Diabetes prevention: economic evaluation of individual case-based and population-wide prevention programmes and implications for public policy

Samantha Roberts

A thesis submitted for the degree of

Doctor of Philosophy in Evidence-Based Health Care

Green Templeton College, Department of Continuing Education

University of Oxford, Hilary 2019

ABSTRACT

Diabetes prevention: economic evaluation of individual case-based and population-wide prevention programmes and implications for public policy

Samantha Roberts

This thesis aims to inform diabetes prevention policy through economic evaluation of individual-case based and population-wide prevention programmes for type 2 diabetes (T2DM). Two broad approaches are described: i) individual case-based programmes focusing on individuals at high risk of T2DM and ii) population-wide programmes that seek to modify an entire population's risk of developing T2DM.

Published evidence on individual case-based interventions is described, with both lifestyle programmes and metformin appearing effective at reducing incidence of T2DM and being cost-effective at a willingness-to-pay threshold of £20,000/QALY. However, key differences were identified between current clinical guidelines/national policy in England and published economic evaluations. The implications of these different approaches to individual case-based programmes, in terms of cost-effectiveness, budget impact and incidence of T2DM, are quantified using a de novo Markov model. This analysis found that whilst current UK national guidance and policy is likely to be cost-effective and have the most favourable budget impact, it will prevent fewer than 5% of incident cases of T2DM over 50 years.

Alternative approaches to diabetes prevention, using population-wide programmes, are therefore identified. Their impact on T2DM, or its major risk factor of adiposity, is summarised through an overview of systematic reviews. Four population-wide actions were associated with lower BMI, including sugar sweetened beverage tax, menu labelling, food store interventions and multi-component community interventions. However, impact on T2DM was impossible to quantify precisely due to lack of primary studies. A pre-existing micro-simulation model was utilised to quantify the potential impact of these interventions on healthcare costs associated with T2DM, QALYs and cumulative incidence of T2DM. This analysis found that these four interventions were associated with reduced costs relating to T2DM and increased QALYs. However, costs and benefits outside the health system precluded meaningful assessment of cost-effectiveness and the interventions resulted in only a small reduction in incidence of T2DM.

These findings support a more comprehensive, complex systems approach to diabetes prevention policy that encompasses both individual case-based and population-wide programmes. They suggest that, even if all the available evidence-based policies described in this DPhil were implemented, they may still be insufficient to substantially reduce the prevalence of T2DM in England. This moves the diabetes prevention policy debate on from considering which single approach to adopt (individual case-based or population-wide) to considering how to implement a combination of programmes concurrently and continuing to search for new, promising interventions at both an individual and population level.

ACKNOWLEDGEMENTS

Professor Trish Greenhalgh provided the academic supervision of this doctoral thesis. Her experience in diabetes prevention, evidence-based medicine and qualitative research provided the scaffolding on which it was developed. Trish is the most generous and astute of supervisors, and worked tirelessly to involve others in my research when my field of interest extended into health economics and modelling.

Prof Gwyn Bevan and Dr Mara Airoldi, from the London School of Economics and Blavatnik School of Government at the University of Oxford respectively, provided me with an early introduction to health economics, in particular the issue of allocative efficiency. They supported the early stages of this DPhil, helping to build a joint programme of enquiry in my doctorate that initially spanned health economic modelling and qualitative research.

Prof Klim McPherson, from the Nuffield School of Primary Care Health Sciences, University of Oxford, supported the later phases of this DPhil providing an introduction to the UK Health Forum and an experienced eye in the evaluation of population-wide interventions.

Prof Dawn Craig, from Newcastle University, welcomed me into her academic unit specialising in health economics just as I was developing my first health economic model and provided an endless source of practical advice as this DPhil progressed.

My DPhil was part-funded by the National Institute for Health Research Biomedical Research Centre, Oxford, grant BRC-1215-20008 to the Oxford University Hospitals NHS Foundation Trust and the University of Oxford.

STATEMENT OF CONTRIBUTIONS

This doctoral thesis is independent and original work of which I am the sole author. My academic supervisor Prof Trish Greenhalgh contributed intellectual guidance on the overall research strategy, analyses and presentation of results.

Other individuals have made contributions in the following ways:

Eleanor Barry (EB): DPhil Student in Primary Care, University of Oxford undertook the initial search for the systematic review in Chapter 3 and reviewed data extraction and quality assessment of a proportion of papers included in this review.

Dawn Craig (DC): Principal Scientist, University of Newcastle provided guidance on structure and key parameter values of the Markov model in Chapter 4.

Louis Pilard (LP): The Centre for Sustainable Healthcare, Oxford reviewed abstracts for inclusions in the overview of systematic reviews in Chapter 5 and checked data extraction and quality assessment of a proportion of papers included in this review.

Quinn Chen (QC): MSc Student in Primary Care, University of Oxford reviewed data extraction and quality assessment of a proportion of papers included in the overview of systematic reviews in Chapter 5.

Jennifer Hirst (JH): Senior Researcher in Primary Care, University of Oxford advised on the methods to complete the meta-analysis in Chapter 5.

Abbygail Jaccard (AJ): Deputy Director of Public Health Modelling, UK Health Forum provided training on the use of the UK Health Forum model, wrote new code for an

intervention to be included in the model and checked parameter values, population data files and results of the analysis in Chapter 6.

Yaling Yang and Lucy Abel: Health Economists in Primary Care, University of Oxford reviewed early drafts of Chapter 6.

Nia Roberts (NR): Information Specialist, University of Oxford, Bodleian Library assisted in developing the search strategy for the overview of systematic reviews in Chapter 5.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
BMI	Body mass index
CCG	Clinical Commissioning Group
DALY	Disability-adjusted life year
EPHPP	Effective Public Health Practice Project
FDPS	Finnish Diabetes Prevention Study
HbA1c	Glycated haemoglobin
ICER	Incremental cost-effectiveness ratio
IEC	International Expert Committee
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
Indian DPP	Indian Diabetes Prevention Programme
Kcal	Kilocalorie
LYG	Life year gained
MCI	Multi-component community intervention
NHS	National Health Service (UK)
NHS EED	NHS Economic Evaluation Database
NHS DPP	National Health Service Diabetes Prevention Programme
NICE	National Institute of Health and Care Excellence
NNT	Number needed to treat
PA	Physical activity
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SSB	Sugar-sweetened beverage
T2DM	Type 2 diabetes mellitus
US DPP	United States Diabetes Prevention Program
US DPPOS	United States Diabetes Prevention Program Outcomes Study
WHO	World Health Organisation

CHAPTER ONE

Introduction

CHAPTER 1: INTRODUCTION

1.1. OVERVIEW OF THESIS

This thesis explores the impact of a range of prevention policies for type 2 diabetes (T2DM) on health system cost, health outcomes of individuals (quality-adjusted life years) and population health (incidence of T2DM).

The high and rising prevalence of T2DM worldwide, and the associated economic costs, are well documented [1]. Consequently, diabetes prevention is a global public health priority [2-4]. The question of whether to target preventive efforts at individuals, populations or both is debated [5]. Preventive efforts targeted at high-risk individuals (e.g. those with intermediate hyperglycaemia, defined in Chapter 2) include lifestyle behavioural change programmes or oral hypoglycaemic medications (metformin) [6]. Population-wide interventions, in contrast, seek to modify the entire population's risk of developing the disease through a range of public health interventions [7].

My DPhil started as an action research project in Newham, East London where a third of the adult population is at high risk of developing T2DM in the next 10 years [8]. I initially planned to undertake economic evaluations of local T2DM prevention programmes using the SocioTechnical Allocation of Resources (STAR) approach [9]. However, my collaboration on a systematic review of efficacy of screen and treat policies for high-risk individuals [10] revealed controversies in individual case-based approaches to prevention. While I was working on that review with others, Healthier You, the NHS Diabetes Prevention

Programme, based on individual case-based interventions, was developed and rolled out across England [3]. These two experiences led me to question whether the NHS Diabetes Prevention Programme was in fact the most effective approach to prevention, given the controversies in the existing literature. I consequently broadened the scope of this DPhil to consider alternative diabetes prevention policies, their impact on cost, quality-adjusted life years (QALYs) and incidence of T2DM and how these compared to current national policy in England and other developed countries.

Beginning with a description of current diabetes prevention policy in England and other high-income countries and an outline of the controversies associated with identifying and managing people at high risk of developing T2DM, my DPhil addresses two groups of policy responses to the challenge of preventing T2DM: i) individual case based programmes targeted at participants at high risk of developing T2DM and ii) population-wide programmes targeting the entire population.

The existing evidence of individual case-based prevention programmes' impact on cost and health outcomes was synthesised through a systematic review. This found some evidence that lifestyle programmes and metformin were cost-effective, but most existing studies did not reflect UK guidelines in both the high-risk population selected and the intensity of lifestyle programme provided. The impact of these differences was examined using a de novo Markov model, which analysed nine alternative approaches to individual case-based prevention. This analysis indicated that, as I had anticipated, different definitions of high-risk populations and different intensities of lifestyle programme do indeed lead to

differences in the cost-effectiveness of diabetes prevention programmes. And whilst low intensity lifestyle programmes, such as the NHS Diabetes Prevention Programme, were the most cost-effective with favourable budget impact, their impact on cumulative incidence of T2DM across a population was likely to be relatively small.

These small gains in population-level incidence of T2DM suggested that population-wide diabetes prevention programmes may be an important part of a wider diabetes prevention policy. I therefore undertook an overview of systematic reviews of population-wide interventions aimed at preventing diabetes or its most important risk factor, obesity. This identified four population-wide actions that appeared promising in terms of reducing BMI: sugar sweetened beverage tax, menu labelling, food store interventions and multi-component community interventions. However, impact on subsequent incidence of T2DM was impossible to quantify precisely due to the dearth of primary studies that had measured this outcome directly. I then undertook an economic evaluation of these population-wide actions using a pre-existing micro-simulation model developed by the UK Health Forum, an independent non-profit research organisation. This model showed that whilst these interventions appeared to reduce overall health system costs, their impact on cumulative incidence of T2DM remained small.

The thesis concludes with a description of the implications of these findings for policy makers.

1.2. AIMS, RESEARCH QUESTIONS, OBJECTIVES AND STUDY DESIGN

The aim of this thesis was to inform diabetes prevention policy through economic evaluation of individual-case based and population-wide diabetes prevention programmes.

The research questions were:

a) What is the efficacy and cost-effectiveness of individual case-based interventions for prevention of T2DM?
b) What is the impact of alternative approaches to individual case-based prevention programmes on T2DM-related health system costs and health outcomes?
c) What is the efficacy of population-wide prevention programmes targeting T2DM or its key risk factor, obesity?
d) What is the impact of population-wide prevention programmes on T2DM-related health system costs and health outcomes?
e) What are the implications of this research for policy makers developing T2DM prevention programmes?

The research objectives were to:

a) Synthesise existing evidence of efficacy and cost-effectiveness of individual case-based interventions for prevention of T2DM

b) Quantify the impact of alternative approaches to individual case-based T2DM prevention programmes on health system cost and health outcomes

c) Synthesise existing evidence of efficacy of population-wide prevention programmes targeting T2DM or its key risk factor, obesity

d) Quantify the impact of population-wide prevention programmes on T2DM-related health system costs and health outcomes

e) Draw out the implications of this research for policy makers developing T2DM prevention programmes

This thesis includes six main study designs:

a) Narrative review of current approaches to T2DM prevention to describe the most common types of individual case-based prevention programmes and their efficacy;
b) Systematic review of economic evaluations of individual case-based T2DM prevention programmes to determine the cost-effectiveness of these programmes;
c) Review of systematic reviews to define population-wide programmes that are effective in preventing T2DM or its main risk factor, obesity;
d) Economic evaluation, creating a de novo Markov model, to determine the effect of alternative definitions of high risk populations and intensity of interventions

on cost, health outcomes and cost-effectiveness of individual case-based programmes;

e) Economic evaluation, using a pre-existing microsimulation model, to quantify the impact of a range of population-wide prevention programmes on health system costs and health outcomes;

f) Meta-analysis of studies describing population-wide programmes' impact on body mass index (BMI) to determine parameter values for the economic evaluation of population-wide programmes outlined above.

1.3. STRUCTURE OF THESIS

CHAPTER 2: Current approaches to diabetes prevention (narrative review of the literature)

T2DM prevention policies are formed in a context of lack of international consensus regarding how to identify high risk participants and different judgements regarding the efficacy and affordability of interventions. The aim of this narrative review was to: i) describe why diabetes prevention is important to policy makers and how those who have prioritised diabetes prevention have chosen to respond, ii) outline the range of approaches used to identify high-risk participants and iii) summarise evidence of efficacy of the most common elements of T2DM prevention policy.

CHAPTER 3: Individual case-based approaches to preventing T2DM: Current evidence of cost-effectiveness and budget impact (systematic review)

Chapter 3, which is based on a published systematic review in BMJ Open on which I was lead author [11], summarises the current evidence of cost-effectiveness of individual case-based

interventions (lifestyle programmes and metformin) and the extent to which this evidence supports current diabetes prevention policy in England. Based on existing literature, metformin and lifestyle interventions in people at high risk of developing T2DM (due to intermediate hyperglycaemia) appear to be cost-effective but not cost saving, and impact on incident cases of diabetes is limited (0.1-1.6% reduction in incident cases). National T2DM prevention policy in the UK and US advocates pragmatic lifestyle programmes (less than 3 years in duration), and in the UK the use of HbA1c or fasting plasma glucose is recommended for identifying eligible participants for these programmes. However, most cost-effectiveness studies relate to different eligibility criteria for participants and a higher intensity of intervention, which limits the direct applicability of findings.

CHAPTER 4: Individual case-based approaches to preventing T2DM: Economic evaluation of alternative programmes (economic evaluation using a Markov model)

Chapter 4, which is based on a published paper in BMC Medicine on which I was lead author [12], explores the difference in cost-effectiveness related to different intensities of lifestyle programmes and different definitions of eligibility for T2DM prevention programmes, to address the gap in the literature regarding the most cost-effective diagnosis-intervention pairs identified in Chapter 3. An economic evaluation of nine alternative individual case-based prevention programmes was undertaken using a de novo decision tree and Markov model, including analysis of impact at an individual level (e.g. ICERs) and a population level in England. This analysis found that different eligibility criteria (defined by different types of intermediate hyperglycaemia) and different intensities of lifestyle programme do lead to differences in the cost-effectiveness of T2DM prevention programmes. Whilst a programme like the NHS Diabetes Prevention Programme (low intensity lifestyle intervention in people

with elevated HbA1c or IFG) was the most cost-effective and had the most favourable budget impact, an England-wide programme was unlikely to have a large impact on incident cases of T2DM (<3.5% reduction in cumulative incidence over 50 years).

CHAPTER 5: Population-wide prevention programmes: Overview of population-level interventions aimed at reducing T2DM or BMI (overview of systematic reviews and meta-analysis)

This chapter, based on a paper in press for Obesity Reviews on which I am lead author, takes account of the limited population-level impact of individual case-based prevention programmes and explores which interventions could be promising elements of population-wide diabetes prevention policies. An overview of systematic reviews was undertaken to identify population-wide programmes that are associated with prevention of T2DM or modification of its major risk factor, obesity. This identified a number of population-wide actions associated with a significant reduction in population-level BMI (sugar sweetened beverage tax, reduction in fruit and vegetable prices, menu labelling, food store interventions and multi-component community interventions). However, impact on T2DM was impossible to quantify precisely due to lack of primary studies. Meta-analysis of studies describing population-wide programmes' impact on body mass index (BMI) was undertaken to determine parameter values required for the economic evaluation of population-wide programmes outlined in Chapter 6.

CHAPTER 6: Population-wide prevention programmes: Economic evaluation of population-wide obesity or diabetes prevention programmes (economic evaluation using microsimulation)

Chapter 6 describes the potential impact of the promising population-wide policies described in Chapter 5 on health system costs and health outcomes (QALYs and cumulative incidence of T2DM). The findings of an economic evaluation (using a pre-existing micro-simulation model) of four population-wide policies (sugar sweetened beverage tax, menu labelling, food store interventions and multi-component community interventions) are summarised. This analysis found that sugar sweetened beverage tax, menu labelling, food store interventions and multi-component community interventions lead to substantial gains in QALYs at a population level (176,722-544,678 QALYs gained over 50 years), a small reduction in T2DM-related health system costs (<0.1% T2DM-related direct healthcare costs over 50 years) and a small impact on cumulative incidence of T2DM (1.1-3.3% reduction over 50 years).

CHAPTER 7: Conclusions and implications for policy makers

Chapter 7 summarises the thesis and its contribution in the field of diabetes prevention policy. Methodological strengths and limitations of the thesis and implications for future research are outlined. The implications for those tasked with developing diabetes prevention policy are then discussed from two perspectives. Firstly, the evidence-based argument for a far more comprehensive approach to diabetes prevention policy (embracing individual case-based and population-wide approaches) is described based on the findings in Chapters 3 to 6. Secondly, I offer my personal reflections as a national policy maker on the

challenges of developing evidence-based policy in this area and a potential framework for action.

CHAPTER TWO

Current approaches to type 2 diabetes prevention

2. CURRENT APPROACHES TO TYPE 2 DIABETES PREVENTION – NARRATIVE REVIEW

The content of this chapter is based partly on material published previously in the following peer-reviewed journal articles:

- Roberts S, Barry E, Craig D, Airoldi M, Bevan G, Greenhalgh T. Preventing type 2 diabetes: systematic review of studies of cost-effectiveness of lifestyle programmes and metformin, with and without screening, for pre-diabetes. *BMJ Open*. 2017;7(11):e017184.

  My role: I conceptualised the study, led on the study design and data extraction, wrote the first draft of the paper and collated responses from other authors. I am the corresponding author and guarantor for the paper.

- Barry E, Roberts S, Oke J, Vijayaraghavan S, Normansell R, Greenhalgh T. Efficacy and effectiveness of screen and treat policies in prevention of type 2 diabetes: systematic review and meta-analysis of screening tests and interventions. *BMJ*. 2017;356:i6538.

  My role: I was second reviewer on this paper. I checked abstracts for inclusion and undertook duplicate data extraction and quality assessment on a proportion of included studies.

2.1. BACKGROUND, AIMS AND OBJECTIVES

T2DM prevention policies are formed in a context of lack of international consensus regarding how to identify high risk participants and different judgements regarding the efficacy and affordability of interventions [1]. The aim of this chapter is to: i) describe why diabetes prevention is important to policy makers, ii) outline the range of approaches to identifying people at high risk of T2DM, iii) summarise evidence of efficacy of the most common elements of diabetes prevention policy and iv) describe existing diabetes prevention policies in countries that have national or regional diabetes prevention programmes.

Diabetes is a global health priority, with 415 million known adult cases worldwide, of which 91% are T2DM [2]. Ageing of the population is predicted to drive substantial increases in prevalence (estimated to have increased to 642 million by 2040) [3], with particularly rapid increases in low- and middle-income countries [4]. The burden of complications in diabetes is high, including heart disease, stroke, neuropathy, nephropathy and retinopathy [5]. Type 2 diabetes develops as a result of genetic, environmental and behavioural factors, including sedentary lifestyle and energy-rich, nutrient-poor diet, both of which predispose to obesity [6].

Diabetes takes a significant toll on health budgets around the world, accounting for 5-20% of total healthcare expenditure in many countries [2]. Both absolute costs and proportion of overall health budgets for T2DM are set to increase further in future decades as prevalence rises, in the context of a marked reduction in the proportion of the population who are

economically active (e.g. in the UK, the relative economic burden per worker is expected to increase by 40-50% by 2060 [7]). Cost-effective treatment and prevention strategies, with acceptable budget impact, will therefore become increasingly important as resources become stretched.

Given the potential impact on populations and health budgets, the burden of T2DM is a key issue for policy makers. In response, countries, including the US and UK, have developed national diabetes prevention programmes [8-11]. The design of large-scale prevention programmes incorporates a number of important choices: i) whether to modify the risk of high-risk individuals or the risk of the entire population, ii) if focusing on high risk individuals, whether to screen a portion of the population for diabetes risk or focus on people who are already known to be at high risk, iii) if no screening programme is in place, how to identify participants who may benefit from a diabetes prevention programme and iv) the role of different types of interventions (lifestyle programmes or metformin) and v) the optimum intensity and duration of these programmes [12,13].

2.2. IDENTIFYING PEOPLE AT HIGH RISK OF TYPE 2 DIABETES

Type 2 diabetes is often preceded by a phase of abnormal glucose regulation (called intermediate hyperglycaemia or prediabetes). Intermediate hyperglycaemia is a generic term that includes impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and HbA1c in the 'at risk' range [14]. One individual may have one, two or all three types of

intermediate hyperglycaemia. Table 2.1 describes these different definitions of intermediate hyperglycaemia, how they are diagnosed and current diagnostic guidelines [15-17].

The distinction between types of intermediate hyperglycaemia is important for three reasons. Firstly, different definitions of intermediate hyperglycaemia are associated with distinct physiological changes. Impaired fasting glucose is associated with reduced hepatic insulin sensitivity, and first phase insulin response; impaired glucose tolerance is associated with reduced peripheral insulin sensitivity and second phase insulin response and HbA1c reflects aggregated blood glucose levels over time [18]. Secondly, progression to diabetes ranges from 3.6% to 7.6% annually depending on the type of intermediate hyperglycaemia [19]. Thirdly, impaired glucose tolerance is associated with increased risk of microvascular disease whereas the relationship is less clear for other types of intermediate hyperglycaemia [14]. Finally, there is evidence that people with different types of intermediate hyperglycaemia respond differently to the same intervention. For example, in a large US trial, the US Diabetes Prevention Program, lifestyle programs were less effective and metformin more effective in participants with IGT *and* HbA1c in the 'at risk range' compared to the entire cohort which were identified on the basis of IGT [20].

Table 2.1. Diagnostic criteria for intermediate hyperglycaemia/prediabetes

Type of pre-diabetes	***Description***	***Diagnostic test used***	***Criteria for diagnosis***			***Incidence of T2DM (per person-year)*** [19]
			***WHO** [15]*	***ADA*** [16]	***IEC*** [17]	
Impaired glucose tolerance	High blood glucose 2-hours after a drink containing 75g of sugar (e.g. Lucozade)	Oral glucose tolerance test	2-hour post-load glucose of 7-11.1 mmol/L	2-hour post-load glucose of 7-11.1 mmol/L	N/A	0.045
Impaired fasting glucose	High blood glucose following a period of fasting	Fasting plasma glucose	6.0-6.9 mmol/L	5.6-6.9 mmol/L	N/A	WHO criteria: 0.047 ADA criteria: 0.036
HbA1c 'at risk' range	Glycated haemoglobin which estimates blood glucose levels over the previous 2-3 months	HbA1c	6.0-6.4%	5.7-6.4%	6.0-6.4%	WHO criteria: 0.036
Impaired glucose tolerance AND impaired fasting glucose	As above	Fasting plasma glucose AND oral glucose tolerance test	2-hour post-load glucose: 7-11.1 mmol/L and Fasting plasma glucose: 6.0-6.9 mmol/L	2-hour post-load glucose: 7-11.1 mmol/L and Fasting plasma glucose: 5.6-6.9 mmol/L	N/A	WHO criteria: 0.70

WHO: World Health Organisation, IEC: International Expert Committee, ADA: American Diabetes Association.

2.3. DEVELOPING PROGRAMMES FOR PEOPLE AT HIGH RISK OF T2DM

Intermediate hyperglycaemia is almost always asymptomatic. It tends to be diagnosed incidentally (when blood tests are performed for other reasons) or as part of a pro-active screening programme delivered either to an entire population or to selected individuals. Most commonly, screening blood tests are offered to people identified as at high risk of

developing T2DM based on demographic variables (e.g. age, ethnicity), survey questions (e.g. family history of T2DM, personal history of gestational diabetes) or biomarkers (e.g. body mass index, blood pressure), typically combined in a 'T2DM risk score' [21]. People diagnosed with intermediate hyperglycaemia may be offered a lifestyle programme (to encourage a healthy diet and increased physical activity) or metformin [22]. These interventions have been shown to delay or prevent type 2 diabetes in a significant proportion of participants in large randomised trials in the US [23], Europe [24], China [25] and India [26]. Lifestyle programmes in these trials were intensive and sustained: 3-10 years of individual and group sessions provided by specialist staff (dieticians or exercise physiologists with annual physician review). Participants of these four large trials were all selected on the basis of impaired glucose tolerance (IGT), a test for intermediate hyperglycaemia that is not used in routine clinical practice.

Subsequent translation of these findings into large-scale community-based programmes produced interventions that were both shorter (3-12 months) and less intense (e.g. they offered less sessions and were delivered to groups rather than individuals by non-specialist staff such as lay workers or prevention managers). These large-scale community-based programmes have been offered to populations of similar age and BMI to the large trials but with different selection criteria (e.g. selection based on elements of the metabolic syndrome rather than the criteria of impaired glucose tolerance seen in the large trials) [27]. There is some evidence that these pragmatic interventions offered to a real-world population deliver more limited and less sustained benefits than were seen with more intensive interventions in trial populations [28].

The efficacy of diabetes prevention programmes is typically measured by a reduction in relative risk of T2DM. Recent meta-analyses have found both the length of the lifestyle programme and the method for identifying eligible participants to be associated with differences in relative risk reduction. A recent meta-analysis [12] found that lifestyle programmes reduce the relative risk of developing T2DM by 32% (95% CI: 15-45%) for interventions lasting 1-2 years and by 37% (95% CI: 18 to 46%) for interventions lasting 3-6 years. A subsequent meta-analysis that I undertook [29] found that studies that identified participants based on IGT and provided lifestyle programmes >=3 years, reduced the relative risk of T2DM by 45%, but in studies that identified participants on the basis of IFG and provided participants with lifestyle programmes of >=3 years duration, the relative risk reduction was 38%. No studies in these meta-analyses used HbA1c alone as the diagnostic criteria for selecting participants. Meta-analysis evaluating the impact of metformin [12] showed a relative risk reduction of 26% (95% CI: 16 to 35%) whilst participants were on this medication. To my knowledge, there are no follow up studies evaluating persistence of benefit once metformin had been discontinued.

2.4. CURRENT NATIONAL OR REGIONAL DIABETES PREVENTION PROGRAMMES

Given the prevalence of T2DM and its associated costs, some countries have developed large scale (national or regional) diabetes prevention programmes. Finland was the first country to launch a national diabetes prevention programme in 2003, combining lifestyle programmes for high risk individuals with an early treatment strategy for people with screen detected T2DM and a population strategy aimed at increasing awareness of diabetes and its risk factors [11]. In 2007, Australia launched a state-wide programme across Victoria focusing on a lifestyle programme for people aged 50-70 years at high risk of T2DM [10,30].

In 2012, the Centre for Disease Control was tasked with deploying the National Diabetes Prevention Programme in the US, working with 220 provider organisations in 40 states, also focusing on a lifestyle programme for participants with intermediate hyperglycaemia [8]. Most recently, in 2016, Healthier You, the NHS' Diabetes Prevention Programme, a 9-month lifestyle programme was launched in England [9] (Table 2.2).

Table 2.2. Description of large-scale national or regional diabetes prevention programmes

Country, year of introduction and programme	*Core components*	*Participant identification*	*Components of lifestyle programme*	*Effect*
Finland, 2003 **National Programme for the Prevention of Type 2 Diabetes [11]**	1. Lifestyle programmes for high-risk individuals 2. Early treatment for those with screen-detected T2DM 3. Population strategy to increase awareness	Opportunistic screening with diabetes risk score (FINDRISC) in healthcare centres, pharmacies and public events Blood test (OGTT) in people with FINDRISC score >=15	1-2 nurse-led baseline visits Average of 2.9 intervention visits in first year – including individual or group education and counselling sessions	At 12 months: Weight: -1.2kg (p<0.0001) BMI: -0.4 kg/m2 (p<0.0001)
Australia, 2007 **Evaluated by the Melbourne Diabetes Prevention Study [10,30]**	Lifestyle programme for high-risk individuals	Screening with diabetes risk score (FINDRISC) in people aged 50-70 years recruited through health providers, pharmacies, community organisations and events Blood test (FPG or OGTT) in people with FINDRISC>=15	6 sessions in 12 months: • Initial 30-45 min individual session • Four 90-minute group lifestyle sessions at 2-weekly intervals • Fifth session at 8 months	At 12 months: Weight: -1.13kg (p=0.016) No significant change in measures of intermediate hyperglycaemia (FPG or 2-hour measurement in OGTT)

US, 2012 **National Diabetes Prevention Program** **[8]**	Intensive lifestyle programme for high-risk individuals	Blood test (FPG, HbA1c or OGTT)	Up to 22 sessions in 12 months (average number attended = 14): • 16 hourly-sessions at weekly intervals in first 6 months • 6 sessions at monthly intervals for the next 6 months	At four years: Weight: -4.2% of body weight
England, 2016 **Healthier You** **NHS Diabetes Prevention Programme** **[9]**	Lifestyle programme for high-risk individuals	Blood test (FPG or HbA1c) during: • NHS Health Check • Routine clinical care	13 face-to-face group-based sessions over 9 months (at least 16 hours of contact time)	Not yet reported

Despite a common focus on individual case-based approaches (namely lifestyle programmes less than 12 months' duration), national or regional prevention programmes differ in terms of the eligible population and intensity of the intervention. And whilst the programmes in Finland, Australia and the US have shown promising early results in terms of weight loss, no studies have yet examined the impact on population-level incidence and prevalence of T2DM resulting from these large-scale programmes.

My primary concern in undertaking this DPhil was the implications of findings for England's diabetes prevention policy. Whilst Chapters 3 and 5 review the international literature on alternative approaches to diabetes prevention, chapters 4 and 6 quantify the impact of alternative diabetes prevention policies on the English population. However, given the

similarity in approach between England's Diabetes Prevention Programme and those of other high-income countries, the findings described in this thesis may be generalizable at a high level.

2.5. SUMMARY AND CONCLUSION

T2DM is a global public health priority due to high prevalence, significant impact on quality and length of life due to micro- and macro-vascular complications, and is a source of substantial costs in health systems around the world.

This narrative review has summarised three findings from the published literature. Firstly, seminal studies in the US, Finland, China and India found that T2DM can be prevented through lifestyle programs or an oral hypoglycaemia medication (metformin), that is individual case-based programmes targeted towards high-risk individuals. However, subsequent studies of effectiveness of lifestyle programmes have illustrated more modest effects on T2DM incidence, compared to trial-based studies of efficacy. Secondly, there is a lack of consensus on how to identify participants for individual-case based prevention programmes, with three different blood tests used to identify intermediate hyperglycaemia, which is associated with an increased risk of developing T2DM. Different types of intermediate hyperglycaemia are associated with different pathophysiological changes, incidence of T2DM and response to preventative programmes. Thirdly, governments in Finland, Australia, the US and England have developed national or regional diabetes prevention programmes, predominantly focusing on lifestyle programmes in high-risk

individuals. These programmes differ in both the intensity of the intervention provided and the method for identifying eligible participants.

These findings raise a number of unanswered questions about the efficacy, costs and cost-effectiveness of diabetes prevention programmes, which I go on to address in the next four chapters. First, the gap between existing evidence of cost-effectiveness of individual case-based interventions and current diabetes prevention policies is explored in Chapter 3. Second, an economic evaluation of alternative approaches to individual case-based interventions is summarised in Chapter 4. I then turn to examining population-wide prevention programmes, with Chapter 5 summarising population-wide programmes that have an impact on BMI (an important risk factor for T2DM) and Chapter 6 undertaking an economic evaluation of these programmes. This thesis concludes with a summary of findings and their implications for policy makers developing diabetes prevention programmes.

CHAPTER THREE

Individual case-based approaches to preventing T2DM:

Current evidence of cost-effectiveness and budget impact

3: INDIVIDUAL CASE-BASED APPROACHES TO PREVENTING T2DM – SYSTEMATIC REVIEW OF CURRENT EVIDENCE OF COST-EFFECTIVENESS AND BUDGET IMPACT

The content of this chapter is based partly on material published previously in the following peer-reviewed journal articles:

- Roberts S, Barry E, Craig D, Airoldi M, Bevan G, Greenhalgh T. Preventing type 2 diabetes: systematic review of studies of cost-effectiveness of lifestyle programmes and metformin, with and without screening, for pre-diabetes. *BMJ Open*. 2017;7(11):e017184.

  My role: I conceptualised the study, led on the study design and data extraction, wrote the first draft of the paper and collated responses from other authors. I am the corresponding author and guarantor for the paper.

3.1. BACKGROUND, AIMS AND OBJECTIVES

As summarised in chapter 2, T2DM is a global public health priority with governments around the world aiming to stem the tide of T2DM-related morbidity, mortality and costs by developing diabetes prevention programmes. Seminal studies in the US, Finland, China and India found that T2DM can be prevented through individual case-based programmes targeted at high-risk individuals (lifestyle programs or metformin). But there is a lack of consensus on how to identify participants for individual-case based prevention programmes, with three different blood tests used in published evidence and clinical practice. Governments in Finland, Australia, the US and England have developed national or regional diabetes prevention programmes, predominantly focusing on lifestyle programmes

in high-risk individuals. But these programmes differ in both the intensity of the intervention provided and the method for identifying eligible participants.

These findings raise a number of unanswered questions about the efficacy, costs and cost-effectiveness of existing diabetes prevention programmes. The aim of this chapter is to summarise the current evidence of cost-effectiveness of individual case-based interventions and the extent to which this evidence supports current diabetes prevention policy in England, through a systematic review of the literature. Given the different definitions of individuals at risk of T2DM and the differences in intervention design outlined in Chapter 2, research questions addressed in this chapter include:

- What is the evidence on cost-effectiveness of lifestyle programmes or metformin in prevention of T2DM?
- What is the impact of the following factors on the cost-effectiveness of these interventions?
    a. Type of intermediate hyperglycaemia (IFG, IGT or 'at risk' HbA1c)
    b. Intensity of lifestyle intervention: Including three different measures of intensity, each of which was examined separately: i) frequency of contact in initial 'core' teaching/coaching sessions, ii) duration of core and maintenance intervention and iii) group or individual format of sessions
    c. Inclusion of screening: Studies of intervention-only on a predefined high-risk population *or* screening for T2DM risk followed by intervention.

d. Years of follow-up to evaluate diabetes incidence: fewer than 10 years and more than 25 years.

- What are the implications of these findings for policy makers and health insurers?

3.2. METHODS

A systematic review of economic evaluations was undertaken using PRISMA criteria (see Appendix 3.1. for PRISMA checklist).

3.2.1. Search strategy and inclusion criteria

I utilised the database search of Embase, PreMedline and Medline for peer-reviewed articles on pre-diabetes and diabetes prevention undertaken by Eleanor Barry (EB), outlined in Chapter 2, as a starting point for this review. Search terms were developed by EB and are outlined in Appendix 3.2. My co-author EB and I screened abstracts for inclusion, identifying eligible papers published between 2004 and 2014. I identified further papers for inclusion (published between 2004 and 2016) by searching NHS EED and undertaking citation tracking and screening of references (in included studies and review articles).

To meet our inclusion criteria, studies needed to include full economic evaluations (cost-effectiveness, cost-utility or cost benefit analysis) that:

- Evaluated the treatment of people identified as high-risk of developing T2DM with either metformin and/or lifestyle programmes (that addressed diet *and* physical activity) against a base case of no intervention;

- Included 12 months or more of intervention and follow up;
- Quantified outcomes (such as change in quality-adjusted life years, disability-adjusted life years, life years gained or numbers needed to treat to prevent one case of T2DM);
- Described the method used to classify people as high-risk of developing T2DM (hence eligible for interventions), including blood tests for intermediate hyperglycaemia, screening questionnaires, diabetes risk algorithms or presence of particular risk factors.

I reviewed full papers meeting the above criteria and developed a data extraction spreadsheet in Excel. This included assessment of study type, population included, type of intervention, costs of intervention, impact on health gain (quality-adjusted life years (QALYs), disability-adjusted life years (DALYs), life years gained (LYG) and numbers needed to treat (NNT) to prevent 1 case of T2DM). Appendix 3.3 and 3.4. include these completed data extraction worksheets. I extracted data from included papers and data extraction for a third of papers was checked by a second reviewer (EB).

3.2.2. Quality assessment

A checklist developed by the International Society for Pharmaco-economics and Outcomes Research [1] was used to evaluate the relevance and credibility of modelling studies for decision-making by policy makers. An example of this assessment is reproduced in Table 3.1. below.

