



Cardiovascular consequences of diabetes mellitus

ISBN 90-9012737-2

Cover design: Christine Hooft

Layout: Bon Mot

Printed by: Print Partners Ipskamp, Enschede

© C.A. Baan, 1999

No part of this thesis may be reproduced, stored in a retrieval system or transmitted in any form or by any means, without permission of the author, or, when appropriate, of the publishers of the publications.

Cardiovascular consequences of diabetes mellitus

Cardiovasculaire consequenties van diabetes mellitus

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof.dr. P.W.C. Akkermans, M.A.
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 22 september 1999 om 11:45 uur

door

Caroline Astrid Baan

geboren te Delft

Promotiecommissie

- Promotores : Prof.dr. P.J. van der Maas
Prof.dr.ir. D. Kromhout
- Co-promotores : Dr. J.J. Barendregt
Dr.ir. E.J.M. Feskens
- Overige leden : Prof.dr. A.F. Casparie
Prof.dr. L.J. Gunning-Schepers
Prof.dr. M.G.M. Hunink

Acknowledgements

Financial support for the publication of this thesis by the Netherlands Heart Foundation and the Netherlands Diabetes Fund is gratefully acknowledged. Additional financial support by the Department of Public Health is gratefully acknowledged.

Contents

Part I

BACKGROUND AND RESEARCH QUESTIONS

1. General introduction 3

Part II

RISK FACTORS FOR DIABETES MELLITUS

2. Obesity and physical inactivity as risk factors for diabetes mellitus 19
3. Physical activity in elderly subjects with impaired glucose tolerance or newly diagnosed diabetes mellitus 41
4. Performance of a predictive model for identifying undiagnosed diabetes mellitus in a health care setting 59

Part III

BASIC ELEMENTS OF DIABETES EPIDEMIOLOGY:

INCIDENCE, PREVALENCE, MORTALITY OF DIABETES MELLITUS IN THE NETHERLANDS

5. Prevalence of diabetes mellitus in The Netherlands. A quantitative review 77
6. The burden of mortality of diabetes mellitus in The Netherlands 93
7. An indirect estimate of NIDDM incidence 105

Part IV

THE DIABETES – CARDIOVASCULAR DISEASE MODEL

8. Estimating the age-specific cardiovascular morbidity and mortality of diabetes mellitus in The Netherlands 121

Part V

APPLICATIONS

9. Increasing cardiovascular comorbidity among diabetic subjects 147
10. Effect of primary prevention of diabetes mellitus on cardiovascular morbidity and mortality 163

Part VI

DISCUSSION AND SUMMARY

11. General discussion	187
12. Summary	205
13. Samenvatting	213
 Dankwoord	 221
Curriculum vitae	225

Publications and manuscripts reprinted in this thesis

Chapter 3

Baan, CA; Stolk, RP; Grobbee, DE; Witteman, JCM; Feskens, EJM. Physical activity in elderly subjects with impaired glucose tolerance or newly diagnosed diabetes mellitus. *Am J Epidemiol* 149:219-227,1999

Chapter 4

Baan, CA; Ruige, JB; Stolk, RP; Witteman, JCM; Dekker JM; Heine RJ; Feskens, EJM. Performance of a predictive model for identifying undiagnosed diabetes mellitus in a health care setting. *Diabetes Care* 22: 213-219,1999

Chapter 5

Baan, CA; Bonneux, L; Ruwaard, D; Feskens, EJM. Prevalence of diabetes mellitus in The Netherlands. A quantitative review. *Eur J Public Health* 8:210-216, 1998

Chapter 6

Baan, CA; Nusselder, WJ; Barendregt, JJ; Ruwaard, D; Bonneux, L; Feskens, EJM. The burden of mortality of diabetes mellitus in The Netherlands. *Epidemiology* 10:184-187, 1999

Chapter 7

Barendregt, JJ; Baan, CA; Bonneux, L. An indirect estimate of NIDDM incidence. *Submitted for publication*

Chapter 8

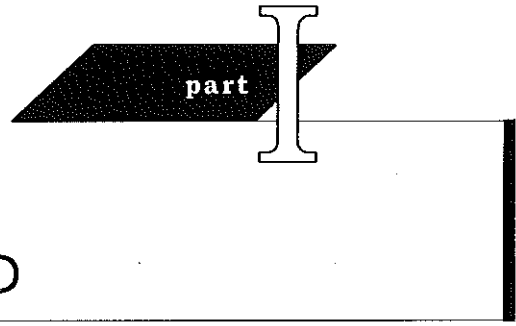
Baan, CA; Barendregt, JJ; Bonneux, L. Estimating the age-specific cardiovascular morbidity and mortality of diabetes mellitus in the Netherlands. *Submitted for publication*

