. (142, 143, 147, 148, 150, 153, 154, 158, 163, 165, 166, 171). These multi-faceted interventions ranged from multiple component interventions such as electronic coaching, staff training, algorithm driven care, reminders, alerts and audits, all in different combinations to the targeting of multi-disciplinary teams, such as nurse case managers, diabetes specialist nurses, general practitioners, community pharmacists, community health workers and dieticians.

Table 1: Cluster Randomised Trials

Interventions targeting General Practitioners/Primary Health Physicians

Author	Year	Patient population	Number of patients	Interventions	Outcome	Results
Piatt, G.A (154)	2006	Underserved urban Community- USA	89	Provider-based diabetes education offered to all providers via attendance at one problem based learning session.	HbA1c	0
		USA			SBP	0
					LDL-C	0
Reutens, A.T (155)	2012	Asia-Pacific region	386	Educational meetings, reminders, medical record summary sheets and patient result cards.	HbA1c	0
					SBP	0
					LDL-C	0
Saenz, A (156)	2012	Adult people with diabetes in Madrid-Spain	697	Computer application to help primary care professionals make decisions about the insulin handling of patients with diabetes.	HbA1c	+
					LDL-C	0
Smith SA (157)	2008	Mayo clinic USA	639	Specialist telemedicine intervention for improving diabetes care.	HbA1C	0
					SBP	0
					LDL-C	0
Sperl-Hillen, J.M (159)	2010	Adult patients with diabetes in Minnesota-USA	3417	Customised simulated cases with feedbacks	HbA1c	+
					SBP	0
					LDL-C	0
King AB (160)	2009	People with Diabetes in rural California-USA	135	Algorithm-directed care, midlevel practitioner–administered, electronically coached, treatment.	HbA1c	0
					SBP	0
					LDL-C	0

Guldberg, T.L (161)	2011	Adults with type 2 diabetes in Denmark.	2716	Electronic feedback system on type 2 diabetes population, giving them the option either to use the data during individual diabetes consultations or to gain an overview of the quality of their diabetes care and compare it with the corresponding quality in their colleagues' practices.	HbA1c	0
					LDL-C	0
Foy, R (162)	2011	People with Diabetes, Newcastle-UK	8690	Brief educational messages, typically of less than 30 words, added to the returned results of laboratory tests ordered by clinicians on patients with diabetes.	HbA1c	0
					SBP	0
					LDL-C	0

Systolic Blood Pressure (SBP), Total Cholesterol or LDL Cholesterol (LDL-C) 0= No statistically significant improvement, += statistically significant effect

Multifaceted Interventions

Author	Year	Patient population	Number of	Interventions	Outcome	Results
Belary, S (153)	2008	Adult patients of south Asian origin with type 2 diabetes -UK	1486	Additional time with practice nurse and support from a link worker and diabetes-specialist nurse. Prescribing support from GP and training of nurses.	HbA1c	0
					SBP	0
					LDL-C	0
Olivarius, N. (163)	2008	Adult patients with Diabetes-Denmark	848	Regular follow up and individualised Goal setting supported by prompting of doctors, clinical guidelines, feedback, and continuing medical education.	HbA1c	+
					SBP	+
					LDL-C	+
Smith, SM (158)	2003	Adult patients with diabetes in North Dublin-Ireland	183	Pathway redesign, 3-monthly routine reviews, Professional education, referral	HbA1c	0
					SBP	0
Peterson, KA (164)	2008	Adult patients with type 2 diabetes in Minnesota-USA	7101	Electronic diabetes registry, visit reminders, and patient-specific physician alerts. A site coordinator facilitated pre-visit planning and a monthly review of performance with a local physician champion.	HbA1c	+
					SBP	+
					LDL-C	+
Maislos, M (165)	2003	Adult patients with Diabetes-Israel	82	Interdisciplinary approach	Hba1c	+

O'Connor, PJ (166)	2005	Adult patients with type 2 diabetes. Minnesota USA.	754	Physician, a nurse, and other clinic staff interested in diabetes. Training of staff.	Hba1c	0
					SBP	0
					LDL-C	0
Piatt, GA (154)	2006	Underserved urban Community-USA	89	Chronic Care Model	HbA1c	+
					LDL-C	+

Systolic Blood Pressure (SBP), Total Cholesterol or LDL Cholesterol (LDL-C) 0= No statistically significant improvement, += statistically significant effect

Nurse Interventions

Author	Year	Patient population	Number of patients	Interventions	Outcome	Results
Blackberry, I. (167)	2013	Adult patients with type 2 Diabetes-Australia	473	Use of nurse for telephone coaching	HbA1c	0
					SBP	0
					LDL-C	0
Juul, L. (168)	2014	Adult patients with type 2 diabetes in Denmark	4034	Intervention practices were offered a 16-hour Self-determination theory – based course including communication training for general practice nurses delivered over 10 months.	HbA1c	0
					LDL-C	0

Systolic Blood Pressure (SBP), Total Cholesterol or LDL Cholesterol (LDL-C) 0= No statistically significant improvement, += statistically significant effect

Pharmacist Interventions

Author	Year	Patient population	Number of patients	Interventions	Outcome	Results
Krais, I (169)	2007	Adult patients with type 2 diabetes Australia	289	Pharmacists delivered a diabetes service to patients. They checked adherence, interactions, hypoglycaemia and lifestyle.	HbA1c	+
					SBP	0
					LDL-C	0

Systolic Blood Pressure (SBP), Total Cholesterol or LDL Cholesterol (LDL-C) 0= No statistically significant improvement, += statistically significant effect

Table 2: Randomised Control Trials:

Multi-faceted intervention

Author	Year	Population	Number of patients	Interventions	Outcome	Results
Rothman, RL (147)	2005	Adult Patients with diabetes. USA	217	Pharmacists and care coordinator who provided diabetes education, algorithms for managing glucose and cardiovascular risk factors, and addressed barriers to care.	HbA1c	+
					SBP	+
					LDL-C	0
De Pue, JD (143)	2013	Participants with type 2 diabetes from a community health centre in American Samoa.	268	Nurse-CHW team intervention.	HbA1c	+
				Staff was hired early to help conduct formative focus groups and to develop the intervention	SBP	0
Hiss, RG (148)		Adult patients with type 2 diabetes. Detroit	197	Nurse care manager with primary care physicians in patients with type 2 diabetes	HbA1c	+
					SBP	0
					LDL-C	+
Cohen, LB (142)	2011	Adult males with type 2 diabetes.	99	Pharmacists, dieticians, nurses, and physical therapists provided educational and behavioural interventions	HbA1C	+
					SBP	+
					LDL-C	0
Shea, S (150)	2009	Adult patients with diabetes in New York-USA	1665	Telemedicine, consisting of a web-enabled computer with modem connection to an existing telephone line	HbA1c	+
					SBP	+
					LDC-L	+

Systolic Blood Pressure (SBP), Total Cholesterol or LDL Cholesterol (LDL-C) 0= No statistically significant improvement, += statistically significant effect, Community Health Worker (CHW)

Pharmacists Interventions

Author	Year	Patient population	Number of patients	Interventions	Outcome	Results
Ali, M. (149)	2012	Adult patients with type2 diabetes in Bedfordshire UK	46	Use of pharmacist to provide education and counselling.	HbA1c	+
					SBP	+
					LDL-C	0
Clifford, RM (141)	2005	Adults with type 2 diabetes from the Fremantle Diabetes Study - Australia	180	Use of pharmacist for counselling and telephone coaching.	HbA1c	+
					SBP	+
Odegard, P.S (146)	2005	Adult patients with type 2 diabetes. USA.	77	Pharmacists made care plans and did weekly visits or telephone calls to facilitate diabetes management and adherence.	HbA1c	0
Doucette, WR. (144)	2009	Adults with type 2 diabetes who had completed at least 2 diabetes education sessions at a local diabetes education centre-USA	78	Discussing medications, clinical goals, and self-care activities with patients and recommending medication changes to physicians.	HbA1c	0
					SBP	0
					LDL-C	0

Systolic Blood Pressure (SBP), Total Cholesterol or LDL Cholesterol (LDL-C) 0= No statistically significant improvement, += statistically significant effect

Community Health Worker Interventions

Author	Year	Patient population	Number of patients	Interventions	Outcome	Results
Spencer, MS (151)	2011	African American and Latino adult participants recruited from 2 health systems in Detroit, Michigan-USA.	183	Culturally tailored CHW assistance with self-management and education.	HbA1c	+
					SBP	0
					LDL-C	0

Systolic Blood Pressure (SBP), Total Cholesterol or LDL Cholesterol (LDL-C) 0= No statistically significant improvement, += statistically significant effect, Community Health Worker (CHW).

Dietician Interventions

Author	Year	Patient population	Number of patients	Interventions	Outcome	Results
Huang, MC (152)	2010	type 2 diabetes patients in primary care clinics in Taiwan	154	Dietician–led intervention on diabetic self-management education every 3 months over 12 months.	HbA1C	0
					SBP	+

Systolic Blood Pressure (SBP), Total Cholesterol or LDL Cholesterol (LDL-C) 0= No statistically significant improvement, += statistically significant effect

Interventions targeting nurses

Author	Year	Patient population	Number of patients	Interventions	Outcome	Results
Houwelling, ST (111)	2010	Patients with type 2 diabetes from north-east region of The Netherlands	230	Glucose levels, blood pressure and lipid profile according to a specified protocol	HbA1c	0
					SBP	0
					LDL-C	0

Systolic Blood Pressure (SBP), Total Cholesterol or LDL Cholesterol (LDL-C) 0= No statistically significant improvement, += statistically significant effect

Interventions targeting General Practitioners/Primary Health Physicians

Author	Year	Patient population	Number of patients	Interventions	Outcome	Results
Hermans, M (170)	2011	Adult patients with type 2 diabetes in six European countries.	3996	Feedback benchmarked against other centres	HbA1c	0
					SBP	+
					LDL-C	0

Systolic Blood Pressure (SBP), Total Cholesterol or LDL Cholesterol (LDL-C) 0= No statistically significant improvement effect, += statistically significance

2.6b Study quality

Each of the studies had identifiable methodological limitations (Table 3). Even though all the studies included were either cluster randomised trials or randomised control trials, in 20 of them the description of allocation concealment was either not done or was not reported (141-144, 146, 148, 150, 151, 154-156, 158-160, 163, 165-167, 169, 171). These 20 studies did not necessarily consistently show a positive result. Some of them showed significant improvements from baseline while others did not. Since blinding to intervention of the participants in the intervention groups is not possible, the trials were appraised based on whether researchers evaluating the outcomes were blinded to the intervention to minimize detection bias. Only four of the trials adequately described a blinded evaluation process (150, 157, 158, 167). Again, the presence of adequate description of blinding at the evaluation process did not necessarily predict an improvement of the outcomes from baseline as only one study out the four showed a reduction in HbA1c and SBP from baseline (150). There was a wide range in the number of subjects in each study (Table 1); lowest number being 46 (149) and largest 8690 (162). Smaller studies are usually likely to be underpowered to detect statistically significant effects. However, in our review there was no suggestion that studies with relatively large number of subjects necessarily produced improvements in the risk factors any more than those with small number of subjects. Out of the six studies with less than hundred subjects (142, 144, 149, 154, 165), four (66.7%) had at least one statistically significant reduction from baseline in the risk factors considered (142, 149, 154, 165). Out of the sixteen studies with subjects from 100 to 1000(111, 141, 143, 147, 148, 151, 152, 155-158, 160, 163, 166, 167, 169) nine (56.3%) of them showed at least one statistically significant reduction in risk factor control from baseline (141, 143, 147, 148, 151, 152, 156, 163, 169). In addition, out of the eight studies with more than one thousand subjects, (150, 153, 159, 161, 162, 164, 168, 170), four (50%) had at least one statistically significant reduction in the outcomes from baseline (150, 159, 164, 170).

Study	Blinding at evaluation	Standardised reporting of outcomes.	Allocation concealment described	Duration (Months)
De Pue, JD	Not reported	Yes	unclear	12
Doucette ,W.R.	Not reported	Not reported	unclear	12
Foy, R	Not reported	No reported	Yes	34
Guldberg, T.L.	Not reported	Not reported	yes	15
Hermans, M	Not reported	No	yes	12
Hiss, RG	Not reported	Yes	unclear	6
Houwelling, ST	Not reported	Yes	yes	14
Huang, MC	Not reported	Yes	yes	12
Cohen LB	Not reported	Not reported	unclear	6
Clifford, RM	Not reported	Not reported	unclear	12
Blackberry, I	YES	Not reported	yes	18
Ali,M.	Not reported	Yes	yes	12
King, AB	Not reported	not reported	unclear	12
Kras I	Not reported	not reported	unclear	6
O'Connor, PJ	Not reported	No	unclear	18
Maislos, M	Not reported	not reported	unclear	6
Odegard, P.S	Not reported	Yes	unclear	6
Peterson, KA	Not reported	Yes	unclear	12
Piatt, G.A.	Not reported	Yes	unclear	12
Piatt, G.A.	Not reported	Yes	unclear	12
Reutens, A.T	Not reported	Yes	No	6
Rothman, RL	Not reported	Yes	yes	12
Saenz, A	Not reported	Not reported	unclear	18
Shea, S	YES	Yes	unclear	60
Smith S	YES	Yes	unclear	18
Smith, SA	YES	Not reported	yes	21
Spencer, M.S	Not reported	Not reported	unclear	6
Sperl-Hillen, J.M.	Not reported	Not reported	unclear	12
Belary, S.	Not reported	Not reported	No	24
Olivarius, N	Not reported	Yes	unclear	72
Juul, L	Not reported	Not reported	yes	18

Table 3: Study quality properties of trial

2.6c Outcome effects based on the type of intervention

The detailed findings from each study were examined according to the primary care professionals targeted, the intervention methods used and the type of outcomes measured. A summary of these findings is shown in Tables 1 and 2.

Educational interventions even when they were coupled with clinician reminders did not seem to have a positive impact on the HbA1c, systolic blood pressure and lipid profiles (145, 154, 155, 158, 162).

The use of telemedicine showed mixed results; when used with a nurse case-manager, there were improvements in HbA1c, LDL-cholesterol and systolic blood pressure levels compared with controls (150). However, when this intervention was directed at family practitioners with specialist advice and evidence-based messages regarding medication management for cardiovascular risk, there was no improvement in HbA1c, systolic blood pressure and LDL-cholesterol (157).

Clinician reminders in the form of a computer application to help primary care professionals make decisions about the glucose lowering therapy in diabetes patients produced significant improvements in HbA1c levels when compared to controls. (156).However algorithm-directed care and electronically coached treatment did not lead to improvements in HbA1c, systolic blood pressure or LDL-cholesterol (160)

The use of feedback to primary care professionals had a significant impact on reduction in HbA1c when it was given after a customised simulated patient interaction (159)but not when it was given after performance was benchmarked against other centres (170), even though systolic blood pressure improved. No improvement in HbA1c or cholesterol was noted compared to control when feedback was given electronically (161)

2.6d Effects based on primary care professional groups

Targeting general or family physicians was largely ineffective in improving the cardiovascular risk factors considered (154, 155, 157, 160-162, 170), except when using a computer application on insulin handling of type 2

diabetes or customised simulated cases with feedbacks (156, 159). Similarly, interventions targeting nurses did not improve outcomes compared to standard care (111, 145, 167).

The use of pharmacists produced mixed results in terms of improving the outcomes in the intervention groups. HbA1c improvement was not achieved in the intervention group by pharmacists discussing medications, clinical goals, and self-care activities with patients and recommending medication changes to physicians when appropriate (144). The use of clinical pharmacists to establish and initiate a diabetes care plan followed by weekly visits or telephone calls to facilitate diabetes management and adherence also did not lead to improvements in HbA1c control (146). However, the use of clinical pharmacists for counselling, patient education and telephone coaching as well as management and regular reviews to support self-monitoring of blood glucose, adherence support, and reminders of checks for diabetes complications led to improvements in HbA1c (141, 149, 169). The use of a clinical pharmacist to provide education and counselling to patients also showed mixed results; improvements in systolic blood pressure was noted when compared to controls in 2 studies(141, 149) although 2 other studies showed no improvements in blood pressure (144, 169). In terms of improvement in cholesterol from baseline, when compared to controls, pharmacist interventions have largely not been successful (144, 149, 169).

The use of a registered dietician to provide on-site diabetic self-management education every 3 months over 12 months failed to lead to improvements in HbA1c(152).

Using community health workers to provide a culturally tailored assistance with self-management and education led to reductions in HbA1C but not systolic blood pressure or lipids (143, 151).

2.6e Multi-component interventions and Multi-disciplinary organisational changes

Eight of the twelve studies that considered multi-disciplinary organisational changes mixed with various interventions reported

improvements in HbA1c (142, 143, 147, 148, 154, 163-165). These included clinically significant reductions of 1.8% (172), 0.8% (147), 0.6% (154), and 0.53% (143) from baseline. The improvements in systolic blood pressure from baseline when compared to control groups were however inconclusive; four studies reporting improvements in systolic blood pressure (142, 147, 163, 171)and another three failing to show any improvements (143, 148, 154). Similarly, improvements in lipids were also inconclusive; five studies (142, 147, 153, 163, 166)showing no effect and another three showing an improvement (148, 154, 164).

2.7 Discussion

Multi-component interventions generally appear to lead to statistically and clinically significant improvements in HbA1c in people with diabetes as opposed to mono-component interventions. This finding was typified by the one study that compared a multi-faceted intervention (Chronic Care Model) and professional education to standard care (154). Both the professional education and standard care interventions did not show improvements in HbA1c; however, the multifaceted interventions showed a marked decline in HbA1c. Practitioner education even when combined with reminders did not demonstrate a significant improvement in the levels of HbA1c, blood pressure and LDL-cholesterol from baseline. This finding is consistent with earlier publications on this subject (173). The lack of efficacy of general practitioner education has been attributed to the fact that the generalists tend to consider factors such as the diabetes management costs, insufficient time, lack of financial incentives and patient refusal of insulin as barriers to effective control of diabetes (155).