Table 3.1. Example of data extraction using questionnaire to assess relevance and credibility of modelling studies for decision makers

QUESTIONS	HELPER QUESTIONS	Example of data extraction - Herman, 2005
ASSESSMENT OF RELEVANCE		
1 Is the population relevant?	Are the demographics similar?	45% members of minority groups (see Knowler, 2002)
	Are risk factors similar?	IGT *and* IFG, BMI>24kg/m2
	Are behaviours similar?	72% participants took at least 80% of required metformin
	Is the medical condition similar?	Yes
2 Are any critical interventions missing?	Does the intervention analysed in the model match the intervention you are interested in?	High-intensity lifestyle intervention over 2.8 years
	Have all relevant comparators been considered?	Low intensity lifestyle intervention not included
	Does the background care in the model match yours?	US based care
3 Are any relevant outcomes missing?	Are the health outcomes relevant to you considered?	Yes, QALYs
	Are the economic end points relevant to you considered?	Yes, incremental cost-effectiveness ratio
4. Is the context (settings and circumstances) applicable?	Is the geographic location similar?	US-based
	Is the health care system similar?	US-based
	Is the time horizon applicable to your decision?	Lifetime simulation
	Is the analytic perspective appropriate to your decision problem?	Health system perspective
ASSESSMENT OF CREDIBILITY		

Validation		
Is external validation of the model sufficient to make its results credible for your decision?	Has the model been shown to accurately reproduce what was observed in the data used to create the model?	Centre for Disease Control and Prevention and Research Triangle Institute International model used
	Has the model been shown to accurately estimate what actually happened in one or more separate studies?	Not reported
	Has the model been shown to accurately forecast what eventually happens in reality?	Not reported
Is internal verification of the model sufficient to make its results credible for your decision?	Have the process of internal verification and its results been documented in detail?	Not reported
	Has the testing been performed systematically?	Not reported
	Does the testing indicate that all the equations are consistent with their data sources?	Not reported
	Does the testing indicate that the coding has been correctly implemented?	Not reported
Does the model have sufficient face validity to make its results credible for your decision?	Does the model contain all the aspects considered relevant to the decision?	Yes
	Are all the relevant aspects represented and linked according to the best understanding of their characteristics?	Yes
	Have the best available data sources been used to inform the various aspects?	Yes
	Is the time horizon sufficiently long to account for all relevant aspects of the decision problem?	Yes, lifetime simulation
	Are the results plausible?	Yes, similar to a majority of other included studies

	If others have rated the face validity, did they have a stake in the results?	Not reported
Design		
Is the design of the model adequate for your decision problem?	Was there a clear, written statement of the decision problem, modelling objective, and scope of the model?	Yes
	Was there a formal process for developing the model design (e.g. influence diagram, concept map)?	Not reported, pre-existing model used
	Is the model concept and structure consistent with, and adequate to address, the decision problem/objective and the policy context?	Yes
	Have any assumptions implied by the design of the model been described, and are they reasonable for your decision problem?	Yes
	Is the choice of model type appropriate?	Yes
	Were key uncertainties in model structure identified and their implications discussed?	Partially. Sensitivity analyses included cost of interventions and different discount rates. No sensitivity analysis of duration of treatment effect or reduction in relative risk of T2DM was undertaken
Data		
Are the data used in populating the model suitable for your decision problem?	All things considered, do you agree with the values used for the inputs?	Partially: • Relative risk reduction based on USDPP is reasonable • Lifestyle intervention provided until onset of T2DM and that health and QOL benefits associated with interventions remain constant and persist until diabetes onset could overstate intervention effect
Analysis		

Were the analyses performed using the model adequate to inform your decision problem?		Yes
Was there an adequate assessment of the effects of uncertainty?		Yes
Reporting		
Was the reporting of the model adequate to inform your decision problem?	Did the report of the analyses provide the results needed for your decision problem?	Yes
	Was adequate nontechnical documentation freely accessible to any interested reader?	Yes
	Was technical documentation, in sufficient detail to allow (potentially) for replication, made available openly or under agreements that protect intellectual property?	Not in published paper
Interpretation		
Was the interpretation of results fair and balanced?		Yes
Conflict of interests		
Were there any potential conflicts of interest?		No
If there were potential conflicts of interest, were steps taken to address these?		NA

3.2.3. Assumptions and calculations

All the economic evaluations included in this review were cost-effectiveness analyses (including cost-utility analyses), which measure both the cost of the intervention and the impact of the intervention on participants' quality and/or length of life [2]. No full cost-benefit analyses were identified. For this review I used a willingness to pay threshold of £20,000/QALY when defining whether an intervention was cost-effective.

The measure of cost-effectiveness (incremental cost-effectiveness ratios or ICERs) are reported from two different perspectives: health system and societal perspective. The health system perspective includes only direct medical costs such as: i) staff, facilities, medication and consumables costs required for provision of the intervention, and ii) general healthcare of participants. In addition, studies of cost-effectiveness from a societal perspective include some or all elements of i) indirect costs of the intervention (e.g. exercise equipment, food preparation equipment), ii) participant time (travelling to and participating in intervention's activities), iii) lost productivity due to absence from work and iv) disability benefits payments.

I used purchasing power parity and currency exchange rates from the CCEMG - EPPI-Centre Cost Converter to convert costs into British pounds 2015 [3]. This tool converts currencies both by year (e.g. US dollars 2007 to US dollars 2015) and well as by purchasing power parity between currencies (e.g. US dollars 2015 to British pounds 2015).

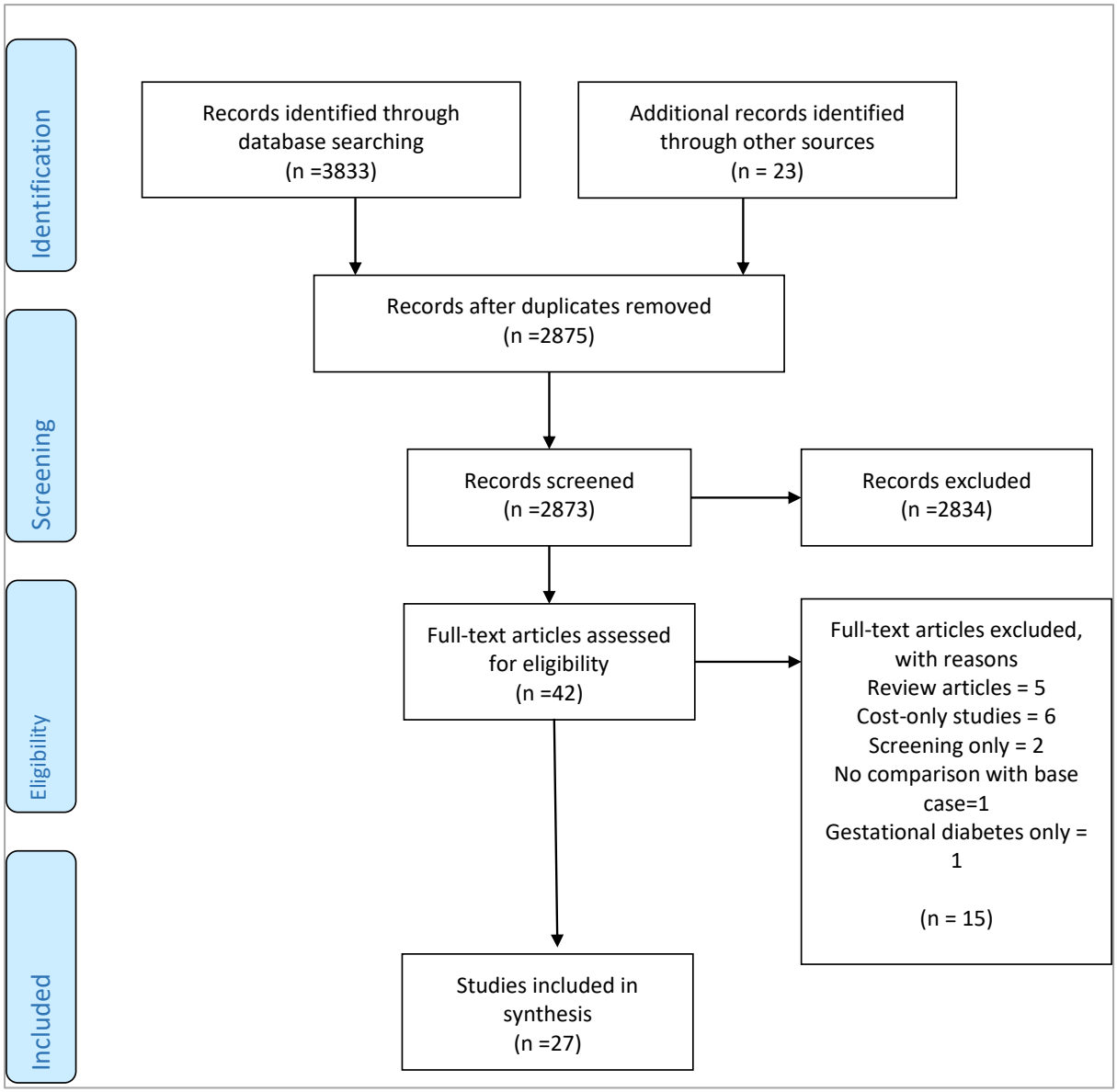
I grouped studies on a number of dimensions to identify key drivers of differences through subgroup analysis. Subgroups examined included: type of prediabetes, intensity of lifestyle

intervention (defined by number of sessions in 'core' intervention, duration of core and maintenance program, group vs. individual format), inclusion of screening, years of follow-up to evaluate diabetes incidence.

3.3. RESULTS

42 full papers were reviewed and 15 were excluded for reasons outlined in Figure 3.1.

Figure 3.1. PRISMA Flow Diagram



In total, 27 studies of diabetes prevention programmes with economic evaluations have been published from 15 countries between 2004 and 2016 [4-30]. 6 of the economic evaluations were within-trial cost-utility analyses and 21 were modelling studies (16 Markov models, two simulation models, two decision trees and one combination Markov model and decision tree). Within the modelling studies there were a wide range of model structures, parameters and parameter values which in part drive the variability observed in study results [31].

3.3.1. Type of intervention

All 27 studies evaluated lifestyle interventions and 12 also evaluated the oral hypoglycaemic drug metformin (Appendix 3.3). 13 reported interventions in a population previously identified as having intermediate hyperglycaemia (people with IFG, IGT or high HbA1c) and 14 reported screening of a broader population and subsequent intervention on those identified as high risk of developing type 2 diabetes. The majority of studies evaluated intensive trial-based interventions, although there was a great deal of heterogeneity in the type of lifestyle interventions evaluated. Table 3.2. describes some of the dimensions on which lifestyle programmes differed: frequency of contact, duration, staff providing intervention, individual vs group interventions and frequency of contact.

3 studies [11,20, 25] did not specify the details of their lifestyle interventions.

Table 3.2. Lifestyle programmes evaluated in studies in this systematic review

A. INTENSIVE TRIAL-BASED LIFESTYLE PROGRAMMES					
Clinical trial on which intervention is based	**Included studies in this review**	**Number of sessions**	**Length of intervention**	**Staff delivering programme**	**Group or individual**
US Diabetes Prevention Program (US DPP)	Palmer, 2004 Eddy, 2005 Herman, 2005 Ackermann, 2006 Hoerger, 2007 Schaufler, 2010 Mortaz, 2012 Png, 2014	16 core sessions Monthly follow-up	2.8 years	Exercise physiologists, dieticians, case managers	Predominantly individual
US Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study (US DPP and DPPOS)	DPPRG, 2012 Palmer, 2012 Dall, 2015 Herman, 2013	Years 1-3: 16 core sessions, monthly follow up Year 4: 16 session group programme Years 5-10: Quarterly 1-hour group sessions, 2 additional 'BOOST' sessions per year for participants originally randomised to lifestyle group	10 years	Exercise physiologists, dieticians, case managers	Individual and group
Finnish DPS lifestyle program (FDPS)	Caro, 2004	Year 1: 7 visits Year 2 onwards: 4 visits p.a. YMCA gym membership to enable 2 supervised exercise sessions per week	5 years	Dietician	Individual dietician visits, group exercise sessions

	Lindgren, 2007	Year 1: 7 visits Year 2 onwards: 4 visits p.a. Supervised circuit type training	6 years	Nutritionist	Individual visits, group exercise sessions
	Bertram, 2010	Weekly visits for 1 month, monthly for a further 3 months, quarterly thereafter	As long as participant has IGT	Dietician, exercise physiologist	Individual
Indian Diabetes Prevention Programme (IDPP)	Ramachandran, 2007	Individual sessions twice a year Monthly phone calls	3 years	Dieticians, social workers and helpers	Individual
Da Qing Lifestyle Program	Liu, 2002	Individual counselling by physicians or group counselling in 9 sessions/year	6 years	Physicians	Individual and group
Diabetes in Europe – applied to Catalonia	Sagarra, 2013	4x90 minute teaching sessions Reinforced with telephone calls, text messages, letters and interviews every 6-8 weeks.	4.2 years	Doctors and nurses	Individual or group
TRANSLATIONAL COMMUNITY-BASED LIFESTYLE PROGRAMMES					
Community-based translations of USDPP	Icks, 2007	16 core sessions in community setting Monthly follow-up	3 years	Diabetologists and dieticians	NR
	Zhuo, 2012	Nation-wide program Year 1: 16 core sessions, post-core sessions every 6 months Year 2: 8 maintenance sessions Year 3: 1-2 sessions	3 years	Lifestyle coaches in year 1 and 2, any health care provider thereafter	Group
	Smith, 2010	12 sessions	12-14 week intervention, 1 year follow up	Health professionals, lay workers	Group

Hypothetical lifestyle program	Neumann, 2011	8 core sessions Follow up: quarterly sessions, monthly calls or emails, newsletter, quarterly journal	5 years	Prevention managers	Group
UEA-IFG	Irvine, 2011	4 core education sessions and group exercise sessions Peer support groups Telephone peer support from volunteers	7 months	Physiotherapists, diabetes prevention facilitators, volunteers (people with T2DM for more than 2 years)	
Kalmar Metabolic Syndrome Program	Feldman, 2013	NR	1 year	NR	NR

Intensive trial-based lifestyle programmes: 18 of the 24 studies that did describe the lifestyle intervention being evaluated were based on intensive trial-based lifestyle interventions (8 based on the US Diabetes Prevention Program, 4 on the US Diabetes Prevention Program together with the US Diabetes Prevention Program Outcome Study, 3 on the Finnish Diabetes Prevention Study, one on the Da Qing study, one on the Indian Diabetes Prevention Programme and one on the Diabetes in Europe study applied to Catalonia, Spain) and 3 were based on community translation of these intensive interventions lasting 3-5 years. The primary studies were generously resourced, included 300-3000 participants and provided lengthy interventions (3-10 years' duration) including 7-16 initial contacts in the 'core programme' delivered by specialist staff (dieticians, exercise physiologists and annual medical review).

Translational community-based programmes: 3 of the 24 studies were based on community translation of these intensive interventions lasting 3-5 years and 3 studies were based on other published studies covering much smaller populations (<150 participants) and providing less intensive interventions (ranging from 12 weeks to 1 year in duration), delivered by non-specialist staff (diabetes prevention facilitators and lay workers).

3.3.2. Target population – demographics and type of intermediate hyperglycaemia

The target population for 16 of the 27 studies were overweight individuals with impaired glucose tolerance (IGT), with or without impaired fasting glucose (IFG). 4 used IFG alone [8, 18, 22, 29], 2 used IGT *or* IFG [10, 17], 1 used IFG or HbA1c [19], 1 used HbA1c alone [5] and 3 used other methods of screening (such as diabetes risk algorithms, BMI or other elements of metabolic syndrome) [7, 9, 11]. 17 out of 27 studies included participants based on a BMI

greater than or equal to 24kg/m^2, 3 included participants based on a BMI greater than or equal to 30mg/kg2 and the remainder did not state a BMI cut-off for participation. A wide range of ages (from 18 years and older) were included.

3.3.3. Benefits of interventions

In the studies included in this review the primary benefit of diabetes prevention programmes was reduction in incidence of type 2 diabetes and its associated complications, measured in the number needed to treat to delay or prevent a case of T2DM or improvements in quality adjusted life years (QALYs), disability adjusted life years (DALYs) and life years gained (LYG), as summarised in Appendix 3.4.

Lifestyle interventions: 21 studies reported change in quality-adjusted life-years associated with lifestyle interventions with a median 0.159 (range: 0.003-2.91) increase in QALYs and 13 reported life-years gained with a median increase of 0.30 (range: 0.04-0.84) relative to usual care. Four studies reported numbers needed to treat with lifestyle programmes to prevent 1 case of type 2 diabetes with results ranging from 4.2-30.

Metformin: 8 studies measured change in quality-adjusted life-years associated with metformin therapy with a median of 0.105 (range: 0.01-2.83) increase in QALYs and 5 studies reported increase in life-years gained with a median gain of 0.14 (range: 0.05 to 0.3). Two studies reported number needed to treat with metformin to prevent 1 case of type 2 diabetes as 6.9 and 27.9.

3.3.4. 'Value for money'

Policy makers may consider a range of economic factors when considering a new programme: cost-effectiveness, budget impact, effect on incident cases of the disease and equity of healthcare provision [32]. All studies included in this review considered cost-effectiveness, reporting incremental cost-effectiveness ratios, 5 described budget impact, 2 modelled impact on incident cases of diabetes and none considered impact on equity of healthcare provision.

Cost-effectiveness: Overall, lifestyle interventions and metformin appeared to be cost-effective in preventing diabetes in high-risk individuals, as summarised in Table 3.2, though there was wide variation in economic estimates between studies. Substantial differences in participant selection and intervention design, which reflect the different eligibility criteria (e.g. intermediate hyperglycaemia, diabetes risk score) and different types of interventions, as well as differences in model structure, parameters and parameter values make comparison between studies difficult.

Table 3.2. Incremental cost-effectiveness ratios

ICERS - LIFESTYLE INTERVENTION								
Author, year of publication	**Duration of analysis**	**ICER in 2015 GBP Health system perspective**			**Cost elements included in ICER from societal perspective**	**ICER in 2015 GBP Societal perspective**		
		Range (in base case)	**Mean ICER**	**Unit**		**Range** (base case)	**Mean ICER**	**Unit**
Herman, 2005 – DPP	Lifetime	1,057	1,057	£/QALY				
Eddy, 2005	30 years	134,420	134,420	£/QALY	Not specified	58,844	58,844	£/QALY
Diabetes Prevention Programme Research Group, 2012	10 years	7,628	7,628	£/QALY	Participant time, food, food preparation and exercise equipment and classes.	10,917	10,917	£/QALY
Ackermann, 2006	Lifetime	1,210-1,480	1,345	£/QALY				
Palmer, 2012	Lifetime	Cost saving	Cost saving	£/QALY				
Png, 2014	3 years	12,544	12,544	£/QALY	Participant time, transport costs, fitness equipment, food costs and food preparation costs, days of work lost due to T2DM	26,764	26,764	£/QALY
Lindgren, 2007	Lifetime				Participant time, travel and work absence	-8,709	-8,709	£/QALY
Hoerger, 2007	Lifetime	7,526-8,750	8,138	£/QALY	Not specified	15,037-17,275	16,156	£/QALY

Liu, 2013	Lifetime simulation				Transport, lost income, cost of home care	Cost saving (-1190 to -2,933)	Cost saving (-2,062)	£/QALY
Gilles, 2008	50 years	7,490	7,490	£/QALY				
Neumann, 2011	Lifetime				Participant transport	Cost saving (-15,259 to-31,721)	Cost saving (-23,490)	£/QALY
Smith, 2010	3 years	3,215	3,215	£/QALY				
Feldman, 2013	Simulation until 85 years of age	3,140 - 17,802	10,471	£/QALY	Participant and transport and non-healthcare organisations costs	Cost saving to £17,281	8,641	£/QALY
Jacobs Van der Bruggen, 2007	70 years	3,822-5,390	4,606	£/QALY				
Irvine, 2011	1 year	76,566	76,566	£/QALY				
Sagarra, 2013	4 years	3,275	3,275	£/QALY				
Schaufler, 2010	Lifetime	573	573	£/QALY				
Mortaz, 2012	10 years	10,416	10,416	£/QALY				
Zhuo, 2012	25 years	Cost saving (-6,149)	Cost saving (-6,149)	£/QALY				
Herman, 2013	10 years	15,191	15,191	£/QALY	Food, food preparation equipment, exercise classes, gym memberships, personal trainers and exercise equipment, transport, participant time	2,459	2,459	£/QALY

Dall, 2015	10 years intervention and analysis				Years of employment, household and personal income, missed work days and disability benefit payments	NR	NR	£/QALY
Palmer, 2004	Lifetime	Cost saving to 8,614	1,783	£/LYG				
Caro, 2004	10 years	577	577	£/LYG				
Bertram, 2010	Age 100 or death	15,460	15,460	£/DALY				
Colagiuri, 2008	10 years				Not specified	37,285	37,285	£/DALY
Icks, 2007	3 years	4,003	4,003	£/case of T2DM avoided	Participant and healthcare professionals' time	23,183	23,183	Cost per case of T2DM avoided

ICERS – METFORMIN							
		METFORMIN - ICER in 2015 GBP Health system perspective			**METFORMIN - ICER in 2015 GBP Societal perspective**		
Author, year of publication	**Duration of analysis**	**Range** (base case)	**Mean**	**Unit**	**Range** (base case)	**Mean**	**Unit**
Herman, 2005	Lifetime	29,409	29,409	£/QALY			
Eddy, 2005	30 years	32,430	32,430	£/QALY	33,392	33,392	£/QALY
Diabetes Prevention Programme Research Group, 2012	10 years	Cost saving	Cost saving	£/QALY	Cost saving	Cost saving	£/QALY
Palmer, 2012	Lifetime	5,477	5,477	£/QALY			

Png, 2014	3 years	15,371	15,371	£/QALY	4,648	4,648	£/QALY
Gilles, 2008	50 years	8,428	8,428	£/QALY			
Schaufler, 2010	Lifetime	332	332	£/QALY			
Herman, 2013	10 years	15,339	15,339	£/QALY	Cost saving (-10,735)	Cost saving (-10,735)	£/QALY
Palmer, 2004	Lifetime simulation	7,290	7,290	£/LYG			
Caro, 2004	10 years	Cost saving (-5,495)	Cost saving (-5,495)	£/LYG			
Bertram, 2010	Age 100 or death	14,960	14,960	£/DALY			
Icks, 2007	3 years	16,296	16,296	Cost per case of T2DM avoided	27,281	27,281	Cost per case of T2DM avoided

There is insufficient evidence to suggest that lifestyle interventions or metformin will be cost saving. Out of 27 studies, lifestyle interventions were found to be cost saving in 2 studies from a health system perspective [19, 23], cost saving from a health system perspective in some countries but not others in 1 study [13] and cost saving from a societal perspective in 3 studies [18, 22, 28]. Of the 12 studies evaluating metformin, 2 studies concluded metformin was cost saving from a health system perspective [6, 12], 1 study concluded metformin was cost saving from a health system perspective in some countries but not others [13] and 2 concluded that metformin was cost saving from a societal perspective [6, 27].

Lifestyle interventions: Of the 16 studies measuring effectiveness as £ per quality adjusted life years (£/QALY), the median incremental cost-effectiveness ratio (ICER) from a health system perspective was £7,490/QALY (range: cost saving to £134,420/QALY). Only 2 studies reported lifestyle interventions that were not cost-effective (>£20,000/QALY); of these, one used a model substantially different in structure to other modelling studies included (the Archimedes model, which analyses changes in biological variables, such as insulin resistance, rather than transitions between disease states, such as intermediate hyperglycaemia, which are used by other models) [14] and the other included analysis lasting only 1 year therefore the benefits of reduced incidence of diabetes were not included [8].

Metformin: Of the 7 studies measuring effectiveness as £/QALY, the median ICER from a health system perspective was £8,428/QALY (range: cost saving to £32,430/QALY). 2 studies reported metformin to not be cost-effective (>£20,000/QALY): of these, one used a model substantially different in structure to other modelling studies included (the Archimedes

model described above) [14] and the other was the first economic model of the US Diabetes Prevention Programme (USDPP) [15]. The subsequent models based on the USDPP and its follow up study have found metformin to be cost saving or cost-effective [6].

Comparing lifestyle programmes and metformin: Twelve studies compared lifestyle programmes and metformin directly. From a health system perspective, neither intervention appears more cost-effective than the other with 6 studies reporting lifestyle programmes more cost-effective than metformin [12, 15, 20, 23, 24, 26], 5 studies [5, 6, 9, 13, 21] reporting metformin more cost-effective than lifestyle programmes and one [28] showing less than 1% difference in cost-effectiveness between the two. However, from a societal perspective, metformin appears more cost-effective than lifestyle programmes, with four [6, 14, 24, 28] out of the five studies undertaking this analysis finding metformin more cost-effective. This is because the cost of participants' time travelling to and attending lifestyle programme sessions is included in most calculations of cost from a societal perspective, but not from a health system perspective.

Sub-group analysis: Given the range of screening and lifestyle interventions provided, and the range of cost-effectiveness ratios, studies which reported ICERS as £/QALY from a health system perspective were grouped on a number of dimensions to identify key drivers of differences. These analyses revealed that:

1) Screening plus intervention studies tended to be less cost-effective than intervention-only studies on average, but both approaches were associated with a wide range of ICERs highlighting current uncertainties. Of the 10 studies that reported £/QALY from a health system perspective for intervention-only studies the

median ICER was £4,606/QALY (range: cost saving to £134,420/QALY). And the median ICER for the 8 screening-plus-intervention studies was £7,814/QALY (range: £573 - £76,566/QALY). However, evaluations that did not include systematic screening may under-state the cost of identifying patients who were diagnosed with intermediate hyperglycaemia based on ad hoc or opportunistic screening. In addition, the costs and benefits of identifying people with T2DM through systematic screening will be understated in evaluations that focus solely on diabetes prevention.

2) In general, the longer the period evaluated the more cost-effective the interventions appeared. Studies that measured cost-effectiveness over a period of 25 years or more appeared more cost-effective (median ICER: £2,976/QALY) than studies that measured cost-effectiveness over 10 years or less (median ICER: £10,416).
3) There were insufficient studies in each sub-group to draw conclusions based on: programme duration, frequency of sessions, group or individual format or types of participants included

Other measures impacting the 'value for money' judgement: Cost-effectiveness analysis measures costs and benefits of an intervention for an individual participant. Policy makers, who are responsible for overall health budgets and the health of the population as a whole, may consider other measures (such as budget impact, impact on equity and impact on incident cases of the disease) when evaluating the impact of an intervention. In terms of budget impact, three studies [11, 25, 26] estimated the cost of implementing a national diabetes prevention programme to be between 0.13 and 0.2% of annual national health expenditure in the Netherlands, Germany and Australia. Two studies [19, 25] modelled

annual expenditures for lifestyle programmes, showing that net savings only exceeded net expenditures 9-14 years after initiating the prevention programme.

Non-attendance at screening, non-enrolment in an intervention and low compliance with an intervention means that the number of cases of diabetes prevented is lower than might be anticipated when extrapolating from trials. As a result of these factors, as well as the partial and finite impact of interventions, two studies [11, 26] estimated that only 0.2-1.6% of incident cases of diabetes would be prevented by a population-wide programme in the Netherlands and a region of Germany.

As an example of how this population-wide impact is calculated, Icks [26] calculated that 29% of incident cases of diabetes in 3 years would be due to people with pre-diabetes (defined as impaired glucose tolerance in this study). Of this pre-diabetic population, 30% of people would attend the screening test (OGTT), 40% and 59% would participate in the lifestyle intervention and metformin respectively. 32% of these would develop diabetes in 3 years with no intervention and 9.3% and 28.8% would develop diabetes with lifestyle and metformin respectively which resulted in 0.2% of incident cases of diabetes being prevented by metformin and 0.8% by lifestyle programmes.

3.3.5. **Quality, relevance/applicability and credibility of existing economic evaluations for current healthcare decision making**

Given the variety of lifestyle programmes and different definitions of eligible population, we examined the extent to which the included studies reflect national guidance in the UK [33,

34] and the US [35, 36], and the areas in which they differ (Table 3.4). Evaluation of studies against ISPOR's Questionnaire to Assess Relevance and Credibility of Modelling studies for Healthcare Decision Making [1] was undertaken which raised a number of issues. The most important of these for policy makers are outlined below. No studies were excluded on the basis of this evaluation.

Table 3.4: Relevance of included studies

(Numbers refer to the number of studies in this review in each category. Some studies may be included in more than one category, for example if the study took place across multiple countries or used multiple diagnostic tests).

HEALTH SYSTEM CONTEXT								
	US	UK	Europe	Australia	Canada	Singapore	India	China
Which health system?	9	3	8	3	2	1	1	1
TARGET POPULATION								
	IGT (+/- IFG)	IFG	IFG or IGT	HbA1c	Other (e.g. risk score)	*Current guidance*		
Which diagnostic test for intermediate hyperglycaemia?	16	5	2	2	3	**UK [34]**: IFG or HbA1c for diagnosis **ADA [35]:** IFG, IGT, or HbA1c for diagnosis		
TYPE OF INTERVENTION/S EVALUATED								
	Trial-based lifestyle programme	Pragmatic lifestyle programme	Not stated	*Current guidance*				
Trial-based lifestyle or pragmatic lifestyle?	18 trial based 3 translations of trials	3	3	**UK: Pragmatic lifestyle programmes [33] -** Group lifestyle programme with 16 hours of contact time over 9-18 months and regular follow up for up to 2 years **US**: **Pragmatic lifestyle programmes [36]-** Counselling, coaching and extended support relating to diet and physical activity for at least 3 months provided by trained staff in clinical or community settings **ADA [35]:** Intensive diet and physical activity behavioural counselling programme adhering to the tenets of the Diabetes Prevention Programme (DPP) targeting a loss of 7% of body weight and an increasing moderate-intensity physical activity (such as brisk walking) to at least 150 min/week				

- *Health system context:* 24 out of 27 studies were undertaken in high-income, predominantly Caucasian nations. Two studies [28, 30] were undertaken in China and India.
- *Target population:* Only 6 [5, 8, 18, 19, 22, 29] out of 27 studies used diagnostic tests for intermediate hyperglycaemia that are in line with current UK guidance, that is HbA1c and fasting plasma glucose. The majority of studies, 16 out of 27 included participants with a positive oral glucose tolerance test (with or without fasting blood glucose) which is not recommended in the UK.
- *Type of intervention:* 21 of the 27 studies evaluated intensive trial-based interventions or intensive translations of trial interventions, which reflect current ADA guidance (lifestyle interventions modelled on the USDPP, targeting 7% weight loss) [35]. However, reviews of community translations of the US DPP trial showed that whilst these translational programs cost less to implement they were also less effective [37, 38]. The modelling studies based on the USDPP trial data may therefore not be relevant comparators for a USDPP-based community programme. In contrast, the National Institute of Clinical Excellence in the UK and the Community Preventative Services Task Force in the US advocate a more pragmatic approach to lifestyle programmes. Only 3 studies [7-9] in this review are relevant comparators in terms of duration and intensity of lifestyle intervention and they report a wide range of cost-effectiveness ratios (from £3,215/QALY to £76,566/QALY).
- *Credibility of models in included studies:* Two key issues emerged with the assessment of the credibility of the modelling studies included in this review: i) areas where updated evidence is available that may impact the evaluation and ii) areas where uncertainty persists and a range of assumptions are observed:

Availability of updated meta-analyses: 12 of the 21 modelling studies assumed reductions in diabetes incidence equivalent to that achieved in the USDPP or FDPS trials (relative risks of 0.50 at 3 years [39] and 0.40 at 6 years [40] respectively). However, two recent meta-analyses of randomised controlled trials [41, 42], have shown a relative risk of diabetes of 0.59 and 0.64. And a meta-analysis of pragmatic lifestyle interventions [43], excluding large trials, showed a relative risk of 0.74. The higher the relative risk, the less the effect of the intervention; therefore, these recent meta-analyses suggest that models based on DPP or DPS trial data will over-state the impact of interventions.

Key uncertainties regarding modelling assumptions: Firstly, uncertainty remains over the extent to which the reduction in diabetes incidence persists once the intervention has ended. Studies included in this review made a wide range of assumptions on this point, ranging from no effect after the intervention ended to effects persisting until the participant developed type 2 diabetes or died. One recent meta-analysis [41], showed relative risks of 0.80 at up to 20 years follow up. However, this analysis includes predominantly the large trials (US DPP, FDPS and Da Qing) as long term follow up data is not available on community-based translational studies. Therefore, this relative risk likely overstates the long term benefits of interventions outside the trial context. Secondly, variability persists over the percentage of people that fail to enrol in lifestyle interventions following screening. Reflecting this uncertainty, 5 studies included in this review assumed 100% enrolment, 2 assumed between 50 and 99% and 5 assumed less than 50%

enrolment. A recent systematic review [43] found that enrolment in interventions varies widely (from 0.28% to 100%) depending on method of communication, setting, and type of intervention.

3.4. DISCUSSION

3.4.1. Principal findings

This systematic review of economic evaluations of T2DM prevention programmes has produced seven major findings. First, that numerous economic evaluations have been undertaken in 15 different countries and produced diverse results, due to differences in model structure and parameter values and to differences in health systems, different definitions of eligible populations and types of lifestyle interventions included. Second, that the majority of evaluations relate to intensive trial-based interventions in populations in high-income countries identified with oral glucose tolerance tests. Third, that with these caveats in mind, both metformin and lifestyle interventions in people at high risk of developing T2DM appear to be cost-effective but not cost saving, with median ICERs of £8,428/QALY and £7,490/QALY respectively. To place this figure in context, smoking cessation services are estimated by NICE to have ICERs ranging from cost-saving to £984/QALY [44] and breast cancer screening is estimated to have an ICER of £20,800/QALY by the UK Panel on Breast Cancer Screening [45]. Fourth, that metformin and lifestyle programmes appear equally cost-effective when only the costs of the health system are taken into account, but metformin is more cost-effective when costs of participants' time (participating in and travelling to programme activities) are taken into account. Fifth,

systematic screening-plus-intervention programmes were less cost-effective on average than intervention-only programmes. Both approaches (systematic screening-plus-intervention and intervention-only) were associated with a wide range of cost-effectiveness ratios and the population benefit of screening in identifying people with previously undiagnosed prediabetes and T2DM is not taken into account in a cost-effectiveness calculation. Sixth, there is insufficient evidence to deduce what intensity, duration or format or lifestyle programmes are more cost-effective than others. Finally, programmes that evaluated costs and benefits over 25 years or more were more cost-effective than those that looked at 10 years or less.

3.4.2. Updated search following publication of systematic review

In an updated search of Medline (in December 2018), 74 additional titles were identified using the search strategy identified in Appendix 3.1, updated to include only studies with 'cost-effective', 'cost utility' or 'economic evaluation' in their title or abstract. Of these additional studies, 4 met inclusion criteria [46-49]. These studies reached similar conclusions to those outlined in the rest of this chapter. They included one cost-utility analysis alongside a randomised controlled trial (RCT) [48], two studies by the same author which used the same micro-simulation model [46, 47] and one Markov model [49]. Three of these studies were based on English populations [46-48] and one on a Swedish population [49]. All studies had a lifetime horizon except the in-trial analysis which reported cost-effectiveness at 3 years. All four studies examined lifestyle programmes, one alongside an RCT of a low-intensity lifestyle programme [48], two (by the same author) based on theoretical low-intensity lifestyle programmes [46,47] and one a high-intensity lifestyle programme based

on the Finish Diabetes Prevention Programme [49]. One study defined eligible participants based on a diabetes risk score, one on HbA1c [46], one on IGT and/or IFG [49] and one considered six different groups based on measures of intermediate hyperglycaemia or other risk factors [47]. The benefits of lifestyle programmes ranged from 0.046-0.61 QALYs gained per participant in the two studies in which this was reported [48, 49] and 0.0003-0.0009 QALYs gained per person in the general population in the other two studies [46, 47]. Two of the studies were cost-utility analyses that reported lifestyle programmes as cost-effective (ICERs of £3,643/QALY [48] and €3,833-€9,215 /QALY [49] and two studies by the same author found lifestyle programmes to be cost saving (one in a cost-utility analysis [47] and one in a cost-benefit analysis [46]. The two studies that found lifestyle programmes to be cost saving utilised a model that included a large number of health states that could be modified by weight loss (e.g. cancer, osteoarthritis, depression) which may account for the more promising findings.

In conclusion, the studies published since the submission of this systematic review for publication have not altered the overall findings or conclusions set out above.

3.4.3. Implications for policy makers

Guidance in the UK and the US advocate lower intensity pragmatic lifestyle programmes and there is a small amount of evidence that these are cost-effective. Historical studies are likely over-stating treatment effects (based on results of recent meta-analyses) and uncertainty over duration of impact limits accurate long-term modelling. Guidance in the UK advocates the use of fasting plasma glucose or HbA1c in identifying people who are at high risk of

T2DM. There is currently insufficient data to conclude that interventions in people identified solely with HbA1c are cost-effective. There is insufficient evidence to suggest that metformin is more cost-effective than lifestyle programmes.

In addition to these considerations of cost-effectiveness, policy makers may need to balance impact on health budgets, incident cases of T2DM and equity of healthcare provision. In the few studies where these were modelled, budget impact was moderate (prevention programmes required 0.13-0.2% of respective countries total healthcare budget), financial payoffs were delayed (net expenditure on treatment and prevention of diabetes only declined after 9-14 years) and impact on incident cases of diabetes was limited (0.1-1.6% reduction in incident cases). This suggests that other avenues to reducing incident cases of diabetes will need to be explored if substantial inroads are to be made in controlling the T2DM epidemic. These may include population-wide measures to address obesity, a primary determinant of progression to type 2 diabetes in a person with intermediate hyperglycaemia [50].

3.4.4. Comparison with previous systematic reviews

The findings outlined in this chapter confirm those of previous systematic reviews [51-55] which have shown that lifestyle interventions are generally cost-effective, but with a wide range of cost-effectiveness ratios, reflecting heterogeneity of interventions, target populations and modelling approaches. They have shown that lifestyle interventions appear more cost-effective if group, rather than individual sessions, are provided and a long time-horizon is adopted for analysis. They have raised the issue of the limited number of studies in developing countries, the concern that real-life implementation of programmes will be

less effective than trial-based interventions, and the uncertainty that persists regarding long-term efficacy of these interventions.

3.4.5. Strengths and limitations

To my knowledge, this was the largest and most up-to-date summary of economic evaluations of diabetes prevention programmes at the time of publication. It was also the first review to: summarise the cost-effectiveness of metformin, compare screening-plus-intervention against intervention-only studies and consider the relevance and credibility of studies for decision makers. It was also the first review to undertake a detailed analysis of key parameter values (e.g. relative risk reductions) underpinning modelling studies and to compare these both with findings from clinical trials and with current diabetes prevention policies in the UK and US. The addition of new material up to December 2018 means that the findings remain up-to-date.

This review has a number of limitations. First is its relevance to policy makers in the US and UK as there are only a small number of economic evaluations included that reflect prevailing national policies. Second is the preponderance of studies from wealthy predominantly Caucasian countries, which may limit the applicability of findings to more diverse populations. Third is the comparison of costs and QALYs across studies. Costs were converted to GBP using purchasing power parity at a national level between the study country and the UK, but this may not adequately reflect purchasing power parity of health system costs between countries, leading to inaccuracies in comparison. QALYs were

compared across studies even though different instruments may have been used to calculate utility values across different studies. This means that the comparison of QALYs may not have been comparing utilities that were alike. Finally, this review may not include all relevant papers as the search strategy did not include Econlit and Tufts cost effectiveness register.