Chapter 9

Baan, CA; Barendregt, JJ; Bonneux, L; Feskens, EJM. Increasing cardiovascular comorbidity among diabetic subjects. *Submitted for publication*

Chapter 10

Baan, CA; Barendregt, JJ; Bonneux, L; Feskens, EJM. The impact of obesitas and physical inactivity as risk factors for diabetes and cardiovascular disease: potentials for prevention. *Submitted for publication*



BACKGROUND AND RESEARCH QUESTIONS

General introduction

DIABETES MELLITUS: AN INTRODUCTION

Diabetes mellitus comprises a clinically and genetically heterogeneous group of disorders that have one common feature: abnormally high levels of glucose in the blood. The most common form is non-insulin dependent diabetes mellitus (NIDDM); about 80-90% of all diabetic patients has NIDDM. Other forms of diabetes are insulin-dependent diabetes mellitus (IDDM) and gestational diabetes.

In 1985, the World Health Organization (WHO) defined new criteria for diabetes mellitus based upon the oral glucose tolerance test (OGTT) (1). During the OGTT test the fasting glucose level is measured, followed by the measurement of the glucose level, 2 hours after an intake of 75 g glucose. Depending on whether the glucose levels have been measured in the blood, plasma or serum, cut-off values have been defined (Table 1). Three diagnoses can be made: normal glucose tolerance, impaired glucose tolerance (IGT) or diabetes mellitus.

The OGTT is often used in epidemiological research. However, in clinical practice, the diagnosis diabetes is usually based on the presence of the classic symptoms of diabetes (polyuria, hunger, thirst, weight loss, tiredness) combined with a single abnormal blood glucose level, or on two abnormal levels without complaints measured on different occasions.

In 1995, an expert group of the American Diabetes Association (ADA) started to develop a new classification system for diabetes mellitus, based upon current knowledge (2). They proposed a system founded on the disease aetiology

Table 1
Diagnostic values for the oral glucose tolerance test (1)

	Glucose concentration (mmol/l)	
	Whole blood	Plasma
	Capillary	Venous
Diabetes mellitus		
Fasting value	≥ 6.7	≥ 7.8
2 hr value	≥ 11.1	≥ 11.1
Impaired glucose tolerance (IGT)		
Fasting value	< 6.7	< 7.8
2 hr value	7.8-11.1	7.8-11.1
Normal glucose tolerance		
Fasting value	< 6.7	< 7.8
2 hr value	< 7.8	< 7.8

instead of, as is presently the case, mainly on the type of treatment used. They also suggested eliminating the terms "insulin dependent diabetes mellitus" and "non-insulin dependent diabetes mellitus" as they have been confusing and have frequently resulted in classifying the patient based on treatment rather than aetiology. Instead of "IDDM" and "NIDDM", the terms "type 1 diabetes" and "type 2 diabetes" should be used. The topic is still very much under discussion (2-4). We have used the old classification and criteria for the studies in this thesis.

Non-insulin dependent diabetes is characterised by initial insulin resistance and hyperinsulinemia with secondary beta-cell failure. At the time of diagnosis, most patients can be treated with a diet and/or oral hypoglycaemic agents, although many patients ultimately need insulin injections in order to maintain adequate glycaemic control. Subjects with diabetes have a high risk for several complications, such as retinopathy, nephropathy, diabetic foot and cardiovascular complications. The occurrence of the symptoms and complications can severely reduce life expectancy and quality of life.

By far the largest burden of comorbidity in patients with NIDDM is caused by cardiovascular complications. Subjects with diabetes have a 2-5 times higher risk of developing coronary heart disease or stroke (5-7), while case-fatality is also significantly higher (8-10). This risk is highly age-dependent, with large relative risks at younger ages, which decrease with age. While women suffer less and at a later age from cardiovascular diseases, this protective effect is eliminated in diabetes (11, 12). Part of the increased risk is due to the fact that diabetes clusters with several other cardiovascular risk factors, such as obesity, hypertension and hypercholesterolaemia (6, 13). Yet even after adjustment for these risk factors, diabetic subjects continue to have a higher risk of CVD (6, 14).

Several risk factors for developing NIDDM have been identified, some modifiable and some not. One of the non-modifiable risk factors is age. In The Netherlands, the incidence of diabetes increases with age by about 7% per year for men and about 7.7% per year for women (15). Next to age, the presence of NIDDM in a family member is an established risk factor for NIDDM. Subjects with a first degree relative with diabetes mellitus have about a 3 times greater chance of developing diabetes mellitus compared to someone without a relative with diabetes mellitus (16). However, migrant studies have shown that genetic factors as such are not decisive for developing NIDDM. Prevalence rates of NIDDM in groups of emigrants are comparable with those of the host country, which implies a complex interaction of genetic and environmental factors (17).

