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Modeling chronic diseases: the diabetes module
Justification of (new) input data

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Rapport in het kort

Modelleren van chronische ziekten: de diabetes module
Verantwoording van (nieuwe) invoer

Om effecten van verschillende preventieve maatregelen voor diabetes te kunnen berekenen, is het RIVM Chronische Ziekten Model geactualiseerd en aangepast. Het Chronische Ziekten Model is een instrument om effecten van veranderingen in het vóórkomen van risicofactoren, bijvoorbeeld overgewicht en roken, voor chronische ziekten (o.a. hart- en vaatziekten) te schatten op ziektelast en sterfte. Dit rapport geeft de verantwoording van de nieuwe diabetesmodule in dit model. Met deze diabetesmodule kunnen zowel primaire preventiestrategieën als maatregelen in de zorg (=betere behandeling van diabetes en cardiovasculaire risicofactoren) worden doorgerekend en het effect op de volksgezondheid worden geschat. Dit geeft beleidsmakers en zorgverleners inzicht in hoeveel gezondheidswinst er te behalen zou zijn door preventie en het kan ondersteunen bij het prioriteren van verschillende preventiestrategieën.

Alle diabetes-gerelateerde informatie in het Chronische Ziekten Model is geactualiseerd. Roken is toegevoegd als risicofactor voor diabetes. HbA1c (een maat voor het bloedglucose niveau) is toegevoegd als risicofactor voor cardiovasculaire complicaties. Nieuwe modelgegevens bij patiënten met diabetes zijn het voorkomen van cardiovasculaire complicaties, het voorkomen van cardiovasculaire risicofactoren (HbA1c, hoge bloeddruk, roken, cholesterol en overgewicht) en de relaties tussen deze risicofactoren en het ontstaan van cardiovasculaire complicaties.

Trefwoorden - Diabetes mellitus, hart- en vaatziekten, preventie, behandeling, modelering

Abstract

Modeling chronic diseases: the diabetes module
A justification of (new) input

The RIVM chronic disease model (CDM) is an instrument designed to estimate the effects of changes in the prevalence of risk factors for chronic diseases on disease burden and mortality. To enable the computation of the effects of various diabetes prevention scenarios, the CDM has been updated and adapted. The present report presents a justification of the new diabetes module and the data used.
The diabetes module allows the computation of both primary prevention scenarios and care scenarios (i.e. treatment of diabetes and cardiovascular risk factors) and the assessment of the effect on public health. The outcome provides policy makers and health professionals with insight into the potential prevention-associated health gain and may aid them in prioritising prevention scenarios.

All diabetes-related information in the CDM has been updated. Smoking has been added as a risk factor for diabetes. HbA1c (a measure of blood glucose level) has been added as a risk factor for cardiovascular complications. New model data regarding patients with diabetes include the prevalence of cardiovascular complications, the prevalence of cardiovascular risk factors (HbA1c, high blood pressure, smoking, cholesterol and overweight) and the relationships between these risk factors and the development of cardiovascular complications.

The literature shows that in trials focusing on the prevention of diabetes, the diabetes incidence drops by 60%. Trials focusing on improved treatment of diabetes patients show that the incidence of cardiovascular diseases falls by 25-50%, depending on the type of treatment and research setting.

Keywords - Diabetes mellitus, cardiovascular diseases, prevention, treatment, modeling

Voorwoord

Dit rapport is een mijlpaal binnen de kennisvraag diabetes uit 2004 (kennisvraag 2.3.3). De kennisvraag Diabetes is een lopend project dat uitgevoerd wordt door het centrum Preventie en ZorgOnderzoek (PZO) van het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) in opdracht van het Ministerie van Volksgezondheid, Welzijn en Sport (VWS). Deze kennisvraag is onderdeel van programma 2 'Beleidsondersteuning Volksgezondheid en Zorg'.

Het doel van het project is het wetenschappelijk onderbouwen van diverse preventieve maatregelen om diabetes en complicaties ten gevolge van diabetes te voorkómen. Om deze vraag te beantwoorden wordt gebruik gemaakt van het RIVM Chronische Ziekten Model. Het Chronische Ziekten Model was tot nog toe vooral geschikt om primaire preventiestrategieën door te rekenen, maar door diverse aanpassingen is het nu ook mogelijk om effecten van preventiestrategieën in de zorg voor diabetes te schatten met het Chronische Ziekten Model. Het huidige rapport geeft een inhoudelijke verantwoording van de aanpassingen die in de diabetesmodule van het Chronische Ziekten Model zijn uitgevoerd.

Het onderzoek is uitgevoerd in nauwe samenwerking met het project 'Budgetallocatie: methode-ontwikkeling voor prioritering van interventies bij chronische ziekten' dat binnen het MAP SOR-onderzoeksprogramma 'Methodologie optimale gezondheidswinst en kwaliteit van zorg' wordt uitgevoerd. De conceptuele en formele opzet van het model is beschreven in het rapport 'A conceptual framework for budget allocation in the RIVM Chronic Disease Model. A case study of Diabetes Mellitus'(rapportnummer 260706001/2005).

Met het hier beschreven diabetesmodel kunnen berekeningen van effecten van diverse preventiestrategieën worden gemaakt in termen van ziektelast, sterfte, zorggebruik en kosten. De eerste resultaten zullen naar verwachting eind 2005 gepubliceerd worden.

Hierbij wil ik iedereen bedanken die heeft bijgedragen aan het tot stand komen van het diabetesmodel en aan deze rapportage.

Caroline Baan
Projectleider

Contents

Summary

Background
The RIVM Chronic Disease Model (CDM) is a computer program designed to compute the effects of changes in risk factor prevalence on disease specific morbidity and mortality over a prespecified number of years. The RIVM was asked to compare the potential benefits of prevention interventions targeted at diabetes and cardiovascular diabetes complications, using the CDM. This report describes the diabetes module in the CDM and gives a justification of (new) diabetes-related input data in the CDM.

Methods
Data regarding the incidence and prevalence of diabetes and diabetes mortality were based on Dutch general practitioner registrations. Prevalence of risk factors for diabetes incidence was retrieved from national surveys. Prevalence of risk factors for cardiovascular complications, in diabetes patients, was estimated from the CDM or based on data from Dutch diabetes care projects. Relative risk estimates for risk factors for diabetes incidence and diabetes complications were estimated from the international literature. A literature review was performed to identify effective prevention interventions targeted at diabetes and cardiovascular complications.

Results
All diabetes-related input data in the CDM were updated. Smoking was added as a risk factor for diabetes incidence. HbA1c (a measure of blood glucose control) was added as a risk factor for diabetes complications. Among diabetes patients, new input data in the CDM comprised the prevalence of cardiovascular complications (acute myocardial infarction, coronary heart disease, congestive heart failure and stroke), the distribution of cardiovascular risk factors (body mass index, physical inactivity, smoking, total cholesterol, blood pressure and HbA1c), and the relative risks between these risk factors and cardiovascular complications. International studies showed that lifestyle programs may reduce diabetes incidence with up to 60% in three to five years, while strict pharmacological treatment of blood pressure or serum cholesterol in diabetes patients may prevent approximately 25% of the cardiovascular complications.

Conclusion
The CDM has been adapted to allow for the comparison of the benefits of prevention interventions aimed at diabetes or diabetes complications. Ongoing activity is needed to update, expand and validate the diabetes module in the CDM.

1. Introduction

CA Baan, G Bos, MAM Jacobs-van der Bruggen

Diabetes is a substantial and growing public health problem and has been appointed one of the spearheads of Dutch policy for the coming years. The National Institute for Public Health and the Environment (RIVM) was asked to explore which intervention strategies and measures are most effective in preventing diabetes and diabetes related (macrovascular) complications.
The Chronic Disease Model (CDM) has been developed by RIVM as a tool to generate structured data on the effects of autonomous changes (demography) as well as interventions on chronic disease risk factors in terms of expected morbidity and mortality in the future. The merits of using a model like the CDM to evaluate interventions are that the consequences can be extrapolated to the Dutch diabetes population, that long term effects can be computed, and that costs and effects of different interventions can be consistently compared. The CDM will be used to compare the potential benefits of several intervention scenarios aimed at primary prevention (preventing new cases of diabetes) or tertiary prevention (reducing complications in diabetic patients). Secondary prevention (screening for new diabetes patients) is beyond the scope of this report. The effects of prevention will be described in terms of reduced morbidity and mortality and also in expected health care demands, costs and quality of life (disability adjusted life-years).
The CDM is in constant development with regular structural changes and updates implemented for different applications. For this extensive diabetes project all input data regarding diabetes in the “old CDM” (CDM-2003) is updated. Also, more specific information is needed. For example, the prevalence of risk factors within the diabetes population (how many diabetes patients have overweight or obesity) was not included in the CDM-2003. Furthermore several structural changes and extensions to the model are needed to model diabetes prevention. For example, HbA1c has to be added as a risk factor for diabetes complications in patients with diabetes. The adaptations with regard to diabetes will be partly implemented in the “new CDM model” (CDM-2005-01), a model version which is available in march 2005. All other diabetes adaptations described in this report are implemented in a CDM version which is available later in 2005 (CDM-2005-02). The CDM-2005-02 will be used for modeling diabetes prevention.
In this report we focus on type 2 diabetes as most of the Dutch diabetes patients (>85%) have type 2 diabetes, and risk factors for this type of diabetes are better understood and more suitable for prevention as compared to type 1 diabetes.

The objective of this report is twofold. First we outline the structure of the CDM-2003 in relation to diabetes and the extensions and developments to the model that were needed to model diabetes interventions. We describe the diabetes specific input data in the CDM-2005-02 and how these data were collected. Secondly this report reviews the results of primary and tertiary diabetes intervention trials from the international literature. This review gives an indication as to which interventions are potentially beneficial and worth modeling.

This report is divided into four parts. In part 1, we briefly describe the CDM-2003 in general and in relation to diabetes. The interrelationships between diabetes, its risk factors, its cardiovascular complications and other risk factors for cardiovascular complications are outlined. We explain how the model was extended to enable the evaluation of interventions to prevent diabetes and its complications. The diabetes specific input data requirements for the

CDM-2005-02 are summarized. For a more elaborated description of diabetes in the CDM-2005-02 we refer to another RIVM report published in 2005 [1].

In Part II we describe the input data regarding diabetes prevalence, incidence and mortality as well as health care utilization, health care costs and quality of life. We summarize the parameters which were already included in CDM-2003 and their justification. Some of these parameters have been updated. Methods of data collection, the resources that were used (or excluded) and the data that were finally selected for the CDM-2005-02 are discussed. For some new data that should be added to the model (health care and costs) insufficient data are available. We discuss which information is still needed and how we plan to collect this information in 2005.

In Part III and IV we focus on risk factors for diabetes incidence (Part III) and risk factors for the development of macrovascular complications of diabetes (Part IV). In Part III we justify the input data regarding prevalence of risk factors in the Dutch population and the strengths of the relations between those risk factors and diabetes incidence in terms of relative risks. In Part IV, a description of all new parameters is given. We describe how the prevalence of cardiovascular complications, the prevalence of risk factors for complications in the Dutch diabetes population and the relative risks between these risk factors and complications in patients with diabetes were retrieved. In addition we review the results of primary (Part III) and tertiary (Part IV) diabetes intervention trials found in the international literature. This gives us some insight in the potential effects of different intervention strategies. Intensive trials however do not mirror real life (health care) practice. The results of these trials still have to be translated into realistic scenarios for the Dutch health care setting. Moreover, many of these trials include pharmacological treatment while medication is not incorporated in the CDM (yet). The results of defining and modeling intervention scenarios will be reported in 2005 and 2006.

Part I The Chronic Disease Model and diabetes

2. The Chronic Disease Model (CDM) and diabetes

RT Hoogenveen, TL Feenstra

The RIVM Chronic Disease Model (CDM) has been developed as a tool to describe the effects of changes in chronic disease risk factors on morbidity and mortality while taking into account integrative aspects. The CDM-2003 contains the following risk factors: body mass index (BMI), physical activity, smoking, alcohol, total cholesterol and systolic blood pressure. It models 28 chronic diseases: cardiovascular diseases (subdivided in acute myocardial infarction, other coronary heart disease, stroke, and congestive heart failure), COPD, asthma, diabetes mellitus, dementia, arthrosis (knee, hip and other), osteoporosis, low back pain and 15 different forms of cancer.
The model is structured in such a way that new diseases and risk factors can be added relatively easily. The mathematical model structure, which is called a multi-state transition model, is based on the life table method. The model states defined are the risk factor classes and disease states. State transitions are possible between classes for any risk factor, incidence, remission and progress for any disease, and mortality. The model describes the life course of cohorts in terms of changes between risk factor classes and changes between disease states over the simulation time period. Risk factors and diseases are linked through relative risks on disease incidence. The main model parameters are:

- the population numbers (in the year at which we start modeling),
- initial class prevalence rates and transition rates for all risk factors,
- initial prevalence, incidence and excess mortality for all diseases, and remission rates (if applicable) and
- relative risk values specified by risk factor and chronic disease.

All model parameters and variables are specified by gender and 5-year age-classes. The time step used for modeling is 1 year. The main model outcome variables are incidence, prevalence and mortality numbers specified by disease, and integrative measures such as total and disability-adjusted life years. Examples of the integrative aspects of the model are the joint effects of combined risk levels, different causes of morbidity and mortality being distinguished, the effects of mortality selection and the statistical modeling of dependent competing risks.
For further details on the Chronic Disease Model in general, we refer to a recently published technical report [1].

Diabetes is modeled in the CDM both as a disease and a risk factor for a number of cardiovascular diseases, which are the most important macrovascular complications of diabetes. The same holds for some cardiovascular diseases. Figure 2.1 shows the dependency structure between diabetes and cardiovascular diseases.

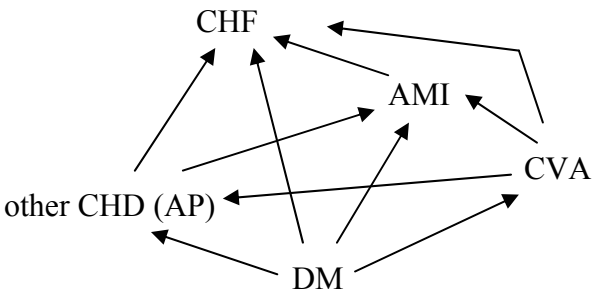


Figure 2.1 Dependency relations between diabetes mellitus and several cardiovascular diseases CHF=Congestive Heart Failure, AMI= Acute Myocardial Infarction, other CHD=other Coronary Heart Diseases, AP=Angina Pectoris, CVA=Stroke, DM=Diabetes Mellitus

The following risk factors included in the CDM-2003 are important for the modeling of diabetes and macrovascular complications of diabetes: body mass index (BMI), physical inactivity, smoking, alcohol, total cholesterol, and systolic blood pressure (SBP). For all risk factors, the model distinguishes several classes (table 2.1).

Table 2.1 Definition of risk factor classes in CDM-2003

Risk factor	**Definition of categories**
Bodyweight (BMI)	• Normal weight (BMI < 25 kg/m^2) • Overweight (BMI 25-30 kg/m^2) • Obese (BMI ≥ 30 kg/m^2)
Physical activity	• Active (30 minutes of activity of moderate intensity on at least 5 days of the week) • Moderately active (30 minutes of activity of moderate intensity on 1 to 4 days of the week) • Inactive (30 minutes of activity of moderate intensity on 0 days of the week)
Smoking	• Non smoking • Former smoking • Current smoking
Alcohol	Men • less than 1 drink per day • 1 to 4 drinks per day • 4 to 6 drinks per day • ≥ 6 drinks per day Women • less than 1 drink per day • 1 to 2 drinks per day • 2 to 4 drinks per day • ≥ 4 drinks per day
Total cholesterol	• < 5.0 mmol/l • 5.0-6.5 mmol/l • 6.5-8.0 mmol/l • ≥ 8.0 mmol/l
Blood pressure	• <120 mmHg • 120-140 mmHg • 140-160 mmHg • ≥160 mmHg • antihypertensive medication

In the CDM-2003, BMI and physical activity are risk factors for diabetes incidence as well as for some cardiovascular diseases. Smoking, alcohol, cholesterol and SBP are modeled as risk factors for cardiovascular diseases only. Adding these risk factors for diabetes and macrovascular complications of diabetes to figure 2.1, a rather complex structure results:

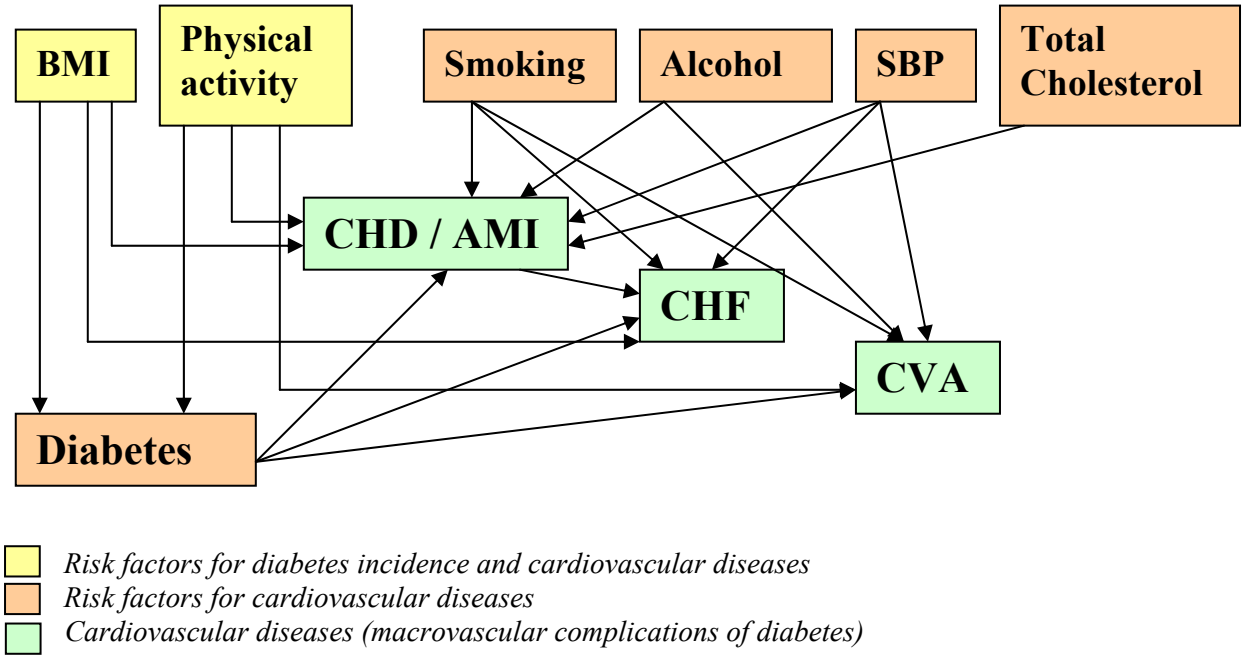


Figure 2.2 Dependency relations between risk factors, diabetes mellitus and several cardiovascular diseases

Given this structure, the following input data directly related to diabetes are included in the CDM-2003:

- diabetes prevalence, incidence and mortality rates,
- for each risk factor for diabetes incidence (BMI and physical activity), the distribution in the Dutch population over each risk factor class (prevalence), and the transition rates between these classes (e.g. probability to loose or gain weight),
- for BMI and physical activity, per risk factor class the relative risks for diabetes incidence, and
- for each combination of diabetes with a cardiovascular disease, relative risks for people with diabetes on incidence of the cardiovascular disease.

All these data are age- (5-year age-classes) and sex-specific. Prevalence data apply to the Dutch population, and are therefore based on the most appropriate, recent Dutch registry data (for diabetes) or survey data (for the risk factors). Relations between risk factors and diseases (relative risks) are estimated on the basis of data from the international literature.
The relative risks should be independent of risks associated with other risk factors that are modeled. This means that the relative risk has to be adjusted for other confounding factors included in the model to prevent double counting. For example, people who are physically inactive have a higher risk to develop diabetes as compared to active people. However a part of this relation is explained by a higher body mass index in inactive people. BMI in itself is a strong risk factor for diabetes, which is already accounted for in the model. Therefore, the relative risk estimates for physical activity on diabetes incidence need to be adjusted for BMI.

In the CDM-2003 version, diabetes is included as a single stage disease, that is, the only distinction made is between diabetes and no diabetes. The model takes into account the links between risk factors, diabetes and macrovascular complications of diabetes, but does not distinguish between the risk factor distribution among people with or without diabetes (figure 2.3).

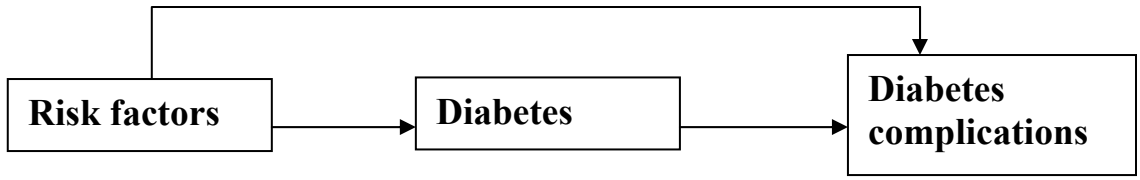


Figure 2.3 Dependency relations between risk factors, diabetes and macrovascular complications of diabetes in CDM-2003

3. Adaptations to the CDM with respect to diabetes

RT Hoogenveen, TL Feenstra

The CDM-2003 is suited to evaluate the effects of primary prevention, since the effect of changes in risk factor prevalence on diabetes and on cardiovascular complications can be estimated. However, it is not suited to evaluate the effect of tertiary prevention, that is, the prevention of cardiovascular complications in patients with diabetes. The link between diabetes treatment (resulting in improved risk profiles among patients with diabetes) and cardiovascular complications is not modeled. All people with diabetes are modeled as average diabetes patients, with average life expectancy and average risks for cardiovascular complications. Again, the distribution of risk factors (for example blood pressure) for cardiovascular complications among diabetes patients is not included in the CDM-2003. Hence, an extension of the model is needed to allow for the evaluation of tertiary prevention. Besides these changes, some further extensions to the model are considered with respect to the model outcomes (quality of life, health care and costs) as well as the implementation of new risk factors for diabetes incidence (smoking and alcohol). An overview of all diabetes input data (old and new) described in this report is given in table 3.1.

To be able to evaluate prevention of macrovascular complications of diabetes, the model must be extended to include the prevalence of risk factors for cardiovascular complications in patients with diabetes, as follows:

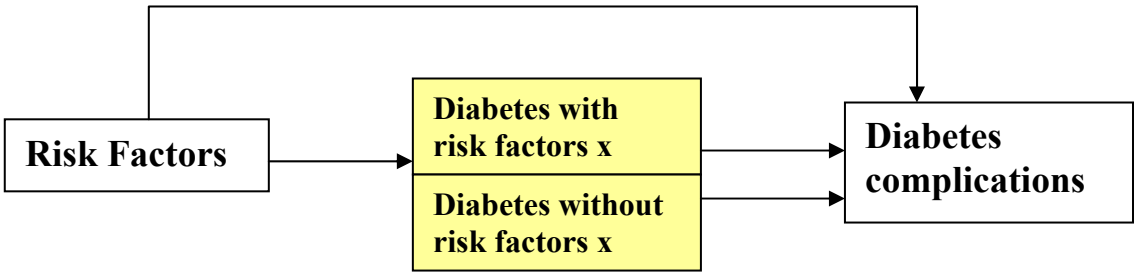


Figure 3.1 Dependency relations between risk factors, diabetes and macrovascular complications of diabetes in CDM-2005-02

That is, in the CDM-2005-02, the diabetes population is divided into risk factor classes. This enables us to evaluate the effect of treatment aiming at risk reduction in patients with diabetes to reduce the incidence of cardiovascular complications. For the formal model, this new structure implies that the model needs to be reformulated, keeping track of risk factor prevalence, once people get diabetes. The CDM-2005-02 requires the following extra input data as compared to the CDM-2003:

- information regarding quality of life and (costs of) health care utilization in patients with diabetes
- if applicable, prevalence of smoking and alcohol consumption in the Dutch population, transition rates between risk factor classes, and relative risks between these risk factors and diabetes incidence
- the prevalence of macrovascular diseases (AMI, CHD, CHF CVA) in patients with diabetes

- for each risk factor for cardiovascular complications, the distribution of the diabetes population over risk factor classes (prevalence) and transition rates between those classes
- relative risks for these risk factors in a diabetes population for incidence of cardiovascular diseases

All these parameters are age- and sex-specific. The risk factors for cardiovascular complications in patients with diabetes to be included in the CDM-2005-02 are BMI, physical activity, total cholesterol, systolic blood pressure and smoking. HBA1c, which is a measure of blood glucose control during the past three months, is a new parameter in the CDM and will only be included for the diabetes population.

In the current report we document updates of the input data already included in the CDM-2003, as well as new estimates for the model parameters in the CDM-2005-02 (table 3.1).

Table 3.1 Overview of the contents of this report

	Parameter	**Update or new**	**Section**
Diabetes input data	incidence, prevalence	update	4.3
	mortality	update	4.4
	health care	new	5.1
	costs	new	5.2
	quality of life	new	5.3
Risk factors for diabetes incidence (prevalence, relative risk and PAR)	methods		6.1
	BMI	update	7.1
	physical activity	update	7.2
	smoking	new	7.3
	alcohol	new	7.4
	combination	new	7.5
Macrovascular complications	methods		9.2
prevalence of complications	AMI, CHD, CHF, CVA	new	9.3
Risk factors for complications (prevalence, relative risks)	BMI	new	10.1
	physical activity	new	10.2
	smoking	new	10.3
	total cholesterol	new	10.4
	SBP	new	10.5
	HbA1c	new	10.6
Interventions	methods		6.2 / 9.2
	primary interventions		8
	tertiary interventions		11

Part II Diabetes input data in the CDM

4. Incidence, prevalence and mortality of diabetes

RT Hoogenveen, CA Baan

4.1 Introduction

In 2000, incidence, prevalence and mortality rates were estimated for all chronic diseases included in the RIVM Chronic Disease Model [2]. For reasons of comparability, the same approach was used for all chronic diseases included in the CDM. At this moment, more recent incidence and prevalence data have become available that enable us to update the Chronic Disease Model parameters. In the current report the analysis made for diabetes mellitus is described. First, the disease modeling analyses (Dismod method) will briefly be introduced and then the recent data on prevalence and incidence of diabetes used will be presented. In the two last sections we will focus in more detail on the methods used for estimating the mortality estimates and discuss the results of mortality estimates.

4.2 The Dismod method

The dismod method is defined as the assessment of disease incidence, prevalence and mortality rates in an incidence-prevalence-mortality (IPM) model. The main advantage of IPM models is that incidence, prevalence and mortality figures are linked through the causal chain of a disease process, and this chain limits the possible combinations of incidence, prevalence and mortality rates [3]. Limits are imposed because any prevalent case must have become incident at some younger age and any person dead with a disease must have become incident previously and have been prevalent, al least shortly. Jointly estimated incidence, prevalence and mortality rates using a causal model are therefore internally consistent [4]. Since the three disease parameters are related through the IPM model, one of them can be calculated given the other ones.

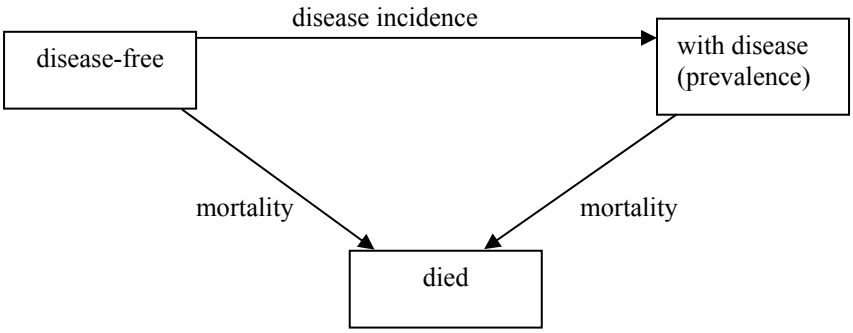


Figure 4.1 Incidence Prevalence Mortality model

The dismod analysis for all diseases included in the CDM consists of calculating disease related mortality from given incidence and prevalence rates from selected registers in general practice [2].

4.3 Incidence and prevalence data

At the internet site the Public Health Compass 2004, Dutch data (age-standardized) on incidence and prevalence of diabetes are presented, both from general practitioner (GP) registrations as well as from epidemiological studies [5]. The validity of all data from the GP has been assessed by evaluating the degree of representativeness, continuity, completeness and freedom from ambiguity of each source.

The data sources used in the IPM-model have been selected from all studies presented at the internet site, using the following criteria:

1. The observation period is around year 2000
2. The study must be a GP study since we want to assess the effect of diseases in terms of health care use (i.e. known by the general practitioner)
3. The number of participants in the study must be over 10,000
4. The registration period has to be sufficiently long in order to include patients who rarely visit the general practitioner (registration period ≥ 1 year)

For diabetes, five data sources have been selected (table 4.1). More detail about the registration projects are given at the internet site The Public Health Compass 2004 [6].

Table 4.1 Registration projects in general practice used for Dismod analysis diabetes mellitus

Registration projects in general practice	Region	Type of registration	Period	Period used	Size
2nd National Study (NS2)	National	Contact registration	2000-2002	2000-2002	395,000
Continuos Morbidity Registration (CMR)	Region Nijmegen	Contact registration	Since 1971 continuous	1996-2000	12,000
Transition Project - 1	Multi-regional	Episode-registration	Since 1985	1985-2000	170,000 py
Registration Network General practices (RNH)	Region Limburg	Problem list	Since 1988 continuous	1997-2000	79,000
Registration Network University general practices Leiden and environs (RNUH LEO) -2	Region Leiden	Problem list	Since 1989	1998-2000	30,000

Diabetes incidence and prevalence estimates for men and women are presented in figures 4.2-4.5.

Incidence

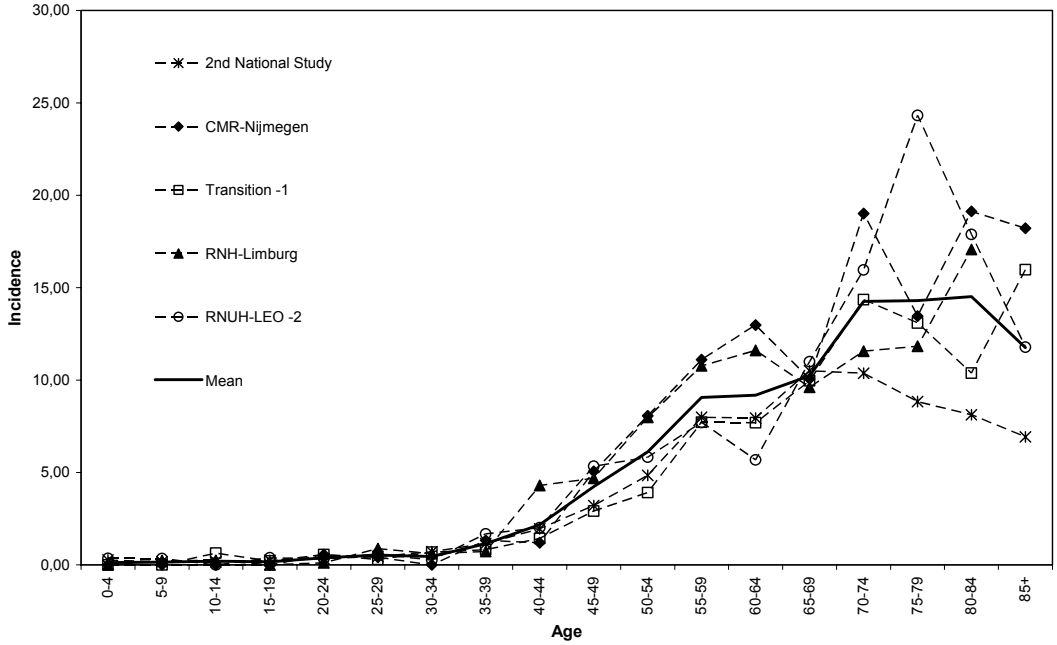


Figure 4.2 Incidence estimates of diabetes mellitus in the 5 data sources selected and the mean of these estimates (men)

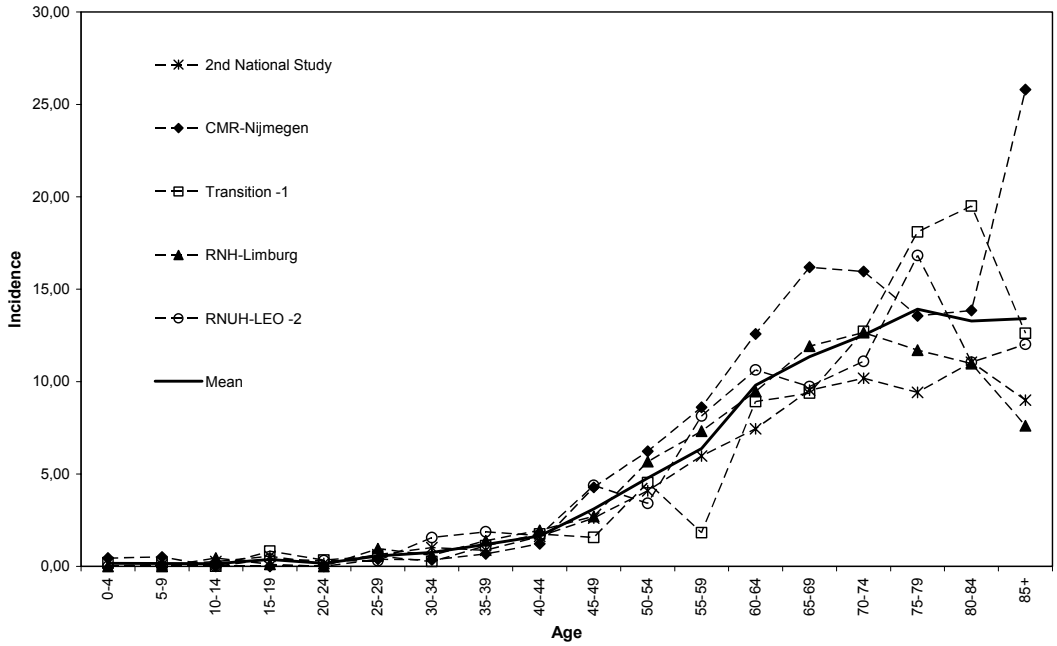


Figure 4.3 Incidence estimates of diabetes mellitus in the 5 data sources selected and the mean of these estimates (women)

Prevalence

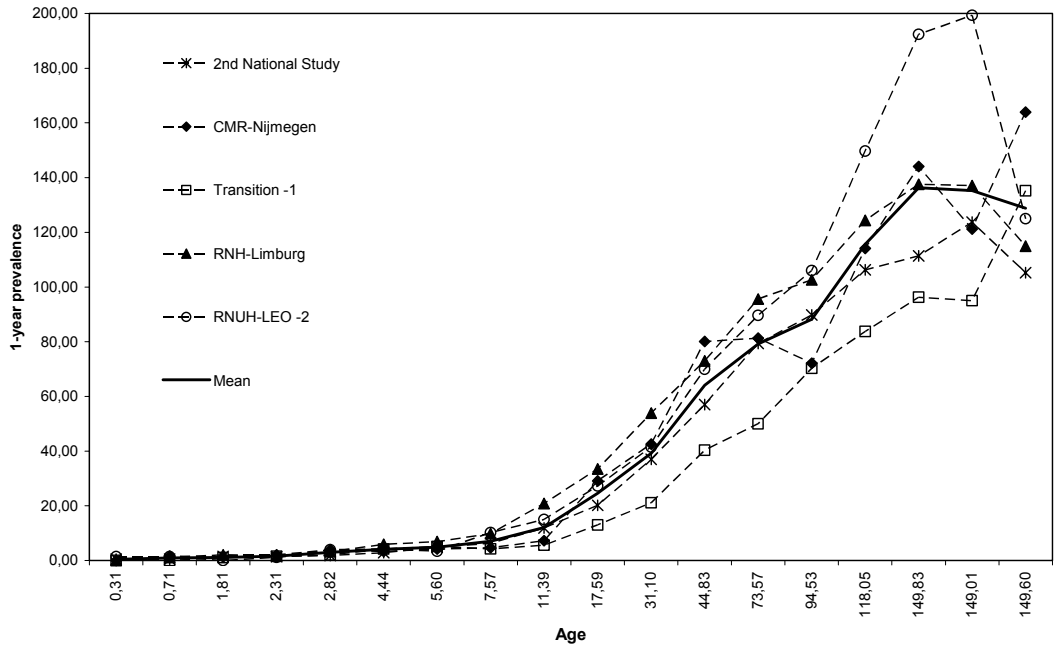


Figure 4.4 Prevalence estimates of diabetes mellitus in the 5 data sources selected and the mean of these estimates (men)

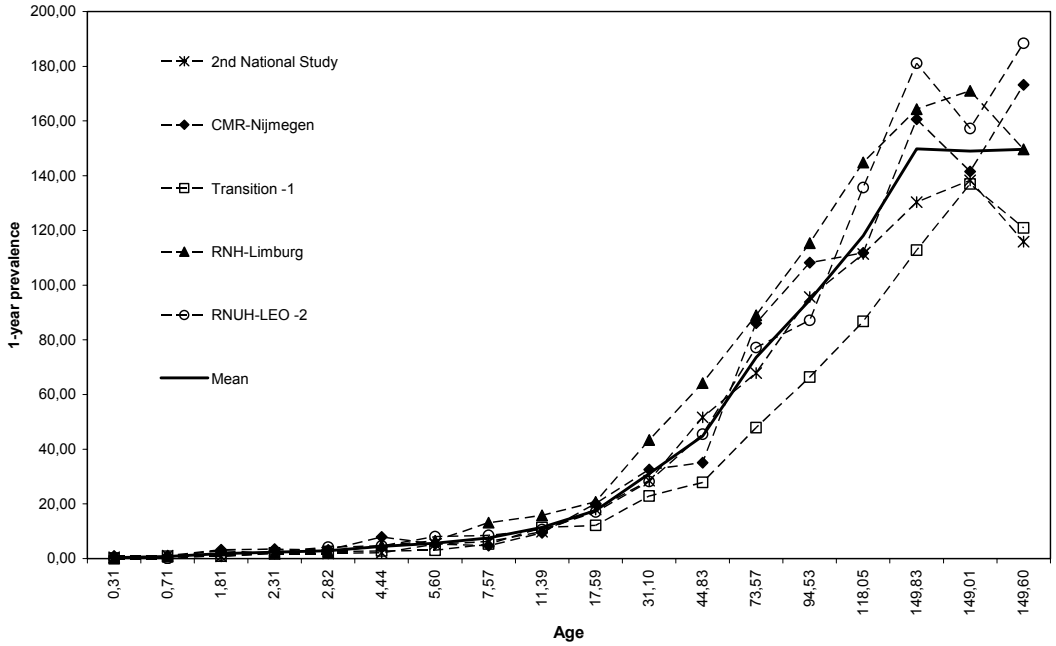


Figure 4.5 Prevalence estimates of diabetes mellitus in the 5 data sources selected and the mean of these estimates (women)

4.4 Mortality data

Mortality is divided in mortality with diabetes and mortality without diabetes. The mortality rates with diabetes are specified by age and sex, but unadjusted for other confounders such as epidemiological risk factors and co-morbid diseases.