3.5. SUMMARY AND CONCLUSION

This systematic review has summarised three findings from the published literature. Firstly, metformin and lifestyle interventions in people at high risk of T2DM appear to be cost-effective but not cost saving, with median ICERs of £8,428/QALY and £7,490/QALY respectively. Secondly, in the few studies where these were modelled, budget impact was moderate, financial payoffs were delayed and impact on incident cases of diabetes was limited. Thirdly, national diabetes prevention policy in the UK and US advocates pragmatic lifestyle programmes (less than 3 years in duration), and in the UK the use of HbA1c or fasting plasma glucose is recommended for diagnosing intermediate hyperglyacaemia. However, the majority of cost-effectiveness studies relate to a different definition of hyperglycaemia and a higher intensity of intervention, which limits the direct applicability of findings.

Additional research is required to explore differences in cost-effectiveness related to different intensities of lifestyle programmes and different definitions of intermediate hyperglycaemia as there are insufficient existing studies to draw conclusions on the most cost-effective diagnosis-intervention pairs.

CHAPTER FOUR

Individual case-based approaches to preventing T2DM:

Economic evaluation of alternative programmes

4: INDIVIDUAL CASE-BASED APPROACHES TO PREVENTING T2DM – ECONOMIC EVALUATION OF ALTERNATIVE POLICIES

The content of this chapter is based partly on material published previously in the following peer-reviewed journal article:

- Roberts S, Craig D, Adler A, McPherson K, Greenhalgh T. Economic evaluation of type 2 diabetes prevention programmes: Markov model of low- and high-intensity lifestyle programmes and metformin in participants with different categories of intermediate hyperglycaemia. *BMC Med.* 2018; 30;16(1):16

  My role: I conceptualised the study, created the model, undertook the analysis, wrote the first draft of the paper and collated responses from other authors. I am the corresponding author and guarantor for the paper.

4.1. BACKGROUND, AIMS AND OBJECTIVES

Diabetes prevention guidance issued by the National Institute of Health and Care Excellence (NICE) in the UK and the Preventative Services Task Force in the US favours low-intensity lifestyle programmes [1,2], focused on participants with IFG (or HbA1c in the 'at risk range' in the UK). However, there are few existing economic evaluations of these type of interventions as outlined in Chapter 3. Most economic evaluations use treatment effects drawn from trials of high-intensity lifestyle programmes in participants with IGT. But the generalisability of this assumption has not been validated. No existing evaluation compares a pragmatic lifestyle programme with metformin or compares programmes for participants

with HbA1c in the 'at risk' range with those offered to participants with other types of intermediate hyperglycaemia.

The aim of this chapter is to evaluate the gap between existing evidence and current policy regarding individual case-based T2DM prevention programmes. The objectives are to examine the costs and effects of different intensity lifestyle programmes and metformin in participants with different categories of intermediate hyperglycaemia. This is achieved by modelling the cost and consequences (in terms of quality-adjusted life years [QALYs]), incident cases of T2DM and average number of years with T2DM) for:

1. Three different definitions of intermediate hyperglycaemia (IFG, HbA1c, IGT) used to select participants for T2DM prevention programmes
2. Three types of T2DM prevention programme (metformin, intensive trial-based lifestyle programme, low-intensity pragmatic lifestyle programme)

4.2. METHODS

I constructed a de novo economic model (decision tree and Markov model) in TreeAgePro (TreeAge Software Inc.) to undertake the analysis described in this chapter. I chose the model type based on what was most commonly utilised in existing economic evaluations of diabetes prevention policy. As more than 80% of economic evaluations summarised in the Chapter 3's systematic review of the literature used Markov models, I elected to develop a Markov model for this analysis. Most of existing studies using Markov models (described in

Chapter 3) utilised either TreeAgePro or Excel for modelling and I elected to use TreeAgePro as it is less error-prone than Excel and enables clearer presentation of results than other software tools [3]. I undertook training in Basic and Advanced Healthcare modelling with TreeAge Pro before I commenced.

I developed the model structure initially based on the health states of interest (IFG, IGT, HbA1c in the 'at risk' range and T2DM) and verified key elements of the structure with the multi-disciplinary clinical team in Newham, East London, who were engaged in developing their borough-wide T2DM prevention programme. The more technical aspects of model design were tested by presenting modelling work in progress at seminars in the Heath Economics Research Centre at the University of Oxford and the Institute of Health and Society at Newcastle University and seeking expert advice from a health economist (Dawn Craig) at Newcastle University (who became a co-author on the paper covering the findings in this chapter).

The model comprised four health states (normoglycaemia, intermediate hyperglycaemia [either IFG, IGT or HbA1c], T2DM and death). A health system perspective was adopted. The price year was 2015, as this was the most recent data available within the tool used for converting costs using purchasing power parity [4], and were reported in Great British Pound Sterling (£). The outcomes of the analysis were cost per QALY gained with QALYs calculated using SF-6D utility values. I adopted a 50-year time horizon, with annual cycles. Costs and utilities were discounted by an annual rate of 3.5% per year, which is the rate recommended by NICE [5].

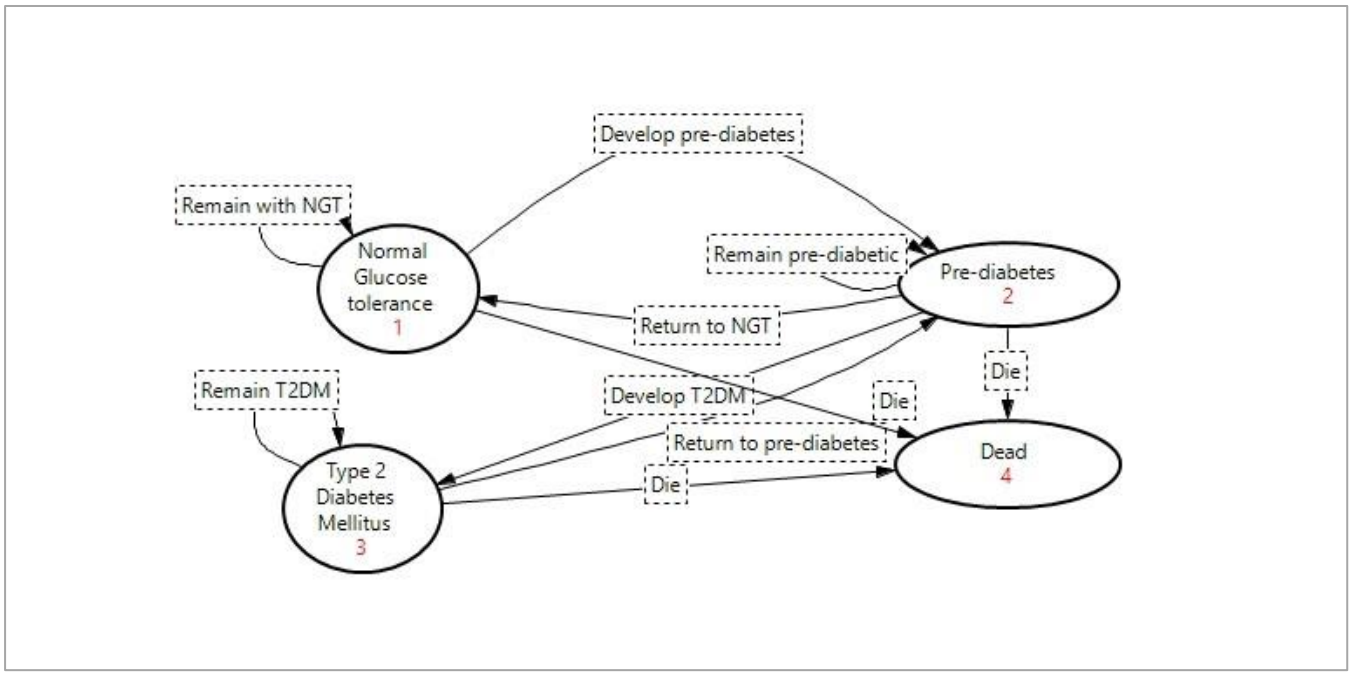
I evaluated both deterministic and probabilistic models; the probabilistic model was used to account for non-linearity, correlations in parameters and to characterise decision uncertainty. Deterministic sensitivity analysis was undertaken to evaluate alternative scenarios where there are differences in definitions (e.g. American Diabetes Association or World Health Organisation diagnostic criteria) or where primary clinical data is not available (e.g. long-term effect of interventions).

Three populations are evaluated in the model, individuals with IFG, IGT and HbA1c in the 'at risk range', across twelve different diagnosis-treatment pairs: IGT_low intensity lifestyle, IGT_intensive lifestyle, IGT_metformin, IGT_no intervention, IFG_low intensity lifestyle, IFG_intensive lifestyle, IFG_metformin, IFG_no intervention, HbA1c_low intensity lifestyle, HbA1c_intensive lifestyle, HbA1c_metformin, HbA1c_no intervention.

4.2.1. Model structure

I assumed the population entered the model with a diagnosis of intermediate hyperglycaemia (IFG, IGT or HbA1c) and could transition to type 2 diabetes, normoglycemia or death, with the probability of transitioning between states modified by the type of intervention the participant receives. Participants who were normoglycemic could transition to intermediate hyperglycaemia or death, but not directly to T2DM. To reflect disease progression/ clinical reality participants who transitioned to T2DM remained in this state until the end of the modelling period or death (Figure 4.1).

Figure 4.1: Markov model - State transition diagram



For the population-level case study of England, I assumed all adults aged 50-59 with diagnosed IFG, IGT or HbA1c would be offered an intervention, but that only 50% of the population with intermediate hyperglycaemia would be diagnosed and 50% who were offered an intervention would fail to enrol. These assumptions match those utilised by NICE in the costing template for T2DM prevention guidance [6], as primary studies of enrolment and compliance in this area show a very wide range of participation rates [7]. I assumed that intermediate hyperglycaemia was diagnosed in one of two ways: i) an incidental finding when blood tests were taken for another purpose or ii) through assessment of glycaemic status during a NHS Health Check, a clinical assessment offered to all 40-74 year olds in England without pre-existing diabetes or cardiovascular disease (with coverage of 13.7%-22.4% reported nationally in in the 50-59 year age-group) [8].

4.2.2. Model parameters

IFG, IGT and HbA1c are distinct physiological states, and differ in terms of epidemiological parameters, cost of care and health utilities (Table 1). However, a single individual may have one, two or three types of intermediate glycaemia concurrently.

Clinical and epidemiological parameters: Diagnostic criteria for intermediate hyperglycaemia reflected those of the NHS Diabetes Prevention Programme [1]: World Health Organisation (WHO) diagnostic criteria for HbA1c and IGT [9] and American Diabetes Association (ADA) criteria for IFG [10] (Table 4.1). Prevalence of IFG, IGT and HbA1c in the 'at risk' range and the combinations of different types of intermediate hyperglycaemia were extracted from a UK-based study [11] and the annual probability of transitioning to T2DM was obtained from a meta-analysis, with different transition probabilities assumed for IFG, IGT and HbA1c [12]. All-cause age-standardised mortality rates were obtained from the Office of National Statistics in England [13], with increased risk of death calculated for participants with intermediate hyperglycaemia or T2DM [14].

Table 4.1: Baseline population – key parameter values.

Parametric form and standard error of distribution used in probabilistic sensitivity analysis in italics

Health state	Diagnostic test	Diagnostic criteria	Prevalence	Annual incidence of T2DM	Annual cost of care (£, 2015)	Utility (QALYs)
Normoglycaemia (NGT)	Any of fasting blood glucose, post-load glucose or glycated haemoglobin	Fasting glucose: <5.6 mmol/L Post-load glucose: <7.0mmol/L HbA1c: <6.0 mmol/mol			£773 *[Gamma distribution, SE: £102.63]*	0.768 *[Beta distribution, SE: 0.10]*
Impaired fasting glucose (IFG)	Fasting blood glucose	Fasting glucose: 5.6-6.9 mmol/L	Isolated IFG: 12.76% IFG+IGT: 1.49% IFG+HbA1c: 6.61% IFG+IGT+HbA1c: 1.06%	3.55% *[Beta distribution, SE: 0.006]*	£869 *[Gamma distribution, SE: 104.56]*	0.759 *[Beta distribution, SE: 0.11]*

Impaired glucose tolerance (IGT)	Post-load glucose	2 hour post-load glucose: 7.0-11.1 mmol/L	Isolated IGT: 7.50% IGT+HbA1c: 3.31%	4.54% *[Beta distribution, SE: 0.004]*	£946 *[Gamma distribution, SE: 101.52]*	0.746 *[Beta distribution, SE: 0.10]*
HbA1c	Glycated haemoglobin	6.0-6.4 mmol/mol	Isolated HbA1c: 7.53%	3.56% *[Beta distribution, SE:0.017]*	£869 *[Gamma distribution, SE: 104.56]*	0.759 *[Beta distribution, SE: 0.11]*
Type 2 Diabetes Mellitus (T2DM)	Any of fasting blood glucose, post-load glucose or glycated haemoglobin	Fasting glucose: >6.9 mmol/l 2 hour post-load glucose: >11.1 mmol/L			£1,179-£2,939 Increasing linearly from Year 1-15 *[Gamma distribution, SE: 270.00]*	0.738 *[Beta distribution, SE: 0.12]*

Sources: Diagnostic criteria for HbA1c and IGT [9] and for IFG [10], prevalence [11], annual incidence type 2 Diabetes [12], costs [15-18], utilities [19].

For IFG and IGT, relative risks of developing T2DM or reverting to normoglycaemia with lifestyle interventions were derived from meta-analyses [20-22]. Relative risks for metformin were drawn from the US Diabetes Prevention Program Outcomes Study (USDPPOS) for metformin therapy as this is the only long-term follow up study of this intervention [23]. To my knowledge there is only a single RCT (a sub-group analysis of the US Diabetes Prevention Program [USDPP]) [24] which reported relative risks of participants identified on the basis of HbA1c, and my model drew from this single analysis. I assumed that the reduction in risk related to metformin was constant over 15 years for participants with IGT and IFG and 10 years for participants identified on the basis of HbA1c, as these were the longest periods of follow up that have been published for each population [23, 24]. Based on an up-to-date meta-analysis I assumed that reduction in risk declined following cessation of the intensive lifestyle programme [21] and ceased ten years after the intervention commenced. As no long-term follow-up studies of low-intensity lifestyle programmes had been undertaken, we conservatively assumed the risk reduction persisted only for the duration of the intervention. Finally, we assumed that adherence was equivalent to that seen in the clinical trials from which relative risks were derived.

Interventions: The low-intensity lifestyle programme was based on NICE guidance [25] and includes a core component of 13 group education sessions in the first year followed by 7 maintenance sessions over the following two years, delivered by diabetes prevention facilitators, with annual review by a general practitioner and blood tests by a practice nurse. The high-intensity lifestyle programme was based on the US DPP [26] and includes 16 one-to-one education sessions delivered by a dietician and 4 exercise sessions supervised by a

physiotherapist in the first year and 12 individual visits and 4 supervised exercise sessions in the second and third year as well as 1-2 reminder phone calls a month and annual clinical review and blood tests. In terms of metformin, a dosage of 850mg twice a day was assumed, in line with the USDPP, with annual titration review and blood tests by a practice nurse and annual review by a general practitioner [26]. Low-intensity lifestyle intervention lasted 2 years, the high-intensity lifestyle intervention lasted 3 years and I assumed that metformin therapy continued as long as the participant had intermediate hyperglycaemia. The base case of no intervention assumed that people with a diagnosis of intermediate hyperglycaemia received no additional treatment, as was the case in the majority of England before the commencement of the national pilots in diabetes prevention in 2017.

Costs (Appendix 4.1): I calculated the costs of lifestyle programmes by applying Personal Social Services Research Unit (PSSRU) staff cost estimates [27] to constituent activities described in publications regarding the USDPP [26] and NICE guidance [25] and using published estimates of diagnostic test costs [28]. I used the British National Formulary to calculate medication costs [15]. As an NHS perspective was adopted I did not include indirect costs such as productivity loss or participants' out of pocket costs.

Costs of T2DM were determined from a UK study of resource utilisation in diabetic care [16]. I assumed costs of diabetes would increase linearly over 15 years from the time of diagnosis to reflect the increasing cost of diabetic complications over time, in line with the approach taken by NICE [6]. Costs of other health states were calculated as proportions of

T2DM costs, derived from two European studies [17, 18]. All costs were inflated to 2015 values. Unrelated healthcare costs (not related to T2DM or its complications) that accrue due to prolonged life were not included in the base case, but were considered in sensitivity analysis.

Utilities: Utilities were measured in quality-adjusted life years and were derived for each health state from a Swedish study which utilised SF-36 questionnaires, converting responses via the SF-6D index to utilities [19]. This is the only source of utilities, to my knowledge, that measured quality of life in IFG and IGT separately. Incremental utilities associated with each intervention were drawn from the USDPP [26], with both low- and high-intensity lifestyle programmes assumed to be associated with the same incremental utility.

Table 4.2 outlines the key parameter values with Appendix 4.2 outlining data sources, assumptions and limitations of these values.

Table 4.2: Interventions – key parameter values: Parametric form and standard error of distribution used in probabilistic sensitivity analysis in italics

Intervention	Annual cost of intervention (£, 2015)	Incremental utility associated with intervention (QALY)	Relative risk of developing T2DM
Low-intensity lifestyle programme	Yr 1: £203.44 Yr 2: £80.02	0.0189 *[Beta distribution, SE: 0.001]*	During intervention: IFG: 0.74/IGT: 0.74/HbA1c: 0.74 *[Lognormal distribution, SE: 0.11]*
High-intensity lifestyle programme	Yr 1: £1225 Yr 2: £689 Yr 3: £671	0.0189 *[Beta distribution, SE: 0.001]*	During intervention: IFG: 0.63/IGT: 0.55/HbA1c: 0.71 *[Lognormal distribution, SE: 0.10 (IFG), 0.07 (IGT), 0.10 (HbA1c)]* Up to 7 years post- intervention: IFG: 0.80/IGT: 0.80/HbA1c: 0.71 *[Lognormal distribution, SE: 0.06 (IFG), 0.06 (IGT), 0.10 (HbA1c)]*
Metformin	£124.25	0.0031 *[Beta distribution, SE: 0.002]*	IFG: 0.82/IGT: 0.82/HbA1c: 0.62 *[Lognormal distribution, SE: 0.05(IGT), 0.05 (IFG), 0.10 (HbA1c)]*

Sources: *Intervention costs (calculated – see Appendix 4.1), incremental utilities [26], relative risks [21, 24, 22, 20, 29]*

4.2.3. Analyses

I undertook two types of analyses: 1) impact on an individual participant in a prevention programme, 2) impact of a nation-wide prevention programme, using England as a case study.

Analyses of individual participants included: i) discounted cumulative healthcare costs (including costs of diagnostic tests and primary and secondary care associated with the intervention, intermediate hyperglycaemia, T2DM and complications of T2DM), ii) discounted quality-adjusted life-years, iii) incidence of T2DM, iv) average number of years with T2DM iv) cost-effectiveness ratios in £/QALY and v) incremental cost-effectiveness ratios, in £ per QALY (for non-dominated interventions). Individuals are frequently diagnosed with more than one type of intermediate hyperglycaemia (Table 4.1). All participants with each type of intermediate hyperglycaemia (alone or in combination with other types of intermediate hyperglycaemia) were analysed in each arm of the model. For example, the IGT arm includes participants with either IGT in isolation, IGT *and* IFG, IGT *and* HbA1c and IGT *and* IFG *and* HbA1c in the 'at risk' range.

Analyses of a nation-wide prevention programme included: i) discounted annual incremental costs, ii) discounted cumulative incremental costs, iii) discounted incremental costs as a percentage of total national diabetes expenditure [30] and iv) cumulative incidence of T2DM. To account for individuals with more than one type of intermediate hyperglycaemia,

the costs and effects in the IGT arm of the analysis were assumed to represent all individuals with a diagnosis of IGT (participants with IGT in isolation, IGT *and* IFG, IGT *and* HbA1c in the 'at risk' range and IGT *and* IFG *and* HbA1c in the 'at risk' range), the costs and effects in the IFG arm of the analysis were assumed to represent all individuals with isolated IFG and IFG and HbA1c in the at risk range and the costs and effects of the HbA1c arm of the analysis were assumed to represent all individuals with isolated HbA1c in the 'at risk' range.

Sensitivity analyses: I assessed parameter uncertainty with: i) deterministic one-way sensitivity analysis, altering all parameter values by +/-10%, ii) probabilistic sensitivity analysis and iii) deterministic scenario analyses where primary clinical data was not available to create a distribution (e.g. duration of intervention effect) or differences in clinical definitions existed (e.g. IFG diagnosed by WHO criteria).

4.2.4. Validation

I validated the model in accordance with the AdVISHE checklist [31]. Three clinical experts tested the face validity of the model structure, inputs and outputs and their suggestions were incorporated in the final model. I undertook extreme value testing and audit of Markov cohort traces and the structure of formulae were reviewed in a session with the TreeAge support team. Model outputs were validated against empirical data, including mortality data for England and estimates of current prevalence of T2DM by age group.

4.3. RESULTS

4.3.1. Outcomes for individual participants in a prevention programme

The base case results of the deterministic analysis are presented in Tables 4.3, 4.4 and cost-effectiveness ratios in Table 4.5. In participants with all types of intermediate hyperglycaemia, pragmatic lifestyle programmes, intensive lifestyle programmes and metformin increased costs, improved QALYs and reduced incidence of T2DM compared with no intervention.

Incremental cost-effectiveness ratios (ICERs) - comparison with the next best alternative (Table 4.5): For all three populations, the low-intensity lifestyle programme was the most cost-effective option with ICERs of £44/QALY, £195/QALY and £186/QALY in populations with IGT, IFG and HbA1c in the 'at risk' range respectively. At the current NICE willingness to pay threshold of £20,000/QALY, intensive lifestyle interventions were cost-effective relative to the next best alternative (low-intensity lifestyle programme) with ICERs of £3,707/QALY and £11,219/QALY for IGT and IFG respectively. For the population with HbA1c in the 'at risk' range, metformin was also found to be cost-effective relative to the next best alternative (low-intensity lifestyle programmes) with an ICERs of £600/QALY; this was the only population for which metformin was not extendedly dominated (a combination of low-intensity and high-intensity lifestyle interventions was not more cost-effective than metformin) [Table 4.5, Figure 4.2]. However, due to effect sizes in participants with HbA1c being derived from a single clinical study, results for this population should be treated cautiously.

Table 4.3: Costs and consequences for individual participants in a prevention programme

Method of identifying participants	Intervention	Total cost (£,2015)	Total QALYs	Prevalence of T2DM after 50 years (%)	Average number of years lived with T2DM after 50 years
IGT	No intervention	17,772	11.53	42%	5.75
	Pragmatic lifestyle programme	17,774	11.59	41%	5.43
	Intensive lifestyle programme	18,423	11.76	33%	3.97
	Metformin	17,988	11.60	38%	5.03
IFG	No intervention	17,429	12.13	38%	5.34
	Pragmatic lifestyle programme	17,440	12.19	37%	5.07
	Intensive lifestyle programme	18,452	12.28	31%	3.98
	Metformin	17,908	12.20	35%	4.68
HbA1c	No intervention	17,436	12.13	38%	5.35
	Pragmatic lifestyle programme	17,446	12.19	37%	5.08
	Intensive lifestyle programme	18,507	12.27	31%	4.03
	Metformin	17,475	12.23	33%	4.18

Table 4.4: Diabetes incidence and risk reduction over 10 years and 50 years

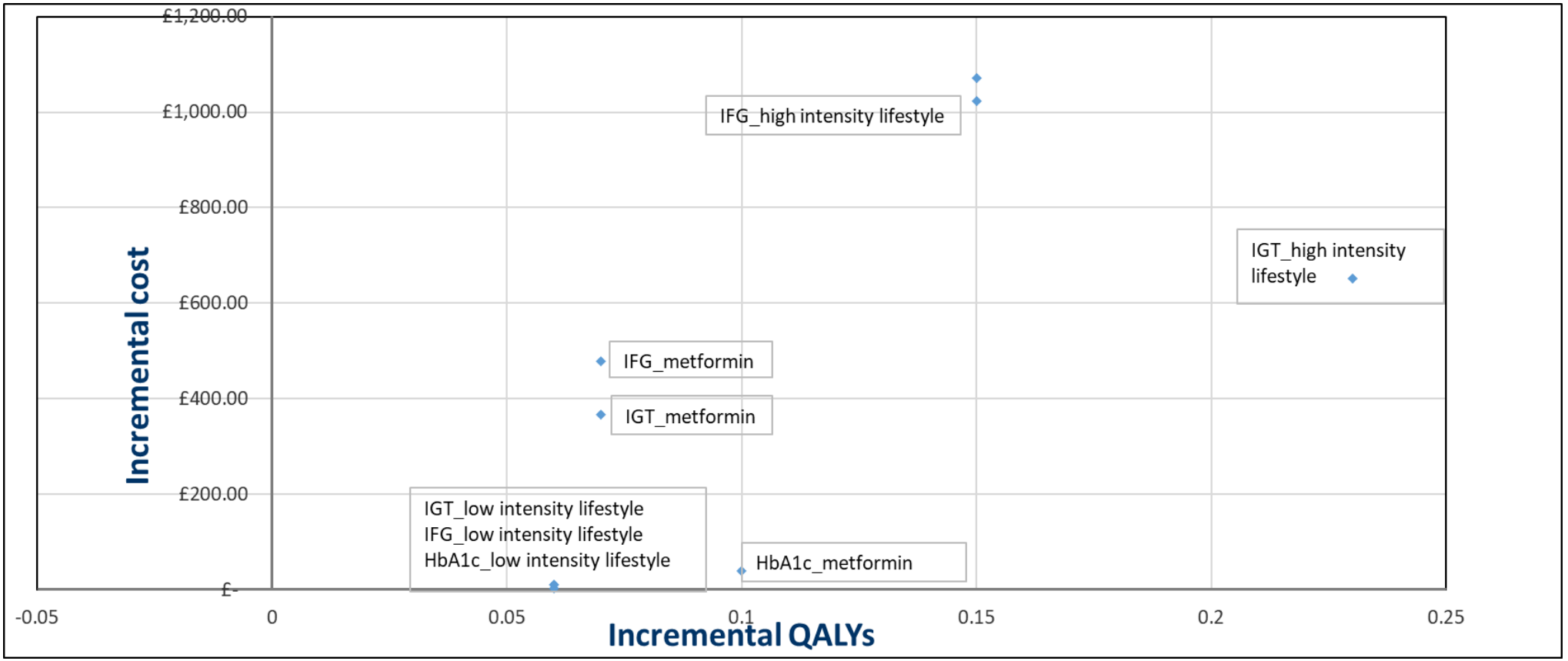
Method of identifying participant	No intervention		Low intensity lifestyle programme				High intensity lifestyle programme				Metformin			
	Incidence T2DM		Incidence T2DM		Relative risk reduction		Incidence T2DM		Relative risk reduction		Incidence T2DM		Relative risk reduction	
	After 10 years	After 50 years	After 10 years	After 50 years	At 10 years	At 50 years	After 10 years	After 50 years	At 10 years	At 50 years	After 10 years	After 50 years	At 10 years	At 50 years
IGT	23%	42%	22%	41%	7%	3%	14%	33%	39%	21%	20%	38%	16%	9%
IFG	19%	38%	18%	37%	7%	3%	13%	31%	35%	17%	16%	35%	16%	9%
HbA1c	19%	38%	18%	37%	7%	3%	13%	31%	35%	17%	13%	33%	35%	14%

The 10-year incidence of T2DM in people with IGT in this model (23%) is in line with that observed in the Diabetes Prevention Programme Outcomes Study (25%) [23]. The 10-year incidence of T2DM in people with IFG in this model (19%) is higher than observed in a German study of diabetes incidence (15%) [34]. However, meta-analyses of progression to T2DM for people with different types of intermediate hyperglycaemia [12] report wide ranges of incidence between studies which may be accounted for by differences in other risk factors, such as BMI.

Table 4.5: Incremental cost-effectiveness ratios and cost-effectiveness relative to no intervention for individual participants in a prevention programme

Method of identifying participants	Intervention	Incremental cost-effectiveness ratio (ICER) *(relative to next best intervention)*				Cost-effectiveness ratio (CER) *(relative to no intervention)*			
		Increm-ental cost (£, 2015)	**Incremental effect** (QALYs)	**ICER** (£/QALY)	**Probability ICER< £20,000/QALY**	**Cost vs no intervention** (£, 2015)	**Effect vs no intervention** (QALYs)	**CER** (£/QALY)	**Probability CER< £20,000/QALY**
IGT	**No intervention**	-	-	-	-	-	-	-	-
	Low-intensity lifestyle	3	0.06	44	98.19%	3	0.06	44.33	98.19%
	Metformin	Subject to extended dominance				367	0.07	5,224	75.86%
	High-intensity lifestyle	649	0.18	3,707	74.58%	652	0.23	2,775	80.5%
IFG	**No intervention**	-	-	-	-	-	-	-	-
	Low-intensity lifestyle	11	0.06	195	98.5%	11	0.06	195	98.5%
	Metformin	Subject to extended dominance				479	0.07	6,842	76.28%
	High-intensity lifestyle	1,012	0.09	11,219	75.09%	1,023	0.15	6,820	81.44%
HbA1c	**No intervention**	-	-	-	-	-	-	-	-
	Low-intensity lifestyle	11	0.06	186	97.79%	11	0.06	186	97.79%
	Metformin	28	0.05	600	50.40%	39	0.10	372	77.89%
	High-intensity lifestyle	1,032	0.04	25,481	40.38%	1,071	0.15	7,376	71.28%

Figure 4.2: Cost-effectiveness plane of all interventions – incremental costs and QALYs compared to no intervention



At a willingness to pay threshold of £20,000/QALY, the probability of being cost-effective relative to the next best alternative was 98%, 99%, 98% for low-intensity lifestyle programmes and 75%, 75% and 60% for high-intensity lifestyle programmes for participants with IGT, IFG and HbA1c respectively. The probability that metformin was cost-effective relative to the next best alternative was 50% for participants with HbA1c (Appendix 4.3).

Cost-effectiveness ratios (CERs) – comparison with no intervention: Compared to no intervention, the low-intensity lifestyle programme was the most cost-effective option with CERs of £44/QALY, £195/QALY and £186/QALY in populations with IGT, IFG and HbA1c in the 'at risk' range respectively. Intensive lifestyle interventions cost £2,775/QALY, £6,820/QALY and £7,376/QALY and metformin £5,224, £6,842 and £372/QALY relative to no intervention for IGT, IFG and HbA1c respectively. At a willingness to pay threshold of £20,000/QALY, the probability of being cost-effective was 98%, 99%, 98% for low-intensity lifestyle programmes, 81%, 81% and 71% for high-intensity lifestyle programmes and 76%, 76% and 78% for metformin in participants with IGT, IFG and HbA1c respectively.

Effect on diabetes prevalence: With no intervention, 42% of the IGT population and 38% of the IFG and HbA1c population developed T2DM over 50 years. Incidence of T2DM was reduced to 41%, 33% and 38% in the IGT population, 37%, 31% and 35% in the IFG population and 37%, 31% and 33% in the HbA1c population with low-intensity lifestyle programmes, high-intensity lifestyle programmes and metformin respectively [Table 4.4].

4.3.2. Outcomes of a nationwide prevention programme

Incident cases of T2DM would reduce by 0.3 to 1.5 % over 50 years in 50-59 year olds if a pragmatic lifestyle programme was offered to everyone with either IFG, IGT or HbA1c in the at risk range in this age group in England [Table 4.6]. A national intensive lifestyle programme would lead to the greatest population health benefits with a 1.9 to 3.1% reduction in diabetes incidence and 2.7 to 3.4% reduction in the number of years with T2DM in this cohort. The type of intermediate hyperglycaemia has a significant impact on population-level outcomes due to of the substantially higher prevalence of IFG and high HbA1c than IGT.

Table 4.6: Outcomes for an England-wide prevention programme

Method of identifying participants	Intervention	Reduction in incident cases of T2DM (number of cases)	% reduction in incident cases of T2DM	Reduction in average number of years lived with T2DM (number of years)	% reduction in average number of years lived with T2DM (%)
IGT	Pragmatic lifestyle programme	2,938	0.3%	0.03	0.5%
	Intensive lifestyle programme	20,494	1.9%	0.15	2.7%
	Metformin	9,388	1.9%	0.07	1.3%
IFG	Pragmatic lifestyle programme	11,582	1.1%	0.04	0.7%
	Intensive lifestyle programme	32,119	3.0%	0.19	3.4%

	Metformin	20,863	1.9%	0.11	2.0%
HbA1c	**Pragmatic lifestyle programme**	15,856	1.5%	o.03	0.6%
	Intensive lifestyle programme	33,027	3.1%	0.15	2.8%
	Metformin	29,163	2.7%	0.14	2.5%

Annual incremental costs are negative from year 3 for pragmatic lifestyle programmes, year 4 for intensive lifestyle programmes and from year 10 for metformin, relative to no intervention (Figure 4.3). Cumulative costs remain positive over the 50-year modelling period relative to no intervention (Figure 4.4). Assuming no existing diabetes services are displaced, an England-wide prevention programme requires an investment (as a % of total diabetes costs) of 0.5 to 0.9% in Year 1, 0.2 to 0.3% in Year 2 for a low-intensity lifestyle programme and 3.1 to 5.2% in Year 1, 1.4 to 2.3% in Year 2 and 1.0 to 1.8% in Year 3 for a high-intensity lifestyle programme, depending on the type of participants targeted (Appendix 4.4).

For an average-sized CCG, this would equate to a reduction in incident cases of T2DM between 12-67 in the case of low-intensity lifestyle programmes, 86-139 in the case of intensive lifestyle programmes and 35-123 in the case of metformin at a cost in year 1 of £194,000-£319,000 for pragmatic lifestyle programmes, £1.17million-£1.9million for intensive lifestyle programmes and £ £118,000-£194,000 for metformin.