Obesity is the most important modifiable risk factor for diabetes mellitus (18-23). At the onset of the disease, about 80% of all subjects are overweight

(18). Different aspects of obesity play a role in the association obesity and diabetes mellitus, such as the level of obesity, the duration of obesity (24, 25) or the location of the body fat, expressed in a waist-to-hip ratio (WHR) (26, 27).

Obesity causes insulin resistance, but in obese subjects with normal beta-cell function, the beta-cells secrete sufficient insulin to overcome insulin resistance and prevent the occurrence of diabetes. Diabetes is thought to develop when the increased insulin resistance is accompanied by beta-cell dysfunction through exhaustion of the beta-cells or other internal and external causes (19, 22).

Another known risk factor for NIDDM is physical inactivity (28-31). Physical activity has an effect on the onset of diabetes mellitus, independent from other risk factors, due to increased insulin sensitivity of the muscle cells and adipose tissues. Besides, physical activity may lead to weight reduction and thus also influence the risk of developing NIDDM (18, 32).

Recent studies indicate that smoking and alcohol may also be risk factors for diabetes, although the results are not consistent (33-38). It is assumed that smoking reduces the glucose tolerance and increases insulin sensitivity (39). Alcohol consumption has been suggested as a possible independent risk factor for NIDDM, either because of its effects on the liver and pancreas, or simply because additional energy results in increased weight and the formation of abdominal adipose tissue. Also dietary factors have proven to play a role, independent of their impact on obesity (40). These areas requires further investigation.

The onset of NIDDM is generally gradual, which implies that many subjects go through the process of developing diabetes without knowing it. Several studies have shown that about 50% of all diabetic subjects are undiagnosed (41-44). Although these subjects do not have severe complaints, they have an increased risk of complications. At the time of diagnosis, 10-20% of the subjects have retinopathy (45, 46). Based on the extrapolation of data on the prevalence of retinopathy, it has been estimated that onset of NIDDM may occur as long as 4-7 years before the clinical diagnosis of NIDDM (45). Microvascular complications of diabetes begin to develop during this period before clinical diagnosis, and the risk for macrovascular complications is probably also increased (47, 48).

The prevalence of known diabetes in adults aged ≥ 20 years in the developed countries was an estimated 6% in 1995 and is expected to rise to 7.5% by the year 2025 (49). This means that the number of adults with diabetes in the developed countries will rise from 51 million in 1995 to 72 million in 2025. In The Netherlands, the prevalence rates vary between 7-14 per 1000 for women

and between 5-15 per 1000 for men in the age group 30-74 years (43, 44, 50-59). Incidence estimates in the few Dutch studies performed vary between 1.5-4 per 1000 (50, 51, 60, 61).

RATIONALE FOR THIS THESIS

Given the complexity of the onset of non-insulin-dependent diabetes mellitus and its complications, it is difficult to estimate the burden of the disease. Comprehensive information on basic epidemiological elements, such as incidence, prevalence and mortality of diabetes are scarce, incomplete or inconsistent with other studies. The combination of changes in life style variables (such as obesity and physical inactivity) and changes in the natural history of complications of diabetes (such as cardiovascular disease) through medical interventions, produces a variety of possible changes in diabetes incidence, prevalence and mortality.

The objectives of this thesis are:

- to describe the incidence, prevalence and mortality of diabetes mellitus, and the relation with its risk factors and its cardiovascular complications;
- to study the effects of trends in cardiovascular diseases on the occurrence of diabetes, and the effects of preventive strategies for diabetes on its cardiovascular complications.

We are interested in type 2 diabetes, as this is the most common form of diabetes. However in most studies no clear distinction is made in the type of diabetes. All analysis in this thesis started from age 30 years. The incidence and prevalence of NIDDM are by far the greatest at older ages (62, 63). The percentage of insulin-dependent diabetes patients diagnosed before age 30 years, but who were older than 30 years when the studies carried out, is expected to be low and decreased with age. In a prevalence study in which a discrimination could be made between NIDDM and IDDM based on age of diagnosis and treatment with insulin, the percentage of IDDM patients decreased from 30% at age 30 years to less than 10% at age 80 years (52). Therefore, the results of our analysis mainly concern NIDDM patients.

As cardiovascular complications are by far the most important complications in type 2 diabetes mellitus, we have confined ourselves to the association between diabetes and cardiovascular diseases. We concentrated on obesity and physical inactivity as risk factors for diabetes, as they are the two main modifiable risk factors for the onset of diabetes.

We opted for an approach in which a simulation model was used to answer the two research questions. A disease model can be helpful in making sense out of many sources of information by combining knowledge from various sources. In addition, a simulation model provides the opportunity to estimate the effect of changes in risk factor for diabetes mellitus all through the cardiovascular disease epidemiology.