Similarly, the use of other mono-component interventions like feedback, clinical reminders, and telemedicine alone have not consistently led to improvements in the HbA1c, SBP and total or LDL-cholesterol possibly because they are delivered in isolation without much organisational support to enhance patient-provider interactions. Studies in which these mono-component interventions have yielded some improvements in cardiovascular risk factors had other components of the multi-faceted

interventions like the use of case managers trained in diabetes management (150). Even the Quality and Outcomes Framework in the UK which is one of the world's largest pay-for-performance schemes, rewarding general practitioners for the quality of care they provide, only had limited impact on improving health outcomes (174, 175). The coupling of customised patient specific feedback bench-marked against the performance of other clinicians and financial incentives led to improvements in outcomes (159). The organisation of care as a whole delivery system design with the revision of roles of primary care professionals, aided with decision support, and information technology and other community linkages should be done in a structured manner in order to improve outcomes. Improving the cooperation between various primary care professionals is likely to be effective if each team member works to achieve improvements in similar outcomes. Previous studies have reported that interactive education, audit and feedback, reminders, academic detailing and other outreach visits were the most effective in changing physician care and patient outcomes (131, 176, 177), whereas simple distribution of clinical practice guidelines and use of opinion leaders were less effective (176).

Since consistency in association of improved cardiovascular risks and the types of primary care professionals used at the forefront of diabetes care was found, the use of practice nurses, pharmacists, dieticians or general practitioners could all be considered in various settings provided the organisation and delivery of diabetes care is done in structured manner. In areas where there are more nurses than other primary care professionals it will be better to use them as case managers aided by telemedicine (150). When community pharmacists have to be used, it is better to combine their educational updates with regular patient reviews counselling of patients on self-monitoring of blood glucose, adherence support, and reminders of checks for diabetes complications (141, 149, 169). Interventions targeting patients have not been considered in this review, as there is ample evidence on the effectiveness of these interventions on various health

outcomes. It is therefore reasonable to consider advocating patient targeted interventions in combination with the multi-faceted health care professional interventions in order to maximise improvements in outcomes.

2.7a Strengths and Limitations

This is the first attempt to consider both primary care and community-based interventions in a systematic review on diabetes patients. A large number of studies from multiple databases were identified. The quality of the studies included was appraised in a systematic manner.

Several factors may affect the study outcomes thus limiting applicability of the findings in clinical practice. Firstly, the rigor and quality of the various interventions are questionable. Like most complex interventions, the chances of practitioners consulting with colleagues and networking and thus increasing the risk of contamination in the standard care groups can occur.

Secondly, even though an attempt was made to get a homogenous number of studies for this review with clear inclusion and exclusion criteria in terms of the study types and outcomes, there were still wide variations in the population of patients and target health care professions. Even the interventions studied varied widely in terms of duration, delivery methods and care systems. This could affect the generalisability of the review.

Thirdly the review was limited by the quality of the studies included. Inadequate information about concealment of allocation, lack of standardised reporting of the outcomes, inadequate information on blinding at outcome evaluation and wide differences in length of follow ups are markers of poor qualities in the studies.

Also, it is possible that if the patient targeted interventions were considered in this review, the generally negative results seen in the mono-component health care professional interventions would have been positive. This is because the lack of statistically significant improvements in the risk factors could be as a result of lack of engagement from patients.

Lastly, the literature search did not identify any unpublished studies, thus raising the possibility of publication bias in some of the studies that reported improvements in outcomes.

2.7b Implication for practice

There was a lack of good quality evidence of cardiovascular risk factor improvement when mono-component interventions were targeted at primary care or community based professionals, irrespective of their roles. When planning diabetes implementation programmes in primary care settings, it is therefore important to avoid using single stand-alone methods like healthcare professional education, telemedicine, clinician reminders and audits. This approach can be expensive to deliver and may not yield the desired outcomes. Instead a collaborative approach, involving the use of multifaceted interventions targeting various professionals in a structured fashion should be considered in all cases. This systematic review shows that a complex structure will yield improvements in outcomes when customised to the needs of local populations. For example, in the primary care setting the use of pharmacists in areas where this resource abounds can yield improvements in diabetes intermediate outcomes provided this is done in a structured collaborative manner.

2.8 Conclusion

This systematic review on interventions targeting primary care or community based professionals on diabetes and other cardiovascular risk factor control has not shown consistency for single stranded interventions on the healthcare professionals. Multi-disciplinary team collaborations mixed with various interventions reported some consistency in improvements in HbA1c. The impact of this on systolic blood pressure reduction and cholesterol reduction has however not been consistently positive. As alluded to in the chapter one, the extent of this HbA1c reduction in people with type 2 diabetes has been of some considerable

debate over the past couple decades. Also, despite the major reductions in cardiovascular outcomes seen in patients receiving tight control of blood pressure compared with those receiving conventional control if the base line blood pressure was high (79, 80) there is still some doubt on the benefits of tight control of systolic BP among patients with diabetes and coronary artery (81). An increased mortality in intensively treated newly diagnosed people with diabetes has been noted and therefore caution in lowering blood pressure too aggressively is recommended in these patients (82). Even in the case of cholesterol reduction where there is overwhelming evidence on the reduction in CVD events (major coronary events, coronary revascularisation and ischaemic stroke) (83) among patients at increased diabetes risk, (those with baseline evidence of impaired fasting glucose, metabolic syndrome, severe obesity, and elevated HbA1c) the risk of development of diabetes among statin-treated patients appears to be raised. However, the overall cardiovascular and mortality benefits of statin therapy exceed the risk for developing diabetes (84). Nevertheless, this finding introduces another complexity in cardiovascular risk management in diabetes in the primary care setting. In the next chapter, the impact intensive glycaemic control alone or as part of a multifactorial cardiovascular risk reduction on cardiovascular and mortality outcomes will be considered in more detail

Chapter 3

Effects of glucose lowering and multifactorial interventions on cardiovascular and mortality outcomes - A systematic review and meta-analysis of randomised control trials.

3.1 Synopsis of chapter 3

The effect of intensive glycaemic control alone or as part of a multifactorial intervention on cardiovascular and mortality outcomes is not fully understood. Also, the interaction of duration of diabetes on cardiovascular and mortality outcomes is unclear.

The aim of this chapter was to quantify the effect of intensive treatment (intensive glucose lowering either alone or as part of a multifactorial intervention) on mortality and vascular outcomes. Also, the association between the treatment effect and the trial-level characteristics was investigated.

Searches on Medline, Embase and the Cochrane Central Register of Controlled Trials without language restrictions from inception to May 13th 2015 were conducted. Randomised controlled trials that evaluated intensive treatment in adult patients with type 2 diabetes were included. Using random effects meta-analysis, rates were pooled across studies and study-level covariate associations were investigated using Bayesian meta-regression.

A total of 19 RCTs (n=84,460) were included. Intensive treatment reduced the risk of non-fatal MI (RR 0.90, 95% CI 0.83 to 0.96) while multi-factorial interventions alone reduced non-fatal strokes (RR 0.53, 95% CI 0.32 to 0.0.87). The effect of intensive treatment on cardiovascular and mortality outcomes was not associated with age, duration of diabetes and gender. Intensive treatment reduced CVD mortality in populations where the average 10-year CVD risk is greater than 6.3%.

In conclusion, part from non-fatal MIs, intensive treatment did not change the risk of cardiovascular and mortality outcomes. It is likely to be beneficial in populations with a higher baseline incidence of CV mortality. Multi-factorial interventions resulted in significant reductions in non-fatal strokes.

3.2 *Background to meta-analysis of randomised control trials Effects of glucose lowering and multifactorial interventions on cardiovascular and mortality outcomes*

Following the results of recent major trials; Action to Control Cardiovascular Risk in Diabetes (ACCORD) (56), Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) (57) and Veterans Affairs Diabetes Trial (VADT) (55) and recent meta-analyses (178, 179) intensive glucose-lowering therapy has been shown not to decrease risks for major CV events or mortality in patients with long duration of type 2 diabetes. Various national and international guidelines have responded to these results by suggesting that less intensive glycaemic control is appropriate for certain patient groups including those with history of advanced micro-vascular and macro-vascular complications, long duration of diabetes and severe hypoglycaemic events (180). However, another meta-analysis conducted by the investigators of the four main trials (UKPDS, ACCORD, ADVANCE and VADT) showed a 9% reduced cardiovascular risk, mainly driven by a 15% reduction in risk of myocardial infarction (181). A recent meta-analysis suggests a lack of uniformity of the effect of intensive therapy across the world with a possible potential harm (mortality) specific to North American trials but not trials from other regions of the world (182). In another recent meta-analysis, even though an increase in the risk of heart failure by the various glucose lowering agents or strategies was shown, there was no significant effect on cardiovascular and all-cause mortality, stroke, unstable angina, or coronary revascularisation (183).

The results of ACCORD, ADVANCE, and VADT do not apply to patients with newly diagnosed type 2 diabetes as evidence suggests such patients benefit from intensive glucose-lowering therapy (184). Multifactorial pharmacological interventions including blood pressure control and lipid lowering with glycaemic control in these patients have demonstrated a significant reduction on vascular complications, cardiovascular and all-cause mortality (185). To date, there are no meta-analyses comparing the effects of intensive multi-factorial interventions with intensive glycaemic control on CV and mortality outcomes in patients with type 2 diabetes. The duration of diabetes is particularly of interest as it has been shown in recent analysis to be one of the two primary biological drivers linked to HbA1c in addition to age at diagnosis (186). In another report examining predictors of the effect of intensive glycaemic control on macro-vascular complications, people on intensive therapy showed a reduction in CV events if the duration of diabetes was 15 years or less but these events increased in those with longer duration (187). Despite these findings, a further exploration of this complex relationship between the duration of diabetes and impact of intensive glucose lowering or multifactorial interventions on macro-vascular complications, CV and all-cause mortalities is still required. This is because, people with long duration of diabetes are also likely to have other multi-morbidities and also be on more complex glucose lowering therapies that are less likely to be received. These could confound the impact of duration of diabetes on the outcomes. A subgroup analysis of the aforementioned meta-analysis suggested the possibility of a better effect for major cardiovascular events in participants without macrovascular disease compared to those with macrovascular disease (181). Therefore, it is also important to evaluate the effects of baseline population CV risk on these outcomes.

The aim of this systematic review and meta-analysis of randomised controlled trials was to determine the effects of both glycaemic control and multifactorial interventions on vascular and mortality outcomes in patients with type 2 diabetes. A further aim was to explore the association

between treatment effect and study-level characteristics such as mean duration of diabetes since diagnosis, mean age, proportion of male patients across trials and the control group event rate which we used as a proxy for the baseline population risk of non-fatal MIs, non-fatal strokes, CV mortality and all-cause mortality.

3.3 Methods

3.3a Data sources and searches

Searches on Medline, Embase and the Cochrane Central Register of Controlled Trials (Central) without language restrictions were conducted from their inception to 14th May 2015. Articles searched included those not published yet, but in the process of publication and non-indexed citations. We used combination of subject headings: 'type 2 diabetes', 'diabetes mellitus', 'cardiovascular disease', 'coronary heart disease', 'stroke', 'peripheral vascular disease', 'hypoglycaemic agents', 'glucose control', 'glycaemic control', 'tight control', 'multifactorial' and 'risk factor lowering'. We also performed hand searches of the reference citations of identified reviews and original articles selected for the full text retrieval. The review was registered on PROSPERO (registration number 42014013860) and is within the scope of the Centre for Reviews and Dissemination.

3.3b Data extraction and quality assessment

Only randomised controlled trials in adults (≥18 years old) with type 2 diabetes of any duration (mean duration had to be specified) were included. The included trials had to be comparing intensive glucose lowering alone (including the pleotropic effects of the drugs being tested) or as part of a multifactorial intervention, to control groups (standard care, placebo, or glycaemic control of reduced intensity). Intensive glycaemic control was defined either by a specified HbA1c target (achieved through pharmacotherapy) or by purposeful treatment intensification algorithms.

Multifactorial interventions included studies on glycaemic control together with blood pressure control and lipid lowering. All studies had to have outcome data on at least one of 4 outcomes considered in the analysis. The following variables were extracted into a pre-formatted spread sheet: Author, name of study, year of publication, linked paper (the same papers were reported in different journals), journal, intensive glucose lowering or multifactorial intervention, cardiovascular outcomes, duration of type 2 diabetes, duration of follow up, randomisation, allocation concealment, double blinding, flow of patients, glycaemic target, mean age, percentage male, number randomised, number followed up and all-cause mortality. Of the Major Adverse Cardiovascular Events (MACE), we included only non-fatal MI, non-fatal stroke and CV mortality. Mortality and cardiovascular morbidity definitions were taken as described in the various articles. Generally, mortality events were classified as cardiovascular if the deaths occurred within 30 days after an MI or a stroke or invasive cardiovascular procedures. Data extraction and quality assessment based on the pre-defined criteria were carried out independently and in duplicate by two investigators. The Cochrane Collaboration's tool for assessing risk of bias was used for quality assessment. Two reviewers (SS and FA) working independently screened the titles and abstracts of all initially identified studies according to the selection criteria. Full texts were retrieved from studies that satisfied all selection criteria. The discrepancies were resolved by consensus and in consultation with a third reviewer (KK). The methodological quality of studies was assessed according to the Jadad score (188); a score of more than 3 given to double blind randomised placebo controlled trials, and 3 or less given to open randomised trials.

3.3c Statistical analysis

The number randomised, the reported number of events and the follow-up period in control and treatment arms of each study was used to calculate separate rate ratios (RR) for non-fatal MI, non-fatal stroke, CV mortality

and all-cause mortality. If the unadjusted hazard ratio (HR) or relative risk was available but the actual summary count data were not, this was used. Throughout the analysis, it was assumed that relative risks and HRs were equivalent and the logarithmic transformed rate ratios across studies were pooled using random effects meta-analysis to allow for heterogeneity between studies. One of the trials (ADDITION study) included in the analysis is a cluster-randomised trial. The effect of clustering in this trial was accounted for by inflating the variance of the treatment size from this trial by 1.09, the design effect reported for this study (189).

A subgroup analysis investigating whether or not the rate ratios in trials of multi-factorial intervention differed from rate ratios in trials of intensive glycaemic control alone was conducted.

An investigation was done on the association between the pooled treatment effect (i.e. the effect of intensive glucose lowering and multifactorial interventions on CV and mortality outcomes) and mean duration of type 2diabetes, mean age and % male using random effects meta-regression. It is known that Diabetes screening results in cases being identified on average 3.3 years earlier than when screening is not done prior to diagnosis (190). Therefore, duration was set at -3.3 years for studies of screen detected diabetes and 0 for newly diagnosed. For all the other studies, the stated mean duration of diabetes at recruitment was used. The association between the treatment effect and the 'control group risk' or 'baseline risk' (which was defined as the incidence rate (per 1000 person-years) in the control arm of each study was investigated. Adjusting for the control group risk accounted for: i) the fact that the control treatment varied across studies as stated above (i.e. control treatment could be standard care, placebo, or glycaemic control of reduced intensity) and ii) any known or unknown patient level characteristics/risk factors/variables that collectively determine disease severity and therefore a patient's response to treatment (191). Heterogeneity of outcomes was assessed and quantified using the I-squared statistic and the between-study variance parameter, tau-squared (τ^2). Publication bias was

assessed by visual inspection of funnel plots for evidence of asymmetry and the Egger's test (192). The random effects meta-analysis models were fitted in Stata (version 13.0, Texas, US). The meta-regression analyses were conducted in WinBUGS (193) which allows for degree of flexibility in incorporating the measurement error in the baseline risk covariate. Minimally informative prior distributions were specified for the WinBUGS models. The statistical analysis was conducted by FA.

3.4 Results

3.4a Study selection and characteristics

The selection process is outlined in the flow chart in Figure 3. Our search on Medline, Embase and the Cochrane Central Register of Controlled Trials (Central) and manual reviews of articles cited in the identified and related publications retrieved 5712 relevant articles. Of these, 5619 were excluded because they did not fulfil our criteria for inclusion. The full text of the remaining 93 articles were obtained and reviewed. Of these, 74 were excluded after the full text screening. Of these 74 articles, two did not consider pharmacotherapy or the multifactorial intervention referred to just included lifestyle and behavioural change. Another ten did not set out to consider treatment intensification or multi-factorial intervention, thirty-four articles had no CV or mortality outcomes, ten reported only micro-vascular complications, 12 were linked articles and six articles were duplicated (Figure 3).

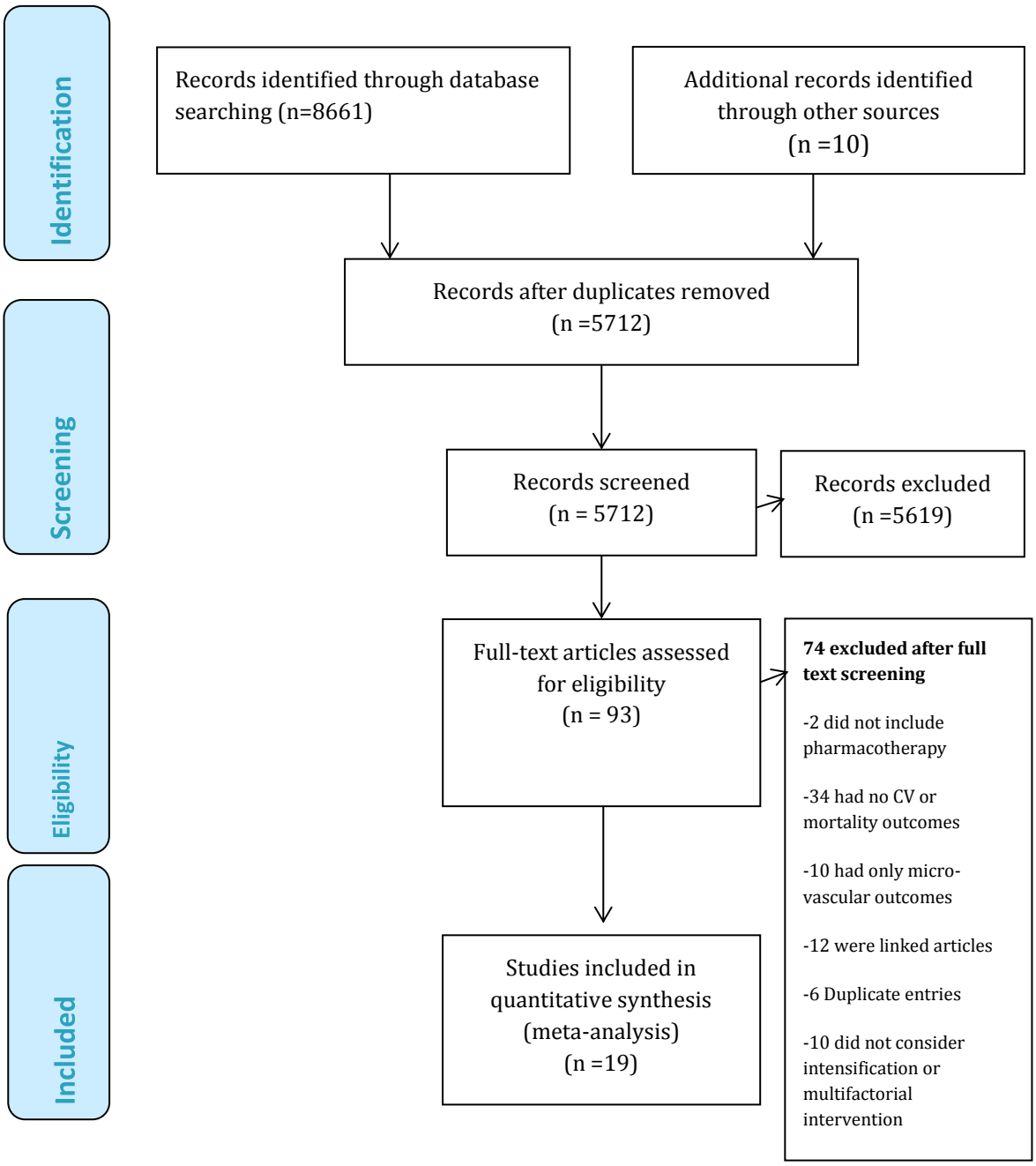


Figure 3: Flow chart indicating the identification and selection of trials for inclusion in the meta-analysis

Of the 19 studies (n=84,460) included, 16 examined non-fatal MI (n=79,595), 14 non-fatal stroke (n=78,568), 18 examined cardiovascular mortality (n=83,938) and 18 all-cause mortality (n=84,266). As with previous meta-analysis on this subject (178), the UGDP studies, using tolbutamide (194) and phenformin (195) were combined and UKPDS 33 (184) and 34 (196) studies were also combined. The latter UGDP (197) looking at the effect of intensive versus standard insulin therapy in people with diabetes was analysed separately. Only 4 studies, STENO-2 (185), Anglo-Danish-Dutch study of Intensive Treatment In people with screen detected diabetes in primary care (ADDITION) (189), PROFIT-J (198) and Rachmani et al (199) were included in the studies examining multifactorial interventions. The rest of the studies assessed only intensive glycaemic control. The selected trials are summarised in Table 4.