Figure 4.3: Annual costs of an England-wide programme

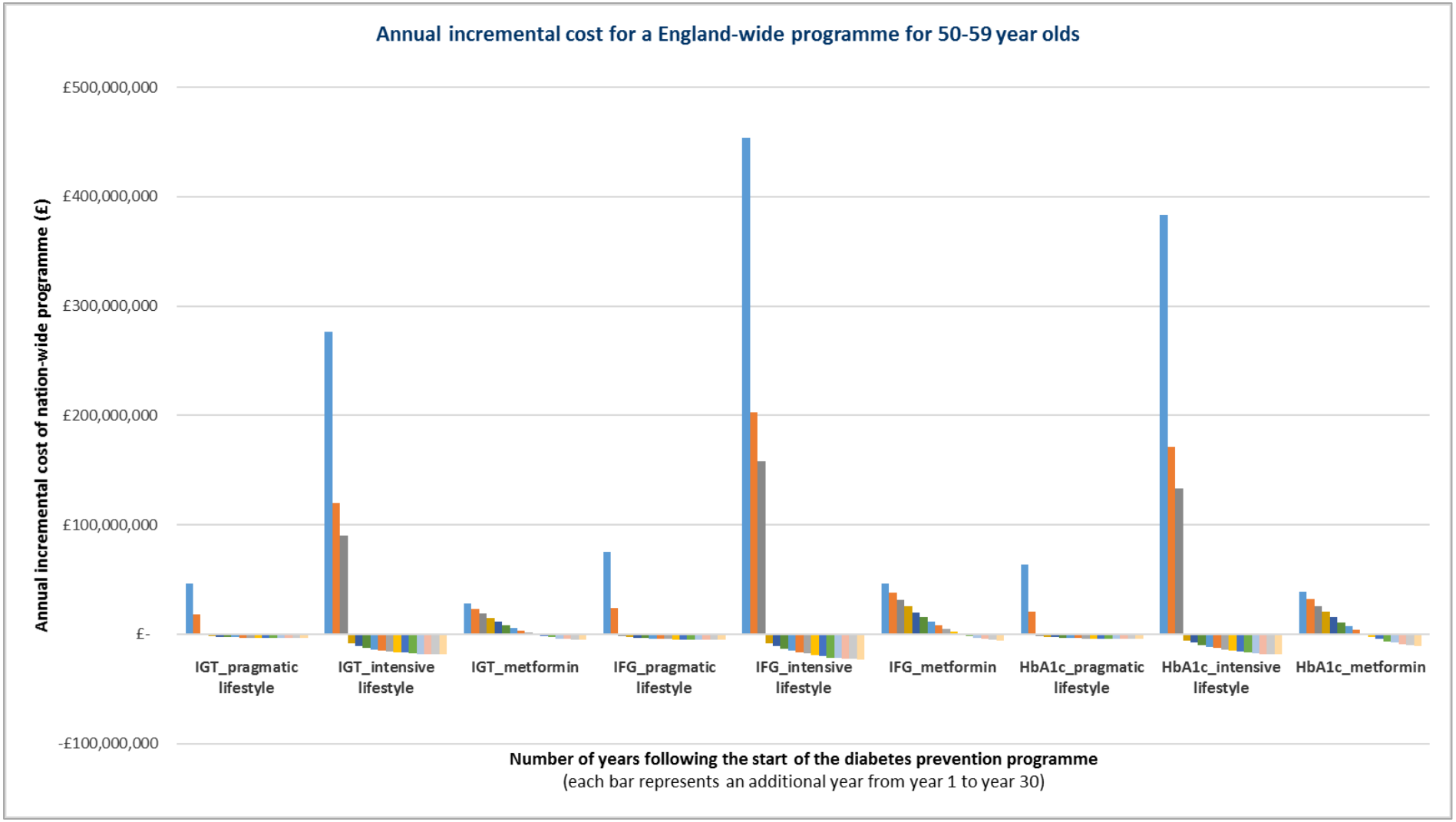
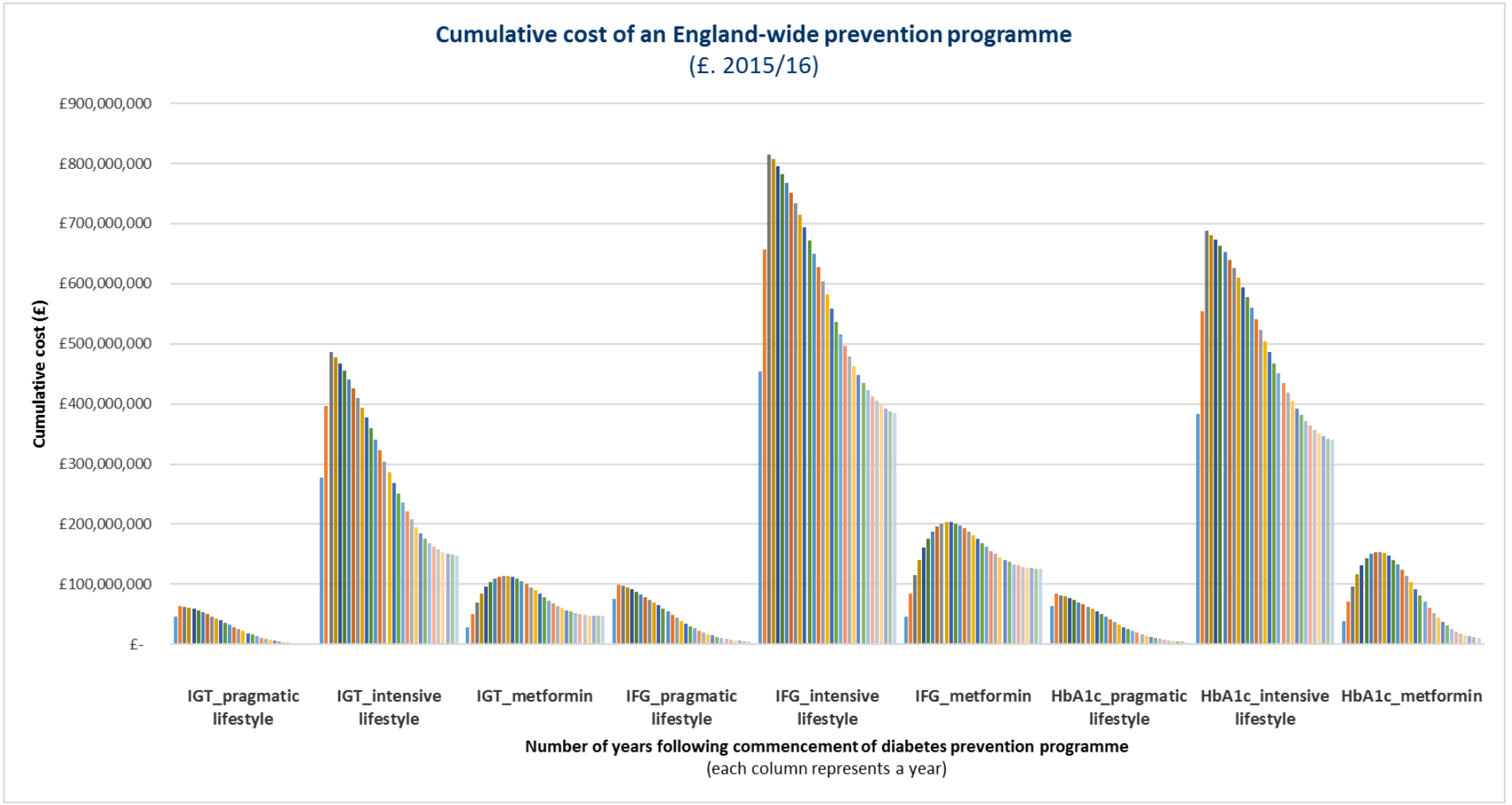


Figure 4.4. Cumulative cost of an England-wide programme



4.3.3. Sensitivity analysis

Key factors impacting cost-effectiveness calculations in one-way sensitivity analysis were health state utilities, hazard ratios of death, relative risks of T2DM and costs of the interventions. Additional scenarios examining extended duration of intervention effect, use of WHO criteria to diagnose IFG, increased/decreased intervention cost and inclusion of unrelated healthcare costs (Appendix 4.5) resulted in the following differences from the base case analysis: i) low-intensity lifestyle programmes are cost-saving in all participants when intervention effect is extended, ii) low-intensity lifestyle programmes are cost saving if the WHO criteria are used to diagnose IFG, with reduced budget impact at a population level but fewer cases of T2DM prevented, iii) metformin is cost saving in participants with HbA1c when intervention effect is extended and iv) high-intensity lifestyle programmes are cost-effective in participants with HbA1c when intervention costs were decreased by 20%. All interventions remained cost-effective relative to no intervention when unrelated healthcare costs were included in the analysis.

An assessment of the validity of this model is summarised in Appendix 4.6.

4.4. DISCUSSION

4.4.1. Principal findings

This analysis produced six major findings. Firstly, low-intensity lifestyle interventions are the lowest cost diabetes prevention programme over a participant's lifetime in all types of intermediate hyperglycaemia. Secondly, high-intensity lifestyle interventions deliver the greatest health benefit in terms of reducing diabetes incidence, years lived with T2DM and QALYs gained in participants with all types of intermediate hyperglycaemia. Thirdly, at a population-level, the type of intervention has the greatest impact on costs while the type of intermediate hyperglycaemia has the greatest impact on % reduction in incident cases. Fourthly, low- and high-intensity lifestyle programmes are very cost-effective in participants with IFG and IGT, while metformin is not a cost-effective option in these populations. These results were consistent across a range of parameter values. Fifthly, while budget impact as a % of total diabetes expenditure is small, these interventions require a net increase in diabetes expenditure (assuming existing services are not displaced) over 2, 3 and 9 years in the case of low-intensity lifestyle programmes, high-intensity lifestyle programmes and metformin respectively. Subsequent savings due to reduced incidence of T2DM are insufficient to entirely offset this increased expenditure. Finally, impact on incidence of T2DM at a population level is small, due to lack of overlap between different types of intermediate hyperglycaemia and issues with participation in screening tests, adherence to interventions and attenuation in the treatment effect over time. For example, if IGT is used to identify participants, only 25% of people with intermediate hyperglycaemia who develop T2DM will be identified. I assume only 50% of those with IGT are identified opportunistically and only 50% of those identified will attend a lifestyle programme. Therefore, only 6.25% of

those with intermediate hyperglycaemia will attend a lifestyle programme. Their risk of T2DM is 15% over the two years of a low intensity lifestyle programme, which in turn reduces this risk by 26%. Therefore, there is a reduction in risk of 4% for 6.25% of the relevant population, leading an absolute reduction in incidence of T2DM of 0.25%.

These results are comparable with previously published economic evaluations of diabetes prevention programmes, as outlined in Chapter 3, which found ICERs ranging from cost saving to £134,420/QALY, with a median value of £7,490/QALY for lifestyle programmes and ranging from cost saving to £32,430/QALY with a median value of £8,428/QALY for metformin in comparison to no intervention. Differences in assumptions regarding intervention cost and effect and uncertainty regarding key parameter values (e.g. duration of intervention effect), account for the range of ICERs in published economic evaluations.

4.4.2. Implications for policy makers

This analysis provides a quantification of a number of key tensions in diabetes prevention policy: 1) whether to select participants for which interventions will be the most cost-effective (those with IGT) or participants identified by tests that are widely used in current clinical practice (those with high HbA1c or IFG), 2) whether to target interventions at populations with the most attractive ICERs (those with IGT) or populations in which the greatest population-wide impact could be achieved (those with IFG according to ADA criteria), 3) whether to minimise budget impact by providing low-intensity lifestyle programmes or maximise reduction in incidence of T2DM and quality-adjusted life-years gained by providing high-intensity lifestyle programmes.

On balance, this analysis suggests that current English national policy of targeting prevention programmes at participants with IFG or HbA1c, and not recommending metformin as first-line prevention, will be cost-effective and have the most favourable budget impact. However, the modest reduction in incidence of T2DM suggests that, importantly, this approach will be insufficient to address the substantial growth in diabetes forecast for the coming decades. The search for additional interventions should continue.

I did not formally evaluate costs and effects in other countries. However, effect sizes in this model are drawn from international studies, therefore conclusions regarding gains in QALYs, reduction in incidence of T2DM and years with T2DM should be broadly generalizable, assuming equivalent prevalence of intermediate hyperglycaemia.

4.4.3. Strengths and limitations

This analysis adds to previous economic evaluations by: i) quantifying the impact of different types of intermediate hyperglycaemia and different intensities of lifestyle programme and ii) estimating costs and consequences at an individual participant-level and a national programme-level, using a case study of England. This study's limitations include: the availability of primary clinical data and the structure and scope of the Markov model. In terms of data availability, there were limited primary clinical data from trials to: i) model participants with intermediate hyperglycaemia identified by HbA1c, ii) quantify the long-

term effect of pragmatic lifestyle interventions, iii) differentiate the reduction in diabetes incidence due to low intensity lifestyle interventions by type of intermediate hyperglycaemia, iv) evaluate the long term effects of metformin in isolation by age-group, as the US DPPOS data used in this analysis relates to a cohort that received lifestyle advice in addition to metformin from year 4 of the 10-year intervention. Another major shortcoming is the absence of evidence on the impact of lifestyle interventions on endpoints important to patients, for example, the complication of diabetes and death. In terms of the model structure, I elected to use a Markov model to compare our findings with those of previous economic evaluations, the majority of which use Markov models. However, the underlying physiological changes in intermediate hyperglycaemia and diabetes (fasting glucose, post-load glucose or HbA1c) are continuous variables, which are better suited to simulation modelling. However, this requires more detailed data which were not available for all types of participants and interventions modelled. In terms of the scope of the model, we modelled only costs and QALYs relating to diabetes and its complications, whereas interventions may have beneficial effects on other types of disease (e.g. obesity-related cancers, dementia), that are not captured, but would likely improve the cost-effectiveness of lifestyle programmes. In addition, we did not explicitly model adverse effects of metformin, which we assumed were accounted for in the lower incremental utilities associated with metformin relative to lifestyle programmes.

4.5. SUMMARY AND CONCLUSION

This modelling study has confirmed that in individual case-based interventions for diabetes prevention the type of intermediate hyperglycaemia and the intensity of lifestyle

intervention do have an effect on the cost, health impact and cost-effectiveness of the intervention. In participants with all types of intermediate hyperglycaemia, low-intensity lifestyle interventions are the lowest cost diabetes prevention programme over a participant's lifetime whereas high-intensity lifestyle interventions deliver the greatest health benefit (in terms of reducing diabetes incidence, years lived with T2DM and QALYs gained). Low- and high-intensity lifestyle programmes are very cost-effective in participants with IFG and IGT, while metformin is not a cost-effective option in these populations but is in participants with HbA1c in the 'at risk' range. All individual case-based prevention programmes require an increase in diabetes expenditure, with subsequent savings being insufficient to entirely offset this expenditure, and the impact on incidence of T2DM at a population level is small.

This analysis suggests that current English national policy of low-intensity lifestyle programmes in participants with IFG or HbA1c will be cost-effective and have the most favourable budget impact, but will prevent only a fraction of cases of T2DM. Additional approaches to prevention need to be investigated urgently. Chapter 5 reviews the literature on population-wide interventions to identify additional approaches to diabetes prevention. And Chapter 6 considers these interventions' impact on health system costs and outcomes (cumulative incidence of T2DM and QALYs).

CHAPTER FIVE

Population-wide approaches to preventing T2DM or obesity:

Current evidence of efficacy

5: POPULATION-WIDE APPROACHES TO PREVENTING T2DM OR OBESITY – OVERVIEW OF SYSTEMATIC REVIEWS TO ASSESS CURRENT EVIDENCE OF EFFICACY

The content of this chapter is based partly on material published previously in the following peer-reviewed journal article:

- Roberts S, Pilard L, Chen J, Hirst H, Rutter H, Greenhalgh T. Efficacy of population-wide diabetes and obesity prevention programmes: an overview of systematic reviews on proximal, intermediate and distal outcomes and a meta-analysis of impact on BMI. *Obesity Reviews (in press)*

  My role: I conceptualised the study, undertook the searches and data extraction, performed the meta-analyses, wrote the first draft of the paper and collated responses from other authors. I am the corresponding author and guarantor for the paper.

5.1. BACKGROUND, AMIS AND OBJECTIVES

Prevention of T2DM is a global health priority due to high and rising prevalence and associated health system costs. Many policy makers, including those in England, are developing T2DM prevention policies based on individual-case based programmes, typically lifestyle interventions, as outlined in Chapter 2. Chapters 3 and 4 explored the effect of these policies on costs and health outcomes finding that, whist they are efficacious and cost-effective, they have a small impact on cumulative incidence of the disease. The next two chapters (chapter 5 and 6) will examine the potential impact of another approach to

T2DM policy: population-wide prevention programmes. These are rooted in the ecological approach to public health [1] which invites consideration of a far broader range of population-wide actions, aimed at altering physical, economic, policy or socio-cultural components of either micro-(e.g. schools, workplaces) or macro- (e.g. town, region, nation) environments [2]. Population-wide programmes aim to address the risk factors for the disease as far 'upstream' as possible and across the entire population. In the case of T2DM, the most commonly associated risk factors are body mass index (BMI), waist circumference and hypertension [3, 4], with measures of adiposity the only factors shown to be causally related to T2DM incidence [5].

This chapter aims to evaluate the efficacy of population-wide obesity and diabetes prevention programmes that operate at the level of the macro-environment. Evidence of efficacy is considered at three levels:

i) Proximal indicators of behaviour change (e.g. increased physical activity in a particular setting or increased choice of healthy food options);
ii) Intermediate indicators of change in energy balance (e.g. increase in total physical activity or reduced total calories consumed);
iii) Distal anthropometric indicators (e.g. reduction in BMI, prevalence of overweight/obesity or T2DM)

The objectives are to review the existing literature on population-wide T2DN or obesity prevention interventions, categorise these according to type of action or policy and

summarise the effect of each type of intervention on the proximal, intermediate and distal indicators outlined above.

5.2. METHODS

I undertook an overview of systematic reviews, which synthesizes the results of multiple systematic reviews, due to the breadth of the area under study and the multiple interventions examined. I pre-specified the study protocol and registered with PROSPERO (CRD42017084364) and reported findings according to the PRISMA statement [6] (Appendix 5.1). Meta-analysis of primary studies reporting change in BMI was undertaken as each review only included a small number of primary studies reporting this endpoint and there was limited overlap between these included studies.

5.2.1. Search strategy

To identify search terms, I started with two seminal reviews of obesity prevention[7, 8] and undertook citation tracking and follow-up of references (see Appendix 5.2 for terms used). Our department librarian (NA) provided advice on which databases to use, checked that I had correctly entered search terms and checked the results of searches. I searched eight databases (Embase, Medline, CINAHL, DoPHER, DARE, NHS EED, HTA, Cochrane Library) for systematic reviews describing population-wide interventions for T2DM or obesity prevention before February 2017. No restrictions were applied to the publication status of reviews, both peer-reviewed publications and grey literature were included. All abstracts were exported into EndNote, duplicates removed and independently reviewed by myself

and a second reviewer (LP) to identify papers for full review. I undertook citation tracking and screening of references which identified an additional 133 papers for full paper review. Inclusion criteria were i) systematic reviews, ii) describing population-wide interventions aimed at preventing T2DM or obesity in adults, and iii) reporting effect of interventions on proximal indicators of behaviour change, intermediate indicators of change in energy balance or distal anthropometric indicators. Exclusion criteria included: i) interventions aimed at individuals identified as being at high risk of T2DM or obesity (e.g. medications, surgery, individual lifestyle programmes, tailored print or technology-based interventions), ii) interventions aimed at specific population sub-groups (e.g. pregnant or post-partum women, women with gestational diabetes) or specific micro-environments (e.g. schools or workplaces), iii) interventions aimed only at children (e.g. time-based restrictions on food advertising) and iv) studies reviewing different end-points (e.g. awareness, intention or attitudes). Only interventions for which there was a significant body of literature were included to keep the number of possible interventions manageable, therefore I only included interventions that were summarised in two or more systematic reviews.

5.2.2. Data extraction

I grouped interventions described in included reviews according to the Analysis Grid for Environments Linked to Obesity framework [2], which categorises elements of the obesogenic environment according to: i) primary mechanism of action (increasing energy expenditure or decreasing energy consumption), ii) level at which they operate (micro- or macro-environments) and iii) type of environment (physical, economic, policy or sociocultural). For reviews in each category, I created an Excel worksheet for data extraction

including: aim of review, databases searched, number and type of papers included, specific areas of focus (country or age groups), interventions, type of analysis, proximal, intermediate and distal outcomes reported and conclusions. I undertook the initial data extraction and this was checked for accuracy by one of two additional reviewers (LP, QC).

5.2.3. Quality assessment

Quality of systematic reviews was assessed by two reviewers, myself and one of two additional reviewers (LP or QC) using the AMSTAR tool [9]. Disagreements were resolved by discussion. AMSTAR was chosen because of its rigorous development process, explicit criteria and wide use among researchers. AMSTAR2, an updated version of AMSTAR, had not been published at the time this work was carried out. I summarised methods used to assess quality of primary studies in included reviews and the results of these assessments in the data extraction worksheets.

5.2.4. Meta-analysis

I undertook meta-analysis of 22 empirical primary studies that reported impact on BMI in an intervention population versus a comparator population within included reviews. Results of modelling studies were not included in the meta-analysis. I extracted data on mean difference in BMI between intervention and comparator groups and standard error of the difference from studies which reported data in a comparable way and entered these into RevMan (Review Manager version 5.3) using inverse variance random-effects meta-analysis. Jennifer Hirst provided advice on data entry, imputation of data, type of analysis and formatting of forest plots and checked the final analysis. Interventions compared in meta-

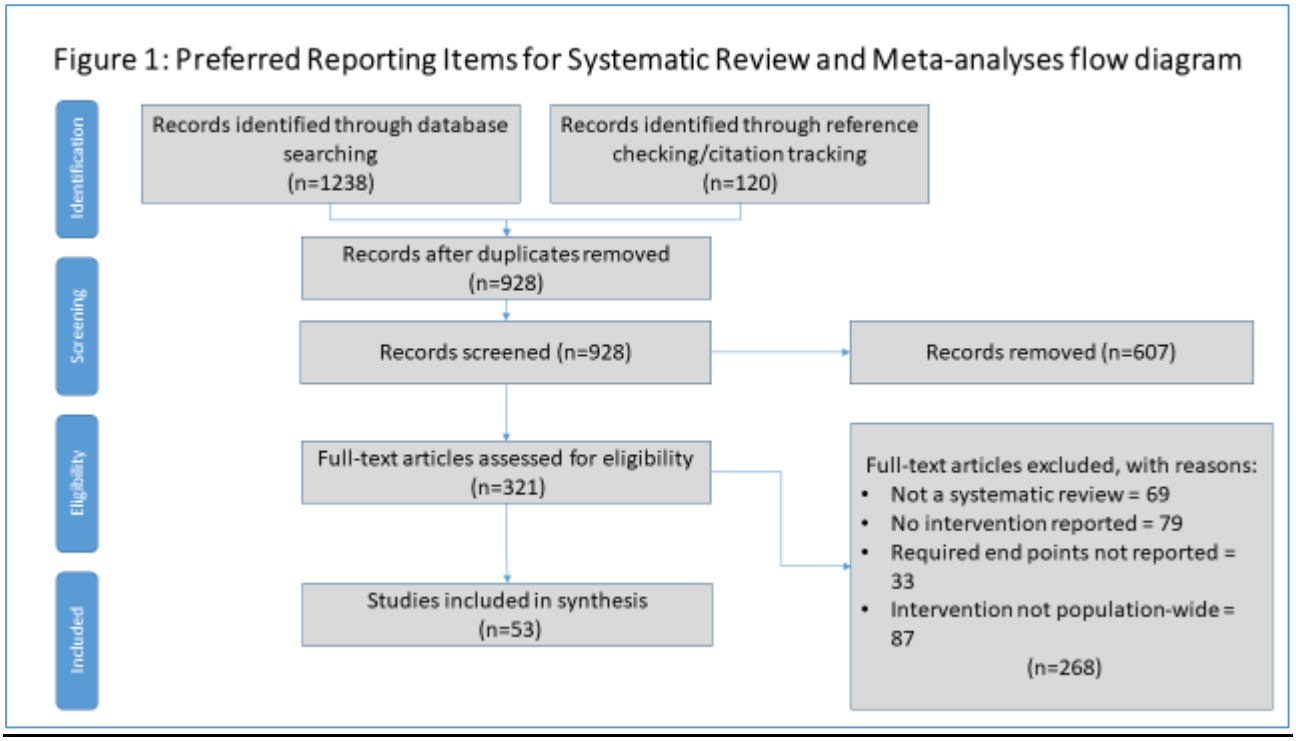
analysis were increasing SSB and fast food prices and decreasing fruit and vegetables on BMI as well as menu-labelling, grocery store interventions and multi-component interventions. Random effects analyses were selected to reflect different study populations, settings and intervention type and duration between included studies. Where standard error of the difference between groups was not reported, or the reporting of the standard error was thought to be incorrect [10], I imputed these by averaging the standard errors of other studies which compared the same intervention and outcome, as recommended in the Cochrane Handbook [11].

5.3. RESULTS

5.3.1. Description of dataset

The initial search identified 1238 papers. Following removal of duplicates and abstract screening, 321 papers underwent full review. 268 papers were excluded for failing to meet the inclusion criteria, leaving 53 systematic reviews included in this review (Figure 5.1.). Inter-rater reliability in applying the AMSTAR tool was high (joint probability of agreement > 90%) and all discussions over disagreements culminated in consensus.

Figure 5.1. Preferred reporting items for systematic review and meta-analysis flow diagram



The requirement for interventions to be mentioned in two or more previous systematic reviews led to the exclusion of a review on policies to reduce trans fats [12] and one on calorie labelling in vending machines[13]. Included reviews described macro-environmental interventions within the following categories of the ANGELO framework:

1. Reducing energy consumption through:
    a. Economic measures:
        i. Sugar sweetened beverage prices (nine reviews)
        ii. Fast food prices (five reviews)
        iii. Fruit and vegetable prices (six reviews)

b. Policy measures – labelling nutritional information in foods purchased in:
    i. Grocery stores and convenience stores – ‘food labelling’ (two reviews)
    ii. Restaurants and other food service establishments – ‘menu labelling’ (12 reviews)
c. Combination of economic, policy and physical measures:
    i. Changing the layout or food provided or promoted in food stores – ‘grocery store interventions’ (seven reviews)

2. Increasing energy expenditure through:
    a. Sociocultural measures:
        i. Mass media campaigns encouraging physical activity (nine reviews)
    b. Physical measures:
        i. Park and playground renovations (four reviews)
        ii. Point of decision prompts to encourage stair usage (five reviews)
    c. Combination of economic and physical measures:
        i. Encouraging active travel, that is walking or cycling rather than using motorised transport (seven reviews)
3. Increasing energy expenditure and decreasing energy consumption
    a. Combination of physical, policy, sociocultural and economic measures:
        i. Multi-component community-based interventions (nine reviews)

The 53 reviews in this sample provide relatively recent summaries of the literature, with only 11 published before 2010 (five of which evaluated mass media campaigns) and almost half (26 reviews) published since 2014. The vast majority of included studies were from the US, except in the areas of multi-component community interventions which were from a

wide variety of countries and point of decision prompts to encourage stair use which were mostly from Europe. Details of methods employed in included reviews (type of synthesis, number and type of included papers, quality assessment) are summarized in Appendix 5.3. A number of reviews included more than one intervention.

5.3.2. Methodological quality and quality of evidence in included systematic reviews

AMSTAR-assessed quality of included reviews [9] is summarised in Table 5.1. Of 53 included reviews, 24 were assessed as good quality (scoring 8 or more out of 11), 24 fair (scoring >= 5 and <8) and 5 poor (scoring 4 or less). No reviews were excluded on the basis of this quality assessment. All reviews stated their research question and inclusion criteria and provided evidence of 'a priori design'. 46 of the 53 reviews undertook comprehensive search and 36 undertook duplicate study selection and data extraction, 50 described characteristics of included studies and 52 combined findings of studies appropriately, though only 8 of the 53 estimated the likelihood of publication bias and 8 listed excluded studies. Most reviews undertook narrative synthesis rather than meta-analysis owing to heterogeneity of included studies.

Table 5.1: Quality assessment of included reviews using AMSTAR criteria.

Intervention	Total number of studies	Number of reviews assessed as reporting										
		1. A priori design provided	2. Duplicate study selection and data extraction	3. Two or more electronic sources searched	4. Status of publication used as inclusion criteria	5. List of included and excluded studies provided	6. Characteristics of included studies described	7. Scientific quality of included studies assessed	8. Scientific quality of studies used when formulating conclusions	9. Method used to combine studies appropriate	10. Likelihood of publication bias assessed	11. Conflict of interests included
Sugar sweetened beverage tax	9	9	6	9	6	0	8	3	3	9	2	5
Food labelling	2	2	0	2	1	1	1	1	1	2	1	1
Menu labelling	11	11	6	9	5	3	11	7	5	11	2	8
Food store interventions	5	5	4	3	3	1	5	4	4	5	0	3
Mass media campaigns	9	9	6	8	6	0	8	4	6	9	2	2
Active travel	6	6	5	6	2	1	6	4	3	5	0	5
Park and playground renovations	2	2	2	2	0	0	2	2	2	2	0	1
Point of decision prompts to increase stair use	4	4	3	3	1	1	4	2	2	4	0	3

Multi-component interventions to increase physical activity	5	5	4	4	2	1	5	3	2	5	1	4
Total	53	53	36	46	26	8	50	30	28	52	8	32

Thirty of the 53 reviews undertook quality assessment of included studies (Appendix 5.3). Most included studies were either natural experiments or econometric analyses of national survey data. Reflecting the difficulty of assessing bias in these types of studies, a wide a variety of tools were used by reviewers. Common concerns regarding study quality across reviews were lack of a control population, failure to account for confounding influences, failure to blind outcome assessors and the use of un-validated tools for outcome measurement (particularly for self-reported physical activity).

Details of review findings and conclusions are summarised below, with additional detail in Appendices 5.4 - 5.7. Summary of findings of primary studies included within reviews that reported impact on BMI, weight or prevalence of overweight and obesity are summarized below, with additional data in Appendix 5.8.

5.3.3. Interventions aimed at reducing energy consumption

Studies of interventions aimed at reducing energy consumption reported efficacy at three levels: i) proximal indicators of behaviour change such as quantity of food or beverage selected, purchased or consumed in response to change in price (own price elasticity of demand), labelling or availability, ii) intermediate indicators of a change in net energy balance such as reduction in total calories consumed and iii) distal indicators of anthropometric changes at the individual level (change in weight or BMI) or at the population level (change in prevalence of overweight, obesity or T2DM). Table 5.2. summarises the combined findings of included reviews.

Table 5.2: Interventions to reduce energy consumption: summary of review findings

		Proximal indicators	Inter-mediate indicators	Distal effects		
Category	**Intervention**	**Selection/purchase/consumption of food**	**Total calories consumed**	**BMI or body weight**	**Prevalence of obesity or overweight**	**Incidence of T2DM**
ECONOMIC MEASURES	**SSB tax**	Reduced purchase with increased price	NR	Small effects on BMI associated with increased price	Insufficient evidence of impact on probability of obesity/overweight	NR
	Fast food tax	Reduced purchase with increased price	NR	Insufficient evidence of impact on BMI	Insufficient evidence of impact on probability of obesity/overweight	NR
	Fruit and vegetable subsidy	Increased purchase with reduced price	NR	Insufficient evidence of impact on BMI	Insufficient evidence of impact on probability of obesity/overweight	NR
POLICY MEAS-URES	**Menu labelling**	Impact on calories ordered only in some contexts/labelling formats/study types	Insufficient evidence in real-world settings	NR	NR	NR
	Food labelling	Increased selection of healthy options	Insufficient evidence	NR	NR	NR
PHYSICAL AND ECONOMIC MEASURES	**Food stores**	Increased selection of healthy options	NR	Some evidence of weight loss particularly in studies including discounts on healthy food	NR	NR

A. Economic measures (e.g. taxes, subsidies):

Increasing consumption of highly processed, energy dense food (which tends to be cheaper than less energy dense food) is associated with increasing prevalence of obesity [14]. Changes to food prices aim to either increase consumption of healthy foods such as fruit and vegetables, or to reduce consumption of unhealthy foods, for example sugar-sweetened beverages (SSBs) which are a substantial source of calories (almost half of calories from added sugar in the US[15]) but have nearly no nutritional value. Nine systematic reviews examined economic measures aimed at decreasing energy consumption, focusing on prices of SSBs, fast food or fruit and vegetables. Nine reviews, including 78 papers, summarised the effect of changes in price of SSBs, fast food or fruit and vegetables. Up to 65% of included studies in these reviews were common across two or more reviews.

A1. Taxation of sugar sweetened beverages: 9 reviews[12, 16-24] examined the effect of change in price of SSBs, including 3 meta-analyses. Findings of the three reviews that had an AMSTAR score of greater than or equal to 8 [16, 20, 21] demonstrated that price elasticity of demand for SSBs was between -0.56 and -1.2 (indicating that for every 10% increase in price, there was a decrease of between 5.6%-12% in quantity of SSBs purchased) The wider dataset of 9 reviews had broadly similar findings. Reviews covered a total of 53 primary studies, 27 based on models and the remainder empirical. All the reviews showed a negative relationship between price and quantity of SSBs purchased. Six reviews reported on price elasticity [16, 17, 19, 20, 23, 24], which ranged from -0.67 to -1.30 (see above for explanation). Only one review [19] reported on cross-price elasticity of demand, with increased prices of SSBs associated with increased quantities of milk and fruit juices

purchased but decreased quantities of diet drinks purchased, suggesting that SSBs may be substituted with other high-energy drinks. Reviews included eight primary empirical studies reporting impact on weight related outcomes [25-29] [30] [28, 31-33] which showed small positive changes or no change.

Meta-analysis of four primary studies [25-27, 29] included in reviews that reported association between a 1% increase in SSB price and BMI found an association of borderline significance (Mean difference in BMI associated with 1% increase in SSB price: -0,02; 95% CI: -0.04; 0.00; I^2=37% (Figure 5.2a)). Of the four primary studies included in reviews that reported an association between SSB price and probability of overweight/obesity, two found no significant association [32, 33], one found an association with a random effects model but not a fixed effects model (suggesting time-varying individual characteristics such as work and marital status may over-ride the effect of changes in prices) [31] and one found a 1% increase in price of SSBs was associated with a statistically significant 0.01% and 0.02% absolute reduction in probability of obesity and overweight respectively.

A2. Increased prices of fast food: The only review that we ranked as good quality (and the only meta-analysis) which examined the effect of change in price on purchase of fast-food and/or weight outcomes [16] found that, overall, a 1% increase in the price of fast food was associated with a 0.3% absolute decrease in consumption but not with statistically significant changes in BMI. Similar small but positive effects on proximal and intermediate outcomes but non-significant effect on distal outcomes were found across the full dataset of

5 reviews addressing this question [16, 17, 22-24]. Reviews included 19 primary studies (11 on adults, 4 on adolescents and 6 on children).

Fast food consumption appeared less responsive to price changes than SSBs, with 3 reviews reporting price elasticity of demand between -0.32 and -0.8).

Meta-analysis of four primary studies [10, 34-37] included in reviews that reported association between a $1 change in fast food price and BMI found a non-significant association (mean difference in BMI with $1 increase in price: -0.23; 95% CI: -0.61,0.14; I^2=0%) (Figure 5.2b). One additional primary study [10] that reported a different outcome (association between BMI per 1% difference in fast food price) also found an inverse relationship, but significance was not reported. Of the three primary studies included in reviews that reported association between fast food price and probability of overweight/obesity, one found no significant association[34], one found an association with a random effects model but not a fixed effects model [31] and one found a 0.07% decrease in the probability of obesity of uncertain significance associated with a 1% increase in price of fast food[10].

Figure 5.2a: Association between price of SSBs and BMI (difference in BMI associated with 1% increase in SSB price)

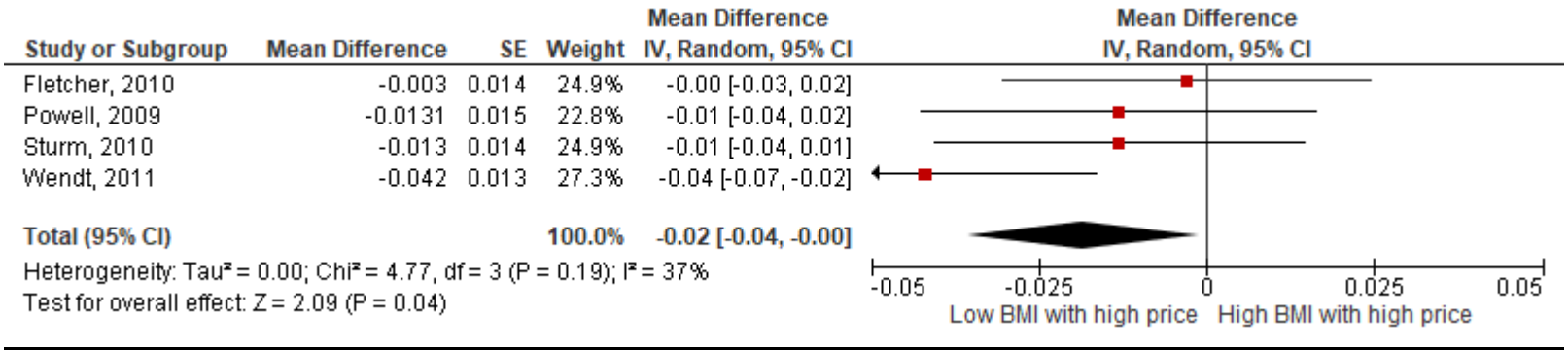


Figure 2b: Association between price of fast food and BMI (difference in BMI associated with $1 increase in fast food price)

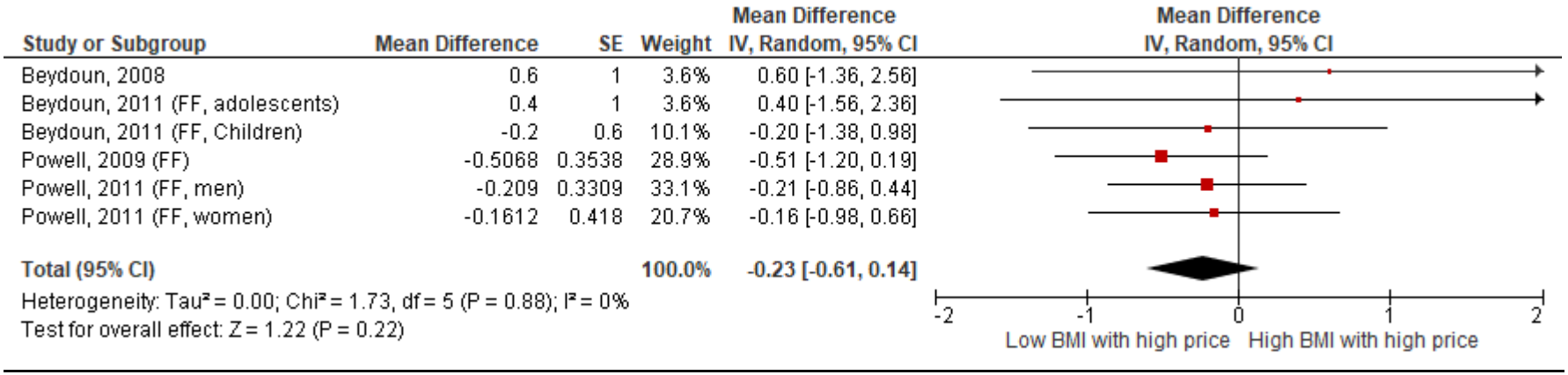
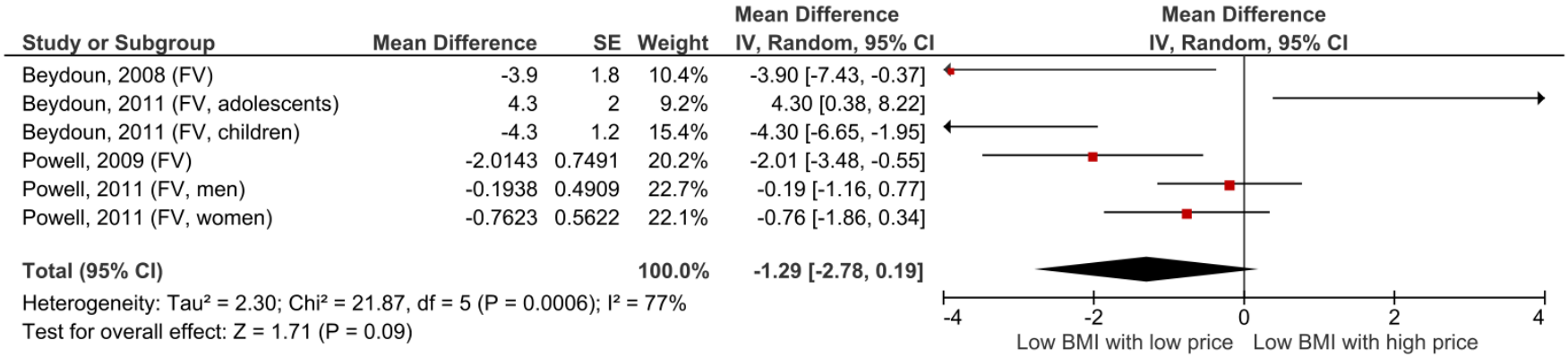


Figure 2c: Association between price of fruit and vegetables and BMI (difference in BMI associated with $1 decrease in fruit and vegetable price)



A3. Fruit and vegetable prices: Two reviews addressing this question were ranked as good-quality using AMSTAR criteria. One [16] found demand for fruit and vegetables to be price elastic (for every 10% decrease in price of fruit and vegetables, quantity purchased increased by 14%) and an association with non-significant decreases in BMI. The second good-quality review [20] found inelastic demand for fruit and vegetables (-0.53 to -0.67) with less elastic demand in high income families and high income countries. Findings of other included reviews [16, 17, 20, 22-24] were in line with this second review (demand elasticity -0.49 to -0.7). The 24 primary studies covered by these reviews were heterogeneous in design and included 7 modelling studies.

