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Opportunities for preventing diabetes and its cardiovascular complications

A modelling approach

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Abstract

Opportunities for preventing diabetes and its cardiovascular complications: a modelling approach

If interventions aimed to reduce overweight and promote physical activity would be implemented on a national scale in the Netherlands, between 1% and 2% of new cases of diabetes would be prevented over a 20-year period. More intensive treatment of persons with diabetes would prevent 5% to 10% of new cases of macrovascular complications. In order to prevent the burden of disease due to diabetes, prevention is crucial.

In this study the long-term efficacy of various interventions in preventing diabetes and its complications was investigated. In addition the costs and cost-effectiveness of these interventions were evaluated. This was done with the help of a computer model that was designed to track the evolution of the Dutch population over time, with regard to risk factors, chronic diseases and mortality.

Reducing the prevalence of overweight is the most powerful tool in preventing diabetes. As the interventions currently available allow the realisation of not more than a small part of the potential health gains, it is mandatory to continue to invest in identifying and developing effective measures to loose weight in a sustainable manner. Smoking cessation does not contribute to preventing diabetes. But, of course, it does prevent other diseases. In treating indivuals with diabetes, interventions aimed at lowering cholesterol and blood pressure result in greater health gains than intensifying blood sugar control.

Succesful prevention of diabetes and its complications leads to higher overall costs of care due to the fact that people live longer and as a consequence incur healthcare costs in life years gained. However, in all interventions evaluated, health gains justify the extra costs.

Key words:
diabetes, prevention, cardiovascular complications, chronic disease model

Rapport in het kort

Kansen voor de preventie van diabetes en de cardiovasculaire complicaties: een modelstudie

Als interventies gericht op verminderen van overgewicht en bevorderen van lichamelijke activiteit op landelijk schaal worden ingevoerd, zouden de komende 20 jaar 1 à 2% van de nieuwe gevallen van diabetes kunnen worden voorkomen. Daarnaast zouden de komende 20 jaar 5 à 10% van de nieuwe macrovasculaire complicaties bij mensen met diabetes kunnen worden voorkomen door intensievere behandeling. Preventie is essentieel om de toekomstige ziektelast van diabetes zoveel mogelijk te beperken.

Van verschillende maatregelen is berekend in welke mate zij bijdragen aan het voorkómen van diabetes of diabetescomplicaties op de lange termijn. Daarnaast zijn voor deze maatregelen de kosten en kosteneffectiviteit geschat. Hierbij is gebruikgemaakt van een computermodel dat in staat is de ontwikkelingen van de Nederlandse bevolking, voor wat betreft risicofactoren, chronische ziekten en sterfte, te volgen over de tijd.

Terugdringen van overgewicht is het belangrijkste wapen in het voorkomen van diabetes. Omdat met de bestaande interventies slechts een fractie van de mogelijke gezondheidswinst wordt gerealiseerd, moeten we blijven investeren in het identificeren en ontwikkelen van effectieve maatregelen om (blijvend) af te vallen. Stoppen met roken draagt niet bij aan preventie van diabetes maar wel aan preventie van andere chronische aandoeningen. Bij mensen met diabetes levert behandeling gericht op cholesterol- en bloeddrukverlaging een grotere bijdrage aan de preventie van macrovasculaire complicaties dan verder intensiveren van bloedsuikerbehandeling.

Succesvolle preventie van diabetes en diabetescomplicaties leidt tot hogere totale zorgkosten doordat mensen langer leven en zorgkosten maken in gewonnen levensjaren. Echter, voor alle bestudeerde maatregelen geldt, dat de gezondheidswinst de extra kosten rechtvaardigt.

Trefwoorden: diabetes, preventie, cardiovasculaire complicaties, modellering, kosteneffectiviteit, Chronische Ziekten Model

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Voorwoord

Dit rapport werd geschreven in het kader van Programma 2 ‘Beleidsondersteuning Volksgezondheid en Zorg’ en heeft betrekking op kennisvraag 4 ‘Diabetes’ (2007).

Diabetes is al sinds enkele jaren een speerpunt van het beleid van het Ministerie van Volksgezondheid, Welzijn en Sport. Het beleidskader is vastgelegd in de nota ‘Langer gezond leven’ en in de beleidsbrief aan de Tweede Kamer ‘kiezen voor gezond leven’. Via het Nationaal Diabetes Actieprogramma wil het ministerie tot een samenhangende aanpak komen om de sterke toename in het aantal mensen met diabetes tegen te gaan. De directie Publieke Gezondheid heeft het RIVM verzocht om de kosteneffectiviteit van diverse preventiemaatregelen door te rekenen. Het huidige rapport beschrijft de effecten op de volksgezondheid en de daarmee gepaard gaande kosten van diverse scenarios gericht op het voorkomen van diabetes of diabetescomplicaties. Het is een interessant en informatief rapport geworden dat een belangrijke basis kan bieden voor de verdere uitwerking van het Nationaal Diabetes Actieprogramma.

Wij zijn de volgende personen zeer erkentelijk voor het becommentariëren van (delen van) een eerdere versie van dit rapport: dr. P.H.M. van Baal, mw. dr. H.C. Boshuizen, mw. dr. ir. W.J.E. Bemelmans.

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Samenvatting

Ontstaan en verloop van type 2-diabetes worden beïnvloed door een aantal risicofactoren. Sommige hebben vooral effect op het krijgen van de ziekte (incidentie), andere juist op het optreden van complicaties. Door het ontwikkelen en toepassen van maatregelen om deze risicofactoren te beïnvloeden, kan de ziektelast van diabetes worden verminderd.

In dit rapport onderzoeken we in hoeverre bepaalde maatregelen, gericht op het bestrijden van risicofactoren, kunnen bijdragen aan het voorkómen van diabetes enerzijds of het voorkómen van het optreden van complicaties bij mensen met diabetes, anderzijds. Tevens is gekeken naar de kosten en kosteneffectiviteit van de maatregelen.

De studie is uitgevoerd met behulp van het Chronische Ziekten Model (CZM) dat op het RIVM is ontwikkeld. Dit model simuleert de ontwikkelingen van de Nederlandse bevolking voor wat betreft risicofactoren, chronische ziekten en sterfte over de tijd.

Uitgangspunt van de analyses is steeds een specifieke risicofactor. Voor iedere risicofactor is eerst gekeken naar de theoretisch te behalen gezondheidswinst, bij volledige verwijdering van de risicofactor onder de bevolking in een theoretisch ‘maximum scenario’. Vervolgens is een haalbaar geachte interventie gesimuleerd in een ‘realistisch scenario’. In het realistische scenario is bijvoorbeeld rekening gehouden met het bereik van een interventie (welk deel van de populatie), bewezen effectiviteit en interventiekosten.

Deel 1 van dit rapport beschrijft een aantal preventieve interventies, gericht op het terugdringen van overgewicht, lichamelijke inactiviteit en roken, met als doel om het ontstaan van diabetes te vookomen. De scenario’s worden gesimuleerd voor een cohort, representatief voor de Nederlandse bevolking in de leeftijdsgroep 20 tot 80 jaar in 2005 (n=11,8 miljoen). De simulatie stopt als iedereen in het cohort is overleden. De uitkomsten voor de theoretisch maximale en realistische scenario’s worden vergeleken met een referentiescenario, waarin de huidige situatie (zonder interventie) wordt gesimuleerd. Het verwachte aantal nieuwe gevallen van diabetes in de Nederlandse bevolking in het referentiescenario tot aan 2025 is ongeveer 1,7 miljoen.

Als iedereen een gezond gewicht zou hebben en voldoende zou bewegen (maximum scenario), zou het aantal nieuwe gevallen van diabetes in Nederland in de komende 20 jaar ongeveer 50% minder zijn. Daarvoor zouden mensen met ernstig overgewicht (obesitas) echter gemiddeld 25 kilo moeten afvallen en mensen met overgewicht 10 kilo. Uitgaand van feitelijke ervaring met leefstijlinterventie is een gewichtsverlies van gemiddeld 0,5 tot 3,0 kilo haalbaar, afhankelijk van de intensiteit van de interventie. In de realistische scenario’s zijn de effecten op het voorkómen van diabetes dan ook veel kleiner dan in het maximum scenario; 2% minder nieuwe diabetesgevallen in de komende 20 jaar bij een combinatie van maatregelen gericht op de gehele gemeenschap en op mensen met obesitas.

In tegenstelling tot overgewicht, is er een relatief zwakke invloed van roken op het ontstaan van diabetes. Als niemand zou roken (maximum scenario), zou het aantal nieuwe gevallen van diabetes in Nederland in de komende 20 jaar ongeveer 3% minder zijn. Net als blijvend afvallen is blijvend stoppen met roken erg moeilijk en bovendien zijn de negatieve effecten van roken niet zomaar verdwenen. Een realistische inschatting van het effect van maatregelen om stoppen met roken te bevorderen, is dat dit nauwelijks effect zal hebben op de incidentie van diabetes. Wel is het natuurlijk zo, dat anti-rookmaatregelen belangrijk blijven voor de preventie van andere chronische ziekten (hart- en vaatziekten en kanker). Tegenover het relatief bescheiden effect van de interventies gericht op

gewichtsvermindering en stoppen met roken staat dat de kosten niet hoog zijn. De kosteneffectiviteitratio's zijn heel gunstig.

Deel 2 van dit rapport beschrijft interventies gericht op betere controle van bloedsuiker, cholesterol en bloeddruk bij mensen met diabetes, met als doel het voorkomen van macrovasculaire complicaties (hart- en vaatziekten). In tegenstelling tot deel 1, waarin leefstijlaanpassingen centraal staan, gaat het hier om farmacologische interventies. De scenario's worden gesimuleerd voor een cohort, representatief voor mensen met diabetes in Nederland in de leeftijdsgroep 30-75 jaar, in 2005 (n=398.000). Bij voortduren van de huidige situatie zullen in dit cohort tot 2025 naar verwachting 63.000 beroertes optreden en 220.000 gevallen van hart- en vaatziekten. In de nieuwste richtlijnen evenals de Nederlandse Zorgstandaard voor diabetes (www.diabetesfederatie.nl), wordt aangeraden om alle risicofactoren voor het krijgen van diabetescomplicaties zoveel mogelijk te behandelen. Hoewel het dus om een totaal risicoprofiel gaat, hebben we de behandelingen gericht op optimaliseren van bloedsuiker, cholesterol en bloeddruk ook afzonderlijk geanalyseerd om een beeld te krijgen van de relatieve bijdrages van de behandelingen gericht op individuele risicofactoren.

Als alle mensen met diabetes in de laagste risicocategorie zouden zijn van hetzij bloedsuiker, hetzij cholesterol, hetzij bloeddruk, (maximum scenario's) zou dat een vermindering betekenen in het optreden van hartziekten met respectievelijk 7%, 20% en 33% over een periode van 20 jaar. Voor beroertes zou dat respectievelijk 10%, 8% en 47% zijn. Optimaal instellen van de bloeddruk bij diabeten biedt de grootste potentiële winst. Hiervan is ongeveer 10% te realiseren (3% reductie in hartziekten en 5% voor beroertes) wanneer de helft van alle nu nog onbehandelde patiënten antihypertensiva zou krijgen (realistisch scenario). Een grotere winst is mogelijk, als daarnaast de patiënten die al behandeld worden met antihypertensiva een meer optimale medicatie zouden krijgen. De verwachte reductie in complicaties, wanneer meer mensen met diabetes cholesterolverlagende medicatie zouden krijgen, is ook 3% voor hartziektes en 5% voor beroertes. In het realistische scenario voor bloedsuiker worden alle patiënten die ondanks behandeling met twee orale bloedsuikerverlagende middelen toch een te hoog bloedsuiker hebben, overgeschakeld op insuline. In Nederland zijn de patiënten over het algemeen relatief goed 'ingesteld'. Het gaat daarom slechts om een klein deel van de patiënten (12%). Bij dit scenario wordt in de komende 20 jaar 1% van de hartziekten en 1% van de beroertes voorkomen. Het verwachte effect van een (realistische) gecombineerde aanpak van bloedsuiker, cholesterol en bloeddruk is bij benadering gelijk aan de som van de behandelingen gericht op de individuele risicofactoren.

Succesvolle preventie van diabetes en diabetescomplicaties leidt tot hogere totale zorgkosten doordat mensen langer leven en zorgkosten maken in gewonnen levensjaren. Echter, voor alle bestudeerde maatregelen geldt dat de gezondheidswinst de extra kosten rechtvaardigt. Verder onderzoek is gewenst naar kosten en effecten van leefstijlinterventies bij mensen met diabetes en de effecten van verschillende preventieve maatregelen op microvasculaire complicaties. Andere aspecten die aandacht verdienen zijn effecten van interventies in de dagelijkse praktijk, langetermijneffecten van interventies, determinanten van therapietrouw, bijwerkingen van medicatie en de impact van (meervoudig) medicijngebruik op de kwaliteit van leven.

Concluderend, om diabetes te voorkomen verdient het de aanbeveling om maatregelen gericht op gewichtsvermindering zoveel mogelijk te bevorderen. Maatregelen gericht op stoppen met roken voorkomen geen diabetes maar zijn wel belangrijk voor het terugdringen van andere chronische ziekten. De huidige maatregelen gericht op gedragsverandering leveren een fractie op van de potentiële gezondheidswinst. Het is daarom van belang (nieuwe) effectieve leefstijlinterventies te identificeren en te optimaliseren. Wat betreft preventie van macrovasculaire complicaties bij mensen met diabetes,

biedt behandeling van cholesterol en bloeddruk meer gezondheidswinst dan een verdere intensivering van de bloedglucosebehandeling bij mensen die matig zijn ingesteld. Vanuit dit perspectief dient er terughoudendheid betracht te worden in het overzetten van patiënten op insuline. Mede omdat overschakelen op insuline behoorlijk ingrijpend kan zijn in het dagelijkse leven van de patiënt, en deze behandeling relatief duur is.

1 Introduction

In the Netherlands, 600,000 persons had diagnosed diabetes in 2003. Due to aging of the population and unfavourable lifestyle trends, this number is expected to increase to nearly a million in 2025 [57]. Diabetes has a large impact on quality of life, while the remaining life expectancy for a 45 year old person with diabetes is reduced by approximately ten years compared to a healthy person [57]. Furthermore, the health care burden of diabetes is high. For example, the direct health care costs for diabetes and related complications in the year 2003 were estimated at 735 million euro, which is 1.3% of the total Dutch health care budget [57].

Several modifiable risk factors, such as obesity, physical inactivity and, to a lesser degree, smoking, play an important role in the development of type 2 diabetes. If favourable changes in these lifestyle factors are achieved, the disease can be prevented or delayed. Moreover, favourable lifestyle changes may also decrease the incidence of other chronic diseases such as cardiovascular disease and cancer. Prevention can either be targeted at the general population or at high risk groups. In this report we use the terms 'universal prevention' and 'selective prevention'. Universal prevention targets the entire population and aims to improve lifestyle related health. Selective prevention aims to identify specific high risk groups and to conduct targeted prevention programs to improve health.

However, many persons already have diabetes and many among them will develop microvascular complications such as neuropathy, retinopathy or nephropathy as well as macrovascular complications such as coronary heart disease (CHD) and stroke. Cardiovascular disease is one of the most frequent complications of diabetes and the predominant cause of death among persons with diabetes [23]. In order to prevent or delay diabetes complications, treatment for persons with diabetes should be intensive and multifactorial. This implies aiming at a healthy lifestyle (weight, activity and smoking) of the patient in combination with good glycaemic control and appropriate treatment of other important cardiovascular risk factors such as dislipidemia and hypertension. At this moment not all persons with diabetes are treated according to the most recent guidelines and thus current care is not optimal [42]. The term 'care-related' prevention will be used throughout this report. Care-related prevention is an essential and integral part of high quality care for persons with (multiple) health problems. It aims to prevent, reduce or delay complications and to support self-management.

Our purpose in this report is to explore the potential effects of measures aimed to prevent the development of diabetes or macrovascular complications in persons with diabetes. Although many trials have been conducted to evaluate the efficacy of various preventive interventions, these trials are generally carried out under well-controlled conditions, in selected populations and with a limited duration of follow-up. Thus, although these studies may show favourable effects on risk factor levels or short-term disease incidence, the long-term consequences for morbidity, mortality and health care costs, in the population as a whole, are unclear. Therefore we used a modeling approach to calculate the long-term health effects for different prevention scenarios. Furthermore, the long-term consequences for health care costs and the cost-effectiveness of several interventions were explored. The results from this report will hopefully provide meaningful insights into the extent to which specific measures may contribute to minimizing the growing burden of diabetes and diabetes related complications.

In the methods section we describe the basic structure and content of the Chronic Diseases Model (CDM), the populations of interest and the scenarios considered. Furthermore, we will describe the general approach used in chapter one to six. Part one of the report deals with the universal and selective prevention of diabetes through measures aimed at weight loss and increased activity (chapter 1) and

interventions to promote smoking cessation (chapter 2). Part two deals with the prevention of macrovascular complications in persons with diabetes through intensified medical care (care-related prevention). We will address more intensive control of blood glucose (chapter 3), cholesterol-lowering treatment (chapter 4), antihypertensive treatment (chapter 5) and a combination of these (chapter 6). Part three gives a summary of the main findings and a discussion of methodological issues and implications (chapter 7).