Table 4: Summary Characteristics of included studies

Study name / name of first author	Publication Year	Jadad score	Standard Arm						Intensive arm					
			Glycaemic target	Intervention	Mean age (years)	% male	Mean duration of T2DM (years)	Mean / median duration of follow up (years)	Intervention	Glycaemic target	Mean age (years)	% male	Mean duration of T2DM (years)	Mean / median duration of follow-up (years)
UGDP	1976	4		Standard	52	29	0	10	Intensive		52	29	10	0
UGDP	1982	3		Standard	52	29	0	10	Intensive		52	29	10	0
VACS	1997	2		Standard	60	100	7.8	2.3	Intensive		60	100	2.3	7.8
UKPDS	1998	3	FPG<15	Standard	53.4	61.9	0	10.1	Intensive	FPG<6	53.2	59.4	10.1	0
PROactive	2004	5		Standard	61.6	65.6	9.6	2.8	Pioglitazone		61.9	66.6	2.8	9.4
Rachmani*	2005		9.6	Standard	56.8	47.1	6.3	7.1	Intensive	9.5	57.4	50.7	7.1	6.2
Dargie*	2007	5		Placebo	63.9	79.1	4	1	Intensive		64.3	84.3	1	4.5
ADVANCE	2008	3		Standard	66	47.7	8	5	Intensive	hBa1C<6.5%	66	47.4	5	7.9
ACCORD	2008	3	7.0-7.9%	Standard	62.2	61.6	10	3.5	Intensive	<6%	62.2	61.3	3.5	10
STENO-2	2008	3		Standard	55.2	70	6	13.3	Intensive		54.9	75	13.3	5.5
VADT	2009	3		Standard	60.3	97.1	11.7	5.6	Intensive	1.5% reduction in HbA1C	60.5	97.1	5.6	11.8
HOME	2009	4		Insulin / placebo	59	50	12	4.3	Insulin / metformin	64	41.3	4.3	14	0
RECORD	2009	2		Metformin / Sulfonylurea	58.5	51.8	7.1	5.5	Rosiglitazone	58.4	51.4	5.5	7	7.8
ADDITION	2011	4	HbA1c <7%	Placebo	60.2	57.3	-1	5.3	Intensive		60.3	58.5	5.3	-1
ORIGIN	2012	3		Standard	63.5	63.3	5.3	6.2	Glargine	FBS < 5.3	63.6	66.8	6.2	5.5
EXAMINE	2013	5	8	Standard	61	68	7.3	1.5	Intensive	8	61	67.7	1.5	7.1
SAVOR-TIMI 53	2013	5	8	Standard	65	67.3	10.3	2.1	Intensive	8	65.1	66.6	2.1	10.3
AleCardio	2013	5	7.8	Standard	61	72.5	8.6	2	Intensive	7.8	61	73.1	2	8.6
PROFIT-J	2014	2	7.43	Standard	68.9	66	11.5	1.85	Pioglitazone	7.43	69	63.2	1.85	11.1

3.4b Results of meta-analysis

The meta-analysis (Table 6 and Figure 4) indicated that compared to standard care, intensive glucose lowering and multi-factorial intervention reduced the risk of non-fatal MI (RR 0.89, 95% CI 0.83 to 0.96) but not non-fatal stroke (RR 0.96, 95% CI 0.86 to 1.07), CV mortality (RR 1.01, 95% CI 0.91 to 1.13) or all-cause mortality (RR 1.01, 95% CI 0.94 to 1.08). Results of subgroup analysis investigating whether or not the rate ratios in trials of multi-factorial intervention differed from rate ratios in trials of intensive glycaemic control alone are presented in Table 6 and as forest plots in Figures 5 to 8. Compared to standard care, multi-factorial interventions reduced non-fatal strokes (RR 0.53, 95% CI 0.32 to 0.87) but not non-fatal MI (RR 0.66, 95% CI 0.38 to 1.03), CV mortality (RR 0.72, 95% CI 0.46 to 1.14) or all-cause mortality (RR 0.82, 95% CI 0.64 to 1.05). When the analysis was restricted to trials of intensive glycaemic control alone, there was a smaller but significant reduction in non-fatal MI (RR 0.90, 95% CI 0.84 to 0.97) but there was no reduction in non-fatal stroke (RR 0.99, 95% CI 0.89 to 1.10), CV mortality (RR 1.02, 95% CI 0.92 to 1.13) and all-cause mortality (RR 1.01, 95% CI 0.95 to 1.08).

Outcome	RR (95% confidence intervals)			
	All trials	Intensive glycaemic control alone	Multi-factorial intervention	P-value†
Non-fatal MI	0.90 (0.83, 0.96)	0.90(0.84, 0.97)	0.65 (0.42, 1.03)	0.0816
Non-fatal stroke	0.96 (0.86, 1.07)	0.99 (0.89, 1.10)	0.53 (0.32, 0.87)	0.0142**
CVD mortality	1.00 (0.90, 1.10)	1.02 (0.92, 1.13)	0.72 (0.46, 1.13)	0.1508
All-cause mortality	1.00 (0.94, 1.06)	1.01 (0.95, 1.08)	0.82 (0.65, 1.05)	0.1018

RR = Risk ratio
†=2-sided p-value testing that hypothesis that the risk ratio for intensive versus standard treatment is not different from the risk ratio for multi-factorial versus standard treatment. ** statistically significant result at the 5% significance level

Table 5: Effect of intensive glucose lowering and multi-factorial interventions on cardiovascular and mortality outcomes in patients with type 2 diabetes: Random effects meta-analysis

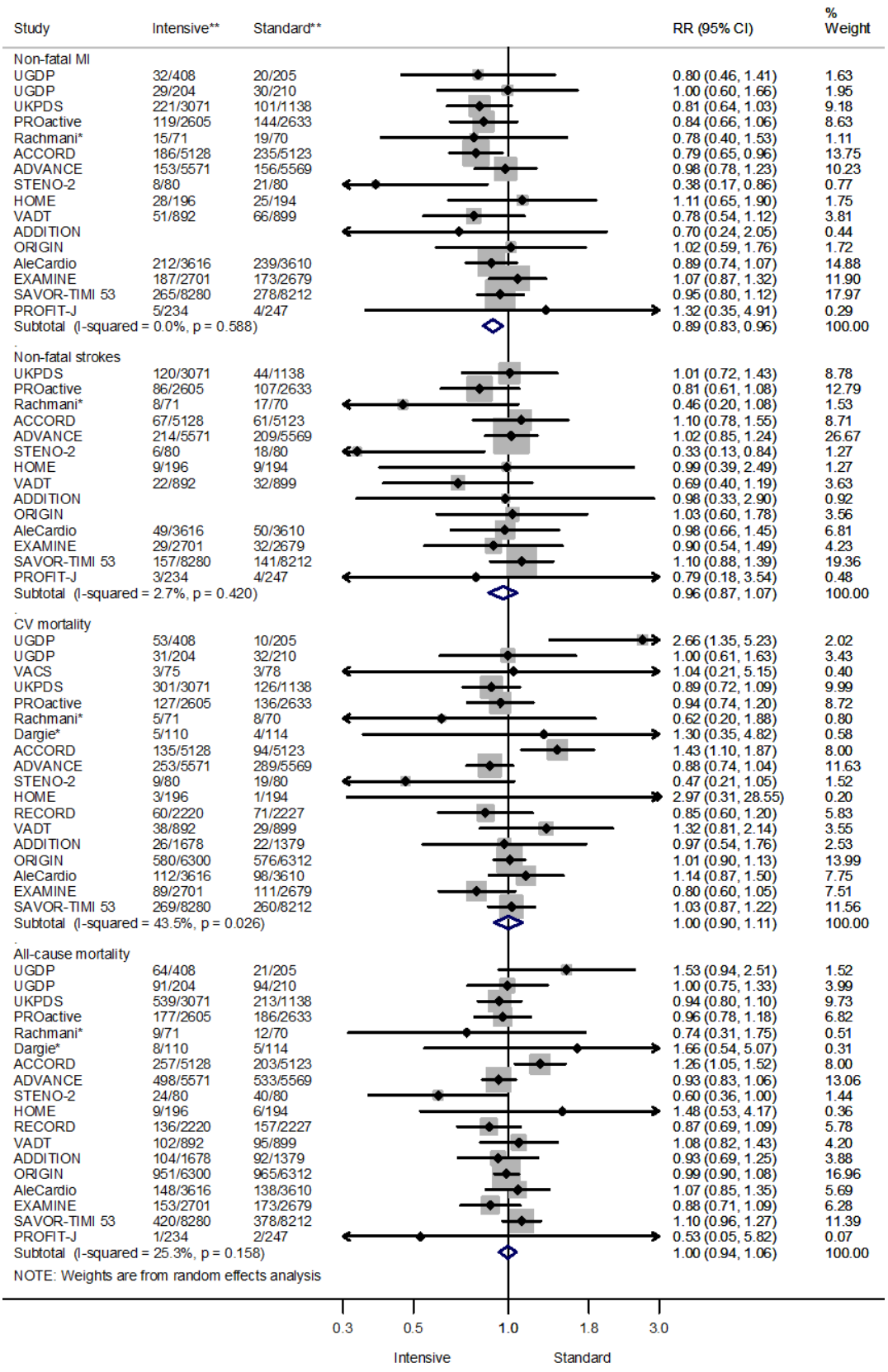


Figure 4: Association between the effect of intensive glucose lowering and multifactorial interventions on cardiovascular and mortality outcomes and the mean duration of type 2 diabetes ** Number of events/total number randomised in the standard and intensive treatment groups not available for ADDITION and ORIGIN trials.

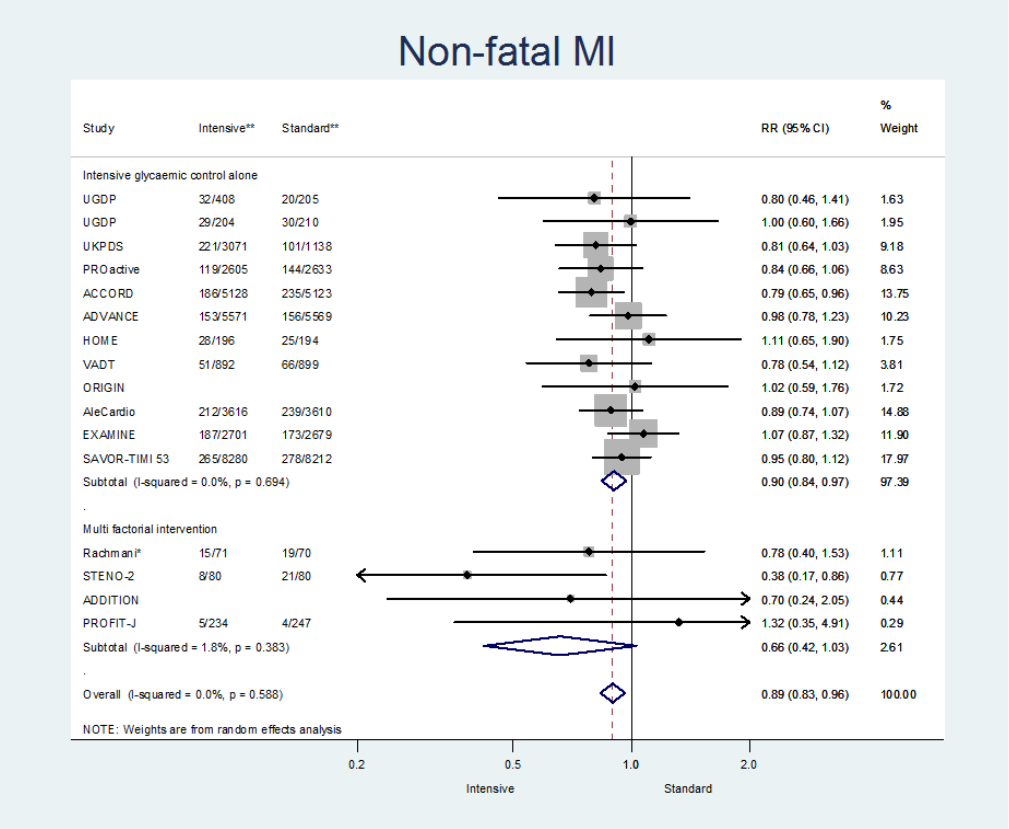


Figure 5: Subgroup analysis investigating the effectiveness of intensive glycaemic control alone or multifactorial intervention to reduce non-fatal myocardial infarction in people with type 2 diabetes. The comparator is standard care

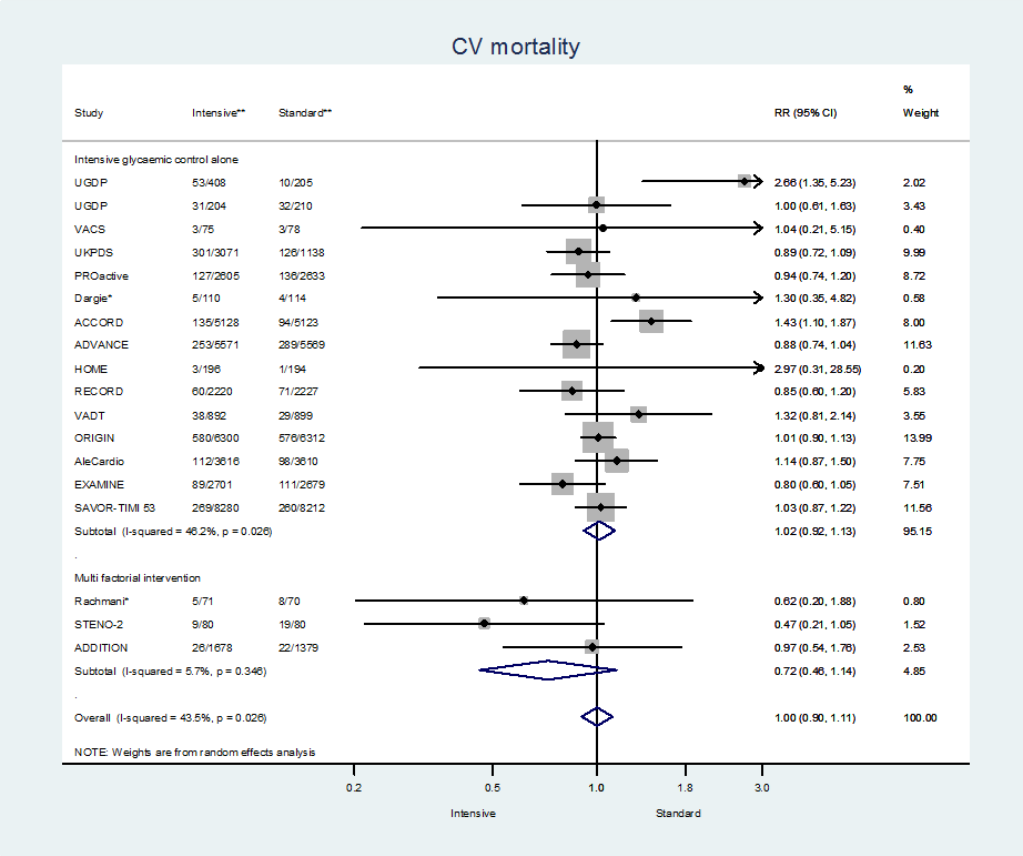


Figure 6: Subgroup analysis investigating the effectiveness of intensive glycaemic control alone or multifactorial intervention to reduce CV mortality in people with type 2 diabetes. The comparator is standard care