Meta-analysis of four primary studies[34-37] included in reviews that reported association between BMI and a $1 difference in price found non-significant effects and substantial heterogeneity between studies (mean difference in BMI associated with $1 difference in price: -1.29; 95% CI: -2.78, 0.19, I^2=77%) (Figure 2c). Of the three primary studies reporting change in probability of obesity or overweight, one found no significant association [34], one found a significant effect on obesity (OR: 0.856) but not overweight [38] and one found no significant effect with a fixed effects model but a statistically significant 16.7% increase in probability of obesity in women for every $1 increase in price using a random effects model [31].

No review reported impact of changes in SSB, fast food or fruit and vegetable prices on incidence of type 2 diabetes.

Quality assessment of included studies in reviews of economic measures: Quality assessment of included studies was undertaken by only four reviews in our sample, with 3 using bespoke criteria [20, 21, 24] and one using the American Health Association, US Preventive Services Task Force and CDC Community Guide Criteria [16]. Reviewers considered that limitations in study quality were predominantly related to study type. Prospective cohort studies were ranked by them as highest quality but accounted for a minority of studies. Most empirical studies were cross-sectional, which can be associated with over-estimation of effect and regression models used to analyse observational data may not sufficiently account for confounding variables. Another limitation was that in some cases, modelling studies used price elasticity data to simulate large price changes which were well outside observed data ranges.

B. Policy measures:

One of the contributors to an obesogenic environment is excess calorie availability in both food stores and food service establishments. In high-income countries, eating outside the home is increasing in frequency with food away from home accounting for 30% of weekly food spending in the UK [39] and 50% in the US [40]. Increased consumption of food away from home is associated with higher fat and energy intake leading to increased risk of weight gain, obesity and insulin resistance, which increases the risk of T2DM [41]. This has led to interest in labelling the nutritional content of food purchased from stores or menu items served in food service establishments, with the aim of increasing selection of healthy food options and reducing calorie consumption.

Two important of sources of heterogeneity are reported in nutritional labelling studies, and examined to different degrees in the included reviews:

1. Type of label: which can be informative (providing nutrient content amounts only, such as total calories per menu item), contextual (providing additional information that places nutritional information in context, such as calories per menu item as a % of recommended daily calories per person) or interpretive (providing additional information that interprets nutritional information, such as traffic light labels or energy equivalence labels)
2. Study setting: whether it occurred in real-world settings (e.g. restaurants, fast-food outlets, cafeterias, grocery stores) or artificial settings (e.g. laboratories, online surveys)

Two reviews, with 28 studies between them, summarised the effect of food labelling and 12 reviews, with 75 studies between them, summarised the effect of menu labelling. The maximum number of primary studies in common between reviews was 82% for reviews of food labelling and 34% for reviews of menu labelling.

B1. Food labelling: One review, including a meta-analysis, was assessed as good quality [42] and found a positive relationship between food labelling and selection of healthier food options across all study types, but no significant relationship in studies in real-world settings or on calories consumed. Meta-analysis across all study types in this review found 17.95% of purchasers select healthier food products (CI: 11.24% to 24.66%) following the introduction of any kind of food labelling, with the introduction of traffic light labelling being the most effective (29.36%; CI: 19.73% to 39.00%) but this is not associated with a significant reduction in calories consumed (-3.6% [95% CI: -8.90% to 1.72%]). The other included

review, which included only real-world studies, found positive effects on purchase or consumption in 14 of 19 included studies, but did not report the magnitude or statistical significance of effect reported in primary studies [42, 43]. Reviews included 28 primary studies. Neither review reported impact on BMI, prevalence of overweight/obesity or T2DM because these outcomes were rarely measured in primary studies. Whilst Cecchini's [42] review was of good quality, no systematic assessment of the quality of included studies was undertaken. However, he did raise concerns about study quality including small sample sizes, limited external validity of laboratory studies and heterogeneity of study outcomes limiting the ability to compare studies. Freudenberg's [43] review did assess quality of included studies, with 15 out of 19 rated as moderate quality using modified GRADE criteria.

B2. Menu labelling: Four reviews were assessed as good quality [44-47], but reached different conclusions due to differences in study inclusion criteria. These included two meta-analyses [44, 46] (one, including only recent studies (2012-2014) [46]) which found statistically significant reductions of 43-78 kcal ordered and 41-100kcal consumed; one narrative synthesis [45] of papers published between 2006-2011 which reported no effect on food ordered or consumed and one narrative synthesis [47] of real world studies which found mixed effects. Similarly mixed findings were reported across the eight other systematic reviews that examined this question: 3 reported mixed findings [43, 48, 49], 3 positive findings predominantly in studies in simulated settings [50-52], 1 positive findings predominantly in universities and worksites [53] and 1 no significant overall effect[54]. These reviews included 75 papers, with limited overlap between reviews.

No review summarized the effect of calorie labelling on anthropometric measures. However, two reports [55-57] evaluating the impact of New York City's calorie labelling laws on BMI were referenced in general discussion. Based on cross-sectional analysis of counties with and without menu labelling one found a statistically significant 0.4kg/m2 reduction in BMI associated with menu labelling [57] and the other found only a statistically significant reduction of -0.31kg/m2 in men, but not women.[55]. Meta-analysis of the results of these two studies (Figure 5.3b) found a difference in BMI of -0.25kg/m2 (95% CI: -0.40, -0.10; I^2=50%).

Overall, review findings are heterogeneous but suggest that menu labelling influences behaviour in some people in some contexts, and that longer study time horizons are required to understand the impact of these interventions on health outcomes, which may be mediated by a learning effect [58, 59] and mitigated by compensatory over-eating [60].

Of the five reviews that reported quality of included studies, four assessed more than 60% of included studies to be of moderate quality, one assessed more than 60% of studies to be weak. Concerns relating to study quality included lack of a comparison group (particularly in real-world settings), differences between comparator groups that were not reported or adjusted for, possibility of confounding, small sample sizes (<150 participants) limiting the ability to detect small effects and short-term measurement of changes in selection and consumption of labelled menu items.

C. Physical measures*:*

Most food is purchased from grocery stores with three quarters of UK households visiting once or more per week[61]. The availability and promotion of healthy food choices is associated with healthy eating patterns in consumers who frequent these stores [62].

Seven reviews summarised food store interventions, incorporating 67 studies. There was a small degree of overlap between studies included in reviews, with a maximum of 24% of studies in common across two or more reviews.

C1. Food store interventions: Food store interventions incorporated a range of initiatives to encourage selection of healthy food, including: i) improving affordability (e.g. discounts or coupons), ii) increasing access or availability (e.g. increased shelf space, more prominent placement, improved refrigeration) or iii) information and advertising (e.g. leaflets, supermarket tours, food demonstrations, shelf labelling). Seven reviews reported effects of food store interventions, with three assessed as good quality. Two of these good quality reviews found food-store interventions increased purchase of healthy food, but that a range of intervention components was required, with economic incentives associated with the greatest effect and information-only campaigns rarely influencing behaviours [63, 64]. And the third good quality review found mixed results but included only two papers on this topic [65]. Three of four other included reviews reported increased purchasing of healthy food in the majority of included studies [43, 64, 66, 67] and one found mixed results (but only included papers up to 2003 [53]). Reviews included 67 studies.

Meta-analysis of the two primary studies included in reviews that reported change in BMI (Figure 5.3a) found small but significant effects (Mean difference in BMI:-1.13; 95% CI: -1.70.,-0.56, I^2=0%) [68, 69], as did a third primary study included in reviews which reported effect on BMI (-1.4 kg four weeks post-intervention) [70] .

Six of the seven reviews evaluated quality of included papers. Concerns regarding quality of included studies related to lack of objective outcome measurements such as sales data, absence of a control population, short term interventions and small sample sizes.

Figure 5.3: Effect of population-wide interventions on BMI (mean difference in BMI)

Figure 5.3a: Grocery store interventions - mean difference in BMI between intervention and control groups

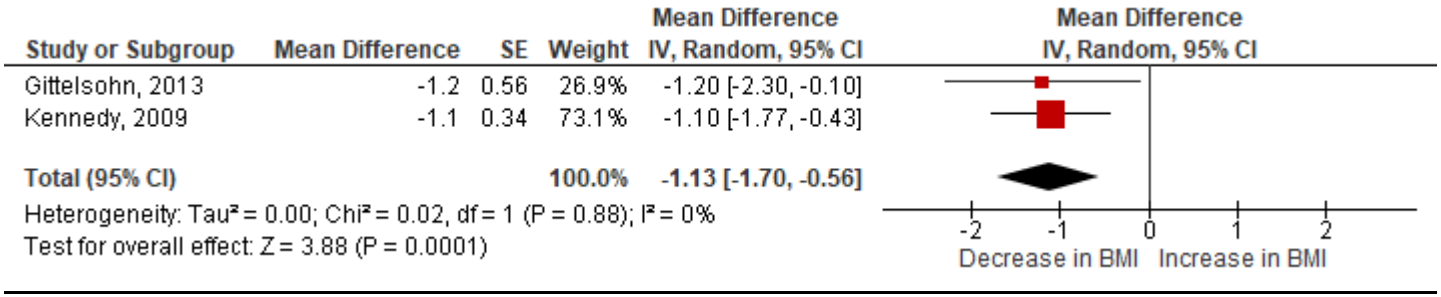
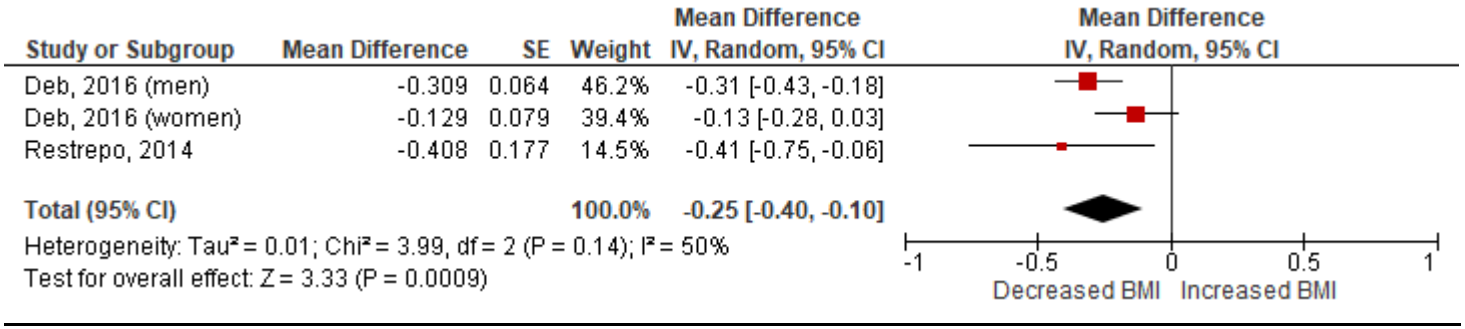


Figure 5.3b: Menu labelling - difference in difference analyses



5.3.4. Interventions aimed at increasing energy expenditure

Included reviews describe three types of interventions aimed at increasing energy expenditure through increased physical activity: 1) socio-cultural (e.g. mass media campaigns promoting physical activity), 2) physical (e.g. investment in parks and recreational areas, point of decision prompts to increase stair usage) and 3) combined economic and physical (e.g. active travel – walking or cycling instead of using motorized transport). Efficacy of these Interventions was reported at three levels: proximal indicators of behavioural change such as increased park use, cycling to work or stair climbing in public places; intermediate indicators of a change in net energy balance such as increased total physical activity (per day/week/year); and distal indicators of anthropometric changes at the individual level (change in weight or BMI) or at the population level (change in prevalence of overweight, obesity or T2DM). Table 5.3 summarises the combined findings of included reviews.

Table 5.3. Interventions to increase energy expenditure: summary of review findings

		Proximal indicators	Inter-mediate indicators	Distal effects		
Category	**Intervention**	**Activity related to intervention**	**Total physical activity**	**BMI or body weight**	**Prevalence of obesity or overweight**	**Incidence of T2DM**
SOCIO-CULTURAL MEASURES	**Mass media campaigns**	NA	Insufficient evidence	NR	NR	NR
PHYSICAL MEASURES	**Park and play-ground renovations**	Increases in park use following intervention	**Insufficient evidence**	NR	NR	NR
	Point of decision prompts	Increase in stair use following intervention	NR	NR	NR	NR
ECONOMIC AND PHYSICAL MEASURES	**Active travel**	Overall, insufficient evidence. Tailored interventions aimed at households likely to change behaviour most promising	Insufficient evidence	Insufficient evidence	Insufficient evidence	NR

D. Socio-cultural measures:

Nine reviews summarised mass media campaigns, incorporating 66 studies. A maximum of 26% of primary studies included in reviews were common across two or more reviews.

D1. Mass media campaigns: Mass media campaigns are large scale, intensive campaigns that deliver messages about a topic through a variety of media channels with the aim of informing or motivating a population to alter their behaviour, in this case primarily to increase their levels of physical activity, or to increase other health-related behaviours (e.g. adopting a healthier diet). Key messages can be delivered via television, radio, billboards, newspapers, magazines, campaign websites and social media channels, with or without accompanying community events and educational sessions. Nine systematic reviews[71-79] examined the effect of mass media campaigns, including one quantitative synthesis[77] and one meta-analysis[78]. The four reviews assessed as good quality [71, 77-79] found mass media campaigns had modest and inconsistent effects on physical activity, with insufficient evidence to support their effectiveness as stand-alone campaigns. They included: one meta-analysis which found significant effects on promoting moderate intensity walking (RR=1.53, 95% CI: 1.25-1.87, I^2=0%, pooled across 3 studies), but insufficient to help participants achieve sufficient levels of physical activity [78]; and one quantitative synthesis which found a median absolute increase in physical activity of 3.4% (IQI: 2.4-4.2%) and median relative increase of 6.7% (IQI: 3.0-14.1%) across 10 studies [77], concluding that intervention effects were modest and inconsistent. In addition, one high quality review [71] noted that media campaigns as a component of other effective interventions (e.g. multi-component community interventions) might provide additional benefits. The findings of the other five included reviews were broadly similar, reporting either inconsistent findings, insufficient

evidence or limited impact. 66 primary studies were included in reviews. No reviews reported impact on weight-related outcomes or T2DM.

Four of the nine reviews assessed quality of included studies. Quality concerns specific to mass media campaigns included failure to report number and duration of media exposures and to use validated outcome measures or objective measures of activity (e.g. accelerometer), with most studies utilizing self-reported physical activity.

E. Physical measures:

Four reviews summarised investment in parks and recreational areas, incorporating 25 primary studies, and five reviews summarised point of choice prompts to increase stair use, incorporating 60 primary studies. A maximum of 26% and 56% of primary studies included in reviews were common across two or more reviews of investment in parks and point of choice prompts respectively.

E1. Investment in parks and recreational areas: Four systematic reviews, three of good quality [65, 80, 81] and one of moderate quality [82], examined the effect of park and playground renovations on physical activity, including interventions that improved park or playground equipment, paths or trails, seating areas and promotion of facilities in green spaces. Across all reviews, park and playground renovations appeared effective in increasing park use, but there was insufficient evidence of impact on overall physical activity. Three of the four reviews [65, 81, 82], including two assessed as good quality, reported increases in park use following intervention, but one good quality review, focusing only on children and adolescents, found limited evidence of effect [80]. Three reviews reported effect on overall

physical activity. Of these, one good quality review [65] found an increase in total physical activity in 2 of 5 included studies, another good quality review found no increase in all three included studies [80] and one review of moderate quality [82] included only one primary study which found an increase in overall physical activity. No reviews reported change in anthropometric data.

25 primary studies were included in reviews. All of the reviews reported risk of bias in the included studies. Weaknesses in study designs included failure to account for confounding variables, non-random allocation, absence of blinding (of participants and/or assessors), short follow-up times (most studies were two years or less) and missing data. Reviews commented on poor description of mediators and moderators of physical activity, making the causal chain between intervention and effect unclear.

E2. Point-of-decision prompts to increase stair use:

Stair climbing is an attractive target for increasing physical activity as more energy is expended than during even vigorous exercise, such as jogging [83].Point of decision prompts in public spaces aim to increase stair use as part of people's daily routine. Five reviews considered the efficacy of point of decision prompts on either overall stair use (ascent and descent) [71, 84, 85] or stair-climbing [83, 86], all but one [86] undertaking quantitative synthesis. Three reviews assessed as good quality [71, 84, 85] found point-of-choice prompts to be effective at increasing stair use, with an absolute increase in people using stairs of 2% to 6% [71, 84, 85]. Due to low baseline rates of stair-climbing, this equates to

between 50-54% median relative increase in stair use [71, 84]. One of these reviews[85] found point -of-choice prompts to be more effective in public settings than workplaces, with the combination of directional and motivational prompts in workplace settings associated with greater increases in stair use than directional prompts alone. Findings of other included reviews, not assessed as good quality, were broadly similar. One of these reviews found prompts effective when the alternative is an escalator but not when it is an elevator [86] a finding that was confirmed by re-analysis of another of the included reviews [87]. Whilst stair-use prompts may be a useful adjunct to achieving overall daily activity requirements, they are unlikely to impact health outcomes in isolation, partly because associated energy expenditure is relatively small [88]. No included review summarized effect on anthropometric measures. Reviews included 50 papers covering 60 studies, predominantly of interrupted time series design.

Three of 5 reviews assessed study quality. Concerns regarding study quality included: inadequate follow up to assess whether behaviour change was maintained, the number of floors of stairs climbed was not objectively measured, total stair use rather than stair climbing (which expends twice as much energy as stair descent) was measured and stair use was measured at aggregate population- rather than individual-level.

F. Physical and economic measures:

Seven reviews summarised active travel, incorporating 67 primary studies. A maximum of 42% of primary studies included in reviews were common across two or more of these reviews.

F1. Active travel - Increasing walking and cycling as a means of transport:

Seven reviews [65, 80, 89-93] examined active travel interventions which aimed to encourage walking or cycling. Interventions evaluated included: upgrading cycle route networks and walking trails, providing walking/cycling maps and other educational and promotional materials, subsidized non-car transport (e.g. free bus passes), disincentives for car transport (e.g. tolls) and a variety of planning initiatives such as pedestrianising city centres, traffic calming zones and opening a new rail station. Three of the four reviews rated as good quality [65, 80, 89, 92] found increased walking or cycling as a means of travel in the majority of included studies and the other good quality review found the most promising interventions to be tailored marketing interventions targeted at households most likely to change behaviour [92] . In most cases, tailored marketing interventions were a branded package of marketing materials, information (e.g. bus routes and timetables) and incentives (e.g. free bus tickets) to households interested in changing travel behaviour. There was limited evidence that increase in walking or cycling as a mode of transport increased total physical activity or reduced BMI. Both reviews that considered change in total physical activity reported mixed results [65, 92], but the small number of studies reporting these outcomes precludes any firm conclusion. Findings of reviews not assessed as good quality were consistent with the conclusions outlined above.

Three primary studies reporting weight-related outcomes were included in reviews: two European studies of active commuting found no significant effect on BMI [94, 95], one US pre-post study of a new light rail system found light rail users had 1.18kg/m2 lower BMI ($p<0.05$) and 81% reduced odds of becoming obese ($p<0.05$) compared to non-rail users

[96]. No review reported impact on prevalence of T2DM. 67 studies were included in reviews, including a significant proportion of grey literature.

Five reviews assessed quality of included papers. Concerns included inconsistencies in the definition of active travel depending on what is considered 'normal' in different settings, use of self-reported activity tools of unknown validity and reliability, weakness in or absence of statistical analysis, failure to control for baseline differences, short study periods (typically less than 12 months) and uncertainty over whether increases in active travel occur in those who are sedentary (where public health benefits may be substantial) or in those who are already moderately active (where public health benefits would be less).

5.3.5. Interventions to increase energy expenditure and decrease energy consumption

Table 5.4 summarises the combined findings of included reviews.

G. Combined socio-cultural, policy, economic and physical measures:

G1. Multi-component community-based interventions:

Nine reviews evaluated evidence regarding multi-component community-based or 'whole of community' interventions [71, 80, 82, 89, 97-101], incorporating 83 primary studies. A maximum of 36% of primary studies included in reviews were common across two or more reviews.

Multi-component community-based interventions combine multiple elements to encourage healthy diet and increased physical activity across the entire population living within a geographically defined area, such as a city, village or region. Intervention components work at the personal, interpersonal and community level and include: communications (e.g. media campaigns), social support (e.g. self-help groups), risk factor screening, counselling and education about nutrition and physical activity in worksites, schools and at community events as well as changes to the built environment (e.g. cycle lanes) and local policy (e.g. reduced prices on healthy foods, restaurant and menu labelling). Of the 9 reviews, 3 evaluated outcomes solely in terms of increases in physical activity [71, 82, 97], 1 in terms of increasing walking [89] and the remaining 5 weight-related measures. One review incorporated a meta-analysis [100] but noted a high degree of heterogeneity between studies, two undertook quantitative synthesis [71, 97] and the remainder were narrative syntheses. Reviews incorporated 83 primary studies, many with multiple publications, including 34 with pre-post design and comparison group, 24 cluster RCTs, 8 repeat cross-sectional studies and the remainder employing a variety of study designs.

Multi-component community interventions appear to be promising in reducing BMI within participating communities in a wide variety of countries, although their effect on physical activity and prevalence of overweight and obesity is uncertain. Of the 4 good quality reviews that reported effect on physical activity, the three most recent reviews did not find a positive effect in most included studies [80, 89, 97] and one review [71] which included papers up to the year 2000 found a median net increase in the percentage of people being active of 4.2% (range, -2.9% to 9.4%). Five good quality reviews [71, 80, 98, 100, 101] which

reported impact on BMI or weight found positive findings in most included studies. Two good quality reviews reported no change in the prevalence of overweight/obesity [80, 98, 101], but included only a small number of studies.

Three included reviews were not rated as good quality. Two of these drew similar conclusions[82, 98] to those outlined above. And the third review found limited evidence of effect on physical activity, BMI or prevalence of overweight and obesity [99] but included only a small number of studies. No review reported change in incidence of T2DM.

Meta-analysis of three primary studies in adults [102-104] and 7 in children or adolescents [105-111] found a mean change in BMI of -0.40 (95%CI: -0.58;-0.22; I^2=45%) in adults and mean change in BMIz of -0.08 (95%CI: -0.14;-0.02) with substantial heterogeneity between studies (I^2=91%) in children or adolescents(Figure 5.4).

Seven reviews assessed the quality of included studies. The four reviews that used Cochrane risk of bias tools reported between 42 and 58% of included studies to be at high risk of bias due to failure to randomise allocation of communities, high rates of attrition and poor quality of outcome measures. Reviews that used other quality assessment tools found between 40-80% of studies to be of moderate quality.

Figure 5.4a: Multi-component community interventions – children and adolescents (mean difference in BMIz-score)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Chomitz, 2010	-0.04	0.029	14.3%	-0.04 [-0.10, 0.02]
Economos, 2009	-0.07	0.013	15.8%	-0.07 [-0.10, -0.04]
Fotu, 2011	-0.03	0.03	14.2%	-0.03 [-0.09, 0.03]
Kremer, 2011	0.02	0.02	15.3%	0.02 [-0.02, 0.06]
Millar, 2011	-0.07	0.03	14.2%	-0.07 [-0.13, -0.01]
Sanigorski, 2008	-0.11	0.05	11.7%	-0.11 [-0.21, -0.01]
Taylor, 2007	-0.26	0.028	14.5%	-0.26 [-0.31, -0.21]
Total (95% CI)			**100.0%**	**-0.08 [-0.14, -0.02]**

Heterogeneity: Tau² = 0.01; Chi² = 69.62, df = 6 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.44 (P = 0.01)

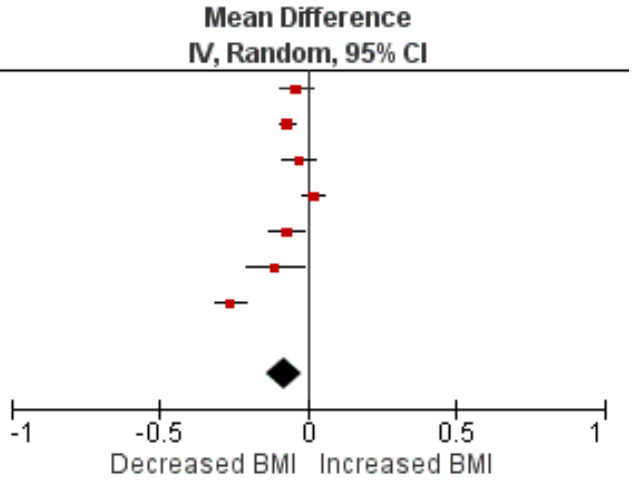


Figure 5.4a: Multi-component community interventions – adults (mean difference in BMI)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
Carleton, 1995	-0.62	0.31	7.7%	-0.62 [-1.23, -0.01]
Schuit, 2006 (men)	-0.36	0.09	37.8%	-0.36 [-0.54, -0.18]
Schuit, 2006 (women)	-0.25	0.1	34.9%	-0.25 [-0.45, -0.05]
Taylor, 1991	-0.68	0.17	19.6%	-0.68 [-1.01, -0.35]
Total (95% CI)			**100.0%**	**-0.40 [-0.58, -0.22]**

Heterogeneity: Tau² = 0.01; Chi² = 5.43, df = 3 (P = 0.14); I² = 45%
Test for overall effect: Z = 4.39 (P < 0.0001)

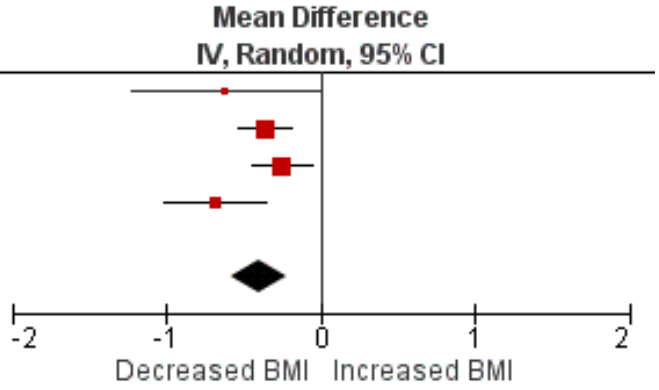


Table 5. 4. Interventions to increase energy expenditure and reduce calorie intake: summary of review findings

		Proximal indicators	Inter-mediate indicators	Distal effects		
Category	**Intervention**	**Increased activity related to intervention or change in purchase/consumption of healthy/unhealthy food**	**Total physical activity or total calories consumed**	**BMI or body weight**	**Prevalence of obesity or overweight**	**Incidence of T2DM**
SOCIO-CULTURAL, POLICY, ECONOMIC & PHYSICAL MEASURES	**Multi-component community-based interventions**	NR	Insufficient evidence	Positive effect on BMI	Insufficient evidence	NR

5.4. DISCUSSION

5.4.1. Principal findings

This review has four principal findings. Firstly, in terms of *proximal indicators of behaviour change*: increased price of SSBs and fast food, decreased price of fruit and vegetables, food labelling, food store interventions and menu labelling (in some contexts) were associated with positive effects (increased purchase or consumption of healthy foods or decreased purchase or consumption of unhealthy foods). Park and playground renovations, point-of-choice prompts to increase stair use and active travel interventions were associated with increased park use or stair use or increased walking or cycling respectively. Secondly, in terms of *intermediate indicators of change in energy balance*: there was a lack of evidence of effect on total calories consumed or total physical activity. Thirdly, in terms of *impact on distal health markers*: increasing price of SSBs, menu labelling, food store interventions and multi-component community interventions appeared to have positive effects on reduction in BMI or weight loss. However, effect on BMI appeared insufficient to translate into an

impact on prevalence of obesity or overweight at a population-level. Reductions in BMI (0.04 to 0.4 kg/m2) achieved through population-level interventions were, for many interventions, an order of magnitude less than those achieved in individual case-based diabetes prevention programmes (0.6kg/m2 for the average English person [112]). Fourthly, no review reported on the impact of these interventions on incident cases of T2DM. These findings are consistent with previous overviews which found point-of-choice prompts to be effective in increasing stair use [113], reducing food prices to be effective at increasing consumption [114] and interventions aimed at improving diet alone or diet together with physical activity (e.g. in multi-component interventions) to be more effective in terms of weight-related outcomes than interventions focusing solely on physical activity [115].

The nature of most primary studies (largely natural experiments or cross-sectional studies of national data) along with small samples in experimental studies and short follow-up periods means that many were categorised by reviewers as poor or moderate methodological quality and as having high risk of bias. The ability of such studies to assess long-term outcomes such as incidence of T2DM is low, therefore the absence of evidence should not be interpreted as 'evidence of absence'. Most studies included in reviews were studies of effectiveness (impact of intervention in usual or field conditions), not of efficacy (impact of interventions in ideal conditions), with relatively low internal validity but relatively high external validity. It is noteworthy that the vast majority of papers in included reviews were from the US or other high-income countries, so findings of this overview may not apply to middle- or low-income countries.

Overweight, obesity and T2DM are all patterned by socio-economic status. Reviews included in this study found that where effects of point-of-choice prompts, menu labelling and multi-component interventions were reported by demographic or socio-economic subgroup, no consistent difference in effects was found. Conversely, increasing SSB or fast food prices is regressive (a disproportionate burden is borne by individuals with lower income), but as elasticities are higher in lower socio-economic groups, the potential for health gain in these groups is also higher. Therefore, the long-term health benefits to those in lower socio-economic groups may well outweigh the short-term regressive effects of the tax.

5.4.2. Updated search following publication of systematic review

In an updated search of Medline (in February 2019), 27 additional titles were identified using the search strategy identified in Appendix 5.2. An updated search of the Cochrane Systematic Review database identified one new systematic review. Of these new reviews, two met my inclusion criteria [116, 117]. These reviews comprised a systematic review of multi-component community interventions (a narrative review of ecological approaches to obesity interventions in Hispanic/Latino youth [116]) and a systematic review of nutritional labelling for food and non-alcoholic drinks on purchasing and consumption [117]. They reached similar conclusions to those outlined in the rest of this chapter.

The review of multi-component community interventions in Hispanic children and adolescents found a reduction in BMz score in three of five included studies, but noted that these interventions were less efficacious than targeted interventions provided in primary

care [116]. The systematic review of nutritional labelling [117] found a statistically significant reduction in calories purchased in a meta-analysis of three included RCTs of menu-labelling in restaurants (mean difference: −46.72 kcal, 95% CI: −78.35, −15.10), but the quality of these studies was rated as low. The findings of this meta-analysis are supported by the only two included studies at low risk of bias in this review (which were not included in the meta-analysis). The same review examined the effect of menu labelling in laboratory settings as well as the effect of menu labelling on calories consumed, neither of which was associated with a statistically significant reduction in kilocalories purchased or consumed. These findings are consistent with those summarised earlier in this Chapter.

5.4.3. Implications for policy makers

Most primary studies covered in these reviews found small positive associations between population-level interventions and proximal (and sometimes intermediate) outcomes, and in some cases small positive associations with distal individual-level outcomes (e.g. BMI) but not distal population-level outcomes (e.g. prevalence of overweight or obesity). Whilst individual case-based interventions may have larger effects on BMI for participating individuals [112], they are only available to a small portion of the population – those who are identified as eligible, who agree to participate, and for whom such interventions are practically and financially feasible. Conversely, population-wide interventions may shift the distribution curve of the whole population, which, even when changes are small, can lead to important population level health benefits [118]. In addition, obesity and its sequelae are now recognized to be the products of multiple factors operating at multiple levels in a complex adaptive system [7]. The 'complex system' view of obesity and diabetes prevention

rejects the notion that single interventions can meaningfully be considered in isolation, and proposes that their impacts should be measured in the context of the wider system taking account of adaptations in the system that are likely to attenuate the impact of any intervention. Multiple small changes – in menu labelling, food and drink prices, grocery stores – may combine and reinforce one another (or, in some cases, work against each other) to generate both immediate and longer-term impacts (some of which will be measured and some not). The finding that so many macro-level interventions appear to have *some* effect suggests that there are good reasons for implementing and evaluating those considered acceptable and affordable.

5.4.4. Strengths and limitations

The review draws together and extends previous secondary research on population-wide obesity or T2DM prevention programmes, many of which were less comprehensive (e.g. addressing primarily case-based programmes [113-115, 119], rural communities [120], specific countries [121] or only studies reporting effects by socio-economic position [122]). Additionally, it is the first review of its type to summarise the effect on anthropometric measures reported in primary studies included in reviews.

Limitations include the predominance of research from high-income countries which precludes conclusions about other settings. Additionally, despite the broad scope of this review, it is possible that relevant reviews were missed. Limitations of methods used to summarise findings include: i) differences in the degree to which the same primary studies are included within reviews of the same topic which in turn affects the degree to which

reviews reach similar conclusions and ii) small numbers of included studies with the meta-analyses and substantial heterogeneity in both the intervention and context in which it was introduced. Finally, a review is only as reliable as the primary studies on which it is based, and methodological quality of many included studies was rated by review authors as medium or poor.

There is another potential limitation to this review – at a more philosophical level. The numerous quality scores and frameworks used by authors of those reviews to assess primary studies were all built on the assumption that 'quality' is defined primarily in terms of internal validity and minimization of bias. 'Poor quality' primary studies, as assessed by the included reviews in my sample, were characterized by features that included lack of a control population and failure to blind participants and assessors. These, and similar criteria, work well when the goal is to undertake a controlled experiment, but are arguably questionable when the goal is to gain insights about multiple interventions introduced in a complex adaptive system. This point is expanded on in the final chapter of this thesis.

5.5. CHAPTER SUMMARY AND CONCLUSIONS

A wide variety of population-level interventions increase healthy food choices and influence physical activity, with a small group of interventions (changes in SSB and fruit and vegetable prices, menu labelling, grocery store interventions and multi-component community interventions) appearing to contribute to reductions in BMI. Whilst the absolute effect of these interventions is small, their sphere of action – the whole population – is large. Taken

together, these interventions provide important components of a system-level response to the complex systems problem of obesity, in which the focus should be on both changing the environments in which we live, and changing the ways in which we respond to those environments.

Chapter 6 examines the potential effect of these promising population-wide actions on cumulative incidence of T2DM and T2DM-related costs on an English population. It also considers the implications of these findings for diabetes prevention policy.

CHAPTER SIX

Population-wide approaches to preventing T2DM:

Economic evaluation of alternative programmes

6. POPULATION-WIDE APPROACHES TO PREVENTING T2DM – ECONOMIC EVALUATION OF ALTERNATIVE POLICIES

6.1. BACKGROUND, AIMS AND OBJECTIVES

Population-wide programmes aim to control upstream causes of increased incidence and prevalence, such as environmental, social or economic factors. They aim to shift the entire population's exposure to these upstream causes of disease. They may be conceptualized as preventing T2DM directly or reducing factors that increase a person's risk of developing the disease. BMI, waist circumference and hypertension are the most consistently measured modifiable risk factors associated with incidence of T2DM [13, 14], with reduction in BMI the factor most frequently reported as causally related to T2DM incidence [15].

Chapter 5 summarised the findings of an overview of systematic reviews which identified a suite of population-wide interventions that appear to have a positive effect on BMI, but none where an effect on T2DM is reported. This chapter summarises the findings of an economic evaluation of these promising population-wide interventions, using a simulation model to analyse their effect on incidence of T2DM, QALYs and T2DM-related healthcare costs in England.

The aims of this economic evaluation were to describe the impact on an English population of the four population-wide interventions associated with reduction in BMI (described in Chapter 5), relative to no intervention:

i) sugar sweetened beverage (SSB) tax

ii) menu labelling

iii) grocery store interventions

iv) multi-component community interventions (MCIs)

Outcomes include incremental healthcare costs incurred, incremental QALYs gained and cumulative incidence of T2DM. The full health system and societal cost of each intervention could not be estimated within the scope of this DPhil, as they encompass a wide variety of direct and indirect costs (e.g. cost of intervention, reduction in taxes receipts due to reduced sales of unhealthy food or additional costs associated with improving grocery store layout). Cost-effectiveness ratios are therefore not reported; in the absence of detailed description of the various costs associated with each intervention, any ICER would be only partial.

Previously published economic evaluations have analysed a suite of obesity prevention programmes [17, 18]. To my knowledge, this is the first to model the impact of menu labelling and food store interventions, and draws on up-to-date pooled results from primary studies, described in the previous chapter, to determine effect size.

6.2. METHODS

I used a pre-existing microsimulation model developed by the UK Health Forum for this analysis. This is a multi-disease, multi-risk factor simulation model, initially developed as part of the UK Government's Foresight Report into tackling obesity [19]. The model is used to simulate a virtual population and analyse the incidence of obesity-related diseases, QALYs and direct healthcare costs associated with these diseases. The BMI risk-factor module was used. This module incorporates different relative risks of developing obesity-related diseases for different ranges of BMI, enabling analysis of the effect of BMI-reducing interventions.

I used the BMI risk-factor module to analyse the effect of interventions on: i) incidence of T2DM, ii) direct healthcare costs of T2DM and iii) quality-adjusted life-years (QALYs) associated with T2DM, coronary heart disease, hypertension and stroke. A healthcare perspective was adopted for the analysis, the price year was 2015 and the costs were reported in Great British Pound Sterling (£). QALYs were drawn from publications which calculated utility vales using EQ5D-3L. I adopted a 50-year horizon, with annual cycles. Costs and utilities were discounted by an annual discount rate of 3.5% per year, which is the rate recommended by NICE[20].