This report is the first of several publications that explore the costs and effects of different scenarios for prevention and treatment of diabetes.

2 General description of methods used

2.1 The Chronic Disease Model (CDM)

The CDM is a Markov-type, multistate transition model, developed at the Dutch National Institute for Public Health and the Environment (RIVM) and can be used to model developments in the Dutch general population [15 4 28 16 27 68]. In short, the model describes the development over time of demography, risk factor prevalence, disease incidence and mortality in the Dutch population. A representation of the associations between risk factors and diseases in the CDM, relevant for this report, is given in Figure 1 below.

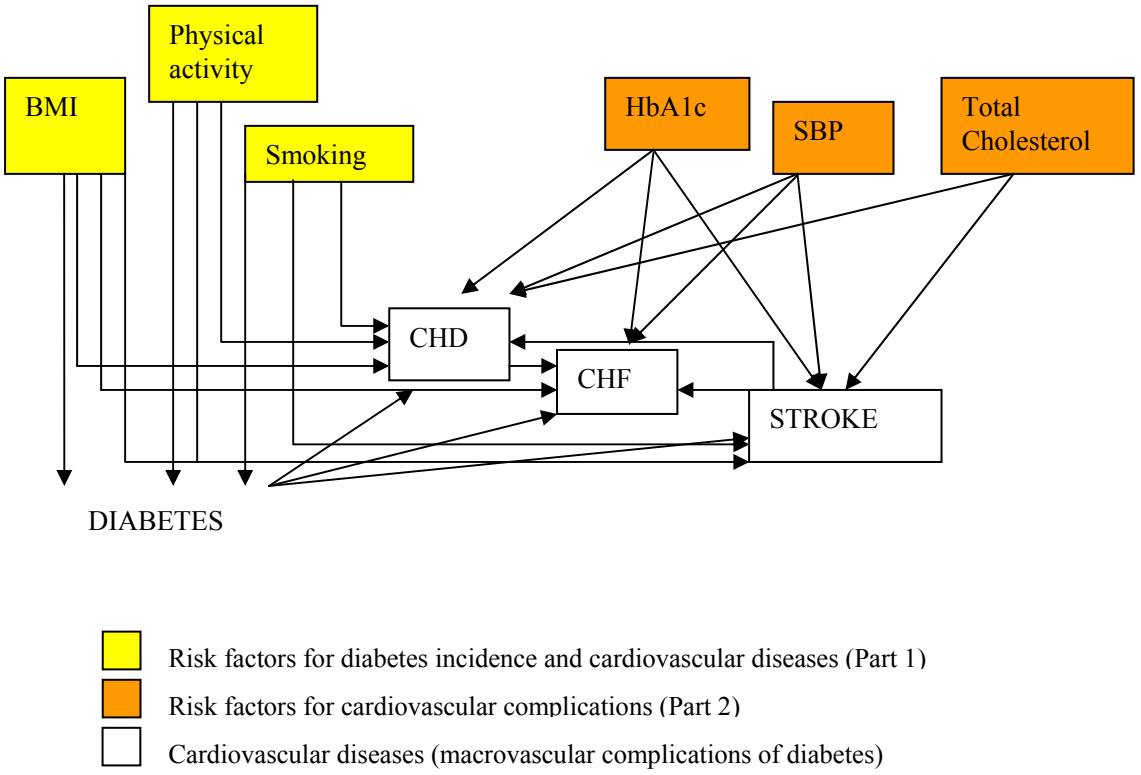

Figure 1 Schematic representation of the interrelations between the relevant risk factors and diseases included in the Chronic Disease Model

BMI=Body Mass Index, HbA1c=Hemoglobin A1c (blood glucose control), SBP=Systolic Blood Pressure, CHD= Coronary Heart Disease, CHF=Chronic Heart Failure

The CDM can also be used for projections, confined to the Dutch diabetes population. A justification of the input data used for diabetes has been given by Baan et al. [4]. It is important to note that microvascular diabetes complications are not included in the model. Furthermore, the model does not include recurrent cardiovascular events. Thus, a person who survives a stroke may develop another cardiovascular complication but not a second stroke.

The associations between risk factors and disease incidence (relative risks) that are used as input parameters in the CDM are based on international cohort- and intervention studies. Input parameters for risk factor- and disease prevalence, mortality rates and transition rates between risk factor classes apply to the Dutch population. All data are age- and sex specific [74].

The Global and Dutch Burden of Disease studies were used to derive the parameters needed to compute health effects in terms of quality-adjusted life-years (QALYs) [74 49 67 43 73]. Health care costs in the model are based on the Dutch costs of illness study 2003 [65] (More details about costs and economic evaluations with the CDM can be found in two articles by Van Baal et al. [74 72]). The price year for all costs is 2005. Cost-effectiveness ratios (CER) for the interventions will be expressed as costs (intervention costs + total health care costs) per quality adjusted life year gained. Because we use a life-time perspective, costs and effects (QALYs) are discounted with 4.0% and 1.5%, respectively as recommended in Dutch guidelines. This means that future costs (and effects) have less weight than costs and effects within the first years. For example, costs count for 100% in year 1, for 47% in year 20 and for 7% in year 70, while effects count for 100% in year 1, for 75% in year 20 and for 36% in year 70.

Information about the CER of an intervention, besides other considerations, may be helpful to policy makers in deciding whether an intervention should be implemented. The threshold value for cost-effectiveness differs between countries. In the Netherlands, (preventive) interventions with a CER under €20,000 /QALY are generally considered cost-effective. The World Health Organization bases the CER threshold on the gross domestic product (GDP). Interventions with a CER lower than the GDP per capita (in the Netherlands 30,000 euro in 2004, CBS statline) are considered very cost-effective, interventions with CER one to three times GDP are considered cost-effective and interventions with CER more than three times GDP (about €90,000 /QALY in the Netherlands) are considered not cost-effective.

2.2 Simulation cohorts

The simulation cohort used to model the effects for universal and selective prevention resembles the Dutch population, 20 to 80 years, in 2005 (n=11.8 million). We use the entire adult population because universal prevention may have an impact on all adults. The simulation cohort used to model the effects of care-related prevention resembles the Dutch diabetes population, 30 to 75 years, in 2005 (n=398.000). Here the age-range is confined to 30-75 because there are few young persons with diabetes who will require pharmacological treatment as considered in this report, and information about risk factor distribution and treatment effects, needed for the calculations, is limited for persons over the age of 75. Characteristics for both cohorts are displayed in Table 1.

Table 1 Characteristics of the 'general population' and the 'diabetes cohort'

	General population	Diabetes cohort
N	11.82 million	398 016
Age (range)	20-80 years	30-75 years
Men (%)	50	53
BMI 25 to 30 kg/m^2 (%)	36	41
BMI ≥30 kg/m^2 (%)	14	40
Current smokers (%)	29	25
Former smokers (%)	33	48
Moderately active (%)	35	27
Inactive (%)	10	14
Total cholesterol ≥ 6.5 mmol/l (%)	19	37
Systolic blood pressure ≥ 140 mmHg (%)	22	67
Coronary Heart Disease (%)	6	21
Stroke (%)	1	4
Hemoglobin A1c ≥ 8.5% (%)	-	15

2.3 Risk factors in the CDM

Body Mass Index (BMI) is categorized into three classes: normal (BMI<25 kg/m^2), overweight (BMI 25 to 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2). A higher BMI increases the risk for all cause mortality, diabetes, cardiovascular diseases, musculoskeletal disorders and cancers.

Physical activity is modeled as a discrete variable with three classes: active (30 minutes of activity of moderate intensity on at least five days of the week), moderately active (30 minutes of activity of moderate intensity on one to four days of the week) and inactive (less than one day a week of at least 30 minutes of moderate intensity activity). Low physical activity increases the risk for all cause mortality, diabetes, cardiovascular diseases, and cancers.

Smoking is modeled according to status as never smoker, former smoker or current smoker. Smoking increases the risk for all cause mortality, diabetes, cardiovascular diseases, COPD and cancers. In addition, time-dependency of relapse risk and relative risk decrease after smoking cessation have been incorporated into the model.

Blood glucose (HbA1c) is categorized into three classes: < 7.0%, 7.0% to 8.5% and ≥ 8.5%. A higher HbA1c increases the risk for cardiovascular diseases.

Cholesterol classes are defined based on the blood level of total cholesterol (TC): < 5 mmol/l, 5.0 to 6.5 mmol/l, 6.5 to 8.0 and ≥ 8.0 mmol/l. Patients with a higher level of total cholesterol have an increased risk for coronary heart disease (CHD). Furthermore, each TC level based category is further subdivided according to whether or not patients are being treated with cholesterol-lowering medication (mostly statins). Patients with cholesterol-lowering treatment have lower risks for CHD and stroke, compared to untreated patients with the same TC level [11].

Blood pressure classes are defined based on the level of systolic blood pressure (SBP): <120 mmHg, 120 to 140 mmHg, 140 to 160 mmHg and ≥ 160 mmHg. Patients with a higher blood pressure level have an increased risk for cardiovascular diseases. Again, each category is further divided according to whether or not patients are being treated with antihypertensive treatment. Patients with treatment have lower risks for cardiovascular diseases compared to untreated patients [70].

2.4 General approach

In this report we explore the potential effects of measures aimed to prevent the development of diabetes (universal and selective prevention) or aimed to prevent macrovascular complications in persons with diabetes (care-related prevention). Chapters one to six deal with specific risk factors for diabetes or diabetes complications. We use a similar approach in these chapters, to describe and explore the risk factors and preventive measures of interest. A description of this general approach is given below.

Firstly, each chapter starts with an introduction in which we describe: 1) the strength of the association between the risk factor and the associated disease (diabetes and/or cardiovascular disease); 2) the current prevalence of the risk factor in the Dutch population. Furthermore, we provide a brief overview, based on the international literature, of the current status of interventions targeted at the risk factor considered, with respect to its contents, target population, effectiveness and costs.

After this introduction we explore the theoretically maximum gain in health that could be achieved if the risk factor would be totally eliminated. This means that results for a reference scenario ('natural developments in the population') are compared to the results for a scenario where everybody is and stays in the lowest risk factor class for the risk factor considered. This hypothetical ideal will be referred to as the 'maximum scenario'. The health gains in these scenarios are determined by the size of the target population, the disease incidence rates in the population as a whole and the strength of the association between the risk factor and the disease (relative risk). For example, the maximum number of incident diabetes cases that would be prevented if everyody had a normal weight depends on by the number of people who are overweight, diabetes incidence rates in the general population and the strength of the association between body weight and diabetes development (i.e. the additional risk due to overweight). The purpose of these theoretical scenarios is to define the 'maximum space for improvement'. Although knowing the 'maximum space for improvement' provides meaningful insight, it is not realistic to assume that the maximum health gains, as derived from these theoretical scenarios, can be achieved. Several factors may limit the effect that can be reasonably attained in practice, such as the efficacy of an intervention as reported in intervention trials (how much weight loss is achieved on average through a lifestyle intervention) or the participation rate (how many people can be reached and how many can be expected to participate).

Thus, following the theoretical scenario, we define at least one realistic scenario. In these scenarios issues such as efficacy and participation rate are addressed as adequately as possible. Again, results are

compared to the reference scenario. In addition, the costs associated with the intervention are estimated. Evidence for the efficacy, participation rate and costs of interventions are derived from the international literature, but sometimes we rely on ad-hoc assumptions. We explore the impact of the particular assumptions by studying the results, when using alternative assumptions (sensitivity analyses).

After describing the maximum and realistic scenarios, we present the outcomes for health and health care costs as calculated with the CDM. We present the difference in cumulative number of incident cases of diabetes, stroke and coronary heart disease (CHD) between the reference scenario and the scenario of interest, as well as the effects on total numbers of life years lived by the (diabetes) cohort. For costs, we report differences in health care costs for diabetes and cardiovascular diseases between the reference scenario and the scenario of interest as well as differences in total health care costs. Total health care costs include costs for diabetes and cardiovascular disease but also costs for other diseases such as cancer and dementia. Cost-effectiveness ratios are provided for the realistic scenarios. Each chapter ends with a brief summary of the results.

2.5 Scenarios

An overview of all the scenarios presented in this report is given in Table 2. In the subsequent chapters the scenarios will be described in more detail. The realistic scenarios are based on actual interventions that have been reported in the (international) literature and for which there is sufficient evidence of effectiveness and costs. All scenarios describe results for closed cohorts. The model starts with the general cohort or diabetes cohort as described in Table 1, and follows this cohort until extinction.

Table 2 Overview of scenarios

Scenario	Assumptions
Part 1: Universal and selective prevention of diabetes	
1: Weight reduction and increased physical activity	
'Normal weight' scenario	All Dutch adults (20-80 years) normal weight (BMI < 25 kg/m^2)
'Normal weight and active' scenario	All Dutch adults (20-80 years) normal weight (BMI < 25 kg/m^2) and physically active
'Community-based intervention' scenario	80% of Dutch adults (20-80 years) are reached by a 5-year lifestyle program. Average weight loss is 0.5 kg. Ten percent of inactive persons become moderately active.
'Lifestyle program obese adults' scenario	10% of Dutch obese adults (= 1.4% of Dutch adults 20-80 years) participate in a 3-year lifestyle intervention. Average weight loss is 3 kg. Fifty percent of inactive persons become moderately active and ten percent of moderately active persons become active.
2: Smoking cessation	
'No smokers' scenario	All Dutch adults (20-80 years) are non-smokers
'Smoking cessation intervention' scenario	Combined public health and individual-based interventions
Part 2: Care-related prevention in persons with diabetes	
1: Intensified blood glucose treatment	
'Low blood glucose' scenario	All diabetes patients (30-75 years) have a HbA1c < 7.0%
'Intensified blood glucose treatment' scenario	Diabetes patients (30-75 years with HbA1c > 7.0) using two oral agents switch to insulin treatment
2: Cholesterol lowering treatment	
'Low cholesterol' scenario	All diabetes patients (30-75 years) have a total cholesterol < 5.0 mmol/l and are treated with statins
'Cholesterol treatment' scenario	Statin treatment for 50% of untreated diabetes patients (30-75 years) with total cholesterol > 5.0 mmol/l
3: Antihypertensive treatment	
'Low blood pressure' scenario	All diabetes patients (30-75 years) have a systolic blood pressure (SBP) < 120 mmHg and receive antihypertensive treatment
'Blood pressure treatment' scenario	Antihypertensive treatment for 50% of currently untreated diabetes patients (30-75 years) with SBP ≥ 140 mmHg.
4: Intensified multifactorial treatment	
'Low CVD-risk' scenario	All diabetes patients (30-75 years) are in the lowest risk factor classes for HbA1c, cholesterol and blood pressure
'Multifactorial treatment' scenario	Blood glucose-, cholesterol- and blood pressure treatment scenarios combined

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PART 1: UNIVERSAL AND SELECTIVE PREVENTION OF DIABETES

3 Weight loss and increased physical activity

The most important modifiable risk factor for diabetes is a high body weight [18 37]. Epidemiological studies have shown that with every one-unit increase in BMI, corresponding to a weight gain of approximately 3 kg, the risk of developing type 2 diabetes increases by approximately 10% to 30% [25]. The risk of developing diabetes for a severely overweight adult (< 50 years) is more than 10 times higher than for a person with a normal weight. Physical inactivity is also an important risk factor for diabetes [30 29 38 79 81]. Inactive persons have an approximately twofold risk for diabetes compared to active persons. A part of the protective effect of physical activity on diabetes incidence is explained by a lower BMI and a more favourable body composition. The remaining part, however, is independent of body weight and is associated with better glucose metabolism. (This 'remaining effect' of physical activity, independent from BMI, is used in the CDM).

In the Dutch population cohort in the model 51% has a normal weight, 36% is moderately overweight and 13% is obese at the start of the simulations (2005). With respect to physical activity, 55% is active, 35% is moderately active and 10% is inactive.

Effects of interventions aimed at weight loss and increased physical activity have been evaluated in different target populations. A large amount of data is available about the effects of interventions within the general population (community-based lifestyle programs) and within high risk groups [34 77 48 6]. Generally, treatment and follow-up duration are five years or less, although results after seven years were recently reported for the Finnish Diabetes Prevention Study [40].

Typically, community-based programs comprise mass media campaigns, and a range of activities to promote a healthy diet and physical activity in the general population. These programs have been conducted with varying results [77 5]. In general, effects on weight are modest, the largest effect was found in the Stanford Five City Project [69]. This study found that after 5 years, weight increase was 0.7 kg less in intervention communities compared to control regions (with an average weight of 1.3 kg in control regions). Most community-based programs fail to achieve substantial effects on physical activity, but some do achieve small reductions in the prevalence of physical inactivity [54 7].