The mortality rates with and without diabetes are fully defined within the IPM model context. This definition has several consequences:

1) the definition does not imply that the mortality rates with diabetes equal the empirical diabetes mortality rates based on death registrations with diabetes as primary or secondary cause of death,
2) the mortality rates with diabetes may result from co-morbid diseases. For diabetes mortality, rates result largely from macro-vascular complications. Thus, aggregating the mortality rates with diabetes and mortality rates with cardiovascular disease results in double counting,

The dismod analyses for diabetes consisted of the following steps:

1) calculate a mean incidence and prevalence rate based on the sources selected (presented above in section 4.3)
2) calculate point prevalence rates by subtracting the incidence rates from the 1-year period prevalence rates obtained in step 1
3) estimate mortality rates with diabetes from these mean incidence and point prevalence rates using the IPM model
4) estimate excess mortality rates using relative risk values presented in epidemiological studies
5) compare the results from step 3 with estimates of mortality with diabetes obtained in step 4 and selection of the mortality rates with diabetes used in the CDM
6) Validation of mortality rates

Ad 3: Estimating excess mortality rates from these mean incidence and point prevalence rates using the IPM model

In an IPM model, mortality can be estimated by the incidence and prevalence with the following equation [7]:

$$mortDM(t) = \frac{inc(t) - \frac{\partial}{\partial(t)} prev(t)}{prev(t)(1 - prev(t))} \qquad (4.1)$$

With t: time (age) parameter; d/dt: instantaneous change over time; prev: prevalence rate; inc: incidence rate; mortDM: mortality rate with diabetes.

The time parameter *t* in the IPM model describes changes over both age and time simultaneously. This means it describes the course of a cohort. This can be illustrated with the Lexis diagram (figure 4.6).

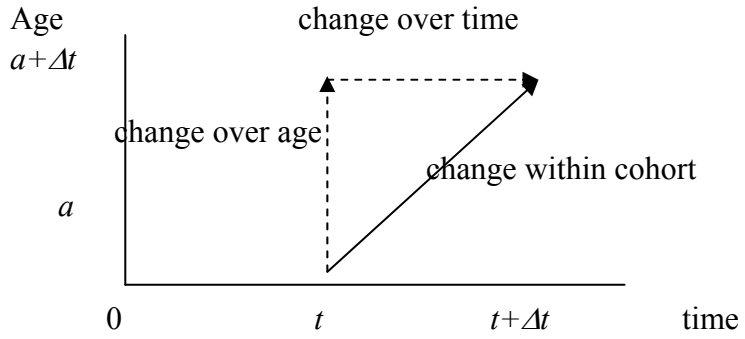


Figure 4.6 Lexis diagram: the relation between time, age and cohort

The Lexis diagram describes a population in terms of changes over age for fixed time (vertical line, age-effects), changes over time for fixed age (horizontal line, period effects), and changes within cohorts (diagonal line).

The incidence and prevalence rates available from registries in general practice describe the changes over age and thus follow the vertical line. One study, the CMR-Nijmegen, estimates the incidence and prevalence continuously over a longer period. With these estimates it is possible to estimate age-standardized changes over time of disease prevalence rates and thus follow the horizontal line. Combining these two estimates (horizontal and vertical) gives the change of diabetes prevalence rate during a 1-year time interval. The mortality rate with diabetes is then calculated using:

$$mortDM(t)\frac{inc(t)-\left(\frac{\partial}{\partial a}+\frac{\partial}{\partial t}\right)prev(t)}{prev(t)(1-prev(t))} \qquad (4.2)$$

With δ/δa: age-change for fixed year; δ/δt: time change for standardized age.
The time changes for standardized age were derived from CMR Nijmegen. We calculated the 1-year relative changes specified by gender and by age. The relative changes were calculated by weighted linear regression on the calculated empirical 1-year relative changes.

Δ prev (a)/prev (a) is the relative change of the disease prevalence rates over time for given age. α is the autonomous change (intercept) β describes the relation with age. If $\beta > 0$ the yearly increase is larger (or the decrease is smaller) for higher ages, if $\beta < 0$ the yearly increase is smaller (or the decrease is larger).The regression model applied was:

$$\frac{\Delta prev(a)}{prev(a)} = (\alpha + 0.01\beta)a \qquad (4.3)$$

With a: age (years); prev: disease prevalence rate; Δ change over time; α intercept; β age regression coefficient.

The results are presented in table 4.2. For men aged 40 years, the prevalence rate has increased with 15.5% per year over the period 1990-2000, for women aged 40 years the prevalence rate has increased with 7.1% per year over the period 1990-2003.

Table 4.2: The relative changes of the diabetes prevalence over the period 1990-2003 and calculated values for age 40 and 60 years

	Men		Women	
Parameter values	α	β	α	β
	0.251	-0.241	0.0978	-0.0677
Calculated values for age (%)	40	60	40	60
	15.5	10.6	7.1	5.7

Ad 4: Estimating mortality rates with diabetes by using relative risk values presented in epidemiological studies.

Mortality for diabetes is also calculated with use of mortality risks obtained from the literature. This method has been described in more detail by Baan and collegues [8].
The excess mortality can be estimated by using:

$$mortDM = \frac{mort_{tot}(RR-1)}{(1+prev(RR-1))} \qquad (4.4)$$

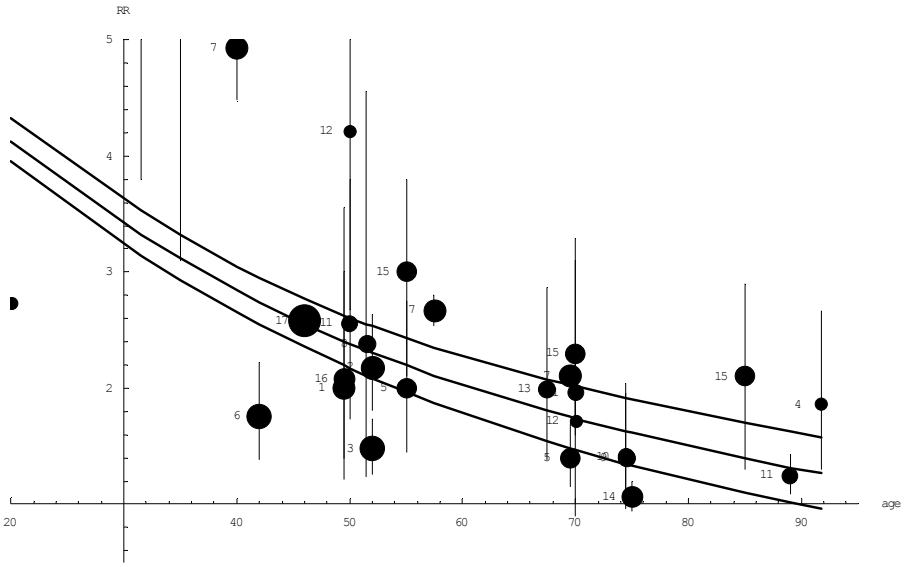
With $Mort_{tot}$: population all cause mortality rates; prev: diabetes prevalence rate; RR: relative risk for total mortality for diabetic versus non-diabetic subjects; mortDM: mortality rate with diabetes.

The relative risks for total mortality for diabetic versus non-diabetic subjects are based on prospective population studies and specified by gender and age. A literature search was performed in Medline. For inclusion in our analysis, studies have to fulfill the following criteria:

- Studies have to be performed after 1980 (either started after 1980 or started before 1980 but with a follow-up period after 1980)
- The study population is Caucasian
- The reference population is the non-diabetic population
- The diabetic population is not a selected subgroup (for instance only hospitalized diabetic patients, or only insulin treated patients)
- The relative risk is reported for men and women separately
- The relative risks are reported for age groups not wider than 30 years
- The relative risks are not corrected for BMI

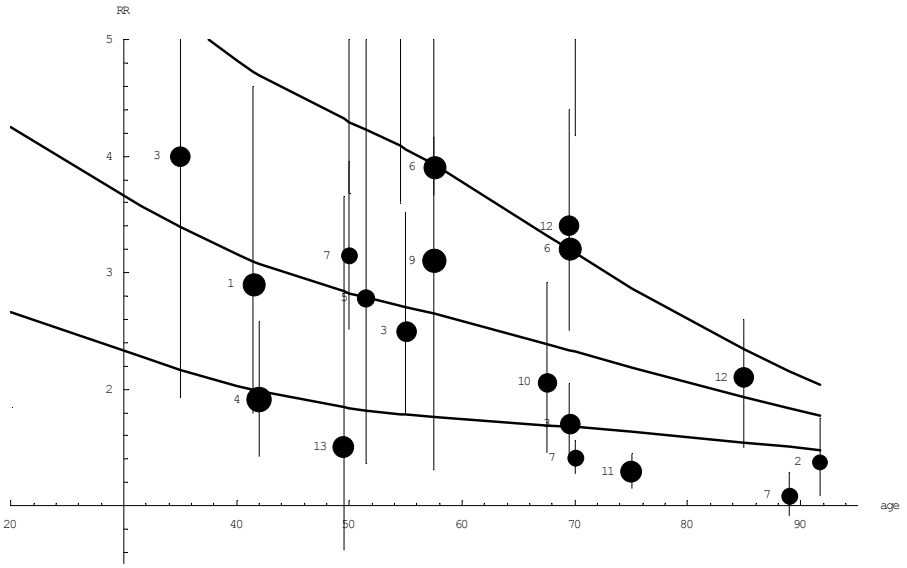
Fourty two studies are identified in the medline search, 18 studies are included in the analysis. Details of these studies are summarized in Appendix I. Of the 24 studies not included in the analysis six are excluded because of the study period [9-14]. Six of the 24 studies excluded were based on a selective diabetes population [15-20]. Four studies used the general population as the reference [21-24], four studies reported relative risks for men and women together [25-27] [28], and three studies corrected for BMI [29-31]. In addition to the published relative risks, results from one Dutch study are used (CB-project) which are unpublished.

All cause mortality rates are obtained from Statistics Netherlands.
The relative risks for all cause mortality for diabetics versus non-diabetics are given in figures 4.7 (males) and 4.8 (females).



1. Balkau, Br Med J, Paris Prospective, 1993
2. Davey Smith, Am J Epid, Whitehall, 1992
3. Ebi, J Clin Epid, Whitehall, 1992
4. Fraser, Arch Intern Med, Adventist Health, 1997
5. Gu, Diab Care, NHANESI, 1998
6. Houterman, Unpublished results, CB Project, 2000
7. Koskinen, AJPH, Social Insurance Finland, 1998
8. Laukkanen, Arch Intern Med, Kuopio, 2001
9. Menotti, J Clin Epid, Seven Countries Netherlands, 2001
10. Menotti, J Clin Epid, Seven Countries Finland, 2001
11. Roper, Diab Care, South Tees UK, 2002
12. Roper, Diab Care, South Tees UK, 2002
13. Simons, Med J Aust, Dubbo, 2000
14. Tan, Diab Care, Tayside Scotland, 2004
15. Tierney, AJPH, North Dakota, 2001
16. Tunstall-Pedoe, Br Med J, Scottish Heart, 1997
17. Vaccaro, Arch Intern Med, MRFIT, 2004

Figure 4.7: All cause mortality risks for males (unadjusted for BMI)



1. Engstrom, JECH, Malmo Cohort Women, 2000
2. Fraser, Arch Intern Med, Adventist Health, 1997
3. Gu, Diab Care, NHANESI, 1998
4. Houterman, Unpublished results, CB Project, 2000
5. Johansson, Eur Heart J, Goteborg BEDA, 2003
6. Koskinen, AJPH, Social Insurance Finland, 1998
7. Roper, Diab Care, South Tees UK, 2002
8. Roper, Diab Care, South Tees UK, 2002
9. Schopman, Thesis, DOM, 1991
10. Simons, Med J Aust, Dubbo, 2000
11. Tan, Diab Care, Tayside Scotland, 2004
12. T ierney, AJPH, North Dakota, 2001
13. Tunstall-Pedoe, Br Med J, Scottish Heart, 1997

Figure 4.8: All cause mortality risks for females (unadjusted for BMI)

Ad 5: Comparing the mortality rates with diabetes obtained by the IPM model (step 3) with estimates of mortality rates with diabetes using relative risk for mortality (step 4) and selection of the mortality rates with diabetes used in the CDM (figure 4.9).

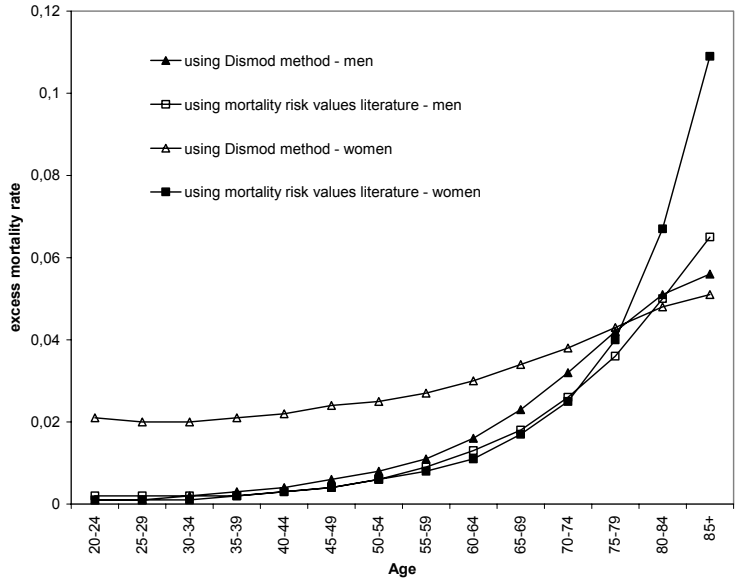


Figure 4.9 Excess mortality of diabetes using different methods

The estimations using Dismod method versus the method using mortality risk values from the literature are more or less equal for men but not for women. At higher ages, the difference between the two methods is larger for both men and women.

The excess mortality based on the method using relative risk values from the literature will be used as input in the diabetes module

Ad 6: Validation of mortality rates with diabetes

To get an idea of the confidence of the estimates of the mortality rates with diabetes, two validation methods are performed.
First, disease prevalence rates are calculated from given incidence rates and mortality risks, adjusted for past incidence trends. These past incidence trends were assessed in the same way as the prevalence time trends (see step 3). The relative incidence trend values used were 0.04 (men) and 0.03 (women). This means that the incidence is increasing with 4% for men and 3% for women per year for all ages. The prevalence rates are calculated using the life table method.

As seen in figure 4.10 the calculated prevalence rates (= “evenwichtsprevalentie”) is higher as compared to the empirical prevalence. This is probably due to the CMR-Nijmegen trend used.

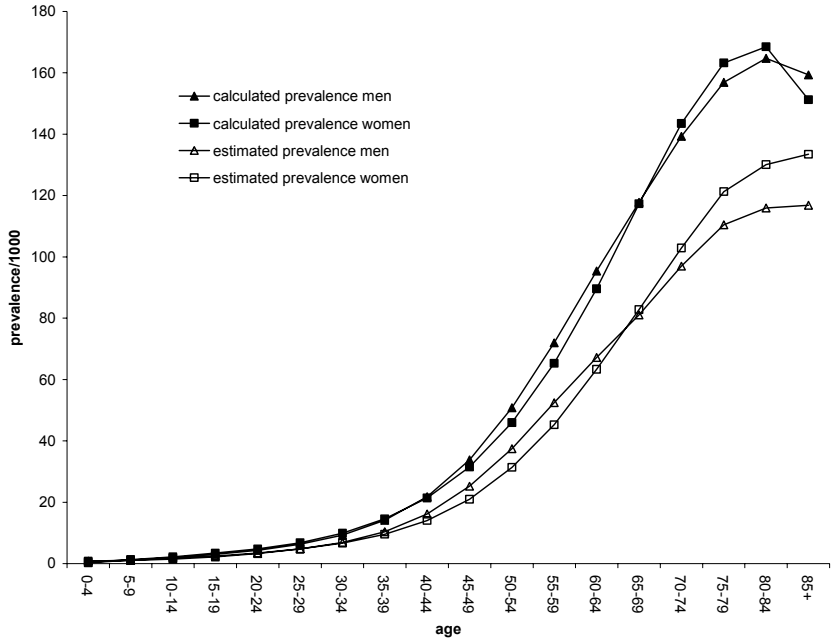


Figure 4.10: Prevalence of diabetes in the Netherlands using the mortality risk from literature method (calculated) versus registrated in general practices (estimated).

Second, we estimated the disease duration of diabetes in the different studies used, with the IPM-method and when using the relative risk method (table 4.3).

Table 4.3 Diabetes incidence and prevalence rates and disease duration values for age range 20-85 years for men and women.

Studies	Men				Women			
	Incidence	Prevalence	Disease duration IPM	RR	Incidence	Prevalence	Disease duration IPM	RR
CMR Nijmegen 1996-2000	5.7	32.5	9.9		5.9	36.2	8.6	
Transition Project – 1 1985-2000	4.1	21.4	9.3		4.5	25.5	7.9	
RNH Limburg 1997-2000	5.2	38.4	13.0		4.7	44.3	15.2	
RNUH LEO-2 1998-2001	5.1	40.0	11.1		4.9	38.6	12.1	
2nd National Study 2000-2002	3.9	30.3	13.3		3.9	33.8	12.8	
Total	4.9 *	32.4 *	11.7	11.4	4.7	35.6	12.8	12.2

* mean value of the 5 studies

The incidence of CMR-Nijmegen is higher as compared to the other studies. In the period 1999-2001 the general practitioners have screened their population for undiagnosed diabetes resulting in an high incidence in that period. Disease duration is more or less comparable between the different studies

Disease duration obtained by using the relative risk method is very comparable with the mean disease duration of the 5 studies. Disease duration can be interpreted with life expectancy. In a recent publication, the life expectancy of persons with diabetes is estimated to be 64.7 for

men and 70.7 for women, respectively 12.8 and 12.2 years less than for men and women without diabetes [32 33].

Discussion

To calculate excess mortality from diabetes using an incidence-prevalence-mortality model results in rather robust estimates. There are differences in estimates depending on what data/method is used for input in the IPM-model. Based on face –validity and comparing with observed prevalence rates and disease duration, the excess mortality calculated using relative risks for mortality from literature are chosen for implementation in the CDM.

There is one major weakness in our dismod analysis. As mentioned before, the trend in incidence of diabetes used in the analyses was based upon the CMR-study. However it is likely that this trend can not be extrapolated to the whole Dutch population due to the screening study they have performed in 1999-2001. We have used the period 1996-2003 which might have dilute the trend effect of the screening study. However, at this moment we do not have other data which we could use for estimating a trend in incidence of diabetes. In 2005 we will perform sensitivity analysis on this specific part of the model.

5. Diabetes health care utilization, costs and quality of life

JNS Struijs, SMC Vijgen, PHM van Baal

5.1 Diabetes health care utilization

As yet the health care utilization of patients with diabetes mellitus has been insufficiently quantified. Detailed information of multidisciplinary health care utilization of diabetes mellitus patients is not collected systematically in the Netherlands.
In order to explore the potential benefits of policy interventions, it is necessary to have insight into the use of multidisciplinary health care services of patients with diabetes mellitus. An overview of current knowledge of health care utilization of diabetes mellitus patients is given in Appendix II. Data for Appendix II were obtained from the Dutch Second National Survey of General Practice (DSNGP-2) [34], the National Medical Register [35] and the National Register of ambulatory care [36]. Furthermore, available Dutch studies in the literature with quantitative information were used [37-39].

General Practitioner care
GP care is quantified in "number of complaints expressed to the GP per year" i.e. partial contacts. A partial contact can be a telephone consult or a physical visit. A visit comprises on average 1.4 partial contacts. Male diabetes patients have on average 10.5 partial contacts a year and female patients 13.3, compared to non-diabetics who have on average 2.9 and 4.8 contacts. Of these contacts, only 3.3 (for men) and 3.2 (for women) are related to diabetes mellitus.
A clear age gradient is observed in the use of GP care. The younger diabetes patients visit their GP less frequently than diabetes patients in the older age classes, which is in line with other diseases [38].

Pharmaceuticals
Over 80% of the diabetes patients use prescribed medication versus only one third in non-diabetics. Diabetics are issued 25.8 prescriptions per year by their GPs versus 7.6 prescriptions a year for non-diabetic patients. The vast majority of the prescriptions (18.6) are not related to diabetes mellitus but to other complaints.

Medical specialist
Yearly, about three-quarters of type 2 diabetes mellitus patients consult a medical specialist [37]. For type 1 diabetes mellitus patients the percentage is 96%. The mean number of visits to the medical specialist is slightly higher for women than for men, i.e. 2.7 for women versus 2.6 for men.

Hospital care
Yearly, about 10.3% of all diabetes patients are admitted to the hospital. This percentage varies from 10.1 for men to 10.5 for women. Male patients who are admitted to the hospital are admitted 2.4 times a year, while female patients who are admitted to the hospital are admitted 2.3 times a year. The average length of stay is 7.0 days for male diabetic patients and 8.0 days for female patients. For the average length of stay a clear age gradient is observed for women, while for men the average length of stay drops in the oldest age class. Most of the discharge diagnoses correspond to complications of diabetes.

Other health care services
Yearly, between 13% and 28% of the patients consult a dietician [37 39]. The utilization of a dietician can not be specified for age and gender, although a distinction was made for diabetes patients under the age of 44 years (8.2%) and above the age of 44 (13.2%)[39].
About one fifth of the diabetes patients uses home care. The same percentage of diabetes mellitus patients visits a physiotherapist [37]. Both numbers can not be specified by age and gender.

Data about nursing home care for diabetes patients are lacking. A tentative estimation is that about 20-30% of the nursing home residents have diabetes mellitus [40].

Summary and future research
The health care utilization of patients with diabetes mellitus has been quantified for GPs, pharmaceuticals, the medical specialists and hospital care.
Current knowledge of health care utilization with regard to other health care services such as home care, dietician, physiotherapist, podiatrist and nursing home care is insufficient. Also, the actual use of the diabetic nurse is still unclear. Therefore, additional data sources and registers need to be investigated to fill up current question marks in Appendix II.
Furthermore, a distinction between the health care utilization of diabetes patients with and without complications needs to be made, since the patterns of health care utilization of these different patient groups (with and without complications) differ considerably [41-43]. Additional research is necessary.

5.2 Diabetes costs

To be able to quantify the potential effect of prevention strategies in terms of preventable (health care) costs, accurate and recent data on the costs of diabetes are required. Although several studies have been performed in the past 10 years, new calculations are necessary. In this section we describe the studies that have been performed so far and the methods we use for our cost analysis.

In the Netherlands, four diabetes cost studies have been performed in the past 10 years (table 5.1). Two different estimation procedures have been used in these studies; the top-down method and the bottom-up method. A bottom-up study lists the disease-related care activities (of care for diabetes) and relates these activities to costs. This is a labour intensive way of calculating costs, and can lead to a large variety in cost estimates[14]. The Code-2 study [44] is such a bottom-up study. In this study the data were collected by primary health care providers, who registered the resource utilization of their patients with type 2 diabetes. With this method it is difficult to determine the complete resource utilization of all diabetic patients in the Netherlands, and to determine which care activities are related to diabetes. The “cost of illness studies” by Polder et al. [45 46] are top-down studies. Top-down studies determine the total costs of a disease by allocating costs to specific combinations of health care services with diagnostic groups, based on the most suitable registrations. For diabetes this method results in an underestimation of the total costs, because costs of (some) complications are not allocated to diabetes but to cardiovascular diseases for example.

Table 5.1 Cost-studies of diabetes mellitus in the Netherlands (costs in euros)

Study, author and year of publication	Code-2-study, Redekop et al., 2002 [44] (only DM2)	Cost of illness study, Polder et al., 1997 [45]	Cost of illness study, Polder et al., 2002 [46]	iMTA, 1998 [47]
Year of data collection	1998	1994	1999	1994
Total direct medical costs related to DM	577 mln.	332.6 mln.	430.6 mln.	340.86 mln.
Total direct medical costs related to non-diabetes specific complications	Idem	-	-	364.14 mln.
Total direct medical costs	**577 mln.**	**333 mln.**	**431 mln.**	**705 mln.**
Total non-medical costs	83 mln.	-	-	90.76 mln (costs of absenteeism)
Total costs	**660 mln.**	**333 mln.**	**431 mln.**	**795.76**
Direct medical costs per patient	1680	-	-	-
Non-medical costs per patient	-	-	-	-
Costs of non- diabetes specific complications mentioned	Yes	No	No	Yes

The cost of illness studies by Polder et al.[45 46] estimated diabetes costs at 333 and 431 million euro, respectively. For both studies this amounted to 1.2% of the total Dutch health care costs in the respective years. The costs relate to diabetes and specific diabetes complications. When comparing the cost of illness studies concerning the years of 1994 and 1999, it appears that within five years time the costs of care for diabetes increased with 100 million euros. However, in the 1999 study the costs of more diabetes specific complications were included than in the 1994 study (polyneuropathy, diabetic retinopathy, nephrotic syndrome, chronic glomerulonephritis, nephritis and nephropathy).

The two cost of illness studies did not take into account the costs of macrovascular complications (like coronary heart disease and stroke) and a number of (non-diabetes specific) microvascular complications caused by diabetes.
In the iMTA study [47] the outcomes were corrected for the underestimation due to not taking into account the costs of all of the complications consequent to using the top-down method. They used the cost of illness study of 1997 to calculate the costs of diabetes and added fractions of the costs of diabetes-related diseases (co-morbidity and complications). Fractions were based on a GP registration.

A complete list of micro- and macrovascular complications of diabetes with their International Classification of Diseases 9 (ICD-9) codes is shown in table 5.2 [47 48]. Table 5.2 also shows the proportion from the total diabetes costs that can be attributed to the individual

complication, as calculated by iMTA in 1998. Diabetes itself (specific complications included) and the macrovascular complications caused the largest amount of costs (91%).

Table 5.2 List of all diabetes complications with ICD- 9 codes

Complication	**ICD-9-codes**	**Proportion of the costs iMTA 1998**
Diabetes and specific complications included	250	48%
Microvascular		*9%, of which*
Ophthalmologic complications		4% (362 included)
Cataract	366	
Partially sighted and blindness	369	
Neurological complications		1% (357 included)
Peripheral autonomic neuropathy	337	
Myasthenia syndrome	358	
Peripheral vascular disorders	443	1%
Gangrene	785	
Amputation	895-897	
Skin and strengthening complications		2%
Chronic Neurophatical ulcer	707	
Cellulites	682	
Diseases of the genitourinary		1% (581 en 583 included)
Nephropathy, nephrotic syndrome	581	
Nephritis	583	
Chronical kidney failure	585	
Proteinuria	791	
Urinary infections	599	
Macrovascular		*43%*
Hypertension	401-404	
Coronary heart disease	410-414	
Stroke	430-438	
Congestive Heart Failure	428-429	

The cost-of illness studies and the iMTA study have their limitations. The iMTA study that allows for correction of the underestimation of costs due to complications seems to be preferred to the cost of illness studies. The iMTA [47] study was based on the cost of illness study of 1997. To have more recent estimates of diabetes costs in this years cost calculations, we will use the iMTA method and apply this method to the costs of the cost of illness study 2002. This can not be done directly, because in 2002 more diabetes complications were included in the cost of illness study. Besides, the representativeness of the fractions used is doubtful. Therefore in our study we will use relative risks from the literature instead of a GP registration to determine these fractions.

To find out what part of every complication is caused by diabetes, population attributable risks (PAR) will be used. The next formula enables the calculation of the PAR of a complication caused by diabetes:

$$PAR = P*(RR-1)/(P*(RR-1)+1) \quad (5.1)$$

with P: prevalence of diabetes in the Netherlands in 1999; RR: relative risk for diabetic patients to develop a complication as compared to non-diabetics.
These population attributable risks have been multiplied by the costs for that complication, resulting in costs that could be attributed to diabetes.

The prevalence data of diabetes will be standardized to the age- and sex distribution of the Netherlands in 2004. The relative risks for complications implemented in the Chronic Disease Model will be used. These relative risks will be updated first. The etiological fractions will then be calculated for men and women separately in 5-year age classes. The PARs will be multiplied by the total costs of the complications as calculated in the cost of illness study 2002. The costs in 1999 will be corrected for inflation by using the consumer price indexes of Statistics Netherlands in 2004. The results of this study will be presented in 2005.

5.3 Diabetes Quality of life

The CDM is used to compare scenarios not only in terms of mortality but also in terms of morbidity. Two metrics that are often used to combine morbidity and mortality are quality adjusted life years (QALYs) and Disability Adjusted Life Years (DALYs). QALYs and DALYs have in common that they use a "weight" to correct for a health state that is less perfect. This weight is either called a disability weight (using DALYs) or a quality weight (using QALYs). A chronic disease with a severe impact on quality of life could have a disability weight of 0.9 on a scale of 0 (perfect health state) to 1 (death). Correspondingly, this disease would be valued with a quality weight of 0.1 on a scale of 0 (death) to 1 (perfect health state). QALYs aggregate the actual health quality over time, DALYs aggregate the loss of health compared to perfect health. In the CDM we use DALY weights instead of QALY weight to calculate the health quality of time for several reasons:
- daly weights are more easily available for more diseases;
- the same methodology is used to derive Daly weights for all diseases so the ranking is more consistent;
- the use of DALY weights is common within the RIVM to calculate burden of disease.

How the quality adjusted life years are estimated in the CDM, is described in more detail in the RIVM report 260706002 [49]. In 2005 a review of the literature on quality of life for diabetes patients will be finished. The results of the review will be used to put the estimated quality adjusted life years into perspective.

Part III Prevention of diabetes

6. Risk factors for diabetes incidence and primary prevention

MAM Jacobs-van der Bruggen

6.1 Introduction

This part of the Technical Report focuses on factors concerning the primary prevention of diabetes mellitus. Primary prevention strategies intend to prevent or delay the development of new cases of diabetes by modifying risk factor exposure in a diabetes-free population. We focus on the risk factors body mass index (BMI), physical inactivity, smoking, and alcohol. These risk factors were already included as risk factors for diabetes (BMI and physical inactivity) or other diseases (smoking and alcohol) in the CDM-2003. The distribution of risk factors in the Dutch population (prevalence), and their relation with diabetes incidence (relative risks) are input variables in the model. The purpose of this part of the report is to justify the updated or new diabetes related input in the CDM, and to review international results of - primary prevention of diabetes - trials.

6.2 Methods

Prevalence of risk factors for diabetes incidence in the Dutch population
Prevalence data of risk factors in the Dutch population were retrieved from Dutch registries. For overweight, physical inactivity and alcohol consumption, data were used from the lifestyle monitoring surveys (Permanent Onderzoek Leefstijl, POLS) from Statistics Netherlands (CBS). Smoking data were obtained from the Dutch organization for public health and smoking (Stichting Volksgezondheid en Roken, STIVORO).

Relative risks of risk factors for incident diabetes
Relative risks for diabetes incidence for BMI, physical inactivity, smoking and alcohol consumption were determined from the international literature. Relevant studies were obtained through Pubmed searches, RIVM diabetes-experts, and references tracking of the articles and reviews retrieved. Studies were used to estimate the relative risk of the risk factor involved if the following criteria were met:

- publication year 1990-2004
- prospective longitudinal cohort study on diabetes incidence
- at least 50 incident cases of diabetes
- Caucasian population
- measurement of risk factor in units or categories equal or convertible to categories in the CDM
- diabetes incidence rate < 10% if risk estimates are reported as odds ratios because odds ratios cannot be interpreted as relative risks if the incidence is > 10%, and
- if the number of publications is sufficient: sex-specific relative risks

Dutch monitoring studies
Relative risks for body mass index, physical inactivity, smoking and alcohol consumption on diabetes incidence were also determined for a Dutch population for which data were available at the RIVM. These calculated relative risks were compared to the updated or new input in the CDM (as estimated from the international literature) for validation. If the results differ substantially, sensitivity analysis will be performed when modeling diabetes scenarios to quantify the variation in outcomes when using different relative risks.

The study population comprises Dutch people aged 20-59 years at baseline from Doetinchem and Maastricht, who participated in monitoring studies between 1987 and 2002. The monitoring studies were conducted in three rounds (Peilstationsproject Hart- en vaatziekten, 1987-1991 [50], MORGEN-project, 1993-1997 [51 52] and the Doetinchem Cohort Study, 1998-2002 [53]) and took place at the Municipal Health Service in each town. Respondents filled in two self-administered questionnaires and underwent a medical examination.
Inhabitants from Doetinchem who participated in the "Peilstationsproject Hart- en vaatziekten", between 1987 and 1991 were invited for reevaluations 6 and 11 years later in the monitoring studies of 1993-1997 and 1998-2002. Baseline data for Doetinchem participants (collected during 1987-1991) consisted of demographic characteristics, presence of chronic diseases, risk factors for chronic diseases and anthropometric measurements. Self-reported diabetes status, year of diagnosis and familial diabetes were retrieved from the latest follow-up survey available (i.e. 1993-1997 or 1998-2002).
In Maastricht, cross-sectional samples were drawn in 1987-1992 and 1993-1997 in which baseline data were collected. Self reported diabetes status and year of diagnosis were assessed with a short questionnaire that was sent to the participants in 1998.

Baseline and follow-up data were linked for 21,939 people. From this dataset we excluded individuals with baseline diabetes, pregnancy or cardiovascular disease. Furthermore we excluded individuals with probable type 1 diabetes at follow-up, individuals who were not Dutch and individuals with missing values for risk factors on diabetes incidence. The dataset for the analysis comprised 20,103 Dutch subjects of whom 292 developed diabetes. Duration of follow-up ranged from 0.5 to 14 years with an average of 7.7 year.