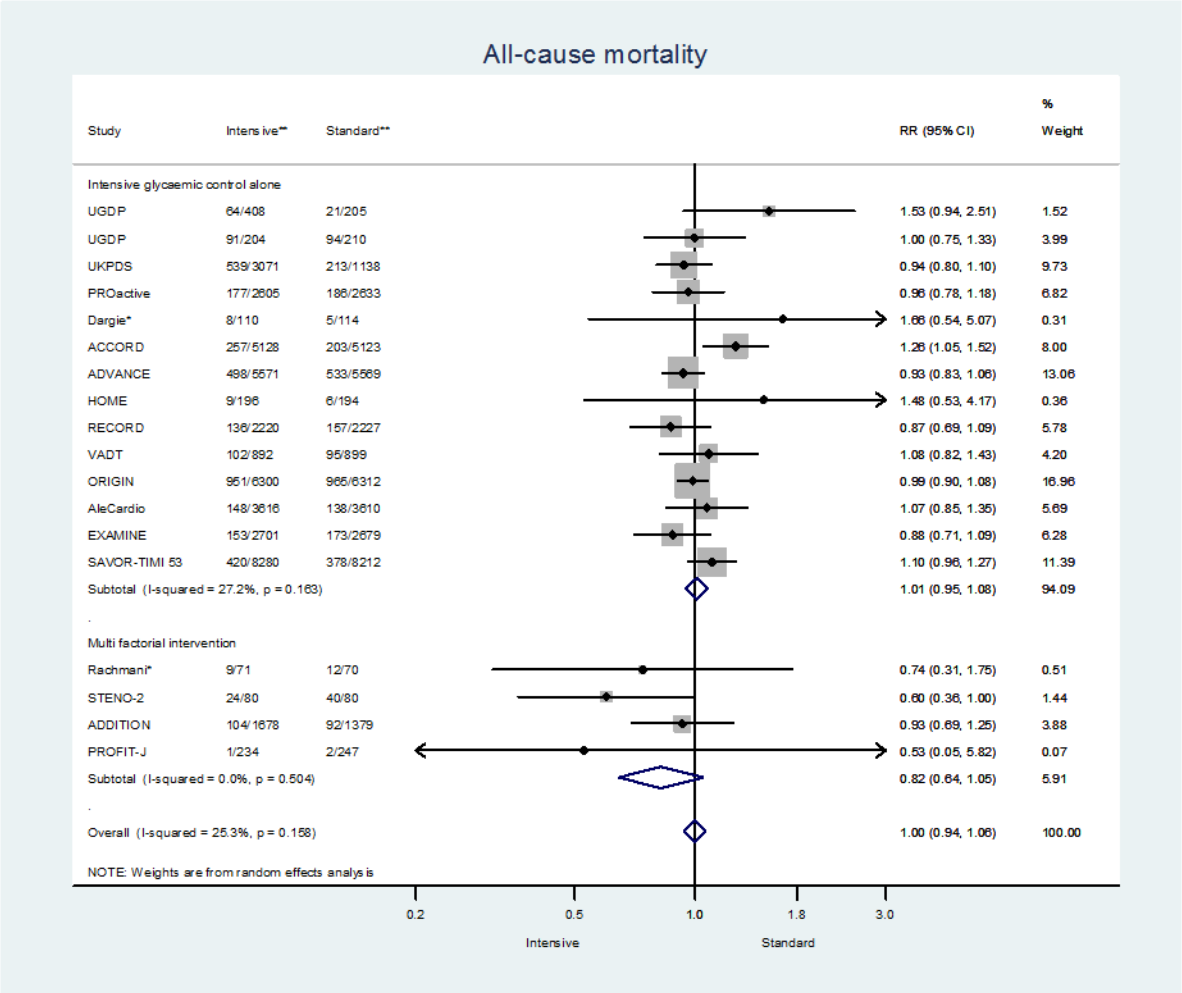


Figure 7: Subgroup analysis investigating the effectiveness of intensive glycaemic control alone or multifactorial intervention to reduce all-cause mortality in people with type 2 diabetes. The comparator is standard care

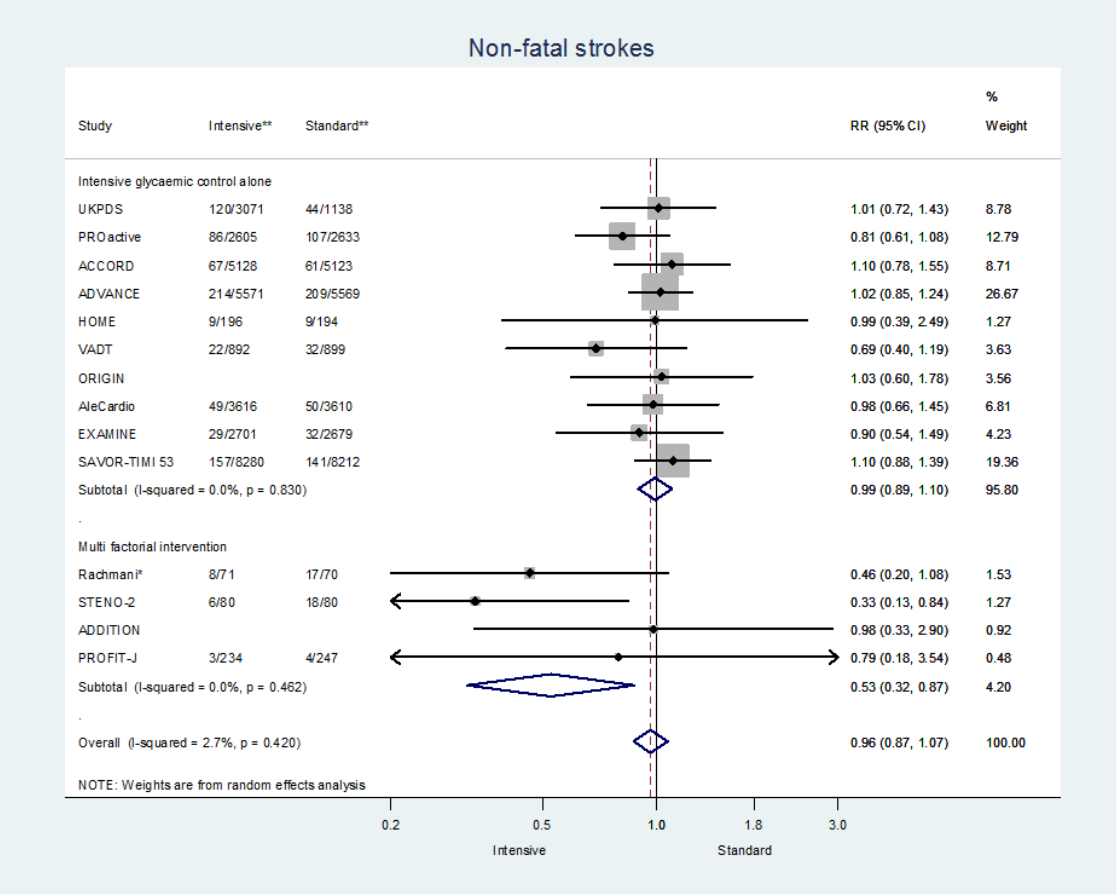


Figure 8: Subgroup analysis investigating the effectiveness of intensive glycaemic control alone or multifactorial intervention to reduce non-fatal stroke in people with type 2 diabetes. The comparator is standard care

3.4c Results of meta-regression

There was no evidence to suggest that the effect of intensive glucose treatment on CV and mortality outcomes was associated with mean age, mean duration of type 2 diabetes and gender (as the percentage of male participants in each study) (Table 7). There was no evidence indicating that rate ratios for non-fatal MI and non-fatal stroke were associated with the underlying risk of non-fatal MI, non-fatal stroke and all-cause mortality but there was evidence to suggest that risk ratios varied with the control group CV mortality rate (interaction term/ratio of hazard ratio= 0.81, 95% credible interval (CrI) 0.65 to 0.99). Figure 9 shows a plot of the risk ratios for MI, stroke and the mortality outcomes against each outcomes' control group event rate. The plots for non-fatal MI and non-fatal strokes are flat

and almost parallel to the horizontal axis but the plots for the mortality outcomes indicate an increased benefit of intensive treatment in populations with higher baseline incidence of cardiovascular and all-cause mortality.

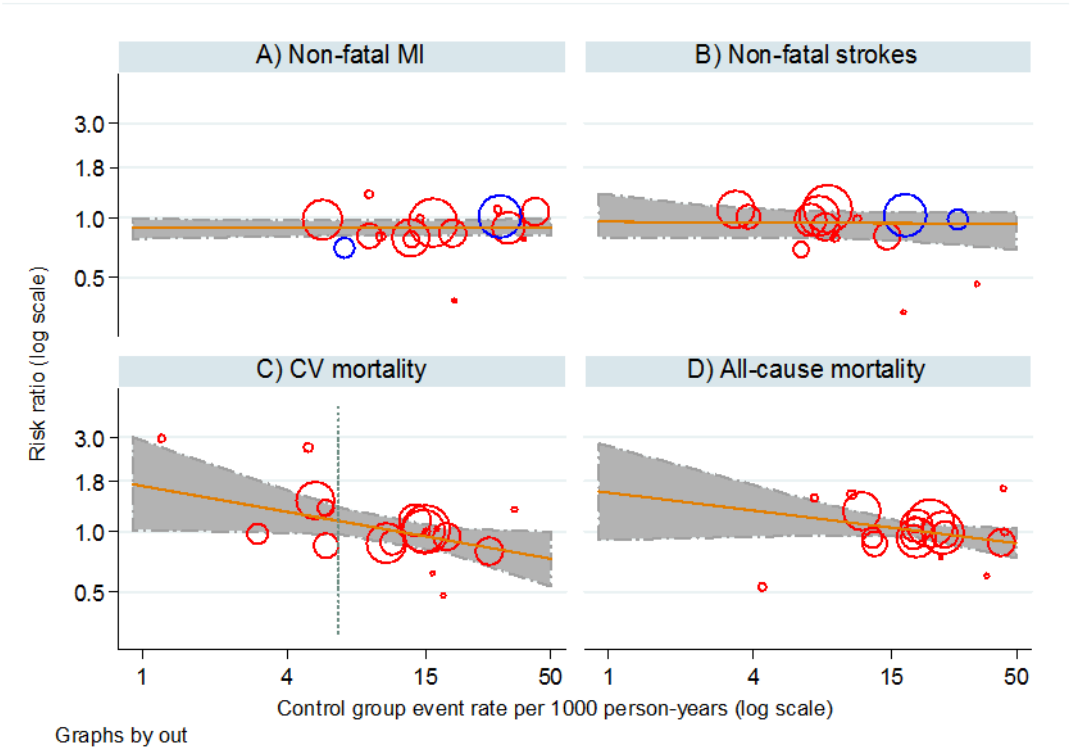


Figure 9: Association between the effect of intensive glucose lowering on cardiovascular and mortality outcomes and baseline incidence of disease.

Solid lines indicate predicted mean risk ratio. Shaded regions indicate predicted 95% credible intervals. The dotted lines indicate control group rate at which the risk ratio changes from favouring standard glycaemic control to favouring intensive glycaemic control.
The circles indicate the observed risk ratio and the error bars indicate 95% confidence intervals. The size of the circles is proportional to the study's weight in the random effects meta-analysis (i.e. inverse of the variance of study-specific estimate plus estimated between-study variance).

Study/population level characteristics	Interaction terms (95% credible intervals in brackets) for the association between study-level characteristics and the effect of intensive glucose lowering on cardiovascular and mortality outcomes in patients with type 2 diabetes			
	Non-fatal MI	Non-fatal strokes	CV Mortality	All-cause mortality
Mean Age (years)	1.015 (0.994, 1.037)	1.022 (0.989, 1.064)	0.999 (0.968, 1.030)	1.004 (0.969, 1.030)
% Male	0.797 (0.416, 1.547)	0.595 (0.202, 1.705)	0.968 (0.380, 2.157)	1.046 (0.579, 1.737)
Control group event rate	1.001 (0.979, 1.039)	0.999 (0.859, 1.021)	0.805 (0.653, 0.989)	0.860 (0.721,1.029)
T2DM duration (Years)	1.005 (0.982, 1.031)	1.001 (0.961, 1.044)	1.008 (0.974, 1.039)	1.010 (0.991, 1.028)

[l]nteraction terms are ratio of hazard ratios and are interpreted as the percentage change in hazard/risk ratio per unit change in covariate (for example the interaction term for the effect of duration on non-fatal MI indicates a 0.2% increase in the risk ratio for every year that a person lives with diabetes).

Table 6: Association between the effect of intensive glucose treatment on cardiovascular and mortality outcomes and the study-level characteristics mean age, mean duration of type 2 diabetes, control group event rate and proportion of study participants for are male

3.4d Assessment of Heterogeneity and publication bias

Heterogeneity in the treatment effect was assessed to be low for non-fatal MI (I^2=0.0%, p=0.588) and non-fatal stroke (I^2=2.7%, p=0.420) but moderate to high for CV mortality (I^2=43.5%, p=0.026) and all-cause mortality (I^2=25.3%, p=0.158) as indicated in Figure 9. Visual inspection of the funnel plots displayed in Figure 10 does not appear to show marked evidence of asymmetry for all 4 outcomes. The Egger test for publication bias which was not statistically significant (for non-fatal MI, Eggers test t=-0.93, p=0.369; for non-fatal stroke, Eggers test t= 1.63, p= 0.128; for CV mortality, Eggers test t=-0.57, p= 0.577 and for all-cause mortality, Eggers test t= -0.16, p= 0.878).

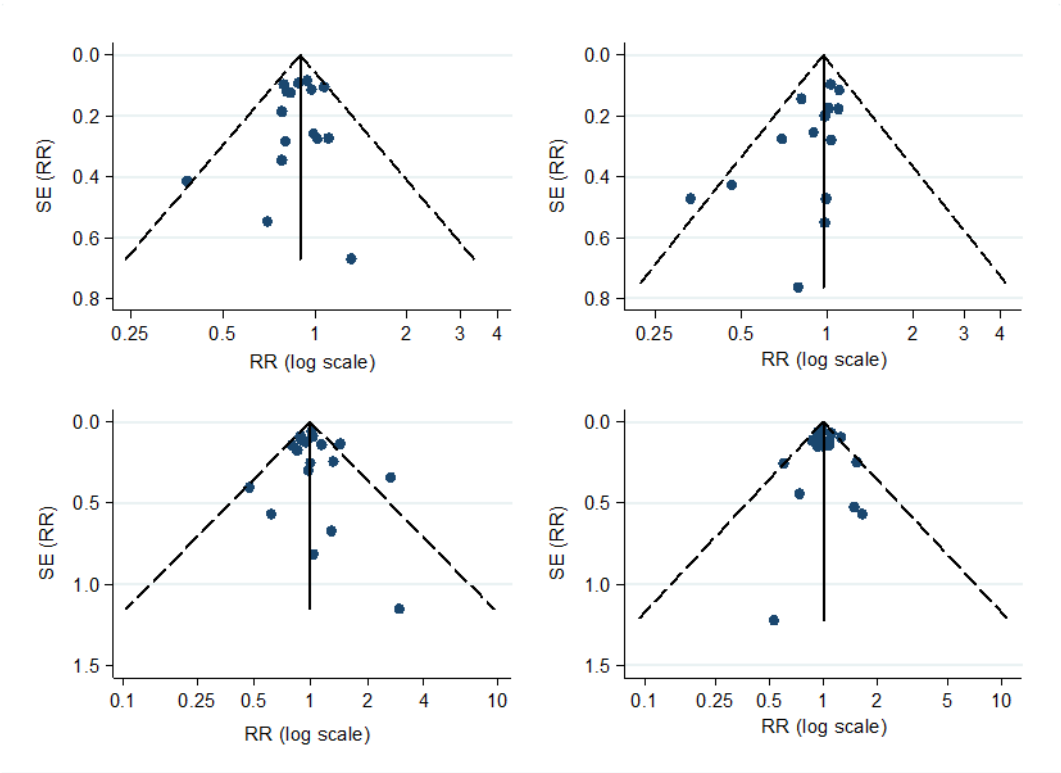


Figure 10: Funnel plots of standard error of risk ratio (SE (RR)) versus risk ratio (RR) on the log scale for non-fatal MI, non-fatal stroke, CV mortality and all-cause mortality.

The dotted lines represent pseudo 95% confidence intervals.

3.5 Discussion

3.5a Summary of findings

In this systematic review and meta-analysis of well conducted randomised controlled trials, a comparison of the effect of intensive glucose control and multifactorial interventions versus standard glucose lowering on major cardiovascular and mortality outcomes in patients with type 2 diabetes was conducted. The association between the treatment effect with 4 study-level characteristics: i) the mean age, ii) the mean duration of type 2 diabetes, iii) the % male and iv) the control group event rate was investigated. The primary analysis showed mixed results –evidence suggesting that intensive treatment reduced the risk of non-fatal MI but

not non-fatal stroke, CVD mortality or all-cause mortality was found. This finding is not dissimilar to other meta-analysis on this topic (178).

The results of the additional analysis were also equally mixed with respect to the covariate associations that were investigated. Firstly, there was evidence suggesting that intensive glucose lowering becomes increasingly effective at reducing mortality outcomes with increasing disease severity (as measured by the control group event rate). A similar finding has been reported before in the post-hoc analysis of ACCORD (200). The strength of the association is especially strong for CVD mortality. The predictions indicated that, intensive glucose lowering is more likely to be beneficial in populations where the baseline incidence of CVD mortality is greater than 6.3 deaths per 1000 person-years. Assuming that the risk of CVD remains constant over a 10-year period, this should translate into a 10-year CVD risk of 6.3%. Control group event rate or baseline risk have traditionally been used as a study-level 'proxy' covariate for measured and unmeasured patient level characteristics that collectively determine how a patient responds to treatment (201) As such, the control group rate may be taken as a measure of disease severity. The clinical implications of this finding is that if in severe disease we are able to reduce HbA1c to target through intensive treatment, there are likely to be benefits in terms of reductions in cardiovascular outcomes.

Secondly, there was no evidence of an association between the treatment effect and the mean duration of type 2 diabetes, which appears at first (at least on face-value) to be contrary to current clinical guidelines and understanding of the impact of intensive glucose lowering (180, 187, 202). Because the duration of diabetes (i.e. how long an individual has diabetes) is individual covariate, we believe a potentially more robust analysis than the one reported here would require individual patient data (IPD) to allow for realistic modelling of patient level association between covariate and health outcomes. Factors such as background event rate, multi-morbidities and complex glucose lowering therapies could also be considered in this more detailed IPD meta-analysis. In a prospective cohort study of older

men using IPD, increasing duration of diabetes was found to predict stable increases in all-cause and MI-related mortality and an even higher risk of stroke mortality (202). With long duration, there may be other factors (which have not been explored in this analysis) such as increased hypoglycaemia rates, which could account for the increased mortality in intensive treatment (203). For instance, the UKPDS analyses using homeostatic model assessment (HOMA) of insulin sensitivity and beta-cell function demonstrated an annual steady decline in beta cell function of 4% (204). As a result of this, patients with longer duration of diabetes are more likely to be on more intensive treatment regimens including insulin therapy and a combination of other glucose lowering agents, which increase the risk of hypoglycaemia. It has been shown that there is some statistical colinearity between diabetes duration and insulin therapy (186)

The benefits from multifactorial intervention seem to be more pronounced with the reduction in non-fatal stroke in this group being 47%. Also, even though there were no statistically significant benefits in the reductions in mortality in both intensive glycaemic control and multifactorial interventions, there were trends towards a reduction in event rates of CV mortality and all-cause mortality in the multi-factorial intervention sub-groups. On the contrary, there was a trend towards an increase in mortality in both CV and all-cause mortality in patients in which only intensive glycaemic control alone were used. The clinical implication of this finding could be that in the setting of uncertain risks or beneficial effects of intensively controlling blood glucose in some patients, focusing more broadly on multifactorial interventions including blood pressure and lipid control may be preferable. In an analysis using Mendelian Randomisation, even though Single Nucleotide Polymorphisms associated with HbA1c were associated with an increased risk of coronary artery disease that the effect was attenuated after adjustments were made for dyslipidaemia, blood pressure and weight (205).