Interventions to reduce weight and promote physical activity in persons at high-risk for developing diabetes (persons with obesity and abnormal glucose metabolism) are typically implemented in a health care setting and comprise dietary advice, exercise programs and/or behavior modification therapy for individuals or groups. These interventions can reduce diabetes risk with 50-60% [13 41]. Weight loss appears to be the primary factor resulting in reduced diabetes incidence. Subsequent analyses from the US Diabetes Prevention Program showed that, for every kilogram of weight loss the risk for developing diabetes was reduced by approximately 16%, while increased physical activity helped to sustain weight loss and reduced diabetes risk in those persons who did not lose weight [24 12]. With these interventions, average weight losses of approximately 4 to 6 kg can be achieved within one year [6]. However, the effects are generally smaller at longer term follow-up [48 13 83 66 41 14 53]. After three years effects on weight range from 1.9 kg [61] to 4.5 kg [13 14]. Intervention programs favorably affect physical activity as they have been shown to improve maximum oxygen uptake [14], increase the time spent on physical activities [13 41] and reduce physical inactivity [41].

3.1 Description of the lifestyle scenarios

'Normal weight' scenario

In this scenario we compare the outcomes for a Dutch cohort (20-80 years) in which everybody has a normal weight with the outcomes for a Dutch cohort (20-80 years) in the reference scenario.

'Normal weight and active' scenario

In this scenario we compare the outcomes for a Dutch cohort (20-80 years) in which everybody has a normal weight and, in addition, is physically active, with the outcomes for a Dutch cohort (20-80 years) in the reference scenario.

'Community-based intervention' scenario

In this scenario we calculate outcomes for a community-based lifestyle program with duration of five years, focusing on nutrition and exercise and targeted at the general population. The effects we assume are based on average results obtained in (international) trials [77 69 54].

We assume that the intervention reaches 80% of the Dutch adult population and that the intervention results in an average weight loss of 0.5 kg. Furthermore, we assume that 10% of the inactive persons become moderately active. Effects are achieved within the first year and maintained during and after the intervention period.

Intervention costs

Costs are based on a Dutch community based program 'Hartslag Limburg' (Heart Health Limburg) [62]. This program aimed to decrease the incidence of cardiovascular diseases in the general population. Total intervention costs for activities focusing on nutrition and physical activity for five years were approximately €6 per 20+ adult in the target area [60 33]. For 80% of Dutch adults (9.4 million), total costs for the 5-year intervention in our scenario were 56 million euro.

'Intervention program obese adults' scenario

In this scenario we project the outcomes for an intensive intervention focusing on diet and exercise, implemented in a health care setting, with duration of three years. The effects we assume are based on average results obtained in international trials [13]. We assume that 10% of the Dutch obese adults (20-80 year) participate in the intervention resulting in an average weight loss of 3 kg. Furthermore we assume that fifty percent of inactive persons become moderately active and 10% of moderately active persons become active. Effects are achieved within the first year and maintained during and after the intervention period.

Intervention costs

Costs are based on the Dutch 'Study on Lifestyle intervention and Impaired glucose tolerance Maastricht (SLIM)'. This lifestyle intervention aimed to improve lifestyle in overweight subjects with impaired glucose tolerance by means of 3-year dietary advice and an exercise program [51 50]. Intervention costs are estimated at €700 per participant, assuming that 50% of the intervention

participants participate in the exercise program [33]. Total costs for the 3-year intervention for 160,000 participants are 112 million euro.

3.2 Long-term effects on health outcomes

Reference scenario

The total number of new cases of diabetes that is expected in a Dutch cohort (20-80 years) over a period from 10 and 20 years starting in 2005 is 816,000 and 1.66 million, respectively. These and other health outcomes for each scenario are given in Table 3. Total life-years expected for the cohort (that is followed until extinction) is 416 million, meaning an average life-expectancy of a cohort member is 35.3 years (416 million/11.8 million). Average life-expectancy for a 40-year old person is 40.45 years.

Table 3 Effects of lifestyle interventions on the cumulative incidence of cardiovascular disease and diabetes

	10-years incidence (until 2015)	20-years incidence (until 2025)	80-years incidence (until 2085)
	Reference scenario: Dutch cohort 20-80 years (n=11.8 million)		
	expected number of (first) cases		
Diabetes	816 000	1.66 million	3.96 million
Stroke	452 000	1.00 million	3.14 million
CHD	1.35 million	2.97 million	8.93 million
	'Normal weight' scenario		
	number of (first) cases prevented:		
Diabetes	379 000 (46%)	709 000 (43%)	1.17 million (30%)
Stroke	21 000 (4.4%)	37 000 (3.6%)	+70 000 (2.2%)
CHD	151 000 (11%)	322 000 (11%)	598 000 (6.7%)
	'Normal weight and active' scenario		
	number of (first) cases prevented:		
Diabetes	416 000 (51%)	785 000 (47%)	1.33 million (33%)
Stroke	102 000 (22%)	221 000 (22%)	564 000 (18%)
CHD	257 000 (19%)	540 000 (18%)	1.01 million (11%)
	'Community-based intervention' scenario		
	number of (first) cases prevented:		
Diabetes	14 000 (1.7%)	24 000 (1.4%)	30 000 (0.8%)
Stroke	3 000 (0.7%)	5 000 (0.5%)	4 000 (0.1%)
CHD	8 000 (0.6%)	16 000 (0.5%)	22 000 (0.2%)
	'Lifestyle program obese adults' scenario		
	number of (first) cases prevented:		
Diabetes	5 000 (0.6%)	8 000 (0.5%)	9 000 (0.6%)
Stroke	500 (0.1%)	800 (0.1%)	100 (< 0.01%)
CHD	2 000 (0.1%)	3 000 (0.1%)	3 000 (0.03%)

Diabetes=Diabetes Mellitus type 2; CHD=Coronary Heart Disease.
The figures for the reference scenario represent the expected numbers of new cases. Those for the other scenarios represent the numbers of cases prevented. A positive sign means more cases than in the reference scenario

'Normal weight and active' scenario

Almost half of the 20-year cumulative incidence of diabetes and 20% of the incidence of cardiovascular disease is prevented if everybody would have a normal weight and is physically active (Table 3), while the expected life years for the Dutch cohort would increase by 6.5%. Almost the entire reduction in diabetes incidence and a large part of the reduction in CHD incidence can be attributed to the elimination of body weight as a risk factor, while the major part of the reduction in stroke incidence can be attributed to the elimination of physical inactivity. Average life expectancy for a 40-year old person increases by 2.3 years from 40.45 to 42.75 years.

'Community-based intervention' scenario

A lifestyle intervention results in a reduction in the 20-year cumulative incidence of diabetes of 1.4% (24,000 cases), while 0.5% of the new cases of stroke and CHD are prevented (Table 3).

The intervention has no significant effect on average life expectancy.

'Lifestyle program obese adults' scenario

A lifestyle intervention for obese adults results in a reduction in the 20-year cumulative incidence of diabetes of 0.5% (8,000 cases), while 0.1% of the new cases of cardiovascular disease are prevented (Table 3). The intervention has no significant effect on average life expectancy of a 40-year old person in the total population, but life expectancy increases by 1.1 years for 40-year intervention participants.

3.3 Long-term effects for health care costs

In the reference scenario, the expected life-time costs for diabetes and cardiovascular disease (related costs) in the Dutch population (20-80 years) are €205 billion. The expected life-time total health care costs are €1,200 billion (discounted with 4% annually). This means that life-time health care costs per persons are €101,400 of which €17,400 can be attributed to diabetes and cardiovascular disease. The effects on health care costs over time for the scenarios are illustrated in Figures 2a and 2b. The area under the curve represents the (cumulative) life-time costs for the cost categories of interest.

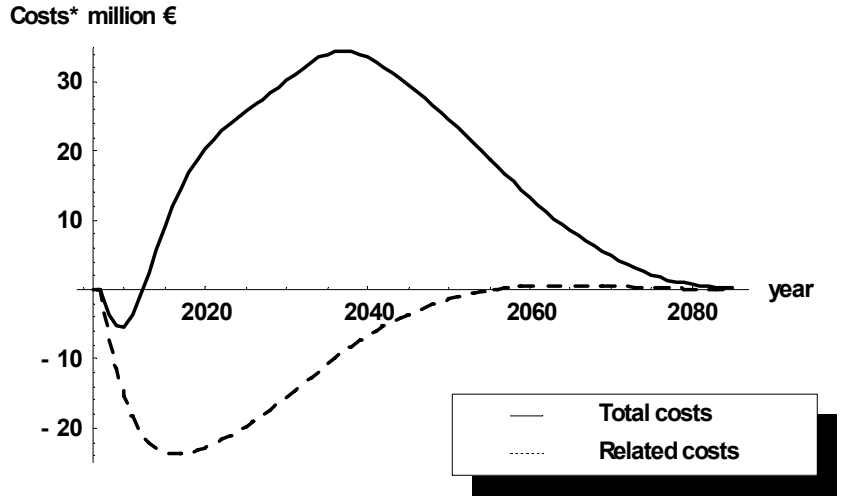

Figure 2a Difference in expected health care costs for 'diabetes and CVD' (=related costs) and life-time total health care costs between the reference scenario and the 'community-based intervention' scenario over time (discounted with 4% annually)

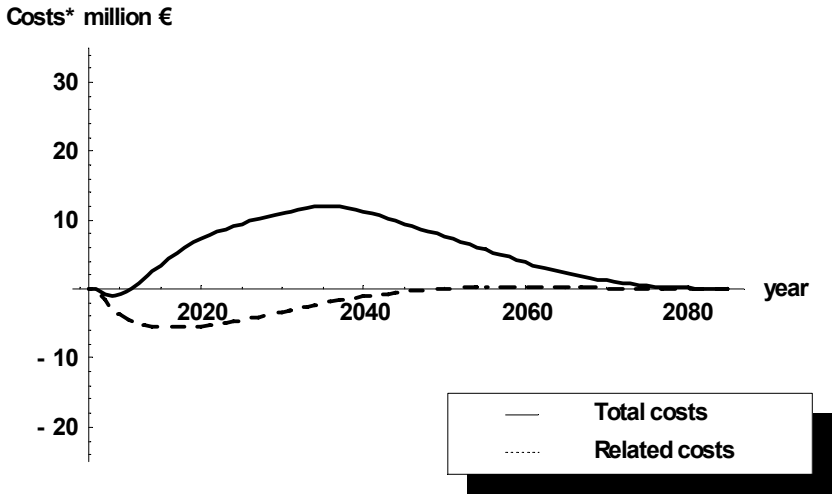

Figure 2b Difference in expected health care costs for 'diabetes and CVD' (=related costs) and life-time total health care costs between the reference scenario and the 'intervention program obese adults' scenario over time (discounted with 4% annually)

Starting a community-based intervention in 2005 would reduce the expected health care costs for diabetes and cardiovascular disease (related costs) for 2010 with approximately 15 million, and the expected related costs for 2015 with 25 million. On the other hand, the expected total health care costs for 2040 increase by approximately 35 million, due to the intervention.

In both intervention scenarios, there is a substantial, initial decrease in the health care costs for diabetes and cardiovascular diseases. However, after about 40 years these costs are a little higher in the intervention scenarios compared with the reference scenario. More people of the cohort survive

(compared to the reference scenario) and many of these persons will eventually develop diabetes or CVD, which is highly prevalent at advanced age. For total health care costs there is a small initial decrease compared to the reference scenario because prevented costs for diabetes and CVD are higher than additional costs for other diseases. However, within 10 years total health care costs are higher for the intervention scenario because more people survive and these people get other diseases.

The results for intervention costs, life-time health care costs and cost-effectiveness are given in Table 4. If everybody would have a normal weight and was physically active, life-time costs for diabetes and CVD would be €23 billion lower than the expected costs in the reference scenario, meaning that the expected costs would be reduced by 11%, corresponding to approximately €2,000 per Dutch adult. A lifestyle intervention for the general population reduces the expected costs by €581 million (€52 per Dutch adult, or on average €62 per 'participant') and an intervention for obese adults reduces these costs by €123 million (€10 per Dutch adult, or on average €800 per participant). However, total health care costs increase.

Table 4 Expected life-time costs and efficy of lifestyle interventions

Scenario		**Costs (millions)**		**Effects**	**Cost-effectiveness**
	Intervention	*Savings in healthcare for related disease*	*Net costs**	*QALYs gained (millions)*	*Euro/QALY*
Normal weight	N/A	17 000 (8%)	27 000 (2%)	8.3	N/A
Normal weight and active	N/A	23 000 (11%)	77 000 (7%)	12.3	N/A
Community-based intervention	56	581 (0.3%)	1 257 (0.1%)	0.28	5 000
Lifestyle program obese adults	112	123 (0.06%)	426 (0.04%)	0.08	7 000

* Net costs are derived by subtracting cost savings in healthcare for related diseases from the additional costs due to healthcare for unrelated diseases (in particular in life years gained).
Costs have been discounted at a rate of 4% and effects at 1.5%. No intervention costs can be assigned to the 'maximum' scenarios and therefore also no cost-effectiveness ratios.

Adults in the Dutch population would gain 12.3 million quality adjusted life-years (on average 1.05 per person) if everybody would have a normal weight and was physically active. A lifestyle intervention for the general population would result in a gain of 280,000 QALYs and the intervention for obese adults would add 80,000 QALYs (on average 0.5 per intervention participant). Both 'realistic' intervention scenarios can be considered 'highly cost-effective' with ratios of 5,000 and 7,000 euro/QALY, respectively.

3.4 Sensitivity analyses

We performed several sensitivity analyses in which effects, costs, time horizon and discount rates were varied.

'Community-based intervention' scenario

1. Effect on BMI and physical activity: 50% (i.e. half of the effect assumed in the reference scenario).

2. Intervention costs double (€12 per adult as compared to €6).

3. Relapse in the effect on BMI and physical activity after the intervention (i.e. a gradual 50% decline in the initial effect in the first 5 years after the end of the intervention, Appendix 1).

4. Discount rates 0% or 4% for both effects and costs.

5. Time horizon 5, 10 or 20 years.

The results for the sensitivity analyses are summarized in Table 5.

Table 5 Sensitivity analysis for the 'community-based intervention' scenario

Scenario variant	Prevented over time period considered			QALYs gained	Cost-effectiveness
	Diabetes	*Stroke*	*CHD*		
Base-case*	24 000	5 000	16 000	280 000	5 000
Effect 50%	12 000	2 000	8 000	139 000	5 000
Intervention costs double	24 000	5 000	16 000	280 000	5 000
Relapse of effect	17 000	4 000	12 000	181 000	5 000
All discount rates 0%	24 000	5 000	16 000	424 000	13 000
All discount rate 4%	24 000	5 000	16 000	156 000	8 000
Time horizon 5 years	7 000	2 000	4 000	12 000	3 000
Time horizon 10 years	14 000	3 000	8 000	39 000	2 000
Time horizon 20 years	24 000	5 000	16 000	109 000	3 000

* Base case: time horizon 20 years for cases prevented, and 80 years for QALYs and cost-effectiveness; intervention costs €6 pp; no relapse of effect; discount rates 1.5% for QALYs and 4% for costs.
Except for the last three rows, the time horizon is that of the base case.

'Lifestyle program obese adults' scenario

1. Effect on BMI and physical activity 50%.

2. Intervention costs €2000 per participant as compared to €700 (i.e. the approximate costs for an intensive lifestyle program in the US, the Diabetes Prevention Program).

3. Relapse in the effect on BMI and physical activity after the intervention. (i.e. a 25% decline in the initial effect in the first 3 years after the end of the intervention and another 12% decline in the three consecutive years, Appendix 1).

4. Discount rates 0% or 4% for both effects and costs.

5. Time horizon 5, 10 or 20 years.

The results for the sensitivity analyses are summarized in Table 6.

Table 6 Sensitivity analysis for the 'lifestyle program obese adults' scenario

Scenario variant	Prevented over time period considered			QALYs gained	Cost-effectiveness
	Diabetes	*Stroke*	*CHD*		
Base-case*	8 000	800	3 000	77 000	7 000
Effect 50%	4 000	400	2 000	39 000	8 000
Intervention costs 2000 pp	8 000	800	3 000	77 000	10 000
Relapse of effect	6 000	700	3 000	57 000	8 000
All discount rates 0%	8 000	800	3 000	116 000	16 000
All discount rate 4%	8 000	800	3 000	44 000	12 000
Time horizon 5 years	2 000	300	800	3 000	32 000
Time horizon 10 years	5 000	500	2 000	11 000	11 000
Time horizon 20 years	8 000	800	3 000	31 000	6 000

* Base case: time horizon 20 years for cases prevented, and 80 years for QALYs and cost-effectiveness; intervention costs €700 pp; no relapse of effect; discount rates 1.5% for QALYs and 4% for cost.
Except for the last three rows, the time horizon is that of the base case.