Analysis,
Body mass index was modeled continuously (per unit BMI) as well as in the CDM categories; moderately overweight (BMI 25-30) versus normal weight (BMI<25), and obese (BMI ≥30) versus normal weight (BMI<25). The analysis were adjusted for age, physical inactivity and smoking.
Physical inactivity was modeled as active (at least 4 hours of physical activity each week) versus inactive. From the available data it was not possible to make (three) categories according to the CDM. The analysis were adjusted for age, BMI (continuously) and smoking.
Smoking was categorized according to the CDM classes as never, former or current smoking. Analysis were adjusted for age BMI and physical inactivity.
Alcohol consumption was modeled in the sex-specific CDM-categories. However, because of the low prevalences in the highest category (excessive drinking), heavy and excessive drinking were combined. The analysis were adjusted for age, BMI and smoking.

Population Attributable Risk (PAR)
The PAR is a measure that expresses (in percentages) how many of the cases of diabetes can be attributed to unhealthy behavior (having the risk factor), or stated otherwise; how many of the new cases of diabetes could be prevented if the risk factor concerned would be totally

removed (for example, how many new cases of diabetes could be prevented if everybody had a normal weight). The PAR depends on the prevalence of the risk factor in the population and the relative risk of this risk factor on diabetes incidence, in formula:

$$PAR = p(RR-1)/(p(RR-1)+1) \quad (6.1)$$

With RR: relative risk of the risk factor on diabetes incidence; p: prevalence of the risk factor in the population

Because this report focuses on type 2 diabetes, the PAR will refer to preventable new cases of diabetes in the adult population (20 years and older) which is almost equal to the total type 2 diabetes incidence. The PAR is computed age and sex-specific. Within gender, PARs for all 10-year age-classes are added in which each age-specific PAR is weighted by the relative diabetes incidence in that class. Total PAR is computed by adding up the PARs for men and women, weighted for diabetes incidence (0.486 for men and 0.514 for women [54]).

Primary prevention
A literature search was done searching for primary intervention studies. Studies were included if they met the following criteria:

- published between 1990-2003
- study aim: prevention of diabetes incidence
- at least 50 people in the intervention group
- inclusion of a control group
- relevant outcome data available (change in risk factor level or prevention of diabetes incidence)
- follow-up at least 1 year
- Caucasian population

This review of the literature provides information on what primary intervention strategies appear to be effective. Based on this information we can determine which strategies are interesting to model with the CDM. However, issues such as feasibility of implementation in the Netherlands, costs of the intervention and translation of trial results into realistic scenarios need to be addressed.

7. Risk factors for diabetes incidence

MAM Jacobs-van der Bruggen, RT Hoogenveen

Known risk factors for diabetes incidence which are modifiable (as opposed to genetic factors such as ethnicity) are a high weight and physical inactivity. These risk factors were already modeled in CDM-2003. Less well known but potentially interesting modifiable risk factors for diabetes incidence are smoking and alcohol consumption. In this chapter we will update the input data for BMI and physical inactivity and we will explore whether smoking and alcohol consumption should be implemented as new risk factors for diabetes incidence in the CDM-2005-02. We will also determine the potential benefit of prevention strategies which focus on each of these risk factors by means of calculating the population attributable risk (PAR).

7.1 Body Mass Index

A high weight is an important risk factor for diabetes [55-57]. The most commonly used measure of relative weight is the Body Mass Index (BMI), which is computed as weight in kilograms divided by height in meters squared. A BMI between 18 and 25 is regarded as normal weight. Individuals with a BMI of 25 to 30 or more than 30 are considered moderately and severely overweight (obese), respectively [58]. The risk of diabetes is also dependent on the distribution of fat over the body [56 59-61]. Accumulation of fat around the waist gives a higher risk of diabetes as compared to accumulation of fat around the hips. Furthermore, duration of overweight and changes in weight are independent risk factors for diabetes incidence [62-64].

In the CDM-2003, BMI is modeled in three classes: normal weight (BMI<25), moderately overweight (BMI 25-30) and obese (BMI ≥30). There are several potential sources of information on prevalence of overweight in the Dutch population[1]. In a Dutch monitoring study (Monitoring risico factoren en gezondheid Nederland, MORGEN), bodyweight was measured, but the information is outdated (1993-1997). Data from a Dutch survey conducted by Statistics Netherlands (CBS-POLS), are more recent, but a disadvantage of this data source is that bodyweight is self-reported. Furthermore, bodyweight and height was reported in classes only. Dependent on actual weight and gender, bodyweight tends to be underreported. We chose the most recent data (CBS 2000-2002) to update the prevalence of overweight in the CDM-2005-01, but upgraded the percentages of overweight and obesity with approximately 3 percent points to correct for the tendency of people to underreport their weight. How this was done is described in an internal report [65]. The calculated prevalence of being moderately overweight or obese for Dutch men and women is illustrated in figure 7.1. Overall, about 36% of the Dutch people > 20 year (40% of the men and 31% of the women) are moderately overweight and about 13% (12% of the men and 15% of the women) are obese (standardized to the age distribution of the Dutch population in 2003). The new prevalence input data, with the accompanying transition rates are documented in input file “BMIinput010305.txt”.

[1] The update of prevalences of overweight and physical inactivity was performed within the framework of project V/260301, prevention of overweight.

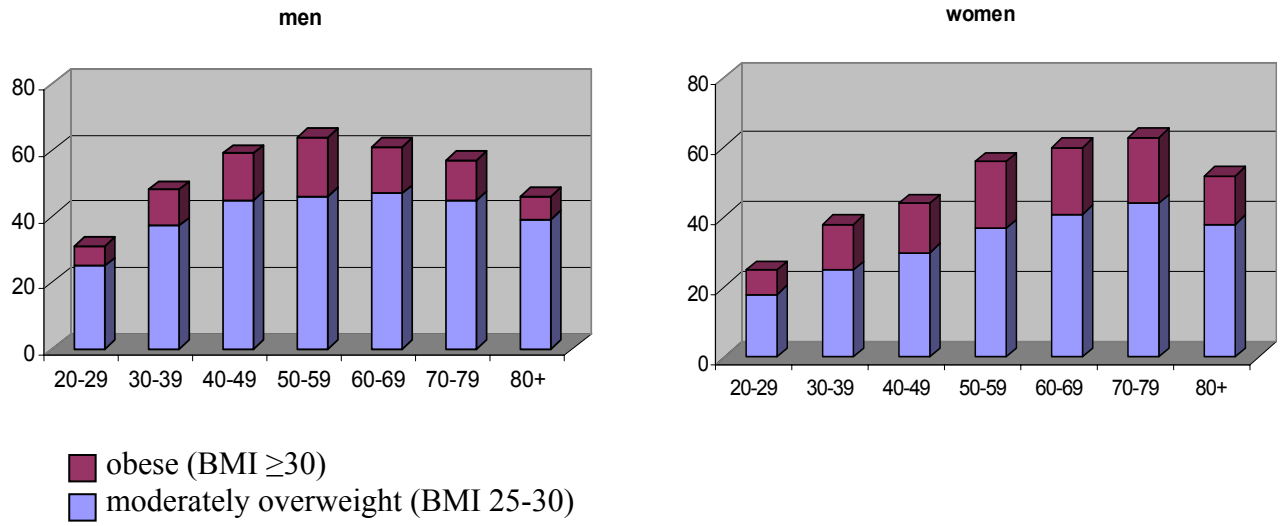


Figure 7.1 Prevalence of being overweight in Dutch men and women.
Source: CBS POLS 2000-2002, corrected for underreporting of bodyweight

To determine the relative risk (RR) for BMI on diabetes incidence we performed a literature search (see methods section 6.1) and included studies in which:

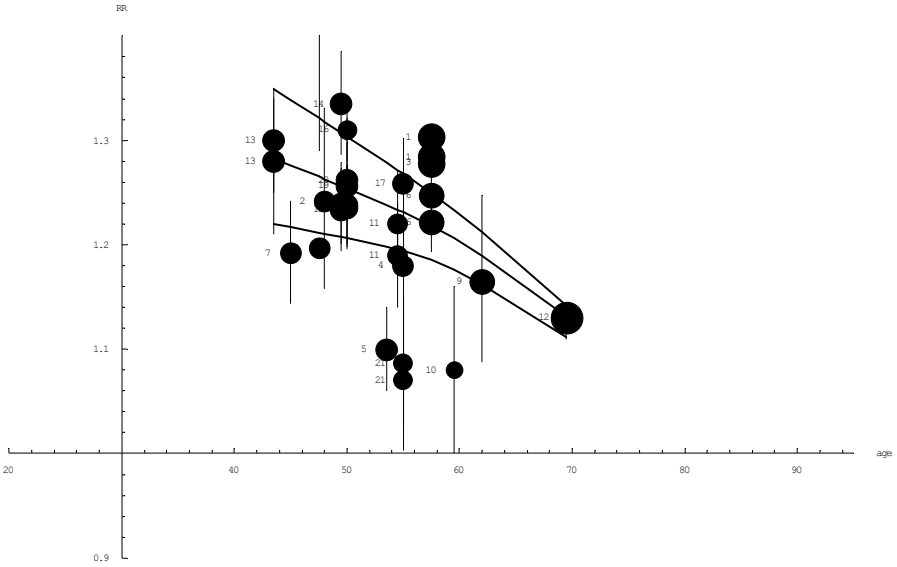
- the effect of BMI is expressed in units, or in categories of which the borders and sample sizes are known,
- relative risks are sex-specific, and
- relative risks are adjusted for at least age, and not adjusted for other measures of bodyweight or body composition (such as waist hip ratio). All relative risks were used, independent of adjustment for other lifestyle factors or factors such as cholesterol or blood pressure.

Including studies with adjustment for at least age, physical inactivity and smoking would mean that only 10 instead of 29 studies could have been included. In modeling BMI as a risk factor for diabetes incidence, sensitivity analysis will be performed to quantify the effect of using relative risk estimates derived from both methods (independent of confounding on lifestyle factors and with adjustment for lifestyle factors).

We included 29 publications in which relative risk estimates for BMI on diabetes incidence were reported [55 56 60 62 64 66-89]. Another eleven prospective studies regarding BMI and diabetes incidence were found but rejected because they had no sex-specific relative risk estimates [61 90-96], comprised less then 50 diabetes cases [93 97 98] or presented only risk estimates adjusted for waist-hip ratio [99]. Results and characteristics of the included studies are summarized in Appendix III. Figure 7.2 illustrates the relative risks per BMI unit that were found in these studies [2]. The lines represent the selected CDM input values and confidence intervals specified by age. All studies show a consistent higher risk on diabetes incidence with increasing BMI. Relative risk estimates vary roughly between 1.1 and 1.35 per unit BMI (kg/m^2). At low ages the effect of BMI on diabetes is somewhat greater for men than for women, while the relative risk decreases for both with advancing age.

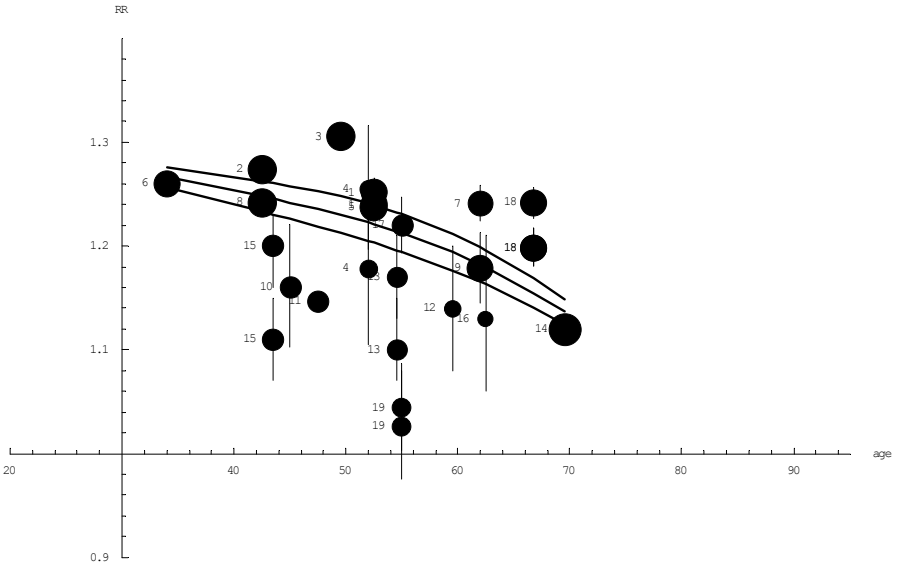
[2] One additional study (Meyer 1995) is shown in the figures. This study estimated the relative risk of BMI on diabetes mortality and was used to estime the relative risk at high ages.

Men



1. Chan, Diab Care, Health Professionals, 1994
2. Eckardstein, J Clin Endocrin Metab, Munster Heart PROCAM, 2000
3. Field, Arch Intern Med, Health Professionals, 2001
4. Freeman, Diabetes, WoSCoPS, 2002
5. Helmrich, NEJM, Pennsylvania Alumni, 1991
6. Koh-Banerjee, Am J Epid, Health Professionals, 2004
7. Kumari, Arch Intern Med, Whitehall, 2004
8. Lipton, Am J Epid, NHANESI, 1993
9. Manson, JAMA, Health Professionals, 1992
10. McPhillips, Am J Epid, Rancho Bernardo, 1990
11. Meisinger, Arch Intern Med, MONICA Augsburg, 2002
12. Meyer, Epidemiology, NHSS Norway, 1995
13. Njolstad, Am J Epid, Finnmark, 1998
14. Perry, Br Med J, British Regional Heart, 1995
15. Shaper, Br Med J, British Regional Heart, 1997
16. Skarfors, Br Med J, Uppsala, 1991
17. Stevens, Obes Res, ARIC, 2001
18. Strandberg, Nutr Metab Card Dis, Helsinki Businessmen, 2000
19. Wannamethee, Diab Care, British Regional Heart, 1999
20. Wannamethee, JECH, British regional Heart, 2005
21. Wilson, Arch Intern Med, Framingham, 2002

Women



1. Carey, Am J Epid, Nurses Health, 1997
2. Colditz, Am J Epid, Nurses Health, 1990
3. Colditz, Ann Intern Med, Nurses Health, 1995
4. Dotevall, Diabet Med, BEDA, 2004
5. Field, Arch Intern Med, Nurses Health, 2001
6. Field, Obes Res, Nurses Health II, 2004
7. Folsom, Arch Intern Med, Iowa Women Health, 2000
8. Hu, NEJM, Nurses Health, 2001
9. Kaye, J Clin Epid, Iowa Women Health, 1991
10. Kumari, Arch Intern Med, Whitehall, 2004
11. Lipton, Am J Epid, NHANESI, 1993
12. McPhillips, Am J Epid, Rancho Bernardo, 1990
13. Meisinger, Arch Intern Med, MONICA Augsburg, 2002
14. Meyer, Epidemiology, NHSS Norway, 1995
15. Njolstad, Am J Epid, Finnmark, 1998
16. Snijder, AJCN, Hoorn, 2003
17. Stevens, Obes Res, ARIC, 2001
18. Weinstein, JAMA, Womens Health, 2004
19. Wilson, Arch Intern Med, Framingham, 2002

Figure 7.2: Relative risk estimates for BMI on diabetes incidence, no restriction on adjustment for lifestyle factors, for men and women, respectively

From Dutch monitoring studies (see methods section 6.2) the relative risks for body mass index on diabetes incidence were 1.29 (1.24-1.34) and 1.21 (1.17-1.25) per unit BMI for Dutch men and women, respectively (adjusted for age, smoking and physical inactivity). The relative risks for moderately overweight versus normal weight and obesity versus normal weight were 5.5 (3.1-9.9) and 19.9 (10.8-36.8) for men and 3.4 (2.0-5.5) and 12.2 (7.4-20.1) for women. These figures are consistent with estimates found in the international literature.

After determining the age- and sex-specific relative risks for BMI in units/m^2 we translated the relative risks per unit into relative risks for the BMI-categories in the CDM. That is for people who are overweight or obese relative to people with normal weight. We used data from Dutch population studies (MORGEN and "Erasmus Rotterdam Gezondheid en Ouderen", ERGO) to determine sex- and age-specific mean levels of BMI within the classes defined in the CDM. Data from the MORGEN study 1993-1997 were used for the age-classes < 60 years and data from the ERGO study 1990-1992 for the age classes 60+. The differences between mean BMI levels were used to convert the relative risks per unit BMI to relative risks for the classes in the CDM.

For example, for Dutch men 40-45 years:

- The relative risk for diabetes incidence is 1.31 per unit BMI.
- The mean levels of BMI for normal weight, overweight and obesity are 22.7, 26.9 and 32.5 respectively.
- The relative risk for overweight versus normal weight is $1.31^{(26.9-22.7)} = 4.2$
- The relative risk for obesity versus normal weight is $1.31^{(32,5-22,7)} = 14.1$

The updated age- and sex-specific relative risks are documented in input file "RRBMIinput010305.txt"

The population attributable risk of being (severely) overweight on diabetes incidence is shown in table 7.1.

Table 7.1 Population attributable risk of being (severely) overweight on diabetes incidence for Dutch men and women

	Prevalence	RR	PAR
men			
moderately overweight (BMI 25-30)	0.25-0.47	1.1-3.6	31.1
obese (BMI>30)	0.06-0.18	1.1-16.2	37.4
women			
moderately overweight (BMI 25-30)	0.18-0.44	1.1-3.3	25.3
obese (BMI>30)	0.07-0.19	1.1-13.3	38.6

The percentage of new cases of diabetes (>20 years) that is attributable to being overweight is 66%; 68% for men and 64% for women. Being moderately overweight causes 28% of the diabetes cases and obesity 38%.

7.2 Physical inactivity

Physical inactivity is a known and modifiable risk factor for diabetes. The risk of diabetes increases with increased duration of inactivity (for example number of hours spent watching television) [100 101], and decreases with increased frequency of physical activity [101-103]. Being in good conditional shape protects against diabetes incidence [104 105]. There are two factors to

consider when determining the impact of physical inactivity on diabetes incidence. First, a part of the protective effect of physical activity on diabetes incidence is explained by an accompanying reduction in body mass index and changes in body composition. Another part, however, is independent of reductions in bodyweight and is associated with improved glucose metabolism. Secondly, there are numerous ways of defining and categorizing inactivity which makes it difficult to compare studies.

In the CDM-2003, physical inactivity is modeled in three classes: people who are active (30 minutes of activity of moderate intensity on at least 5 days of the week), people who are insufficiently active (30 minutes of activity of moderate intensity on 1-4 days of the week) and people who are inactive (30 minutes of activity of moderate intensity on less than 1 day a week). Recent information about the prevalence of physical inactivity was retrieved from Statistics Netherlands 2001-2003. The prevalence of physical inactivity for Dutch men and women is illustrated in figure 7.3. The new prevalence input data for physical inactivity and the transition rates for the CDM-2005-01 are described in an internal report [106] and documented in input file "lichactCBS010305.txt" [3].

In the Netherlands, about 45% of the population > 20 year (46% of the men and 45% of the women) does not comply to the Dutch guidelines for physical activity of "at least 30 minutes of physical activity of moderate intensity on at least five but preferably all days of the week" [107]. In the guideline, "moderate intensity" is defined age-dependent. As a result, walking is included as an activity of moderate intensity in people who are 55+, but not in younger people. This explains the relatively low prevalence of elderly people (60-80) who are insufficiently active. Approximately 11% of the Dutch population is inactive; 10% of the men and 12% of the women (standardized to the age distribution of the Dutch population in 2003).

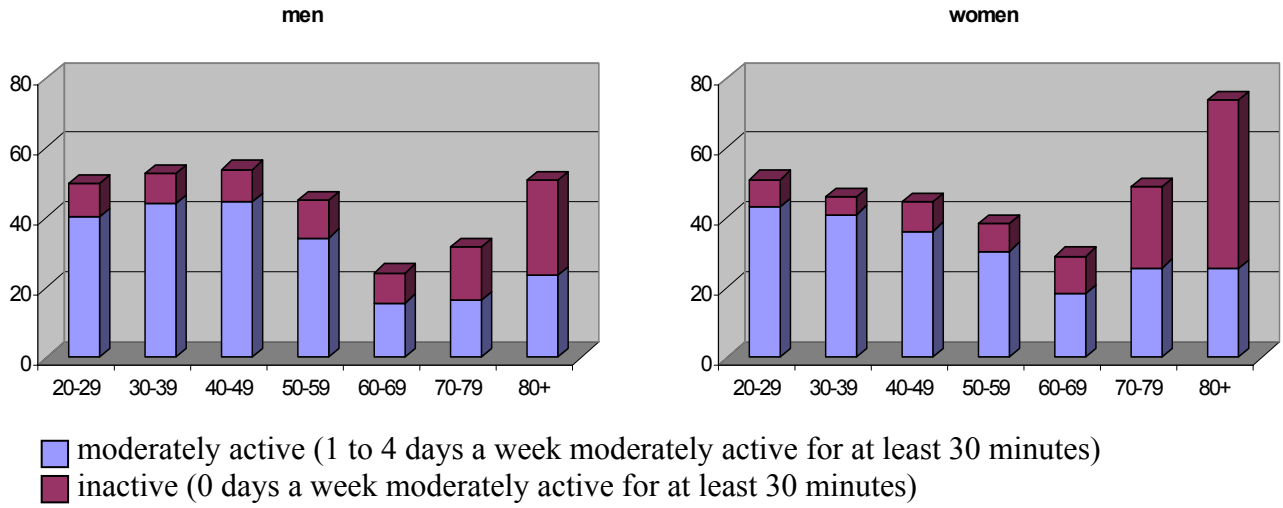


Figure 7.3 Prevalence of physical inactivity in Dutch men and women
Source: Statistics Netherlands 2001-2003

[3] The update of prevalences of overweight and physical inactivity was performed within the framework of project V/260301, prevention of overweight.

To determine the relative risk for physical inactivity on diabetes incidence we included studies in which:

- physical activity is specified in at least three categories (specifying frequency, duration and/or intensity of physical activity during leisure time),
- relative risks are adjusted for at least age, with or without adjustment for BMI and irrespective of confounding on other factors.

We exclude studies which relate cardio-respiratory fitness to diabetes incidence. We calculate two different relative risks, one for the overall effect of physical activity, without adjustment for BMI for calculating a population attributable risk, and one for the effect independent of changes in body mass index to be used in the CDM.
As expected, physical activity was categorized in different ways and in unequal numbers of classes in the studies we included. To be able to convert these results into relative risks for the classes defined in the CDM (inactive versus active and insufficiently active versus active) we made the most active category in each study the reference group and the least active group became the inactive group. All categories in-between were taken together and represented the insufficiently active group. This method is also used in a recent meta-analysis on the effect of physical activity on the incidence of stroke [108].
We included 13 publications in which relative risk estimates for physical inactivity on diabetes incidence were reported, 3 studies in men [84 109 110], 5 studies in women [56 70 75 86 111] and 5 studies in both men and women with separate estimates for each gender [67 79 83 112 113]. Another 17 prospective studies examining the relation between inactivity and/or cardio-respiratory fitness and diabetes incidence were found but rejected because they did not meet our criteria [61 66 72 77 82 85 90 92 93 105 114-120]. Results and characteristics of the selected publications are summarized in Appendix VIa.

All studies show a consistent higher risk for diabetes incidence for inactive versus active people, and a small increase in risk for people who are only moderately active. Because we did not find a substantial change in relative risk with increasing age, we decided to remove the highest and lowest estimates and took the weighted mean of the remaining studies as the relative risk in our model (Appendix VIb). The calculated relative risks are 1.53 and 1.36 for inactive versus active people for men and women, after adjustment for BMI, and 1.91 for both men and women without adjustment for BMI. The corresponding relative risks for moderately active versus active are 1.14 and 1.18 with adjustment for BMI and 1.31 and 1.35 without adjustment for BMI. The new relative risk estimates for physical inactivity on diabetes incidence for the CDM-2005-01 are stored in input file “RRlichactinput010305.txt”.

From Dutch monitoring studies (see methods section 6.2) the relative risk for diabetes incidence could only be analysed for people who are physically active for less than 4 hours per week versus people who are more active. The corresponding relative risks were 1.47 (1.05-2.05) and 1.19 (0.83-1.70) for men and women after adjustment for age, BMI and smoking, and 1.83 (1.33-2.53) and 1.53 (1.08-2.17) for men and women with adjustment for age and smoking only. This is in the same order of magnitude as the risks found in the international literature.

The population attributable risk of physical inactivity on diabetes incidence is shown in table 7.2.

Table 7.2 Population attributable risk of physical inactivity on diabetes incidence for Dutch men and women

	Prevalence	RR	PAR	RR	PAR
		unadjusted for BMI		adjusted for BMI	
men					
moderately active	0.16-0.45	1.31	7.5	1.14	3.5
inactive	0.09-0.27	1.91	9.8	1.53	6.0
women					
moderately active	0.18-0.43	1.35	8.3	1.18	4.5
inactive	0.05-0.48	1.91	13.7	1.36	6.1

The percentage of new cases of diabetes (>20 years) that is attributable to not being active is 20%; 17% for men and 22% for women. A large part can be explained by the higher weight in inactive people. However, even increased physical activity without weight changes could prevent approximately 10% of the diabetes cases.

7.3 Smoking

There is accumulating evidence that current as well as former smokers are at increased risk for diabetes incidence. In current smokers the risk increases with the mean number of cigarettes smoked each day in most [102 121-124] but not all large studies [125]. The risk also increases with the total number of pack-years smoked [122 123 126]. For former smokers the risk decreases with time since stopping; after 5 to 10 years the risk is no longer significantly increased [121 122 125]. In the CDM-2003, smoking is included as a risk factor for cardiovascular disease and several forms of cancer but it is not directly related to diabetes incidence. Smoking is categorized as non-smoking, current smoking and former smoking.

Prevalence data for smoking were retrieved from STIVORO (2004) and are illustrated in figure 7.4. In the Netherlands 28% of the 20+ population smoke; 32% of the men and 25% of the women. Thirty-four percent of the 20+ population are former smokers; 38% of the men and 31% of the women (standardized to the age distribution of the Dutch population in 2003).

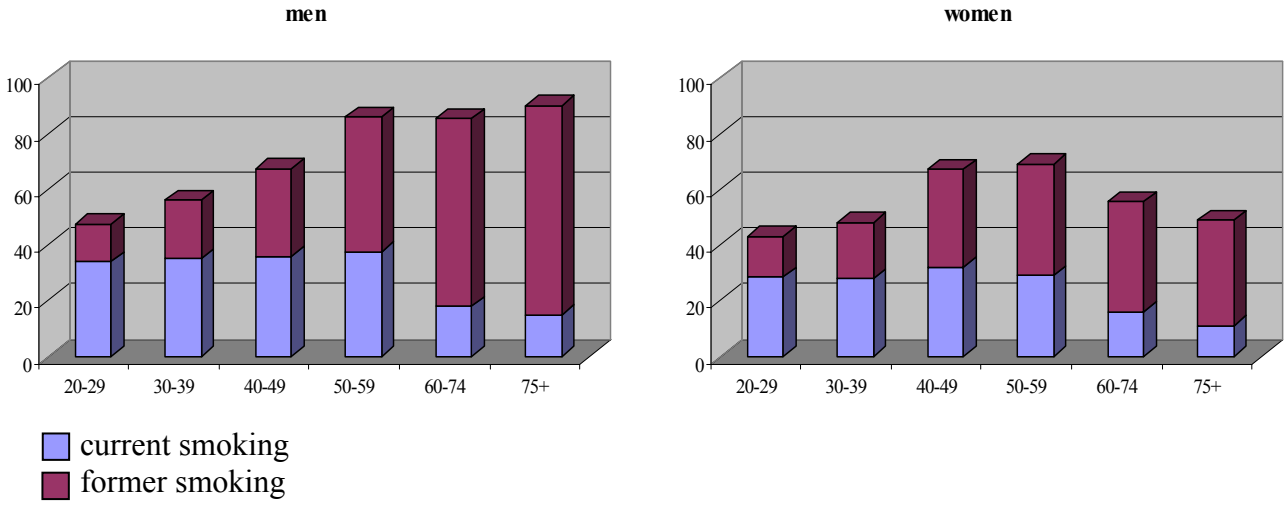


Figure 7.4 Prevalence of current and former smoking in Dutch men and women
Source: STIVORO (2004)

To determine the relative risk for smoking on diabetes incidence we included studies in which:

- the effect of smoking is expressed in categories (current smoking versus non smoking or former smoking versus non smoking)
- relative risks are adjusted for at least age and BMI. Adjustment for lifestyle (physical activity) and biological factors (blood pressure and cholesterol) did not substantially influence risk estimates so all relative risks were used, independent of adjustment for these factors
- follow-up is at least 5 years, because it takes some time fore smoking to cause its harmful effects

Because there were only two studies with sex-specific relative risks for women, and we have no reason to believe that the risks are substantially different between men and women, we combined all risk estimates regardless of gender.

We included 10 out of 27 publications in which relative risk estimates for smoking on diabetes incidence were reported [67 75 82 99 121 127-131]. The other 17 studies were excluded because of a non-Caucasian population [115 116 132-134], less than 50 incident diabetes cases [93 98 135], classification of smoking as yes versus no [72, 77 79 134 136] effect of smoking in cigarettes/day [92] or duration of follow-up less than 5 years [86]. In three studies relative risk estimates for smoking were not presented because smoking prevalence at baseline was not different between future diabetes cases and non-cases [66 83 88]. All studies included reported on current as well as former smoking. Results and characteristics of these publications are summarized in Appendix V.
Figure 7.5 illustrates the relative risks that were found in these studies. The lines represent the selected CDM input values and confidence intervals specified by age. All studies, except one [67] show a consistent higher risk of diabetes incidence for people who (used to) smoke. Relative risk estimates vary roughly between 1.0 and 1.8 for current smokers and 1.0 and 1.4 for former smokers. The relative risk for diabetes incidence for smoking is rather consistent over age and the weighted mean values 1.15 for current smokers and 1.09 for former smokers were selected as input data for the CDM-2005-02.

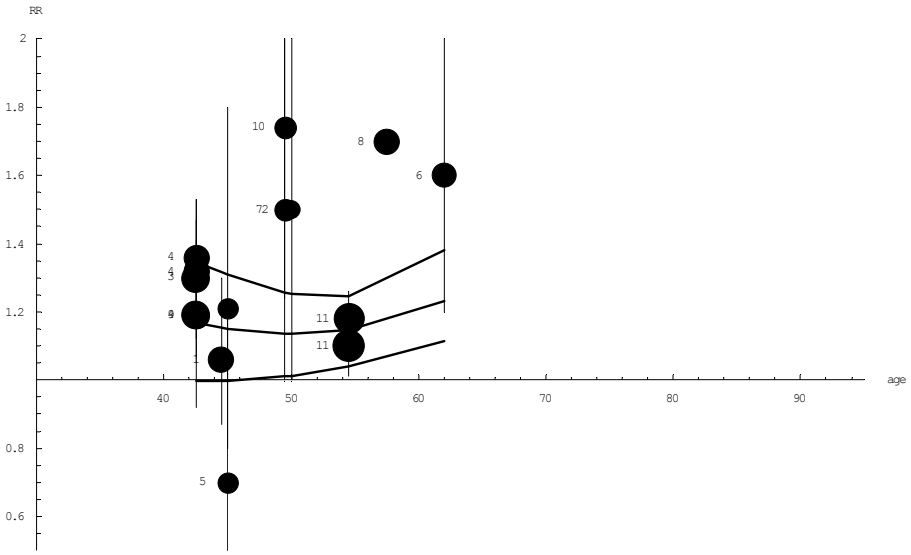
From Dutch monitoring studies (see methods section 6.2) the calculated relative risks for incident diabetes were 1.14 (0.72-1.82) and 1.13 (0.76-1.67) for male and female current smokers and 1.33 (0.86-2.04) and 0.62 (0.37-1.04) for male and female former smokers (adjusted for age, BMI and physical inactivity). The relative risks for current smokers are very similar to the selected values from the international studies. The relative risk found for female former smokers is surprisingly low.

The population attributable risk of current and former smoking on diabetes incidence is shown in table 7.3.

Table 7.3 Population attributable risk of current and former smoking on diabetes incidence for Dutch men and women

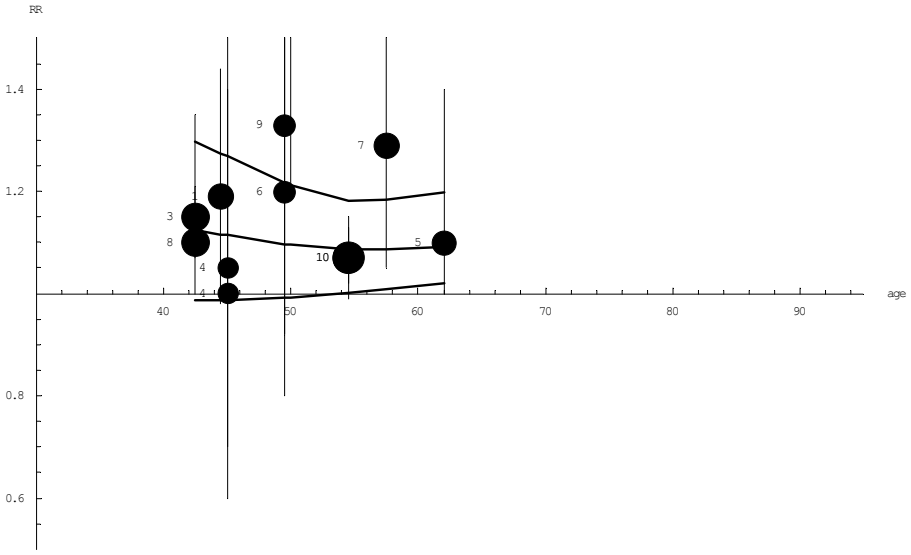
	Prevalence	RR	PAR
men			
current smoking	0.15-0.38	1,15	5.9%
former smoking	0.13-0.75	1,09	9.9%
women			
current smoking	0.11-0.32	1,15	4.6%
former smoking	0.14-0.40	1,09	5.6%

Current smokers



1. Carlsson, Diabetologia, Nord-Trondelag, 2004
2. Cassano, Am J Epid, Normative Aging, 1992
3. Hu, NEJM, Nurses Health, 2001
4. Hu, NEJM, Nurses Health, 2001
5. Kumari, Arch Intern Med, Whitehall, 2004
6. Manson, Am J Med, Physicians Health, 2000
7. Perry, Br Med J, British Regional Heart, 1995
8. Rimm, Br Med J, Health Professionals, 1995
9. Rimm, AJPH, Nurses Health, 1993
10. Wannamethee, Diab Care, British Regional Heart, 2001
11. Will, Int J Epid, CPSI, 2001

Former smokers



1. Carlsson, Diabetologia, Nord-Trondelag, 2004
2. Cassano, Am J Epid, Normative Aging, 1992
3. Hu, NEJM, Nurses Health, 2001
4. Kumari, Arch Intern Med, Whitehall, 2004
5. Manson, Am J Med, Physicians Health, 2000
6. Perry, Br Med J, British Regional Heart, 1995
7. Rimm, Br Med J, Health Professionals, 1995
8. Rimm, AJPH, Nurses Health, 1993
9. Wannamethee, Diab Care, British Regional Heart, 2001
10. Will, Int J Epid, CPSI, 2001

Figure 7.5 Relative risks for current and former smokers on diabetes incidence

The percentage of new cases of diabetes (>20 years) that is attributable to smoking is 13%; 16% for men and 10% for women. Current smoking causes 5% of the cases and former smoking 8%. The impact of former smoking for men is relatively high because the percentage of former smokers among elderly men is very high.

Based on the accumulating evidence for a relation between smoking and diabetes incidence we decided to include smoking as a risk factor for diabetes incidence. The new input data for smoking prevalence and transition rates are stored in input file "Smokinput160305.txt", the relative risks for smoking on diabetes incidence are documented in input file "RRsmok160305.txt".

7.4 Alcohol

Alcohol is a potential modifiable risk factor for diabetes incidence. Moderate alcohol consumption protects against diabetes risk as compared to not drinking or excessive drinking [137]. Results are inconsistent with respect to possible differential effects for different kinds of alcohol [138-141]. Frequent drinking (of moderate amounts) appears to be better then binge drinking [138 140 142].