3.5b Study strengths and limitations

This meta-analysis used 19 studies (n=84,460), making it more powered and robust for conclusions to be drawn. Previous analyses on this topic (178, 179, 181-183) did not include as many participants as ours and did not look at multi-factorial interventions, thus giving our study a unique perspective on this area. Adjusting for the control group risk allowed us to account for the variations in the control group treatment and any known or unknown patient level characteristics that could collectively determine disease severity and therefore a patient's response to treatment.

The main limitation of our study is the fact that we limited intensive glycaemic control to only pharmacotherapy. Treatment intensification can also be achieved with changes in diet and bariatric surgery for example. Also multifactorial interventions go beyond lipid, blood pressure and glycaemic control. Studies looking at other very relevant contributors to cardiovascular outcomes like medication adherence, smoking, patient education and physical activities were not included. We acknowledge that the number of trials of multifactorial interventions alone (four trials) is relatively small to allow robust conclusions to be drawn from the respective subgroup analysis.

The duration of diabetes in this analysis was assumed to be the duration since diagnosis. In reality we would never really know how long a patient has had diabetes prior to diagnosis and so the duration since diagnosis is only at best a "proxy" for duration of diabetes. In the context of the finding of lack of duration effect in this study, it would have been reasonable to have considered the various classes of glucose lowering therapies used in the various trials, comparing the side effect profiles, to see if other characteristics, like hypoglycaemia could account for any increase event rates. However longer outcome trials are needed to answer this question in future.

Finally, the findings on lack duration effect should be interpreted with caution as we used aggregate data (i.e. mean duration of diabetes) in the analysis. As stated in our earlier discussion of this issue above, a recent

longitudinal cohort studies using IPD suggest evidence of an association between duration of T2DM and CV and mortality outcomes even though the focused population was only elderly males (202).

3.6 Conclusion

This study found evidence to suggest that intensive glucose control and multifactorial intervention reduced the risk of non-fatal MI but not non-fatal stroke, CVD mortality or all-cause mortality. Multi-factorial interventions had very pronounced reduction in non-fatal stroke. No evidence of an association between intensive glucose control and multifactorial intervention and mean duration of type 2 diabetes was found; however, there was evidence suggesting that the effectiveness of intensive therapy to reduce mortality outcomes in patients with type 2 diabetes increases with increasing background cardiovascular risk in the population.

It has already been established in chapter 2 that targeting multi-disciplinary team collaborations mixed with various interventions reported some consistency in improvements in HbA1c in the primary care or community based settings. Having now further explored the benefits intensive glucose control and multifactorial interventions, it is logical to consider a model of diabetes care that increases the reliable use of these evidence based interventions through the organisation of work using of multi-faceted interventions targeting multiple professionals all in the primary care setting. These proposed multidisciplinary teams will be closer to the patients' homes. Diabetes care delivery can be delivered by a range of professionals such as physicians, practice and specialist nurses, dieticians, community pharmacists, health-care assistants and in some cases community champions functioning as a primary care team. The other advantage of such a model could diabetes care delivery at lower cost yet maintains continuity of care, as it is wholly primary care based. Attempts have already been made to decrease the overreliance of specialist centres in the management of glycaemia and cardiovascular risk factors through the use of multidisciplinary services that provides diabetes care closer to

home for patients with poor glycaemic control. The have mainly been various versions of the chronic care model or intermediate primary care models that use both primary and specialist care staff, thus potentially comprising the continuity of care for these patients.

In the next chapter, the impact of an enhanced primary care based package of care on unplanned hospitalisations and length of stay for patients with diabetes will be assessed in comparison to intermediate care clinics for diabetes. The first outpatient attendance for diabetes and admission with type 2 diabetes and non-fatal myocardial infarction, non-fatal stroke, major foot amputations and hypoglycaemia in the same spell will also be assessed.

Chapter 4

Evaluating the impact of an enhanced primary care diabetes service on diabetes outcomes: a before-after study in a large multi-ethnic Clinical Commissioning Group.

4.1 Synopsis of chapter 4

Diabetes is an ambulatory care-sensitive condition and a high quality primary care or risk factor control can lead to a decrease in the risk of non-elective hospitalisations while ensuring continuity of care with usual primary care teams.

In this before and after study, eight primary care practices providing enhanced diabetes care in Leicester UK, were compared with matched neighbouring practices with comparable demographic features providing integrated specialist –community care diabetes service. The primary objective at twelve months was to demonstrate equivalence in non-elective bed days. The enhanced practices had primary care physicians and nurses with an interest in diabetes who attended monthly diabetes education meetings and provided care plans and audits. The control practices provided an integrated primary-specialist care service.

The difference between the mean change in the non-elective bed days from baseline and at follow up in core and enhanced practices was not statistically significant (mean = 2.20 per 100 patients, 95% CI = -0.92 to 5.31 per 100 patients, p = 0.14). The analogous change for first outpatients' attendance were 0.23 per 100 patients (95% CI = -0.47 to 0.52 per 100 patients p=0.92) and for diabetes related complications admissions was 0.30 per 100 patients (95% CI = -0.85 to 1.45 per 100 patients p=0.55).

It was concluded that a model of enhanced primary care based diabetes care appears unlikely to increase hospitalisations, outpatients' attendance or admissions for diabetes related complications.

4.2 Background to the evaluation of the before and after study of the impact of an enhanced primary care diabetes service on diabetes outcomes.

People with diabetes are at greater risk for cardiovascular disease, renal disease, endocrine/metabolic complications, and other chronic complications. A portion of health care use associated with these medical conditions exerts considerable pressure on health care (206). Diabetes is a primary care –sensitive or ambulatory care-sensitive condition and a high quality primary care or risk factor control can lead to a decrease in the risk of non-elective hospitalisation due to these conditions. In the UK, between October and December 2014, there were 1.4 million emergency admissions to hospital; 4.3 million people attended a first outpatient appointment. Moreover, ten percent of patients admitted as emergencies stayed for more than two weeks, but these patients accounted for 55 percent of bed days (207). In the USA in 2004, US$2.4bn was estimated to have been spent on potentially preventable hospitalisations due to uncontrolled diabetes (208).

Since diabetes can cause several acute and chronic complications, which could potentially lead to hospitalisations, focusing on reducing the number and/or duration of admissions for people with diabetes has a huge potential for reducing hospital bed use. Emergency admissions resulting from diabetes or its complications are an unexpected health event and could represent poor outcomes or failure to initiate or augment the management of a patient with diabetes at the appropriate time (209). The resultant effect of this is not only economic loss to healthcare systems, but it puts a strain on patients and their families. Although some emergency admissions may be unavoidable, some may be preventable, and inability to prevent them could indicate an inefficient use of healthcare resources and negatively impact on patients' quality of life. Reducing bed days could be a key indicator of healthcare quality and underpins appropriate allocation of resources and assessment of the impact of secondary prevention activities.

In recognition of the fragmentation of care of people with diabetes between specialist and primary care teams resulting in poor and costly outcomes, many centres have devised various models of diabetes care to suit their local populations (210). These models are usually multi-component interventions targeting multi-faceted health care professionals' interaction in an integrated fashion to improve outcomes. The Chronic Care Model is an example of this integrated care and is based on a paradigm shift of dealing with acute care issues to a system that is prevention based (211-213). The model works on the basis that quality diabetes care is not delivered independently and can be enhanced by system redesign, community resources, self-management support, decision support, clinical information systems, and organizational support working in tandem to enhance patient-provider interactions (211, 212, 214). An evaluation of this model in the US suggests that its implementation in the community is effective in improving clinical and behavioural outcomes in patients with diabetes (154, 215). Many such models are being implemented in other countries including the UK (210). In Leicester UK, the City Clinical Commissioning Group recently reconfigured diabetes services. A care model that aimed to achieve an integrated diabetes service across community, primary and acute care resulting in a more cost-effective, accessible and high quality service for all patients was developed. General practices in the city were classified as "enhanced" or "core". The enhanced practices used general practitioners and nurses with an interest in diabetes to provide the diabetes service within their practices. The core practices provided a primary-specialist care service, delivered by usual general practitioners but supported by diabetes specialist nurses, dieticians and podiatrists, working under the supervision of diabetes specialists in the secondary care units in an integrated manner.

This evaluation focuses specifically on the impact of enhanced care package (a key part of the service redesign) on unplanned hospitalisations and length of stay for patients with diabetes (non-elective bed days). Our

primary objective was to demonstrate that the service provided by the enhanced practices does not lead to an increase in non-elective bed days over and above the core service. We chose to evaluate non-inferiority instead of superiority because core care in the city of Leicester is provided by intermediate care clinics for diabetes (ICCD) (216), which is a multidisciplinary service that provides diabetes care closer to home for patients with poor glycaemic control. Even though the ICCD has not been found to produce significant reductions in intermediate outcomes and yet incurring significantly higher primary care and community clinic costs (216), locally in Leicester UK, the service had already been evaluated and appeared to be effective in reducing hospital admissions and numbers of ambulance call-outs for treatment of hypoglycaemia (217). In this service, diabetes specialist nurses, dieticians and podiatrists usually support the clinicians in the core practices, with supervision from diabetes specialist physicians from the secondary care units in an integrated manner. They operate from strategically located community health centres to serve various sections of the city.

As a result of the success of the ICCD locally, our alternative service redesign, which is cheaper, should not reduce the quality of the care. A secondary objective was to examine whether there was also equivalence in first outpatient attendance for diabetes between the practices providing Enhanced and Core care. We also evaluated the impact of the enhanced care package on diabetes related comorbid bed days (admission with type 2 diabetes as primary diagnosis and at least one of the following comorbidities: non-fatal myocardial infarction, non-fatal stroke, major foot amputations and hypoglycaemia in the same spell).

4.3 Patients and Methods

This was a before and after study. Data from all diabetes patients older than 17 years of age registered in eight selected general practices providing enhanced diabetes care in the city of Leicester, UK were used in this evaluation. These data were compared with eight matched general practices drawn from the city of Leicester with comparable benchmarks in

population demographics namely percentage of patients older than 65 years of age, average deprivation (Index of Multiple Deprivation 2010) scores, percentage of patients with at least one co-morbidity (non-fatal myocardial infarction or non-fatal stroke or major foot amputations). For each of the eight enhanced practices, there was a suitably matched practice within one mile. If there were more than one, the practice most similar in terms of the matching characteristics was used. Ethnicity data are poorly coded and were not included in the matching process. A predominantly south-Asian population as opposed to the west inhabits the east of Leicester. Therefore, since matched Core and Enhanced practices were within one-mile vicinity, they were assumed to consist of similar ethnicity composition. The evaluation was done on the care delivered prior to April 2013 (before) and April 2014 (after).

4.3a Exposure of Interest

In the practices offering the Enhanced care, the lead general practitioner had to have an interest in diabetes and be studying towards or have completed an MSc in Diabetes or updating their diabetes knowledge through our locally accredited programme (Effective Diabetes Education Now (EDEN)). A practice nurse with similar or equivalent diabetes qualifications supported them. These teams were charged with identifying patients who could be discharged from secondary care and managed effectively in primary care, and with targeting patients with an HbA1c greater than 8% (64mmol/mol) for care planning. They also focused on care planning for those diabetes patients with multi-morbidities and those who were housebound. The teams met up once a month for clinical discussions around complex diabetes cases selected from their practices. Monthly audits of outpatient attendances and hospital admissions were also discussed and fed back to practices. The lead general practitioners discussed stable patients still under specialist care with the specialists in charge of the patient's care, and if it was appropriate and the patients were in agreement, they were discharged back to primary care. Clinicians

followed clinical care pathways for various aspects of diabetes care and referrals, and received telephone-based support for complex cases, depending on the needs of the general practitioner. The enhanced practices therefore had all the resources to successfully manage the repatriation of patients from specialist care to primary care. The non-elective bed days (as opposed to all bed days) was chosen as the primary outcome in an attempt to rule out admissions due to the specialist level conditions such as antenatal diabetes, diabetic foot care, renal, insulin pumps, Type 1/adolescent diabetes inpatient diabetes care (210), and complex unstable diabetes patients since the admissions from these should have been electively arranged by hospital specialists.

4.3b Comparator Group

In the Core practices, basic diabetes care was provided as usual by general practitioners. In order to limit a two tier system of care for patients in the city and thus avoid the widening of variation in the quality of care provided, the clinicians in the core practices were supported by diabetes specialist nurses, dieticians and podiatrists, working under the supervision of diabetes specialists in the secondary care units in an integrated manner.

4.3c Data Sources

The outcome data were non-elective bed days, first outpatients' appointments and admission with type diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations in the same spell. These data were drawn primarily from the Hospital Episode Statistics (HES) database. The HES database is made up of many data items relating to admitted and outpatient care delivered by NHS hospitals in England with diagnoses coded using the WHO's International Classification of Diseases 10th revision [ICD-10].

To ensure independence, the team analysing the data did not perform the data extraction. A third party extracted the data using the same approach as the NHS uses in England to produce cost data based on a coding system called Healthcare Resource Group (HRG) to reimburse hospitals for the

treatment they deliver. HRG is a grouping system where patient events or spells consuming a similar level of resource are allocated a cost. In order to maintain patient confidentiality, no patient's name or unique identifier is present in this tool.

For the diabetes related non-elective admissions, we searched admissions with only type 2 diabetes as a primary diagnosis using E11 code. Similarly, for the admissions with type 2 diabetes and co-morbidities we searched E11 code and non-fatal myocardial infarction or non-fatal stroke**,** not specified as haemorrhage or infarction or major foot amputations or hypoglycaemia in the same spell using I21 or I22 or I64 or E16.2 or S88 or S98 or T13.6 or T05.2-6.

The baseline data variables analysed were diabetes prevalence, percentage male, percentage of people aged over 65, deprivation and percentages achieving targets on the various cardiovascular risk factors. We estimated the quality of cardiovascular risk factor control by computing mean percentage of people achieving all four cardiovascular risk factors (HbA1c ≤ 8%, blood pressure ≤140/80mmHg, total cholesterol ≤5mmol/L and being treated with renin angiotensin system inhibitors if a patient has micro-albumuria). All these baseline variables were drawn from publicly available data on general practices in England (218). Because the data were extracted from publicly available data sources without any patient identifiers, ethical clearance for these analyses was deemed unnecessary.

4.3d Statistical analysis

Baseline characteristics of the two groups (Enhanced and Core) were summarised separately using means and standard deviations. Paired t-test analyses were used to compare the baseline characteristics between enhanced and core practices.

The change in the number of diabetes related non-elective bed days between 2013 and 2014 in the enhanced and the core practices was computed. Since evaluation of non-inferiority between the enhanced care and core care was being considered, a lower confidence interval of not

more than zero indicated a lack of increase for the outcomes. A paired t-test analysis was conducted to compare the change from baseline (2013) between the two groups. Non-elective hospitalisation (bed-days) is an undesirable outcome. If the change in the non-elective bed days from baseline to follow up in core or enhanced practices is positive, it means there were more of these hospitalisations at follow-up. If it is negative, then the hospitalisations were less at follow-up. If the difference between the mean change in non-elective bed days between matched core and enhanced practices is positive, it could mean therefore that there was a more favourable change in the non-elective bed days in the enhanced practices after the follow up.

For the secondary outcomes, again, the change in the first outpatients' attendance, admissions of patients with diabetes and non-fatal myocardial infarctions, major foot amputations and non-fatal strokes between 2013 and 2014 in the enhanced and the core was computed. A paired t-test analysis was conducted to compare the change from baseline between the two groups. Even though the diabetes related non-elective bed days refer to patients admitted with diabetes as a primary diagnosis, it is possible that some of the admissions for these diabetes patients were for other reasons unrelated to their diabetes or its complications. A sensitivity analysis was conducted using all admissions for diabetes patients with diabetes as either a primary diagnosis or secondary diagnosis to compute the bed days and then conducted paired t- tests again to see if the results differed from the findings of the primary analysis. All the outcome data were expressed per hundred adult patients ≥18 years of age due to differences in patient list size between the practices. Statistical analyses were performed using SPSS (version 22.0, Chicago, IL, US).

4.4 Results

4.4a Sample characteristics

The normality testing was done for the entire baseline characteristics considered for comparison between the core and enhanced practices.

For deprivation scores (IMD), Shapiro Wilk's test ($p>0.05$) (219, 220) and visual inspections of their histograms, normal Q-Q plots and box blots showed that deprivation scores (IMD) were approximately normally distributed for both the core and enhanced practices with a skewness of 0.06 (SE=0.75) and Kurtosis of 0.58 (SE= 1.48) for the enhanced practices and skewness of 1.13 (SE=0.75) and Kurtosis of -0.44 (SE= 1.48) for the core practices (221-223)

In the case of the percentage male patients, Shapiro Wilk's test ($p>0.05$) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed for both the core and enhanced practices with a skewness of -0.658 (SE=0.75) and Kurtosis of -0.642 (SE= 1.48) for the enhanced practices and skewness of -0.275 (SE=0.75) and Kurtosis of -1.50 (SE= 1.48) for the core practices.

Also, in the case of the percentage of patients aged ≥65 years, Shapiro Wilk's test ($p>0.05$) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed for both the core and enhanced practices with a skewness of 2.25 (SE=0.75) and Kurtosis of 5.72 (SE= 1.48) for the enhanced practices and skewness of 1.15 (SE=0.75) and Kurtosis of 1.21 (SE= 1.48) for the core practices.

The average of percentage of people achieving all four cardiovascular risk factor targets (HbA1c =/ <8% or 64 mmol/mol, blood pressure =/<140/80 mmHg, total cholesterol =/<5mmol/L, and being treated with ACE-I if there is microalbumuria) was used as a quality of care indicator score. Again, for this score, Shapiro Wilk's test ($p>0.05$) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed for both the core and enhanced practices with a skewness of -0.52 (SE=0.75) and Kurtosis of -1.83 (SE= 1.48) for the enhanced practices and skewness of -0.13 (SE=0.75) and Kurtosis of 1.61 (SE= 1.48) for the core practices.