3.5 Summary

Body weight is the most important modifiable risk factor for diabetes. If all Dutch adults would have a normal weight and were physically active, the impact would be enormous with a decrease in the expected long-term incidence of diabetes of approximately 50%. However, this would imply an average weight loss of approximately 25 kg in obese adults and 10 kg in persons who are moderately overweight, as opposed to average weight losses of 0.5 kg and 3.0 kg as estimated for our realistic scenarios simulating a community-based intervention and lifestyle program for obese adults, respectively. We know that weight loss is not easily achieved nor maintained [2]. Based on results obtained in intervention trials, we estimated that large scale implementation of lifestyle interventions, could prevent 1.4% (community-based intervention) or 0.5% (lifestyle program for obese adults) of the 20-year cumulative diabetes incidence in the Dutch population. With these realistic interventions, the life-time costs related to diabetes and cardiovascular disease decrease, while the total health care costs increase due to longer life expectancies. The community-based intervention is cost-effective under a wide range of assumptions. An intervention for obese adults is also cost-effective, except when a time-span shorter than 10 years is considered because the short-term health effects are insufficient to counterbalance the intervention costs.

4 Smoking cessation

Smoking has been reported to increase diabetes risk, with an approximately 15% higher risk among current smokers as compared to non smokers [19]. Furthermore, the finding that heavy smoking is associated with higher risks than light smoking indicates that there is a dose-effect relationship [55 82 31 59 58 45 80 56 9 17]. The risk among ex-smokers remains increased (9%), but this elevated risk disappears gradually over time. Although the association between smoking and diabetes is not strong, smoking is a major risk factor for cardiovascular disease. As the risk of cardiovascular disease is already increased considerably among individuals with diabetes, it is crucial to eliminate as much as possible any other factor that adds to the total cardiovascular risk score. Moreover, the deleterious effects of smoking might even be stronger in an already compromised cardiovascular system.

Thus, it seems that reducing smoking in the general population can have two types of benefit with regard to diabetes. Firstly, it might reduce the incidence of diabetes. Second, by reducing the proportion of smokers amongst those who do develop diabetes it might have a favourable impact on the occurrence of cardiovascular complications. However, attempts to bring down the prevalence of smoking have, so far, been met with limited success. Hence, when estimating the relative strengths of various preventive strategies, it is especially important to take a realistic perspective on the possibilities of anti-smoking interventions.

We shall focus on attempts to stimulate smoking cessation. In this respect, a distinction can be made between interventions involving the whole population, such as mass media campaigns, and those that are aimed at the individual. We shall consider an approach in which interventions at both levels are applied simultaneously. The scenarios described in the following section, therefore, are all ‘combined scenarios’.

4.1 Description of scenarios

Maximum scenario

In the maximum scenario we compare the outcomes for a Dutch cohort (aged 20-80 years) in the reference scenario with those of an otherwise similar cohort consisting of individuals who have never smoked and never start smoking.

Realistic scenario

We assumed that a public health policy targeting smoking would not be restricted to one type of intervention and would entail an integral approach. It makes sense to combine various types of measures that have impact on different spheres of societal interactions. We considered a combination of the following interventions, which have been described more extensively elsewhere [75].

- Increased tobacco taxes (ITT): a 5.4% increase in 2008 (25 cents), followed by an increase of 5.1% in 2010, assuming a price-elasticity of -0.2. The assumption is that the tax increase will lead to a price increase depending on the hight of the additional tax increase and of supply.
- Mass media campaigns (MMC): Publicity by television, radio and newspapers; large-scale distribution of leaflets and flyers, postings on billboards and educational messages, leading to a decrease of smoking prevalence with 0.2 percentage points, in 2008 and 2010.

- Minimal counseling (MC): a brief individual smoking cessation advice given by a GP or assistant during a single visit of 1-12 minutes duration, offered to 25% of smokers.
- GP support (GPS): individual smoking cessation advice given by a GP or assistant during one or two visits, according to a 5-step protocol. GP support (GPS), offered to 5% of all smokers.
- Intensive counseling (40-110 minutes) by a trained counselor combined with nicotine replacement therapy for a period of 12 weeks on average (IC+NRT), offered to 7% of all smokers.

In contrast to the maximum scenario, the modeled population in the realistic scenario is a dynamic one in which individuals may start, stop and re-start smoking. A feature implemented in the CDM is that it accounts for relapse and that the risk of relapse depends on time since smoking cessation. Moreover, also the relative risks for smoking-related diseases depend on time since cessation.

In order to estimate effects on CVD prevention, implementation of these interventions was compared with usual practice. The input prevalence in the CDM for current and former smoking were derived from 5-year age class and sex specific data from yearly population monitoring studies (STIVORO) conducted between 1997 and 2000. Start, cessation and restart rates were also derived from this source. As efficacy measure of the interventions, 12-month prolonged abstinence was taken as the end-point, assuming that this is almost equal to cessation.

Efficacy estimates and intervention costs are summarized in Table 7 below. Costs of the combined intervention were €6 per person. We assumed that there is no interaction between efficacy and costs of interventions when they are combined.

Table 7 Efficacy and costs of the smoking cessation interventions

Intervention	Control group	Cessation ratesintervention group	Difference in cessation rates versus control	Costs per person
MMC	None	0.2%-2.1%	0.2%-2.1%	€3
ITT	None	3%-10%	3%-10%	€3
MC	No advice	4.4% (2.5-6.2)	0.9% (0.3-2.2)	€5
GPS	No advice	7.9% (4.2 – 15)	4.8% (1.1-12)	€26
IC+NRT	IC + placebo	22% (17-27)	6.3% (4.0-8.5)	€390

MMC; Mass Media Campaign; ITT: Increased Tobacco Taxes; MC: Minimal Counceling; GPS: General Practitioner Support; IC: Intensive Counseling; NRT: Nicotine Replacement Therapy.

4.2 Long-term effects of smoking cessation on health outcomes

Maximum scenario

Almost one out of every 5 cases of CHD in a 20-year period would be prevented if nobody smoked, and 3% of new diabetes cases (Table 8). Average life expectancy for a 40-year old person increases with 2.12 years.

Realistic scenario

The results for the realistic scenario consisting of the combination of public health and individual-based interventions described above are presented in Table 8 below. Average life expectancy for a 40-year old person increases only marginally.

Table 8 Effects of smoking cessation interventions on cardiovascular disease and diabetes incidence

	10-years incidence (until 2015)	20-years incidence (until 2025)	80-years incidence (until 2085)
	'No smokers' scenario number of (first) cases prevented:		
Diabetes	39 000 (5%)	48 000 (3%)	+75 000 (2%)
Stroke	76 000 (17%)	117 000 (12%)	+51 000 (2%)
CHD	290 000 (22%)	509 000 (17%)	480 000 (5%)
	'Smoking cessation' scenario number of (first) cases prevented:		
Diabetes	300 (< 0.1%)	+100 (< 0.1%)	+2 200 (< 0.1%)
Stroke	2 500 (0.6%)	4 300 (0.4%)	2 800 (0.1%)
CHD	6 100 (0.5%)	9 900 (0.3%)	5 500 (0.1%)

Diabetes=Diabetes Mellitus type 2; CHD=Coronary Heart Disease.
All figures represent differences compared to the reference scenario. Figures for the reference scenario are given in Table 3. A positive sign means more cases than in the reference scenario.

4.3 Smoking cessation and health care costs

The differences in health care costs over time between the "Smoking cessation" scenario and the reference scenario are illustrated in Figure 3. The area under the curve represents the (cumulative) life-time costs for the cost categories of interest.

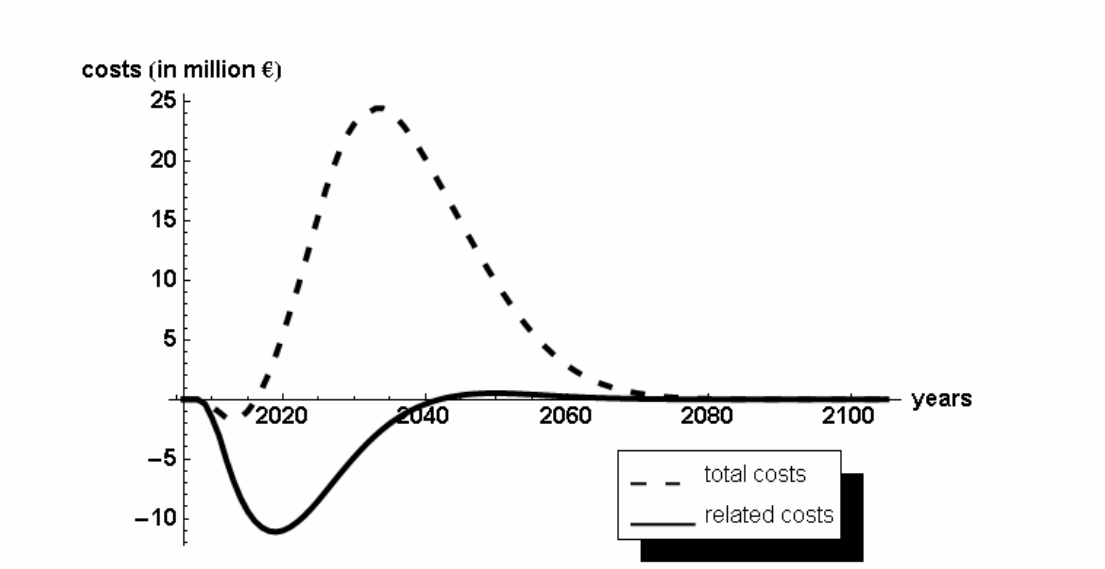

Figure 3 Difference in expected health care costs for 'diabetes and CVD' (= related costs) and life-time total health care costs between the 'No smoker' scenario and the reference scenario for the general population over time (discounted with 4% annually).

Table 9 below summarizes the results regarding costs, QALYs gained and cost-effectiveness.

Table 9 Expected life-time costs and efficacy of smoking interventions

Scenario	Costs (millions)			Effects	Cost-effectiveness
	Inter-vention	*Savings related disease*	*Net costs**	*QALYs gained*	*Euro/QALY*
No smokers	N/A	4 000 (4%)	51 000 (7%)	9.9 million	N/A
Smoking cessation	334	180 (< 0.02%)	611 (0.06%)	0.13	7 000

* Net costs are the difference between costs savings in healthcare for related diseases and additional costs due to healthcare for unrelated diseases (in particular in life years gained).
Costs have bee discounted at a rate of 4% and effects at 1.5%. No intervention costs can be assigned to the 'maximum' scenarios and therefore also no cost-effectiveness ratios.

4.4 Sensitivity analyses

For the smoking cessation intervention in the general population we performed the following sensitivity analyses.

1. All effects reduced.
2. All effects increased.
3. Discount rates 0% or 4% for both effects and costs.
4. Time horizon 5, 10 or 20 years.

The results of using these alternative assumptions are displayed in Table 10.

Table 10 Sensitivity analysis for the 'smoking cessation' scenario

Scenario variant	Prevented over time period considered			QALYs gained	Cost-effectiveness
	Diabetes	*Stroke*	*CHD*		
Base-case*	+100	4 300	9 900	130 000	7 000
Effects increased	+55	2 600	6 000	76 000	7 000
Effects decreased	+420	17 000	39 000	511 000	6 000
All discount rates 0%	+100	4 300	9 900	314 000	14 000
All discount rate 4%	+100	4 300	9 900	44 000	62 000
Time horizon 5 years	130	820	2 100	440	760 000
Time horizon 10 years	280	2 500	6 100	9 000	36 000
Time horizon 20 years	+100	4 300	9 900	50 000	8 000

* Base case: time horizon 20 years for cases prevented, and 80 years for QALYs and cost-effectiveness; discount rates 1.5% for QALYs and 4% for costs, time horizon 80 years.
Except for the last three rows, the time horizon is that of the base case. A positive sign means more cases than in the reference scenario.

4.5 Summary

Eliminating smoking would prevent roughly 15 to 20% of cardiovascular events over a period of 20 years with only a small effect on the incidence of diabetes. However, in reality it is very difficult to reduce the proportion of smokers in the general population. In the realistic scenario, we assumed that a combination of measures would be implemented targeting smoking, both at the level of the general population and at the level of the individual who has decided to attempt smoking cessation. The overall effect of such efforts is rather limited and the numbers of cardiovascular events prevented do not exceed 1 in 1,000 and 1 in 10,000 for diabetes incidence. However, the costs of these and similar interventions are relatively low. Therefore, investing in smoking prevention may be considered a sensible choice.

PART 2: CARE-RELATED PREVENTION OF COMPLICATIONS

5 Blood glucose: intensive control

As the name indicates, the aim in treating diabetes with anti-glycaemic drugs is to lower the blood glucose level. Although completely normalizing the amount of sugar in the blood is -at least currently- unattainable, it seems rational to bring the glucose level as closely as possible within the normal range.

The percentage glycosylated hemoglobin in whole blood (HbA1c in the following) has become a widely used and well-accepted measure of diabetes 'control'. HbA1c more or less reflects the average level of blood glucose during the three months preceding the test. High values indicate that the effects of treatment in maintaining blood glucose within desirable bounds are insufficient. Moreover, the HbA1c level has prognostic significance. Thus, much evidence exists that the level of hyperglycemia (and thus also of HbA1c) in diabetic patients is associated directly with a greater risk of occurrence of microvascular complications, such as retinopathy, nerve disease and kidney disease. However, the evidence is more tenuous that HbA1c level is an independent risk factor for macrovascular complications. Although there is a two-fold to four-fold increased risk of cardiovascular death in diabetic patients, this increased risk is often ascribed to the greater prevalence among diabetics of other cardiovascular risk factors, such as obesity, hypertension and dysplipidedemia, rather than to the hyperglycemia itself. One meta-analysis of a small number of prospective cohort studies reported a relative risk for coronary heart disease or stroke of 1.18 (95% CI: 1.10-1.26) for a 1-percentage point increase in HbA1c [63]. Other observational studies have shown that this correlation between CVD and glucose also exists at glucose levels that are below the thresholds used to define diabetes [36].

Assuming that there indeed is an independent relation between increased HbA1c and cardiovascular risk, the next question is whether improving long-term glycemic control reduces the risk for cardiovascular disease events. Evidence of the UKPDS trial, which was the only one specifically designed to test the hypothesis that more intensive glucose-lowering therapies may reduce the risk for cardiovascular morbidity, has largely been interpreted as negative [71]. Currently new studies are underway that have been designed to answer this question, in particular the ACCORD trial [21].

On the other hand, the recognition that strict glycaemic control can reduce miscrovascular complication is in itself sufficient to make effective anti-glycaemic treatment a priority. Most guidelines—including the Dutch standard for diabetes care (Zorgstandaard)—advise to aim at HbA1c levels of under 7% and that levels above 'should serve as a call to action to initiate or change therapy' [52]. As the clinical course of type 2 diabetes is generally characterized by a gradual decline in β-cell function and hence worsening of glycaemic control, consecutive treatment adjustments often need to be made. This process can be conceived of as a 'step-wise' approach, starting with lifestyle modifications, followed by oral monotherapy (usually metformin), oral combination therapy (the addition of sulfonylureas, thiazolidinediones, or one of the newest generation drugs), and finally treatment with insulin, either as add-on to oral treatment or as monotherapy. Often, the next step is taken after dose adjustments have failed. It is obvious that to be able to implement such a course of action more intensive monitoring and more frequent visits to physicians or specialized nurses is required. Especially when the switch to insulin is made, the patient's life becomes strongly medicalized, with the need to daily self-inject insulin and to regularly monitor blood glucose. Other disadvantages of insulin therapy are the greater risk of hypoglycemia, the almost unavoidable weight increase, and finally the costs.

In this part of the study we estimate the costs and effects of a tighter control of blood glucose. Translated into a modeling scenario, this implies increasing the proportion of patients who meet target HbA1c values by 'switching' part of the patients to more intensive treatment. As mentioned previously,

HbA1c is modeled as a categorical variable with three levels (< 7% (Class 1); 7%-8.5% (Class 2); > 8.5% (Class 3)). Moreover, fluctuation over time and age dependency of relative risks associated with HbA1c are neglected.

5.1 Description of scenarios

Reference scenario

The Dutch diabetic population with its current distribution over HbA1c classes and treatment schedules was taken as the reference population. Data for these variables were derived from sources that have been described in more detail previously [4].

Maximum scenario

The outcomes of a hypothetical cohort of Dutch individuals with diabetes (30-75 years) who all have target HbA1c levels of 7.0% or less, were compared to the outcomes in the reference scenario.

Realistic scenario

A realistic scenario was largely based on a recent Dutch study [22]. This study concerns a trial conducted in a general practice setting, in which patients with insufficient control of their diabetes despite the use of at least two oral anti-glycemic agents, were randomized to one of two insulin regimens: insulin monotherapy or insulin in combination with oral drugs. Based on the results of this trial, we assumed that switching to insulin monotherapy would result in an average HbA1c reduction of 1 percentage point. Moreover, still based on this study, we assumed that 10% of cases switching to insulin would result in treatment failure, either due to a lack of effect in some patients or to difficulties self-administering insulin. Thus, the scenario we defined includes an intervention in which all patients using 2 oral agents and who's HbA1c > 7.0% are started on insulin monotherapy. Further details of the scenario and intervention costs are provided in Appendix 2. Suffice it here to mention, that all 'candidates for switching to insulin' were in HbA1c category 7.0 to 8.5%, and that 39.000 patients switched to HbA1c class < 7%, as a result of the intervention. Total intervention costs were 148 million.