Abbygail Jaccard (AJ), the Deputy Director of Modelling at the UK Health Forum, and I undertook this analysis together. I undertook training provided by the UK Health Forum, enabling me to set up the model for the analysis we wished to undertake, import the

necessary baseline population data files, identify which interventions to model and their associated parameter values, create interventions to be analysed where a pre-existing intervention profile could be used (e.g. SSB tax, food store interventions and MCI) and analyse and write up model results. Together, AJ and I: reviewed key parameter values currently used in the model (and I suggested updated data sources for a handful of parameters) and reviewed results from a preliminary run of the model to identify any erroneous results. AJ wrote the code for a new profile of intervention which was required for menu labelling and sent me the model outputs once the simulations were complete.

6.2.1. Model structure and parameter values

In the start year of the simulation (2015), the distribution of the English population in terms of age, sex, and BMI was used as the starting population (Table 6.1). The health experience of one individual at a time from the start year, 2015, until the final year, 2065, is simulated, with the expected value resulting from 20 million individual simulations reported in this chapter. For each simulation, an individual is randomly selected from the starting population and initialised with a BMI and a set of diseases based on incidence and prevalence estimates. Each year an individual's BMI is updated based on: i) change in BMI in the baseline population (estimated through categorical nonlinear multivariate regression analysis of BMI data reported in the Health Survey for England between 2004 and 2014) and ii) changes in BMI specific to the intervention being modelled.

In addition, each year an individual can develop one or more of the following diseases: T2DM, stroke, coronary heart disease and hypertension; or die. Incidence of each disease is modified by relative risks associated with BMI, drawn from the World Obesity Federation's

DYNAMO study [21]. Individuals with hypertension or T2DM can develop coronary heart disease or stroke, individuals with coronary heart disease may also develop hypertension or T2DM and individuals with stroke do not develop other clinical conditions. Each year an individual has the chance of acquiring a new disease, dying from an existing disease or from other causes. Costs and QALYs are derived from an individual's disease status.

During each annual cycle, transitions between current health states (e.g. T2DM) and new health states (e.g. stroke, coronary heart disease) are determined by generating a random number between zero and one for each potential new health state. If the random number is less than or equal to the transition probability for progression to the new health state, the transition to this new health state occurs and is irreversible. If the random number is greater than the transition probability of the new health state, no change to health state occurs. This process is repeated annually for each individual for 50 years.

Parameter values for disease states were not shared by the UK Health Forum due to concerns regarding intellectual property.

Figure 6.1. Model structure

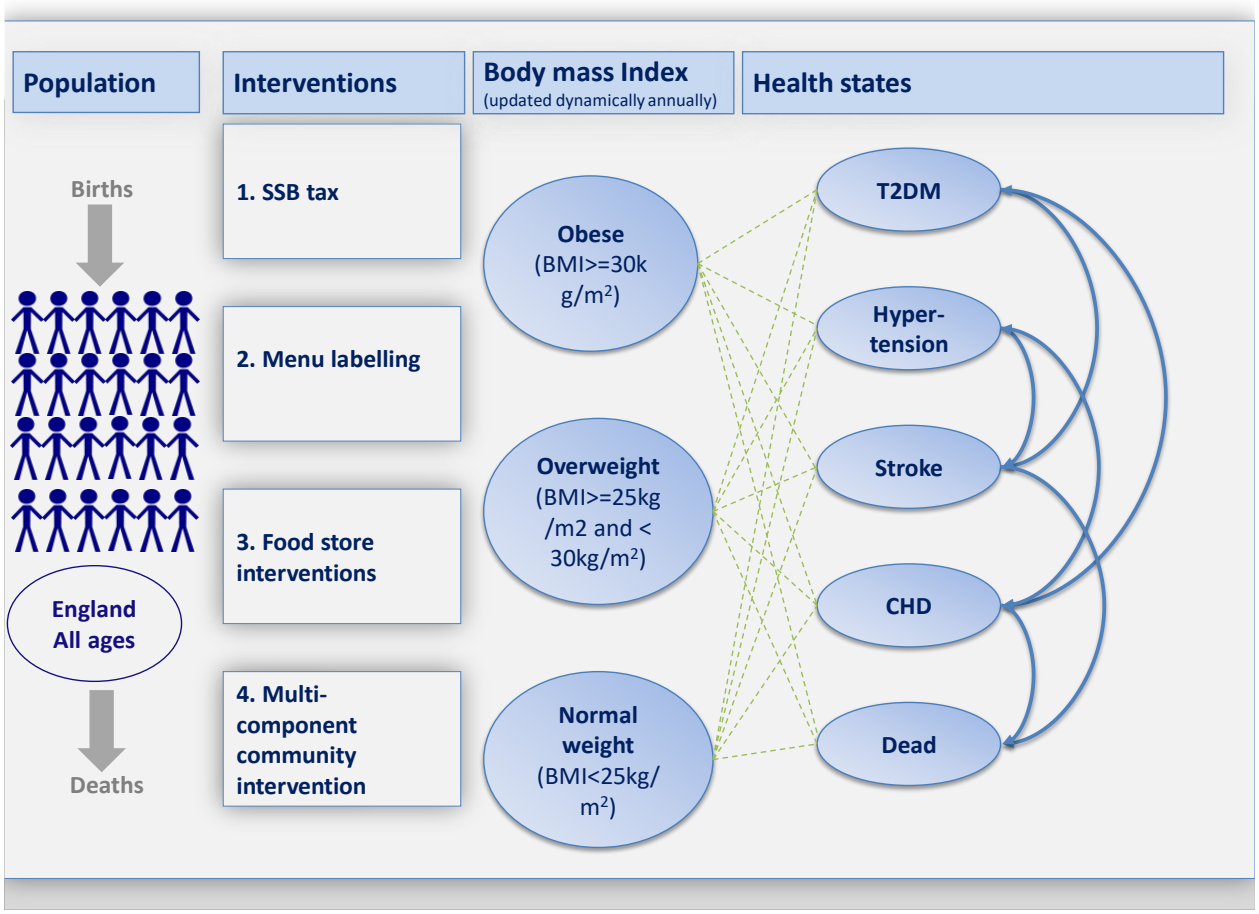


Table 6.1. Parameter values of baseline population

Parameter	Source	Year
Population distribution by age and sex	Office for National Statistics[22]	2015
Total fertility rate	Office for National Statistics[23]	2015
Birth rates by mothers age	Office for National Statistics[24]	2015
Mortality rates by age and sex	Office for National Statistics[22]	2015
BMI distributions by age and sex	Health Survey for England[25]	2004-2014

6.2.2. Interventions

Four interventions were evaluated against a base case of no intervention (Table 6.2), including:

- Sugar sweetened beverage (SSB) tax: a 20% tax charged on the price of soft drinks (both concentrated and not concentrated, not low calorie) in England. Shortly before this analysis was undertaken the UK government announced a sugar sweetened beverage tax would be introduced in April 2018 [38]. The levy will be imposed on industries importing or manufacturing SSBs based on two tiers of sugar content. Drinks with ≥8 g of sugar per 100 mL are charged £0.24 per litre and those with ≥5 g but <8 g per 100 mL are charged £0.18 per litre. Alcoholic drinks, milk-based drinks and pure fruit juices are exempt irrespective of sugar content. As the effects of this policy are still to be evaluated, the intervention modelled in this chapter is a hypothetical tax.
- Menu labelling: mandatory calorie posting on menus in chain restaurants with more than 15 stores nationwide, based on New York City's menu labelling legislation [38].
- Grocery-store interventions: a range of initiatives to encourage selection of healthy food, including: i) improving affordability (e.g. discounts or coupons), ii) increasing access or availability (e.g. increased shelf space, more prominent placement, improved refrigeration) or iii) information and advertising (e.g. leaflets, supermarket tours, food demonstrations, shelf labelling).
- Multi-component community interventions (MCI): which combine multiple elements to encourage healthy diet and increased physical activity across the entire population living within a geographically defined area, such as a city, village or

region. Intervention components may include: communications (e.g. media campaigns), social support (e.g. self-help groups), risk factor screening, counselling and education about nutrition and physical activity in worksites, schools and at community events as well as changes to the built environment (e.g. cycle lanes) and local policy (e.g. reduced prices on healthy foods).

Table 6.2. Interventions – parameter values

Intervention	Description	Impact on BMI	% of population affected	Proportion of intervention effect modelled each year
SSB tax	20% tax on soft drinks with added sugar	-0.07 (95%CI: -0.05, -0.09) [40]	100%	Over 10 years: 90% in first year 5% in second year 5% in 3rd -10th year (assumption)
Menu labelling	Interpretive nutrition labelling on menus in chain restaurants	-0.25 (95%CI: -0.40, -0.10) [Meta-analysis in Chapter 5]	50%	100% within 1 year [41]
Grocery store interventions	Improvements in information, accessibility and affordability of healthy food in food stores	-1.13 (95%CI: -1.70, -0.56) [Meta-analysis in Chapter 5]	10%	100% in the second year (assumption)
Multi-component community intervention	Intervention with multiple components focused on population living in a geographically defined region	-0.40 (95%CI: -0.58, -0.22) [Meta-analysis in Chapter 5]	50%	100% in the second year (assumption)

Intervention effect: I assumed interventions only affected adults. This was because parameter values for intervention effect of menu labelling and food store interventions were based on studies which only reported results for adults. Parameter values for menu

labelling, food store interventions and MCIs' impact on BMI were drawn from pooled findings of empirical studies from the overview of systematic reviews outlined in Chapter 5. Where UK-based estimates from a single study were available (for SSB tax) they were used, as patterns of consumption differ between countries [40].

Substantially different types of evidence inform these parameter values. Differences in BMI associated with SSB tax are based on a modelling study [40], which uses empirical data on price elasticity of demand derived from cross-sectional studies of panel data to identify changes in consumption in the UK, with the effect on BMI subsequently calculated from these changes in consumption. Impact of menu labelling on BMI is based on two evaluations of New York State's menu labelling legislation which was implemented in different counties at different times over a number of years. Both evaluations used econometric analyses of cross-sectional panel data [41, 42]. BMI change associated with grocery store interventions [43-45] and MCIs [46, 47] were based on a meta-analysis of studies with pre-post design with comparators. Substantial heterogeneity was observed when pooling study results (I^2=65% for grocery store interventions) potentially due to substantial differences in intervention components in included studies.

Regain in BMI could not be estimated as studies used for deriving intervention effect either used cross-sectional data (e.g. SSB tax, menu labelling) or had short follow-up periods (e.g. food store interventions). Primary studies used to derive intervention effect for MCI had long follow-up periods (5 to 8.5 years), therefore the intervention effect likely includes some

element of weight regain. The results reported in this chapter assume no weight regain, which may overstate the effect of food store interventions.

Proportion of population affected: I estimated the proportion of the population affected by each intervention, based on the nature of the intervention and the type of study from which intervention effect was derived. I assumed taxes and menu labelling affect 100% of the population as these policies are usually enacted at a regional or national level and studies of intervention effect are based on national or state-wide data sets. Multi-component community interventions were assumed to affect 50% of the population because they require local implementation, but studies of intervention effect draw on region-wide data to derive intervention effect. Grocery store interventions were assumed to affect 10% of the population because they require local implementation and studies of intervention effect draw on study participants only. The estimates of population sizes affected are uncertain, but there is no primary data to validate these assumptions, to my knowledge.

6.2.3. Outcome measures

Results from the simulation are reported per population of 100,000 in England. To aid interpretation, I performed secondary analysis in Excel to report results at two additional levels: 1) impact per individual in the English population, 2) impact across all adults in England. Outcome measures at an individual level include direct healthcare costs of T2DM and QALYs. Outcomes measures per population of 100,000 in England and across the English adult population include cumulative incidence of T2DM, direct healthcare costs of T2DM

and QALYs. Reported results are the expected value following 20 million individual simulations.

The UK Health Forum will not disclose both base case and post-intervention outcomes for each intervention because of intellectual property concerns. Therefore, only changes in incidence of T2DM and QALYs are reported. This limited my ability to assess the face validity of reported outcomes in the base case.

6.2.4. Sensitivity analyses

No sensitivity analysis was undertaken. The UK Health Forum model is unable to perform probabilistic sensitivity analysis. No deterministic sensitivity analysis was undertaken because the staff member at the UK Health Forum with whom I was working left the organisation and the remaining team was unable to re-run the model with a range of alternative parameter values.

6.2.5. Validation

I validated the model in accordance with the AdVISHE checklist [51]. Two experts (Prof Susan Jebb from the University of Oxford and Prof Jonathan Valabhji, the National Clinical Director for Obesity and Diabetes at NHS England) tested the face validity of the model structure, inputs and outputs and their suggestions were incorporated in either the final

model or the description of strengths and limitations. Audit of traces was undertaken by Abbygail Jaccard (AJ) and myself. Cross-validity testing of the UKHF model has been undertaken previously [52].

6.3. RESULTS

Results of the simulation are outlined in Table 6.3.

All interventions reduced cumulative incidence of T2DM, increased QALYs and reduced T2DM-related costs relative to no intervention.

6.3.1. Individual-level outcomes

Effect on T2DM-related costs per adult in England: Cumulative direct healthcare costs of T2DM are reduced on average per individual by £34, £60, £24 and £73 for SSB tax, menu labelling, food store interventions and MCI at 50 years.

Effect on QALYs per adult in England: Cumulative incremental QALYs gained per adult in England due to reduced incidence of T2DM, coronary heart disease, hypertension and stroke were small for population-wide interventions, ranging from 0.004 to 0.014 at 50 years.

6.3.2. Population-level outcomes

Effect on cumulative incidence of T2DM: All interventions reduce cumulative incidence of T2DM. At 50 years, reduction in incident cases of T2DM ranges from 44,528 to 134,778. Given prevalence of T2DM (diagnosed and undiagnosed) in England was 4.05 million in 2016 [53]. These represent small changes in the number of prevalent cases per annum (between 1.1 and 3.3% of all cases of T2DM at 50 years).

Effect on costs relative to no intervention: SSB tax, menu labelling, food store interventions and MCIs reduce cumulative direct T2DM-related healthcare costs by £1.35bn, £2.39bn, £0.96bn and £2.91bn respectively over 50years. Given direct costs of T2DM related care were estimated as £8.8 billion p.a. in 2010/11 [54], cost savings of population-wide interventions over 50 years are small (<0.1% T2DM-related healthcare costs over 50 years).

Effect on QALYs relative to no intervention: Because of the size of the population affected by population-wide programmes, QALYs gained were substantial, ranging from 176,722 to 544,678 over 50 years.

This analysis focuses on England and I did not formally evaluate costs and effects in other countries. Effect sizes in this model are drawn from international studies, but conclusions regarding gains in QALYs and reduction in incidence of T2DM will only be generalizable if

distributions of overweight and obesity are similar between the comparator population and the English population.

Table 6.3. Impact of population-wide programmes at 50 years

		1. SSB tax		2. Menu labelling		4. Food store interventions		5. Multi-component community interventions (MCIs)	
		Mean	**Standard error**	**Mean**	**Standard error**	**Mean**	**Standard error**	**Mean**	**Standard error**
Outcomes per population of 100,000	Reduction in cumulative incident cases of T2DM - per population of 100,000 (number)	147	27	263	30	112	27	339	29
	Cumulative incremental direct costs of T2DM - per population of 100,000 (£, million)	- 3.40	1.06	- 6.00	1.06	- 2.42	1.06	- 7.33	0.11
	Cumulative incremental QALYs - per population of 100,000 (QALYs)	639.5	-	1139	-	444.5	-	1370	-
Population-level outcomes	Reduction in cumulative incident cases of T2DM – adults in England (number)	58,444	-	104,562	-	44,528		134,778	
	Cumulative incremental direct costs of T2DM - adults in England (£, million)	-£1,352	-	-£2,386	-	-£964		-£2,914	
	Cumulative incremental QALYs- adults in England (QALYs)	254,249	-	452,838	-	176,722		544,678	
Individual-level outcomes	Incremental costs of T2DM (vs. no intervention) per individual (£)	-£34.00	-	-£60.01	-	-£24.24	-	-£73.30	-
	Incremental QALYs (vs. no intervention) per individual (QALY)	0.00640	-	0.01139	-	0.00445	-	0.0137	-

6.3.3. Consideration of intervention cost

The direct costs of implementing population-wide interventions may not be borne by the health system (e.g. with a SSB tax) and there are indirect costs that would not be identified through analysis from a health system perspective (e.g. costs to industry leading to a reduction in profitability and a reduction in tax receipts or employment). Within the timescale of this DPhil, it was not possible to identify all the direct and indirect costs associated with the four interventions examined in this chapter. Therefore, only the effect on T2DM-related costs is reported, rather than the net effect on costs having deducted the total cost of each intervention. Similarly, no cost-effectiveness analysis is undertaken as incremental costs have not been calculated. However, a high-level examination of costs associated with these interventions is summarised in the following paragraphs.

SSB taxes could be associated with the direct cost of administering the tax [48], and the indirect costs of reduced employment and tax receipts from the beverages sector. Where SSB taxes have been implemented (e.g. individual states in the US), the revenue collected exceeds the cost of implementation [48]. And when the UK's SSB tax was announced in 2016, Her Majesty's Treasury calculated that it would generate £520m in additional revenue which would be spent on increasing school sports [38]. This suggests that SSB taxes may be cost-saving.

Where menu labelling has been mandated in the US the costs largely fall on the food service sector [49]. When the Food and Drug Administration in the US introduced menu labelling

legislation, they estimated that the average cost of labelling per restaurant chain would be $45,720 with 1,640 restaurant chains affected, leading to an estimated national cost of almost $75 million. A rough extrapolation to England, based on respective population sizes and conversion to 2015 GBP [55], would indicate a cost of £9m for the food sector each time menu items are labelled. Assuming menu items are labelled twice a year, over 50 years the discounted cost of menu labelling could be approximately £422 million. Given an estimated £2.4 billion is saved in T2DM-related healthcare costs, this programme may be cost saving overall.

The direct costs of multi-component community interventions (MCIs) will differ depending on the core components of the intervention, and may incur indirect costs for local businesses due to reduced sales of unhealthy food and beverages. Of the studies of MCIs included in the meta-analysis of intervention effect in Chapter 5, only one has published a costing study to estimate the direct cost of the intervention. [50]. This is a Dutch study that cost € 900,000 for a population of 180,000 over 5 years between 1999 and 2003. Extrapolating this cost to 2015 GBP [55] and applying it to the 50% of the English population assumed to be affected by MCIs in the calculations above, would lead to a cost of £135.75 million over 5 years. The MCI modelled in this chapter would reduce T2DM-related costs by £86m over 5-years and £2.9 billion over 50 years, suggesting that MCIs may not be cost-saving in the short-term but may be over a longer timeframe.

No costing study of grocery store interventions could be identified, therefore I could not estimate the likely cost of this intervention.

6.4. DISCUSSION

6.4.1. Principal findings

This analysis has produced three major findings. Firstly, SSB tax, menu labelling, food store interventions and MCIs all have potential to reduce incidence of T2DM, but the effect of individual interventions is small (reduction of 1.1-2.6% of prevalent cases over 50 years). Secondly, SSB tax, menu labelling, food store interventions and MCIs reduce T2DM-related costs, but the effect on annual direct healthcare costs of T2DM over 50 years is small (<0.1% of direct healthcare costs of T2DM). Thirdly, all interventions modelled lead to substantial increases in QALYs at a population level, but QALYs gained at an individual level are small (<0.014 QALYs gained over 50 years). Finally, absence of data on all elements of intervention costs limits the ability to report net effect on health system and societal costs or cost-effectiveness ratios.

I am aware of only one other published economic evaluation of population-wide programmes' effect on T2DM-related costs and outcomes published by the School of Health and Related Research, University of Sheffield [17]. This study found SSB tax reduced T2DM-related costs and increased QALYs. However, the reduction in healthcare costs (£4.80 per individual vs £34 in this analysis) and QALYs gained (0.0003 QALYs gained per individual versus 0.006 in this analysis) following introduction of an SSB tax were significantly lower in the Sheffield model. This is potentially due to three main differences between the Sheffield analysis and my analysis. In terms of model structure, risk of T2DM in the Sheffield model is based on both HbA1c and BMI values whereas in the UKHF model it is based solely on BMI.

In terms of baseline cohorts, Breeze used the Whitehall cohort and did not model changes in BMI in the baseline population as was the case in this analysis. This could lead to lower estimates of transition to T2DM as the baseline population will not be 'gaining weight' each year as they do in this analysis. Finally, Breeze's model stratified intervention effect according to age group whereas this analysis did not. I utilised an average intervention effect in this model, but as SSB tax has the greatest effect on children, which were excluded from the model used in this analysis, this intervention effect may well be over-stated leading to over-estimation of the impact of SSB tax on T2DM-related costs and outcomes.

6.4.2. Strengths and limitations

This analysis adds to previous economic evaluations by linking the effect of obesity prevention programmes with a well-established simulation model to quantify their long term impact on T2DM incidence, T2DM-related healthcare costs and QALYs at individual- and population-levels, including: i) estimating the impact of menu labelling and food store interventions on T2DM incidence, T2DM-related costs and QALYs for the first time, ii) using up-to-date information from a comprehensive overview of systematic reviews to determine effect sizes, iii) extrapolating findings to determine the impact of adoption of policies/programmes at a national level in England.

The approach to evidence used to inform parameter values in this analysis is in line with NICE's methods to inform public health guidance [56], which notes that a randomised controlled trial may not be available or appropriate to evaluate complex, multi-agency, large-scale interventions and recommends the use of observational studies to determine the effectiveness of interventions in real life.

This analysis has four principal limitations: limited consideration of costs, uncertainty regarding duration of intervention effect and size of effected population, inability to perform sensitivity analysis and lack of transparency regarding model structure and function. Firstly, the full health system and societal cost of each intervention could not be estimated within this analysis, as they encompass a wide variety of direct and indirect costs, therefore reduction in T2DM-related costs is not net of the intervention cost, which may overstate the cost savings at the level of the overall economy. Additionally, costs avoided by reducing incidence of other obesity-related diseases (e.g. cardiovascular disease, stroke, hypertension, obesity-related cancers, musculoskeletal conditions) are not included in this analysis, therefore impact on reducing healthcare costs may be under-stated. Secondly, data on effect size was based on cross-sectional data or longitudinal data with follow up of short duration (with the exception of intervention effect in MCIs). This could over-state the intervention effect as the full weight regain following the intervention may not have occurred. Additionally, the size of the population affected in menu labelling, food store interventions and MCIs is based on an assumption, no primary data is available to inform these parameter values. Thirdly, neither deterministic or probabilistic sensitivity analysis could be performed which means that the uncertainty in results reported in this chapter is understated. Finally, the UK Health Forum simulation model remains a 'black box'. Key equations and parameter values are not published and insufficient data is provided in reported results to allow external validation.

This concern was discussed at length with my internal examiners during my Confirmation of Status viva. We considered whether updating the Markov module used in Chapter 4 with a

'BMI module' would be a better modelling approach as this could provide results that could be more reliably validated. However, on balance we agreed that I should continue to use the UK Health Forum's model for two reasons. Firstly, the value of baseline BMI modelling and weight gain in the UK population was an important element of the analysis that a Markov model would not replicate. Secondly, the widespread use of the UK Health Forum model by policy makers and charities in multiple countries provided some confidence in its utility for informing policy making. However there remains a considerable risk associated with basing economic analysis or public policy on models which are not fully in the public domain as both the model structure and results cannot be validated.

6.4.3. Implications for policy makers

The results of this analysis suggest that SSB tax, menu labelling, food store interventions and MCIs could be promising population-wide elements of national diabetes prevention policy. Even though effect sizes appear small, SSB tax, menu labelling and MCIs are likely to be acceptable, affordable, and can be implemented simultaneously. Considering the effect of each intervention in isolation is not wholly consistent with the 'complex system' view [19] of obesity and diabetes prevention as implementation of all interventions in a coordinated way may lead to attenuation or amplification of effect, depending on the nature of their interactions. However, current empirical methods used to determine intervention effect limit our ability to estimate the combined effect of multiple interventions, leaving policy makers to draw conclusions based on only small changes of individual interventions, as described in this paper.

6.5. SUMMARY AND CONCLUSION

This chapter has examined the potential costs and effects of a range of population-wide programmes targeting upstream risk-factors for T2DM, notably those related to adiposity. Using a pre-existing multi-disease, multi-risk factor microsimulation model developed by the UK Health Forum, four population-wide prevention programmes (versus no intervention) were analysed from a health system perspective, namely: i) sugar sweetened beverage tax; ii) menu labelling; iii) grocery-store interventions and iv) multi-component community interventions. All four interventions are associated with reduced incidence of T2DM, reduced T2DM-related healthcare costs and increased QALYs, but the effect of individual interventions is small. Further assessment of direct and indirect costs of these interventions is required before drawing conclusions on cost-effectiveness.

CHAPTER SEVEN

Discussion and Conclusion

7. DISCUSSION AND CONCLUSION

7.1. SUMMARY OF CHAPTER FINDINGS

This thesis argues for a more comprehensive, complex systems approach to diabetes prevention policy that encompasses both individual case-based and population-wide programmes. My findings strongly suggest that, even if all the available evidence-based policies described in this DPhil were implemented, they may still be insufficient to substantially reduce prevalence of T2DM in England. This moves the diabetes prevention policy debate on from considering which is the single right approach (individual case-based or population-wide) to implementing a combination of programmes concurrently and continuing to search for new, promising interventions at both an individual and population-level.

Chapter 1 described how this thesis was developed at the same time as 'Healthier You', the NHS Diabetes Prevention Programme, was being launched in England. It highlights how controversies relating to current national policy were initially explored through my collaboration on a literature review of screen and treat policies for people with intermediate hyperglycaemia. This understanding of the gap between existing literature and current policy led to a broadening of the scope of this thesis to consider alternative diabetes prevention policies and their impact on health system cost, health outcomes of individuals (QALYs) and population health (incidence of T2DM). This DPhil framed two potential policy responses to the challenge of preventing T2DM: i) individual case-based programmes targeted at participants at high risk of developing T2DM (e.g. the NHS Diabetes Prevention Programme) and ii) population-wide programmes targeting the entire population at risk. Each approach is examined in turn, utilising a combination of literature reviews and health economic modelling.

Chapter 2 presented a narrative review of the importance of diabetes prevention to policy makers, how those who have prioritised diabetes prevention chose to respond, and a summary of individual case-based interventions and issues related to identifying participants at high risk of T2DM. Three main findings from the published literature are summarised in this chapter. Firstly, seminal studies in the US, Finland, China and India found that T2DM can be prevented through lifestyle programmes or an oral hypoglycaemia medication (metformin), that is individual case-based programmes targeted towards high-risk individuals. However, subsequent studies of effectiveness of lifestyle programmes illustrated more modest effects on diabetes incidence, compared to trial-based studies of efficacy. Secondly, the primary literature is characterised by a lack of consensus on how to identify participants for individual-case based prevention programmes, with three different blood tests used to identify intermediate hyperglycaemia. Each of these different types of intermediate hyperglycaemia is associated with different pathophysiological changes, incidence of T2DM and response to preventative programmes. Thirdly, governments in Finland, Australia, the US and England have developed national or regional diabetes prevention programmes, predominantly focusing on lifestyle programmes in high-risk individuals. These programmes differ in both the intensity of the intervention provided and the method for identifying eligible participants. These findings raise unanswered questions about the efficacy, costs and cost-effectiveness of diabetes prevention programmes, which I go on to address in the remainder of the thesis.

Chapter 3 summarised the current evidence of cost-effectiveness of individual case-based interventions and the extent to which this evidence supports current diabetes prevention policy in England. Four main findings from a systematic review of the literature are presented in this chapter. Firstly, metformin and lifestyle interventions in people at high risk of T2DM appear to be cost-effective but not cost saving, with median ICERs of £8,428/QALY and £7,490/QALY respectively. Secondly, in the few studies where these were modelled, budget impact was moderate (prevention programmes required 0.13-0.2% of respective countries total healthcare budget), financial payoffs were delayed (net expenditure on treatment and prevention of diabetes only declined after 9-14 years) and impact on incident cases of diabetes was limited (0.1-1.6% reduction in incident cases). Thirdly, most published economic evaluations relate to intensive trial-based interventions in populations in high-income countries identified with oral glucose tolerance tests. Finally, national diabetes prevention policy in the UK and US advocates pragmatic lifestyle programmes (less than 3 years in duration), and in the UK the use of HbA1c or fasting plasma glucose is recommended for diagnosing intermediate hyperglycaemia. However, most cost-effectiveness studies relate to a different definition of hyperglycaemia and a higher intensity of intervention, which limits the direct applicability of findings. These findings suggested that additional research was required to explore differences in cost-effectiveness related to different intensities of lifestyle programmes and different definitions of intermediate hyperglycaemia, which are explored in Chapter 4, as there are insufficient existing studies to draw conclusions on the most cost-effective diagnosis-intervention pairs.

Chapter 4 explored the differences in cost-effectiveness related to different types of individual case-based interventions, to address the gap in the literature regarding the most cost-effective diagnostic-treatment pairs outlined in Chapter 3. Six main findings from an economic evaluation of nine alternative diagnostic-treatment pairs are summarised in this chapter. Firstly, in individual case-based interventions for diabetes prevention, the type of intermediate hyperglycaemia and the intensity of lifestyle intervention do influence cost, health impact and cost-effectiveness of the intervention. Second, that in participants with all types of intermediate hyperglycaemia, low-intensity lifestyle interventions are the lowest cost diabetes prevention programme over a participant's lifetime whereas high-intensity lifestyle interventions deliver the greatest health benefit (in terms of reducing diabetes incidence, years lived with T2DM and QALYs gained). Third, that low- and high-intensity lifestyle programmes are very cost-effective in participants with IFG and IGT, while metformin is not a cost-effective option in these populations but is in participants with HbA1c in the 'at risk' range. Fourth, that all individual case-based prevention programmes require an increase in diabetes expenditure, with subsequent savings being insufficient to entirely offset this expenditure. Fifth, that the impact on incidence of T2DM at a population level is small. Finally, this analysis suggests that current English national policy of low-intensity lifestyle programmes in participants with IFG or HbA1c will be cost-effective and have the most favourable budget impact, but will prevent only a fraction of cases of T2DM. Additional approaches to prevention need to be investigated urgently.

Chapter 5 identified additional approaches to diabetes prevention through an overview of systematic reviews of population-wide diabetes or obesity prevention programmes acting at

a community, regional or national level. This review identified literature on eleven types of programmes: i) increase in sugar sweetened beverage (SSB) tax prices, ii) reduction in fast food prices, iii) reduction in fruit and vegetable prices, iv) food labelling in grocery stores, v) menu labelling in restaurants, vi) interventions in food stores, vii) mass media campaigns, viii) park and playground renovations, ix) point of decision prompts to increase stair usage, x) encouraging active travel and xi) multi-component community-based interventions (MCIs). Four main findings from this overview of systematic reviews are summarised in this chapter. Firstly, in terms of *proximal indicators of behaviour change*, increased price of SSBs and fast food, decreased price of fruit and vegetables, food labelling, food store interventions and menu labelling (in some contexts) were associated with positive effects (increased purchase or consumption of healthy foods or decreased purchase or consumption of unhealthy foods). Park and playground renovations, point-of-choice prompts to increase stair use and active travel interventions were associated with increased park use or stair use or increased walking or cycling respectively. Secondly, in terms of *intermediate indicators of change in energy balance*: there was a lack of evidence of effect on total calories consumed or total physical activity. Thirdly, in terms of *impact on distal health markers*: increasing price of SSBs, menu labelling, food store interventions and MCIs appeared to have positive effects on reduction in BMI or weight loss. However, effect on BMI appeared insufficient to translate into an impact on prevalence of obesity or overweight at a population-level. Reductions in BMI (0.04 to 0.4 kg/m2) achieved through population-level interventions were, for many interventions, an order of magnitude less than those achieved in individual case-based diabetes prevention programmes (0.6 kg/m^2 for the average English person). Fourthly, no review reported on the impact of these interventions on incident cases of T2DM.

Chapter 6 examined the potential effect of the promising population-wide actions identified in Chapter 5 (increasing price of SSBs, menu labelling, food store interventions and MCIs) on QALYs, cumulative incidence of T2DM and T2DM-related costs in an English population. Four principal findings from this economic evaluation are summarised in this chapter. Firstly, SSB tax, menu labelling, food store interventions and MCIs all have potential to reduce incidence of T2DM, but the effect of each intervention is small (reduction of between 1.1 and 3.3% of prevalent cases after 50 years). Secondly, SSB tax, menu labelling, food store interventions and MCIs reduction of annual direct healthcare costs of T2DM is small (<0.1% direct healthcare costs of T2DM over 50 years). Thirdly, all interventions modelled led to substantial increases in QALYs at a population level, but QALYs gained at an individual level are small (<0.014 QALYs gained over 50 years). Identifying the full range of direct and indirect costs associated with these interventions was beyond the scope of this DPhil, therefore analysis of cost-effectiveness was not undertaken. Finally, the analysis described in this chapter does suggest that a small number of population-wide interventions may be a useful adjunct to diabetes prevention programmes, such as those in England, that are currently focused predominantly on individual case-based interventions.

7.2. STRENGTHS AND LIMITATIONS

7.2.1. Strengths

This thesis is one of the most comprehensive examinations of a wide range of potential diabetes prevention policies that has been undertaken. It includes an assessment of: the efficacy and cost-effectiveness of 9 alternative individual case-based interventions, the

efficacy of 11 population-wide prevention programmes and the impact on cost and health outcomes of four of these. By quantifying the likely impact of each programme on cumulative incidence of T2DM, these analyses illustrate how relatively ineffective each policy will be in isolation and argue for both a more comprehensive, multi-pronged approach to diabetes prevention policy and urgent development and evaluation of additional programmes that could augment those described in this thesis.

Specific strengths of this thesis include the range of diabetes prevention policies examined, use of systematic literature reviews to inform model development and parameter values, the use of relatively robust methods to undertake economic evaluations and the consistent extraction of the policy implications of these analyses.

In terms of evaluating a wide range of diabetes prevention policies, Chapter 4 summarises findings from the first economic evaluation to compare low-intensity lifestyle programmes with high-intensity programmes and metformin in participants with different definitions of intermediate hyperglycaemia. Chapter 5 and 6 summarise the most comprehensive overview of systematic reviews to date which is used to identify potentially effective population-wide diabetes and obesity prevention programmes and includes the first assessment of menu labelling and food store interventions' impact on costs and incidence of T2DM.

In terms of using systematic reviews to inform model structure and parameter values, Chapter 4 was the first economic evaluation to draw key parameter values (e.g. relative risks of T2DM) from pooled results of recent meta-analyses of intervention effect and to identify different parameter values for different types of intermediate hyperglycaemia. Likewise, Chapter 6 was the only economic evaluation of population-wide interventions, to my knowledge, to derive parameter values of intervention effect from meta-analysis of findings from primary studies.

Finally, relatively robust methods were used to undertake economic evaluations and the policy implications of these analyses were consistently extracted. In terms of robust methods for economic evaluations, the Markov model described in Chapter 4 was the first of those used to analyse diabetes prevention programmes that was comprehensively validated using the AdViSHE tool. In addition, these analyses were the first to my knowledge to extract the implications for UK policy makers in terms of % of health budget expended or saved and % cumulative incidence of T2DM reduced. Existing publications either reported impact at an individual level (e.g. ICER) or impact per 100,000 population, which makes the potential impact of any health policy at a national level hard to discern.

7.2.2. Limitations

However, this thesis encompasses several limitations: heterogeneity of the population examined, some omissions in the range of programmes considered, availability of evidence

to inform key parameter values, the structure and function of models employed, and modelling of discrete interventions operating in a complex system.

Firstly, heterogeneity of the population effected by alternative diabetes prevention programmes was only partially reflected in the modelling approaches used in this thesis. In the Markov model described in Chapter 4, heterogeneity of the population in terms of type of intermediate hyperglycaemia was explicitly modelled, but other potentially important sources of heterogeneity (e.g. baseline weight) was not. This is because the model was structured to reflect transitions between different levels of hyperglycaemia rather than different categories of weight. In the simulation model described in Chapter 6, population heterogeneity in terms of baseline weight was explicitly modelled but other potential sources of heterogeneity that may affect an individual's response to an intervention was not (e.g. level of deprivation may be relevant when levying a regressive tax such as that on SSBs).

Secondly, the full range of diabetes prevention programmes was not considered. This thesis considers all 'first-line' individual case-based programmes, but the use of metformin as a 'second-line' programme in those who are unable to or choose not to enrol in or complete lifestyle programmes, was not modelled. There is no primary data on the effect of metformin when used post-lifestyle intervention, so modelling the impact of this policy would include a good deal of uncertainty. This thesis also considered all population-wide programmes acting at a macro-level (i.e. population, region or community level) for which there were more than one systematic review. There may be population-wide interventions for which no systematic review has been undertaken or, given the breadth of the subject

area and the inconsistency of terminology used across this vast field, there may be systematic reviews that my search did not identify. In addition, there are potentially relevant programmes acting at a meso-level (e.g. school or workplace) which may be relevant but were not included in the scope of this thesis.

Thirdly, the evidence used to inform some key parameter values in the economic evaluations have limitations. In some instances, there was no available data to inform key parameter values (e.g. persistence of the effect of lifestyle interventions), therefore a range of values were tested in sensitivity analyses. Some values were derived from meta-analyses that illustrated a good deal of heterogeneity in terms of intervention effect, reflecting variation in specific interventions and differing contexts. These parameters were incorporated in probabilistic sensitivity analysis of individual case-based programmes, but the lack of sensitivity analysis in the modelling of population-wide programmes means that the true level of uncertainty around these estimates is not characterised. In population-wide programmes, most primary studies are from the US which may limit their applicability to the UK. Finally, variables that are continuous (e.g. weight, HbA1c) are presented as categorical (e.g. overweight/obese, IFG/T2DM) in both models. If the distribution of the underlying continuous variable (e.g. weight) in the population from which the intervention effect is derived is substantially different from that of the population being modelled, this will also lead to inaccuracies in transition probabilities attributed to categorical variables (e.g. overweight/obese).