In the CDM-2003, alcohol is modeled as a risk factor for all cause mortality, coronary heart disease, stroke and several forms of cancer. Alcohol is categorized in 4 categories for men (less than 1 drink per day, 1 to 4, 4 to 6, and more than 6 drinks per day) and 4 categories for women (less than 1 drink per day, 1 to 2, 2 to 4, and more than 4 drinks per day) based on the categorization used in the Australian recommendations on responsible drinking [32].

Prevalence data were retrieved from Statistics Netherlands (2002). Prevalence of alcohol consumption for Dutch men and women according to age is illustrated in figure 7.6. In the Netherlands 57% of the 20+ population drink less than one glass of alcohol per day, 42% of the men and 71% of the women (standardized to the age distribution of the Dutch population in 2003). The prevalence of excessive drinking is highest in middle-aged men but does not exceed 4%.

To determine the relative risk for alcohol on diabetes incidence we included studies in which:
- the effect of alcohol was expressed in at least three categories, with a range that covered a substantial part of the categories in the CDM. This means that studies were excluded if the highest category was >1 drink/day
- relative risks are adjusted for at least age and BMI (or weight / WHR / or waist-circumference)
- relative risks are sex-specific

Non-drinkers and ex-drinkers (if treated separately) were taken together and represent the reference category.

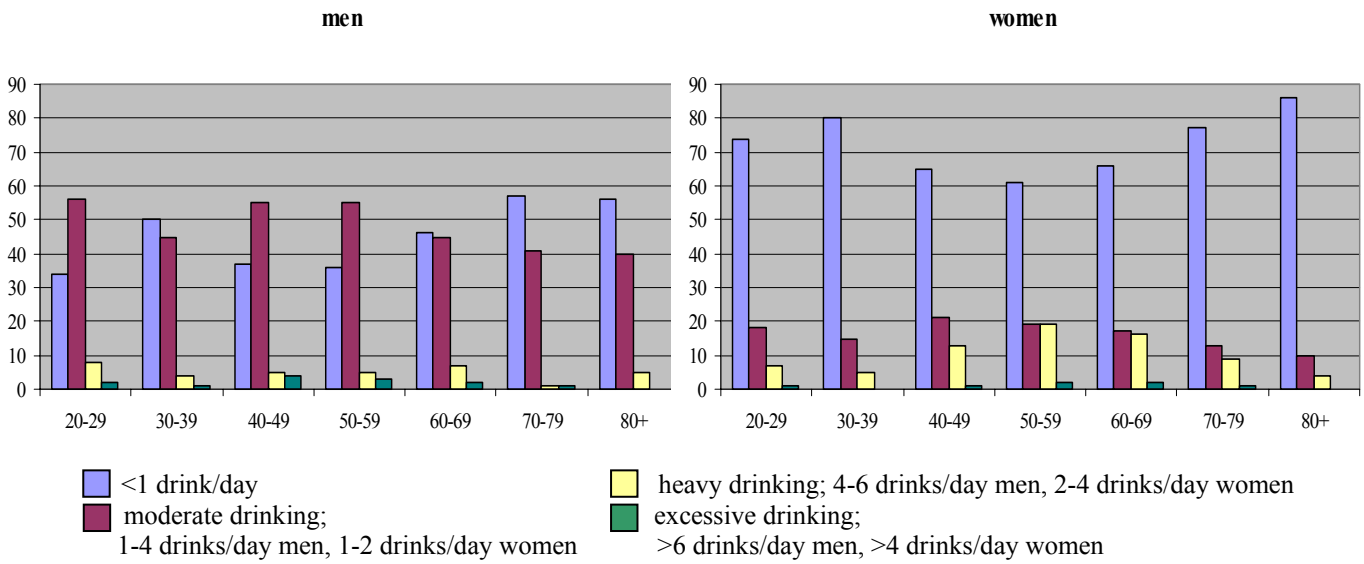


Figure 7.6 Prevalence of alcohol consumption in Dutch men and women
Source: Statistics Netherlands (2002)

We included 8 out of 24 publications in which relative risks for alcohol on diabetes incidence were reported [72 130 138-141 143 144]. Results and characteristics of these publications are summarized in Appendix VI. The other sixteen prospective studies on alcohol consumption and diabetes incidence were excluded because: alcohol consumption was modeled linearly in units/week [92 145 146], the highest category had only a moderate level of consumption (>10 gram/day) [75 147 148], the study comprised a non-Caucasian population [115 116 134 149-151], there were less then 50 incident diabetes cases [116 117], relative risks were not reported because alcohol consumption was not related to diabetes incidence [77 83] or results were reported for men and women combined [96]. The included studies show a consistent lower risk of diabetes incidence for people who drink moderately. Relative risk estimates vary roughly between 0.6 and 0.8 for moderate drinkers as compared to non-drinkers. There is no convincing evidence for an increased risk with heavy drinking (as compared to not drinking).

From the Dutch monitoring studies (see methods section 6.2) the relative risks on diabetes incidence for moderate drinking versus drinking less than one drink per day were 0.80 (0.57-1.12) and 0.33 (0.13-0.82) for men and women (adjusted for age, BMI, smoking and physical inactivity). Heavy and excessive drinking combined had relative risks of 0.66 (0.37-1.17) and 0.71 (0.34-1.47) for men and women, compared to drinking less than one drink per day. These results are in line with the figures found in the international literature.

There seems to be substantial evidence that moderate drinking protects against diabetes incidence. However, because there are not enough studies in the higher ranges of alcohol consumption, we cannot define a valid risk function to estimate relative risk parameters for the alcohol classes in the CDM. We decided not to include alcohol consumption as a risk (or protective) factor for diabetes incidence yet.

7.5 Combination of risk factors

Besides estimating the effect of individual risk factors, it is interesting to look at the influence of risk profiles in which risk factors are combined. For women in the Nurses Health Study

who did not fit into the low risk profile for diabetes (BMI < 25, healthy diet, moderate physical activity for at least 30 minutes per day, no smoking and moderate consumption of alcohol) the risk for diabetes incidence was more than 10 fold the risk for women with the low risk profile [102]. Although interesting, modeling risk profiles in the CDM-2005-02 (with different combinations of risk factors and accompanying prevalence- and relative risk- input data) is not yet feasible.

7.6 Conclusion risk factors for diabetes incidence

In the preceding sections we described the updated input data for BMI and physical inactivity in the CDM-2005-02. The relative risks for BMI and physical inactivity on diabetes incidence in the Dutch monitoring study were consistent with the input data estimated from the international literature.
Accumulating evidence suggests that smoking affects diabetes risk and smoking is added to the model as a risk factor for diabetes incidence. The relative risks found for smokers in the Dutch monitoring study were very similar to the estimate from the international literature except for female former smokers, where no evidence for an increased diabetes risk was found in the Dutch study. When we model our scenarios we will perform sensitivity analysis in which the relative risk for female former smokers on diabetes incidence will be set to 1.00 (no increased risk), as opposed to 1.09 as found in the international literature.
Alcohol consumption, although related to a reduced diabetes incidence, is not modeled yet because of insufficient data to quantify model parameters.

The population attributable risks for the risk factors are summarized in table 7.4.
With regard to prevention the highest potential gain is by reducing bodyweight. The optimal goal of intervention strategies however would be to induce positive changes in the general risk profile by intervening on combinations of risk factors. The results of primary prevention trials found in the international literature are reviewed in chapter 8.

Table 7.4 Summary of population attributable risks for risk factors for diabetes incidence

risk factor	PAR total	PAR men	PAR women
being overweight (BMI >25)	66.2	68.5	63.9
being moderately overweight (BMI 25-30)	28.1	31.1	25.3
being severely overweight (BMI ≥30)	38.0	37.4	38.6
smoking	9.1	11.6	6.6
current smoking	4.3	4.9	3.7
former smoking	4.8	6.7	2.9
physical activity	19.7	17.2	22.0
through reduced weight	9.6	7.7	11.4
independent of reduced weight	10.1	9.5	10.6

8. Primary prevention

MAM Jacobs-van der Bruggen, LCM Limburg

Primary prevention strategies intend to prevent or delay the development of new cases of diabetes, by modifying risk factor exposure in a diabetes-free population. Besides evidence of effectiveness of interventions as described in this chapter, we should consider policy relevance of the interventions, feasibility and costs, and our ability to model the strategy with the CDM. Furthermore, trial outcomes need to be translated into realistic expectations, when implemented into the Dutch health care setting, before we can define definite scenarios in 2005.

Primary prevention of diabetes entails trying to delay or prevent the development of diabetes by means of (lifestyle or pharmacological) interventions. In the international literature we found 13 studies that fulfilled our criteria for inclusion (see section 6.2). Four studies focused on lifestyle interventions (with diet and/or physical activity) [152,153 154] four on pharmacological interventions [155-158], two studies included both a lifestyle and a pharmacological intervention [159,160 161] and two studies used surgery as a means to loose weight for severely obese individuals [162 163]. All studies were aimed at individuals at a high risk of diabetes, that is individuals with high bodyweight and/or high levels of blood glucose, or individuals at high risk of cardiovascular disease [156]. The characteristics of the individuals selected in the intervention trials are important to consider when translating the results of these trials into prevention scenarios for the (general) Dutch population.

8.1 Lifestyle interventions

The results of the lifestyle intervention studies are summarized in Appendix VIIa. Significant improvements in lifestyle were attained and these changes were accompanied by reduced bodyweight, improved blood glucose control and reduced diabetes incidence of about 50-60%% in three to six years [154 152 159]. These programs may even have long term beneficial effects. In men with impaired glucose tolerance (IGT) who participated in the Malmo prevention trial, 12-year mortality was similar to that in normal glucose controls and significantly lower than that in the IGT routine treatment group [164].

The intensity of a lifestyle program appears to be an important determinant of success [152 159]. Intervention that comprised diet and physical activity appeared to be more effective than diet or physical activity alone [153]. In the Netherlands a lifestyle program to improve glucose metabolism is conducted in Maastricht. The intervention comprises 3-monthly nutritional advise from a dietician and subjects are encouraged to increase physical activity. Participants are enabled and stimulated to participate in supervised activities for at least one hour per week, without costs. The Dutch study, the “Study on Lifestyle-intervention and Impaired glucose metabolism Maastricht” (SLIM), has a planned duration of 6 years. The intervention comprises 3-monthly nutritional advise from a dietician and subjects are encouraged to increase physical activity. Participants are enabled and stimulated to participate in supervised physical activities for at least one hour per week. The control group only received yearly general information on the importance of a healthy diet and physical activity. Preliminary results of SLIM showed significant improvements (for intervention versus control) in body weight, BMI and glucose tolerance at the two years follow-up [165]. In the “fasting hyperglycemia study” [161] weight nor blood glucose were improved.

The feasibility of reducing bodyweight by lifestyle programs is moderate. The aim of the Finnish Diabetes Prevention Study (DPS) [152], reducing weight by at least 5%, was attained by 43% of the participants in 1 year. The aim of the US Diabetes Prevention Program (DPP) [159], reducing bodyweight by at least 7%, was attained by 50% in 2 years. Besides reducing bodyweight it is at least as important that these reductions in weight can be sustained [166]. In general it appears that the largest reduction in bodyweight is achieved within the first year of treatment after which the mean bodyweight tends to increase slowly [154 159 161 167]. The percentage of people in whom weight was still 7% lower than baseline weight one year after concluding the DPP was still 38%, whereas in the Malmo study [154], 71% of the participants were able to maintain an overall weight reduction for over 5 years. The results of the DPP indicated that about 7 people at high risk for diabetes should be treated for 3 years to prevent one case of diabetes [159].

8.2 Pharmacological interventions

The results of the pharmacological intervention studies are summarized in Appendix VIIb. Treatment with metformin [159], orlistat [155 157] ramipril or acarbose were all found to be effective in preventing diabetes incidence, with risk reductions from 24% to 37% percent in the larger studies.

Metformin is an oral medicine used to control blood glucose levels by increasing insulin sensitivity of the tissues. Metformin is frequently used in obese patients with type 2 diabetes because of its proven effectiveness [168] and because, as opposed to other oral diabetes medications, it does not cause weight gain [169]. In the US DPP, treatment with metformin resulted in weight reduction and reduced levels of blood glucose compared to placebo, while diabetes incidence was reduced with 24%. However, with risk reductions of 51% and 24% respectively, intensive lifestyle intervention for two years in the same study was more effective in preventing diabetes than treatment with metformin [159].

Orlistat is a medicine that inhibits dietary fat absorption, promotes weight loss and may reduce the risk of developing diabetes in obese individuals. In a large international study, obese individuals treated with orlistat had significant reductions in weight as compared to placebo treated controls. The risk of developing diabetes in 4 years was reduced with 37% [157]. In another study, obese individuals treated with orlistat for 2 years (in addition to a low energy diet) lost more weight than individuals treated with diet and placebo [155]. Significantly less participants with normal glucose tolerance at baseline progressed to impaired glucose tolerance (IGT) or diabetes in the orlistat group as compared to the placebo group (18/273 versus 30/249). Individuals with IGT at baseline who were treated with orlistat were less likely to develop diabetes as compared to placebo treated controls (2/67 versus 4/53). In addition glucose tolerance had improved to normal values in 72% of the orlistat treated IGT-patients as compared to 49% in controls.

Ramipril is an ACE inhibitor and is generally used for the treatment of hypertension. ACE inhibitors also seem to have beneficial effects on glucose metabolism. In a large international study individuals (55+) with evidence of vascular disease who were treated with ramipril had a significant 34% reduced risk of developing diabetes in 4.5 years [156].

Acarbose is an oral medication used in patients with type 2 diabetes. Acarbose slows down the action of enzymes that are active in digesting food, thereby slowing the appearance of sugar in the blood after a meal. In people with IGT, treatment with acarbose reduced the risk of developing diabetes with 25% in 3 years and significantly increased reversion from IGT to normal glucose tolerance. However, acarbose treatment was frequently accompanied with

side effects such as flatulence and diarrhea which made 31% of the acarbose participants discontinue treatment early [158].
Treatment with sulfonylurea was accompanied by significant weight gain and showed no indication for reduced diabetes incidence [160].
Bariatric surgery is effective in loosing weight and preventing diabetes cases. However this intervention option is of less interest from a public health (political) perspective.

8.3 Primary prevention conclusions

Primary prevention of diabetes in individuals at high risk for diabetes appears to be feasible, the development of diabetes can be delayed or postponed. Lifestyle interventions seem to be more effective than pharmacological interventions with reductions in diabetes incidence of up to 60% in five years. However, these programs are intensive and costly, with (individually supervised) diet and exercise programs for several years. How the trial results, obtained in individuals at high risk for diabetes can be translated into realistic scenario outcomes, when implemented in Dutch health care settings, will be studied in 2005. One limitation to consider with respect to the CDM, when modeling a prevention scenario targeted at individuals with impaired glucose tolerance, is that glucose levels of individuals without diabetes are not included in the model.

Part IV Prevention of diabetes complications

9. Macrovascular complications of diabetes and tertiary prevention

G Bos

9.1 Introduction

In this part of the Technical Report we focus on factors concerning tertiary prevention. Tertiary interventions intend to prevent or delay the development of complications of people having diabetes, by modifying high exposure to cardiovascular risk factor(s) in diabetes patients. We focus on the risk factors overweight, physical activity, smoking, total cholesterol, and systolic blood pressure. These risk factors are involved in development of diabetes and cardiovascular complications, and are already included as risk factors for diabetes and other diseases in the primary prevention part of the CDM. HbA1c (a measure of blood glucose control in diabetes patients) is added to the model as a new factor. To calculate tertiary prevention scenarios, it is necessary to specify the distribution of risk factors for the diabetes population. The distribution of risk factors and complications in Dutch diabetes patients (prevalence), and the relation of risk factors with macrovascular complications (relative risks) are thus new input in the model. The purpose of this part of the report is to justify the new diabetes related input in the CDM, and to review international results of tertiary intervention trials.

9.2 Methods

Prevalence of cardiovascular disease in diabetes
The prevalence of cardiovascular disease in individuals with diabetes was obtained from estimates by the CDM. Based on the prevalence of AMI, CHD, CHF and stroke in the general population and the relation of these diseases with incidence of diabetes, the prevalence of cardiovascular disease was calculated in subjects with and without diabetes. The estimated prevalences from the model were validated by experimental data.

Prevalence of cardiovascular risk factors
The prevalence of cardiovascular risk factors for diabetes, i.e. overweight, smoking and physical inactivity in individuals with diabetes was obtained from estimates by the CDM. Based on the prevalence in the general population and the relation between risk factor and incidence of diabetes, the prevalence of risk factors was calculated in subjects with and without diabetes.
The estimated prevalences from the model were validated by experimental data, because of internal consistence in the model. The prevalences for total cholesterol, blood pressure and HbA1c were based on empirical data, because these factors are not included as risk factors for incidence of diabetes in the CDM. Data on the distribution of risk factors in people with diabetes are scarce. First a literature search was performed to find data from Dutch studies, and to determine all diabetes populations in the Netherlands. A list of large studies and projects was composed (table 9.1). Based on this list, data were retrieved to be able to

estimate age- and sex-specific prevalence of complications and risk factors in diabetes patients. Inclusion criteria were:

- N>1000 subjects with diabetes
- Start year>1995
- Availability of raw data (within 2 months, limited costs)

The data of three Diabetes Care Projects (Westfriesland, SHL Breda and Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC)) and two large GP registrations (second Dutch National Survey of General Practice (DNSGP-2) and Nijmeegs Monitoring Project (NMP)) did meet these criteria. The populations of the Diabetes Care Projects have been described previously [170]. Prevalence data published in the literature were used for validation. It was not possible to obtain data about physical activity in diabetes patients in the used data sources. Therefore, only a description of physical activity in Dutch diabetes patients in the literature was given.

Table 9.1 List of Dutch studies with diabetes patients

Study	Period	Diabetic patients	Setting	Reference	In/exclusion
Hoorn study	1989-1992	N=255	Population based cohort Hoorn	Mooy *et al.* 1995	Exclusion: N too small/old
Hoorn study	2000-2001	N=412	Population based cohort Hoorn	Dekker, Heine, VUMC	Exclusion: N too small
MORGEN	1993-1998	N=377	Amsterdam, Doetinchem, Maastricht	Verschuren, RIVM	Exclusion: N too small
Doetinchem	1998-2002	N=139	Doetinchem	Verschuren, RIVM	Exclusion: N too small
Diabeteszorg West-Friesland	2002 - now	N=2221	Annual care of patients detected by GP or the Hoorn study	Nijpels, Diabetes Onderzoek Centrum	Inclusion
Stichting Huisartsen Laboratorium Breda	1998 - now	N=20437	Annual care in Breda region	Hessen, SHL Breda	Inclusion
ZODIAC, Zwolle	1998 - now	N=2624	Annual care GPs in East Netherlands	Ubink-Veltmaat *et al.* 2003	Inclusion
Matador	2000 - now	N~3000	45 GPs	Frederiks, Jöbses	Exclusion: data not available
Dissertation Carry Renders	1992, 1993	N=516	GP's in Enschede, Hengelo and Amsterdam/Amstelveen	Renders *et al.* 2001	Exclusion: N too small and data < 1995
Diagnosis for health (D4H)	2002 - now	N=10404	Houten	Pijman	Exclusion: data not yet available

Study	Period	Diabetic patients	Setting	Reference	In/exclusion
CMR/NMP, Nijmegen	1996 - now	N=1060	Continuous registration (since 1971) of diabetes patients from GP in Nijmegen region	De Grauw *et al.* 2002	Inclusion
Utrecht diabetes project		N=770	Diabetologist support for 85 GPs	Rutten *et al.* 2001	Exclusion: N too small
Diabetesdienst	1993	N=637	22 GPs in a GP network	Bouma *et al.* 1999, De Sonnaville *et al.* 1997	Exclusion: N too small
CODE-2	1998	N=1371	29 GPs in Europe	Redekop *et al.* 2002	Exclusion: costs of diabetes, not Dutch
	2001-2002	N=895	Electronic medical records of 95 GPs	Schaars *et al.* 2004	Exclusion: N too small
Tweede Nationale studie	2000-2002	N=10129	Patient registration in 104 GPs	Schellevis *et al.* 2003	Inclusion

Definition of risk factors for complications
Body mass index, smoking, cholesterol and physical activity are defined in categories according to the CDM-2003 (see chapter 2, table 2.1).
Blood pressure is already implemented in the CDM-2003, but is changed as follows: in CDM-2003, blood pressure was defined in 4 categories based on systolic blood pressure, and 1 category of antihypertensive medication users. Since the use of antihypertensive medication in diabetes patients is rather high (>50%), we specified the medication users also in 4 blood pressure categories (table 9.2).
The definition of HbA1c is new in the CDM-2005-02. HbA1c in diabetes patients is defined in 3 categories (table 9.2) according to the guidelines of the Zorgstandaard Nederlandse Diabetes Federatie [171].

Table 9.2 Description of newly defined factors in the CDM-2005-02

Factor	Category	Description
Blood pressure	1	<120 and no medication
	2	120-140 and no medication
	3	140-160 and no medication
	4	≥160 and no medication
	5	<120 with antihypertensive medication
	6	120-140 with antihypertensive medication
	7	140-160 with antihypertensive medication
	8	≥160 with antihypertensive medication
HbA1c	1	<7%
	2	7-8.5%
	3	>=8.5%

Relative risks of risk factors for complications in individuals with diabetes
For the input in the CDM, we assumed that the relative risks of all risk factors for CVD in diabetes patients are the same as in subjects without diabetes, and that having diabetes has an multiplicative effect. The relative risk in diabetes patients is modeled as:

*RR (rf→CVD in DM) = RR (DM→CVD) * RR (rf→CVD in general population)* (9.1)

RR= relative risk
rf= risk factor
CVD=complication (AMI, CHD, CHF, stroke)
DM=diabetes

Thus, the effect of having both diabetes and having a risk factor on CVD risk is expressed with no diabetes/no risk factor as reference group. In the next sections, we will discuss whether this assumption is reasonable for all risk factors. We will discuss the possible error made by this assumption, and which correction which should be made.
For HbA1c, which will only be modeled in individuals with diabetes, new relative risks were estimated. Relative risks of overweight, smoking, physical activity, total cholesterol, systolic blood pressure and HbA1c for cardiovascular disease in diabetes patients were determined from the international literature. Relevant articles were retrieved from Pubmed searches, RIVM diabetes-experts and reference tracking of the articles and reviews retrieved. Publications were used to estimate the relative risk of the risk factor involved if the following criteria were met:

- publication year 1990-2004
- prospective longitudinal cohort study in diabetes patients on incidence of complications
- at least 50 incident cases (AMI, CHD, CHF, stroke)
- Caucasian population
- Relative risk in diabetes population reported
- measurement of risk factor in units or categories
- Sex-specific relative risks (if possible)
- Multivariate estimate of relative risk

Tertiary prevention
A literature search was done searching for tertiary intervention studies. Studies were included if they met the following criteria:

- published between 1995-2004
- study aim: prevention of macrovascular complications in patients with diabetes
- at least 50 subjects in the intervention group
- inclusion of a control group
- relevant outcome data available (change in risk factor level or prevention of diabetes complications)
- follow-up at least 1 year
- Caucasian population

This review of the literature provides information on which tertiary intervention strategies in individuals with diabetes appear to be effective. Based on this information we can determine which strategies are potentially interesting to model with the CDM next year. However, relevant aspects such as feasibility of implementation in Dutch health care, costs of the intervention and translation of trial results into realistic scenarios need to be addressed.

9.3 Prevalence of macrovascular complications in individuals with diabetes

Information on the occurrence of macrovascular diseases (disease states) are used in the CDM as initial class prevalence rates (in the year at which we start modeling). The default input for prevalence of macrovascular endpoints in diabetes patients is obtained from calculations by the CDM. Empirical data on macrovascular complications in Dutch diabetes patients for validation are scarce. In the time period of this project, we had data on complications available from NMP and ZODIAC which are relatively small studies where age- and sex-specific prevalence estimates has to be made. The prevalence of all endpoints increase with age when based on estimates from the model. Figure 9.1 illustrates that the prevalences obtained from empirical data were lower than estimated prevalences of myocardial infarction (AMI) in men and women. For CHD, CHF and stroke, the same differences were observed (Appendix VIII). It is likely that the estimates based on the model are an overestimation of the prevalences in older age. This could be due to higher case fatality rate in cardiovascular disease in patients with diabetes than those without diabetes [172]. Case fatality, however, is not included in the CDM. In 2005, we will further explore this issue. The impact of both default input and empirical input on model output will be evaluated by calculations of the CDM.

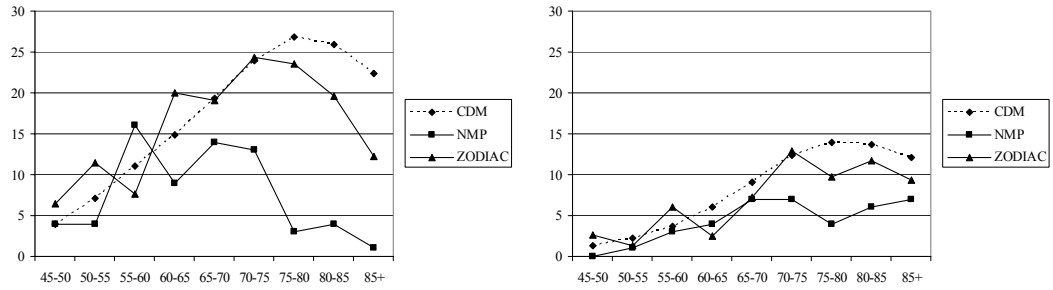


Figure 9.1 Initial class prevalence rates of AMI in diabetes patients in men (left) and women (right) with diabetes, estimated from CDM and empirical data

Default input data for prevalence of macrovascular complications in diabetes patients = estimated prevalences calculated by CDM-2005 in diabetes patients.

The diabetes-specific prevalence input data, with the accompanying transition rates will be documented in input files “ChdDmInput.txt”, “ChfDmInput.txt”, “CvaDmInput.txt”, respectively.

Prevalences international literature

Patients with diabetes have at least two-fold increased risk on cardiovascular disease and mortality compared with non-diabetic subjects [173]. In people with diabetes, cardiovascular complications occur at an earlier age and often result in premature death. The cardiac care has improved in the last decades, which has improved the survival of the diabetes patients as well as non-diabetic patients. The prevalence of cardiovascular disease in diabetes patients is still high. In a Finnish population without cardiovascular disease aged 45-64 years, 35% of the diabetic men and 31% of the diabetic women had developed a major CHD event (CHD death or non-fatal myocardial infarction) compared to 14% in non-diabetic men and 2% in non-diabetic women [174]. In the Heart Protection Study among UK adults with known diabetes

aged 40-80 years, the prevalence of vascular disease at baseline was 19% myocardial infarction and 14% CHD [175]. Also, the Strong Heart Study showed that incidence rates for non-fatal CVD in diabetes patients between the ages of 45 and 74 years were much higher than in non-diabetic patients. Incidence rates per 1000 person years were as follows: for diabetic men 31.8, for non-diabetic men 16.4, for diabetic women 17.9, for non-diabetic women 5.8 [176]. In the UK Prospective Diabetes Study (UKPDS), myocardial infarction occurred in 12% of the subjects with diabetes, of whom 51% were fatal [177]. In the Diabetes Intervention Study, after 11-year follow-up, the prevalence of myocardial infarction was lower being 15%, but this percentage was observed in a cohort of newly detected cases of relatively young diabetes patients in the age of 30-55 years [178]. In general, women with diabetes have higher cardiovascular risk than diabetic men. Although women have a lower risk for most risk factors (associated with lower risk for cardiovascular disease) diabetes tends to eliminate the female advantage [179].
Patients with diabetes also have an increased risk of development of CHF (Nationaal Kompas). The Framingham Heart study observed a relative risk of 1.7 in men (65-94 years old). In women aged 35-64 years, a relative risk of 7.0 was found [180]. Nichols *et al.* studied the prevalence and incidence of CHF in populations with and without diabetes. The prevalence of CHF in diabetes was 12% versus 4.5% in individuals without diabetes after 4 years of follow-up [181]. After 6 years of follow-up, the prevalences were 14% and 6%, respectively [182].
In 27268 women pooled from 9 prospective epidemiological studies in the United States (Women's Pooling Project) 2.3% had a history of previous stoke in the total population. In the participants with diabetes, 95 of 2091 (4.5%) had previous stroke [183]. From our empirical data (NMP) we found that in about 5% of men and women with diabetes stroke occurred. This was in line with findings from other studies. Tuomilehto *et al.* [184] showed that percentages of stroke were 5.1 and 6.0% in men and women with diabetes, respectively, while in non-diabetic subjects stroke percentages of <1% were observed. The Strong Heart study reported that stroke mortality rates were similar in subject with and without diabetes, but numbers of stroke cases were low (large confidence intervals) [176]. The UKPDS reported 4% fatal and non-fatal stroke after 7 years of follow-up in diabetes patients without cardiovascular disease at baseline [177].

Concluding remarks
The numbers of Dutch diabetes patients in which the prevalence of macrovascular disease could be obtained were very small. In 2005, we will validate estimated prevalences calculated by the CDM based on relative risks of diabetes versus non-diabetics for macrovascular disease with the prevalence of complication estimates from empirical data (NMP).

10. Risk factors for macrovascular complications in individuals with diabetes

G Bos, RT Hoogenveen

In this part, we will describe the prevalence of six risk factors for macrovascular disease (overweight, physical activity, smoking, total cholesterol, systolic blood pressure and HbA1c) in diabetes patients, and the association between the risk factors and macrovascular disease in subjects with diabetes. The relation between glucose concentrations and macrovascular events is less powerful than for microvascular complications; smoking, blood pressure, and cholesterol concentration are more important risk factors for macrovascular disease in patients with diabetes than glucose concentration.

10.1 Overweight

Prevalence of overweight and obesity in diabetes patients
Information on the prevalence (risk factor classes) of overweight, defined as body mass index (BMI) 25-30 kg/m^2, and obesity (BMI ≥30 kg/m^2) are used in the CDM as initial class prevalence rates (in the year at which we start modeling). The default input for prevalence of macrovascular endpoints in diabetes patients was obtained from calculations by the CDM. Pooled data from ZODIAC, Westfriesland and NMP were used to validate the input prevalence data for the model. In SHL Breda, BMI was not measured. The empirical prevalences corresponded very well in men and women in the three diabetic populations

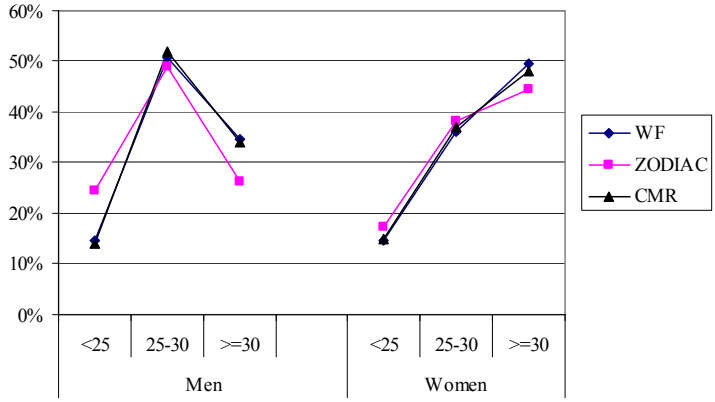


Figure 10.1 Percentage overweight and obesity in three data sources

(figure 10.1). Overweight and obesity are very common in diabetes patients. This was seen for prevalences based on estimates from the CDM as well as prevalences obtained from empirical data (figure 10.2). Figure 10.2 illustrates that empirical and estimated BMI prevalences in men corresponded very well except for younger ages. In women, the same

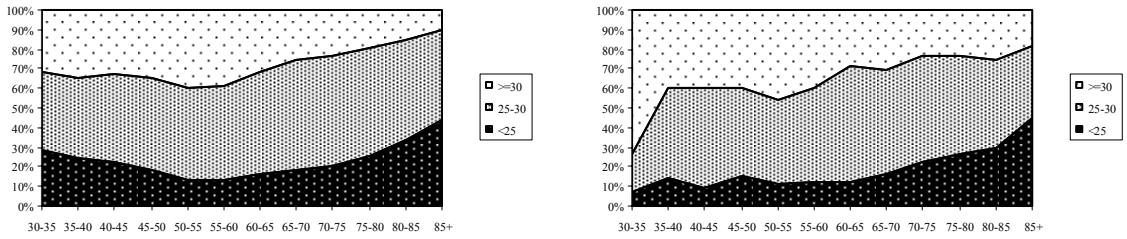


Figure 10.2 Prevalence of normal weight, overweight and obesity in men with diabetes, estimated from the CDM (left), and empirical data (source: NMP, ZODIAC and Westfriesland (pooled data))(right)

agreement was observed (Appendix IX). In both men and women, circa 80% had a BMI > 25 kg/m^2 (table 10.1). In people with diabetes, the prevalence of moderate overweight increased until the age of about 65. In men, the percentage moderate overweight was higher than in women in all age classes (mean 51% in men and 37% in women). Severe overweight or obesity decreased with age, and more women (48%) than men (32%) with diabetes were obese.

Table 10.1 Empirical data for prevalence of overweight and obesity in diabetes patients, age- and sex-specific

			men			women		
	n	n	< 25	25-30	≥ 30	< 25	25-30	≥ 30
25-44	104	91	11	44	45	11	27	62
45-54	339	255	12	44	44	15	25	60
55-64	670	519	12	54	34	11	33	56
65-74	603	700	19	54	27	14	42	44
75+	354	630	29	47	23	22	40	38
Total	2070	2195	17	51	32	15	37	48

Sources: NMP, ZODIAC and Westfriesland (pooled data)

Default input data for prevalence of BMI in diabetes patients = estimated prevalences calculated by CDM-2005 applied to diabetes patients

The diabetes-specific BMI input data are documented in input file “BmiDmInput.txt”.

International literature

In comparison with other European countries and the US, the prevalence of obesity in the Netherlands is relatively low [185]. The range in occurrence of obesity in diabetes patients was 26% in Spain [186], 35% in Brazil [187] to 43% in 9 countries in Europe [188]. In Norway, the prevalence of obesity in men with diabetes was 28% and 46% in diabetic women versus 14% and 18% in non-diabetic men and women [189]. Obesity is more prevalent in women than in men [190]. Besides obesity, circa 35% of the people with diabetes is moderately overweight [190] [191].

Relative risk

Coronary heart disease

Obesity is a well-established risk factor of CHD in the general population. Surprisingly, in most studies of individuals with diabetes, no positive association was found between obesity and CHD death or total mortality [191]. A few studies reported the association of BMI with CHD risk in diabetes patients. In stepwise multivariate Cox models, BMI was not an important risk factor [192]. In about 6000 women with diabetes of the Nurses' Health study, the cardiovascular risk of women having a BMI >=30 was 3-fold higher, compared to women with BMI<20 [191]. They concluded that overweight still contributes to CHD in women with diabetes. However, they used a reference category of BMI<20, which is rather low. A recent study in Finland demonstrated an association of BMI (per unit) with CHD death, but not with all (fatal and non-fatal) CHD events in men. In women, no association was found between BMI and CHD morbidity and mortality [174]. In contrast, the Physicians Health study reported relative risk of overweight in subjects with diabetes with lean subjects (<22 kg/m^2) without diabetes as reference category, with relative risks of 2.9 and 5.4 for overweight and obesity, respectively [18]. Thus, having both diabetes and overweight was associated with CHD with relative risk =5.4. This is in line with Figure 10.3 (relative risks in general population and in diabetes). Preferentially, relative risks of BMI should be obtained for women and men separately, but this was not possible (not enough publications).

For the CDM-2005-02, we assume that the relative risk of overweight and obesity for CHD in diabetes population is the same as in subjects without diabetes, and that having diabetes has an multiplicative effect on the relation between BMI and CHD (figure 10.3). For men, this is plausible (see Physician's Health Study), but for women this might overestimate the effect. Since diabetes and overweight are strongly related, the diabetes-related risk of CHD is partly explained by overweight [193]. We suppose that the assumption will lead to an overestimation of the risk of both overweight and diabetes on macrovascular disease. In 2005, we will further explore this issue.