5.2 Long-term effects for health outcomes

The diabetes population in 2005 comprised 398,000 people 30-75 years, 212,000 men and 186,000 women. The expected cumulative incidence of stroke and CHD in the reference scenario is summarized in Table 11. Average life expectancy for a 40-year old person with diabetes is 30.9 years.

Maximum scenario

The results for prevented cumulative incidence of stroke and CHD, as well as life years gained are summarized in Table 11. In the maximum scenario, the average life expectancy of a 40-year old individual would increase from 30.7 years to 31.4 years, a gain of somewhat more than half a year.

Realistic scenario

The results for prevented cumulative incidence of stroke and CHD, as well as life years gained are also summarized in Table 11. The average life expectancy of a 40-year old individual would increase from 30.72 years to 30.80 years, a marginal gain. The cost-effectiveness ratio is 22,000 euro/QALY.

Table 11 Effects of intensified blood glucose treatment on cardiovascular complications

	10-years incidence (until 2015)	20-years incidence (until 2025)	80-years incidence (until 2085)
	Reference scenario: Dutch cohort of diabetes patients 30-75 years (n=398 000)		
	expected number of (first) cases		
Stroke	39 000	63 000	78 000
CHD	138 000	220 000	271 000
	'Low blood glucose' scenario		
	number of (first) cases prevented:		
Stroke	4 000 (11%)	6 000 (10%)	7 000 (9%)
CHD	12 000 (9%)	16 000 (7%)	18 000 (6%)
	'Intensified blood glucose treatment' scenario		
	number of (first) cases prevented:		
Stroke	500 (1%)	800 (1%)	900 (1%)
CHD	1 400 (1%)	1 900 (1%)	2 000 (1.6%)

CHD=Coronary Heart Disease.
The figures for the reference scenario represent the expected numbers of new cases. Those for the other scenarios represent the numbers of cases prevented.

5.3 Long-term effect on health care costs

The differences in health care costs over time between the 'Intensified blood glucose treatment' scenario and the reference scenario are illustrated in Figure 4. The area under the curve represents the (cumulative) life-time costs for the cost categories of interest.

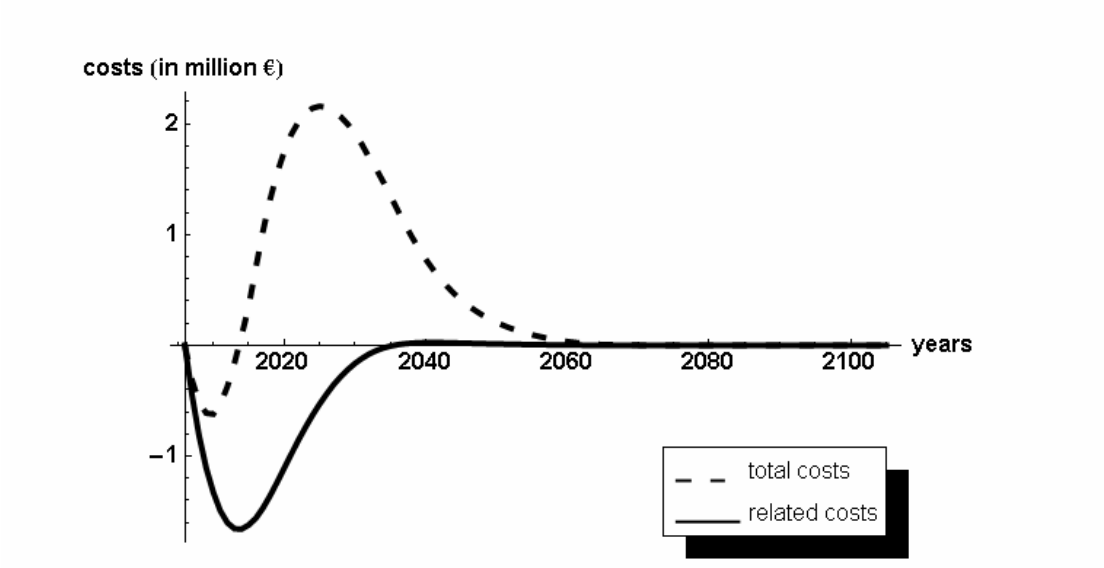

Figure 4 Difference in expected health care costs for 'CVD' (= related costs) and life-time total health care costs between the 'Intensified blood glucose treatment' scenario and the reference scenario for the diabetic population over time (discounted with 4% annually)

The expected costs involved, distinguished into those directly related to the diseases considered and the total health care costs, as well as the QALYs gained and the cost-effectiveness ratio are displayed in Table 12.

Table 12 Expected life-time costs and efficacy of intensified blood glucose treatment

Scenario	Costs (millions)			Effects	Cost-effectiveness
	Intervention	*Savings in healthcare for related disease*	*Net costs**	*QALYs gained*	*Euro/QALY*
Low blood glucose	N/A	205 (2%)	350 (1%)	72 000	N/A
Intensified blood glucose treatment	148	23 (0.2%)	42 (0.1%)	9 000	22 000

* Net costs are the difference between costs savings in healthcare for related diseases and additional costs due to healthcare for unrelated diseases (in particular in life years gained).
Costs have bee discounted at a rate of 4% and effects at 1.5%. No intervention costs can be assigned to the 'maximum' scenarios and therefore also no cost-effectiveness ratios.

5.4 Sensitivity analyses

The sensitivity analyses we performed were based on variations of the following parameters.

1. Greater effect of the intervention: A reduction of HbA1c levels of 1.5 percentage points instead of 1. This would imply that 29% of patients from class 2 would switch to class 1.

2. Different relative risks. As data on the relative risks for different levels of HbA1c values are still scarce, we run the model assuming different relative risks. We assumed that relative risks of CHD and Stroke for HbA1c classes 2 and 3 are a factor 1.5 greater than used as input in the reference scenario.

3. Discount rates 0% or 4% for both effects and costs.

4. Time horizon 5, 10 or 20 years.

The results of using these alternative assumptions are displayed in Table 13. Especially greater relative risks would make a big difference.

Table 13 Sensitivity analysis for the 'intensified blood glucose treatment' scenario

Scenario variant	Prevented over time period considered		QALYs gained	Cost-effectiveness
	Stroke	*CHD*		
Base-case*	800	1 900	8 600	22 000
Greater effect intervention	960	2 500	10 700	19 000
Greater relative risks	3 000	60 000	145 000	5 000
All discount rates 0%	800	1 900	11 300	29 000
All discount rate 4%	800	1 900	5 700	33 000
Time horizon 5 years	300	870	660	132 000
Time horizon 10 years	530	1 400	2 200	52 000
Time horizon 20 years	800	1 900	5 600	28 000

* Base case: time horizon 20 years for cases prevented, and 80 years for QALYs and cost-effectiveness; discount rates 1.5% for QALYs and 4% for costs, time horizon 80 years.
Except for the last three rows, the time horizon is that of the base case.

5.5 Summary

This analysis shows that approximately 1% of cardiovascular events could be prevented by a more 'aggressive' approach in the first line treatment of patients with diabetes type 2. However, the costs involved are relatively high. It should also be considered that switching a greater proportion of patients to insulin has the further disadvantage of increasing medicalization of this population who would otherwise lead relatively normal lives.

It is to be noted that the proportion of patients using two oral agents but no insulin was quite low (approximately 13%). This reflects the fact that in the Netherlands glycemic control in the first line is already quite adequate. Or, in other words, the space for further improvement is limited. Furthermore,

although it has been shown that reduced levels of HbA1c decreases the development of microvascular complications, evidence regarding the relation between HbA1c lowering and cardiovascular disease prevention is still rather scarce. Several trials are still underway which may change the picture, as might developments in drug efficacy (new drugs) and/or drug prices (cheaper drugs).

From the results of our simulation we can conclude that the intensity of blood glucose control in the Netherlands is rather adequate. Further increasing the efforts in this direction would lead to an increase in medicalization with only a small effect on prevention of macrovascular complications. Thus, the current trend to step up the proportion of patients on insulin should be regarded with a critical eye.

6 Cholesterol-lowering treatment

There is substantial evidence that cholesterol-lowering treatment can reduce cardiovascular disease in diabetes patients [11 10 3 78]. The beneficial effects of statin treatment are reported for diabetes patients with and without cardiovascular disease. Furthermore, the relative risk reductions in CVD achieved through statin treatment appear to be virtually independent of the baseline level of cholesterol [26 20]. Several years of statin treatment reduces LDL cholesterol with on average 1.0 mmol/l. The risk reduction for major coronary events is lower for persons over 65 years of age (19%) as compared to younger persons (26%). The risk reduction for stroke is 18% for all ages [10]. Current international as well as Dutch guidelines advise cholesterol-lowering treatment with statins for almost all diabetes patients over 40 years [32 1].

The Dutch multidisciplinary guideline for cardiovascular risk management advises statin treatment for diabetes patients with LDL cholesterol > 2.5 mmol/l or total cholesterol (TC)> 4.5 mmol/l. For 'younger' patients with favourable risk profile and HbA1c< 7%, higher threshold levels of cholesterol can be adopted or treatment can be postponed until a higher age. Statin treatment may also be considered for patients with LDL<2.5, at very high cardiovascular risk.

In the Dutch diabetes population cohort in the model, 85% has total cholesterol over 5.0 mmol/l. Approximately 30% of these patients receive cholesterol-lowering treatment.

6.1 Description of scenarios

Maximum scenario

In the maximum scenario we compare the outcomes for a Dutch cohort of people with diabetes (30-75 years) in the reference scenario with the outcomes for a Dutch cohort of people with diabetes (30-75 years) in which everybody is in the lowest risk factor class for cholesterol (total cholesterol < 5.0 mmol/l and treated with statins).

Realistic scenario

In the realistic scenario we compare the outcomes for a Dutch cohort of people with diabetes (30-75 years) in the reference scenario with the outcomes for a Dutch cohort of people with diabetes (30-75 years) in which 50% of the diabetes patients with total cholesterol > 5 mmol/l who are currently untreated are treated with statins. Effects of statin treatment are based on results from a meta-analysis of international trials as reported in the introduction [10].

Intervention costs

We assume that newly treated patients are treated for the rest of their lives (100% compliance). We assume that 70% of the patients use simvastatin 40mg daily (€175 per patient per year) and that 30% of the patients use 40mg pravastatin daily (€302 per patient per year). Besides medication costs and prescription costs of €24 per patient per year, we assume an additional €51 per patient per year for extra health care use (one visit to the general practitioner €21, tests €12 and two additional visits to a practitioners nurse €18). Total intervention costs are estimated by multiplying the number of

additionally treated patients in each year with yearly intervention costs (€288, discounted with 4% annually) and summing these costs over the subsequent years. Total intervention costs for this scenario are €371 million.

6.2 Long-term effects for health outcomes

Reference scenario

In the reference scenario, 15% of the diabetes patients have a total cholesterol (TC) level < 5.0 mmol/l, 48% have TC 5.0-6.5, 28% have a TC between 6.5 and 8.0 and 9% have TC> 8.0 mmol/l. Within these classes the percentage of patients, treated for high cholesterol is 10%, 19%, 41% and 71%, respectively. Due to limited data, we assume that total cholesterol level is stable over time, that treated patients remain treated and that untreated patients remain untreated (i.e. no transitions).

The expected cumulative incidence of stroke and CHD in the reference scenario is summarized in table 14. Average life expectancy for a 40-year old person with diabetes is 30.9 years.

Maximum scenario

In this scenario, all diabetes patients have a TC< 5.0 mmol/l and all patients receive cholesterol-lowering treatment. If all diabetes patients would be in the lowest risk factor class for cholesterol, 5,000 new cases of stroke and 44,000 new cases of CHD could be prevented within 20 years, corresponding to 8%, respectively 20% reductions in the expected cumulative incidences of stroke and CHD in the reference scenario (Table 13).

Life expectancy for a 40-year old person with diabetes increases with on average 1.7 years, from 30.9 years to 32.6 years.

Table 14 Effects of intensified cholesterol lowering treatment on cardiovascular complications

	10-years incidence (until 2015)	20-years incidence (until 2025)	80-years incidence (until 2085)
	'Low cholesterol' scenario number of (first) cases prevented:		
Stroke	4 000 (10%)	5 000 (8%)	4 000 (5%)
CHD	33 000 (24%)	44 000 (20%)	44 000 (16%)
	'Cholesterol treatment' scenario number of (first) cases prevented:		
Stroke	2 000 (5%)	3 000 (5%)	3 000 (4%)
CHD	5 000 (4%)	7 000 (3%)	7 000 (3%)

CHD=Coronary Heart Disease.

All figures represent differences compared to the reference scenario. Figures for the reference scenario are given in Table 11.

Realistic scenario

In the realistic scenario, 115 700 diabetes patients are additionally treated with statins in the first year. As in the reference scenario, 15% of the diabetes patients have a total cholesterol (TC) level < 5.0 mmol/l, 48% have TC 5.0-6.5, 28% have a TC between 6.5 and 8.0 and 9% have TC > 8.0 mmol/l. Within these classes the percentage of patients, treated for high cholesterol is 10%, 60%, 70% and 86% as compared to 10%, 19%, 41% and 71% in the reference scenario.

Additional cholesterol-lowering treatment for 50% of currently untreated diabetes patients with TC > 5.0 mmol/l would prevent 3,000 new cases of stroke and 7,000 new cases of CHD within 20 years, corresponding to 5%, respectively 3% reductions in the expected cumulative incidences of stroke and CHD in the reference scenario (Table 13).

Life expectancy for a 40-year old person with diabetes increases with on average 0.4 years, from 30.9 years to 31.3 years. For a newly treated 40-year old patient, life expectancy increases with 1.2 years.

6.3 Long-term effects for health care costs

In the reference scenario, the expected life-time costs for diabetes and cardiovascular disease in the Dutch diabetes population (30-75 years) are €11.2 billion and the expected total health care costs are €38.8 billion (discounted with 4% annually).

The difference in health care costs over time between the realistic intervention scenario and the reference scenario are illustrated in figure 5 for costs related to diabetes and CVD (lower line) and total health care costs (upper line).

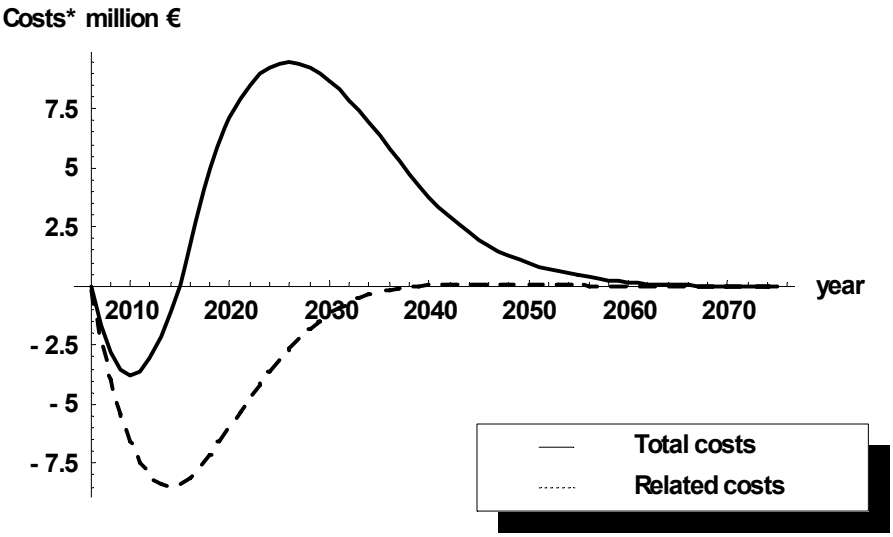

Figure 5 Difference in expected health care costs for diabetes and CHD (related costs) and life-time total health care costs between the realistic intervention scenario for cholesterol-lowering treatment and reference scenario over time (discounted with 4% annually)

In both the maximum and realistic scenario, cumulative life-time health care costs for diabetes and cardiovascular diseases decrease, while total health care costs increase due to increased life expectancy.

If everybody would be in the lowest risk factor class for cholesterol, life-time costs for diabetes and CVD would be €551 million lower as compared to the expected costs in the reference scenario.

Additional treatment of 50% of the currently untreated patients with TC > 5.0 mmol/l would prevent €129 million (Table 15). The intervention is considered cost-effective with a ratio of €14,000/QALY.

Table 15 Expected life-time costs and efficacy of intensified cholesterol treatment

Scenario	**Costs (millions)**			**Effects**	**Cost-effectiveness**
	Intervention	*Savings in healthcare for related disease*	*Net costs**	*QALYs gained*	*Euro/QALY*
Low cholesterol	N/A	551 (4.9%)	886 (2.3%)	210 000	N/A
Cholesterol treatment	371	127 (1.1%)	176 (0.5%)	40 000	14 000

* Net costs are derived by subtracting costs savings in healthcare for related diseases from the additional costs due to healthcare for unrelated diseases (in particular in life years gained).
Costs have been discounted at a rate of 4% and effects at 1.5%. No intervention costs can be assigned to the 'maximum' scenarios and therefore also no cost-effectiveness ratios.