For non-elective bed days per 100 diabetes patients ≥18 years of age at baseline, the Shapiro Wilk's test ($p>0.05$) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed for both the core and enhanced practices with a skewness of -0.51 (SE=0.75) and Kurtosis of -1.18 (SE= 1.48) for the enhanced practices and skewness of 0.72 (SE=0.75) and Kurtosis of 0.12 (SE= 1.48) for the core practices.

Finally for comorbid admission, that is any admission with type 2 diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations in the same spell per 100 diabetes patients ≥18 years in 2013, again the Shapiro Wilk's test ($p>0.05$) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed for both the core and enhanced practices with a skewness of -0.21 (SE=0.75) and Kurtosis of -1.31 (SE= 1.48) for the enhanced practices and skewness of 1.73 (SE=0.75) and Kurtosis of 3.54 (SE= 1.48) for the core practices.

For the main outcome analyses, the differences between the outcomes in 2014 and in 2013 were computed for the core and the enhanced practices. These differences were then used for the paired t-tests between the core and the enhanced practices. To do this, the assumptions of normality for these differences had to be established. For the non-elective bed days in the enhanced practices, the Shapiro Wilk's test ($p=0.10$) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were approximately normally distributed with a skewness of -0.1.24 (SE=0.75) and Kurtosis of 0.56 (SE= 1.48). In the core practices, the Shapiro Wilk's test ($p=0.32$) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed with a skewness of -0.38 (SE=0.75) and Kurtosis of -1.26 (SE= 1.48).

Similarly, normality testing was done for the difference between first out patients' appointment per hundred in 2013 and 2014 in the enhanced

practices. The Shapiro Wilk's test (p=0.67) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed with a skewness of -0.16 (SE=0.75) and Kurtosis of 0.07 (SE= 1.48). In the core practice, the Shapiro Wilk's test (p=0.11) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed with a skewness of -1.61 (SE=0.75) and Kurtosis of 3.38 (SE= 1.48).

For the normality testing of the difference between percentage of any admission with type 2 diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations n the same spell per adult population over 17 years in 2013 and 2014 in the enhanced practices, the Shapiro Wilk's test (p=0.13) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed with a skewness of -1.10 (SE=0.75) and Kurtosis of 0.42 (SE= 1.48). In the core practices the Shapiro Wilk's test (p=0.85) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed with a skewness of 0.36 (SE=0.75) and Kurtosis of 1.00 (SE= 1.48).

In order to carry out the sensitivity analysis, a normality testing was done for the difference between the percentage of admissions with a diagnosis of type 2 diabetes, primary or secondary, in 2013 and 2014 in the enhanced practices. The Shapiro Wilk's test (p=0.46) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed with a skewness of - 0.56 (SE=0.75) and Kurtosis of -1.00 (SE= 1.48). In the core practices the Shapiro Wilk's test (p=0.41) and visual inspections of their histograms, normal Q-Q plots and box blots showed that the percentages were also approximately normally distributed with a skewness of 0.157 (SE=0.75) and Kurtosis of -1.40 (SE= 1.48).

4.4b Main baseline results

Data were available for 8,366 adult patients with type 2 diabetes and aged ≥18 years of age in the sixteen practices. Of these, 6,054 (72.4%) were registered in the eight enhanced practices and 2,312 (27.6%) were registered in eight matched core practices.

The baseline characteristics were similar in both types of practice (Table 8 and Appendix 4.15). There were no significant differences between enhanced and core practices in terms of any of the characteristics examined, apart from the percentage of male patients in the two groups; the percentage of male patients in the enhanced practices (mean [SD] = 49.4% [2.6%]) was less than in the core practices (52.6% [3.7%]; p=0.011). A simple linear regression was calculated to predict the difference in non-elective bed days between the matched core and enhanced practice upon difference between the percentage male in the core practices and the enhanced practices. Preliminary analyses were performed to ensure to ensure there was no violation of assumption of normality and linearity. A non-significant regression equation was found P= 0.89 with an $R^2$of -0.16, Standardised B =0.062 (CI -1.33 to 1.50) (Appendix 4.16). Another simple linear regression was calculated to predict the difference in first outpatient's appointment between the matched core and enhanced practice upon difference between the percentage male in the core practices and the enhanced practices. Preliminary analyses were performed to ensure to ensure there was no violation of assumption of normality and linearity. A non-significant regression equation was found, P= 0.44 with an R^2 of -0.046, standardised B =0.32 CI (-1.41 2.87) (Appendix 4.17). Similarly, another simple linear regression was calculated to predict the difference in admissions with type 2 diabetes (and non-fatal myocardial infarction or non-fatal stroke or foot amputations in the same spell) between the matched core and enhanced practice, upon difference between the percentage male in the core practices and the enhanced practices. Preliminary analyses were performed again to ensure there was no violation of assumption of normality and linearity. A non-significant regression equation was found, P= 0.63 with an $R^2$of -0.12 standardised

B=0.20 CI (-0.41 0.62) (Appendix 4.18). Finally, a simple linear regression was calculated to predict the difference in admission with type 2 diabetes, primary or secondary- sensitivity analysis, between the matched core and enhanced practice, upon difference between the percentage male in the core practices and the enhanced practices. Preliminary analyses were performed to ensure to ensure there was no violation of assumption of normality and linearity. A non-significant regression equation was found P= 0.20 with an R^2 of 0.14, standardised B=-0.51, CI (-3.43 0.87) (Appendix 4.19)

Table 7: Baseline characteristics in practices offering enhanced care and those offering core (usual) care Mean (SD)

Baseline characteristics	Enhanced practices (N = 57,943)	Core practices (N=25,492)	p-value*
Deprivation score (IMD)	34.04 (11.05)	33.33 (12.00)	0.780
Percentage male patients	49.40 (2.55)	52.55 (3.70)	0.011
Percentage of patients aged ≥65 years	14.20 (4.05)	11.31 (3.94)	0.219
Quality of care indicator†	78.09 (5.60)	70.34 (10.61)	0.073
Non-elective bed days ‡	5.62 (2.11)	3.82 (1.62)	0.075
Co-morbid admissions §	0.93 (0.67)	0.78 (0.87)	0.734

IMD: Index of Multiple Deprivation

* P-values compare enhanced and core practices and were estimated using paired t-tests.

†: Average of percentage of people achieving all four cardiovascular risk factor targets (HbA1c =/ <8% or 64 mmol/mol, blood pressure =/<140/80 mmHg, total cholesterol =/<5mmol/L, and being treated with ACE-I if there is microalbumuria)

‡: Non-elective bed days per 100 diabetes patients ≥18 years of age

§: Any admission with type 2 diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations in the same spell per 100 diabetes patients ≥18 years in 2013.

4.4c Main outcome results

The main results are summarised in Table 9 and Appendix 4.20. Whereas in the core practices the mean change in non-elective bed days was 1.29 (2.85) per 100 patients, suggesting an increase in non-elective admission after the follow up periods, in the enhanced practices the mean change in non-elective bed days was -0.91 (2.1) per 100 patients suggesting that there was no increment in non-elective bed days after the follow up period in the enhanced practices. The difference between the non-elective bed days in core practices and that in enhanced practices was not significant (mean = 2.20 per 100 patients, 95% CI = -0.92 to 5.31 per 100 patients, p = 0.14). In the sensitivity analysis, when the analysis included all non-elective admissions for diabetes patients whether diabetes was the primary diagnosis or secondary diagnosis, the difference between the non-elective bed days in core practices and that in enhanced practices was 2.78 per 100 patients (95% CI = -2.71 to 8.27 per 100 patients, p=0.27).

Similarly, differences between the mean first outpatient attendances in the adult population in matched core and enhanced practices also increased over the 12 months of follow up. The difference between the mean first outpatient attendance in the core practices and that in enhanced practices was 0.02 per 100 patients (95% CI = -0.47 to 0.52, per 100 patients p=0.92), suggesting a lack of increment in the first out patients' attendance in the enhanced practices at the end of the follow up period. Admissions with type 2 diabetes complications were measured as the percentage of any admission with type 2 diabetes and non-fatal myocardial Infarction or non-fatal stroke or major foot amputations in the same spell per adult population over 17 years. The difference between this in the matched core and enhanced practices did not increase over the 12 months of follow ups 0.30 per 100 patients (95% CI = -0.85 to 1.45 per 100 patients p=0.55) suggesting a lack of increment in the admissions in the enhanced practices at the end of the follow up period.

Table 8: Effect of enhanced diabetes services on non-elective bed days, first outpatient attendance and hospitalisation with diabetes its complications.

	Change from 2013 to 2014					
Outcome‡	Core practices Mean (SD)	Enhanced practices Mean (SD)	Mean difference	Lower Confidence interval	Upper Confidence interval	P-value *
Non-elective bed days						
Diabetes as primary diagnosis	1.29 (2.85)	-0.91(2.1)	2.20	-0.92	5.32	0.14
Diabetes as primary or secondary diagnosis†	3.85(5.86)	1.06(4.01)	2.78	-2.71	8.27	0.27
First outpatient attendance	-0.10(0.38)	-0.13(0.44)	0.02	-0.47	0.52	0.92
Admission with type 2 diabetes complication §	0.04(1.09)	-0.26(0.60)	0.30	-0.85	1.45	0.55

* Comparing change from 2013 to 2014 between core and enhanced practices estimated using paired t-tests.

†: This analysis includes all non-elective admissions for diabetes patients whether diabetes is the primary diagnosis or secondary diagnosis

‡: All outcome data reported per hundred patient populations over 17 years

§: Admissions with type 2 diabetes complication is measured as any admission with type 2 diabetes and non-fatal myocardial Infarction or non-fatal Stroke or major foot amputations in the same spell.

4.5 Discussion

This analysis demonstrates that, this enhanced care package aspect of our service redesign had similar outcomes to that provided by the more expensive primary-specialist integrated care (216). The prevention of an increment in the non-elective bed days, first outpatient's attendances and admissions with diabetes related complications has the potential to make the practice accreditation more cost-effective as diabetes service delivery in specialist settings tend to be more expensive (224). The choice of the primary-specialist integrated care service as a comparator could have blunted the benefits our enhanced care package. This is because the stated comparator service has already been evaluated and proved to be effective in reducing hospital admissions (217). Probably if our comparator service was another service delivery system, we could have demonstrated superiority in the outcomes. The NHS Portsmouth CCG has similar characteristics such as population density, indices of Deprivation 2010 (average score), percentage of population from Black ethnic groups and percentage of population from Asian ethnic groups, to NHS Leicester City CCG (225, 226). This allows for appropriate benchmarking. This CCG has had its own service re-organisation since 2009 (210). As of December 2013, people with diabetes in NHS Portsmouth CCG were 77.2% more likely to have a myocardial infarction, 33.1% more likely to have a stroke, 85.7% more likely to have a hospital admission related to heart failure and 42.1% more likely to die than the general population in the same area (225). In the same period, people with diabetes in NHS Leicester City CCG were only 38.9% more likely to have a myocardial infarction, 14.8% more likely to have a stroke, 58.7% more likely to have a hospital admission related to heart failure and 24.5% more likely to die than the general population in the same area (226).

These results suggest the enhanced care package is non-inferior to the specialist assisted integrated care provided in the core practices, we can be more confident that through the service redesign, the unintended

consequence of creating a lower quality of care for diabetes patients has not occurred. This supports a recent study in Australia where an innovative integrated primary–secondary model of care for people with complex type 2 diabetes demonstrated fewer admissions for a diabetes-related complication than those receiving usual care (227). This integrated care model consisted of a multidisciplinary, community-based and integrated primary-secondary care diabetes service similar to the care received in the core practices in Leicester City. Another study evaluated this integrated primary–secondary model of care for people with complex type 2 diabetes and showed not only positive impact on quality of the care but also did this at lower cost than usual care (228, 229), hence further supporting the success of the non-inferiority demonstrated by the enhanced practices. In the general population, reviews and meta-analysis of secondary cardiac prevention programmes have shown improved processes of care (230) and improved patient outcomes (231). A more recent meta-analysis showed that organisational interventions led to 21% reduced all-cause mortality and a 26% reduction in cardiac-related mortality. However, not enough data were available to assess for interventions on hospital admissions (232). In these studies however, these benefits tend to diminish as time goes on, thereby leading to doubts on long-term clinical and economic outcomes. The use of well-trained, well-organised primary care teams, offering enhanced diabetes care, which was the basis of the intervention evaluated in this study, could potentially provide longer lasting benefits.

Repeated admissions to hospitals are increasingly being used as a measure of quality of care of patients by primary care teams in most developed countries (233, 234). In the organisation of diabetes models of care, it is important to demonstrate that the service delivery is both safe and of a high enough quality as what is already available before the analysis for any cost savings can be completed. Here we demonstrate that our enhanced care delivery seems to achieve this.

The secondary objective demonstrated a lack of increase in the first outpatient's attendance in the enhanced practices when compared with the core-integrated practices. Therefore, diabetes patients can be managed safely by well-trained primary care teams closer to their homes, potentially at a lower cost. In addition, specialist teams, both physicians and nurses, are spared to focus on more complex diabetes and endocrine conditions in the specialist settings.

4.5a Strengths and weaknesses of the study

The strength of this analysis is the fact that we focused mainly on clinical outcomes and admissions and outpatients' attendances as opposed surrogate markers like HbA1c, blood pressure and cholesterol. Previous studies on structured integrated services redesigns have always focused on these intermediate outcomes (147, 154, 158, 163-165). An attempt was made to match practices in the exposed and control groups according to diabetes related characteristics and population demographics including age, co-morbidities and ethnicity. Admissions of people with diabetes could be for other reasons other than diabetes. Hence in our main analysis, we used cases in which diabetes was stated as a primary diagnosis. Furthermore, we extracted all diabetes admissions, whether diabetes was a primary or secondary diagnosis, and conducted a sensitivity analysis. The results of this further analysis were concordant with our main findings. All the outcome data were collected independently.

The main weakness of this study is that it is an observational study with a small sample size. Also the analysis was hampered due to the lack of access to individual patient clinical data over the study period. Another limitation was the fact that the matching of practices did not take into account practice list sizes and as a result there were more patients in the enhanced practices than in the core practices. This could affect some of the findings, as other factors such as resources allocation could be dependent on practice list size. In the choice of diabetes related complications, only non-fatal myocardial infarction, major foot amputations, hypoglycaemia and unspecified strokes were used (I64). A much broader list of diabetes

related microvascular complications such as renal complications (diabetic nephropathy, intracapillary glomerulonephrosis, Kimmelstiel–Wilson syndrome, ophthalmic complications (cataract, retinopathy), neurological complications (amyotrophy, mononeuropathy, autonomic neuropathy, polyneuropathy) and peripheral circulatory complications (gangrene, ulcer, peripheral angiopathy) should have been considered. Even in the case of the macro-vascular complications considered, only I64 cerebrovascular accidents were considered and these constitute only a small fraction of strokes. I61 and I63 are the main codes for stroke and should have been used for the analysis. Nevertheless, the sensitivity analysis performed; considering admissions with diabetes stated either as a primary or a secondary diagnosis, showed similar findings as the main analysis.

Even though the logic of the service redesign was to enable a cheaper service provision by shifting the care of diabetes patients from secondary to primary care, a further economic evaluation will be necessary to ascertain if there is any cost saving derived from the enhanced care package. Until then it is difficult to tell if the possible cost savings derived from the lack of increase in the non-elective bed days, first outpatient attendances and admissions with diabetes and its complications will be offset by the cost of the enhanced care package.

4.5b Implications for practice

Firstly, these findings are of relevance to policy makers in countries with well-established primary care services who aim to provide a safe and good quality care (235) away from specialist centres, which are associated with increasing costs of delivering hospital inpatient care.

In an attempt to decrease the over dependence on the usually expensive specialist based treatments and to reduce the burden of chronic disease, models of care along the lines of the chronic care model (154) and the primary-specialist care integrated care models have been shown to improve quality outcomes for people with complex conditions (236, 237). In many countries however, services integrations can usually be very

difficult to achieve due to constraints in varying sources of funding for primary and specialist teams. The use of well-trained primary care teams providing service along the lines of our enhance care teams could be an alternative. This could also be welcomed by the patients who would be guaranteed continuity of care from their family physician who in addition to knowing a lot about their diabetes also has good knowledge of the patients' other biopsychosocial aspects of life.

4.6 Conclusion

The analyses indicated that the use of a structured diabetes shared care service redesign, involving enhanced diabetes-skilled primary care physicians, nurses and health care assistants in primary care settings is unlikely to increase hospitalisations, first outpatient's attendance or even admissions for diabetes related complications any more than an integrated specialist–community care core diabetes service.