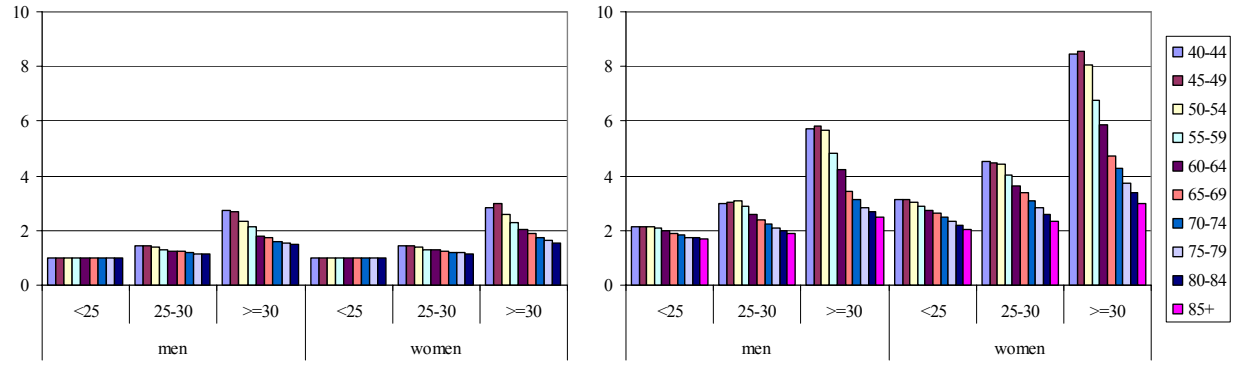


Figure 10.3 The relative risk of CHD in diabetes patients (right) associated with BMI, compared to non-diabetics with normal weight as reference category, is obtained by multiplying the relative risks of overweight with CHD in the general population (left) with the relative risk of diabetes (versus no diabetes) with CHD.

The assumption that the "Relative risk of BMI for CHD in diabetes = Relative risk of diabetes for CHD * Relative risk of BMI for CHD in the general population" will probably lead to an overestimation of the risk of having both overweight and diabetes on macrovascular complications

Heart failure
We found only one study (two publications) in which risks of BMI for CHF was reported. After 6 years of follow-up, the risk associated with 2.5 unit change in BMI was 12% [182], that is 12% increased CHF risk for each 2.5 kg/m^2 increment in BMI. Another publication of the same study after 2.5 years of follow-up [181] reported an association for change in weight, but not BMI, with risk of CHF. Both studies, however, were carried out in a population of both diabetic and non-diabetic individuals. We conclude that there is little evidence to support a strong association between BMI and CHF in diabetes patients. In 2005, sensitivity analysis will be performed to quantify the effect of using relative risk estimates in diabetes patients derived from the model versus relative risks of 1 (no effect) for the purpose of modeling BMI as a risk factor for CHF.

The assumption that the "Relative risk of BMI for CHF in diabetes = Relative risk of diabetes for CHF * Relative risk of BMI for CHF in the general population" will probably lead to an overestimation of the risk of having both overweight and diabetes on macrovascular complications

Stroke
There were only two studies that reported the association of BMI with stroke risk in diabetes patients. Lehto and Tuomilehto did not observe an association between BMI and stroke in subjects with diabetes [184 194]. We did not find clear evidence for an association between BMI and stroke in diabetes patients. In modeling BMI as a risk factor for stroke as a complication of diabetes, sensitivity analysis will be performed to quantify the effect of using relative risk estimates derived from the model versus relative risks of 1 (no effect).

The assumption that the "Relative risk of BMI for stroke in diabetes = Relative risk of diabetes for stroke * Relative risk of BMI for stroke in the general population" will probably lead to an overestimation of the risk of having both overweight and diabetes on macrovascular complications

Concluding remarks
There is a considerable difference in the distribution of BMI in 3 categories between people with and without diabetes. For the CDM-2005-02, we assume equal transition rates between the BMI prevalences in diabetes patients compared to the general population. Because of lack of publications on relative risks of BMI for macrovascular disease in diabetes patients, we will validate the input in the CDM to external data.

10.2 Physical inactivity

Prevalence of (in)activity in diabetes patients
The default input for distribution of active, insufficiently active and inactive diabetes patients is obtained from calculations by the CDM. The prevalence of physical (in)activity in 3 categories in both diabetic and non-diabetic men and women based on estimates from the model is shown in Appendix IX. Physical inactivity is included in the CDM as a risk factor for diabetes. Diabetes patients turned out to be somewhat less active than individuals without diabetes. Unfortunately, we were not able to find a data set in which we could explore physical activity in 3 categories (according to CDM) in the general population in which a large diabetes subpopulation was defined. In the diabetes care projects and GP registrations, no data on physical activity were available. It was not possible to pool data of population studies because of difference in measurement methods of physical activity. Thus, only published information was used to describe physical activity in Dutch diabetes patients. Schuit *et al.* reported the prevalence of physical activity in people with a chronic disease [195]. They found that men and women with diabetes were less physically active at work than people without diabetes and/or CVD. Men with diabetes spend more time on housekeeping, while women spend less time on this activity in comparison to women without diabetes. TNO used data of the Patiëntenpanel Chronische Ziekten (PPCZ) to perform a quick scan on chronic diseases and exercise [196]. The conclusion was that 25% of the diabetic women of 65 years and older were norm active (fulfilled the NNGB guideline). Women of 65 years and older with chronic disease in general had a high prevalence of inactivity (mean 49%). There were no clear differences between men with and without diabetes (figure 10.4). Since physical activity is difficult to measure, and subsequently to compare between different studies, we do not give a comparison of prevalences of physical activity with the international literature.

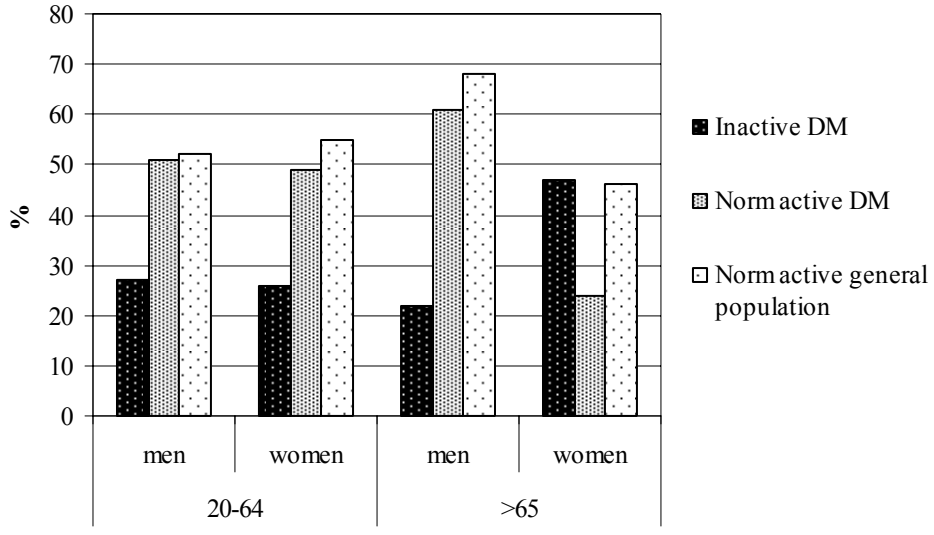


Figure 10.4 Percentage of inactivity in people with diabetes and the general population (source: Scan Chronische Ziekten TNO)

Input data for prevalence of physical activity in diabetes patients = estimated prevalences calculated by CDM-2005 applied to diabetes patients

The diabetes-specific physical activity input data are documented in input file "LichactDmInput.txt".

Relative risk

The possible protective effect of physical activity on macrovascular complications in patients with diabetes is not clear. In US adults with diabetes, walking was associated with lower all cause mortality, but the association with CVD mortality was less clear [197]. In a cross-sectional, case-control study, physical activity (moderate and vigorous) seemed to be associated with a lower prevalence of acute coronary events in the investigated group of diabetic subjects. Light physical activity did not have any significant association with the development of acute coronary events [198]. In univariate analyses, physical activity was protective for AMI, but in stepwise multivariate Cox models, physical activity was not an important risk factor [199]. The diabetic women in the Nurses Health demonstrated a 40% decreased CHD risk with 4 to 7 times moderate to vigorous activity per week [200]. A 26% decrease in stroke was observed in active women, but this was not significant. No other studies reporting a relation between exercise and stroke in diabetes were found. In addition, several studies showed that cardio respiratory fitness was associated with lower cardiovascular risk, but fitness is not included in the CDM. Overall, there was a trend in increased cardiovascular risk with inactivity, but the majority of the associations between exercise and macrovascular endpoints did not reach significance.
For the CDM-2005-02, we assume that the relative risk of physical activity for CHD and stroke in diabetes population is the same as in subjects without diabetes, and that having diabetes has an multiplicative effect on the relation between physical inactivity and CHD and stroke. This assumption will possibly lead to an overestimation of the risk on macrovascular disease, but we did not found evidence to reject the hypothesis that the relation between physical inactivity and macrovascular disease is the same in subjects with diabetes compared to subjects without diabetes.

The assumption that the "Relative risks of physical (in)activity for CHD and stroke in diabetes = Relative risk of diabetes for CHD and stroke * Relative risks of physical (in)activity for CHD and stroke in the general population" will probably lead to an overestimation of the risk of both physical (in)activity on these macrovascular complications in a diabetic population

Concluding remarks

Due to lack of a Dutch (general) population study including sufficient diabetes patients, and a reliable measurement of physical activity, it was not possible to validate the estimated prevalence of physical activity in diabetes patients. When better data are available, we will confirm that the input in the CDM is reliable.
In modeling physical inactivity as a risk factor for macrovascular complications, sensitivity analysis will be performed to quantify the effect of using relative risk estimates derived from the model versus relative risks of 1 (no association).

10.3 Smoking

Prevalence of smoking
The default input for distribution of smoking in diabetes patients is obtained from calculations by the CDM. Smoking is included in the CDM as a (weak) risk factor for incidence of diabetes. The prevalence of smoking in diabetes patients is almost equally to individuals without diabetes (Appendix IX).
Empirical data about smoking in Dutch diabetes patients is scarce. Only ZODIAC and NMP provided data on smoking in diabetes patients, but information about former smoking was missing in NMP. We compared the estimated prevalences derived from the CDM with prevalences of current smoking in ZODIAC and NMP (figure 10.5). There were differences

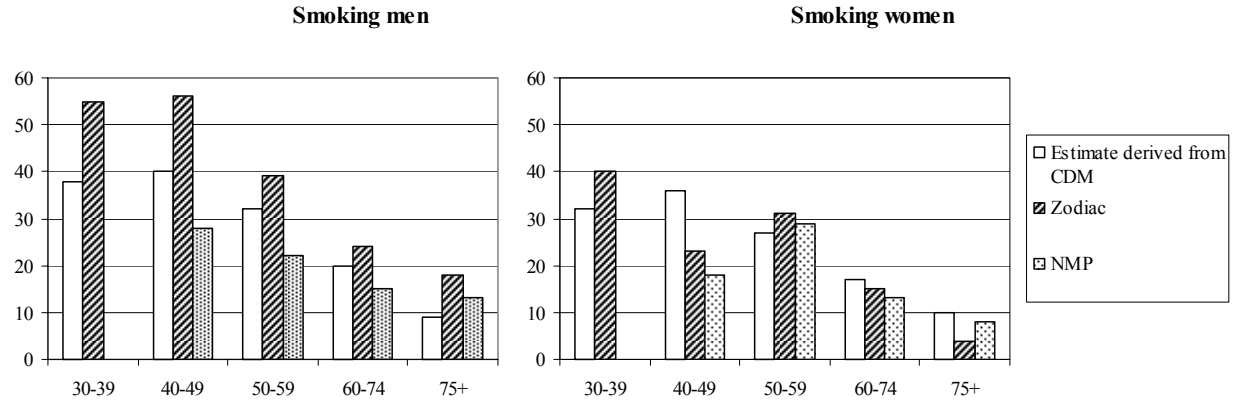


Figure 10.5 Estimated prevalences of current smoking in diabetes patients (white bars) compared to prevalence of current smoking in ZODIAC and NMP

between the estimated and empirical smoking values as well as between ZODIAC and NMP data in men and women. In men, ZODIAC prevalences of smoking were higher and NMP prevalences of current smoking were lower than the estimate derived from the model. This could be due to small numbers (n<50 in age groups <50 y) or to regional differences in smoking habits (Nationale Atlas Volksgezondheid, RIVM, Bilthoven). In table 10.2 the prevalences of former smoking are shown. In men, prevalence of former smoking in CDM increased more with age than in ZODIAC. There were less former smokers among women in ZODIAC than the model-derived prevalences of former smoking. More data on (former) smoking in both subjects with and without diabetes are needed to assess whether smoking habits in Dutch diabetes patients are different from the general population. We conclude that there is not enough evidence to reject the estimates from the model.

Table 10.2 Estimated prevalences of former smoking in diabetes patients compared to prevalence of current smoking in ZODIAC

	Men		Women	
	Estimate derived from CDM	Zodiac	Estimate derived from CDM	Zodiac
30-39	17	14	20	17
40-49	30	21	34	36
50-59	48	43	39	23
60-74	66	56	38	16
75+	81	59	23	10

Default input data for prevalence of smoking in diabetes patients = estimated prevalences calculated by CDM-2005 applied to diabetes patients

The diabetes-specific smoking input data are documented in input file "SmokDmInput.txt".

International literature

There are large international differences in smoking habits, even between European countries (table 10.3). Smoking habits are determined by age, sex, national smoking habits and presence of chronic diseases. It is difficult to compare international smoking prevalences with Dutch prevalences among diabetes patients.

Table 10.3 Summary of international literature regarding prevalence of smoking in diabetes patients

Publication	Population	Smoking
Glumer 1999-2000 [201]	30-60 year (Denmark)	42% (men) 37% (women)
Sender 2000 [186]	mean 66 year (Spain)	12%
Schaan 1999-2000 [187]	mean 53 year (Brasil)	31%
Khaw 1995-1997 [202]	45-79 jaar (UK)	7.5%
EUROASPIRE II 1995-1996 [188]	<70 year (9 countries in Europe)	19% (men) 14% (women)
NHANES-III 1991-1994 [190]	(USA)	22%
Physician's Health Study 1983 [18]	40-84 year (USA)	17% (men)
MRFIT 1973-1975 [19]	35-57 year (USA)	36% (men)
Adlerberth 1973 [203]	51-59 year (Sweden)	41% (men)
Tuomilehto 1972-1977 [184]	(Finland)	51% (men) 11% (women)

Relative risk

Coronary heart disease

In the Multiple Risk Factor Intervention Trial (MRFIT), cigarette smoking was a powerful determinant of CVD mortality in men with diabetes, and had an additive effect to cholesterol or blood pressure [14]. Smoking as a risk factor for AMI and all cause mortality [178]or CHD [204] was also observed by two other studies in people with diabetes. The Physicians Health study reported relative risks of smoking in subjects with diabetes with non-smoking subjects without diabetes as reference category, with relative risks of 3.2, 4.7 and 3.8 for never, current and former smoking, respectively [18]. This was of the same magnitude as the relative risk as calculated by the CDM (figure 10.6).

The combination of smoking and diabetes appear to heighten the development of macrovascular complications [205] by increasing insulin resistance and worsening of diabetes control [206].

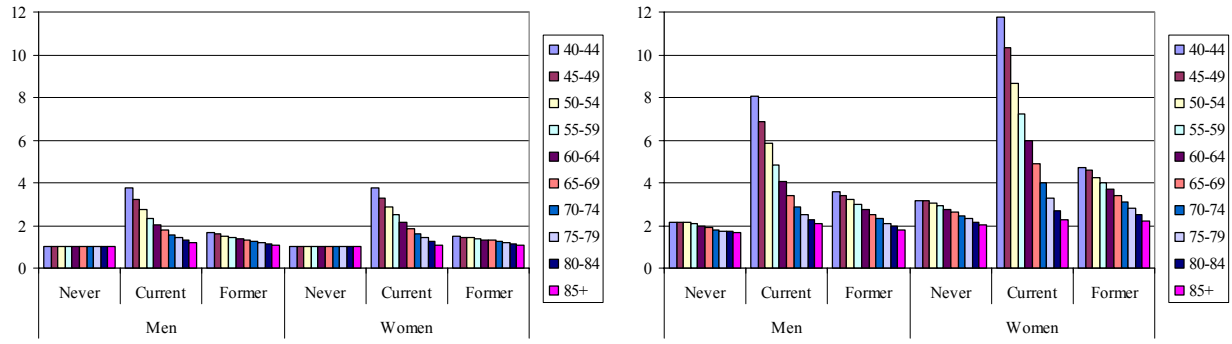


Figure 10.6 The relative risk of smoking for CHD in diabetes patients (right) with never smoking subjects without diabetes as reference category is obtained by multiplying the relative risks of smoking with CHD in the general population (left) with the relative risk of diabetes (versus no diabetes) with CHD.

As input in the CDM, we assumed that the relative risk of current and former smoking as a cardiovascular risk factor is the same subjects with and without diabetes, and that having diabetes has an multiplicative effect. We conclude that there is evidence in the international literature for this assumption.

The assumption that the "Relative risk of smoking for CHD in diabetes = Relative risk of diabetes for CHD * Relative risk of smoking for CHD in the general population" is reasonable for estimating the risk of smoking on macrovascular complications in a diabetic population

Heart failure and stroke

We did not find publications on the role of smoking in the development of CHF in diabetes patients. The publications about stroke were conflicting. The UKPDS showed that smoking is a risk factor for stroke [207]. In contrast, in the London cohort of the prospective WHO Multinational Study of Vascular Disease in Diabetes, smoking was not associated with stroke [208]. In summary, we did not find evidence to assume that the association between smoking with CHF and stroke in diabetes patients is different from the association in the general population.

The assumption that the "Relative risks of smoking for CHF and stroke in diabetes = Relative risk of diabetes for CHF and stroke * Relative risks of smoking for CHF and stroke in the general population" seem to be reasonable for the risk of smoking on macrovascular complications in a diabetic population

Concluding remarks

In future modeling, a validation of smoking input will be performed to quantify the effect of using relative risk estimates the default smoking input derived from the model versus empirical data (ZODIAC). We recommend access to smoking data in a Dutch (general) population study with at least 1000 diabetes patients and measurement of current and former smoking to estimate the prevalence of smoking in both diabetes patients and the general population from the same population.

10.4 Total cholesterol

Prevalence of hypercholesterolemia in diabetes
According to the guidelines of the Zorgstandaard Nederlandse Diabetes Federatie [171], the ratio between total and HDL cholesterol must be < 5. In the CDM, only total cholesterol is included. In empirical data (in pooled data of ZODIAC, Westfriesland, SHL Breda and NMP), mean 6% of men and 13% of women had elevated cholesterol concentrations (>6.5 mmol/l)(data not shown). There were, however, considerable differences in prevalences of hypercholesterolemia between the projects (table 10.4).

Table 10.4 Distribution (%) of total cholesterol in 4 categories in four diabetic populations

		<5 mmol/l	5-6.5 mmol/l	6.5-8 mmol/l	>=8 mmol/l
Men	ZODIAC	34	51	13	1
	Westfriesland	42	47	11	1
	SHL Breda	60	36	4	0
	NMP	49	42	9	0
	CDM (general population)	57	36	7	1
Women	ZODIAC	21	51	24	5
	Westfriesland	30	49	19	1
	SHL Breda	44	46	9	1
	NMP	40	45	14	1
	CDM (general population)	53	36	9	1

Compared to the prevalences in the general population in the CDM, it is not clear whether percentages in each category in diabetes patients differ from the total population. Because of the latter and the fact that people with diabetes do not have higher total cholesterol than non-diabetic individuals in the literature, we decided that the cholesterol input for diabetes patients is the same prevalence as in the general population.

Input data for prevalence of total cholesterol in diabetes patients = input CDM-2005-01. The input data (general population) are documented in input file “cholinput010305.txt”.

International prevalence of hypercholesterolemia
Pyorala *et al.* found that hypercholesterolemia was higher in non-diabetic subjects than in diabetic subjects. 55% of diabetic patients and 59% of non-diabetic patients had cholesterol >= 5mmol/l in EUROASPIRE II (9 countries in Europe) [188]. The Dutch prevalence of hypercholesterolemia seems somewhat lower than in other countries: 28% in Spain [186], 40% in Brazil [187], 34% in the Third National Health and Nutrition Examination Survey (NHANES III) (USA) [190]. The observed (international) difference is mainly due to the fact that most articles do not publish the prevalences of (high) cholesterol according to the 4 categories in the CDM, but the percentage of hypercholesterolemia based on both cholesterol level and use of medication. The medication use and the occurrence of co-morbidity pollutes the estimate of prevalence of high cholesterol in diabetes patients. In diabetic men in the Physicians Health study had 28% high cholesterol versus 13% in men without heart disease and diabetes [18].

Relative risk

Coronary heart disease

The United Kingdom Prospective Diabetes Study showed that increased concentration of total cholesterol was a risk factor for cardiovascular mortality and morbidity in patients with diabetes in a univariate model [199]. In multivariate analyses, LDL and HDL, and not total cholesterol were predictors. In MRFIT, the age-corrected incidence of CHD in diabetic patients was four fold that in non-diabetic subjects at any level of cholesterol [14], but these relative risks were only age-adjusted. The Physicians Health study reported a relative risk of high cholesterol (>=6.7 mmol/l) in subjects with diabetes with normocholesterolemic subjects without diabetes as reference category, with relative risks of 3.0 and 1.8 (versus 1.3 in non-DM) for normal and high cholesterol, respectively [18]. This is remarkable because the risk of diabetes without increased cholesterol is lower than the risk of having both diabetes and high cholesterol. This combination was very unlikely in this study, and the relative risk of 1.8 was based on n=6. In summary, there is an association between total cholesterol and CHD in diabetes patients. Clinical trials have demonstrated that diabetes patients benefit from lipid lowering equally to people without diabetes [175 188 209].

For the input in the CDM, we assume that the relative risk of total cholesterol for CVD in diabetes patients is the same as in subjects without diabetes, and that having diabetes has an multiplicative effect. From the preceding appears that this assumption will give a reliable estimation of the relative risk of total cholesterol with CHD. The *magnitude* of the association of a combination of cholesterol and diabetes as risk factors is less clear, and the proposed multiplication of relative risks possibly will probably give an overestimation (figure 10.7). More research is needed whether including a correction factor in the multiplication of the relative risk in diabetes patients will give better estimates.

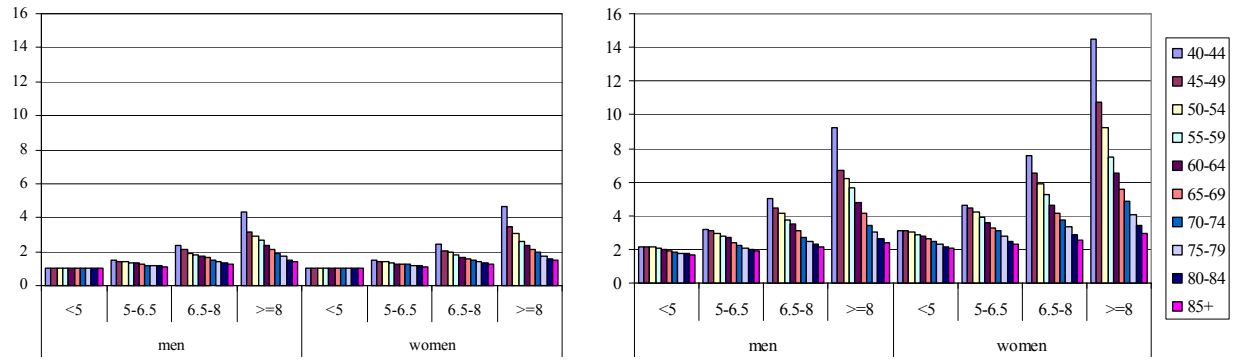


Figure 10.7 The relative risks for total cholesterol and CHD in diabetes patients (right) compared with subjects with no diabetes and low cholesterol is obtained by multiplying the relative risks of total cholesterol with CHD in the general population (left) with the relative risk of diabetes (versus no diabetes) with CHD

The assumption that the "Relative risk of increased total cholesterol for CHD in diabetes = Relative risk of diabetes for CHD * Relative risk of increased total cholesterol for CHD in the general population" will possibly give an overestimation of macrovascular risk associated with increased total cholesterol in diabetic patients

Concluding remarks

Patients with diabetes have no higher total cholesterol than the general population. Diabetes patients often have an unfavourable lipid profile that is characterized by low HDL-cholesterol

and high triglycerides. In 2005, we will investigate the possibility to include other lipid fractions in the CDM.
Diabetes patients often use lipid lowering medication. We also will include lipid lowering medication in the CDM. The rise in use of statins has been huge in the last decades. Statins affect CVD, but it is not entirely clear whether this effect runs via cholesterol. For the input in the CDM this means that new cholesterol categories will be included, and relative risks will be obtained from either results of trials or results from prospective cohorts.

10.5 Hypertension

Prevalences in people with and without diabetes
The presence of a high blood pressure is two times more common in people with than in people without diabetes. Both hypertension and diabetes often occur together. High blood pressure is defined as systolic blood pressure > 140/85 according to the Zorgstandaard voor goede diabeteszorg [171].
In the CDM-2003, blood pressure is categorized in 5 categories based on systolic blood pressure level and one medication group. 45 to 50% of the patients with type 2 diabetes mellitus and hypertension have systolic blood pressure levels above 140 mmHg during antihypertensive therapy [210]. Because of the latter and a high prevalence of medication use in diabetes patients (more than 50% [211 212], we decided to create new blood pressure categories, to be able to distinguish blood pressures within the medication group. In general, women have a lower blood pressure than men. However, women lose that advantage by developing diabetes. Both blood pressure and use of antihypertensives increase with increasing age. Data on both systolic blood pressure and antihypertensive medication use were available from ZODIAC and NMP. In table 10.5, the new input in 8 categories of blood pressure in diabetes patients is shown. Only <5% of the diabetes patients was represented in the lowest blood pressure category (<120 mmHg), even among medication users.

Table 10.5 Empirical input data for distribution (%) of systolic blood pressure (8 categories) in diabetes patients, age- and sex-specific

			No medication				Medication			
		n	<120	120-140	140-160	>=160	<120	120-140	140-160	>=160
Men	25-44	52	10	37	23	8	0	15	4	4
	45-64	520	5	24	20	9	2	10	15	14
	65-74	326	2	14	16	12	2	11	21	21
	75+	223	3	13	16	13	5	9	23	19
	Total	1121	4	19	18	11	2	11	18	17
Women	25-44	40	23	43	15	3	3	8	5	3
	45-64	394	4	18	18	10	4	12	21	14
	65-74	427	2	11	12	14	1	10	27	24
	75+	471	1	8	11	9	2	11	28	29
	Total	1332	2	13	14	11	2	11	25	22

Sources: NMP and ZODIAC (pooled data)

Input data for prevalence of hypertension in diabetes patients = empirical prevalences based on pooled NMP and ZODIAC data

The diabetes-specific hypertension input data are documented in input file “SbpDmInput.txt”.

International literature
It is well known that more than 50% of the patients with diabetes are hypertensive. The prevalences in the Dutch diabetes patients were in line with prevalences in the international literature. A mean of 57% hypertension was reported in a 9 countries study in Europe [188]. In the UKPDS, prevalence of hypertension (systolic blood pressure >=160 or diastolic blood pressure >=90 or antihypertensive medication) was 33% in men and 45% in women, but diabetes patients with cardiovascular disease were excluded [213]. Prevalence of hypertension of 63% was found in NHANES III (USA) [190]. There were no differences between men and women with diabetes.

Relative risk

Coronary heart disease
The role of hypertension as a risk factor of increased cardiovascular risk among diabetes has been extensively investigated. The association of hypertension with CVD in diabetes is strong: mortality is increased 4 to 7-fold in patients with diabetes and hypertension when compared with normotensive non-diabetic subjects [214]. In the UKPDS, the incidence of macrovascular complications in diabetes patients was associated with systolic blood pressure. Each 10 mmHg increase in mean systolic blood pressure was associated with 11% higher risk of AMI [215] and 9% higher risk of CHD [76]. Thus, hypertension is not only more frequent in diabetes patients, but has also a greater impact on CVD than in non-diabetic subjects [14 216]. It is clear that high blood pressure accelerates the development of micro- and macrovascular complications of diabetes. Hypertension also appears to accelerate vascular and cardiac abnormalities in diabetes [217]. A theory is that the hyperglycemic state makes the vessels more vulnerable, even with moderate low blood pressure. If this is true, even diabetes patients with lower blood pressure are at higher risk for CVD. This is supported by the results of the MRFIT study which reported that even at systolic levels <120 mmHg, patients with diabetes have higher risk of CVD mortality than do those without diabetes [14]. Also, clinical trials have demonstrated that treatment of blood pressure in the normotensive range of diabetes is associated with a reduction in cardiovascular disease. Individuals with type 2 diabetes derived more benefit from aggressive blood pressure lowering than did those without diabetes [218-220].
For the CDM, we assumed that the relative risk of hypertension for CVD in diabetes population is the same as in subjects without diabetes, and that having diabetes has an multiplicative effect. There is convincing evidence for this assumption in the literature.

The assumption that the “Relative risk of increased systolic blood pressure for CHD in diabetes = Relative risk of diabetes for CHD * Relative risk of increased systolic blood pressure for CHD in the general population” is a reasonable estimate for the association of increased systolic blood pressure with increased macrovascular risk in diabetic patients

Heart failure
We did not find studies on systolic blood pressure and CHF in diabetes patients that met our criteria. At this moment, it is not possible to evaluate whether it is reasonable to assume that the relative risk of hypertension for CVD in diabetes population is the same as in subjects without diabetes.

The assumption that the "Relative risk of increased systolic blood pressure for CHF in diabetes = Relative risk of diabetes for CHF * Relative risk of increased systolic blood pressure for CHF in the general population" was not rejected as a reasonable estimate for the association of increased systolic blood pressure with increased macrovascular risk in diabetic patients

Stroke
Lewington *et al*. studied the association between 20 mmHg blood pressure lowering and stroke mortality in one million adults in 5 age-groups in a meta-analysis. The relative risk ranged from 0.33 in age 40-49 to 0.68 in age 80-89 in men, and from 0.41 to 0.65 in women [221]. In younger age-groups were obtained stronger associations than in older age. In the UKPDS, increase of 10 mmHg in systolic blood pressure was associated with a relative risk of 1.19 (1.14-1.24) for (non)fatal stroke [215]. In addition, antihypertensive treatment is effective in preventing stroke in diabetes patients [222]. We found some evidence for the assumption that the relative risk of hypertension for CVD in diabetes population is the same as in subjects without diabetes, but the amount of studies was limited.

The assumption that the "Relative risk of increased systolic blood pressure for stroke in diabetes = Relative risk of diabetes for stroke * Relative risk of increased systolic blood pressure for stroke in the general population" is reasonable according to some findings in the literature for the association of increased systolic blood pressure with increased macrovascular risk in diabetic patients

Concluding remarks
Following the new prevalence of systolic blood pressure in 8 categories in diabetes patients, the CDM needs adaptation of the prevalence of blood pressure in the total population in 8 categories also. This will be done in 2005. This also requires adaptations of the relative risks of blood pressure with cardiovascular disease.
CHF is the least well described macrovascular endpoint. There is a clear relation between diabetes and CHF. The relation of blood pressure (and other risk factors) to CHF in diabetes patients needs more attention in future research.

10.6 HbA1c

Glycated hemoglobin (HbA1c) is a measure of mean blood glucose concentrations over about 3 months. Long term increased blood glucose levels leads to micro- and macrovascular complications. In the general population, the risk of macrovascular disease is associated with HbA1c [202]. In the CDM-2005-02, normal HbA1c in diabetes patients is defined as <7% and too high HbA1c as >=8.5% according to the guidelines of the Zorgstandaard Nederlandse Diabetes Federatie [171].

Prevalence of HbA1c in people with diabetes
In two of the three Diabetes care projects, ZODIAC and SHL Breda, 54% of men and 56% of women had elevated HbA1c (≥7%), of which 12 and 13% were badly controlled with an Hba1c >8.5%. In one other care project, in Westfriesland and in NMP the percentage of diabetes patients with an HbA1c below 7% was larger. There was a difference in amount of better controlled patients between populations. In the Dutch literature, the percentage of well controlled patients was even lower (~40%) [211 223 224], and 15 to 30% of the people with diabetes were in the highest category. The prevalence of high HbA1c differs between

populations because the HbA1c level increases with age, and decreases by good glucose control. For the input in the CDM, the pooled prevalences of all four studies will be used (Table 10.6).

Table 10.6 Empirical data for prevalence of HbA1c (3 categories) in diabetes patients, age and sex-specific

	n	n	men			women		
			<7	7-8.5	>=8.5	<7	7-8.5	>=8.5
25-44	368	298	0.46	0.33	0.21	0.39	0.42	0.19
45-64	4162	3323	0.48	0.39	0.13	0.47	0.40	0.13
65-74	3184	3478	0.48	0.42	0.11	0.44	0.45	0.11
75+	2234	4384	0.43	0.44	0.12	0.43	0.44	0.12
Total	9948	11483	0.47	0.41	0.13	0.44	0.43	0.12

Sources: ZODIAC, Westfriesland, SHL Breda, NMP

International publications
The findings in the Dutch situation are in line with the prevalences found in the international literature. A large population study (NHANES) showed a large amount of not well-controlled diabetes patients where 60% had Hba1c above 7% [190]. Of men and women with diabetes in Sweden had 59% and 54% HbA1c below 6.5% in the 60-75 year age group [225].

Validation of empirical HbA1c input data and transition rates
The prevalence of high HbA1c differs between populations, because the HbA1c level increases with diabetes duration, and decreases by good glucose control. Newly diagnosed diabetes patients have generally lower mean HbA1c, with higher percentages of patients in the lowest category (Table 10.7). We therefore estimated the prevalence of HbA1c, by taking into account the prevalence of HbA1c in *incident* diabetes patients.

Table 10.7 Percentages per HbA1c category in prevalent and incident diabetes patients

	Incident diabetes patients (diabetes duration < 1 year)	Prevalent diabetes patients (diabetes duration >=1 year)	Eigenvector
Men	0.53	0.41	0.41
	0.31	0.40	0.43
	0.16	0.19	0.16
Women	0.64	0.38	0.37
	0.25	0.42	0.43
	0.12	0.20	0.20

Transition rates describe the transitions between different categories. Diabetes patients can move from all categories of HbA1c to all categories. Both prevalences and transition rates were stable over age categories in ZODIAC, Westfriesland and SHL Breda. So, the input in the model is not age- and sex-specific. We used ZODIAC data to estimate year-transitions between HbA1c categories, because in ZODIAC also information about diabetes duration was available. The ‘crude’ transition rates can be obtained from table 10.8.

Table 10.8 1-Year transitions between 3 categories of HbA1c

			HbA1c (Year x+1)		
			<7%	7-8,5%	>=8,5%
Men	HbA1c (Year x)	<7%	63.2	30.5	6.3
		7-8.5%	30.7	54.6	14.7
		>=8.5%	12.0	44.0	44.0
Women	HbA1c (Year x)	<7%	61.7	31.0	7.3
		7-8.5%	27.2	51.7	21.2
		>=8.5%	12.4	46.9	40.7

Source: ZODIAC

The prevalences of incident diabetes patients were used as initial class prevalence rates for a theoretical new cohort of diabetes patients. The change per year in the distribution over the HbA1c categories were calculated using the 1-year transition rates, relative risks of HbA1c for mortality and excess mortality in diabetes patients. After about 10 year, the percentage of diabetes patients in that HbA1c category stabilised, until the age of 90 (Figure 10.8). The obtained value can be interpretated as an 'eigenvector' of the mathematical state-transition model equations. The 'eigenvectors' matched well with the empirical prevalences obtained from ZODIAC and were now used as the new initial class prevalence rates for HbA1c.