6.4 Sensitivity analyses

For the cholesterol-lowering intervention for persons with diabetes we performed the following sensitivity analyses:

1. Effect: the benefit of statin treatment, in terms of relative risk reduction for cardiovascular disease, is reduced to the lower boundaries of the confidence intervals as reported by Baigent and colleagues [10].

(coronary heart disease: 21% for persons under 65 years and 12% for persons over 65; stroke: 12%)

2. Intervention costs 457 million (€353 per patient per year which is the average price of simvastatin 40mg (€175 per patient per year), pravastatin 40mg (€302 per patient per year) and atorvastatin 10mg (€291 per patient per year) and one extra visit to the general practitioner.

3. Poor compliance: We assume that 50% of the new patients who start statin treatment stop taking their medication after (on average) two years [46 35]. This implies that there are costs associated with two years of treatment, while we assume that the health benefits can be ignored.

4. Discount rates 0% or 4% for both effects and costs.

5. Time horizon 5, 10 or 20 years.

Results for the sensitivity analyses are given in Table 16.

Table 16 Sensitivity analysis for the 'cholesterol treatment' scenario

Scenario variant	Prevented over time period considered		QALYs gained	Cost-effectiveness
	Stroke	*CHD*		
Base-case*	3 000	7 000	40 000	14 000
Low effect	2 000	5 000	30 000	16 000
Intervention costs €353 pp	3 000	7 000	40 000	16 000
Poor compliance	1 000	3 000	20 000	15 000
All discount rates 0%	3 000	7 000	53 000	20 000
All discount rate 4%	3 000	7 000	27 000	20 000
Time horizon 5 years	500	2 000	3 000	52 000
Time horizon 10 years	900	3 000	10 000	24 000
Time horizon 20 years	3 000	7 000	26 000	15 000

* Base case: time horizon 20 years for cases prevented, and 80 years for QALYs and cost-effectiveness; intervention costs €288 pp; compliance 100%; discount rates 1.5% for QALYs and 4% for costs.
Except for the last three rows, the time horizon is that of the base case.

6.5 Summary

Diabetes patients typically have only slightly raised plasma concentrations of low density lipoprotein (LDL) cholesterol. However, substantial benefits of treatment with a cholesterol lowering drug have been shown in large trials with risk reductions for cardiovascular complications of approximately 20 to 30% [11]. Currently, less then 30% of the Dutch diabetes patients receive cholesterol-lowering treatment, while 37% have relatively high levels of total cholesterol (> 6.5 mmol/l). Eliminating cholesterol as a risk factor for CVD by assuming life-long low levels of total cholesterol and cholesterol-lowering treatment for all patients would reduce the 20-year expected incidence of coronary complications and stroke with 20% and 8% respectively. However, more realistically, additional treatment of 50% of currently untreated patients with a total cholesterol level over 5.0 mmol/l could prevent 7,000 new cases of coronary disease and 3,000 new strokes, corresponding to 5% and 3% of the expected incidence respectively. In this case, life-time costs for cardiovascular disease decrease with 1% while total costs increase by 0.5%. A newly treated 40-year old patient gains more than one life-year as compared to a patient who remains untreated. Although a low effectiveness or poor compliance with statin treatment would results in a substantial reduction in health benefits, the intervention would remain cost-effective. If the time horizon considered is shorter than 10 years, the intervention is no longer cost-effective.

7 Antihypertensive treatment

A high blood pressure increases the risk for cardiovascular disease and many studies have shown that antihypertensive treatment reduces the incidence of coronary heart disease, stroke and chronic heart failure in persons with and without diabetes, as summarized in a meta-analysis [70]. (Intensified) antihypertensive treatment in diabetes patients reduces the risk for stroke with approximately 31%, and the risks for coronary heart disease and chronic heart failure with approximately 20% and 18% [70]. The Dutch multidisciplinary guideline for cardiovascular risk management states that diabetes patients with a systolic blood pressure ≥ 140 mmHg should receive antihypertensive treatment aimed to reduce cardiovascular disease and nephropathy. Diuretics (thiazidediuretics) and ACE inhibitors are the recommended antihypertensive agents among persons with diabetes. Furthermore, the current guideline for general practitioners recommends antihypertensive treatment with an ACE inhibitor for all diabetes patients with micro- or macroalbuminuria.

A high blood pressure is common among Dutch diabetes patients. In the diabetes cohort in our model, 68% have a systolic pressure ≥ 140 mmHg. Only slightly more than half of these patients receive antihypertensive treatment. A recent Dutch study based on a well controlled diabetes population in Zwolle (the Netherlands) revealed that 27% of their patients had micro- or macroalbuminuria and about 33% of these patients did not receive ACE inhibiting treatment [42]. Diabetes patients with antihypertensive treatment used on average two antihypertensive agents.

7.1 Description of scenarios

Maximum scenario

In the maximum scenario we compare the outcomes for a Dutch cohort of people with diabetes (30-75 years) in the reference scenario with the outcomes for a Dutch cohort of people with diabetes (30-75 years) in which everybody is in the lowest risk factor class for blood pressure.

Realistic scenario

In the realistic scenario we compare the outcomes for a Dutch cohort of people with diabetes (30-75 years) in the reference scenario with the outcomes for a Dutch cohort of people with diabetes (30-75 years) in which 50% of the diabetes patients with systolic blood pressure ≥ 140 mmHg who are currently untreated are treated for high blood pressure.

Effects of blood pressure lowering medications are based on a meta-analysis of intervention studies as mentioned in the introduction [70]. Effects are modeled through risk reductions.

Intervention costs

We assume that all newly treated patients are treated with a diuretic (€70 per year) and an ACE inhibitor (€143 per year) for the rest of their lives. Besides medication costs of €213 per patient per year and prescription costs of €48, we assume an additional €38 per patient per year for costs related to additional health care visits; 10 minutes for general practitioner (€21) and two additional visits to a

practitioners nurse (€18). Total intervention costs are estimated by multiplying the number of additionally treated patients in each year with yearly intervention costs of €299 (discounted with 4% annually) and summing these costs over the subsequent years. Total intervention costs are €208 million.

7.2 Long-term effects on health outcomes

Reference scenario

The prevalence in SBP classes 140-160 and > 160 mmHg is 35% and 33%. Within these classes, 48% and 60% are treated with antihypertensive medication. Due to limited data, we assume that systolic blood pressure level is stable over time, and that treatment status does not change (i.e. no transitions).

The expected cumulative incidence of stroke and CHD is summarized in Table 17.

Maximum scenario

If all diabetes patients would be in the lowest risk factor class for blood pressure, 29,000 new cases of stroke and 71,000 new cases of CHD could be prevented within 20 years, corresponding to 46%, respectively 32% reductions in the expected cumulative incidences of stroke and CHD in the reference scenario (Table 17).

Life expectancy for a 40-year old person with diabetes increases with on average 4.0 years, from 30.9 years to 34.9 years.

Table 17 Effects of intensified anti-hypertensive treatment on cardiovascular complications

	10-years incidence (until 2015)	20-years incidence (until 2025)	80-years incidence (until 2085)
	'Low blood pressure' scenario number of (first) cases prevented:		
Stroke	20 000 (51%)	29 000 (46%)	31 000 (40%)
CHD	52 000 (38%)	71 000 (32%)	70 000 (26%)
	'Blood treatment' scenario number of (first) cases prevented:		
Stroke	2 000 (5%)	3 000 (5%)	3 000 (4%)
CHD	5 000 (4%)	7 000 (3%)	6 000 (2%)

CHD=Coronary Heart Disease.

All figures represent differences compared to the reference scenario. Figures for the reference scenario are given in Table 11. A positive sign means more cases than in the reference scenario.

Realistic scenario

In the realistic scenario, 62 100 diabetes patients are additionally treated with antihypertensive agents in the first year. As in the reference scenario, 33% of the diabetes patients have a SBP between 140 and 160 and 33% have a SBP > 160 mmol/l. Within these classes the percentage of treated patients is 74% and 80% respectively as compared to 48% and 60% the reference scenario.

Additional antihypertensive treatment for 50% of currently untreated diabetes patients with SBP ≥ 140 mmol/l would prevent 3,000 new cases of stroke and 7,000 new cases of CHD within 20 years, corresponding to 5%, respectively 3% reductions in the expected cumulative incidences of stroke and CHD in the reference scenario (Table 17).

Life expectancy for a 40-year old person with diabetes increases with on average 0.4 years, from 30.9 years to 31.3 years. For a newly treated 40-year old patient, life expectancy increases with 2.0 years.

7.3 Long-term effects on health care costs

In the reference scenario, the expected life-time costs for diabetes and cardiovascular disease in the Dutch diabetes population (30-75 years) are €11.3 billion and the expected total health care costs are €39.4 billion (discounted with 4% annually).

The difference in health care costs over time between the realistic intervention scenario and the reference scenario are illustrated in figure 6 for costs related to diabetes and CVD (lower line) and total health care costs (upper line).

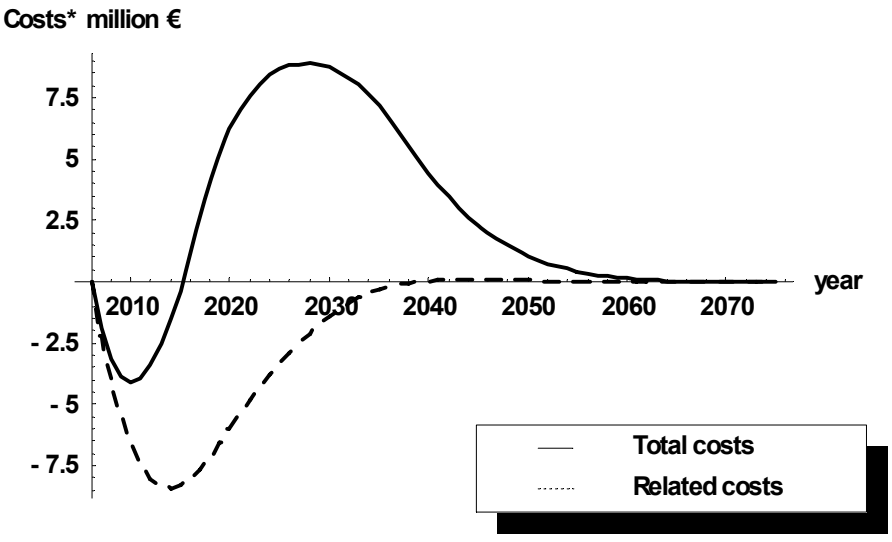

Figure 6 Difference in expected health care costs for diabetes and CHD (related costs) and life-time total health care costs between the realistic intervention scenario for antihypertensive treatment and reference scenario over time (discounted with 4% annually)

In both the maximum and realistic scenario, cumulative life-time health care costs for diabetes and cardiovascular diseases decrease, while total health care costs increase due to increased life expectancy. If blood pressure is eliminated as a risk factor for diabetes, expected life-time costs for diabetes and CVD would be €1,594 million lower as compared to the expected costs in the reference scenario. Additional treatment of 50% of the currently untreated patients with SBP ≥ 140 mmol/l would prevent €129 million (Table 19). The intervention is considered cost-effective with a ratio of €10,000/QALY.

Table 18 Expected life-time costs and efficacy of intensified anti-hypertensive treatment

Scenario	**Costs (millions)**			**Effects**	**Cost-effectiveness**
	Intervention	*Savings in healthcare for related disease*	*Net costs**	*QALYs gained*	*Euro/QALY*
Low blood pressure	N/A	1 594 (14.1%)	2 041 (5.2%)	469 000	N/A
Blood pressure treatment	208	129 (1.1%)	173 (0.5%)	39 000	10 000

* Net costs are the difference between costs savings in healthcare for related diseases and additional costs due to healthcare for unrelated diseases (in particular in life years gained).
Costs have bee discounted at a rate of 4% and effects at 1.5%. No intervention costs can be assigned to the 'maximum' scenarios and therefore also no cost-effectiveness ratios.

7.4 Sensitivity analyses

For the antihypertensive intervention for persons with diabetes we performed the following sensitivity analyses:

1. Effect: the benefit of antihypertensive treatment, in terms of relative risk reduction for cardiovascular disease, is reduced to the lower boundaries of the confidence intervals for diabetes patients, as reported in a meta-analysis [70]: no effect on coronary heart disease and chronic heart failure; 14% on stroke.

2. Intervention costs: We assume that all newly treated patients use three antihypertensive agents and that the associated costs per patient per year are 497 euro. (In addition to costs in base case scenario (€299): a β-blocker €174 per year and four prescriptions €24).

3. Poor compliance: We assume that 40% of the new patients who start antihypertensive treatment stop taking their medication after (on average) two years [76 8 47]. This implies that there are costs associated with two years of treatment, while we assume that the effects can be ignored.

4. Discount rates 0% or 4% for both effects and costs.

5. Time horizon 5, 10 or 20 years.

Results are given in Table 18.

Table 19 Sensitivity analysis for the 'anti-hypertensive treatment' scenario

Scenario variant	Prevented over time period considered		QALYs gained	Cost-effectiveness
	Stroke	*CHD*		
Base-case*	3 000	6 000	39 000	10 000
Low effect	2 000	+ 1 000	7 000	35 000
Intervention costs €496 pp	3 000	6 000	39 000	13 000
Poor compliance	2 000	3 000	20 000	15 000
All discount rates 0%	3 000	6 000	51 000	16 000
All discount rate 4%	3 000	6 000	25 000	15 000
Time horizon 5 years	1 000	2 000	2 000	31 000
Time horizon 10 years	2 000	4 000	8 000	14 000
Time horizon 20 years	3 000	6 000	24 000	10 000

* Base case: time horizon 20 years for cases prevented, and 80 years for QALYs and cost-effectiveness; intervention costs €299 pp; compliance 100%; discount rates 1.5% for QALYs and 4% for costs.
Except for the last three rows, the time horizon is that of the base case. A positive sign indicates that there are more cases in the intervention scenario.

7.5 Summary

About 70% of the persons with diabetes have a systolic blood pressure ≥ 140 mmHg and approximately half of them receive antihypertensive medication. One antihypertensive agent is generally not sufficient to achieve good blood pressure control and most patients use combinations of two or more different classes of antihypertensive drugs [42]. Elimination of blood pressure as a risk factor for cardiovascular complications (maximum scenario) would have a huge effect on the expected cumulative incidences of stroke and CHD, which would be 46% and 32% lower as in the reference scenario. About 10% of this potential health benefit can be realized by starting treatment in 50% of currently untreated hypertensive patients. In this case, life-time costs for cardiovascular disease decrease with 1% while total costs increase by 0.5%. A newly treated 40-year old patient gains two life-years as compared to a patient who remains untreated. Although poor compliance with antihypertensive treatment would results in a substantial reduction in health benefits, the intervention would remain cost-effective. However, if a short-term time-horizon is applied or if the effect of antihypertensive treatment is confined to a 14% risk reduction for stroke, the intervention is no longer cost-effective.

8 Prevention of complications: multifactorial treatment

The above analyses considered various interventions aimed at reducing individual risk factors separately in the prevention of macrovascular diabetes complications. However, it is strongly recommended in all guidelines to take into account the whole risk profile including all relevant risk factors. In this analysis we estimate the benefits and costs of an intensive treatment program in the first line. The aim of such a strategy is to monitor and adequately control blood pressure, blood lipids and HbA1c simultaneously. In analyzing this comprehensive approach, it does not suffice to simply combine the results of the individual scenarios presented in the preceding, for two reasons. Firstly, interaction of effects should be reckoned with, as unfavourable outcomes can only be prevented once. And, secondly, the costs of intervention will not be equal to the sum of the individual interventions, because, for example, one visit to the GP will include consultation for all risk factors simultaneously.

8.1 Description of scenarios

In principle, the multifactorial scenario is simply the sum of the individual scenarios. However, adaptations need to be made in estimating effects and costs for reasons mentioned above. Again, we distinguish a maximum scenario and a realistic one.

Maximum scenario

The maximum scenario consists of an elimination of all three risk factors: all individuals in the lowest risk factor classes for blood pressure, blood lipids and HbA1c.

Realistic scenario

The realistic scenario uses the same factors determining the effects of the interventions on the risk factors class distributions as the individual cases. As the CDM is built upon a model of independency of risk factors, this can be done immediately, without the need for adjustments. The only adaptations that need to be done concern the intervention costs. In particular, it was assumed that the number of contacts with GPs and nurses will be less than the sum of the individual scenarios.

8.2 Long-term effects on health outcomes

The results for the various outcomes that were also considered in the individual scenarios are summarized in the Table 20.