Fourthly, the structure and function of the models described in this thesis have limitations. The Markov model is limited in terms of the disease states that are included in the analysis.

Lifestyle programmes which lead to weight loss will reduce the risk of a wide variety of diseases (e.g. cardiovascular disease, cancer), and in turn have an impact on health system costs and QALYs associated with these diseases. But these disease states are not included in the Markov model, which therefore understates the potential benefit of lifestyle interventions. The UK Health Forum's simulation model is limited by lack of transparency in terms of equations and parameter values used and in the way results are reported. Whilst there has been some cross-validity testing of this model against other models, no comprehensive assessment of internal and external validity has been published. In addition, the outputs of the model only specify the incremental change (B-A) rather than describing both the base case (A) and the post-intervention case (B). This limited my ability to undertake even the most basic assessment of validity of the base case scenario and there remains a considerable risk associated with basing economic analysis or public policy on models which are not fully in the public domain as both the model structure and results cannot be validated.

Finally, the 'complex system' view of obesity and diabetes prevention rejects the notion that single interventions can meaningfully be considered in isolation, and proposes that their impacts should be measured in the context of the wider system taking account of adaptations in the system that are likely to attenuate or exaggerate the impact of any intervention. Multiple small changes – in menu labelling, food and drink prices, grocery stores – may combine and reinforce one another (or, in some cases, work against each other) to generate both immediate and longer-term impacts (some of which will be measured and some not). Because the nature of the primary evidence is intervention-

specific, this thesis assesses the evidence of each intervention in isolation and evaluates the effect of each intervention in isolation. However, in practice, many of the programmes described in this thesis could (and, my findings suggest, should) be implemented concurrently (lifestyle interventions, SSB tax, menu labelling, grocery store interventions, MCIs) and the net impact on T2DM of their concurrent implementation could be more or less than the sum of individual interventions because of the complex adaptive system in which they operate.

7.3. IMPLICATIONS FOR FURTHER RESEARCH

Five promising areas for further research have been identified in this thesis, including research aimed at: i) identifying additional diabetes prevention programmes, ii) characterising heterogeneity in treatment effect of individual-case based programmes, iii) addressing uncertainties in key parameter values outlined above, iv) understanding important interactions between individuals who are participating in case-based diabetes prevention programmes and their environment and v) exploring new modelling approaches.

In terms of identifying additional diabetes prevention programmes, there are three potentially promising areas for research. First is the use of metformin as a 'second-line' programme in those who are unable to or choose not to enrol in or complete lifestyle programmes. There is no primary data on the effect of metformin when used post-lifestyle intervention for those who do not complete their lifestyle programme, or long-term follow-up studies of metformin used alone in participants who cannot or will not participate in

lifestyle programmes. There is substantial resistance to 'medicalising' people with intermediate hyperglycaemia [1] by prescribing a medication such as metformin, but, given the limited effect of existing well-characterised interventions, this may be a promising additional route to investigate. Second is the role of diabetes or obesity prevention programmes acting at a meso-level (e.g. school or workplace) which were not included in the scope of this thesis, but may be a further suite of interventions to incorporate in a multi-tiered, comprehensive diabetes prevention policy. Third is analysis of the direct and indirect costs of grocery store interventions and menu labelling to confirm they are indeed cost-effective prior to developing national policy.

In terms of characterising heterogeneity of treatment effect, the multiple relevant baseline characteristics of each person affected by diabetes prevention policies (e.g. age, race, BMI, socio-economic status, type of intermediate hyperglycaemia) suggest that a more nuanced approach to determining intervention effect may be required. For example, a recent publication on the effect of weight loss interventions on cardiovascular events [2] found that on average there was no significant effect. However, analysis using recursive partitioning revealed that participants with well-controlled T2DM and poor self-reported health experienced negative effects, which masked the positive response in other participant groups, rendering the results neutral.

In terms of uncertainty regarding key parameter values, five areas of additional research could substantially advance our understanding of individual case-based and population-wide interventions. Firstly, evaluating the effect of lifestyle programmes and metformin in

participants identified solely on the basis of HbA1c. Secondly, estimating longer-term follow-up of pragmatic lifestyle programmes to evaluate the duration and profile of the reduction in risk of T2DM. Third, evaluating the impact of lifestyle programmes on the complications of T2DM including death, as this has not been adequately characterised in studies with even long follow up periods. Finally, evaluating multiple population-wide programmes concurrently and over a long period to estimate their net effect on both BMI and prevalence of T2DM.

Qualitative research also has an important role to play in terms of understanding important interactions between individuals at high risk of T2DM, including those who are participating in case-based diabetes prevention programmes, and their environment. During this DPhil I began to explore this by undertaking 'go-along' interviews, which are a hybrid of ethnographic observation and qualitative interviews [3], with residents in Newham East London who were likely to have a high risk of developing diabetes (e.g. first degree relative with diabetes). In a 'go-along' interview a researcher accompanies participants on excursions in their familiar environments, to capture contextual data to elucidate the interaction between the physical and social environment and health-related lifestyle choices. This kind of study could help to synthesise how the food environment, built environment, local geography, social structures and cultural frames interact with, and enable or constrain, individual psychological factors (motivation, self-efficacy, health literacy) to produce (or prevent) actions that reduce or increase risk of T2DM.

Whilst the findings of the 'go-along' interviews I undertook are not included in this DPhil, an early insight from them was the importance of behaviours within the participants' social network. This could open avenues for research using alternative types of health economic modelling. Whilst the Markov and simulation models used in this DPhil have specific limitations outlined above, a general limitation of both these model types is that they treat individuals or cohorts as autonomous. Whereas agent-based models, which incorporate decision rules for how interactions between participants affects their decisions (e.g. to comply with an intervention) and the consequences of these decisions for their health state, enable the influence of social interactions to be included in a model. To my knowledge agent-based models have not been used in diabetes prevention modelling, but may be a useful simulation tool, particularly in planning local implementation of a multi-level diabetes prevention programme.

7.4. IMPLICATIONS FOR POLICY

Since starting this DPhil in 2016, the NHS has expanded 'Healthier You', NHS England's individual case-based diabetes prevention programme and introduced a pilot of very low-calorie diets for reversing T2DM due to some promising recent publications [4] and the government has introduced a sugar sweetened beverage tax [5] and published a childhood obesity strategy [6]. During this time, I have also become a policy maker, working as Director of Innovation, Research and Life Sciences at NHS England, drafting elements of the Long Term Plan for the NHS and endeavouring to develop evidence-based policies for my own area. This recent experience of policy making has helped me to understand how difficult it

would be to act on the conclusions of this DPhil within the fragmented policy-making landscape of the UK.

The over-arching conclusion of this DPhil is that governments should urgently expand national diabetes prevention programmes to encompass a broad range of individual case-based and population-wide initiatives. In the UK, this would involve discrete activities at national policy-, community- and individual clinician level. At a national policy level, menu labelling regulations could be developed (along the lines of those in the US) following an exploration of the likely direct and indirect costs described above. At community or local authority-level, grocery store and multi-component community interventions could be developed, following examination of their direct and indirect costs. At a clinical level, the prescription of metformin should be encouraged in people who have HbA1c in the at-risk range and who refuse to or are unable to participate in lifestyle programmes.

It is not possible to produce a definitive figure for the combined effect size of all the promising individual case-based and population-wide programmes on incidence of T2DM in England, due to the complex system in which diabetes prevention efforts operate. Interactions between different parts of the complex system could mean that the combined result was greater than or less than the sum of any individual programmes. For example, in the Indian Diabetes Prevention Programme the combined effect of metformin *and* a lifestyle programme was less than the effect of lifestyle programmes alone [7], suggesting some negative feedback loop between the two interventions. Conversely, studies of menu labelling have shown some evidence of a positive feedback loop or 'learning effect', with

one study finding reduced calories purchased at food service establishments that did not label menus but shared customers with establishments that had introduced menu labelling [8].

Notwithstanding the difficulty of estimating the combined effect of different programmes, the small effect sizes of each programme suggest that even if all the evidence-based programmes outlined in this DPhil were implemented, they are unlikely to entirely reverse progression of the type 2 diabetes epidemic. This in turn suggests that an urgent search for additional diabetes prevention programmes should continue. However, there is an opportunity to enhance the way in which we identify promising programmes, estimate their effect on obesity or T2DM, and implement diabetes prevention policy.

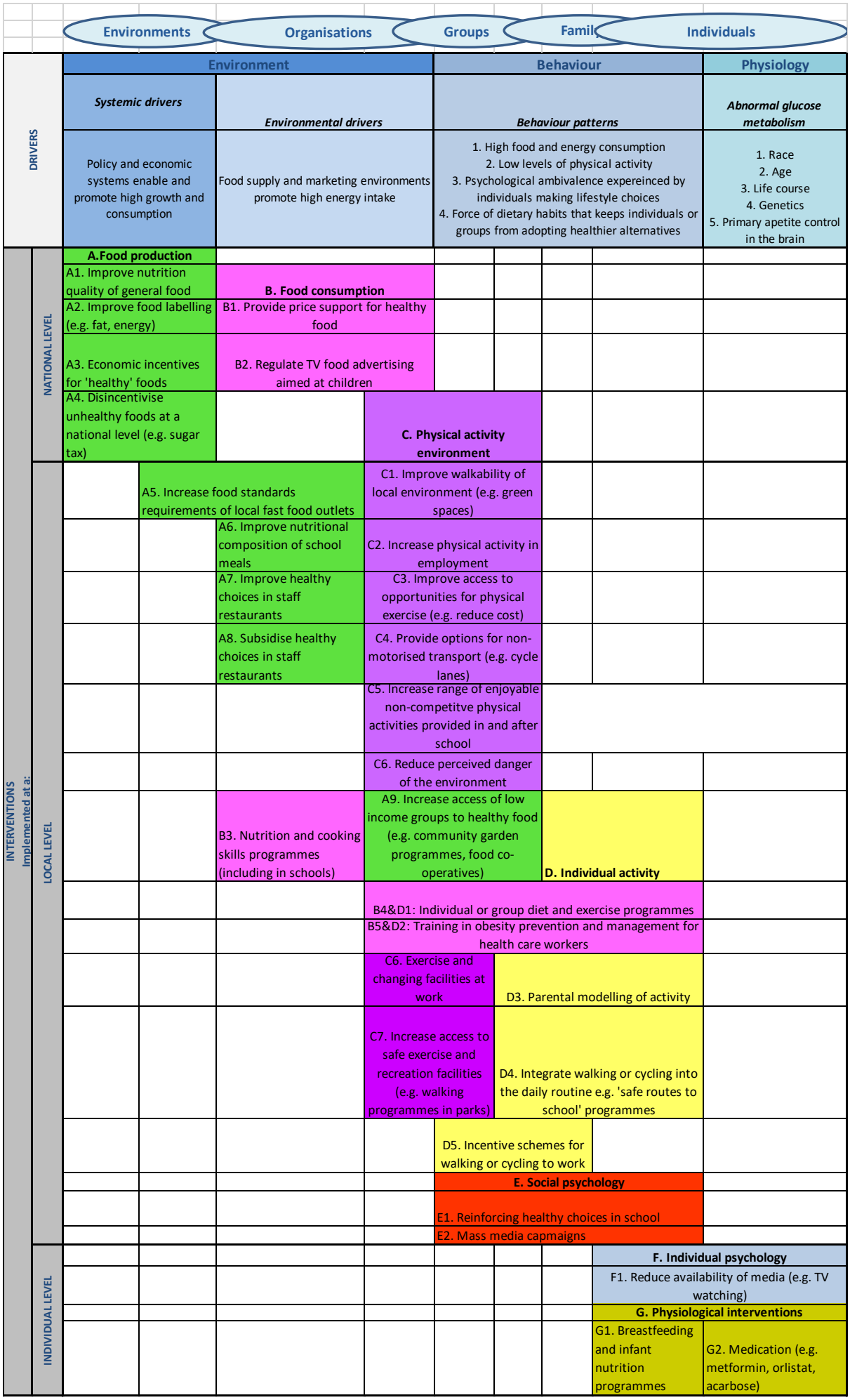
Additional diabetes prevention programmes could be identified through consideration of those that:

- Act at the meso-system level (e.g. school or workplace) but that were not examined in this DPhil
- Have promising effects on proximal indicators of behaviour change but have not been shown to affect BMI both due to the nature of the study design and the likely small effect they would have on overall calories consumed or expended (e.g. decision prompts to increase stair use)

- Have some level of face validity (they are likely to decrease calories consumed or increase calories expended) but have not yet been evaluated for impact on BMI (e.g. tax for other foodstuffs that have a high sugar content such as confectionary).

Figure 7.1. summarises a range of potential diabetes prevention programmes that could be considered by policy makers, based on review of abstracts in the overview of systematic reviews described in Chapter 5.

Figure 7.1. Potential elements of a comprehensive diabetes prevention programmme



There is an opportunity to re-visit how we evaluate the effect of T2DM prevention programmes. Unlike medicines which can be treated as alternatives in trials and the emphasis of evaluation is on reducing confounding variables to establish causation, population-wide diabetes prevention programmes could occur simultaneously and may interact in unexpected ways within the complex adaptive system that is the obesogenic environment. Therefore, the practice of isolating a single intervention and attempting to evaluate its impact in isolation may not be fruitful. An alternative approach is to implement a wide range of programmes simultaneously, such as a selection of those identified in Figure 7.1, some of which will have strong evidence of impact on BMI and others of which will have either face validity or evidence of impact on some elements of behaviour change (calories consumed or expended). Their combined effects could then be evaluated through repeat cross-sectional population-wide measurements. This is an approach that has been taken in Amsterdam's childhood obesity prevention programme, which was associated with a 12% reduction in levels of overweight in children between 2012 and 2015 [9].

There is also an opportunity to re-visit the way in which diabetes prevention policy is formulated and implemented. To date, the primary voices in diabetes prevention policy in England are the national commissioning bodies of the NHS (NHS England and Public Health England), through the publication of the Five Year Forward View [10] and more recently the Long Term Plan [4]. This healthcare-centric view of diabetes prevention lends itself to individual case-based programmes as these are the interventions that the NHS can deliver. However, a truly comprehensive diabetes prevention programme requires collaboration of policy and programme delivery at multiple levels across the private and public sectors,

including: i) nationally within government (including departments responsible for health and social care, education, transport and business), national commissioning organisations (NHS England and Public Health England) and companies with a national footprint, ii) regionally within local authorities, Clinical Commissioning Groups and businesses with a regional footprint and iii) locally within schools, childcare providers, local businesses, workplaces, faith-based organisations and healthcare providers.

Taken together, these proposed approaches to identifying, implementing and evaluating diabetes prevention programmes could amount to a comprehensive, multi-layered modification of behaviours of individuals and communities and the obesogenic environment in which they reside. This would require a significant shift from the current healthcare-focused approach to individual case-based prevention of T2DM.

7.5. CONCLUSIONS

Most countries that have implemented diabetes prevention programmes, including England, have focused on low-intensity individual case-based interventions in people at high risk of T2DM. These are effective, cost-effective and have acceptable budget impact, but are likely to have only a small effect on incidence of T2DM. In addition, there are a small group of population-wide obesity or diabetes prevention programmes (SSB tax, menu labelling, grocery store interventions and multi-component community interventions) which these countries have not uniformly embraced, which are likely to reduce T2DM costs, increase QALYs and have a small effect on incidence of T2DM. Modelling approaches are unable to

estimate the combined effects of these interventions due to uncertainty regarding potential interactions between individual interventions and other elements of the complex system in which they operate. However, given the small effect sizes of individual interventions it is likely that they will be insufficient to entirely stem the tide of increasing diabetes prevalence.

Historically debate has focused on the value of individual case-based programmes versus population-wide programmes. But this DPhil argues that not only are both necessary, but that concurrent implementation of those programmes that have a strong evidence base will probably not be sufficient to curb the exponential increase in prevalence of T2DM forecast for the coming decades. To achieve that goal, consideration of a radically different approach to identifying, evaluating and implementing diabetes prevention programmes is required.

REFERENCES

CHAPTER 1 - REFERENCES

1. International Diabetes Federation, *IDF Atlas, 8th edition, Brussels, Belgium.* International Diabetes Federation, 2017.
2. The Community Guide, *Diabetes Prevention and Control: Combined Diet and Physical Activity Promotion Programmes to Prevent Type 2 Diabetes Among People at Increased Risk. Atlanta, GA.* Accessed on 19th April 2015 at www.thecommunityguide.org/diabetes/supportingmaterials/SScombineddietandpa-econ.html
3. NHS England. NHS Diabetes Prevention Programme. Accessed on 11th December 2017 on https://www.england.nhs.uk/diabetes/diabetes-prevention/
4. Diabetes Australia, *Information on prevention programmes.* Accessed on 21st June 2016 on https://www.diabetesaustralia.com.au/prevention
5. Rose, G., *Sick individuals and sick populations.* International Journal of Epidemiology, 2001. 30(3): p. 427-432.
6. National Institute of Health and Care Excellence, , *Type 2 diabetes: prevention in people at high risk.* NICE Guideline PH 38. Accessed on 2nd January 2019 at https://www.nice.org.uk/guidance/ph38
7. Swinburn, B., G. Egger, and F. Raza, *Dissecting Obesogenic Environments: The Development and Application of a Framework for Identifying and Prioritizing Environmental Interventions for Obesity.* Preventive Medicine, 1999. 29(6): p. 563-570.
8. Gallo V, S.D., Mathur R et al. , *The Diabetes Epidemic in Newham: UCLP Primary Care Programme.* 2015.
9. Airoldi, M., et al., *STAR--people-powered prioritization: a 21st-century solution to allocation headaches.* Med Decis Making, 2014. 34(8): p. 965-75.
10. Barry, E., et al., *Efficacy and effectiveness of screen and treat policies in prevention of type 2 diabetes: systematic review and meta-analysis of screening tests and interventions.* BMJ, 2017. 356: p. i6538.
11. Roberts, S., et al., *Preventing type 2 diabetes: systematic review of studies of cost-effectiveness of lifestyle programmes and metformin, with and without screening, for pre-diabetes.* BMJ Open, 2017. 7(11): p. e017184.

12. Roberts, S., et al., *Economic evaluation of type 2 diabetes prevention programmes: Markov model of low- and high-intensity lifestyle programmes and metformin in participants with different categories of intermediate hyperglycaemia.* BMC Med. 2018. 30:16(1):16

CHAPTER 2 - REFERENCES

1. Fagg, J. and J. Valabhji, *How do we identify people at high risk of Type 2 diabetes and help prevent the condition from developing?* Diabet Med, 2018.
2. International Diabetes Federation*, Diabetes Atlas*, International Diabetes Federation (IDF), 7th edition, 2015
3. Wild S et al. Global Prevalence of Diabetes: estimates for the year 2000 and Projections for 2030. *Diabetes Care* 27. 5 (2004): 1047-1053
4. WHO Diabetes Fact Sheet. Accessed at http://www.who.int/mediacentre/factsheets/fs312/en/ on 1st June 2016
5. Alberti KGMM, Zimmett P, Shaw International Diabetes Federation. A Consensus on Type 2 Diabetes Prevention. Diabet Med. 2007; 24: 451-63
6. P Zimmet, KG Alberti, J Shaw Global and societal implications of the diabetes epidemic. Nature. 2001; 414 (6865):782-787
7. Bagust A, Hopkinson PK, Maslove L, Currie CJ. The projected health care burden of Type 2 diabetes in the UK from 2000 to 2060.Diabet Med. 2002 Jul;19 Suppl 4:1-5.
8. Ely, E.K., et al., *A National Effort to Prevent Type 2 Diabetes: Participant-Level Evaluation of CDC's National Diabetes Prevention Program.* Diabetes Care, 2017. **40**(10): p. 1331-1341.
9. Barron, E., et al., *Progress of the Healthier You: NHS Diabetes Prevention Programme: referrals, uptake and participant characteristics.* Diabetic medicine : a journal of the British Diabetic Association, 2018. **35**(4): p. 513-518.
10. Dunbar, J.A., et al., *Challenges of diabetes prevention in the real world: results and lessons from the Melbourne Diabetes Prevention Study.* BMJ Open Diabetes Res Care, 2015. **3**(1): p. e000131.
11. Saaristo, T., et al., *Lifestyle intervention for prevention of type 2 diabetes in primary health care one-year follow-up of the Finnish National Diabetes Prevention Program (FIN-D2D).* Diabetes care, 2010. **33**(10): p. 2146-2151.
12. Barry, E., et al., *Efficacy and effectiveness of screen and treat policies in prevention of type 2 diabetes: systematic review and meta-analysis of screening tests and interventions.* Bmj, 2017. **356**: p. i6538.
13. Rose, G., *Sick individuals and sick populations.* International Journal of Epidemiology, 2001. **30**(3): p. 427-432.
14. Yudkin J, Montori VM. The epidemic of pre-diabetes: the medicine and the politics. BMJ. 2014; 349: g4485

15. World Health Organization (2011) Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. World Health Organization, Geneva
16. American Diabetes Association. Standards of Medical Care in Diabetes 2016. Diabetes Care. 2016; 39: Suppl
17. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327– 1334
18. Faerch K, Borch-Johnsen K, Holst JJ, Vaag A. Pathophysiology and aetiology of impaired glucose tolerance: does it matter for treatment and prevention of type 2 diabetes. Diabetologica. 2009; 52: 1714-1723
19. Morris DH, Khunti K, Achana F, Srinivasan B, Gray LJ, Davies MJ, Webb D, Progression rates from HbA1c 6.0-6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis. Diabetologica. 2013;56: 1489-1493
20. Diabetes Prevention Program Research Group. HbA1c as a Predictor of Diabetes and as an Outcome in the Diabetes Prevention Program: A Randomized Clinical Trial. Diabetes Care. 2014. Suppl. DOI: 10.2337/dc14-0886
21. Noble D, Mathur R, Dent T, Meeds C, Greenhalgh T. Risk models and scores for Type 2 Diabetes: A systematic review. BMJ 2011;343:d7163
22. National Institute of Health and Care Excellence, *Type 2 diabetes: prevention in people at high risk.* NICE Guideline PH 38. Accessed at https://www.nice.org.uk/guidance/ph38 on 02/01/2019
23. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346:393-403.
24. Lindström J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, et al, Finnish Diabetes Prevention Study Group. The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care. 2003; 26:3230-6.
25. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997; 20:537-44.
26. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V, Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006; 49:289-97.

27. Ali MK, Echouffo-Tcheugui J, Williamson DF. How Effective Were Lifestyle Interventions In Real-World Settings That Were Modeled On The Diabetes Prevention Program? Health Affairs. 2012: 1 (31): 67–75
28. Kahn R, Davidson MB. The reality of Type 2 Diabetes Prevention. Diabetes Care. 2014;37(4):943-949
29. Roberts S, Barry E, Craig D, Airoldi M, Bevan G, Greenhalgh T. Preventing type 2 diabetes: systematic review of studies of cost-effectiveness of lifestyle programmes and metformin, with and without screening, for pre-diabetes. *BMJ Open*. 2017;7(11):e017184.
30. Dunbar, J.A., *Diabetes Prevention in Australia: 10 Years Results and Experience.* Diabetes Metab J, 2017. **41**(3): p. 160-167.
31. The Community Guide. Diabetes Prevention and Control: Combined Diet and Physical Activity Promotion Programmes to Prevent Type 2 Diabetes Among People at Increased Risk. Atlanta, GA: Community Preventive Services Task Force; 2014. Accessed on 19th April 2015 at www.thecommunityguide.org/diabetes/supportingmaterials/SScombineddietandpa-econ.html
32. The NHS Diabetes Prevention Program accessed on 19th April 2015 at https://www.england.nhs.uk/ourwork/qual-clin-lead/diabetes-prevention/
33. Alouki K, Delisle H, Bermudez-Tamayo C, Johri M, Lifestyle Interventions to Prevent Type 2 Diabetes: A Systematic Review of Economic Evaluation Studies Journal of Diabetes Research, 2016
34. Saha S, Gerdtham UG, Johansson P. Economic evaluation of lifestyle interventions for preventing diabetes and cardiovascular diseases. Int J Environ Res Health. 2010 Aug;7(8):3150-95.
35. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. Diabetes Care. 2010 Aug;33(8):1872-94.
36. Li R, Qu S, Zhang P, Chattopadhyay S, Gregg EW, Albright A, Hopkins D, Pronk NP. Economic Evaluation of Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. Ann Intern Med. 2015 Sep 15;163(6):452-60.
37. Radl KI, Ianuale C, Boccia S. A systematic review of the cost-effectiveness of lifestyle modification as primary prevention intervention for diabetes mellitus type 2. Epidemiology Biostatistics and Public Health 2013 (10);2

38. Schaufler TM, Wolff M Cost effectiveness of preventive screening programs for type 2 diabetes mellitus in Germany. Appl Health Econ Health Policy. 2010;8(3):191-202
39. Dall TM, Storm MV, Semilla AP, Wintfield N, O'Grady M, Narayan KM, Value of lifestyle intervention to prevent diabetes and sequelae. Am J Prev Med. 2015 Mar;48(3):271-80

REFERENCES – CHAPTER 3

1. Caro J, Eddy DM, Kan H et al. Questionnaire to Assess Relevance and Credibility of Modeling Studies for Informing Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report. Value in Health. 2014;17: 174-182
2. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. 2006 Oxford University Press
3. http://eppi.ioe.ac.uk/costconversion/default.aspx. Accessed on the 20th September 2016
4. Schaufler TM, Wolff M Cost effectiveness of preventive screening programs for type 2 diabetes mellitus in Germany. Appl Health Econ Health Policy. 2010;8(3):191-202
5. Dall TM, Storm MV, Semilla AP, Wintfield N, O'Grady M, Narayan KM, Value of lifestyle intervention to prevent diabetes and sequelae. Am J Prev Med. 2015 Mar;48(3):271-80
6. Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. Diabetes Care. 2012; 35:723-30
7. Smith KJ, Hsu HE, Roberts MS, Kramer MK, Orchard TJ, Piatt GA, et al. Cost-effectiveness analysis of efforts to reduce risk of type 2 diabetes and cardiovascular disease in southwestern Pennsylvania, 2005–2007. Prev Chronic Dis. 2010; 7:A109.
8. Irvine L, Barton GR, Gasper AV, Murray N, Clark A, Scarpello T, et al. Cost-effectiveness of a lifestyle intervention in preventing type 2 diabetes. Int J Technol Assess Health Care. 2011; 27:275-82
9. Feldman I, Hellström L, Johansson P. Heterogeneity in cost-effectiveness of lifestyle counseling for metabolic syndrome risk groups—primary care patients in Sweden. Cost Eff Resour Alloc. 2013; 11:19
10. Sagarra R, Costa B, Cabré JJ, Solà-Morales O, Barrio F, el Grupo de Investigación DE-PLAN-CAT/PREDICE. Lifestyle interventions for diabetes mellitus type 2 prevention. Rev Clin Esp (Barc). 2014; 214:59-68
11. Jacobs-van der Bruggen MA, Bos G, Bemelmans WJ, Hoogenveen RT, Vijgen SM, Baan CA. Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modelling study. Diabetes Care. 2007; 30:128-34
12. Caro JJ, Getsios D, Caro I, Klittich WS, O'Brien JA. Economic evaluation of therapeutic interventions to prevent type 2 diabetes in Canada. Diabet Med. 2004; 21:1229-36
13. Palmer AJ, Roze S, Valentine WJ, Spinas GA, Shaw JE, Zimmet PZ. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic

implications of the diabetes prevention program in Australia, France, Germany, Switzerland, and the United Kingdom. Clin Ther. 2004; 26:304-21

14. Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. Ann Intern Med. 2005; 143:251-64
15. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, et al, Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med. 2005; 142:323-32
16. Ackermann RT, Marrero DG, Hicks KA, Hoerger TJ, Sorensen S, Zhang P, et al. An evaluation of cost sharing to finance a diet and physical activity intervention to prevent diabetes. Diabetes Care. 2006; 29:1237-41
17. Hoerger TJ, Hicks KA, Sorensen SW, Herman WH, Ratner RE, Ackermann RT, et al. Cost-effectiveness of screening for pre-diabetes among overweight and obese U.S. adults. Diabetes Care. 2007; 30:2874-9
18. Lindgren P, Lindström J, Tuomilehto J, Uusitupa M, Peltonen M, Jönsson B, et al, DPS Study Group. Lifestyle intervention to prevent diabetes in men and women with impaired glucose tolerance is cost-effective. Int J Technol Assess Health Care. 2007; 23:177-83
19. Zhuo X, Zhang P, Gregg EW, Barker L, Hoerger TJ, Tony Pearson-Clarke, et al. A nationwide community-based lifestyle program could delay or prevent type 2 diabetes cases and save $5.7 billion in 25 years. Health Aff (Millwood). 2012; 31:50-60
20. Gillies CL, Lambert PC, Abrams KR, Sutton AJ, Cooper NJ, Hsu RT, et al. Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. BMJ. 2008; 336:1180-5
21. Bertram MY, Lim SS, Barendregt JJ, Vos T. Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care. Diabetologia. 2010; 53:875-81
22. Neumann A, Schwarz P, Lindholm L. Estimating the cost-effectiveness of lifestyle intervention programs to prevent diabetes based on an example from Germany: Markov modelling. Cost Eff Resour Alloc. 2011; 9:17
23. Palmer AJ, Tucker DM. Cost and clinical implications of diabetes prevention in an Australian setting: a long-term modeling analysis. Prim Care Diabetes. 2012; 6:109-21
24. Png ME, Yoong JS. Evaluating the cost-effectiveness of lifestyle modification versus metformin therapy for the prevention of diabetes in Singapore. PLoS One. 2014; 9:e107225

25. Colagiuri S, Walker AE. Using an economic model of diabetes to evaluate prevention and care strategies in Australia. Health Aff (Millwood). 2008; 27:256-68
26. Icks A, Rathmann W, Haastert B et a', Clinical and cost-effectiveness of primary prevention of Type 2 diabetes in a real world routine healthcare setting: model based on the KORA survey 2000. Diabetic Med 2007; 24(5):473-80
27. Herman WH, Edelstein SL, Ratner RE et al, Effectiveness and cost-effectiveness of diabetes prevention among adherent participants. Am J Manag Care 2013; 19(3):194-202
28. Liu X, Li C, Gong H et al, An economic evaluation for prevention of diabetes in a developing country: a modelling study. BMC Public Health 2013; 13(279)
29. Mortaz S, Wessman C, Duncan R, Gray R, Badawi A. Impact of screening and early detection of impaired fasting glucose tolerance and type 2 diabetes in Canada: A Markov model simulation. Clinicoecon and Outcomes Research. 2012;4:91-97
30. Ramachandran A, Snehalatha C, Yamuna A, Mary S, Ping Z. Cost-effectiveness of the interventions in the primary prevention of diabetes among Asian Indians: within-trial results of the Indian Diabetes Prevention Programme (IDPP). Diabetes Care. 2007 Oct;30(10):2548-52.
31. Sculpher MJ, Pang FS et al. Generalisability in Economic Evaluations studies in healthcare: a review and case studies. Health Technol Assess. 2004;8: 1-192
32. Daniels N, Porteny T, Urritia J. Expanded HTA: Enhancing Fairness and Legitimacy. Int J Health Policy Manag. 2016; 5(1): 1–3
33. National Institute for Health and Care Excellence. Type 2 diabetes: prevention in people at high risk. NICE Guideline PH 38. Accessed at https://www.nice.org.uk/guidance/ph38 on 20.3.16.2012
34. National Institute for Health and Care Excellence. Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. Costing template. July 2012. Accessed on 07.09.2016 at https://www.nice.org.uk/guidance/ph38/resources/costing-report-68964013
35. American Diabetes Association. Standards of Medical Care in Diabetes 2016. Diabetes Care. 2016; 39: Suppl
36. The Community Guide. Diabetes Prevention and Control: Combined Diet and Physical Activity Promotion Programmes to Prevent Type 2 Diabetes Among People at Increased Risk. Atlanta, GA: Community Preventive Services Task Force; 2014. Accessed on 19th April 2015 at www.thecommunityguide.org/diabetes/supportingmaterials/SScombineddietandpa-econ.html
37. Ali MK, Echouffo-Tcheugui J, Williamson DF. How Effective Were Lifestyle Interventions In Real-World Settings That Were Modeled On The Diabetes Prevention Program? Health Affairs. 2012: 1 (31): 67–75

38. Kahn R, Davidson MB. The reality of Type 2 Diabetes Prevention. Diabetes Care. 2014;37(4):943-949
39. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346:393-403.
40. Barry E, Roberts S, Oke J, Vijayaraghavan S, Normansell R, Greenhalgh T. Can type 2 diabetes be prevented using screen-and-treat policies? Systematic review and meta-analysis of screening tests and interventions for pre-diabetes. BMJ 2017 4;356:i6538
41. Balk EM et al. Combined Diet and Physical Activity Promotion Programmes to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. Annals of Internal Medicine. 2015;163 doi:10.7326/M15-0452
42. Ashra NB, Spong R, Carter P, et al. *A systematic review and meta- analysis assessing the effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes mellitus in routine practice*. London: Public Health England, 2015. Accessed 01.10.15 on https://www.gov.uk/government/publications/diabetes-prevention-programmes-evidence-review
43. Aziz Z, Absetz P, Oldroyd J, Pronk NP, Oldenburg B. A systematic review of real-world diabetes prevention programmes: learnings from the last 15 years Implementation Science 2015 10:172
44. National Institute of Clinical Excellence. Cost effectiveness of Interventions for Smoking Cessation: Final Report. 2007
45. Pharoah P, Sewell B, Fitzsimmons D, Bennett HS, Pashayan N. Cost effectiveness of the NHS breast screening programme: life table model. BMJ 2013;346:f2618
46. Breeze, P.R., et al., *Cost-effectiveness of population-based, community, workplace and individual policies for diabetes prevention in the UK.* Diabet Med, 2017. **34**(8): p. 1136-1144.
47. Breeze, P.R., et al., *The impact of Type 2 diabetes prevention programmes based on risk-identification and lifestyle intervention intensity strategies: a cost-effectiveness analysis.* Diabetic Medicine, 2017. **34**(5): p. 632-640.
48. Leal, J., et al., *Cost-effectiveness of a pragmatic structured education intervention for the prevention of type 2 diabetes: Economic evaluation of data from the Let's Prevent Diabetes cluster-randomised controlled trial.* BMJ Open, 2017. **7**(1).
49. Neumann, A., et al., *The cost-effectiveness of interventions targeting lifestyle change for the prevention of diabetes in a Swedish primary care and community based prevention program.* The European Journal of Health Economics, 2017. **18**(7): p. 905-919.

50. Cobiac LJ, Veerman L, Vos T. The Role of Cost-Effectiveness Analysis in Developing Nutrition Policy. Annu Rev Netr 2013;33: 373-93
51. Alouki K, Delisle H, Bermudez-Tamayo C, Johri M, Lifestyle Interventions to Prevent Type 2 Diabetes: A Systematic Review of Economic Evaluation Studies Journal of Diabetes Research, 2016
52. Saha S, Gerdtham UG, Johansson P. Economic evaluation of lifestyle interventions for preventing diabetes and cardiovascular diseases. Int J Environ Res Health. 2010 Aug;7(8):3150-95.
53. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. Diabetes Care. 2010 Aug;33(8):1872-94.
54. Li R, Qu S, Zhang P, Chattopadhyay S, Gregg EW, Albright A, Hopkins D, Pronk NP. Economic Evaluation of Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. Ann Intern Med. 2015 Sep 15;163(6):452-60.
55. Radl KI, Ianuale C, Boccia S. A systematic review of the cost-effectiveness of lifestyle modification as primary prevention intervention for diabetes mellitus type 2. Epidemiology Biostatistics and Public Health 2013 (10);2

REFERENCES – CHAPTER 4

1. The NHS Diabetes Prevention Programme. Accessed on 28.10.2016 at https://www.england.nhs.uk/ourwork/qual-clin-lead/diabetes-prevention/

2. The Community Guide. Diabetes Prevention and Control: Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among People at Increased Risk. Atlanta, GA: Community Preventive Services Task Force; 2014. Accessed 14.10.2016 at www.thecommunityguide.org/diabetes/supportingmaterials/SScombineddietandpa-econ.html on 19 April 2015

3. Menn P, Holle R. Comparing three software tools for implementing markov models for health economic evaluations. Pharmacoeconomics. 2009;27(9):745-53.

4. http://eppi.ioe.ac.uk/costconversion/default.aspx. Accessed on the 20th September 2016

5. National Institute of Health and Care Excellence. Guide to the Technology Appraisal Process, 2013. Accessed on 27.10.2016 at https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance. Accessed on 28th October 2016

6. National Institute of Health and Care Excellence. Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. Costing template. July 2012. Accessed on 07.09.2016 at https://www.nice.org.uk/guidance/ph38/resources/costing-report-68964013

7. Aziz Z, Absetz P, Oldroyd J, Pronk NP, Oldenburg B. A systematic review of real-world diabetes prevention programmes: learnings from the last 15 years Implementation Science 2015 10:172

8. Usher-Smith J et al. NHS Health Check Programme rapid evidence synthesis. January 2017. Accessed on 25th September at www.healthcheck.nhs.uk/document.php?o=1251)

9. World Health Organization (2011) Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. World Health Organization, Geneva

10. American Diabetes Association. Standards of Medical Care in Diabetes 2016. Diabetes Care. 2016; 39: Suppl

11. Mostafa SA, Khunti K, Srinivasan BT, Webb D, Gray LJ, Davies MJ. The potential impact and optimal cut-points of using glycated haemoglobin, HbA1c, to detect people with impaired glucose regulation in a UK multi-ethnic cohort. Diabetes research and clinical practice. 2010;90(1):100-8

12. Morris D, Khunti K, Achana F, Srinivasan B, Gray L, Davies M, et al. Progression rates from HbA1c 6.0–6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis. Diabetologia. 2013;56(7):1489-93

13. Office of National Statistics. Deaths registered in England and Wales. 2014

14. DECODE Study Group, European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? Diabetes Care. 2003 Mar;26(3):688-96.