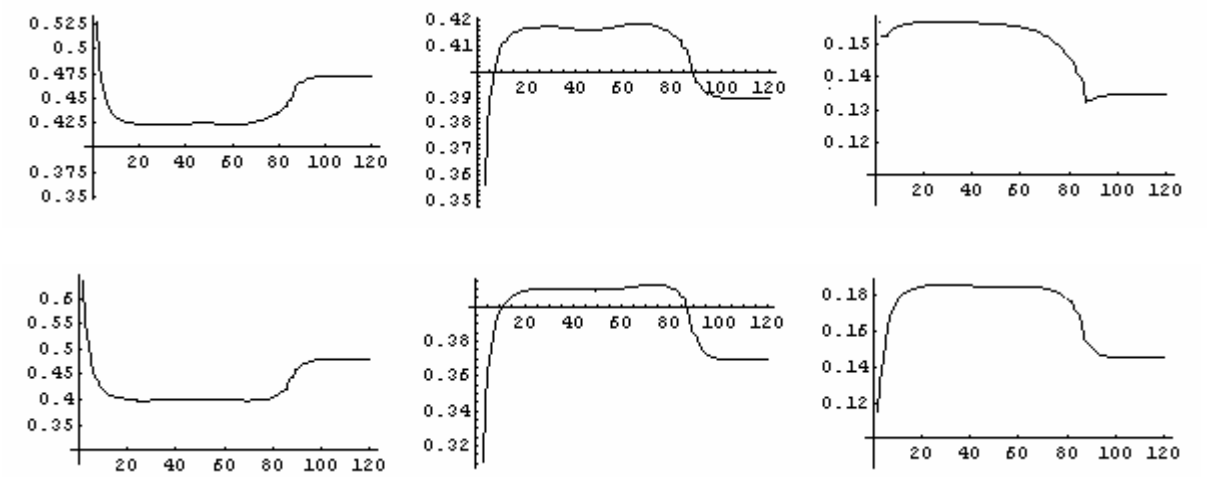


Figure 10.8 HbA1c class prevalences based on the prevalence in a cohort of incident diabetes patients and transition rates and in 1st, 2nd and 3rd (left, middle, right) HbA1c category in men (above) and women (below). The constant 'eigenvector' is the start prevalence for HbA1c categories.

Input data for prevalence of HbA1c in diabetes patients = empirical prevalences based on pooled ZODIAC, Westfriesland, SHL Breda and NMP data. Transition rates are based on year-transitions in ZODIAC.

The diabetes-specific HbA1c input data, with the accompanying transition rates are documented in input file "Hba1cDmInput.txt".

Relative risks
In people with diabetes, chronic hyperglycemia is related to the development of microvascular disease. The relation of HbA1c with macrovascular disease is less clear [226]. In the last decade, few randomized clinical trials, improving glycemic control, aiming at lowering the incidence of cardiovascular complications have been performed [227]. In a meta-analysis performed by Selvin *et al.* [228], the pooled relative risk for cardiovascular disease was 1.18 (1.10-1.26) for a 1-percentage increase in HbA1c in people with diabetes. We used this review to compare with our estimated relative risks. Khaw and colleagues analyzed the relation of HbA1c to incident cardiovascular events in a 6 year cohort study of diabetic and non-diabetic men and women. They proved that HbA1c level is an independent risk factor for incident cardiovascular events, irrespective of diabetes status. Therefore, we decided to select studies performed in both diabetic and non-diabetic subjects. The relative risks obtained from the literature were graphed by age (group), and subsequently relative risks and confidence intervals were estimated from the data.

Coronary heart disease
We found 9 publications in which relative risk estimates for HbA1c on AMI, CHD or CVD incidence were reported. The population characteristics and results of these publications are summarized in Appendix X. All studies show a higher risk on CHD with increased HbA1c. Inclusion of studies (n=3) evaluating risk on CVD (ICD codes 390-459) showed slightly higher relative risks. We therefore excluded these studies from our calculation. The univariate relative risk of HbA1c was about 2 in men and women, however, after adjustment for other risk factors of CHD the range in relative risk by multivariate analyses was between 1.14 and 1.32 per unit HbA1c. The input for the CDM was estimated from these 6 studies. There were not enough studies that reported the results for men and women, separately. Also, there was no effect of age on the relative risks of HbA1c. So, the estimated risks are not age- and sex-specific. The independent risk of increased HbA1c for CHD is estimated 20% percent higher per unit HbA1c (relative risk =1.16 (1.05-1.27). This finding was in line with the pooled relative risk from the meta-analysis, which reported 1.13 (1.06-1.20) for CHD disease and 1.16 (1.07-1.26) for fatal CHD [228]. The same relative risk of 1.13 was used in the UKPDS Diabetes Model [229].

Input data for relative risks of increased HbA1c for CHD in diabetes patients is RR=1.16 in all age groups in men and women. The input data are documented in input file "RRHba1cDm.txt".

Heart failure
We only found two publications in which risks of HbA1c for CHF was reported [181 182]. They were publications of the same study after 2.5 and 6 years of follow-up. Both studies showed an opposite risk on CHF with increased HbA1c, with a decreased risk of CHF after 2.5 years, and an increased risk after 6 years. We conclude that there is not enough evidence to suppose an association between HbA1c and CHF in diabetes patients yet. Therefore, the relative risk input in the model will be 1.

Input data for relative risks of increased HbA1c for CHF in diabetes patients is RR=1 (no association). The input data are documented in input file "RRHba1cDm.txt".

Stroke
We included 2 publications in which risks of HbA1c for stroke were reported. Results of the publications are shown in Appendix X. Both studies show a consistent higher risk on stroke

with increased HbA1c. The relative risk varied between 1.12 and 1.4 per unit HbA1c (mean: 1.14 (1.02-1.27). The pooled relative risk obtained from 3 studies in the review was 1.17 (1.09-1.25) [228]. A relative risk of 1.14 was used in the UKPDS diabetes model [229].

Input data for relative risks of increased HbA1c for stroke in diabetes patients is RR=1.14 in all age groups in men and women. The input data are documented in input file "RRHba1cDm.txt".

Concluding remarks
HbA1c is a new risk factor for macrovascular complications in patients with diabetes, to be included in the CDM. Hba1c is well measured in the several diabetes care projects. The mean HbA1c was in the range of 7.1 to 7.4%, and there were small differences in the distribution over the 3 categories of HbA1c such that the amount of diabetes patients in the lowest category was higher in Westfriesland and NMP. But in these studies still about half of the diabetes patients was represented in the categories > 7%. In the future, we will include HbA1c and/or 2h-glucose for the general population to be able to define individuals with impaired glucose tolerance (pre-diabetes).

11. Tertiary prevention

MAM Jacobs-van der Bruggen

11.1 Interventions to reduce bodyweight

The results of trials that focus on bodyweight reduction in patients with diabetes are summarized in Appendix XIa (lifestyle interventions) and Appendix XIb part D (pharmacological interventions, weight management). Weight loss interventions that are used in patients with diabetes include diet, behavioral therapy, exercise, pharmacological therapy and bariatric surgery [230].

Diet is regarded as one of the cornerstones of therapy in (obese) patients with diabetes. Diets in (obese) diabetic patients may result in weight loss of up to 10% of baseline weight and is accompanied by improvements in metabolic control and lipid profile [57 231 232]. However, a successful weight loss with diet is often difficult to achieve and even more difficult to maintain. Although weight is initially lost, most of this loss may be regained within 5 years [230]. Intensive treatment with very low calorie diets (VLCD) may initially result in promising weight loss and improved metabolic control [57], but these effects are seldom maintained in the long term [230].

Behavioral programs have been shown to be moderately effective in inducing weight loss [231 233]. In a meta-analyses of 18 educational and behavioral intervention programs in diabetic patients, mean weight loss and mean decrease in HbA1c were not significantly different between intervention and usual care or minimal intervention groups [233]. The degree of weight loss achieved and maintained may increase with the length of the program and additional components included in the program such as diet and (supervised) exercise [230 231].

Exercise in (obese) diabetic individuals usually results in only modest weight loss [232 234]. Although diet appears to be more effective in losing weight [232], exercise may have beneficial effects on glycaemic control (HbA1c -0,4 tot -1,8%) [234-236] independent of weight loss and is regarded as an important determinant of long-term maintenance of weight loss [230]. There are however few studies examining the effects of (only) exercise in large groups of diabetic patients [236]. Exercise programs are costly, difficult to implement and have shown variable results.

Pharmacological treatment is effective in reducing bodyweight with about 3 to 5 kg as compared to placebo treatment, within 1 year [237]. These reductions in weight are accompanied by improved glucose control with HbA1c reductions of 0.4-1.0%. However, use of medication is expensive and should be continued to maintain positive effects. Further research is needed to examine the long-term efficacy and safety of these medications.

Current weight-control interventions have shown that short-term weight loss is achievable but no currently available intervention has shown consistent long-term maintenance of major weight loss. The efficacy of programs may improve with the duration and intensity of the program and may increase when several weight-loss strategies are combined [231].

Several Cochrane reviews concerning long-term effects of weight loss strategies (behavior, exercise and/or diet) on risk factors and complications are expected in 2005.

Studies evaluating the effect of weight loss on diabetes complications have not been found. One large trial the “LOOK AHEAD” trial in the US started in 2001 and examines the long-term effects of an intensive lifestyle program, focusing on weight reduction and maintenance, in 5000 overweight diabetic patients on macrovascular complications, quality of life, costs and care. Results are expected in 2012.

11.2 Strict control of blood glucose

The results of trials that focused on strict control of blood glucose levels are summarized in Appendix XIb part A. The potential benefit of intensive blood glucose control on the prevention of diabetes complications was studied in one large study, the UKPDS [168 238] and two smaller studies, the Kumamoto-study [239 240] and the Veterans affairs cooperative study on glycemic control and complications in type II diabetes (VA-CSDM) studies [241 242]. The effects of intensive blood glucose control on diabetes complications are also summarized in a recent review [243] and in a meta-analysis [244].
It appears to be[245 246] feasible to lower blood glucose levels significantly as compared to conventional treatment. HBA1c levels of approximately 7% were reached within 3-6 months and maintained for 2-8 years in the Kumamota and VA-CSDM studies. In the UKPDS, HbA1c levels in newly diagnosed patients dropped in the first year (from 7% to 6%) but increased thereafter up to almost 8% after 15 years. Most people needed multiple therapies to achieve and keep "near-normal blood glucose" [247]. Intensive treatment caused more mild and moderate hypoglycemic events in all studies. Significant weight gain as a result of intensive therapy was only found in the UKPDS.
Significant benefits of tight control of blood glucose on macrovascular complications were not found, except for patients who were overweight and were treated with metformin [168]. For these newly diagnosed patients, diabetes related mortality was reduced with 42% after 11 years of follow-up.
A newer class of agents for the treatment of type 2 diabetes, the thiazolidinediones (TZD) has shown promising results with improved blood glucose control, which is accompanied by reductions in markers of macrovascular complications such as blood pressure and improved lipid profiles [248-251]. Several studies are currently conducted to provide additional support for the benefits of TZDs in minimizing cardiovascular complications [248 250]. Recent research also emphasizes the role of postprandial glucose levels in the development of diabetes complications [252-254]. It appears that peak glucose levels after a meal may be at least as import as mean levels of blood glucose in the development of complications and may be an important target for preventive strategies [252].
Weight loss and exercise training in diabetic patients are accompanied by significant improvements in metabolic control with HbA1c reductions ranging from -0.4% to 1.8% [231 232 234-237 255]. Patient education, behavioral interventions and self-management techniques can improve blood glucose regulation with HbA1c reductions of about 0.3-0.5% as compared to usual care [232 233 256 257]. Whether these interventions are effective in reducing complications in the long term is unknown.

11.3 Blood pressure control

The effects of antihypertensive therapy in diabetic patients on diabetes complications are summarized in several recent reviews and meta-analysis [258] (Appendix XIb, part B)[243 244 259-261].
Mean blood pressure reductions that are attained when comparing intensive treatment with placebo treatment or usual care are -5 mmHg for systolic blood pressure (SBP) and -2 mm Hg for diastolic blood pressure (DBP) [244]. However, depending on population characteristics and choice of medication decrements of -10 to -30 mmHg for SBP [219 262] and -8 to -24 mmHg for DBP [219 263] may be achieved. In the long term most patients will need several antihypertensive medications to attain treatment goals [264 265]. Antihypertensive therapy in diabetic patients significantly reduces macrovascular complications with

approximately 20-40% [244 259 261]. The optimal treatment goal is approximately 130/80. There appears to be no obvious superiority with regard to medication class [260 264 265], although ACE-inhibitors and ARBs may be particularly beneficial for renal protection [258 266, 267 268] with protective effects for the renal system that seem to be independent of the blood-pressure lowering effect [269-271]. ACE-inhibitors may protect renal function even in normotensive diabetic patients [272].
Note that intensive lowering of diastolic blood pressure increases the risk of cardiovascular events in smokers and therefore intensive treatment in diabetic smokers should be accompanied with the greatest effort to induce smoking cessation [273].

11.4 Lipid control

The results of pharmacological management of dyslipidemia in patients with diabetes are summarized in several recent reviews and a meta-analysis [243 244 274-276]. The characteristics and results of the meta-analysis and several large trials are summarized in Appendix XIb, part C.
Statins, aimed at reducing LDL-cholesterol, are the most widely used study-medication, but other agents like gemfibrozil, to reduce triglycerides, or fenofibrates, to increase HDL-cholesterol and to reduce triglycerides, are also used.
Treatment with statins results in a consistent reduction of LDL-cholesterol of approximately 1.0 mmol/l as compared to placebo treatment [274 275]. Lipid-lowering therapy results in a mean reduction in total cholesterol of about 0.6 mmol/l as compared to placebo treatment [244]. Treatment with fenofibrate induces large reductions in triglyceride (-30%) and increments in HDL-levels of about 8%.
With lipid lowering treatment, the risk for macrovascular complications in diabetic patients with or without cardiovascular disease can be significantly reduced with about 20-40% [244 274 275 277 278]. This risk reduction seems to be independent of age, diabetes duration, glycaemic control or baseline levels of LDL-cholesterol of the patients [175 278]. The greatest benefit of lipid lowering therapy can be achieved in diabetic patient at increased risk for macrovascular complications, with a mean absolute risk reduction for cardiovascular events of about 7% [274]. Although combination therapy with different classes of lipid-lowering medication may provide maximal lipid profile modification [279 280], safety issues as well as patient tolerability and compliance should be considered [281-283]. Four ongoing large studies, with 2,000 to 10,000 participants, will provide further evidence for the role of lipid management in patients with diabetes in preventing diabetes complications [276].

11.5 Conclusions tertiary prevention

Although improvements in lifestyle are worth persuing in diabetes patients, there is no evidence for substantial reductions in cardiovascular disease, resulting from (only) lifestyle interventions. Strict pharmacological treatment of cardiovascular risk factors in diabetes patients, on the other hand, may significantly reduce the incidence of cardiovascular disease. Intensified treatment of blood pressure or serum cholesterol, may reduce cardiovascular disease with up to 25%, while intensified treatment of blood glucose reduces cardiovascular disease with about 10%. The highest potential benefit may be gained from multifactorial intervention (Appendix XI part E). In one study in which lifestyle changes and pharmacological treatment of cardiovascular risk factors was combined, the incidence of cardiovascular disease was reduced with approximately 50% [284]. However this was only a small study conducted in a selected diabetes population at high risk of macrovascular

complications. A large trial in the US and Canada “The Action to Control Cardiovascular Risk in Diabetes” (ACCORD) in about 10,000 diabetes patients with cardiovascular disease is currently conducted and will examine the benefits of strict blood glucose control in combination with intensive treatment of blood pressure or cholesterol. Results of this study are expected in 2009 [276].

12. Discussion and conclusions

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In the preceding Chapters we documented updates of the input data that were already included in the CDM-2003 and new estimates for the model parameters in the CDM-2005. In table 12.1 the status of all parameters that have been described in this report is stated.

Table 12.1 Overview of the contents of this report

	Parameter	Input file	To do
Diabetes input data	Incidence, prevalence	DMinput010305.txt	Completed
	Mortality		Completed
	Health care	Not yet	Health care utilization for missing health care services; distinction diabetes with(out) complications (in 2005)
	Costs	Not yet	In 2005
	Quality of life		
Risk factors for diabetes incidence (prevalence, relative risk and PAR)	BMI	BMIinput010305.txt RRBMIinput010305.txt	Completed
	Physical activity	lichactCBS010305.txt RRlichactinput010305.txt	Completed
	Smoking	Smokinput160305.txt RRsmok160305.txt	Completed
	Alcohol	alcoinput010305.txt	
	Combination	Not yet feasable	--
Macrovascular complications			
Prevalence of complications	AMI, CHD, CHF, CVA	ChdDmInput.txt ChfDmInput.txt CvaDmInput.txt	Small N Validation
Risk factors for complications			
Prevalence	BMI	BmiDmInput.txt	Completed
	Physical activity	LichactDmInput.txt	Lack of empirical data
	Smoking	SmokDmInput.txt	Validation
	Total cholesterol	cholinput010305.txt	To be included lipid lowering medication; HDL-cholesterol
	SBP	SbpDmInput.txt	Diabetes-input completed

	Parameter	Input file	To do
	HbA1c	Hba1cDmInput.txt	Completed
Relative risks	BMI	RRBMIinput010305.txt	CHD: sensitivity analyses & validation CHF: too less publications Stroke: sensitivity analyses & validation
	Physical activity	RRlichactinput010305.txt	CHD: sensitivity analyses CHF not included Stroke: sensitivity analyses
	Smoking	RRSBPinput010305.txt	CHD completed CHF: too less publications Stroke completed
	Total cholesterol	RRcholinput010305.txt	CHD completed CHF and stroke not included
	SBP	RRSBPinput010305.txt	CHD, stroke completed; CHF: too less publications
	HbA1c	RRHba1cDm.txt	CHD: input completed. To do: modeling CHF: RR=1 Stroke: input completed. To do: modeling
Interventions	Primary interventions	Overview of literature	In 2005
	Tertiary interventions	Overview of literature	In 2005

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Appendix I Studies reporting relative risk on mortality for diabetic vs non-diabetic subjects

Ref	Study	Period	Population	Follow-up (yr)	Diagnosis dm	Number of events	Age	Relative Risk Men	Relative Risk Women	Confounding
[1]	NHANES I	1973-1993	14,374	22	Self report	3,204	35-44 45-64 65-74	6.2 2.0 1.4	4.0 2.5 1.7	age
[2]	Whitehall Study	1968-1987	11,521	12	OGTT	3,415	40-64	2.18 (1.81-2.63)		age
[3]	Whitehall Study	1968-	17,717	10	OGTT	1670	40-64	1.48 (1.26-1.73)		age, smo, ses, blp, chol, lvh, luf
[4]	Malmo Cohort Women	1977-1991	9,351	10.7	Self report and fasting bloodglucose	286	28-55		3.6 (2.3-5.6)	age
[5]	Verona Study	1986-1991	5,996	5	Med doctor	1,260	45-54 55-64 65-74 75+	2.33 (1.38-3.69) 2.13(1.76-2.56) 1.50 (1.30-1.72) 1.13 (1.00-1.28)	3.43 (1.43-6.77) 2.33 (1.63-3.22) 2.27 (1.92-2.66) 1.32 (1.20-1.44)	age
[6]	Paris Prospective Study	1968-	7,166	15.6	OGTT	975	44-55	2.0 (1.4-3.0)		age
[7]	The Adventist Health Study	1976-1988	603	12	Self report	1,387	85-99	1.86 (1.30-2.66)	1.38 (1.09-1.75)	age, gen, smo, pa, nutr
**	CB project	1977-2000	49,071	20	Self report	3,866	30-54	1.76 (1.39-2.22)	1.91 (1.42-2.58)	age, gen, cho blp, smo
[8]	Gotenborg BEDA	1980-1999	1,372	19	Self report	164	39-64		2,78 (1.36-5.67)	age
[9]	Social Insurance Finland	1980-1985	46,000 dm patients	5	Treatment for diabetes in national drug register	11,215	40-44 45-49 50-54 55-59 60-64 65-69 70-74	5.7 (4.7-6.9) 4.1 (3.5-4.7) 3.6 (3.2-4.0) 2.7 (2.4-2.9) 2.4 (2.2-2.6) 2.3 (2.1-2.4) 2.0 (1.9-2.1)	7.5 (5.3-10.7) 5.6 (4.2-7.5) 4.3 (3.5-5.3) 4.2 (3.7-4.8) 3.7 (3.4-4.0) 3.4 (3.2-3.6) 3.1 (3.0-3.2)	age
[10]	Kuopio	1984-1997	1,294	10.7	?	142	42-61	2.38 (1.24-4.56)		age

Ref	Study	Period	Population	Follow-up (yr)	Diagnosis dm	Number of events	Age	Relative Risk Men	Relative Risk Women	Confounding
[11]	FINE study: Netherlands	1985-1995	887	10	Self report	424	65-84	1.40 (0.96-2.04)		age, dis
[11]	FINE study: Finland	1985-1995	716	10	Self report		65-84	1.41 (1.02-1.96)		age, dis
[12]	Wales Record Linkage	1993-1996	434,000	4	Linkage between different registrations	1,694	25-34 35-44 45-54 55-64 65-74 75-84	5.19 2.60 3.61 2.42 1.38 1.10	5.39 3.63 3.72 2.83 2.42 1.50	age
[13]	South Tees Diabetes Mortality Study: type 2 diabetes	1994-1999	4,842 dm	6	Diabetes register	1,205	40-59 60-79	2.56 (1.73-3.80) 1.96 (1.74-2.21)	3.15 (2.51-3.95) 1.41 (1.28-1.56)	age
[13]	South Tees Diabetes Mortality Study: type 1 diabetes	1994-1999	4,842 dm	6	Diabetes register	1,205	40-59 60-79	4.21 (2.68-6.33) 1.72 (0.90-3.29)	6.20 (3.68-10.43) 7.31 (4.18-12.877)	age
[14]	Dubbo Study	1988-1998	2,805	10	Self report	842	60-75	1.99 (1.38-2.87)	2.06 (1.46-2.92)	age, alc, smo, dis, blp
[15]	Rochester (Mayo Clinic)	1970-1994	85,806	25	Registerd at Mayo Clinic and deseased and DM registered	10,152	45-54 55-64 65-74 75-84 85-94	9.3 2.8 2.1 2.3	4.0 5.0 4.0 2.6 2.3	age, gen
[16]	North Dakota	1992-1996	28,795	5	Death certificates	28,795	45-64 65-74 75+	3.0 (2.1-3.8) 2.3 (1.6-3.1) 2.1 (1.3-2.9)	5.3 (3.6-6.9) 3.4 (2.5-4.4) 2.1 (1.5-2.6)	age
[17]	Scottish Heart Study	1987-1993	11,629	7.6	Self report	591	40-59	2.08 (1.22-3.55)	1.50 (0.62-3.66)	age
[18]	Tayside, Scotland	1993-2002	10,782	4.6	Registry,diabetes diagnosed > 65 yr	2,560	65-99	1.06 (0.94-1.19)	1.29 (1.15-1.45)	age

smo: smoking; blp: blood pressure; nutr: nutrient; pa: physical activity; gen: gender; chol: cholesterol; dis: disease; ses: socio economic status; alc: alcohol; luf: lung function; lvh:left ventricular hypertrophy; funct capacity: functional capacity; gen: gender; *: Type 2 diabetes only; **: Houterman, unpublished results

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Appendix II Care consumption of diabetes mellitus patients in one year

Health care utilization n=9,695	% of pat.	Men								Women							
age-class		20-29	30-39	40-49	50-59	60-69	70-79	>80	All	20-29	30-39	40-49	50-59	60-69	70-79	>80	All
GP care																	
% of patients with contacts	95	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Mean no. of consults, diabetics		6.1	7.1	8.7	9.8	10.4	11.6	14.8	10.5	10.3	10.7	12.4	11.7	12.7	13.9	15.9	13.3
No. of consults related to dm		1.9	2.5	2.9	3.3	3.3	3.2	3.5	3.3	1.7	2.4	3.2	3.3	3.4	3.6	3.3	3.2
Mean no. of consults, non- chronically ill	75	1.6	2.0	2.6	3.3	4.4	6.0	7.3	2.9	3.5	4.0	4.4	4.9	5.7	7.4	8.8	4.8
Pharmaceuticals #																	
% of patients with prescription		82.5	91.5	95.3	95.7	95.7	97.9	98.2	95.8	91.7	96.90	97.8	96.6	96.7	98.6	95.6	96.9
Mean no. of prescriptions		9.1	12.5	16.0	18.7	22.3	25.8	38.9	22.5	11.4	17.9	21.4	24.6	26.8	30.5	37.3	28.7
No. of prescriptions related to dm		5.9	6.1	6.4	7.2	7.6	7.9	9.4	7.1	4.3	6.5	6.9	7.6	7.9	8.0	8.0	7.3
Medical specialist																	
% patients with consult	80	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
% patients with first referral		15.0	14.6	16.6	18.1	19.1	17.1	15.7	17.5	14.9	16.5	18.6	20.3	19.3	18.7	14.5	18.2
Mean no. of consults		2.0	2.5	2.0	2.4	2.7	2.9	2.7	2.6	2.3	2.8	2.7	2.7	2.8	2.7	2.7	2.7
Hospital care																	
% patients with admission		8.3	5.7	8.3	8.7	10.5	12.0	11.4	10.1	6.4	7.6	7.7	10.4	11.1	11.2	10.7	10.5
Mean no. of admissions		1.2	1.5	2.1	2.5	2.4	2.4	2.6	2.4	1.0	1.8	2.4	2.3	2.3	2.5	2.2	2.3
Average length of stay (days)		5.2	6.3	6.7	4.8	7.0	8.2	8.9	7.0	1.33	4.8	4.9	4.7	6.8	9.7	11.6	8.0
Other health care services																	
Home care	12	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Diabetic nurse	23	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Physical therapist	19	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Nursing home care	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Podiatrist	7-13	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Dietitian	13-28	?	<44: 8.1%	>44: 13.8%	?	?	?	?	?	?	?	?	?	?	?	?	?

prescribed by their GP.

Appendix III Relative risks for body mass index (BMI) on diabetes incidence

publication	study follow-up in years	population cases (n)	definition of diabetes cases	definition of BMI	adjusted for	result relative risk
Dotevall 2004 [1]	BEDA study follow-up 18 year 1979-1998	1351 women 39-65 year mean age 49 cases dm 73	self reported blood glucose tested registries	< 22 (ref) 1. 22-24 2. 24-27 3. >27	age physical activity blood pressure triglycerides	age only / multivariate 1. 1.18 (0.39-3.5) / 1.03 (0.34-3.1) 2. 3.21 (1.28-8.1) / 2.41 (0.95-6.1) 3. 8.27 (3.47-19.7) / 4.53 (1.84-11.2)
Field 2004 [2]	Nurses Health 2 follow-up 6 year 133,521 person years 1993-1999	46,634 women 29-47 year mean age 39 cases dm 418	self reported + additional questionnaire to confirm	< 22 (ref) 1. 22-24.9 2. 25-29.9 3. 30-34.9 4. > 34.9	age smoking family dm	1. 1.79 (0.80-4.02 2. 8.29 (4.14-16.6) 3. 28.6 (14.4-56.5) 4. 84.4 (47.3-165)
Koh-Banerjee 2004 [3]	Health Proffesionals follow-up follow-up 4 year 1996-2000	22,171 men 40-75 year in 1986 mean age 53 cases dm 305	self reported	BMI in 1986 <23 (ref) 1. 23,0-24,9 2. 25,0-26,9 3. 27,0-29,9 4. ≥ 30	age smoking alcohol physical activity family dm diet weight change 1986-1996	age / multivariate 1. 2.1 (1.2-3,5) / 2.0 (1.2-3.5) 2. 3.4 (2.0-5.7) / 3.1 (1.9-5.3) 3. 5.6 (3.4-9.4) / 5.0 (3.0-8.3) 4. 14.1 (8.4-23.7) / 10.8 (6.4-18.3)
Kumari 2004 [4]	Whitehall 2 study follow-up 11 year 1985-1995	10,308 civil servants (9,162 white) 35-55 year cases dm men 242 women 119	self reported with blood glucose tested	20.0-24.9 (ref) 1. < 20 2. 25.0-29.9 3. ≥ 30	age lenght of follow-up ethnicity ECG abnormalities employment grade	men (5807) / women (2579) 1. 1.00 (0.5-2.2) / 1.00 (0.4-2.6) 2. 2.14 (1.6-2.9) / 2.15 (1.4-3.4) 3. 5.34 (3.4-8.3) / 4.03 (2.4-6.9)
Weinstein 2004 [5]	Women's Health Study follow-up 7 year from 1992 onward	37,878 women > 45 year mean age 55 cases dm 1361	self reported with control	< 25 (ref) 1. 25-30 2. ≥ 30	age family dm alcohol smoking hormone use physical activity hypertension cholesterol diet	only age / multivariate 1. 3.99 (3.35-4.76) / 3.22 (2.69-3.87) 2. 14.0 (11.9-16.4) / 9.06 (7.60-10.8)

publication	study follow-up in years	population cases (n)	definition of diabetes cases	definition of BMI	adjusted for	result relative risk
Snijder 2003 [6]	Hoorn-study follow-up 6 year 1989-1996/98	619 men cases dm 64 738 women cases dm 68 50-75 year mean age 62	blood glucose tested or medication	per unit BMI	age	men: 1.01 (0.92-1.11) women: 1.13 (1.06-1.21)
Meisinger 2002 [7]	Monica Augsburg Cohort study follow-up 7.6 year 1989-1996/98	3,052 men cases dm 128 3,114 women cases dm 85 35-74 year mean age 51	self reported diabetes or medication	per unit BMI	age uric-acid alcohol smoking dm in family physical activity blood pressure cholesterol	age adjusted: men 1.22 (1.17-1.27) women 1.17 (1.13-1.21) multivariate: men 1.19 (1.14-1.24) women 1.10 (1.07-1.15)
Wilson 2002 [8]	Framingham Heart Study follow-up maximal 44 year men 44,460 p.y. women 62,060 p.y. from 1948/51 onward	men cases dm 29 women cases dm 32 35-75 year mean age 55	blood glucose tested or treatment for diabetes	18.5-24.9 (ref) 1. 25.0-29.9 2. ≥ 30.0 (information on BMI was up- dated regularly)	age smoking blood pressure cholesterol	age adjusted / multivariate men 1. 1.33 (1.02-1.73) / 1.27 (0.97-1.67) 2. 2.12 (1.52-2.96) / 1.85 (1.31-2.61) women 1. 0.97 (0.77-1.21) / 0.91 (0.72-1.15) 2. 1.42 (1.09-1.85) / 1.36 (1.03-1.78)
Freeman 2002 [9]	West of Scotland Coronary Prevention Study follow-up 3.5-6.1 year	5974 men with high cholesterol 45-64 year mean age 55 cases dm 139	blood glucose tested or medication	per unit	age smoking alcohol blood pressure cholesterol glucose other	unadjusted: 1.17 (1.12-1.23) multivariate: 1,09 (0,1.04-1,14)
Hu 2001 [10]	Nurses Health Study follow-up 16 year 1,301,055 person years 1980-1996	84.941 women 35-60 year cases dm 3300	self reported + additional questionnaire to confirm	< 23.0 (ref) 1. 23.0-24.9 2. 25.0-29.9 3. 30.0-34.9 4. > 34.9	age smoking dm in family menopausal status be on pill diet alcohol physical activity	1. 2.67 (2.13-3.34) 2. 7.59 (6.27-9.19) 3. 20.1 (16.6-24.4) 4. 38.8 (31.9-47.2)

publication	study follow-up in years	population cases (n)	definition of diabetes cases	definition of BMI	adjusted for	result relative risk
Field 2001 [11]	Health Professionals Follow-up study follow-up 10 year 1986-1996	44.520 men 40-75 year mean age 55 cases dm 1207	self reported	18.5-21.9 (ref) 1. 22-24.9 2. 25-29.9 3. 30-34.9 4 > 34.9	age smoking ethnicity	1. 1.8 (1.2-2.7) 2. 5.6 (3.7-8.4) 3. 18.2 (12-28) 4. 41.2 (26-65)
	Nurses Health Study follow-up 10 year 1986-1996	75.960 women 40-65 year mean age 53 cases dm 1382				1. 2.2 (1.7-3.1) 2. 8.1 (6.1-11) 3. 17.8 (13-24) 4. 30.1 (23-41)
Stevens 2001 [12]	Atherosclerosis Risk in Communities Study follow-up 8 year from 1986 onward	4.602 men cases dm 573 5.293 women cases dm 440 45-64 year mean age 54	self reported diagnosed diabetes blood glucose tested treatment for diabetes	quartiles 1 (ref)	age smoking physical activity SES	unadjusted / multivariate men 2. 2.0 (1.4-2.8) / 2.0 (1.4-2.9) 3. 2.8 (2.0-4.0) / 2.9 (2.1-4.1) 4. 7.1 (5.2-9.7) / 7.2 (5.2-10) women 2. 2.7 (1.8-4.0) / 2.8 (1.9-4.1) 3. 4.3 (3.0-6.3) / 4.2 (2.9-6.2) 4. 10.2 (7.1-15) / 9.9 (6.8-14)
Folsom 2000 [13]	Iowa Women's Health Study follow-up 11 year 1986-1996	31.702 women 55-69 year mean age 62 cases dm 1578	self reported diagnosed diabetes	quintiles < 22,8 (ref) 1. 22.8-24.9 2. 24.9-27.1 3. 27.1-30.2 4. > 30.2	age smoking alcohol dm in family physical activity diet SES hormone use	only age / multivariate 1. 1.9 (1.4-2.5) 2. 2.9 (2.2-3.8) 3. 6.6 (5.0-8.5) 4. 13.8 (11-18) / 13.1 (9.8-17) multivariate + waist + WHR 4. 6.5 (4.9-8.8)
Von Eckardstein 2000 [14]	Prospective Cardiovascular Munster study follow-up 6 year 22,283 person years 1979-1989	3.737 men 37-60 year mean age 47 cases dm 200	self reported of FPG > 7.0	< 24.4 (ref) 1. 24.4-26.6 2. > 26.6	age	1. 2.14 (1.34-3.43) 2. 3.95 (2.55-6.05)

publication	study follow-up in years	population cases (n)	definition of diabetes cases	definition of BMI	adjusted for	result relative risk
Strandberg 2000 [15]	follow-up 20 year 1974-1995	1.802 men 40-55 year mean age 48 cases dm 94	self reported medical record of blood glucose tested in 1985/86	per unit BMI	multivariate 1 smoking blood pressure triglyceride multivariate 2 (1+) alcohol cholesterol WHR	multivariate 1 1.77 (1.39-2.26) multivariate 2 1.14 (1.04-1.26)
Wannamethee 1999 [16]	British Regional Heart Study follow-up 17 year from 1978/80 onward	6.916 men 40-59 year mean age 50 cases dm 237	self reported confirmed in medical records	< 25 (ref) 1. 25-27.9 2. > 27.9	age	1. 2.24 (1.54-3.23) 2. 5.11 (3.60-7.28) > 5 years overweight on baseline 20-40% higher risk than < 5 years
Njolstad 1998 [17]	Finnmark Study follow-up 12 year 1977-1989	6.098 men cases dm 87 5.556 women cases dm 75 35-52 year mean age 43	hospital records or self reported and confirmed by a medical doctor	< 27.1 (ref) 1. 27.1-28.9 2. 29.0-31.9 3. 32.0-34.9 4. > 34.9	age length smoking physical activity blood pressure cholesterol FPG ethnicity antihypertensive treatment.	age adjusted / multivariate men 1. 3.19 / 2.53 (1.34-4.79) 2. 6.72 / 5.47 (2.97-10.07) 3. 20.04 / 13.05 (6.23-27.32) 4. 42.00 / 27.89 (12.27-63.42) women 1. 7.85 (5.60 (2.36-13.28) 2. 18.94 / 9.23 (4.25-20.02) 3. 14.18 / 6.49 (2.53-16.65) 4. 36.60 / 11.07 (4.63-26.46)
Shaper 1997 [18]	British Regional Heart Study follow-up 15 year 1978-1993	7.575 men 40-59 year cases dm 245 mean age 48	self reported confirmed in medical record	20-21.9 (ref) 1. 22-23.9 2. 24-25.9 3. 26-27.9 4. 28-29.9 5. > 29.9	age smoking physical activity alcohol SES	age adjusted / multivariate 1. 1.06 / 1.12 (0.49-2.55) 2. 1.83 / 1.83 (0.86-3.91) 3. 3.41 / 3.58 (1.71-7.49) 4. 4.95 / 5.20 (2.44-11.0) 5. 9.31 / 9.68 (4.60-20.4)

publication	study follow-up in years	population cases (n)	definition of diabetes cases	definition of BMI	adjusted for	result relative risk
Carey 1997 [19]	Nurses Health Study follow-up 333,384 person years 1986-1994	43.581 women 40-65 year mean age52 cases dm 705	self reported additional questionnaire to confirm	< 21 (ref) 1. 21-22.9 2. 23-24.9 3. 25-26.9 4. 27-28.9 5. 29-30.9 6. >31	age smoking physical activity dm in family	age adjusted / multivariate 1. 1.2 / 1.2 (0.8-1.6) 2. 3.1 / 2.9 (2.0-4.3) 3. 7.0 / 6.5 (4.6-9.4) 4. 9.6 / 8.8 (6.2-12.5) 5. 12.7 / 11.4 (8.0-16.2) 6. 18.1 / 15.9 (11.2-22.6)
Colditz 1995 [20]	Nurses Health Study follow-up 1,490,000 person years 1976-1990	114,824 women 30-55 year mean age 50 cases dm 2204	self reported additional questionnaire to confirm	< 22 (ref) 1. 22-22.9 2. 23-23.9 3. 24-24.9 4. 25-26.9 5. 27-28.9 6. 29-30.9 7. 31-32.9 8. 33-34.9 9. > 35	age	1. 2.9 (2.0-4.1) 2. 4.3 (3.1-5.8) 3. 5.0 (3.6-6.6) 4. 8.1 (6.2-11) 5. 15.8 (13-20) 6. 27.6 (23-34) 7. 40.3 (34-48) 8. 54.0 (46-64) 9. 93,2 (81-107)
Perry 1995 [21]	British Regional Heart Study follow-up 12.8 year 1978/80-1991	7.577 men 40-59 year mean age 49 cases dm 194	follow-up questionnaire medical records death certificates	highest (>27.9) versus lowest quintile (<22.9)	age smoking physical activity alcohol blood pressure cholesterol heart rate uric acid	adjusted age: 11.6 (5.4-16.8) multivariate 7.3 (3.4-15.6)
Chan 1994 [22]	Health Professionals' follow-up study follow-up 5 year 1987-1992	27.983 men 40-75 year mean age 57 cases dm 272	self reported additional questionnaire to confirm	< 22.9 (ref) 1. 23-23.9 2. 24-24.9 3. 25-26.9 4. 27-28.9 5. 29-30.9 6. 31-32.9 7. 33-34.9 8. >35	age smoking dm in family	only adjusted age / multivariate 1. 1.0 / 1.0 (0.5-2.0) 2. 1.6 / 1.5 (0.8-2.9) 3. 2.3 / 2.2 (1.3-3.8) 4. 4.8 / 4.4 (2.6-7.7) 5. 8.1 / 6.7 (3.8-12) 6. 13.8 / 11.6 (6.3-22) 7. 26.9 / 21.3 (11-41) 8. 50.7 / 42.1 (22-81) additional adjustment WHR 8. 31.7 (16-62)

publication	study follow-up in years	population cases (n)	definition of diabetes cases	definition of BMI	adjusted for	result relative risk
Lipton 1993 [23]	NHANES 1 follow-up 16 year 1971-1987	3874 men cases dm 294 5657 women cases dm 377 20-70 year mean age 47	self reported diagnosed diabetes medical record death certificate	per unit BMI	age physical activity social status subscapular /triceps skinfold ratio	men: 1.20 women: 1.13
Manson 1992 [24]	Physicians Health Study follow-up 5 year	21.271 men 40-84 year mean age 53 105,140 person- years cases dm 285	self reported additional questionnaire to confirm	Quartiles < 23 (ref) 1. 23-24.4 2. 24.5-26.4 > 26.4	age smoking alcohol physical activity blood pressure cholesterol other	1. 1.07 (0.64-1.79) 2. 1.73 (1.10-2.74) 3. 3.09 (2.02-4.72)
Helmrich 1991 [25]	old students from University of Pennsylvania follow-up 14 year 98,524 person years 1962-1976	5990 men 39-68 year mean age 53 cases dm 202	self reported	per unit BMI	age physical activity dm in family hypertension	1.10 (1.06-1.14)
Kaye 1991 [26]	Iowa Women's Health Study follow-up 2 year 1986-1987	41.837 women 55-69 year mean age 61 cases dm 399	self reported	< 24.7 (ref) 1. 24.7-29.2 2. > 29.2	age SES WHR	only adjusted age / multivariate 1. 1.9 (1.3-2.6) / 1.2 (1.0-1.5) 2. 6.0 (4.4-8.8) / 3.1 (2.6-3.7)
Skarfors 1991 [27]	Uppsala follow-up 14 year 1970-1984	1.860 men 47-53 year mean age 50 cases dm 77	self reported doctor diagnose medical record blood glucose tested	per unit	physical activity dm in family blood pressure glucose insulin antihypertensive treatment lipids	1.12 (1.00-1.25)

publication	study follow-up in years	population cases (n)	definition of diabetes cases	definition of BMI	adjusted for	result relative risk
Mc Phillips 1990 [28]	Rancho Bernardo California follow-up 10-15 year mean 12 year 1972/74 - 1984/87	795 men cases dm 102 1.052 women cases dm 117 40-79 year mean age 59	blood glucose tested self reported diagnosed diabetes	per unit	age	men 1.08 (1.00-1,16) women 1.14 (1.08-1,20)
Colditz 1990 [29]	Nurses Health Study follow-up 8 year 826,010 person years 1976-1984	113.861 women 30-55 year mean age 42 cases dm 873	self reported additional questionnaire to confirm	BMI in 10 categories	age	BMI is a strong risk factor risk increases with increased BMI

dm=diabetes mellitus; ref=reference category; p.y.= person years; SES=social economic status; WHR=waist-hip ratio; FPG=fasting plasma glucose; NHANES=National Health and Nutrition Examination Survey