Table 20 Effects of intensified multi-factorial treatment on cardiovascular complications

	10-years incidence (until 2015)	20-years incidence (until 2025)	80-years incidence (until 2085)
	'Low CVD risk' scenario number of (first) cases prevented:		
Stroke	25 000 (63%)	36 000 (57%)	40 000 (51%)
CHD	76 000 (55%)	107 000 (48%)	111 000 (41%)
	'Multifactorial treatment' scenario number of (first) cases prevented:		
Stroke	4 400 (11%)	6 300 (10%)	6 800 (9%)
CHD	10 500 (8%)	13 900 (6%)	13 200 (5%)

CHD=Coronary Heart Disease.
All figures represent differences compared to the reference scenario. Figures for the reference scenario are given in Table 11.

8.3 Long-term effect on health care costs

The results for the various outcomes that were also considered in the individual scenarios are summarized in Table 21.

Table 21 Expected life-time costs and efficacy of intensified multifactorial treatment

Scenario	Costs (millions)			Effects	Cost-effectiveness
	Intervention	*Savings in healthcare for related disease*	*Net costs**	*QALYs gained*	*Euro/QALY*
Low blood pressure	N/A	2 200 (20%)	2 900 (7%)	659 000	N/A
Blood pressure treatment	726	276 (2%)	384 (1%)	86 000	13 000

* Net costs are the difference between costs savings in healthcare for related diseases and additional costs due to healthcare for unrelated diseases (in particular in life years gained).
Costs have been discounted at a rate of 4% and effects at 1.5%. No intervention costs can be assigned to the 'maximum' scenarios and therefore also no cost-effectiveness ratios.

8.4 Sensitivity analyses

As separate sensitivity analyses were already carried out for the individual scenarios, we restricted the sensitivity analyses done here to varying discount rates and the time horizon. The results are displayed in Table 22.

Table 22 Sensitivity analysis for the 'multifactorial treatment' scenario

Scenario variant	Prevented over time period considered		QALYs gained	Cost-effectiveness
	Stroke	*CHD*		
Base-case*	6 300	13 900	86 500	13 000
All discount rates 0%	6 300	13 900	115 000	19 100
All discount rate 4%	6 300	13 900	57 000	19 500
Time horizon 5 years	3 000	2 600	5 900	53 500
Time horizon 10 years	4 400	10 500	20 200	23 400
Time horizon 20 years	6 300	13 900	54 500	14 400

* Base case: time horizon 20 years for cases prevented, and 80 years for QALYs and cost-effectiveness; discount rates 1.5% for QALYs and 4% for costs, time horizon 80 years.
Except for the last three rows, the time horizon is that of the base case.

8.5 Summary

Diabetes is a metabolic disease that is associated with an increased prevalence of other cardiovascular risk factors. Moreover, as hyperglycaemia poses a continuous threat to the cardiovascular system, there may well be a deleterious interaction with such other risk factors at the physiological level. Thus, it is now generally recommended that all cardiovascular risk factors should be targeted simultaneously, including blood sugar, cholesterol and blood pressure.

The multifactorial approach leads to substantially greater health benefits than each of the individual approaches. Costs are greater, but in the base-case scenario the cost-effectiveness ratio is still acceptable. An important disadvantage, however, is the strong medicalization of the patients. As already mentioned earlier, insulin treatment requires a daily confrontation with being a patient. In addition, blood pressure control and cholesterol lowering each require extra pills per day, and often combination treatment is necessary. Besides, doctor visits will need to be more frequent for blood pressure and cholesterol monitoring and adjustments of medication schedules, even leaving aside insulin and glucose management.

PART 3 GENERAL DISCUSSION

9 Summary, discussion, and recommendations

9.1 Summary of findings

In this report we explored the costs and potential effects of measures aimed at preventing the development of diabetes (part one) or aimed to prevent cardiovascular complications in persons with diabetes (part two).

In part one, we calculated the costs and effects of interventions, aimed to reduce the expected number of new cases of diabetes and cardiovascular diseases. We modeled the developments over time for a cohort resembling the Dutch general adult population, 20 to 80 years of age. The total number of new cases of diabetes up to 2025 that is expected in this population of 11.8 million persons is 1.66 million. The expected life-time costs for diabetes and cardiovascular disease are €205 billion and the expected life-time total health care costs €1200 billion (discounted with 4% annually). We evaluated what would happen if all Dutch adults would start and stay in the lowest risk factor classes for body mass index and physical activity or for smoking. The extent to which these theoretic scenarios as well as the realistic preventive measures considered, succeed in preventing expected disease incidence as well as their long-term consequences for health care costs are summarized in Tables 23 and 24 and further discussed in Section 9.2 below. Figures 7 and 8 depict the cumulative reduction in diabetes incidence for each of the scenarios.

In part two, we calculated the costs and effects of different pharmacological interventions, aimed to reduce the expected number of cardiovascular complications in persons with diabetes. We modeled the developments over time for a cohort resembling the Dutch population of persons with diabetes, 30 to 75 years of age. The expected incidence of cardiovascular complications up to 2025 in this diabetes population of 398,000 people is 63,000 for stroke and 220,000 for coronary heart disease. Expected life-time costs related to diabetes and cardiovascular complications are €11.2 billion and the expected total health care costs are €38.8 billion (discounted with 4% annually).

The results of the maximum and realistic scenarios, with respect to disease incidence, life-time health care costs and cost-effectiveness ratios, are summarized in Tables 25 and 26 and discussed in Section 9.3 below. Figures 9 and 10 depict the cumulative reduction in cardiovascular disease incidence for each of the scenarios.

Table 23 Summary results universal and selective prevention

Scenario	Cumulative 20-year incidence			Life time Costs	
	DM	*Stroke*	*CHD*	*Related*	*Total*
Normal weight and active	47	22	18	11	7
Community-based intervention	1.4	0.5	0.5	0.3	0.1
Lifestyle program obese adults	0.5	0.1	0.1	0.06	0.04
No smokers	3	12	17	4	7
Smoking cessation intervention	-	0.4	0.3	0.1	0.06

DM: diabetes mellitus type 2; CHD: Coronary Heart Disease.
The table depicts proportional reductions (percentage of expected number of cases) in expected disease incidence, proportional reduction in health care costs for diabetes and CVD (related costs), and proportional increase in total health care costs for the scenarios for universal and selective prevention. Cumulative 20-year incidence refers to the period 2005-2025. Related costs are those related to diabetes and cardiovascular complications. Total costs are the sum of the related costs and the costs for all other diseases, but excluding the costs of the intervention.

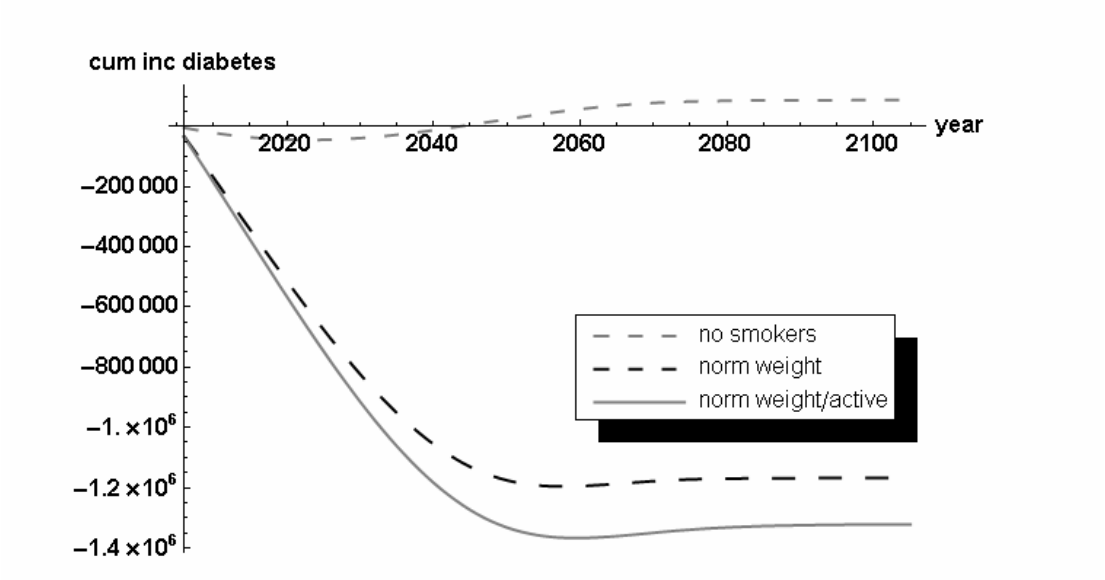

Figure 7 Reduction of cumulative diabetes incidence in maximum scenarios: 'no smokers', 'normal weight', and 'normal weight and active'.

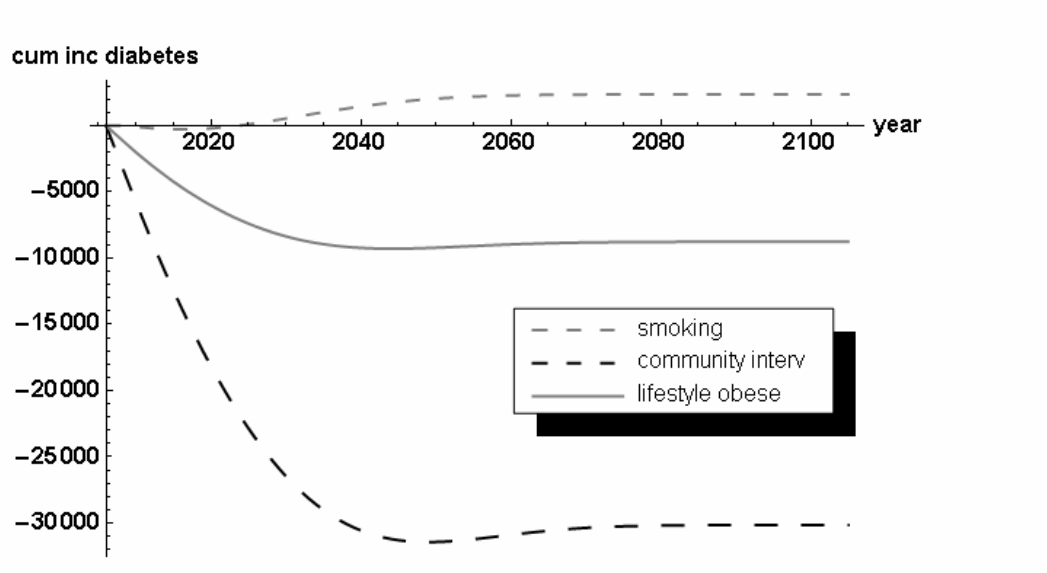

Figure 8 Reduction of cumulative diabetes incidence in the intervention scenarios: 'smoking cessation', 'community intervention', and 'lifestyle program obese adults'

Table 24 Summary of cost-effectiveness results interventions for universal and selective prevention

Scenario	Intervention costs (millions)	QALYs gained	Total costs (millions)	Cost-effectiveness ratio (€/QALY)
Community-based intervention	56	280 000	1 257 (0.1%)	5 000
Lifestyle program obese adults	112	80 000	426 (0.04%)	7 000
Smoking cessation	334	130 000	521 (0.06%)	7 000

The table depicts total intervention costs, QALYs gained over life-time as a result of the intervention, increase in life-time total health care costs due to the intervention and the cost-effectiveness ratio for the intervention: (intervention costs + total costs) /QALYs, for realistic scenarios for universal and selective prevention.

Table 25 Summary results care-related prevention

Scenario	Cumulative 20-year incidence		Life time Costs	
	Stroke	*CHD*	*Related*	*Total*
Low blood glucose	11	8	2.0	2.2
Intensified blood glucose treatment	1	1	0.2	0.1
Low cholesterol	8	20	4.9	2.3
Intensified cholesterol treatment	5	3	1.1	0.5
Low blood pressure	47	33	14.4	5.3
Intensified blood pressure treatment	5	3	1.0	0.5
Low CVD risk	58	49	20.0	8.0
Intensified mulifactorial treatment	10	6	2.5	1.0

CHD: Coronary Heart Disease; CVD: CardioVascular Disease.

The table depicts proportional reductions (percentage of expected number of cases) in expected disease incidence, proportional reduction in health care costs for diabetes and CVD (related costs), and proportional increase in total health care costs for the scenarios for universal and selective prevention. Cumulative 20-year incidence refers to the period 2005-2025. Related costs are those related to diabetes and cardiovascular complications. Total costs are the sum of the related costs and the costs for all other diseases, but excluding the costs of the intervention.

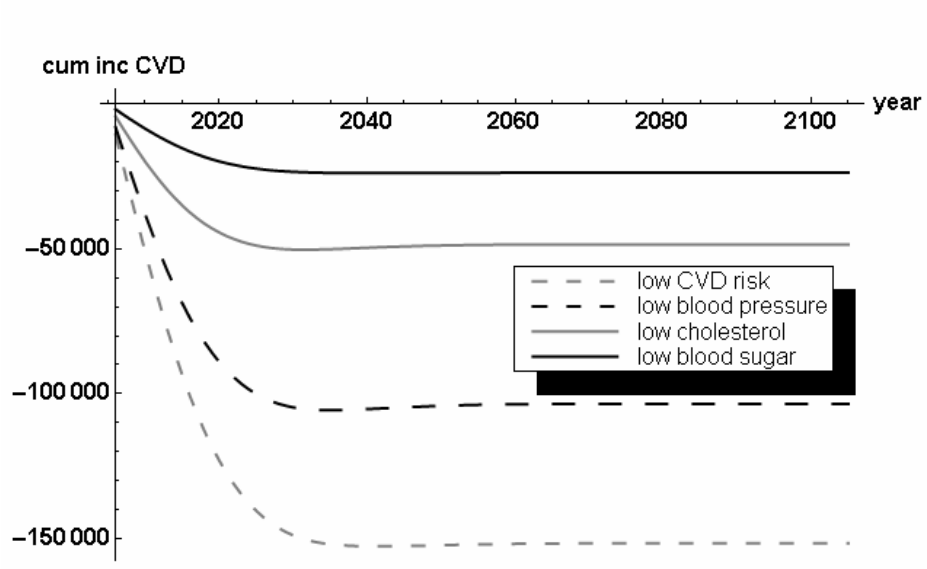

Figure 9 Reduction of the cumulative incidence of CHD (heart and stroke combined) in the maximum scenarios

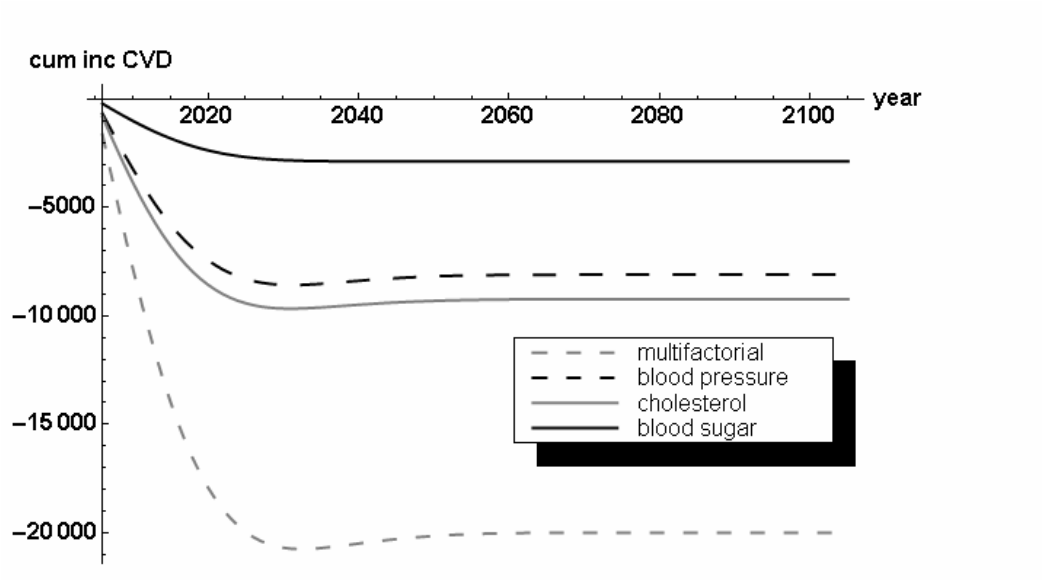

Figure 10 Reduction of the cumulative incidence of cardiovascular disease (heart and stroke combined) in the realistic, intervention, scenarios

Table 26 Summary of cost-effectiveness results care-related prevention

Scenario	Intervention costs (millions)	QALYs gained	Total costs (millions)	Cost-effectiveness ratio (€/QALY)
Intensified blood glucose treatment	148	9 000	42 (0.1)	22 000
Cholesterol lowering treatment	371	40 000	176 (0.5)	14 000
Blood pressure lowering treatment	208	39 000	173 (0.5)	10 000
Multifactorial treatment	726	86 000	384 (1.0)	13 000

The table depicts total intervention costs, QALYs gained over life-time as a result of the intervention, increase in life-time total health care costs due to the intervention and the cost-effectiveness ratio for the intervention: (intervention costs + total costs) /QALYs, for realistic scenarios for universal and selective prevention.

9.2 Highlights and recommendations: prevention of diabetes

Great potential for preventing diabetes by reducing body weight, but a large gap exists between health benefits in the maximum scenario and those attained in the realistic scenario.