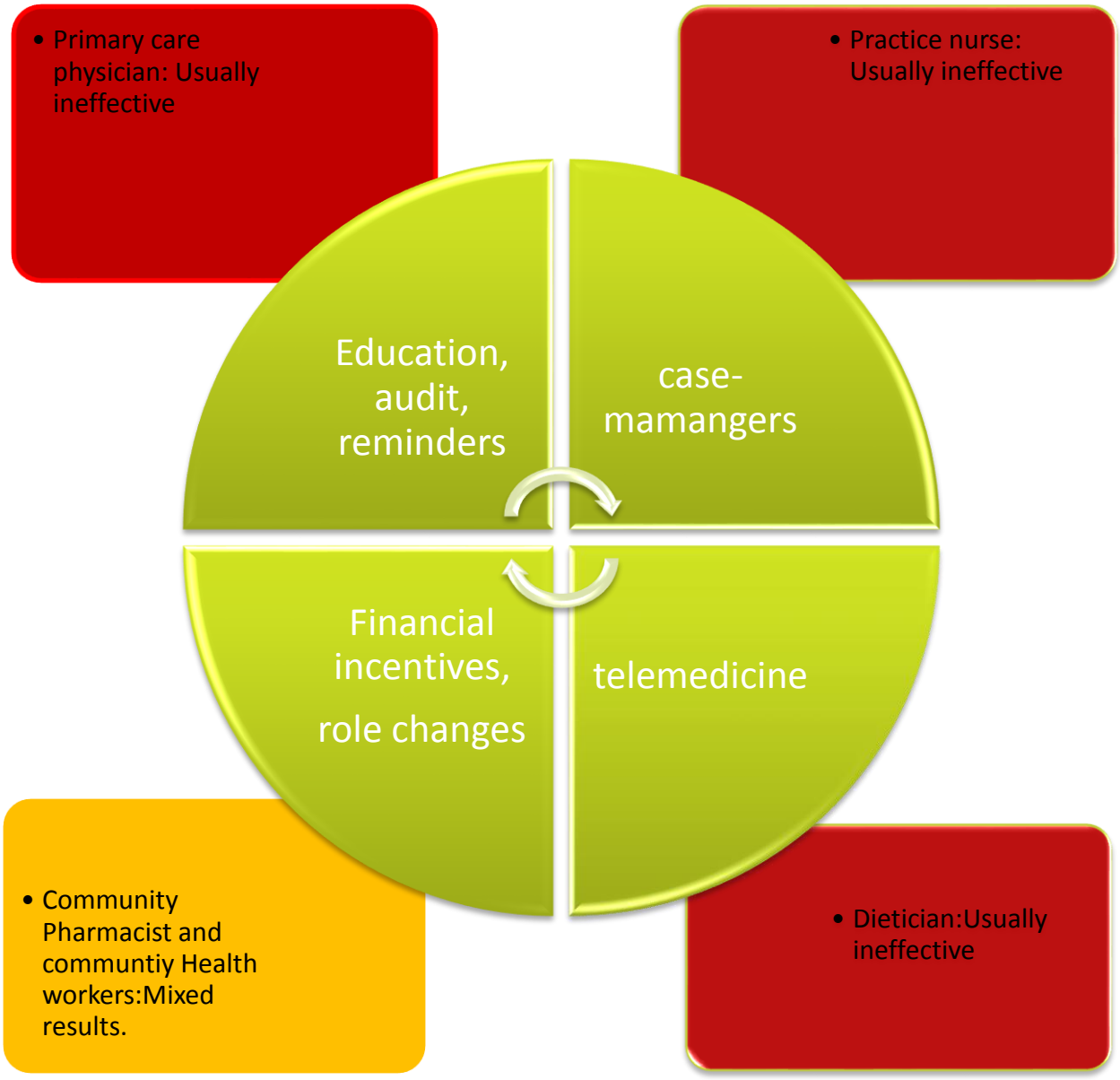
Chapter 5:

The shape of the new model of diabetes care

The translation of evidence from clinical trials into real and equitable improvements in diabetes management in the face of a growing prevalence of the disease tends to focus on changing health care professional behaviours (238). However, these healthcare professionals usually work in established multidisciplinary healthcare units, which usually have established processes in place and the professionals are expected to conform to these. Interdisciplinary teams working across primary and specialist care units, even though have shown positive improvements in outcomes, are usually difficult to establish due to contractual barriers in institutional mergers, problems in back office role merges and concerns around unified pathway adoption.

From the findings in this thesis, a model of diabetes care to increase the reliable use of evidence based multi-faceted interventions through the use of multiple professionals, rather than individual clinicians or isolated interventions, would be more adaptable. This interdisciplinary multifaceted model keeps the "wheels of success" in achievement of HbA1c rolling as illustrated on the green wheel in figure 11. The proposed multidisciplinary teams will be easier arranged in the primary care setting, closer to the patients' homes. A range of professionals functioning as a primary care team can provide diabetes care. This should include, physicians, practice and specialist nurses, dieticians, community pharmacists, psychologists, health-care assistants and in some cases community champions. When interventions are targeted at these groups independently of the other groups or interventions, there are "blocks to successful" achievements of targets, as illustrated in the red blocks in figure 11. A key intervention required to be used in combination with other interventions is the health care professional education. Even though on its own it can be ineffective, when combined with other interventions, an increased awareness of the impact of the ever-changing landscape in diabetes care occurs.

Figure 11: Primary care or community based professionals.



Interventions on the "Red blocks" alone show doubtful or ineffective results- ("block" the improvements in outcomes). The "Green wheel" represents multi-component interventions or multidisciplinary teams and gets achievements of HbA1c "rolling"

5.1 Up skilling of Primary or Community Care Professionals in Multidisciplinary Teams

In an Integrated primary care diabetes model, innovative collaboration between primary care team members can result in the creation of new health care organisations, which can provide integrated diabetes care for their local populations. With the patient in the centre, delivery of care can revolve around them, with the aspiration to have an organisational structure, clinical pathways and financial planning all aligning seamlessly (239). The subsequent care pathway developed should be customised to the wide-ranging needs of the local population and adapted to the evolving needs and the changing national health agendas instead of a 'one size fits all' model. The prime focus of the integrated primary care diabetes service is the integration of a health care system and the co-ordination of services around a patient, bringing together physicians, nurses, dieticians, health care assistants and community workers in setting nearer the patient' home.

In order to successfully maintain or even improve patient outcomes and reduce variation in care, while supporting this "left-shift" of care, up-skilling of general practitioners, practice nurses and health care assistants and on-going support from specialists in this field is required. This comprehensive health care professional up-skilling process needs to be based on psychological theories of learning (240-242) with the necessary knowledge and competency framework. This will hopefully equip the diabetes care workforce with the appropriate knowledge and skills to provide them the confidence to deliver highest quality care and improve patient outcomes.

Possible areas of training could include: mentorship and case management at practice level to support clinical development, training and care planning. Not only should the education and training be available at differing levels, but it needs to be provided by multiple alternative and complementary methods including the workplace based leaning, distance

learning, modular format, journal clubs and mentorship. The multi-disciplinary team creates an adaptable and responsive model with a feedback mechanism, which encourages the improvement of the quality of care through their knowledge of the local needs. Furthermore, and crucial for such an educational programme's longevity, it has to be developed so that it can reflect the continual changing approaches to diabetes management in relation to new therapies and national drivers.

Practices that participate and engage in this training process can gain accreditations based on the breadth and complexity of diabetes care that they provide. A stepwise and on-going accreditation process could start from the provision of a basic core service including screening of all patients at risk of diabetes, diabetes prevention interventions, regular surveillance of all patients with diabetes i.e. measuring and managing HbA1c according to guidance, blood pressure and cholesterol measurements and eye and feet examinations etc, cardiovascular disease risk reduction, evidence based prescribing, auditing care provided, and evidence of referral and attendance of all patients to evidence based patient education interventions/programmes.

A step up on the accreditation ladder will be practices that can provide elements of an enhanced service including the management of complex patients on insulin including in-house initiation and titration for people Type 2 diabetes, management of people with stable Type 1 diabetes, initiation and management of GLP-1 agonist therapies, high quality of care for housebound patients (including nursing/residential homes), and proactive discharge of suitable patients currently under specialist follow-up.

5.2 Focus on cardiovascular risk factor control

The presence of a complex health and illness profile is found to be associated with worse control of cardio-metabolic risk factors independent of regimen intensity and history of CHD (243). This is compounded by the fact that management of the major cardiovascular risk factors in diabetes have all raised questions on the benefits of high risk

factor control. In glycaemic control for example, although early intensive treatment in diabetes results in lasting benefit, including for CVD risk reduction (77), intensive glycaemic control in late diagnosis and in patients of high background cardiovascular disease does not reduce major cardiovascular events and indeed may increase mortality (78). Similarly, even though major reductions in cardiovascular outcomes is seen in patients receiving tight control of blood pressure compared with those receiving conventional control if the base line blood pressure was high (56, 79, 244) tight control of systolic BP among patients with diabetes and coronary artery disease has not been shown to improve cardiovascular outcomes (80). The findings in this thesis show that intensive glucose control and multifactorial intervention could reduce the risk of non-fatal MI but not non-fatal stroke, CVD mortality or all-cause mortality. Even though there were no statistically significant benefits in the reductions in mortality in both intensive glycaemic control and multifactorial interventions, there were trends towards a reduction in event rates of CV mortality and all-cause mortality in the multi-factorial intervention sub-groups. The benefits from multifactorial intervention seem to be more pronounced with the reduction in non-fatal stroke in this group being 47%. The effectiveness of intensive therapy to reduce mortality outcomes in patients with type 2 diabetes increases with increasing background cardiovascular risk in the population.

A good general knowledge and an understanding of the impact of glycaemic control and multifactorial cardiovascular risk management in primary care provides the means of answering a large number of important practical problems. The next hurdle will be how to apply the evidence from this thesis to provide such complete answers. Common clinical pathways through the use of information technology are a pre-requisite. Once up skilled in the handling of the complex glycaemic and cardiovascular risk treatment options in primary care, the primary care professionals will require information technology infrastructures which enable seamless passage of care through different units.

5.3 Enhancement of multidisciplinary teams through the use of Information Technology.

Local information technology (IT) infrastructure can enable records to be shared between primary, community and secondary care. This will also provide secure data centres to facilitate monitoring of clinical outcomes and service improvement. This can assist patients, carers and health care professionals in the choice of therapeutic options, understanding of the disease and its complications and self-management (245). Through the use of integrated IT systems, provision of therapies and services to people with diabetes in different health care regions is made possible by ensuring responsiveness to the needs and preferences of patients, improvements in health care process and intermediate outcomes, patient-clinician communication and access to medical information. Due consideration however needs to be given to potential barriers to the use of IT. Access to the IT infrastructure due to older age of patients, low income, education, cognitive impairment and physicians' concerns about increasing their workload are all potential barriers.

5.4 Expected advantages on primary care based multidisciplinary diabetes team

Diabetes is a chronic disease with a progressive deterioration and association with other co-morbid conditions. As a patient's condition changes, the constitution of the team may change to reflect the changing clinical and psychosocial needs of the patient. It is therefore extremely important that in addition to the wide range of professionals, there exists a range of interventions to be combined appropriately with the teams in order to meet the patients' needs. For example, in the case of the newly diagnosed young type diabetes patients under forty years old other priorities in their daily lives including work and childcare could compromise their compliance to medications. They may spend a long time waiting for clinic appointments (246). The use of the community

pharmacist may focus on medications adherence and home delivery of repeat prescriptions, clinical goals, and self-care activities. They may initiate diabetes care plans followed by telephone calls to facilitate diabetes management and adherence. As these patients progress in age and attain retirement, their needs and pressures also change. They now face the challenge of multi-morbid medical problems. Adherence may not so much be due to the lack of time, but may be due to interactions and side effects of multiple medications (247). The nurse case manager working in collaboration with the physician and the pharmacists, will then be the most useful team member.

Patient lists in primary care means continuity of care. So using primary care teams for this provision of integrated care service for people with diabetes will ensure continuity. The sustained patient-physician partnership is the paramount feature of primary care (248). There is evidence for a positive effect of continuity of care on both physician(249)and patient(250-253)satisfaction with care and patient adherence to medical regimens(254), emergency department and hospital utilization (255-257), overall service utilization, and cost.

Finally, since the cost of interventions are generally lower in the primary care setting, and my work in this thesis managed to demonstrate an equivalent level of effectiveness compared to other integrated community-specialist level models of diabetes care, it is plausible that this model of care is cost effective. Finally, it is important to remember that patient targeting is critical, and that applying interventions closer to the patient's home, where they offer the most benefit, is always going to be a preferred option for patients.

5.5 Areas for future research

Even though care delivery in the primary care setting tends to be less expensive, a further economic evaluation will be necessary to ascertain if there is any cost savings derived from the enhanced care package. Until then it is difficult to ascertain if the possible cost savings derived from the lack of increase in the non-elective bed days, first out-patient attendances and admissions with diabetes and its complications will be offset by the cost of the enhanced care package.

Diabetes is only one of the long term conditions primary care teams manage. Even though this evaluation has confirmed non-inferiority to the specialist-primary care integrative care services in diabetes, it is unclear if this success can be maintained in the long term. Primary care teams, unlike specialist teams, could be side-tracked from diabetes management in the face of competing demands from other disease areas. It will therefore be important to further explore how primary care teams can improve outcomes in patients with diabetes and other multi-morbidities. Several frequent comorbidities like heart diseases and chronic kidney disease depression, among others, are also identified in people with diabetes. These contribute to the problem of non-attainment of targets. In the multi-morbid persons with diabetes, lifestyle measures, medical nutrition therapy, and appropriately prescribed physical activity as well as weight loss for those who are overweight or obese are usually considered. Optimal control of glucose and other cardiovascular risk factors (e.g. smoking, sedentary lifestyle, hypertension, dyslipidaemia and obesity) is essential. Additionally, in the multi-morbid diabetes patient the control of the other chronic illnesses e.g. depression or heart failure, may at any particular clinical encounter be of paramount concern to the patient with diabetes. All interventions should therefore be tailored to the individual and provide on-going support. With a principal goal of treatment being safely achieving glycaemic control at the earliest possible stage with the least risk for adverse events, thereby increasing the likelihood of long-term durability of control and avoidance of complications in the future, there is a clinical need for a personalised algorithm that covers these issues.

Therefore, an important area of further exploration is to establish and test out an individualised algorithm to aid decision making by primary care teams in the management the multi-morbid diabetes patient in the context on their illness, especially in terms of the co-existent diseases. This will also test an implementation strategy of the use of this individualised decision-aid algorithm for reducing all-cause hospitalisations and diabetes related complications.

Chapter 6

Conclusion.

Unlike a new drug that cannot be introduced without exhaustive scientific trials, policy makers usually introduce new models of diabetes care with little or no scientific evaluation. These decisions are often based upon economic and political imperatives and yet seldom evaluate their impact on clinical outcomes like diabetes related hospitalisation for complications (258). If diabetes models of care were subject to the same scrutiny as new drug evaluations, licensing would not be achieved in most instances (258). By critically evaluating the impact of all the primary care interventions and health professions and systemically and quantitatively synthesising data on glucose control and multiple cardiovascular risk control, this thesis was scientifically rigorous enough to inform the use this primary care based model of care in various regions. The management of people with diabetes now largely occurs in the primary care setting (24). Due the high prevalence of diabetes in the primary care, an up skilled comprehensive primary care is less likely to lead to non-elective hospitalisation even after controlling for a variety of patient demographic and disease characteristics. Primary care teams working collaboratively and seamlessly, combining various interventions tailor-made of for their local populations can improve cardiovascular risk control and prevent and increase in hospitalisations due to diabetes related complications.

Previous studies in both industrialized and developing countries around other disease areas show that regions with better primary care have better health outcomes, including total mortality rates, heart disease mortality rates, and infant mortality, and earlier detection of cancers such as colorectal cancer, breast cancer, uterine/cervical cancer, and melanoma (259, 260). The opposite is the case for higher specialist supply, which is associated with worse outcomes (259, 260). Comprehensiveness in primary care is therefore necessary in order not only to avoid unnecessary referrals to diabetes specialists, but also to facilitate the coordination of care and improve continuity of care.

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8.0 Appendices

8.01 Appendix 2.1

Interventions targeting primary care professionals on improvement of diabetes outcomes. (Medline)

	You type in	MeSH headings to be selected from those that display
1	Education	Exp Education, Continuing/ Exp Education, Graduate/ Exp Education, graduate, continuing (note: I have assumed we are not interested in undergraduate education)
2	Audit	Exp Clinical Audit/
3	Feedback	"feedback" MeSH headings are suitable) psychological
4	Financial incentive*	Reimbursement, Incentive/ Physician Incentive Plans/ Reward/
5	Clinician reminder*	Quality of care Reminder system
6	Follow up	Treatment outcomes/
7	Professional roles	Exp Professional Role/
8	Medical records	Exp Medical Records/
9	Reminder systems	Reminder systems/
10	Primary care	Exp Primary Health Care
11	Primary health care	
12	General practice	Exp General Practice/
13	General practitioner*	
14	Nurse practitioner*	Exp Nurse Practitioners/
15	Diabet* nurses.mp.	
16	Diabetes specialist nurses.mp	
17	Community health nurse*	Community Health Nursing/ or Community Health Services/

18	Family practice	(Family Practice/ is included if you explode General Practice/)
19	GP or GPs	
20	Community health clinic	Community Health Centers/
21	Optometry	Optometry/
22	Optometrist*	Optometrist*.mp.
23	Pharmacist*	Pharmacists/
24	Community setting	Community setting.mp.
25	Community care	
26	Diabetes outcome*	Diabetes outcome*.mp.
27	Diabetic outcome*	Diabetic outcome*.mp.
28	Process* of care	Process* of care.mp.
29	Health metric*	
30	HbA1c	Hemoglobin A, Glycosylated
31	Glycosylated and (haemoglobin* or hemoglobin*)	
32	Glycated and (haemoglobin* or hemoglobin*)	
33	Lipids	
34	Exp Lipids/bl	
35	Blood sugar*	Blood Glucose/
36	Blood glucose	
37	LDL	Cholesterol, LDL (Lipoproteins, LDL is also available, and if you explode it you also retrieve Cholesterol, LDL)
38	HDL	Cholesterol, HDL (Lipoproteins, HDL is also available, and if you explode it you also retrieve Cholesterol, HDL)
39	Triglyceride*	Triglycerides/
40	Cholesterol	Cholesterol/
41	Quality of life	“Quality of Life”/
42	SF36 or SF 36	

43	Short form 36	Short form 36.mp
44	Episode* and hypoglyc*	
45	Blood pressure	Blood pressure/
46	Hypertension	Exp Hypertension/
47	Blood pressure measurement	Blood pressure determination/
48	OR/1-9	
49	OR/10-25	
50	OR/26-47	
51	58 AND 59 AND 60	
52	randomized controlled trials as topic/	
53	randomized controlled trial/	
54	random allocation/	
55	double blind method/	
56	single blind method/	
57	clinical trial/	
58	clinical trial phase i.pt.	
59	clinical trial phase ii.pt.	
60	clinical trial phase iii.pt.	
61	clinical trial phase iv.pt.	
62	controlled clinical trial.pt.	
63	randomized controlled trial.pt.	
64	multicenter study.pt.	
65	clinical trial.pt.	
66	exp clinical trial as topic/	
67	or/52-66	
68	(clinical adj trial$).tw.	

69	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	
70	PLACEBOS/	
71	placebo$.tw.	
72	randomly allocated.tw.	
73	(allocated adj2 random$).tw	
74	or/68-73	
75	67 or 74	
76	case report.tw.	
77	letter/	
78	historical article/	
79	or/76-78	
80	75 not 79	
81	49 and 50 and 51	
82	80 and 81	
83	exp Diabetes Mellitus, Type 1/	
84	exp Diabetes, Gestational/	
85	exp Diabetes Mellitus, Type 2/	
86	exp Prediabetic State/	
87	83 or 84 or 85 or 86	
88	82 and 87	131 artilces

Notes

Specific diabetes terms suggested. Enter them as searches 83 onwards and then "OR" those searches together. Then AND the result of that with set 82.

Type in the term in the left column. If a MeSH term is shown in the right column, select it and explode it if "exp" is indicated. Then click continue.