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Appendix IVa Relative risks for physical inactivity on diabetes incidence

publication	study follow-up in years	population incident diabetes cases	definition of diabetes cases	classification physical activity	confounders	result relative risk
Kumari 2004 [1]	Whitehall 2 study follow-up 11 year 1985-1995	10,308 civil servants (9,162 white) 35-55 year cases dm men 242 women 119	self reported and blood glucose tested	vigorous (ref) 1. moderate 2. mild/none	model 1 age etnicity length of follow-up ECG abnormalities employment grade model 2 + BMI height smoking blood pressure dm in family	men / women model 1 1. 1.64 (1.1-2.4) / 1.43 (0.6-3.4) 2. 1.53 (1.0-2.3) / 1.83 (0.8-4.4) model 2 1. 1.66 (1.1-2.4) / 1.38 (0.6-3.3) 2. 1.52 (1.0-2.3) / 1.71 (0.7-4.1)
Weinstein 2004 [2]	Women's Health Study (WHS) follow-up 7 year from 1992 onward	37,878 women > 45 year mean age 55 cases dm 1361	self reported with control	energy expenditure kcal/week 0-199 (ref) 1. 200-599 2. 600-1499 3. > 1499	age BMI family dm alcohol smoking hormone use hypertension cholesterol diet	only age / multivariate 1. 0.72 (0.62-0.82) / 0.91 (0.79-1.06) 2. 0.58 (0.50-0.67) / 0.86 (0.74-1.01) 3. 0.60 (0.52-0.70) / 0.82 (0.70-0.97)
Hu, G 2003 [3]	Finnish men en women follow-up 12 year 1982-1998	6,898 men 7,392 women 35-64 year cases dm 373	hospital records insurance records	low activity in leisure time (ref) 1. moderate intensive physical activity > 4 hours /week 2. intensive activity /sport for at least 3 hours /week	age gender blood pressure smoking education activity at work	multivariate / multivariate +BMI men 1. 0.71 (0.53-0.97) / 0.78 (0.57-1.06) 2. 0.62 (0.38-1.00) / 0.84 (0.52-1.37) women 1. 0.64 (0.46-0.89) / 0.81 (0.58-1.15) 2. 0.58 (0.30-1.12) / 0.85 (0.43-1.66)
Hu, F 2001 [4]	Nurses Health Study follow-up 16 year 1.301.055 person-years 1980-1996	84.941 women 34-59 year cases dm 3300	self reported diagnosed diabetes questionnaire to confirm	moderate / intensive activities: < 0.5 hours / week (ref) 1. 0.5-1.9 2. 2.0-3.9 3. 4.0-6.9 4. >7.0	age BMI dm in family menopausal status hormone therapy diet alcohol	1. 0.89 (0.77-1.02) 2. 0.87 (0.75-1.00) 3. 0.83 (0.71-0.96) 4. 0.71 (0.56-0.90)

publication	study follow-up in years	population incident diabetes cases	definition of diabetes cases	classification physical activity	confounders	result relative risk
Hu, F 2001 [5]	Health Professionals follow-up study follow-up 10 year 1986-1996	37,918 men 40-75 cases dm 1058	self reported diagnosed diabetes questionnaire to confirm	MET hours / week, quintiles Q1: median 2.7 (ref) 1. Q2: median 9.6 2. Q3: median 18.6 3. Q4: median 31.6 4. Q5: median 57.8	age smoking dm in family alcohol vitamin E	multivariate / multivariate + BMI 1. 0.78 (0.66-0.93) / 0.82 (0.69-0.98) 2. 0.65 (0.54-0.78) / 0.72 (0.60-0.86) 3. 0.58 (0.48-0.70) / 0.66 (0.54-0.80) 4. 0.51 (0.41-0.63) / 0.62 (0.50-0.76)
Folsom 2000 [6]	Iowa Women's Health Study follow-up 12 year 350,000 p.y. 1986-1997	34,257 women 55-69 year post menopausal cases dm 1997	self reported diagnosed diabetes	moderate physical activity rare/never (ref) 1. max. 1/week 2. 2-4 /week 3. >4 /week	model 1 age alcohol smoking diet dm in family hormone therapy education model 2 + BMI en WHR	model 1/ model 2 1. 0.80 (0.71-0.90) / 0.90 (0.79-1.01) 2. 0.65 (0.58-0.74) / 0.86 (0.76-0.98) 3. 0.51 (0.43-0.59) / 0.73 (0.62-0.85) no difference in relative risk estimates between age classes
Wannamethee 2000 [7]	British Regional Heart Study follow-up mean 16.8 year	5,159 men 40-59 year cases dm 196	self reported check in medical records	inactive (ref) 1. occasional 2. light 3. moderate 4. moderately vigorous/vigorous	age BMI smoking alcohol SES CHD	only age / multivariate 1. 0.65 (0.42-1.00) / 0.66 (0.42-1.02) 2. 0.60 (0.38-0.95) / 0.65 (0.41-1.03) 3. 0.42 (0.24-0.72) / 0.48 (0.28-0.83) 4. 0.36 (0.21-0.62) / 0.46 (0.27-0.79)
Hu 1999 [8]	Nurses Health Study follow-up 8 year 534,928 person-years 1986-1994	70,102 40-65 year cases dm 1419	self reported diagnosed diabetes questionnaire to confirm	Quintiles of total activity 0-2.0 MET (ref) 1. 2.1-4.6 2. 4.7-10.4 3. 10.5-21.7 4. > 21.7	age BMI dm in family menopausal status hormone therapy hypertension cholesterol alcohol smoking	multivariate / without BMI 2. 0.84 (0.72-0.97) / 0.77 (0.66-0.90) 3. 0.87 (0.75-1.02) / 0.75 (0.65-0.88) 4. 0.77 (0.65-0.91) / 0.62 (0.52-0.73) 5. 0.74 (0.62-0.89) / 0.54 (0.45-0.64)
Njolstad 1998 [9]	Finnmark Study follow-up 12 year 1977-1989	6,098 men cases dm 87 5,556 women cases dm 75 35-52 year mean age 43	hospital record or self reported and confirmed by doctor	self reported low moderate regular training heavy training	age BMI length smoking blood pressure cholesterol FPG hypertension	per unit increase adjusted for age, male/female 0.67 (0.49-0.92) / 0.66 (0.44-0.99) multivariate male / female 0.84 (0.61-1.16) / 0.91 (0.61-1.36)

publication	study follow-up in years	population incident diabetes cases	definition of diabetes cases	classification physical activity	confounders	result relative risk
Haapanen 1997 [10]	Finland follow-up 10 year 1980-1990	891 men cases dm 62 973 women cases dm 54 35-63 year	self reported or death certificate	activity index / total energy expenditure high (ref) 1. moderate 2. low	age	men / women 1. 1.21 (0.63-2.31) / 1.17 (0.50-2.70) 2. 1.54 (0.83-2.84) / 2.64 (1.28-5.44)
Lipton 1993 [11]	National Health and Nutrition Examination Survey (NHANES 1) follow-up 16 year 1971-1987	4,454 men cases dm 361 5,657 white women cases dm 377 20-70 year mean age 47	self reported medical record death certificate	work and leisure very active (ref) 1. moderately active 2. inactive	age BMI sub scapular /triceps skinfold ratio blood pressure education race	men 1. 1.13 (0.87-1.48) 2. 1.21 (0.90-1.62) white women 1. 1.21 (0.89-1.65) 2. 1.46 (1.07-1.98)
Manson 1992 [12]	Physicians Health Study follow-up 5 year 105,140 p.y.	21,271 men 40-84 year mean age 53 cases dm 285	self reported + questionnaire to confirm	activity intense enough to build up a sweat less than once a week (ref) 1. 1 / week 2. 2-4 / week 3. 5+ / week	age BMI	age / age and BMI 1. 0.77 (0.55-1.07) / 0.78 (0.56-1.09) 2. 0.62 (0.46-0.82) / 0.68 (0.51-0.90) 3. 0.58 (0.40-0.84) / 0.71 (0.49-1.03)
Kaye 1991 [13]	follow-up 2 year 1986-1987	37,579 women 55-69 year cases dm 318	self reported	3 levels based on frequency of physical activity in leisure time of at least moderate intensity	age	moderate versus low 0.7 (0.5-0.9) high versus low 0.5 (0.4-0.7)

dm=diabetes mellitus; ref=reference category; BMI=body mass index; p.y.= person years; MET=metabolic equivalent; WHR=waist-hip ratio; SES=social economic status; CHD=coronary heart disease; FPG=fasting plasma glucose; NHANES=National Health and Nutrition Examination Survey

Appendix IVb Calculated relative risks for physical inactivity on diabetes incidence

Calculated relative risks for physical activity, with adjustment for BMI

Men

publication	inactive versus active	moderately active versus active
Kumari [1]	1.52	1.66
Hu,G [3]	1.19	0.93
Hu,F [5]	1.61	1.18
Wannamethee [7]	2.17	1.33
Njolstad [9]	1.69	1.30
Lipton [11]	1.21	1.13
Manson [12]	1.41	1.00
Total*	1.53	1.14

* Weighted mean after exclusion of lowest and highest estimate

Women

publication	inactive versus active	moderately active versus active
Kumari [1]	1.71	1.38
Weinstein [2]	1.22	1.07
Hu,G [3]	1.18	0.95
Hu,F [4]	1.41	1.21
Folsom [6]	1.37	1.21
Hu,F [8]	1.85	1.54
Njolstad [9]	1.33	1.15
Lipton [11]	1.46	1.21
Total	1.36	1.18

Calculated relative risks for physical activity, without adjustment for BMI

Men

publication	inactive versus active	moderately active versus active
Kumari [1]	1.53	1.64
Hu,G [3]	1.61	1.15
Hu,F [5]	1.96	1.31
Wannamethee [7]	2.78	1.61
Njolstad [9]	3.32	1.82
Haapanen [10]	1.54	1.21
Manson [12]	1.72	1.16
Total	1.91	1.31

Women

publication	inactive versus active	moderately active versus active
Kumari [1]	1.83	1.43
Weinstein [2]	1.67	1.08
Hu,G [3]	1.72	1.10
Folsom [6]	1.96	1.43
Hu,F [8]	1.85	1.31
Njolstad [9]	3.48	1.87
Haapanen [10]	2.64	1.54
Kaye [13]	2.0	1.4
Total	1.91	1.35

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Appendix V Relative risks for current and former smoking on diabetes incidence

publication	study follow-up in years	population cases (n)	definition of diabetes cases	definition of smoking	adjustment for	result relative risk
Carlsson 2004 [1]	Nord-trondelag study follow-up 11 year 1984/86-1995/97	37,968 men and women > 20 year cases dm 738	self-reported blood glucose measured in self- reported cases	never (ref) 1. former 2. current	age gender BMI	1. 1.19 (0.98-1.44) 2. 1.06 (0.87-1.30)
Kumari 2004 [2]	Whitehall 2 study follow-up 11 year 1985-1995	10,308 civil servants (9,162 white) 35-55 year cases dm men 242 women 119	self reported blood glucose measured	never (ref) 1. former smoking 2. current smoking	age etnicity length of follow-up ECG abnormalities employment grade BMI height physical activity blood pressure dm in family	men / women 1. 0.95 (0.7-1.3) / 0.94 (0.6-1.6) 2. 1.24 (0.8-1.8) / 0.73 (0.4-1.3)
Hu 2001 [3]	Nurses Health Study follow-up 16 year 1980-1996 1.301.055 person years	84,941 women 34-59 year mean age 43 cases dm 3,300	self reported diagnosed diabetes confirmed with questionnaire	never smoking (ref) 1. former smoking 2. current < 15/day 3. current > 15/day	age BMI diet alcohol physical activity dm in family menopausal status hormone therapy	1. 1.15 (1.07-1.25) 2. 1.20 (1.03-1.41) 3. 1.34 (1.20-1.50)
Wannamethee 2001 [4]	British Regional Heart Study follow-up 16.8 years	7,735 men 40-59 year mean age 50 cases dm 290	self reported confirmed in medical record	never smoking (ref) 1. current 2. current < 20/day 3. current > 19/day 4. former smoking	age BMI alcohol social class physical activity CHD undiagnosed antihypertensives	age / age + BMI / multivariate 1. 1.52 / 1.74 (1.24-1.43) / 1.70 2. 1.59 / 1.79 (1.20-2.68) / 1.80 3. 1.50 / 1.71 (1.19-2.45) / 1.64 4. 1.40 / 1.33 (0.92-1.90) / 1.32
Will 2001 [5]	Cancer Prevention Study 1 follow-up 13 year 1959-1972	275,190 men cases dm 10.634 434,637 women cases dm 14,763 > 30 years mean age 54	self reported or reported in death certificate	never smoking (ref) 1. former smoking 2. current < 20/day 3. current 20-40/day 4. current > 40/day	age BMI alcohol physical activity diet education race	men / women 1. 1.07 (1.02-1.13) / 1.07 (0.99-1.15) 2. 1.05 (0.98-1.12) / 0.98 (0.93-1.03) 3. 1.19 (1.13-1.26) / 1.21 (1.14-1.29) 4. 1.45 (1.34-1.57) / 1.74 (1.49-2.03)

publication	study follow-up in years	population cases (n)	definition of diabetes cases	definition of smoking	adjustment for	result relative risk
Manson 2000 [6]	Physicians Health Study follow-up 12 year 1982-1995 255.830 person years	21,068 men 40-84 year mean age 62 cases dm 770	self reported diagnosed diabetes	never smoking (ref) 1. current < 20/day 2. current > 20/day 3. former smoking	age BMI physical activity history hypertension or cholesterol fam. history of MI alcohol treatment	adjustment age / multivariate 1. 1.4 (1.0-2.0) / 1.5 (1.0-2.2) 2. 2.1 (1.7-2.6) / 1.7 (1.3-2.3) 3. 1.2 (1.0-1.4) / 1.1 (1.0-1.4)
Perry 1995 [7]	British Regional Heart Study follow-up 12,8 year 1978/80-1991	7,735 men 40-59 year mean age 50 cases dm 194	self reported medical records and death certificates	never smoking (ref) 1. former smoking 2. current smoking	age BMI CHD baseline physical activity alcohol cholesterol blood pressure heart rate uric acid	adjustment age en BMI: 1. 1.2 (0.8-1.8) 2. 1.5 (1.0-2.2) amount makes no difference multivariate 2. 1.2 (0.8-1.8)
Rimm 1995 [8]	Health Professionals Follow-up Study follow-up 6 year 1986-1992 230.769 person-years	41,810 men 40-75 year mean age 58 cases dm 509	self reported confirmed with questionnaires or medical record	never smoking (ref) 1. former smoking 2. current 1-14/day 3. current 15-24/day 4. current > 24 /day	age BMI dm in family alcohol physical activity	1. 1.29 (1.05-1.57) 2. 1.37 (0.77-2.43) 3. 2.38 (1.57-3.59) 4. 1.94 (1.25-3.03)
Rimm 1993 [9]	Nurses Health Study follow-up 12 year 1976 - 1.277.589 person years	114,247 women 30-55 year mean age 42 cases dm 2,333	self reported confirmed with questionnaires	never smoking (ref) 1. former smoking 2. current 1-14/day 3. current 15-24/day 4. current > 24 /day	age BMI dm in family alcohol physical activity be on pill menopausal status	1. 1.10 (1.00-1.20) 2. 0.95 (0.76-1.20) 3. 1.19 (0.99-1.43) 4. 1.42 (1.18-1.72)
Cassano 1992 [10]	Normative Aging Study follow-up mean 18 year 1963-1987	1,972 men 22-80 year mean age 50 cases dm 226	medical record and measurement of blood glucose	never smoking (ref) 1. current smoking 2. former smoking	age BMI WHR	1. 1.5 (1.0-2.1) 2. 1.7 (1.2-2.4)

dm=diabetes mellitus; ref=reference category; BMI=body mass index; CHD=coronary heart disease; MI=myocardial infarction; WHR=waist-hip ratio

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Appendix VI Relative risks for alcohol consumption on diabetes incidence

publication	study follow-up in years	population	definition of diabetes cases	classification of alcohol consumption	confounders	result relative risks
Carlsson 2003 [1]	Finnish Twin Cohort Study follow-up 20 year 445,930 person- years 1975-1995	22,778 men and women >17 year mean age 34 cases dm 580	hospital record or prescribed medication	<5.0 gram/day (ref) 1. no alcohol men 2. no alcohol women 3: 5.0-29.9 men 4: 5.0-19.9 women 5: >29.9 men 6: >19.9 women	age BMI	1. 1.1 (0.7-1.5) 2. 1.1 (0.9-1.5) 3. 0.8 (0.6-1.1) 4. 0.7 (0.4-1.1) 5. 0.9 (0.6-1.4) 6. 1.6 (0.8-3.5)
Wannamethee 2003 [2]	Nurses Health study II follow-up 10 year 1989-1999	109,690 women 25-42 year cases dm 935	self reported confirmed with additional questionnaire	no alcohol (ref) 1. 0.1 - 4.9 gram/day 2. 5.0 - 14.9 gram/day 3. 15.0-29.9 gram/day 4. > 30.0 gram/day	age BMI smoking physical activity dm in family blood pressure cholesterol be on pill	1. 0.80 (0.66 - 0.96) 2. 0.67 (0.50 - 0.89) 3. 0.42 (0.20 - 0.90) 4. 0.78 (0.34 - 1.78)
Meisinger 2002 [3]	Monica Augsburg Cohort study follow-up 8 year 1984/1995-1998	3,052 men cases dm 128 3,114 women cases dm 85 35-74 year mean age 51	self reported diabetes or medication	gram/day men 0.1-39.9 (ref) women 0.1-19.9 (ref) 1. no alcohol men 2. no alcohol women 3. > 39.9 men 4. > 19.9 women	age BMI smoking uric acid physical activity dm in family blood pressure cholesterol	age en BMI 1. 1.59 (0.96-2.63) 2. 1.51 (0.92-2.47) 3. 2.06 (1.39-3.04) 4. 0.94 (0.46-1.91) multivariate 3: 1.95 (1.30-2.91) 4. not significant
Wannamethee 2002 [4]	British Regional Heart Study follow-up 17 year 1978/80-1995	5,221 men 40-59 year cases dm 198	self reported medical record death certificate	incidental (ref) 1. no alcohol 2. 1-15 drinks/week 3. 15-42 drinks/week 4. >42 drinks/week	age, BMI physical activity smoking SES CHD	age /multivariate: 1. 1.12 (0.62-2.03) /1.10 (0.61-2.00) 2. 0.75 (0.52-1.09) /0.81 (0.55-1.20) 3. 0.73 (0.49-1.08) /0.66 (0.44-0.99) 4. 1.27 (0.81-1.99) /0.96 (0.60-1.52)

publication	study follow-up in years	population	definition of diabetes cases	classification of alcohol consumption	confounders	result relative risks
Conigrave 2001 [5]	Health Professionals follow-up study follow-up 12 year 1986-1998	46,892 men 40-75 year cases dm 1571	blood glucose tested medication	no alcohol (ref) 1: 0.1-4.9 gram/day 2: 5.0-9.9 gram/day 3: 10.0-14.9 gram/day 4: 15.0-29.9 gram/day 5: 30.0-49.9 gram/day 6: >50 gram/day	age BMI smoking physical activity profession diet dm family history CHD cancer, hypertension or hyper cholesterol	1: 1.05 (0.92-1.20) 2: 0.80 (0.68-0.95) 3: 0.71 (0.59-0.86) 4: 0.64 (0.53-0.78) 5: 0.57 (0.45-0.71) 6: 0.61 (0.43-0.86) its best to drink on many days
Kao 2001 [6]	Atherosclerosis Risk in Communities Study follow-up 3-6 year 1990-1998	12,261 men and women 45-64 year cases dm 239	blood glucose tested medication or self reported	≤ 1 drink/week (ref) 1. no alcohol 2. ex drinkers 3. 1.1-7 4: 7.1-14 5: 14.1-21 6: >21	age BMI race education physical activity dm in family smoking diet hypertension WHR	men / women 1: 1.14 (0.79-1.65) /1.10 (0.84-1.43) 2: 1.06 (0.77-1.47) /1.10 (0.81-1.49) 3: 1.12 (0.82-1.52) /1.09 (0.80-1.49) 4: 0.80 (0.55-1.17) /0.81 (0.47-1.37) 5: 1.07 (0.68-1.69) /0.64 (0.25-1.64) 6: 1.50 (1.02-2.20) /0.41 (0.10-1.77)
Wei 2000 [7]	Cooper Clinic Study follow-up 6 year 52.588 person-years	8,663 men 30-79 year cases dm 149	blood glucose tested	no alcohol + quartiles gram/week Q1: < 62 Q2: 62-123 (ref) Q3: 123-277 Q4: > 277	age dm in family fitness level blood pressure cholesterol smoking glucose level waist- circumference	no alcohol: 1.8 (1.0 - 3.3) Q1 1.4 (0.7 - 2.6) Q3 2.2 (1.2 - 3.9) Q4 2.4 (1.4 - 4.4)
Rimm 1995 [8]	Physicians Health Study follow-up 6 year	41,810 men 40-75 year 230,769 person- years cases dm 509	self reported en confirmed with questionnaire or medical record	no alcohol (ref) 1: 0.1-4.9 gram/day 2: 5.0-9.9 gram/day 3: 10.0-14.9 gram/day 4: 15.0-29.9 gram/day 5: 30.0-49.9 gram/day 6: >50 gram/day	age BMI dm in family smoking physical activity	1: 1.17 (0.91-1.49) 2: 0.88 (0.64-1.20) 3: 0.90 (0.64-1.24) 4: 0.91 (0.67-1.24) 5: 0.61 (0.44-0.91) 6: 0.84 (0.41-1.56)

dm=diabetes mellitus; ref=reference category; BMI=body mass index; SES=social economic status; CHD=coronary heart disease; WHR=waist-hip ratio

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Appendix VIIa Lifestyle interventions and prevention of diabetes incidence

Study and year of publication Duration of follow-up	Inclusion criteria	Population characteristics at baseline	Intervention (number of participants)	Change in weight or BMI	Change in blood glucose	Incident diabetes	Risk reduction
SLIM 2003 [1,2] Follow-up 2 year (planned follow-up 6 years)	> 40 year BMI >25 or dm in family IGT	64% ♂ mean age 57 mean BMI 29 kg/m^2	Intensive lifestyle (51) Lifestyle (51)	BMI -0.8* BMI +0.0	HbA1c +0.0 HbA1c -0.1	-- --	
Diabetes Prevention Program 2002 [3] Follow-up 3 years	>25 year BMI>24 IGT	32% ♂ mean age 51 year mean BMI 34 kg/m^2	Intensive lifestyle (1079) Lifestyle+metformin (1073) Lifestyle+placebo (1082)	-5.6 kg* -2.1 kg* -0.1 kg	HbA1c +0.1* HbA1c +0.05* HbA1c +0.2	4.8/100 py* 7.8/100 py* 11.0/100 py	58% (51%)*[4] 31% (24%)* ref
Diabetes Prevention Study 2001 [4] Follow-up 3 years	40-65 year BMI>25 IGT	33% ♂ mean age 55 year mean BMI 31 kg/m^2	Intensive lifestyle (265) Lifestyle (257)	BMI -1.3* BMI -0.3	HbA1c -0.2* HbA1c -0.0	3.2/100 py* 7.8/100 py	58%* ref
Oslo Diet and Exercise Study (ODES) 1997 [5] Follow-up 1 year	40 year BMI>24	♂ + ♀ mean age 40 mean BMI 29	Diet+physical activity (65) Diet (52) Physical activity (49) Control (43)	BMI -3.7* BMI -1.3 BMI -0.3 BMI +0.4	FPG -0.3* FPG -0.2* FPG -0.1 FPG 0.0	-- -- -- --	
Fasting hyperglycemia study 1997 [6] Follow-up 1 year	IFG	41% ♂ dm 23% mean age 50 year mean BMI 29 kg/m^2	Intensive lifestyle (111) Lifestyle (116)	-0.4 kg -0.2 kg	HbA1c –0.1 HbA1c -0.1	n=-1 n=0	
Malmo feasibility study 1991 [7] Follow-up 5 years	men 47-49 year IGT[5]	100% ♂ mean age 48 mean BMI 27 kg/m^2	Intensive lifestyle (181) Regular care (161)	BMI -2.3* BMI +0.5	2h-PG -13%* 2h-PG +3%	10.6%* 28.6%	63%* ref

SLIM=Study on lifestyle-intervention and impaired glucose tolerance Maastricht; BMI=body mass index; dm=diabetes mellitus; IGT=impaired glucose tolerance; IFG=impaired fasting glucose; py=person years; ref=reference group
* significant difference between groups

[4] between parenthesis are results for white participants
[5] results presented for subgroup with IGT at baseline (81%)

Appendix VIIb Pharmacological interventions and prevention of diabetes incidence

Study and year of publication Duration of follow-up	Inclusion criteria	Population characteristics at baseline	Intervention (number of participants)	Change in weight or BMI	Change in blood glucose	Incident diabetes	Risk reduction
XENDOS 2004 [8] Follow-up 4 year	30-60 years BMI>30	45% ♂ mean age 43 year mean BMI 37 kg/m^2	Orlistat+lifestyle (1640) Placebo+lifestyle (1637)	-5.8 kg* -3.0 kg	FPG +0.1* FPG +0.2	6.2%* 9.0%	37%*
Diabetes Prevention Program 2002 [3] Follow-up 3 years	>25 year BMI>24 IGT	32% ♂ mean age 51 year mean BMI 34 kg/m^2	Metformin+lifestyle (1073) Placebo+lifestyle (1082)	-2.1 kg* -0.1 kg	HbA1c +0.1* HbA1c +0.2	7.8 /100 py* 11.0 /100 py	31% (24%)*[6] ref
Stop NIDDM trial 2002 [9] Follow-up 3 years	40-70 year BMI 25-40 IGT	49% ♂ mean age 54 year mean BMI 31 kg/m^2	Acarbose (682) Placebo (686)	-0.5 kg +0.3 kg	-- --	10.1 / 100 py 12.1 /100 py	25%* ref
Heart Outcomes Prevention Evaluation study (HOPE) 2001 [10] Follow-up 4,5 year	>55 year at risk CVD	80% ♂ mean age 66 mean BMI 27 kg/m^2	Ramipril (2837) Placebo (2883)	+1.0 kg +0.8 kg		3.6%* 5.4%	34%* ref
Heymsfield 2000 [11] Follow-up 2 years	>18 year BMI 30-43	18% ♂ mean age 44 year mean BMI 36 kg/m^2	Orlistat (359) Placebo (316)	-6.7 kg* -3.8 kg	FPG -0.16*[7] FPG -0.04	n=0*[8] n=3	--
Fasting hyperglycemia study 1997 [12] Follow-up 1 year	IFG	41% ♂ dm 23% mean age 50 year mean BMI 29 kg/m^2	Sulfonyluria (112) Control (115)	+0.6 kg* -1.2 kg	HbA1c -0.2* HbA1c -0.0	n=+2 n=-3	--

XENDOS=XENical in the prevention of diabetes in obese subjects (XENDOS); BMI=body mass index; dm=diabetes mellitus; IFG=impaired fasting glucose; FPG=fasting plasma glucose; py=person years; ref=reference group; CVD=cardio vascular disease; NIDDM=non insulin dependent diabetes mellitus
* significant difference between groups

[6] between parenthesis are results for white participants
[7 and 5] results for participants with normal glucose tolerance at baseline (78%)
[8] distribution over normal glucose tolerance, IGT and diabetes after the study is significantly different between groups

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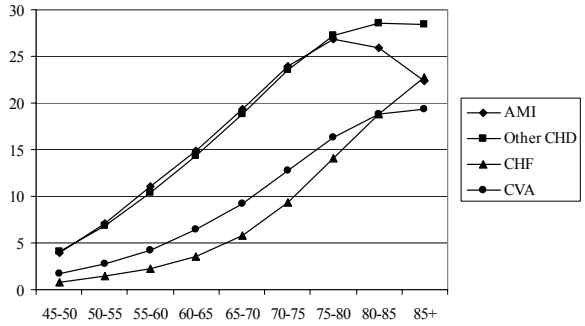
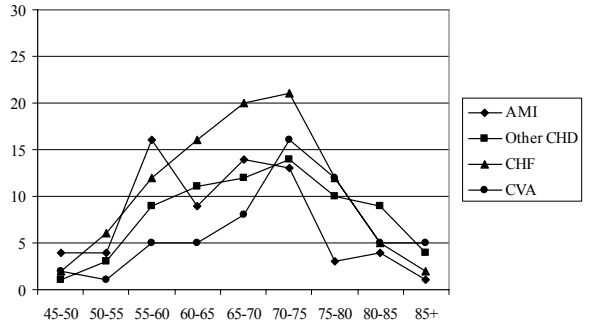
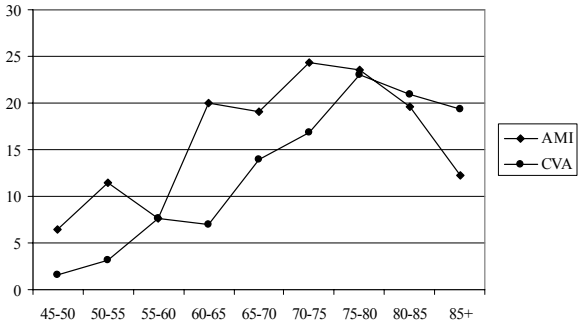
Appendix VIII Prevalence of macrovascular disease in diabetic men and women

based on estimations from the CDM (left) and based on empirical data (sources: Nijmeegs Monitoring Project)(middle) and ZODIAC (right))