The potential to reduce diabetes incidence through reducing bodyweight, is high because overweight is a very strong risk factor for diabetes and overweight is highly prevalent among the Dutch adult population. Our theoretical maximum scenario showed that if everybody would have a normal weight, about half of the diabetes incidence could be prevented. However, this would imply an average weight loss of approximately 25 kg in obese adults and 10 kg in persons who are moderately overweight. In trials using community-based and targeted lifestyle interventions, only modest average weight losses of approximately 0.5 kg and 3.0 kg are found. In addition, there is no evidence that community interventions cause a substantial increase in the mean level of physical activity. Thus, the realistic scenario showed a 2% reduction of diabetes incidence, based on a combination of nation-wide implementation of the community-based intervention and a lifestyle program offered to 10% of the Dutch obese adults.

Although we modeled a once-only implementation of lifestyle programs, we assumed that the lifestyle changes, relative to the control population, were maintained (for life) after the intervention. This is an optimistic assumption, as weight loss is not easily maintained. Repeated implementation of the interventions might be needed to maintain (or even increase) the health benefits that are achieved. Repeated implementation seems a realistic option as our sensitivity analyses showed that even with higher intervention costs (for example due to repeated implementation) the intervention remains cost-effective.

As opposed to the optimistic assumption of weight loss maintainance, as described above, the methods we used might have resulted in an underestimation of the effect of lifestyle interventions. We modeled the effects on diabetes incidence only through changing risk factor distributions of body mass index and physical activity, while other intervention related effects such as weight change, waist-hip ratio or dietary changes may have independent beneficial effects that were not taken into account.

Effects of smoking on diabetes incidence are modest.

Smoking has a modest impact on the risk of developing diabetes and even if everybody would be a non smoker, this would reduce the expected incidence of diabetes by only 3% (maximum scenario). Successful smoking cessation, similar to other lifestyle changes, is not easily achieved nor maintained. Furthermore, if a person stops smoking, the risk for diabetes does not decline to the risk for a non smoker but becomes similar to a former smoker, due to long-lasting harmful effects of previous smoking habits. Despite the high prevalence of smoking, implementing a variety of measures aimed at smoking cessation will therefore not influence the long-term expected incidence of diabetes. Nonetheless, smoking cessation interventions are cost-effective and important for the prevention of other chronic diseases such as cardiovascular diseases and cancers.

Prevention of diabetes results in a decrease in diabetes-related health care costs over life-time, but total health care costs increase.

Both lifestyle- and smoking cessation interventions result in initial decreases in the health care costs for diabetes and cardiovascular diseases. However, as shown in for example Figure 2a, after a certain time these costs become a little higher in the intervention scenarios than in the reference scenarios, because more people of the intervention cohort survive. Many of these survivors will eventually develop diabetes or cardiovascular disease, which is highly prevalent at advanced age (i.e. delay instead of real prevention).

For total health care costs there is a small initial decrease compared to the reference scenario because prevented costs for diabetes and CVD are higher than additional costs for other diseases. However, within a few years, total health care costs are higher for the intervention scenario, because more people survive and other diseases may develop during these life years gained. For example if, due to the intervention, stroke is prevented in a 60 year old woman, and she now lives until age 80, she might develop dementia.

Because the additional total health care costs are predominant at the end of the time horizon, discount rates do have a substantial impact on these costs and the cost-effectiveness ratio. An annual discount rate of 4% (as used in this report, according to Dutch guidelines) means that costs in the final years have a very low weight.

Interventions aimed at weight loss or smoking cessation are both cost-effective under a wide range of assumptions.

The cost-effectiveness ratios of the interventions are fairly robust. Assuming lower treatment effects, relapse in effects after the interventions or higher intervention costs, does not substantially change these ratios. However, it takes some time before the health benefits of prevention reach their full potential. The lifestyle intervention for the general population is cost-effective for all time periods considered with an optimum time horizon of approximately ten years. The lifestyle intervention for obese adults is cost-effective if a time-horizon of at least ten years is applied and smoking cessation interventions are cost-effective with a time horizon of 20 years or more.

9.3 Highlights and recommendations: prevention of complications

Large potential for blood pressure treatment but a large difference between health benefits in the maximum scenario and those attained in the realistic scenario.

If all persons with diabetes would be in the lowest risk factor class for either blood glucose, cholesterol or blood pressure, the cumulative incidences of macrovascular complications would drop by 10%, 8% and 47% respectively, for stroke, and by 7%, 20% and 33% for coronary heart disease (Table 7.2). This implies that the largest potential for the prevention of complications would be in the reduction of blood pressure. This large potential can be explained by the fairly strong association between systolic blood pressure and the incidence of cardiovascular complications. Furthermore, hypertension is highly prevalent in the Dutch diabetes population (about 70% have a systolic blood pressure $\geq$ 140 mmHg) and approximately half of them do not receive antihypertensive treatment, meaning that current treatment is suboptimal. Although elimination of blood pressure as a risk factor (maximum scenario) would have an enormous effect on the development of complications, only about 10% of this potential can be realized by starting new treatments in 50% of currently untreated hypertensive patients as

modeled in our realistic scenario. This means that initiating treatment in untreated patients is not enough. In addition, treatment compliance and treatment regimens should be addressed in patients with high blood pressure levels despite current treatment.

Relative small health benefits of strict blood glucose control

Although it is known that strict control of blood glucose levels reduces the risk for microvascular complications, conclusive evidence that lower levels of HbA1c lead to substantial reductions in the incidence of cardiovascular complications is lacking at present. Furthermore, it should be mentioned that Dutch diabetes patients in current practice are already relatively well controlled. About half of the patients fulfill the goal of a HbA1c level lower than 7%. Given these facts, it is not surprising that our maximum scenario showed only modest potential benefits with respect to the prevention of macrovascular complications. Obviously, the realistic scenario could not do better. The intervention studied in our realistic scenario (switching patients with at least two oral agents to insulin monotherapy), implied that only a limited proportion of patients were eligible for the treatment. Finally, alhough we know that HbA1c levels in persons with diabetes increase with age, and disease progression, the model did not allow for changes of HbA1c levels over time (see also methodological issues), and we could also not include treatment adaptations as a reaction to these changes.

Effects of cholesterol-lowering treatment on stroke

The effect of elimination of cholesterol on stroke incidence in the maximum scenario is relatively limited, but given this limited impact, the effect of the realistic scenario (defined as cholesterol-lowering treatment provided to more patients) is quite large. This can be explained by the way the association between cholesterol and stroke is modeled in the CDM. Because there is no convincing evidence for an association between the level of total cholesterol and stroke incidence from observational studies, this association is not incorporated in the CDM [39]. However, cholesterol-lowering treatment with statins does reduce stroke incidence and this association has been included [39].

Multifactorial intervention: summing up the parts?

Although we addressed treatment of separate cardiovascular risk factors, diabetes treatment should be multifactorial aiming for optimal blood glucose-, cholesterol- and blood pressure control. Our maximum ‘multifactorial’ scenario showed that we cannot simply add the health benefits from the individual maximum scenarios, because a complication can only be prevented once. Because the proportional reduction in complications is much smaller in the realistic scenarios, it appears that here the health benefits do equal the sum of the individual results. It should be mentioned that the risk factors in the model are assumed to be independent, while in reality unfavourable risk factors may cluster within certain persons.

Prevention of diabetes complications results in a decrease in health care costs related to these complications over life-time, but total health care costs increase.

From a health care perspective, prevention does not save money. However, all interventions can be considered cost-effective, meaning that the health gains justify the extra investments.

9.4 General, methodological issues

Using risk factor classes

The Chronic Diseases Model uses risk factor classes, and no continuously distributed risk factor data. As a consequence, people who are already in the lowest class for a specific risk factor are unable to benefit from interventions, targeted at that risk factor. For example, even a substantial weight reduction does not result in any health benefits in a person who weights 80 kg and is 1.8m tall (BMI of 24.7). Significant associations between BMI and disease incidence (for example diabetes) have however been shown even in the lower ranges of BMI [58] [37].

Disadvantages of modeling intervention effects through changing risk factor classes.

In general, the Chronic Diseases Model uses changes in risk factor levels to estimate the long-term effects on diseases that are related to this risk factor. One reason to take such an approach, is that (short-term) intervention trials generally report effects in terms of changes in risk factor levels and not in terms of effects on disease incidence. For example, effects of lifestyle interventions on diabetes incidence are modeled through changing risk factor distributions of body mass index and physical activity. Recent results from lifestyle studies that do report long-term effects on disease outcomes, suggest that our method may results in an underestimation of the 'true' effect of lifestyle changes. In the Finnish Diabetes Prevention Study, a four-year lifestyle intervention, reduced the 7-year incidence of diabetes by 42% [40]. Similar findings were recently presented for the Study of Lifestyle Intervention in patients with glucose intolerance in Maastricht (SLIM). It appeared that the intervention reduced 6-year diabetes incidence, although initial reductions in body weight were not maintained.

Limitations of modeling treatment effects through direct linking with disease incidence.

Cholesterol-lowering and antihypertensive treatments are exceptions to the general method used in CDM. For these interventions sufficient evidence exists to quantify a direct association between treatment and cardiovascular outcomes. However, this method has its own limitations: treatment is dichotomized in the model (yes or no) without specification of the intensity of treatment, or whether treatment is adequate or not.

Due to limited data, transition rates for blood glucose, cholesterol and blood pressure were set to zero.

This means that we assumed that treatment, when initiated, was continued lifelong, while untreated patients remained untreated. On the other hand we assumed that the levels of blood glucose, cholesterol and blood pressure were stable over time (no increase with aging). We may be able to explore the impact of these assumptions as soon as more information on natural development and treatment in current practice becomes available.

In the Chronic Diseases Model, cardiovascular complications are 'chronic' meaning that there are no recurrent events.

In the model a person either dies due to a cardiovascular complication, for example stroke or becomes a 'chronic' (stroke) patient. Consequently although treatment can be beneficial in preventing recurrent events, these effects are not accounted for in the model. This means that the health benefits as predicted for the scenarios for care-related prevention are somewhat underestimated.

9.5 Conclusions

Prevention of obesity seems the key factor in preventing diabetes. Effort should be devoted to identifying and developing effective measures that can bring about long-lasting lifestyle changes. With respect to prevention of macrovascular diabetes complications, more gain is to be expected from intensive treatment of cholesterol and blood pressure than from (further) improvements of blood glucose control of patients with moderate glycaemic control.

The potential effects of lifestyle interventions in preventing macrovascular complications in persons with diabetes and beneficial treatment effects on microvascular complications were not addressed in our study and should be explored in future research. Other aspects that need further attention are long-term treatment effects in day-to-day realistic conditions -as opposed to efficacy in well-controlled trials-, determinants of treatment adherence and treatment success, drug-induced adverse event [44 64] and the impact of (multiple) drug use on a persons quality of life.

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Appendix 1: Sensitivity analyses for lifestyle intervention

Sensitivity analyses: lifestyle intervention for the general population

Relapse:

In the base-case analysis we assume that people who were reached by the lifestyle program have the same probabilities to gain weight as persons who were not reached by the program after the intervention stops, i.e. effects are remained. Our sensitivity analysis includes a scenario in which there is a decline in the initial effect after the intervention ends. Based on a meta-analysis by J. Anderson and colleagues [2] that focused on long-term weight loss maintainance (after hypoenergetic balanced diets), we assume a 50% decline in the initial effect in the first five years after the intervention ends*. The assumed effect on bodyweight over time is illustrated in Figure 1. The same assumptions concerning decline in effect are applied to the effect on physical activity.

* Anderson: Weight loss in intervention participants declines from 9 kg at the end of the intervention to 2 kg five years later. If a 'natural' weight gain of 0.5 kg per year is assumed the intervention effect declines from 9.5 kg (9.0 kg + 0.5 kg, intervention duration 1 year) to 5.0 kg (2.0kg + 6* 0.5kg), which is approximately 50%.

Sensitivity analyses: lifestyle intervention for obese persons

Relapse:

In the base-case analysis we assume that intervention participants and non participants have the same probabilities to gain weight after the intervention stops (i.e. effects are remained). From the long-term evaluation of the Diabetes Prevention Study it appeared that 25% of the intervention effect on weight dissapeared within the 3 years after the intervention stopped [40]. It seems reasonable to assume that the decline after that is more gradual.Therefore we assume a 25% decline in the initial effect on BMI in the first three years after the end of the intervention and another 12% decline in the three consequetive years. The assumed effect on bodyweight over time is illustrated in Figure 2.
The same assumptions concerning decline in effect are applied to the effect on physical activity.

Appendix 2: Input data blood glucose scenario

The choices made to define a realistic scenario for intensified blood glucose lowering treatment were largely based on four Diabetes Care studies conducted in the Netherlands: 1) The Hoorn study; 2) SHL Breda (primary care Breda); 3) ; Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC); 4) The Utrecht region. See the report by Baan et al. [4].

The first three of these studies together provided a database of almost 25,000 diabetes patients, which was used to estimate the baseline distribution of HbA1c values and of anti-diabetic medication use. The proportion of patients using 2 oral agents—a parameter necessary for the scenario definition (see below)— was derived from the Hoorn study, which showed that approximately 28% of patients were using two (or more) oral anti-hyperglycemic drugs but no insulin (Giel Nijpels; personal communication). Moreover, it could be further inferred that almost none of these patients were in HbA1c class 3 (HbA1c > 8.5). With 87.6% in classes 1 and 2 (12.4% in class 3), this means that (0.28/0.876)*100%=32% of patients in classes 1 and 2 use 2 oral agents without insulin.

The Goudswaard study [22] served as the model for the actual definition of the realistic scenario. It concerns a trial conducted in a general practice setting, in which patients with insufficient control of their diabetes despite the use of at least two oral anti-glycemic agents, were randomized to one of two insulin regimens: insulin monotherapy or insulin in combination with oral drugs. Based on the results of this trial, we assumed that switching to insulin monotherapy would result in an average HbA1c reduction of 1 percentage point. Moreover, still based on this study, we assumed that in 10% of cases switching to insulin would be unsuccessful, either due to a lack of effect in some patients or to difficulties self-administering insulin. Thus, the scenario we defined includes an intervention in which all patients using 2 oral agents and who's HbA1c > 7.0% are started on insulin monotherapy.

To estimate the effect of this intervention, again the database of the three first studies was used. When 1 percentage point was subtracted from the HbA1c levels of those whose HbA1c values were in the range 7.0-8.5, 80.5% of the patients originally in class 2 transferred to class 1. However, as we assumed only 32% of the patients with HbA1c 7.0-8.5 were eligible (i.e. used two oral agents and no insulin), and that there would be a treatment failure in 10% of cases, the proportion of patients who transferred from class 7-8.5 to < 7 was calculated to be 0.32*0.9*80.5%=23.2%.

Table 27 Distribution shift over HbA1c categories

	baseline	Post intervention
HbA1c < 7%	45.6%	55.3%
HbA1c 7%-8.5%	42.0%	32.3%
HbA1c ≥ 8.5%	12.4%	12.4%

Sources: ZODIAC, SHL and WestFriesland, supplemented with personal communications (Dr. G. Nijpels)

Intervention costs

We assumed that all patients who are switched to insulin will be treated with insulin monotherapy. Net drug costs thus consist of the difference in cost between insulin and two oral agents. As mentioned above, 32% of the patients in class 2 are eligible for treatment switch. As 42% of patients are in class 2 originally, 0.32*42.0% = 13.4% of patients will be switched to insulin. Of these, 90% will continue treatment. For the 10% of patients experiencing treatment failure (due to a lack of effect in some patients or to difficulties self-administering insulin; see above), we assumed that they would be treated

for half a year after which their costs would be 'costs as usual'. Costs per person for the first and subsequent years are displayed in Table 28.

Table 28 Costs per patient switching to insulin monotherapy

Cost item	Volume in units (V)	Unit price in € (P)	Costs in € (V*P)
	First year		
Mixtard 30/70 insulin (1)	12 months	19.86 – 25.83*	(mean) 274.40
SU-derivatives (2)	7.7 prescriptions	17.09**	131.63
Metformine (3)	7.7 prescriptions	7.18**	55.26
Drug costs net: (1)-(2)-(3)			87.25
Glucose meter + test stips			494
Blood withdrawal materials			42
Nurse instructions	60 minutes	0.86	51.60
Dietician	30 minutes	0.84	25.20
Diabetes diary	1	12.65	12.65
Telephone costs, time	175 minutes (26 weeks*10 minutes+9 months*5 minutes)	0.03	5.25
Nurse's telephone time	175 minutes	0.86	150.50
Telephone costs, subscription			1.50
GP visit	40 minutes (4*10)	2.04	81.60
Total			**952.55**
	Second year		
Drug costs net			87.25
Blood withdrawal materials			42
Visit to diabetes nurse	20 minutes (2*10)	0.86	17.20
Diabetes diary	1	12.65	12.65
Telephone costs, subscription			1.50
(Extra) GP visit	10 minutes	2.04	20.40
Total			**181.00**

* Source; www.cvzkompassen.nl

** GIP2003, prices adjusted to 2004 level