15. British National Formulary Online. Accessed 06.09.2016 on https://www.bnf.org/products/bnf-online/

16. Hex N, Bartlett C, Wright Det al. Estimating the current and future costs of type 1 and type 2 diabetes in the United Kingdom, including direct health costs and indirect societal and productivity costs. 2012. Diabetic Medicine 29: 855–862

17. Bachle C. Direct costs in glucose regulation: results from the population-based Heinz Neixdorf recall study. BMJ Open Diabetes Research and Care. 2016

18. Nichols GA, Arondekar B, Herman WH. Medical Care Costs One Year after Identification of Hyperglycemia below the Threshold for Diabetes. 2008 Medical Caree;46 (3):287-292

19. Neumann A, Schoffer O, Norström F, Norberg M, Klug SJ and Lindholm L. Health-related quality of life for pre-diabetic states and type 2 diabetes mellitus: a cross-sectional study in Västerbotten Sweden. 2014. Health and Quality of Life Outcomes 2014; 12:150

20. Balk EM et al. Combined Diet and Physical Activity Promotion Programmes to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force. Annals of Internal Medicine. 2015;163 doi:10.7326/M15-0452

21. Barry E, Roberts S, Oke J, Vijayaraghavan S, Normansell R, Greenhalgh T. Can type 2 diabetes be prevented using screen-and-treat policies? Systematic review and meta-analysis of screening tests and interventions for pre-diabetes. BMJ 2017 4;356:i6538

22. Roberts S, Barry E, Craig D, Airoldi M, Bevan RG, Greenhalgh. Preventing Type 2 Diabetes: Systematic review of cost-effectiveness of lifestyle programmes and metformin, with and without screening for prediabetes. Submitted for publication

23. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. The Lancet Diabetes & Endocrinology. 2015;3(11):866-75

24. Diabetes Prevention Program Research Group. HbA1c as a Predictor of Diabetes and as an Outcome in the Diabetes Prevention Program: A Randomized Clinical Trial. Diabetes Care. 2014. Suppl. DOI: 10.2337/dc14-0886

25. National Institute for Health and Care Excellence. Type 2 diabetes: prevention in people at high risk. NICE Guideline PH 38. 2012. Accessed on 28.10.2016 at https://www.nice.org.uk/guidance/ph38

26. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, et al, Diabetes Prevention Programme Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med. 2005; 142:323-32

27. Curtis B, Burns A. Unit Costs of Health and Social Care 2015. Personal Social Services Research Unit Accessed 14.10.2016 on http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php [35]

28. Khunti K, Gillies CL, Taub NA, Mostafa SA, Hiles SL, Abrams KR, Davies MJ. A comparison of cost per case detected of screening strategies for Type 2 diabetes and impaired glucose regulation: modelling study. Diabetes Res Clin Pract. 2012 Sep;97(3):505-13

29. Ashra NB, Spong R, Carter P, et al. *A systematic review and meta- analysis assessing the effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes mellitus in routine practice*. London: Public Health England, 2015. Accessed 01.10.15 on https://www.gov.uk/government/publications/diabetes-prevention-programmes-evidence-review

30. Saha S, Gerdtham UG, Johansson P. Economic evaluation of lifestyle interventions for preventing diabetes and cardiovascular diseases. Int J Environ Res Health. 2010 Aug;7(8):3150-95.

31. Vemer P, Corro Ramos I, van Voorn GAK, Al MJ, Feenstra TL. AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users. Pharmacoeconomics.2016;34:349-361

32. NHS Digital. National Diabetes Audit 2015-16. 2016 (Accessed on 21st September 2017 on content.digital.nhs.uk/nda)

33. Diabetes UK. Diabetes Prevalence 2016. November 2016 (Accessed on 21st September 2017 on www.diabetes.org.uk/professionals/position-statement-reports/statistics/diabetes-prevalence-2016/)

34. Kowall B, Rathmann W et al. Incidence Rates of Type 2 Diabetes in People With Impaired Fasting Glucose (ADA vs. WHO Criteria) and Impaired Glucose Tolerance: Results From an Older Population (KORA S4/F4/FF4 Study). Diabetes Care. Feb 2019, 42 (2) e18-e20

CHAPTER 5 – REFERENCES

1. McLaren, L. and P. Hawe, *Ecological perspectives in health research.* Journal of Epidemiology and Community Health, 2005. **59**(1): p. 6-14.
2. Swinburn, B., G. Egger, and F. Raza, *Dissecting Obesogenic Environments: The Development and Application of a Framework for Identifying and Prioritizing Environmental Interventions for Obesity.* Preventive Medicine, 1999. **29**(6): p. 563-570.
3. Zimmet, P., K.G. Alberti, and J. Shaw, *Global and societal implications of the diabetes epidemic.* Nature, 2001. **414**(6865): p. 782-7.
4. Noble, D., et al., *Risk models and scores for type 2 diabetes: systematic review.* BMJ, 2011. **343**.
5. Hamman, R.F., et al., *Effect of weight loss with lifestyle intervention on risk of diabetes.* Diabetes Care, 2006. **29**(9): p. 2102-7.
6. Moher D, L.A., Tetzlaff J, Altman DG, The PRISMA Group, *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLos Medicine, 2009. **6**(7)
7. Foresight., *Tackling obesities: future choices.* Accessed on 11th November 2016 at http:// www.bis.gov.uk/foresight/our-work/projects/published-projects/ tackling-obesities, 2007.
8. Swinburn, B.A., et al., *The global obesity pandemic: shaped by global drivers and local environments.* Lancet, 2011. **378**(9793): p. 804-14.
9. Shea, B.J., et al., *AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews.* Journal of Clinical Epidemiology, 2009. **62**(10): p. 1013-1020.
10. Chou, S.-Y., M. Grossman, and H. Saffer, *An economic analysis of adult obesity: results from the Behavioral Risk Factor Surveillance System.* Journal of Health Economics, 2004. **23**(3): p. 565-587.
11. Higgins JPT, G.S.e., *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].* The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org, 2011.
12. Downs SM, T.A., Leeder SR, *The effectiveness of policies for reducing dietary trans fat: a systematic review of the evidence.* Bulletin of the World Health Organization, 2013. **91**: p. 262-269H.
13. Grech, A. and M. Allman-Farinelli, *A systematic literature review of nutrition interventions in vending machines that encourage consumers to make healthier choices.* Obesity Reviews, 2015. **16**(12): p. 1030-1041.

14. Drewnowski, A., *Obesity and the food environment: dietary energy density and diet costs.* Am J Prev Med, 2004. **27**(3 Suppl): p. 154-62.
15. Welsh, J.A., et al., *Consumption of added sugars is decreasing in the United States.* The American Journal of Clinical Nutrition, 2011. **94**(3): p. 726-734.
16. Afshin, A., et al., *The prospective impact of food pricing on improving dietary consumption: A systematic review and meta-analysis.* PloS one, 2017. **12**(3): p. e0172277.
17. Andreyeva, T., M.W. Long, and K.D. Brownell, *The Impact of Food Prices on Consumption: A Systematic Review of Research on the Price Elasticity of Demand for Food.* American Journal of Public Health, 2010. **100**(2): p. 216-222.
18. Bes-Rastrollo, M., et al., *Impact of sugars and sugar taxation on body weight control: A comprehensive literature review.* Obesity, 2016. **24**(7): p. 1410-1426.
19. Cabrera Escobar, M.A., et al., *Evidence that a tax on sugar sweetened beverages reduces the obesity rate: a meta-analysis.* BMC Public Health, 2013. **13**: p. 1072.
20. Green, R., et al., *The effect of rising food prices on food consumption: systematic review with meta-regression.* Bmj, 2013. **346**: p. f3703.
21. Nakhimovsky, S.S., et al., *Taxes on Sugar-Sweetened Beverages to Reduce Overweight and Obesity in Middle-Income Countries: A Systematic Review.* PloS one, 2016. **11**(9): p. e0163358.
22. Powell, L.M. and F.J. Chaloupka, *Food prices and obesity: evidence and policy implications for taxes and subsidies.* Milbank Quarterly, 2009. **87**(1): p. 229-57.
23. Powell, L.M., et al., *Assessing the potential effectiveness of food and beverage taxes and subsidies for improving public health: a systematic review of prices, demand and body weight outcomes.* Obesity Reviews, 2013. **14**(2): p. 110-28.
24. Thow, A.M., S. Downs, and S. Jan, *A systematic review of the effectiveness of food taxes and subsidies to improve diets: understanding the recent evidence.* Nutrition Reviews, 2014. **72**(9): p. 551-65.
25. Wendt M, T.J., *Economic Research Report Number 118. The Effect of Food and Beverage Prices on Children's Weights.* Economic Research Service, United States Department of Agriculture, 2011.
26. Sturm, R., et al., *Soda taxes, soft drink consumption, and children's body mass index.* Health Aff (Millwood), 2010. **29**(5): p. 1052-8.
27. Powell, L.M., J. Chriqui, and F.J. Chaloupka, *Associations between state-level soda taxes and adolescent body mass index.* J Adolesc Health, 2009. **45**(3 Suppl): p. S57-63.

28. Fletcher, J.M., D. Frisvold, and N. Tefft, *Can Soft Drink Taxes Reduce Population Weight?* Contemporary economic policy, 2010. **28**(1): p. 23-35.
29. Fletcher, J.M., D. Frisvold, and N. Tefft, *Taxing soft drinks and restricting access to vending machines to curb child obesity.* Health Aff (Millwood), 2010. **29**(5): p. 1059-66.
30. Duffey, K.J., et al., *Food price and diet and health outcomes: 20 years of the CARDIA Study.* Arch Intern Med, 2010. **170**(5): p. 420-6.
31. Han, E. and L.M. Powell, *Effect of food prices on the prevalence of obesity among young adults.* Public Health, 2011. **125**(3): p. 129-35.
32. Fletcher JM, F.D., Tefft N, *Taxing Soft Drinks And Restricting Access To Vending Machines To Curb Child Obesity.* Health Affairs, 2010. **29**(5): p. 1059-1066.
33. Kim D, K.I., *Food taxation and pricing strategies to 'thin out' the obesity epidemic.* Am J Prev Med, 2006. **30**(5): p. 430-437.
34. Beydoun, M.A., L. Powell, and Y. Wang, *Fast food, fruits and vegetables' prices' association with dietary intakes among US adults: Is there modification by family income?* Social science & medicine (1982), 2008. **66**(11): p. 2218-2229.
35. Beydoun, M.A., et al., *Food Prices Are Associated with Dietary Quality, Fast Food Consumption, and Body Mass Index among U.S. Children and Adolescents.* The Journal of Nutrition, 2011. **141**(2): p. 304-311.
36. Powell, L.M. and Y. Bao, *Food prices, access to food outlets and child weight.* Economics & Human Biology, 2009. **7**(1): p. 64-72.
37. Powell, L.M. and E. Han, *Adult Obesity and the Price and Availability of Food in the United States.* American Journal of Agricultural Economics, 2011. **93**(2): p. 378-384.
38. An, R., et al., *Eating better for less: a national discount program for healthy food purchases in South Africa.* Am J Health Behav, 2013. **37**(1): p. 56-61.
39. Office of National Statistics, *Family spending in the UK: Financial Year ending March 2016.* Accessed on 31st August 2017 at https://www.ons.gov.uk/peoplepopulationandcommunity/personalandhouseholdfinances/expenditure/bulletins/familyspendingintheuk/financialyearendingmarch2016#main-points, 2016.
40. Variyam, J.N., *Do nutrition labels improve dietary outcomes?* Health Econ, 2008. **17**(6): p. 695-708.
41. Pereira, M., et al., *Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis.* Lancet, 2005. **365**.

42. Cecchini, M. and L. Warin, *Impact of food labelling systems on food choices and eating behaviours: a systematic review and meta-analysis of randomized studies.* Obesity Reviews, 2016. **17**(3): p. 201-10.
43. Freudenberg, N., et al., *The State of Evaluation Research on Food Policies to Reduce Obesity and Diabetes Among Adults in the United States, 2000-2011.* Preventing Chronic Disease, 2015. **12**: p. E182.
44. Sinclair, S.E., M. Cooper, and E.D. Mansfield, *The Influence of Menu Labeling on Calories Selected or Consumed: A Systematic Review and Meta-Analysis.* Journal of the Academy of Nutrition and Dietetics, 2014. **114**(9): p. 1375-1388.e15.
45. Swartz, J.J., D. Braxton, and A.J. Viera, *Calorie menu labeling on quick-service restaurant menus: an updated systematic review of the literature.* International Journal of Behavioral Nutrition & Physical Activity, 2011. **8**: p. 135.
46. Littlewood, J.A., et al., *Menu labelling is effective in reducing energy ordered and consumed: a systematic review and meta-analysis of recent studies.* Public Health Nutrition, 2015. **19**(12): p. 2106-2121.
47. Fernandes, A.C., et al., *Influence of menu labeling on food choices in real-life settings: a systematic review.* Nutrition Reviews, 2016. **74**(8): p. 534-548.
48. Harnack, L.J. and S.A. French, *Effect of point-of-purchase calorie labeling on restaurant and cafeteria food choices: A review of the literature.* International Journal of Behavioral Nutrition and Physical Activity, 2008. **5**(1): p. 51.
49. VanEpps, E.M., et al., *Restaurant Menu Labeling Policy: Review of Evidence and Controversies.* Current Obesity Reports, 2016. **5**(1): p. 72-80.
50. Kiszko, K.M., et al., *The Influence of Calorie Labeling on Food Orders and Consumption: A Review of the Literature.* Journal of Community Health, 2014. **39**(6): p. 1248-1269.
51. Sacco, J., et al., *The influence of menu labelling on food choices among children and adolescents: a systematic review of the literature.* Perspectives in Public Health, 2017. **137**(3): p. 173-181.
52. Long, M.W., et al., *Systematic Review and Meta-analysis of the Impact of Restaurant Menu Calorie Labeling.* American Journal of Public Health, 2015. **105**(5): p. e11-e24.
53. Seymour, J.D., et al., *Impact of nutrition environmental interventions on point-of-purchase behavior in adults: a review.* Preventive Medicine, 2004. **39, Supplement 2**: p. 108-136.
54. Nikolaou, C.K., C.R. Hankey, and M.E. Lean, *Calorie-labelling: does it impact on calorie purchase in catering outlets and the views of young adults?* International Journal of Obesity, 2015. **39**(3): p. 542-5.

55. Deb P, V.C., *Who benefits from calorie labelling? An analysis of its effects on Body Mass.* National Bureau of Economic Research, 2016. **Working Paper 21992**(Accessed on 16th December 2017 at http://www.nber.org/papers/w21992).

56. B., R., *Calorie Labeling in Chain Restaurants and Body Weight: Evidence from New York.* European University Institute Max Weber Programme, 2014. **EUI Working Paper MWP 2014/05**(Accessed on 16th December 2017 at http://cadmus.eui.eu/bitstream/handle/1814/31332/MWP_2014_05.pdf).

57. Restrepo, B.J., *Calorie Labeling in Chain Restaurants and Body Weight: Evidence from New York.* Health Economics, 2017. **26**(10): p. 1191-1209.

58. Bollinger B, L.P., Sorensen A. , *Calorie posting in chain restaurants.* Am Econ J-Econ Polic, 2011. **3**(1): p. 91-128.

59. Krieger, J.W., et al., *Menu labeling regulations and calories purchased at chain restaurants.* Am J Prev Med, 2013. **44**(6): p. 595-604.

60. Roberto, C.A., et al., *Evaluating the Impact of Menu Labeling on Food Choices and Intake.* American Journal of Public Health, 2010. **100**(2): p. 312-318.

61. Prior G, P.R., O'Driscoll C, *Food and You Survey.* Food Standards Agency, 2014. **Accessed on 10th December 2017 at**

https://www.food.gov.uk/sites/default/files/food-and-you-2014-uk-bulletin-1.pdf.

62. Gamba, R.J., et al., *Measuring the food environment and its effects on obesity in the United States: a systematic review of methods and results.* J Community Health, 2015. **40**(3): p. 464-75.

63. Liberato, S.C., R. Bailie, and J. Brimblecombe, *Nutrition interventions at point-of-sale to encourage healthier food purchasing: a systematic review.* BMC Public Health, 2014. **14**: p. 919.

64. Adam, A. and J.D. Jensen, *What is the effectiveness of obesity related interventions at retail grocery stores and supermarkets? -a systematic review.* BMC Public Health, 2016. **16**(1): p. 1247.

65. Mayne, S.L., A.H. Auchincloss, and Y.L. Michael, *Impact of policy and built environment changes on obesity-related outcomes: a systematic review of naturally occurring experiments.* Obesity Reviews, 2015. **16**(5): p. 362-75.

66. Gittelsohn, J., M. Rowan, and P. Gadhoke, *Interventions in Small Food Stores to Change the Food Environment, Improve Diet, and Reduce Risk of Chronic Disease.* Preventing Chronic Disease, 2012. **9**: p. E59.

67. Escaron, A.L., et al., *Supermarket and grocery store-based interventions to promote healthful food choices and eating practices: a systematic review.* Prev Chronic Dis, 2013. **10**: p. E50.
68. Kennedy, B.M., et al., *The "Rolling Store:" an economical and environmental approach to the prevention of weight gain in African American women.* Ethn Dis, 2009. **19**(1): p. 7-12.
69. Gittelsohn, J., et al., *A food store-based environmental intervention is associated with reduced BMI and improved psychosocial factors and food-related behaviors on the Navajo nation.* J Nutr, 2013. **143**(9): p. 1494-500.
70. Geliebter, A., et al., *Supermarket discounts of low-energy density foods: effects on purchasing, food intake, and body weight.* Obesity (Silver Spring), 2013. **21**(12): p. E542-8.
71. Kahn, E.B., et al., *The effectiveness of interventions to increase physical activity.* American Journal of Preventive Medicine. **22**(4): p. 73-107.
72. Marcus, B., et al., *Physical activity interventions using mass media, print media, and information technology.* American Journal of Preventive Medicine, 1998. **15**(4): p. 362-378.
73. Marshall, A.L., N. Owen, and A.E. Bauman, *Mediated approaches for influencing physical activity: update of the evidence on mass media, print, telephone and website delivery of interventions.* J Sci Med Sport, 2004. **7**.
74. Cavill, N. and A. Bauman, *Changing the way people think about health-enhancing physical activity: do mass media campaigns have a role?* J Sports Sci, 2004. **22**.
75. Finlay, S.-J. and G. Faulkner, *Physical activity promotion through the mass media: Inception, production, transmission and consumption.* Preventive Medicine, 2005. **40**(2): p. 121-130.
76. Leavy, J.E., et al., *Physical activity mass media campaigns and their evaluation: a systematic review of the literature 2003–2010.* Health Education Research, 2011. **26**(6): p. 1060-1085.
77. Brown, D.R., et al., *Stand-alone mass media campaigns to increase physical activity: a community guide updated review.* Am J Prev Med, 2012. **43**.
78. Abioye, A.I., K. Hajifathalian, and G. Danaei, *Do mass media campaigns improve physical activity? a systematic review and meta-analysis.* Archives of Public Health, 2013. **71**(1): p. 20.
79. Yun, L., et al., *A Systematic Review of Community-wide Media Physical Activity Campaigns: An Update From 2010.* Journal of Physical Activity and Health, 2017. **14**(7): p. 552-570.
80. Audrey, S. and H. Batista-Ferrer, *Healthy urban environments for children and young people: A systematic review of intervention studies.* Health & Place, 2015. **36**: p. 97-117.
81. Roberts, H., et al., *Identifying Effective Behavior Change Techniques in Built Environment Interventions to Increase Use of Green Space.* Environment and Behavior. **0**(0): p. 0013916516681391.

82. Hunter, R.F., et al., *The impact of interventions to promote physical activity in urban green space: a systematic review and recommendations for future research.* Soc Sci Med, 2015. **124**: p. 246-56.
83. Webb, O.J., F.F. Eves, and J. Kerr, *A Statistical Summary of Mall-Based Stair-Climbing Interventions.* Journal of Physical Activity and Health, 2011. **8**(4): p. 558-565.
84. Soler, R.E., et al., *Point-of-decision prompts to increase stair use. A systematic review update.* American Journal of Preventive Medicine, 2010. **38**(2 Suppl): p. S292-300.
85. Bellicha, A., et al., *Stair-use interventions in worksites and public settings — A systematic review of effectiveness and external validity.* Preventive Medicine, 2015. **70**: p. 3-13.
86. Nocon, M., et al., *Review Article: Increasing physical activity with point-of-choice prompts - a systematic review.* Scandinavian Journal of Public Health, 2010. **38**(6): p. 633-638.
87. Eves, F.F., *Point-of-Decision Prompts to Increase Stair Use.* American Journal of Preventive Medicine, 2010. **38**(5): p. 573-574.
88. Eves, F.F., et al., *Contextual barriers to lifestyle physical activity interventions in Hong Kong.* Med Sci Sports Exerc, 2008. **40**(5): p. 965-71.
89. Ogilvie, D., et al., *Interventions to promote walking: systematic review.* BMJ, 2007. **334**(7605): p. 1204.
90. Ogilvie, D., et al., *Promoting walking and cycling as an alternative to using cars: systematic review.* BMJ, 2004. **329**(7469): p. 763.
91. Scheepers, C.E., et al., *Shifting from car to active transport: A systematic review of the effectiveness of interventions.* Transportation Research Part A: Policy and Practice, 2014. **70**: p. 264-280.
92. Yang, L., et al., *Interventions to promote cycling: systematic review.* BMJ, 2010. **341**.
93. Pucher, J., J. Dill, and S. Handy, *Infrastructure, programs, and policies to increase bicycling: an international review.* Prev Med, 2010. **50 Suppl 1**: p. S106-25.
94. *Arhus BikeBus'ters.* Tools of Change, 1996. **Accessed on 10th December 2017 at http://www.toolsofchange.com/en/case-studies/detail/131**.
95. Oja, P., I. Vuori, and O. Paronen, *Daily walking and cycling to work: their utility as health-enhancing physical activity.* Patient Educ Couns, 1998. **33**(1 Suppl): p. S87-94.
96. MacDonald, J.M., et al., *The effect of light rail transit on body mass index and physical activity.* Am J Prev Med, 2010. **39**(2): p. 105-12.
97. Baker, P.R.A., et al., *Community wide interventions for increasing physical activity.* Cochrane Database of Systematic Reviews, 2015(1).

98. Compernolle, S., et al., *A RE-AIM evaluation of evidence-based multi-level interventions to improve obesity-related behaviours in adults: a systematic review (the SPOTLIGHT project).* Int J Behav Nutr Phys Act, 2014. **11**: p. 147.

99. Fogelholm M, L.-K.M.C.h.-p.i.w.p.a.d.t.a.p.o.S.J.o.N.-. *Community health-promotion interventions with physical activity: does this approach prevent obesity?* Scandinavian Journal of Nutrition/Naringsforskning, 2002. **46**(4): p. 173-177

100. Boelsen-Robinson, T., et al., *A systematic review of the effectiveness of whole-of-community interventions by socioeconomic position.* Obesity Reviews, 2015. **16**(9): p. 806-16.

101. Wolfenden, L., et al., *A systematic review and meta-analysis of whole of community interventions to prevent excessive population weight gain.* Preventive Medicine, 2014. **62**: p. 193-200.

102. Carleton, R.A., et al., *The Pawtucket Heart Health Program: community changes in cardiovascular risk factors and projected disease risk.* American Journal of Public Health, 1995. **85**(6): p. 777-785.

103. Schuit, A.J., et al., *Effect of 5-year community intervention Hartslag Limburg on cardiovascular risk factors.* Am J Prev Med, 2006. **30**(3): p. 237-42.

104. Taylor, C.B., et al., *Effect of Long-term Community Health Education on Body Mass Index: The Stanford Five-City Project.* American Journal of Epidemiology, 1991. **134**(3): p. 235-249.

105. Economos, C.D., et al., *Shape Up Somerville two-year results: a community-based environmental change intervention sustains weight reduction in children.* Prev Med, 2013. **57**(4): p. 322-7.

106. Chomitz, V.R., et al., *Healthy Living Cambridge Kids: A Community-based Participatory Effort to Promote Healthy Weight and Fitness.* Obesity, 2010. **18**(S1): p. S45-S53.

107. Sanigorski, A.M., et al., *Reducing unhealthy weight gain in children through community capacity-building: results of a quasi-experimental intervention program, Be Active Eat Well.* Int J Obes (Lond), 2008. **32**(7): p. 1060-7.

108. Kremer, P., et al., *Reducing unhealthy weight gain in Fijian adolescents: results of the Healthy Youth Healthy Communities study.* Obesity Reviews, 2011. **12**: p. 29-40.

109. Millar, L., et al., *Reduction in overweight and obesity from a 3-year community-based intervention in Australia: the 'It's Your Move!' project.* Obes Rev, 2011. **12 Suppl 2**: p. 20-8.

110. Fotu, K.F., et al., *Outcome results for the Ma'alahi Youth Project, a Tongan community-based obesity prevention programme for adolescents.* Obes Rev, 2011. **12 Suppl 2**: p. 41-50.

111. Taylor, R.W., et al., *APPLE Project: 2-y findings of a community-based obesity prevention program in primary school age children.* Am J Clin Nutr, 2007. **86**(3): p. 735-42.

112. Balk, E.M., et al., *Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force.* Annals of Internal Medicine, 2015. **163**(6): p. 437-51.

113. Brand, T., et al., *What works in community-based interventions promoting physical activity and healthy eating? A review of reviews.* Int J Environ Res Public Health, 2014. **11**(6): p. 5866-88.

114. Faith, M.S., et al., *Toward the reduction of population obesity: macrolevel environmental approaches to the problems of food, eating, and obesity.* Psychol Bull, 2007. **133**(2): p. 205-26.

115. Stephens, S.K., L.J. Cobiac, and J.L. Veerman, *Improving diet and physical activity to reduce population prevalence of overweight and obesity: an overview of current evidence.* Preventive Medicine, 2014. **62**: p. 167-78.

116. Kiraly, C., et al., *Applying Ecological Frameworks in Obesity Intervention Studies in Hispanic/Latino Youth:: A Systematic Review.* Hispanic Health Care International : The Official Journal of The National Association of Hispanic Nurses. **15**(3): p. 130-142.

117. Crockett, R.A., et al., *Nutritional labelling for healthier food or non-alcoholic drink purchasing and consumption.* Cochrane Database of Systematic Reviews, 2018(2).

118. Rose, G., *Sick individuals and sick populations.* International Journal of Epidemiology, 2001. **30**(3): p. 427-432.

119. Luckner, H., J.R. Moss, and C.A. Gericke, *Effectiveness of interventions to promote healthy weight in general populations of children and adults: a meta-analysis.* European Journal of Public Health, 2012. **22**(4): p. 491-7.

120. Calancie, L., et al., *Nutrition-related policy and environmental strategies to prevent obesity in rural communities: a systematic review of the literature, 2002-2013.* Preventing Chronic Disease, 2015. **12**: p. E57.

121. Gao, Y., S. Griffiths, and E.Y. Chan, *Community-based interventions to reduce overweight and obesity in China: a systematic review of the Chinese and English literature.* J Public Health (Oxf), 2008. **30**(4): p. 436-48.

122. Beauchamp, A., et al., *The effect of obesity prevention interventions according to socioeconomic position: a systematic review.* Obesity Reviews, 2014. **15**(7): p. 541-54.

CHAPTER 6 - REFERENCES

1. International Diabetes Federation, *IDF Diabetes Atlas, 8th edition, Brussels, Belgium.* International Diabetes Federation, 2017.
2. NHS England, Accessed on 11th December 2017 on https://www.england.nhs.uk/diabetes/diabetes-prevention/, NHS Diabetes Prevention Programme.
3. The Community Guide, *Diabetes Prevention and Control: Combined Diet and Physical Activity Promotion Programmes to Prevent Type 2 Diabetes Among People at Increased Risk. Atlanta, GA.* Accessed on 19th April 2015 at www.thecommunityguide.org/diabetes/supportingmaterials/SScombineddietandpa-econ.html
4. Diabetes Australia, *Information on prevention programmes.* Accessed on 21st June 2016 on https://www.diabetesaustralia.com.au/prevention
5. Rose, G., *Sick individuals and sick populations.* International Journal of Epidemiology, 2001. **30**(3): p. 427-432.
6. Pan, X.R., et al., *Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study.* Diabetes Care, 1997. **20**(4): p. 537-44.
7. Lindstrom, J., et al., *The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity.* Diabetes Care, 2003. **26**(12): p. 3230-6.
8. Ramachandran, A., et al., *The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1).* Diabetologia, 2006. **49**(2): p. 289-97.
9. Knowler, W.C., et al., *Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin.* N Engl J Med, 2002. **346**(6): p. 393-403.
10. Roberts, S., et al., *Economic evaluation of type 2 diabetes prevention programmes: Markov model of low- and high-intensity lifestyle programmes and metformin in participants with different categories of intermediate hyperglycaemia.* BMC Medicine, 2018. **16**(1): p. 16.
11. Icks, A., et al., *Clinical and cost-effectiveness of primary prevention of Type 2 diabetes in a 'real world' routine healthcare setting: model based on the KORA Survey 2000.* Diabet Med, 2007. **24**(5): p. 473-80.

12. Jacobs-van der Bruggen, M.A., et al., *Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modeling study.* Diabetes Care, 2007. **30**(1): p. 128-34.
13. Noble, D., et al., *Risk models and scores for type 2 diabetes: systematic review.* BMJ, 2011. **343**.
14. Public Health England, *NHS Diabetes Prevention Programme (NHS DPP) Non-diabetic hyperglycaemia.* Accessed on 11/11/2016 on https://www.gov.uk/government/publications/nhs-diabetes-prevention-programme-non-diabetic-hyperglycaemia 2015.
15. Balk, E.M., et al., *Combined Diet and Physical Activity Promotion Programs to Prevent Type 2 Diabetes Among Persons at Increased Risk: A Systematic Review for the Community Preventive Services Task Force.* Annals of Internal Medicine, 2015. **163**(6): p. 437-51.
16. Roberts S, P.L., Chen J, Hirst J, Rutter H, Greenhalgh T, *Efficacy of population-wide diabetes and obesity prevention programmes: an overview of systematic reviews and meta-analysis of impact on BMI.* Submitted for publication, 2018.
17. Breeze, P.R., et al., *Cost-effectiveness of population-based, community, workplace and individual policies for diabetes prevention in the UK.* Diabet Med, 2017. **34**(8): p. 1136-1144.
18. Cecchini, M., et al., *Tackling of unhealthy diets, physical inactivity, and obesity: health effects and cost-effectiveness.* The Lancet, 2010. **376**(9754): p. 1775-1784.
19. Foresight., *Tackling obesities: future choices.* Accessed on 11th November 2016 at http:// www.bis.gov.uk/foresight/our-work/projects/published-projects/ tackling-obesities, 2007.
20. NICE, *Guide to the Technology Appraisal Process.* Accessed on 27.10.2016 at https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance., 2013.
21. World Obesity Federation. *Relative risk Assessments IASO; Prepared for DYNAMO-HIA project*. Available from: http://www.worldobesity.org/site_media/uploads/Appendix_Relative_Risk_Assessments_IASO.pdf; http://www.worldobesity.org/what-we-do/policy-prevention/projects/eu-projects/dynamohiaproject/estimatesrrperunitbmi/.
22. Office of National Statistics, *Population estimates for England, Wales, Northern Ireland and Scotland.* 2014.
23. Office of National Statistics, *Conceptions in England and Wales.* 2015.
24. Office of National Statistics, *Family spending in the UK: Financial Year ending March 2016.* Accessed on 31st August 2017 at

https://www.ons.gov.uk/peoplepopulationandcommunity/personalandhouseholdfinances/expenditure/bulletins/familyspendingintheuk/financialyearendingmarch2016#main-points, 2016.

25. UK Data Service. Health Survey for England 2003-2016. Accessed on 31st August 2017 at https://discover.ukdataservice.ac.uk/series/?sn=2000021. .

26. Smolina, K., et al., *Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. Corrected data on incidence and mortality in 2013 at http://www.bmj.com/content/347/bmj.f7379.abstract.* BMJ, 2012. **344**: p. d8059.

27. British Heart Foundation, *Cardiovascular Disease Statistics 2014*. 2015.

28. Office for National Statistics, *Deaths Registrations Summary Statistics, England and Wales*. 2014.

29. Laires, P.A., et al., *Cost-effectiveness of adding ezetimibe to atorvastatin vs switching to rosuvastatin therapy in Portugal.* J Med Econ, 2015. **18**(8): p. 565-72.

30. National Health Service, *2012-13 programme budgeting PCT benchmarking tool*. 2013.

31. British Heart Foundation, *Stroke Statistics 2009*. 2009.

32. Rivero-Arias, O., et al., *Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome.* Med Decis Making, 2010. **30**(3): p. 341-54.

33. Health and Social Care Information Centre, *Health Survey for England 2012*. 2012.

34. Sullivan, P.W., et al., *Catalogue of EQ-5D scores for the United Kingdom.* Med Decis Making, 2011. **31**(6): p. 800-4.

35. Polder, J.J., et al., *Age-specific increases in health care costs.* Eur J Public Health, 2002. **12**(1): p. 57-62.

36. NHS Digital. *National Diabetes Audit 2015/2016*. 2017; Available from: http://www.content.digital.nhs.uk/catalogue/PUB23241.

37. International Diabetes Federation, *Diabetes Atlas*. 2014.

38 Gauke D. Budget. London: HM Treasury, 2016

38. Bernell, B., *The history and impact of the New York City menu labeling law.* Food Drug Law J, 2010. **65**(4): p. 839-72, iii.

39. Wendt M, T.J., *Economic Research Report Number 118. The Effect of Food and Beverage Prices on Children's Weights.* Economic Research Service, United States Department of Agriculture, 2011.

40. Briggs, A.D.M., et al., *Overall and income specific effect on prevalence of overweight and obesity of 20% sugar sweetened drink tax in UK: econometric and comparative risk assessment modelling study.* BMJ : British Medical Journal, 2013. **347**.
41. Restrepo, B.J., *Calorie Labeling in Chain Restaurants and Body Weight: Evidence from New York.* Health Economics, 2017. **26**(10): p. 1191-1209.
42. Deb P, V.C., *Who benefits from calorie labelling? An analysis of its effects on Body Mass.* National Bureau of Economic Research, 2016. **Working Paper 21992**(Accessed on 16th December 2017 at http://www.nber.org/papers/w21992).
43. Geliebter, A., et al., *Supermarket discounts of low-energy density foods: effects on purchasing, food intake, and body weight.* Obesity (Silver Spring), 2013. **21**(12): p. E542-8.
44. Kennedy, B.M., et al., *The "Rolling Store:" an economical and environmental approach to the prevention of weight gain in African American women.* Ethn Dis, 2009. **19**(1): p. 7-12.
45. Gittelsohn, J., et al., *A food store-based environmental intervention is associated with reduced BMI and improved psychosocial factors and food-related behaviors on the Navajo nation.* J Nutr, 2013. **143**(9): p. 1494-500.
46. Schuit, A.J., et al., *Effect of 5-year community intervention Hartslag Limburg on cardiovascular risk factors.* Am J Prev Med, 2006. **30**(3): p. 237-42.
47. Carleton, R.A., et al., *The Pawtucket Heart Health Program: community changes in cardiovascular risk factors and projected disease risk.* American Journal of Public Health, 1995. **85**(6): p. 777-785.
48. Brownell , K.D., et al., *The Public Health and Economic Benefits of Taxing Sugar-Sweetened Beverages.* New England Journal of Medicine, 2009. **361**(16): p. 1599-1605.
49. *Cost of menu labelling.* Accessed on 25th March 2018 at https://cspinet.org/resource/cost-menu-labeling, 2015.
50. Ronckers, E.T., et al., *Costs of the 'Hartslag Limburg' community heart health intervention.* BMC Public Health, 2006. **6**(1): p. 51.
51. Vemer, P., et al., *AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users.* Pharmacoeconomics, 2016. **34**: p. 349-361.
52. EConDA,, *Work package 7: Model validation.* Accessed on 25th February 2018 on http://www.econdaproject.eu/publications_21_2382981409.pdf, 2015.
53. Diabetes UK, *Diabetes Prevalence 2016.* Accessed on 3rd March 2018 at https://www.diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevalence-2016, November 2016.

54. Hex, N., et al., *Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs.* Diabet Med, 2012. **29**(7): p. 855-62.

55. http://eppi.ioe.ac.uk/costconversion/default.aspx. Accessed on the 20th August 2018

56. National Institute of Health and Care Excellence. Methods for the development of NICE's public health guidance (third edition). 2012. Accessed on 23rd June 2019 at https://www.nice.org.uk/process/pmg4/chapter/introduction#framework-for-public-health-guidance

REFERENCES – CHAPTER 7:

1. Yudkin J, Montori VM. The epidemic of pre-diabetes: the medicine and the politics. *BMJ.* 2014; 349: g4485
2. Baum A, Scarpa J, Bruzelius E, Tamler R, Basu S, Faghmous J. Targeting weight loss interventions to reduce cardiovascular complications of type 2 diabetes: a machine learning-based post-hoc analysis of heterogeneous treatment effects in the Look AHEAD trial. *Lancet Diabetes Endocrinol*. 2017 Oct;5(10):808-815
3. Carpiano RM. Come take a walk with me: the 'go-along' interview as a novel method for studying the implications of place for well-being. *Health Place.* 2009 Mar 15(1):263-72
4. NHS England and NHS Improvement. Long Term Plan for the NHS. January 2019
5. Gauke D. Budget. London: HM Treasury, 2016
6. Department of Health and Social Care. Childhood Obesity: a plan for action. June 2018
7. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V, Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006; 49:289-97.
8. Bollinger B, Leslie P, Sorensen A. Calorie posting in chain restaurants. Am J-Econ Polic. 201;3(1);91-128
9. Review of Amsterdam's Healthy Weight Programme, 2011-2017. Accessed on 30th March 2019 on https://www.amsterdam.nl/sociaaldomein/blijven-wij-gezond/amsterdam-healthy/
10. NHS England. Five Year Forward View. October 2014