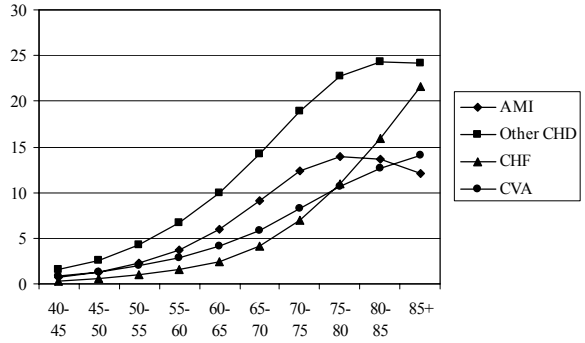
men

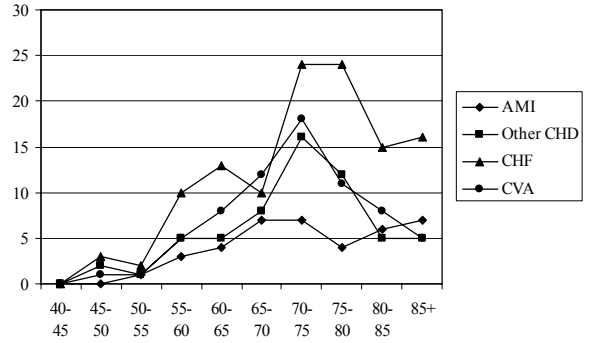


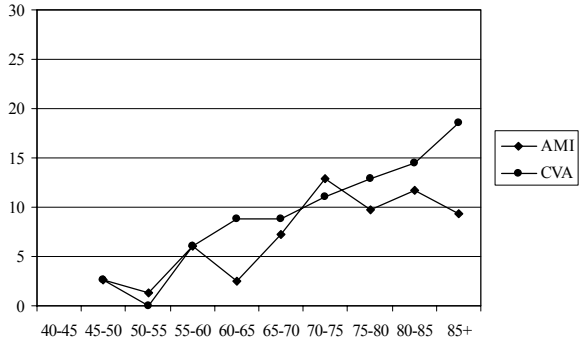




women



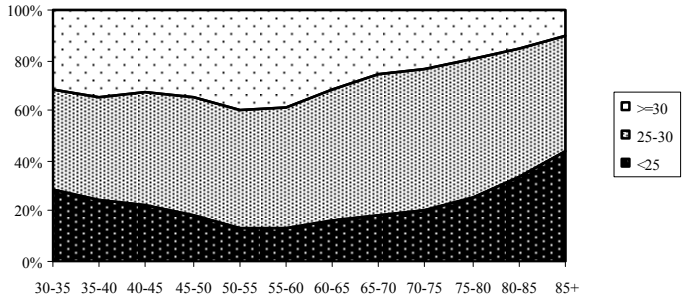


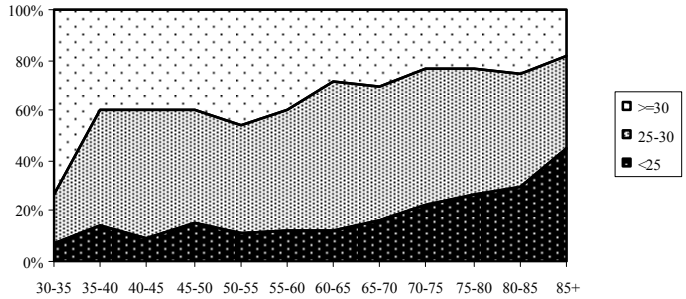


Appendix IX Validation of prevalences of risk factors in diabetes patients based on estimations from CDM

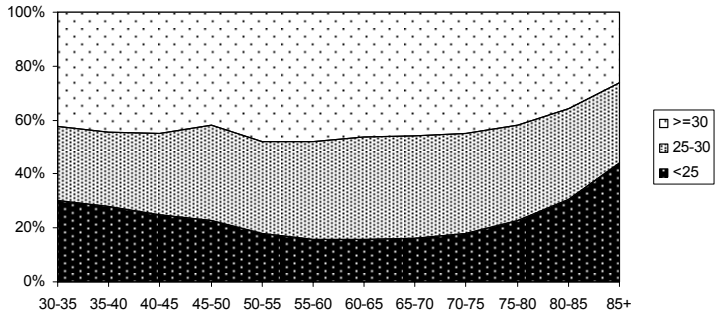
Distribution of BMI in 3 categories in diabetics based on estimations from the CDM (left) and based on empirical data Sources: Nijmeegs Monitoring Project, ZODIAC and Westfriesland (pooled data)(right)

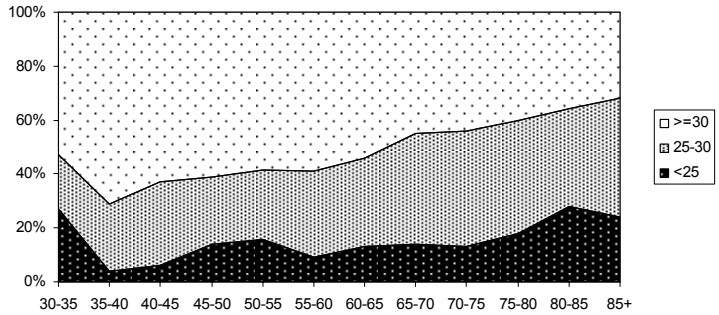
men





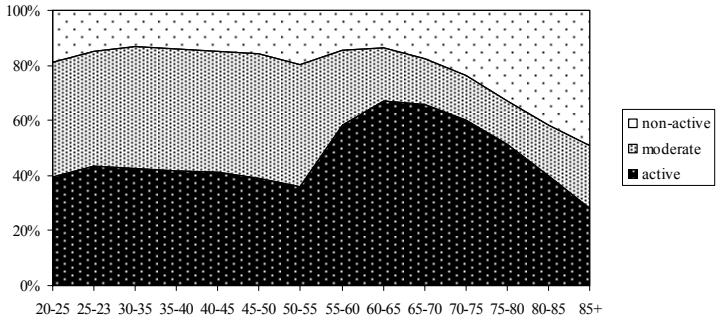
women

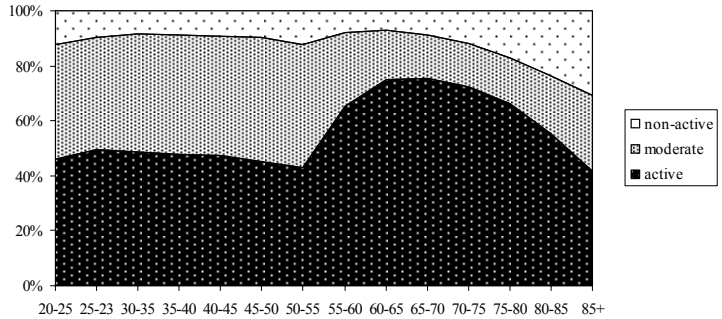




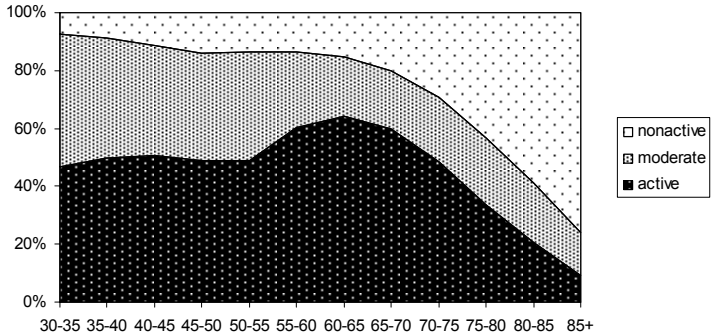
Distribution of physical activity in 3 categories in diabetics (left) compared with non-diabetics (right) based on estimations from the CDM. No empirical data were available for validation

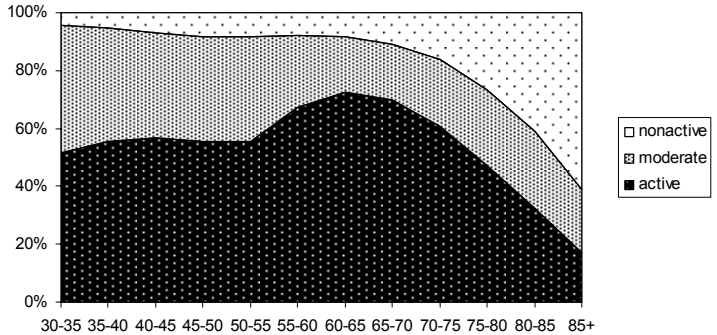
men





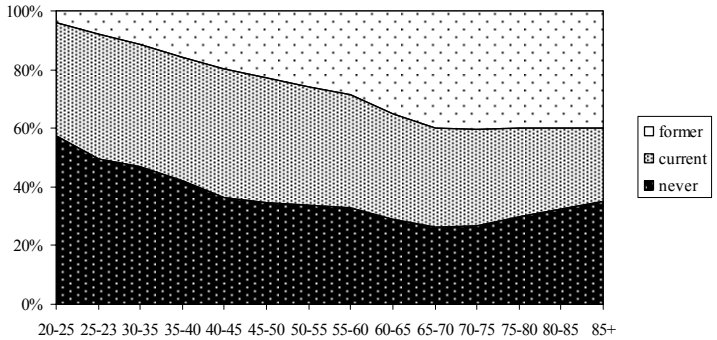
women

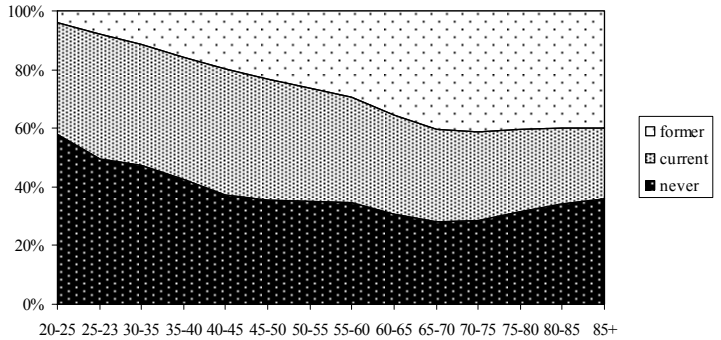




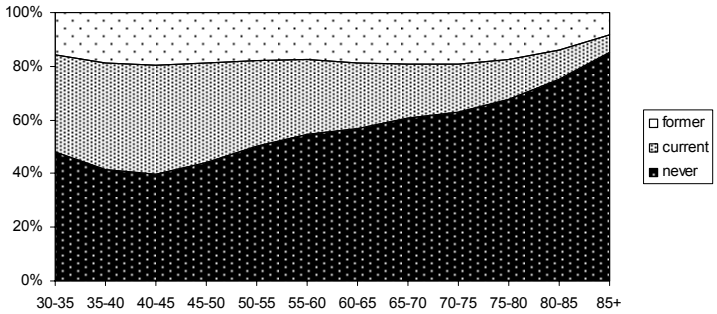
Distribution of smoking in 3 categories in diabetics (left) compared with non-diabetics(right) based on estimations from the CDM. No empirical data were available for validation

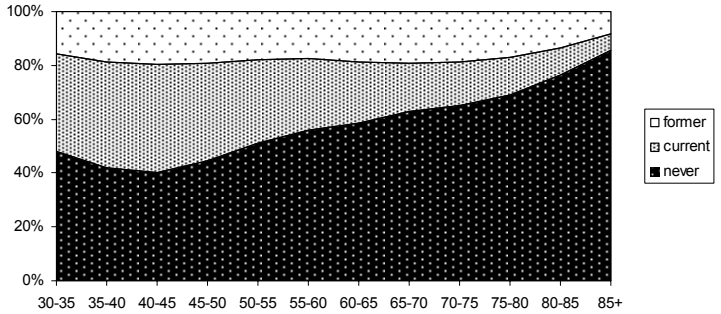
men





women





Appendix X Relative risks for HbA1c on incidence of macrovascular disease in diabetes patients

Study publication	Population follow up in years	Definition of diabetes	Definition endpoint	Determinants Relative risk	Confounders
			CHD		
UKPDS 2000 [1]	25-65 yr; n=3642 dm; med FU 10.5 yr (UK)	2x FPG>6	AMI n=496 cases	1.14 (1.08-1.21)	Sex, age, ethnic group, smoking, HDL, LDL, TG, albuminuria, SBP
UKPDS 2001 [2]	25-65 yr; n=4540 DM; 10.7 yr FU (UK)	2x FPG>6	CHD (non)fatal MI	1.18 (1.11-1.25)	age, sex, ethnic group, smoking, diabetes duration, glycaemia, SBP, lipids
UKPDS 1998 [3]	25-60 yr; n=3055 DM, 10 yr FU (UK)	2x FPG>6	CAD (fatal+non-fatal MI+AP) n=355 cases	1.11 (1.02-1.20)	Age, sex, LDL, HDL, HbA1c, SBP, smoking
Moss 1994 [4]	>30 yr; n=1780 dm; 10 yr FU (US)	Type 2	IHD mortality	1.10 (1.04-1.17)	age, sex, CVD history, urine protein, SBP, packyears smoked, diabetes duration
Khaw 1995-99 [5]	45-79 yr; n=4662 men+5570 women (general population); 6 yr FU (UK)	Diagnosed by GP or self reported	CHD mortality n=342 cases men n=157 cases women	Men women 1.25 (1.14-1.38) 1.13 (0.98-1.30)	Age, BMI, WHR, SBP, cholesterol, smoking, CVD history
Juutilainen 2004 [6]	45-64 yr; 835 dm; 13 yr FU (Finland)	National drug reimbursment register	CHD event n=151 cases men n=126 cases women	Men women 1.05 (0.98-1.13) 1.09 (1.03-1.15)	Age, area, smoking, BMI, SBP, total cholesterol, HDL, FPG, diabetes duration
			CVD		
Khaw 1995-1999 [7]	45-79 yr; n=4662 men; 4 yr FU (UK)	Diagnosed by GP or self reported	CVD mortality ICD 400-438	HbA1c (niet in DM) 1.29 (1.05-1.60) n=60	SBP, total cholesterol, BMI, smoking, history of AMI/stroke
Khaw 1995-99 [5]	45-79 yr; n=4662 men+5570 women; 6 yr FU (UK)	Diagnosed by GP or self reported	CVD mortality ICD 400-438 n=498 cases men	HbA1c (niet in DM) Men women 1.19 (1.10-1.29) 1.21 (1.10-1.34)	Age, BMI, WHR, SBP, cholesterol smoking, CVD history

Study publication	Population follow up in years	Definition of diabetes	Definition endpoint	Determinants Relative risk	Confounders
			n=273 cases women		
Hoorn study 1999 [8]	50-75 yr; n=2363; 8 yr FU (NL)	OGTT known dm excluded	CVD mortality 390-459 n=98 cases	Hba1c in tertiles with highest tertile diveded in two subgroups by the cut off of 6.5% <5.2 (n=752) 1 n=16 5.2-5.5 (n=798) 1.30 (0.71-2.38) n=32 5.5-6.4 (n=730) 1.69 (0.93-3.06) n=39 >=6.5 (n=83) 1.79 (0.77-4.16) n=11	Age, sex, hypertension, WHR, TG, LDL, smoking Univariate: highest category and trend are significant
			CVA		
UKPDS 2000 [1]	25-65 yr; n=3642 dm; med FU 10.5 yr (UK)	2x FPG>6	(non)fatal CVA n=162 events	1.12 (1.01-1.21)	Sex, age, ethnic group, smoking, HDL, LDL, TG, albuminuria, SBP
Moss 1994 [4]	>30 yr; n=1780 dm; 10 yr FU (US)	Type 2	Stroke mortality	1.17 (1.05-1.30)	age, sex, CVD history, hypertension

dm=diabetes mellitus; FU=follow-up; BMI=body mass index; WHR=waist-hip ratio; SBP=systolic blood pressure; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TG=triglycerides; dm=diabetes mellitus; OGTT=oral glucose tolerance test; IFG=impaired fasting glucose; FPG=fasting plasma glucose; py=person years; ref=reference group; CHD=coronary heart disease; AMI=acute myocardial infarctionI;CAD=coronary artery disease; AP=angina pectoris; IHD=ischaemic heart disease;CVD=cardio vascular disease; CVA=cerebro vascular event;

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Appendix XIa Tertiary prevention trials in diabetic patients, lifestyle interventions

Study Duration of follow-up	Population characteristics at baseline	Intervention (number of participants)	Outcome measures	Results Intervention versus control
Education, behavior and self management				
Ellis 2004 [1]	meta-analysis "diabetes patient education" 1990-2000, 21 studies type 2: 14 studies	1. control groups 2. intervention groups	effect of intervention (pre- post) on HbA1c after 12, 24 and 52 weeks HbA1c intervention versus control predictors of positive outcome	 -1.2%* / -0.9%* / –1.5%* positive in all 28 interventiongroups – 0.32% * programms with individual education, cognitive learning and/or exercise
Gary 2003 [2]	meta-analysis until 1999. educational and behavioral interventions in type 2 diabetes 63 studies, 18 included in meta-analysis	1. control groups 2. intervention groups intervention: median 5 months control: usual care: 56% control: minimal intervention: 44% focus: diet (70%), exercise (57%), medication (35%) blood glucose selfmonitoring (26%), foot care (35%) other (61%)	HbA1c weight	-0.51 ns -1.4 kg ns
Norris 2002 [3]	meta-analysis 1980-1999 "effectiveness of disease and case management for people with diabetes" 31 studies	1. control groups 2. intervention groups focus lifestyle: 44% knowledge: 23% skills: 3% mix: 30%	HbA1c directly after intervention after 1 to 3 months after 4 months	 -0.76% * -0.26% ns -0.26% * more contact time gives better results

Study Duration of follow-up	Population characteristics at baseline	Intervention (number of participants)	Outcome measures	Results Intervention versus control
Diet and exercise				
Miller 2004 [4]	effectiveness of physical activity interventions for the treatment of overweight and obesity and type 2 diabetes	besides meta-analysis Boule 2001 another 9 controlled trials on effectiveness of training (sometimes in combination with diet or other treatments)	HbA1c	significant improvement in all 9 studies difference with control 0.4-1.8%
Norris 2004 [5]	meta-analysis until 8-2003. Lifestyle and behavioral weight loss interventions in adults with type 2 diabetes 22 RCT-studies	1. intervention versus usual care 7 studies 585 subjects 2. physical activity versus no or lesser physical activity 2 studies, 53 subjects	weight HbA1c total cholesterol (4 studies)	1. -1.7 kg * / 2. 3.9 kg ns 1. ± -0.5 ns / 2. ± +0.1 ns 1. -0.1 mmol/l ns mean weight loss in people on a low-calorie diet (917 in 12 studies) was 3.7 kg compared to baseline values
Anderson 2003 [6]	meta-analysis “Importance of weight management in type 2 diabetes”	1. VLED, 10 studies 4-6 weeks, obese type 2 (152) 2. LED, 13 studies at least 6 weeks (weight loss in week 12 at least 5%) obese type 2 (376) 3. LED, 18 studies 12 weeks, obese type 2 (342)	weight reduction (% baseline) FPG reduction (% baseline) change in risk profile	1. weight: -9.6% in 6 weeks FPG: -50% in 2-6 weeks 2. weight -14.7% after 16 weeks weightgain of 3 kilo in next 32 weeks FPG-30% in 16 weeks, stable for 8 weeks, gradual increase with increasing weight 3. weight -9.6%, FPG –25.7%, total cholesterol: -9.2%, SBP –8,1%
Boule 2003 [7]	meta-analysis until 3-2002 “effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus”	8 studies with HbA1c measurements n=250 Exercise intensity: range 50->75% VO2 max Exercise volume 8.75-24.75 MET hours per week	difference in mean HbA1c between intervention and control groups after intervention	– 0.71%* effect on HbA1c depends on exercise intensity (r=-0.91* more than on exercise volume (r=-0.46))

Study Duration of follow-up	Population characteristics at baseline	Intervention (number of participants)	Outcome measures	Results Intervention versus control
Boule 2001 [8]	meta-analysis until dec 2000 "Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus" 14 studies	12 studies with aerobic training mean frequency 3.4 /week mean duration 18 weeks 2 studies with resistance training mean frequency 2.5 /week mean duration 15 weeks	difference in mean HbA1c between intervention and placebo groups after intervention difference in mean weight between intervention and placebo groups after intervention	7.65% versus 8.31% / -0.66% * 83.0 versus 82.5 / -0.54 kg ns decrease in HbA1c is not explained by weight loss
Kelley 2001 [9]	review "Effects of exercise on glucose homeostasis in type 2 diabetes mellitus"		% of studies with positive effect of intervention on HbA1c mean HbA1c effect in these studies effects on blood presure effects on blood lipide	65% 0.5-1.0% small effect (1 studie) no effect (2 studies) increase HDL (3 of 4 studies) decrease LDL (2 of 4 studies) improvements approximately 10% of baseline values
Brown 1996 [10]	meta-analysis "weight reduction in type 2 diabetes" mean age 52 year mean weight 96 kg 89 studies, 1800 patients	1. diet (36 studies) 2. behavior (18 studies) 3. exercise (9 studies) 4. 1 + 2 (4 studies) 5. combination 1+2+3 (5 studies) other	 weight (kg) BMI (effect size) HbA1c decrease SBP decrease DBP total cholesterol HDL / LDL triglyceride	effect 1 / 2 / 3 / 4 / 5 9.1 / -2.9 / -1.5 / ? / -3.9 kg 0.6* / 0.6 / 0.5 / ? / 0.4* -2.7% / -1.5% / -0.8% / ? / -1.6% 0.8* / 0.6*/-0.1 / ? / 0.7* 0.7* / ? / 0.0 / ? / ? 0.6* / 0.1 / 0.1 / 0.3 / 0.1 ns 0.6* / 0.1 / 0.2 / 0.4* / 0.3*

ns=not significant; RCT=randomised clinical trial; (V)LED=(very) low energy diet; dm=diabetes mellitus; FPG=fasting plasma glucose; SBP=systolic blood pressure; VO2 max=maximum oxigen uptake; MET=metabolic equivalent; r=correlation coefficient; HDL=high-density lipoprotein; LDL=low-density lipoprotein; BMI=body mass index; DBP=diastolic blood pressure;
* significant difference between groups

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Appendix XIb Tertiary prevention trials in diabetic patients, pharmacological interventions

Study Duration of follow-up	Population characteristics at baseline	Intervention (number of participants)	Outcome measures	Results Intervention versus control
A. Intensive blood glucose control				
Meta-analysis "Glucose lowering therapy in patients with diabetes" 2001 [1]	5 studies: UGDP, VACSDM, Kumamoto, DIGAMI, UKPDS ♂: 27-100% mean age 50-68	1. standard/conventional treatment 2. intensive blood glucose treatment	HbA1c CHD death or non-fatal MI cardiovascular death MI stroke	-0.9%* RR 0.87 (0.74-1.01) RR 0.89 (0.74-1.08) RR 0.91 (0.78-1.05) RR 1.16 (0.85-1.57)
VA-CSDM 2000 [2] Follow-up 2 year	♂: 100% mean age 60 year range 40-69 dm duration 8 year mean HbA1c 9.4% microalbiminuri 38%	1. standard treatment (66) 2. intensive stepwise insulin treatment, HbA1c goal 4.0-6.1% (74)	HbA1c bodyweight cardiovascular event death from all causes changes in retinopathy	-2.1%* (7.1% versus 9.2%) from 6 months onwards no difference between groups 32% versus 20% no differences between groups no differences between groups
Kumamoto Study 2000 [3 4] Follow-up 8 year	♂: 50% mean age 50 year dm duration 8.5 year mean HbA1c 9.1% mild retinopathy and microalbuminuri	1. conventional insulin injection therapy (55) 2. multiple insulin injection therapy, HbA1c goal < 7.0 % (55)	HbA1c bodyweight macrovascular event	-2.2%* from 3 months onwards no difference 0.6/100 py versus 1.3/100 py
UKPDS group 1998 [5] Follow-up 10 year	♂: 61% mean age 53 year range 25-65 newly diagnosed dm mean HbA1c 7.1%	1.conventional treatment diet (1138) 2. intensive treatment, FPG goal <6.0 mmol/l 2a. insulin (1156) 2b. sulphonylurea (1573)	HbA1c bodyweight diabetes related endpoint diabetes related death	during 10 years: -11%* +2.9 kg -12%* -10%

Study Duration of follow-up	Population characteristics at baseline	Intervention (number of participants)	Outcome measures	Results Intervention versus control
UKPDS group 1998 [6] Follow-up 11 year	♂: 47% mean age 53 year range 25-65 newly diagnosed dm with bodyweight >120% ideal weight mean HbA1c 7.2% mean BMI 32	1. conventional treatment diet (411) 2. intensive treatment metformin, FPG goal < 6.0 mmol/l (342)	HbA1c bodyweight diabetes related endpoint diabetes related death death from all causes macrovascular total	-8%* during 10 years no difference between groups -32%* -42%* -36%* -30%*
B. Intensive blood pressure control				
Meta-analysis "treatment of hypertension in patients with diabetes" 2003 [7]		1. studies that compare medication with placebo (SHEP, Syst-Eur, HOPE, RENAAL, IPDM) 2. studies with different blood pressure goals (HOT, UKPDS, ABCD) 3. studies that compare different medications (10 studies)	total cardiovascular events total death optimum treatment goal best choice of medication	RR 0.4 to 0.9 absolute risk reduction 2% to 8 % RR 0.6 to 1.0 absolute risk reduction –1% to 5% ± 135/80 no obvious superiorities in choice of medication; probable first choice: TD, ARB and ACE-inhibitors; multiple therapy needed to reach goals
Meta-analysis "Blood pressure lowering therapy in patients with diabetes" 2001 [1]	♂: 33-63% mean age 51-70 not only patients with diabetes	1. studies that compare intervention versus placebo or usual care (HDFP, SHEP, HOT, UKPDS, Syst-Eur, MICRO-HOPE)	SBP / DBP CHD death or non-fatal MI cardiovascular death MI stroke	-5 mm Hg / -2 mm Hg RR 0.73 (0.57-0.94) RR 0.59 (0.49–0.71) RR 0.78 (0.67-0.92) RR 0.65 (0.53-0.80)
Lewis 2001 [8] Follow up 3 year	♂: 66% type 2 diabetes with nephropathy and hypertension 30-70 year mean age 59	1. placebo (569) 2. ARB (irbesartan) (579) goal 135/85 in all groups	blood pressure during study CVD morbidity or death	140/77 versus 144/80 * ns

Study Duration of follow-up	Population characteristics at baseline	Intervention (number of participants)	Outcome measures	Results Intervention versus control
RENAAL 2001 [9] Follow up 3 year	1513 type 2 diabetes with nefropathy	1. placebo 2. ARB (losartan)	CVD morbidity and death	ns
IRMA-2 study (=IPDM) 2001 [10] Follow-up 2 year	♂: 68% mean age 58 range 30-70 with hypertension and microalbuminuria	1. placebo (201) 2. ARB (irbesartan 150 mg/day) (195) 3. ARB (irbesartan 300 mg/day) (194)	blood pressure non fatal cardiovascular event	during the study gr.2: -1 mm Hg* gr. 3: -3 mm Hg* 4.5% (gr. 3) versus 8.7% (gr. 1) ns conclusion : irbesartan is renoprotective independent of blood pressure lowering effect
ABCD study 2000 [11] Follow-up 5 year	470 diabetes and hypertension (DBP > 90 mm Hg)	1. goal DBP 80-89 mm Hg. 2. goal DBP < 75 mm Hg. with CCB (nisoldipine) or ACE (enalapril)	blood pressure total death	132 / 78 versus 138 / 86 * 5.5% versus 10.7% / RR 0.51 (0.27-0.97)
HOPE 2000 [12] Follow-up 4.5 year	♂: 63% type 2 diabetes at risk for CVD age>55, mean age 65	1. placebo (1722) 2. ACE (ramipril) (1774)	blood pressure SBP / DBP CVD death total death	– 2.4 mm Hg / –1.0 mm Hg * -37% * -24% *
Syst-Eur trial 1999 [13] Follow-up 2 year	♂: 35% diabetes with systolic hypertension age > 60 year	1. placebo (240) 2. CCB (nitrendipine) (+other if needed) (252) goal SBP –20 mm Hg until < 150 mm Hg	blood pressure SBP/DBP total death cardiovascular death cardiovascular event stroke	-8.6 / -3.9 mm Hg *(?) -41% ns -70% * -62% * -69% *
UKPDS group 1998 [14] Follow-up 8 year	♂: 55% mean age 56 range 25-65 newly diagnosed diabetes with hypertension	1. blood pressure control goal <180/105 (390) 2. stricter blood pressure control with ACE (captopril) or BB (atenolol) goal <150/85 (758)	mean blood pressure blood pressure < 150/85 blood pressure < 180/105 mean HbA1c year 1-4 / year 5-8 diabetes related endpoint diabetes related death	144/82 versus 154/87 * 56% versus 37% * 96% versus 91% * 7.2 versus 7.2 / 8.3 versus 8.2 -24% * -32% *

Study Duration of follow-up	Population characteristics at baseline	Intervention (number of participants)	Outcome measures	Results Intervention versus control
Hypertension Optimal Treatment Study (HOT) 1998 [15] Follow-up 4 year	♂: 53% 50-80 year mean age 61 with hypertension (DBP between 100-115)	1. DBP pressure target 90 (501) 2. DBP pressure target 85 (501) 3. DBP pressure target 80 (499) with CCB (felodipine) and ACE or BB or diuretics if needed	mean DBP change (mm Hg) mean SBP change (mm Hg) major CVD event MI CVA CVD death overall mortality	-20, -22, -24 patiets with / without diabetes -26 -28 and -30 patiets with / without diabetes 0.49 (0.29-0.81) 0.50 (0.20-1.23) 0.70 (0.33-1.47) 0.33 (0.14-0.78) 0.56 (0.31-1.02)
Systolic Hypertension in the Elderly Program SHEP 1996 [16] Follow-up 5 year	♂: 50% type 2 diabetes with systolic hypertension age > 60 mean age 70	1. placebo + regular antihypertensive treatment if needed (300) 2. TD (chlorthalidone) (+ other diuretics if needed) (283)	blood pressure SBP / DBP major CVD event nonfatal/fatal stroke major CHD event all cause mortality	-9.8 / -2.2 mm Hg RR 0.66 (0.46-0.94) RR 0.78 (0.45-1.34) RR 0.44 (0.25-0.77) RR 0.74 (0.46-1.18)

ACE=Angiotensin Converting Enzyme Inhibitor; ARB=angiotensin II receptor blocker; BB=beta-blocker; CCB=calcium channel blocker; TD=thiazide diuretic

C. Intensive lipid control

Armitage 2004 [17]	review	summary of results from large statin trials in diabetic patients intervention versus control	LDL reductions in statin trials (AFCAPS/TexCAPS, ALLHAT-LLT, HPS, ASCOT-LLA, 4S, CARE, LIPID, WOSCOPS) risk reduction in first major coronary event (4S, CARE, LIPID) % with major coronary event in 5-6 years (4S, CARE, LIPID)	0.6-1.1 mmol/l risk reduction 27% 19% versus 25%

Study Duration of follow-up	Population characteristics at baseline	Intervention (number of participants)	Outcome measures	Results Intervention versus control
Vijan 2004 [18]	meta-analysis "lipid-lowering therapy in type 2 diabetes" statins: 10 studies gemfibrozil: 2 studies	1. diabetes patients without CVD: 6 studies: AFCAPS/TexCAPS, ALLHAT-LLT, HHS, HPS, PROSPER, ASCOT-LLA mean duration of follow-up 4.3 year 2. diabetes patients with CVD: 8 studies: 4S, CARE, HPS, LIPID, LIPS, Post-CABG, PROSPER, VA-HIT mean follow-up 4.9 year	LDL change CVD event (cardiovascular mortality MI stroke) absolute risk reduction CVD event number needed to treat to prevent one CVD event	0.1-1.0: 3 studies, > 1.0 mmol/l: 10 studies 1. 0.78 (0.67-0.89) / 2. 0.76 (0.59-0.93) 1. 0.03 (0.01-0.04) / 2. 0.07 (0.03-0.12) 1. 35 / 2. 14
CARDS 2004 [19] Follow-up 4 year	♂: 68% type 2 diabetes with CVD risk factor LDL <4.14 mmol/l 40-75 year mean age 62	1. placebo (1410) 2. statin (atorvastatin) (1428)	CVD event (acute CHD event, revascularisation or stroke) CHD event stroke coronairy revascularisation total death	-37%* (1.54 versus 2.46/100 py at risk) -36%* -48%* -31%ns -27% nns
ASCOTT_LLA 2003 [20] Follow-up 3 year	♂: 81% diabetes with hypertension and high CVD risk total cholesterol < 6.5 40-79 year mean age 63	1. placebo (1274) 2. statin (atorvastatin) (1258)	total cholesterol / LDL (year 1) total cholesterol / LDL (year 3) non fatal MI or fatal CHD	-1.3 mmol/l / -1.2 mmol/l* -1.0 mmol/l / -1.0 mmol/l* 0.84 (0.55-1.29)
Heart Protection Study (HPS) 2003 [21] Follow-up 5 year	♂: 70% 5963 diabetes 40-80 year mean age 62	1. placebo 2. simvastatin 40 mg/dag	total cholesterol / triglycerides HDL/LDL major coronary event (non-fatal MI or coronary death) major vascular event (major coronary event, stroke or revascularisation)	-1.1 mmol/l / -0.3 mmol/l + 0.01 / -0.9 mmol/l -27%* -22%*

Study Duration of follow-up	Population characteristics at baseline	Intervention (number of participants)	Outcome measures	Results Intervention versus control
Huang 2001 [1] Follow-up 4 to 6 year	meta-analyses lipid lowering therapy in diabetic patients ♂: 70-100% mean age 49-64	7 studies: Helsinki Heart, AFCAPS/TexCAPS, 4S, CARE, LIPID, Post-CABG, VA-HIT primary prevention: (2 studies) secondary prevention: (5 studies) statines (5 studies) gemfibrozil (2 studies)	total cholesterol LDL / HDL cholesterol triglyceride cardiac event cardiac events (primary) cardiac event (secondary) CVD-death (secondary) MI (secondary) stroke (secondary)	-0.6 mmol/l * -0.7mmol/l / + 0.05 mmol/l * -0.9 mmol/l * RR 0.75 (0.61-0.93) RR 0.44 (0.17-1.20) RR 0.77 (0.62-0.96) RR 0.80 (0.53-1.20) RR 0.60 (0.41-0.87) RR 0.74 (0.44-1.25)
Sacks 2000 [22]	pooled analysis of diabetic patients in WOSCOPS (n=76) CARE (n=586) and LIPID (n=782)	1. placebo 2. pravastatin 40 mg/day	death CVD or non-fatal MI	risk reduction 19% (-2 tot 36)
SENDCAP study 1998 [23] Follow-up 3 year	♂: 71% type 2 diabetes 35-65 year mean age 51	1. placebo + usual care (83) 2. bezafibrate 400 mg/day + usual care (81)	triglyceride HDL LDL total cholesterol definite CHD event (event rate)	-32.5% versus +4.1%* +6.4% versus -2.0%* -9.6% versus +0.6% ns -7.4% versus -0.3%* 22.6% versus 7.4% *
D. Weight management				
Norris 2004 [24]	Meta-analysis “effects of pharmacotherapy on weight reduction in type 2 diabetes” mean age 55 year	1. fluoxetine, 6 studies n=296, follow-up 24-30 weeks 2. orlistat, 4 studies n=1,475, follow-up 52-57 weeks 3. sibutramine, 4 studies n=460, follow-up 12-26 weeks	weight reduction reduction in HbA1c	1. 5.1 kg * 2. 2.6 kg * 3. 4.5 kg * 1. 1.0% * 2. 0.4% * 3. 0.7

Study Duration of follow-up	Population characteristics at baseline	Intervention (number of participants)	Outcome measures	Results Intervention versus control
E. Multifactorial intervention				
Steno-2 study 2003 [25] Follow-up 8 year	♂: 74% type 2 diabetes median duration 6 year with micro-albuminuria mean age 55	1.conventional treatment (n=80) 2.intensive treatment (n=80) behavioral and phamacological focused on overweight, physical activity, smoking, hyperglycaemy, hypertension, dyslipidemia, microalbuminuria	BMI male/female SBP / DBP tot chol / LDL chol HDL chol / triglyceride HbA1c CVD event (HR)	+0.7 versus +0.4 /+2.3 versus +1.3 -14 versus –3 * / -12 versus –8 * -50 versus –3 * / -47 versus –13 * 6 versus 7 / -41 versus + 9 * -0.5 versus +0.2 * 0.47 *

VA-CSDM=Veterans Affairs Cooperative study on glycaemic control and complications in Type 2 Diabetes Mellitus; UKPDS=UK Prospective Diabetes Study; RENAAL=Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; IRMA-2=IRbesartan in patients with type 2 diabetes and MicroAlbuminuria; ABCD=Appropriate Blood Pressure Control in Diabetes; HOPE=Heart Outcomes Prevention Evaluation;Syst-Eur=Systolic Hypertension in Europe Trial Investigators; CARDS=Collaborative AtoRvastatin Diabetes Study; ASCOTT-LLA= Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm; SENDCAP= St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention; Steno-2= Intensified multifactorial intervention and cardiovascular outcome in type 2 diabetes; CHD=coronary heart disease; CVD=cardio vascular disease; MI=myocardial infarction; CVA=cardiovascular accident; RR=relative risk; HR=hazard ratio; BMI=body mass index; dm=diabetes mellitus; IFG=impaired fasting glucose; FPG=fasting plasma glucose; py=person years; ns=not significant; SBP=systolic blood pressure; DBP=diastolic blood pressure; HDL=high-density lipoprotein; LDL=low-density lipoprotein
* significant difference between groups

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