If the term in the left column has an exp or a / then it is a MeSH term and you need to type in the whole string as shown, with the exp and /

For sets 48 onwards, type in the string as shown ("or/1-8" is short way of writing "1 or 2 or 3 or 4 or 5 or 6 or 7 or 8")

8.02 Appendix 4.01 Paired t-tests for baseline characteristics.

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Deprivation in Core Practice	33.3250	8	12.00426	4.24415
	eDepreviation	34.0375	8	11.04613	3.90540
Pair 2	c_%male	52.5525	8	3.69700	1.30709
	e_%male	49.4000	8	2.54895	.90119
Pair 3	c_ % over 65	11.3100	8	3.93740	1.39208
	e_ % over 65	14.2000	8	4.05322	1.43303
Pair 4	c_Mean%achieving all 4	70.3419	8	10.61191	3.75187
	e_Mean%achieving all 4	78.0938	8	5.60271	1.98086
Pair 5	c_% of Any admission with T2 Diabetes and Non-fatal Myocardial Infarction or Non-fatal Stroke or major	.7813	8	.87391	.30898
	e_% of Any admission with T2 Diabetes and Non-fatal Myocardial Infarction or Non-fatal Stroke or major	.9300	8	.66650	.23565
Pair 6	c_% of Non-elective bed days per adult population over 17 years in 2013	3.8175	8	1.62379	.57410
	e_% of Non-elective bed days per adult population over 17 years in 2013	5.5788	8	2.09441	.74049

Paired Samples Correlations				
		N	Correlation	Sig.
Pair 1	Deprivation in Core Practice & eDepreviation	8	.828	.011
Pair 2	c_%male & e_%male	8	.704	.051
Pair 3	c_ % over 65 & e_ % over 65	8	-.147	.729
Pair 4	c_Mean%achieving all 4 & e_Mean%achieving all 4	8	.299	.472
Pair 5	c_% of Any admission with T2 Diabetes and Non-fatal Myocardial Infarction or Non-fatal Stroke or major foot amputations n the same spell per adult population over 17 years in 2013 & e_% of Any admission with T2 Diabetes and Non-fatal Myocardial Infarction or Non-fatal Stroke or major foot amputations n the same spell per adult	8	-.181	.668
Pair 6	c_% of Non-elective bed days per adult population over 17 years in 2013 & e_% of Non-elective bed days per adult population over 17 years in 2013	8	.200	.634

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the				
					Lower	Upper			
Pair 1	Deprivation in Core Practice - eDepreviation	-.71250	6.81688	2.41013	-6.41155	4.98655	-.296	7	.776
Pair 2	c_%male - e_%male	3.15250	2.62451	.92791	.95835	5.34665	3.397	7	.011
Pair 3	c_ % over 65 - e_ % over 65	-2.89000	6.05071	2.13925	-7.94852	2.16852	-1.351	7	.219
Pair 4	c_Mean%achieving all 4 - e_Mean%achieving all 4	-7.75187	10.41443	3.68206	-16.45856	.95481	-2.105	7	.073

Pair 5	c_% of Any admission with T2 Diabetes and Non-fatal Myocardial Infarction or Non-fatal Stroke or major foot amputations n the same spell per adult population over 17 years in 2013 - e_% of Any admission with T2 Diabetes and Non-fatal Myocardial Infarction or Non-fatal Stroke or major foot amputations n the same spell per adult population over 17 years in 2013	-.14875	1.19125	.42117	-1.14466	.84716	-.353	7	.734
Pair 6	c_% of Non-elective bed days per adult population over 17 years in 2013 - e_% of Non-elective bed days per adult population over 17 years in 2013	-1.76125	2.37898	.84110	-3.75012	.22762	-2.094	7	.075

8.03 Appendix 4.02

A simple linear regression was calculated to predict the difference in non-elective bed days between the matched core and enhanced practice upon difference between the % male in the core practices and the enhanced practices. Preliminary analyses were performed to ensure to ensure there was no violation of assumption of normality and linearity. A non-significant regression equation was found F(1,6) =0.023, P= 0.89 with an R2 of -0.16

Descriptive Statistics			
	Mean	Std. Deviation	N
Difference between changed in Non-elective bed days between core and enhanced practices.	-2.1975	3.72902	8
Difference between percentage male in core and enhanced practices	3.1525	2.62451	8

Correlations			
		Difference between changed in Non-elective bed days between core and enhanced practices.	Difference between percentage male in core and enhanced practices
Pearson Correlation	Difference between changed in Non-elective bed days between core and enhanced practices.	1.000	.062
	Difference between percentage male in core and enhanced practices	.062	1.000
Sig. (1-tailed)	Difference between changed in Non-elective bed days between core and enhanced practices.	.	.442
	Difference between percentage male in core and enhanced practices	.442	.
N	Difference between changed in Non-elective bed days between core and enhanced practices.	8	8
	Difference between percentage male in core and enhanced practices	8	8

Variables Entered/Removed[a]			
Model	Variables Entered	Variables Removed	Method
1	Difference between percentage male in core and enhanced practices[b]	.	Enter
a. Dependent Variable: Difference between changed in Non-elective bed days between core and enhanced practices.			
b. All requested variables entered.			

Model Summary[b]				
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.062[a]	.004	-.162	4.02013
a. Predictors: (Constant), Difference between percentage male in core and enhanced practices				
b. Dependent Variable: Difference between changed in Non-elective bed days between core and enhanced practices.				

ANOVA[a]						
Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	.370	1	.370	.023	.885[b]
	Residual	96.969	6	16.161		
	Total	97.339	7			
a. Dependent Variable: Difference between changed in Non-elective bed days between core and enhanced practices.						
b. Predictors: (Constant), Difference between percentage male in core and enhanced practices						

Coefficients[a]								
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	-2.474	2.313		-1.069	.326	-8.134	3.187
	Difference between percentage male in core and enhanced practices	.088	.579	.062	.151	.885	-1.329	1.504
a. Dependent Variable: Difference between changed in Non-elective bed days between core and enhanced practices.								

Residuals Statistics[a]					
	Minimum	Maximum	Mean	Std. Deviation	N
Predicted Value	-2.5535	-1.9041	-2.1975	.23001	8
Residual	-4.96112	4.30210	.00000	3.72192	8
Std. Predicted Value	-1.548	1.275	.000	1.000	8
Std. Residual	-1.234	1.070	.000	.926	8

a. Dependent Variable: Difference between changed in Non-elective bed days between core and enhanced practices.

8.04 Appendix 4.03

A simple linear regression was calculated to predict the difference in first outpatients' appointment between the matched core and enhanced practice upon difference between the % male in the core practices and the enhanced practices. Preliminary analyses were performed to ensure to ensure there was no violation of assumption of normality and linearity. A non-significant regression equation was found F(1,6) =0.69, P= 0.44 with an R2 of -0.046

Descriptive Statistics			
	Mean	Std. Deviation	N
Difference between changed in first outpatient appointment between core and enhanced practices.	-.2250	5.93747	8
Difference between percentage male in core and enhanced practices	3.1525	2.62451	8

Correlations			
		Difference between changed in first outpatient appointment between core and enhanced practices.	Difference between percentage male in core and enhanced practices
Pearson Correlation	Difference between changed in first outpatient appointment between core and enhanced practices.	1.000	.322
	Difference between percentage male in core and enhanced practices	.322	1.000
Sig. (1-tailed)	Difference between changed in first outpatient appointment between core and enhanced practices.	.	.218
	Difference between percentage male in core and enhanced practices	.218	.
N	Difference between changed in first outpatient appointment between core and enhanced practices.	8	8
	Difference between percentage male in core and enhanced practices	8	8

Variables Entered/Removed[a]			
Model	Variables Entered	Variables Removed	Method
1	Difference between percentage male in core and enhanced practices[b]	.	Enter
a. Dependent Variable: Difference between changed in first outpatient appointment between core and enhanced practices.			
b. All requested variables entered.			

Model Summary[b]				
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.322[a]	.104	-.046	6.07180
a. Predictors: (Constant), Difference between percentage male in core and enhanced practices				
b. Dependent Variable: Difference between changed in first outpatient appointment between core and enhanced practices.				

ANOVA[a]						
Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	25.574	1	25.574	.694	.437[b]
	Residual	221.201	6	36.867		
	Total	246.775	7			
a. Dependent Variable: Difference between changed in first outpatient appointment between core and enhanced practices.						
b. Predictors: (Constant), Difference between percentage male in core and enhanced practices						

Coefficients[a]								
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	-2.521	3.494		-.722	.498	-11.070	6.028
	Difference between percentage male in core and enhanced practices	.728	.874	.322	.833	.437	-1.411	2.868
a. Dependent Variable: Difference between changed in first outpatient appointment between core and enhanced practices.								

Residuals Statistics[a]					
	Minimum	Maximum	Mean	Std. Deviation	N
Predicted Value	-3.1837	2.2129	-.2250	1.91140	8
Residual	-6.20202	9.28706	.00000	5.62140	8
Std. Predicted Value	-1.548	1.275	.000	1.000	8
Std. Residual	-1.021	1.530	.000	.926	8
a. Dependent Variable: Difference between changed in first outpatient appointment between core and enhanced practices.					

8.05 Appendix 4.04

A simple linear regression was calculated to predict the difference in admissions with type 2 diabetes (and non-fatal myocardial infarction or non-fatal stroke or foot amputations in the same spell) between the matched core and enhanced practice, upon difference between the % male in the core practices and the enhanced practices. Preliminary analyses were performed to ensure to ensure there was no violation of assumption of normality and linearity. A non-significant regression equation was found F(1,6) =0.26, P= 0.63 with an R2 of -0.12

Descriptive Statistics			
	Mean	Std. Deviation	N
Difference between changed in any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations In the same spell between core and enhanced practices	-.3038	1.37611	8
Difference between percentage male in core and enhanced practices	3.1525	2.62451	8

Correlations			
		Difference between changed in any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or	Difference between percentage male in core and enhanced practices
Pearson Correlation	Difference between changed in any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations In the same spell between core and enhanced practices	1.000	.205
	Difference between percentage male in core and enhanced practices	.205	1.000
Sig. (1-tailed)	Difference between changed in any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations In the same spell between core and enhanced practices	.	.313
	Difference between percentage male in core and enhanced practices	.313	.
N	Difference between changed in any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations In the same spell between core and enhanced practices	8	8
	Difference between percentage male in core and enhanced practices	8	8

Variables Entered/Removed[a]			
Model	Variables Entered	Variables Removed	Method
1	Difference between percentage male in core and enhanced practices[b]	.	Enter
a. Dependent Variable: Difference between changed in any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations In the same spell between core and enhanced practices			
b. All requested variables entered.			

Model Summary[b]				
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.205[a]	.042	-.118	1.45486
a. Predictors: (Constant), Difference between percentage male in core and enhanced practices				
b. Dependent Variable: Difference between changed in any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations In the same spell between core and enhanced practices				

ANOVA[a]						
Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	.556	1	.556	.263	.627[b]
	Residual	12.700	6	2.117		
	Total	13.256	7			
a. Dependent Variable: Difference between changed in any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations In the same spell between core and enhanced practices						
b. Predictors: (Constant), Difference between percentage male in core and enhanced practices						

Coefficients[a]								
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	-.642	.837		-.767	.472	-2.691	1.406
	Difference between percentage male in core and enhanced practices	.107	.210	.205	.513	.627	-.405	.620
a. Dependent Variable: Difference between changed in any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations In the same spell between core and enhanced practices								

Residuals Statistics[a]					
	Minimum	Maximum	Mean	Std. Deviation	N
Predicted Value	-.7401	.0558	-.3037	.28187	8
Residual	-2.45577	1.90755	.00000	1.34694	8
Std. Predicted Value	-1.548	1.275	.000	1.000	8
Std. Residual	-1.688	1.311	.000	.926	8
a. Dependent Variable: Difference between changed in any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations In the same spell between core and enhanced practices					

8.06 Appendix 4.05

A simple linear regression was calculated to predict the difference in admission with type 2 diabetes, primary or secondary- sensitivity analysis, between the matched core and enhanced practice, upon difference between the % male in the core practices and the enhanced practices. Preliminary analyses were performed to ensure to ensure there was no violation of assumption of normality and linearity. A non-significant regression equation was found F(1,6) =2.12, P= 0.20 with an R2 of 0.14

Descriptive Statistics			
	Mean	Std. Deviation	N
Difference between changed in admissions with a diagnosis of T2 diabetes, primary or secondary - for sensitivity analysis between core and enhanced practices.	-2.7822	6.56824	8
Difference between percentage male in core and enhanced practices	3.1525	2.62451	8

Correlations			
		Difference between changed in admissions with a diagnosis of T2 diabetes, primary or secondary - for sensitivity analysis between core and enhanced practices.	Difference between percentage male in core and enhanced practices
Pearson Correlation	Difference between changed in admissions with a diagnosis of T2 diabetes, primary or secondary - for sensitivity analysis between core and enhanced practices.	1.000	-.511
	Difference between percentage male in core and enhanced practices	-.511	1.000
Sig. (1-tailed)	Difference between changed in admissions with a diagnosis of T2 diabetes, primary or secondary - for sensitivity analysis between core and enhanced practices.	.	.098
	Difference between percentage male in core and enhanced practices	.098	.
N	Difference between changed in admissions with a diagnosis of T2 diabetes, primary or secondary - for sensitivity analysis between core and enhanced practices.	8	8
	Difference between percentage male in core and enhanced practices	8	8

Variables Entered/Removed[a]			
Model	Variables Entered	Variables Removed	Method
1	Difference between percentage male in core and enhanced practices[b]	.	Enter
a. Dependent Variable: Difference between changed in admissions with a diagnosis of T2 diabetes, primary or secondary - for sensitivity analysis between core and enhanced practices.			
b. All requested variables entered.			

Model Summary[b]				
Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.511[a]	.261	.138	6.09994
a. Predictors: (Constant), Difference between percentage male in core and enhanced practices				
b. Dependent Variable: Difference between changed in admissions with a diagnosis of T2 diabetes, primary or secondary - for sensitivity analysis between core and enhanced practices.				

Coefficients[a]								
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	1.246	3.510		.355	.735	-7.342	9.835
	Difference between percentage male in core and enhanced practices	-1.278	.878	-.511	-1.455	.196	-3.427	.872
a. Dependent Variable: Difference between changed in admissions with a diagnosis of T2 diabetes, primary or secondary - for sensitivity analysis between core and enhanced practices.								

Residuals Statistics[a]					
	Minimum	Maximum	Mean	Std. Deviation	N
Predicted Value	-7.0599	2.4092	-2.7822	3.35383	8
Residual	-10.03403	8.72247	.00000	5.64745	8
Std. Predicted Value	-1.275	1.548	.000	1.000	8
Std. Residual	-1.645	1.430	.000	.926	8
a. Dependent Variable: Difference between changed in admissions with a diagnosis of T2 diabetes, primary or secondary - for sensitivity analysis between core and enhanced practices.					

8.07 Appendix 4.06

Paired T-TESTS FOR OUTCOMES.

Paired Samples Statistics					
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Difference between % of Non-elective bed days per adult population over 17 years in 2013 and 2014 in core practices	-1.2850	8	2.85396	1.00903
	Difference between % of Non-elective bed days per adult population over 17 years in 2013 and 2014 in enhanced practices	.9125	8	2.09903	.74212
Pair 2	Difference between 1st OP appointment per thousand in 2013 and 2014 in the core practices	1.0250	8	3.82912	1.35380
	Difference between 1st OP appointment per thousand in 2013 and 2014 in the enhanced practices	1.2500	8	4.44169	1.57037
Pair 3	Difference between % of any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations n the same spell per adult population over 17 years in 2013 and 2014 in the core practices	-.0425	8	1.09205	.38610
	Difference between % of any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations n the	.2613	8	.59633	.21084

	same spell per adult population over 17 years in 2013 and 2014 in the enhanced practices				
Pair 4	Difference between the % of admissions with a diagnosis of T2 diabetes, primary or secondary in 2013 and 2014 in the core practices- for sensitivity analysis	-3.8451	8	5.85677	2.07068
	Difference between the % of admissions with a diagnosis of T2 diabetes, primary or secondary in 2013 and 2014 in the enhanced practices- for sensitivity analysis	-1.0629	8	4.07194	1.43965

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	Difference between % of Non-elective bed days per adult population over 17 years in 2013 and 2014 in core practices & Difference between % of Non-elective bed days per adult population over 17 years in 2013 and 2014 in enhanced practices	8	-.113	.790
Pair 2	Difference between 1st OP appointment per thousand in 2013 and 2014 in the core practices& Difference between 1st OP appointment per thousand in 2013 and 2014 in the enhanced practices	8	-.025	.952
Pair 3	Difference between % of any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations n the same spell per adult population over 17 years in 2013 and 2014 in the core practices & Difference between % of any	8	-.265	.525

	admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations n the same spell per adult population over 17 years in 2013 and 2014 in the enhanced practices			
Pair 4	Difference between the % of admissions with a diagnosis of T2 diabetes, primary or secondary in 2013 and 2014 in the core practices- for sensitivity analysis & Difference between the % of admissions with a diagnosis of T2 diabetes, primary or secondary in 2013 and 2014 in the enhanced practices- for sensitivity analysis	8	.162	.701

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Difference between % of Non-elective bed days per adult population over 17 years in 2013 and 2014 in core practices - Difference between % of Non-elective bed days per	-2.19750	3.72902	1.31841	-5.31504	.92004	-1.667	7	.139

	adult population over 17 years in 2013 and 2014 in enhanced practices								
Pair 2	Difference between 1st OP appointment per thousand in 2013 and 2014 in the core practices - Difference between 1st OP appointment per thousand in 2013 and 2014 in the enhanced practices	-.22500	5.93747	2.09921	-5.18885	4.73885	-.107	7	.918
Pair 3	Difference between % of any admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations n the same spell per adult population over 17 years in 2013 and 2014 in the core practices - Difference between % of any	-.30375	1.37611	.48653	-1.45421	.84671	-.624	7	.552

	admission with T2 Diabetes and non-fatal myocardial infarction or non-fatal stroke or major foot amputations n the same spell per adult population over 17 years in 2013 and 2014 in the enhanced practices								
Pair 4	Difference between the % of admissions with a diagnosis of T2 diabetes, primary or secondary in 2013 and 2014 in the core practices- for sensitivity analysis - Difference between the % of admissions with a diagnosis of T2 diabetes, primary or secondary in 2013 and 2014 in the enhanced practices- for sensitivity analysis	-2.78217	6.56824	2.32222	-8.27336	2.70902	-1.198	7	.270

8.08 Appendix 4.07: Peer-reviewed published articles from chapters of thesis