OUTLINE OF THE THESIS

The thesis consists of different parts. Each part represents a further step towards the development of a disease model.

First, I propose to discuss the two main modifiable risk factors for diabetes mellitus, obesity and physical inactivity. The associations between obesity, physical inactivity and the onset of NIDDM are reviewed in chapter 2. This review must be interpreted in the context of the data needed for the model. Input for the model comprises the relative risks of obesity and physical activity on the incidence of diabetes mellitus as well as the prevalence of these risk factors in The Netherlands. As I will estimate in chapter 10, the effect of various preventive strategies as well as the effect of secular trends in the risk factors, the observed trends of the two risk factors and the limited number of trials on primary prevention of diabetes by reduction of body weight and/or increasing physical activity will also be described.

Concerning physical inactivity, most studies to date have focussed on the association with diabetes in middle-aged populations. Only two studies have been conducted in elderly subjects (43, 64). In both studies, physical activity was presented as a single index and no information was reported about specific types of physical activity or the intensity of the activity. In chapter 3 the association between physical activity and NIDDM is estimated in an elderly population, the Rotterdam Study. We estimated the effect of physical activity on the presence of newly diagnosed diabetes mellitus, and specified the intensity or type of activity, which showed the largest association.

In chapter 4, we investigated whether these risk factors could be used to identify subjects with an elevated risk of having undiagnosed diabetes mellitus. In a sub-sample of the Rotterdam Study, three predictive models were developed which contained various levels of required information. The first predictive model contained information routinely collected by the general practitioner, such as gender, age and obesity. The second predictive model also included additional questions related to physical activity, family history and cardiovascular

symptoms as well as smoking habits. A third model included variables that had to be obtained by a physical examination.

The basic epidemiological elements of a disease are incidence, prevalence and mortality rates. Two out of three parameters identify the third in an incidence-prevalence-mortality (IPM) model. However, in the case of diabetes mellitus none of the three parameters is well identified. The third part of this thesis describes how the input data of the basic epidemiological elements of diabetes are estimated.

It turned out to be difficult to determine the prevalence of diabetes mellitus in The Netherlands, as the many studies reporting prevalence rates showed different results. Chapter 5 describes how we arrived at estimates of age-specific prevalence rates of diabetes for men and women in The Netherlands, based upon a pooled analysis of all available prevalence studies.

A valid estimate of diabetic mortality can not be derived from cause-of-death statistics (65, 66). These statistics are based on the concept of a single cause, termed the underlying cause of death. Diabetes is associated at the time of death with other conditions, in particular circulatory and renal disease. It is often difficult to determine the contribution of diabetes mellitus to the "web of causation" leading to death. But the coding may also promote difficulties in interpretation. Coding practices differ between countries and over time, which explain 35% of the variation in the published diabetes mortality rates (67). In chapter 6, we combine the estimated prevalence of diabetes with published relative risks for all cause mortality of diabetes with mortality data from Statistics Netherlands. This results in an estimate of the excess mortality related to diabetes and the loss of life expectancy attributable to diabetes.

As the onset of NIDDM is gradual and many people with diabetes are undiagnosed, the incidence of NIDDM is difficult to estimate. Estimates of incidence become highly dependent on factors other than the true occurrence of disease: patient and doctor awareness and level of case finding. Chapter 7 describes how the incidence is derived from the prevalence estimate and mortality of diabetes in an incidence, prevalence, mortality model (IPM-model). The estimates are compared with the results of the few available Dutch studies.

The fourth part of this thesis describes the diabetes-cardiovascular diseases model. Among the basic data needed are those on cause-specific mortality. However, a valid estimate of diabetes mortality can not be obtained from the cause-of-death registration (65). The underlying cause of death of a diabetic subject who dies of a heart attack will either be registered as a myocardial infarction or diabetes. This not only leads to an underregistration of diabetes mortality, as explained in chapter 6, but also precludes a valid estimate of the

cardiovascular mortality rate among diabetic subjects. In chapter 8, cardiovascular mortality and morbidity among diabetic subjects is estimated, by using a multi-state life table. This is an extension of the standard life table that distinguishes not just between 'alive' and 'dead', but allows for additional states like 'alive, healthy', 'alive, with heart disease', etc (68). In addition to cause-specific mortality rates, the multi-state life table comprises also incidence, prevalence and case-fatality rates.

Part V of the thesis consists of two applications of the diabetes-cardiovascular disease model developed. Recent studies from various countries have reported increases in diabetes prevalence (69-72). There may be several reasons for the increase of prevalence, one of them being improved survival of persons with diabetes. Since the early 1970s, mortality from cardiovascular diseases in the total population has decreased in The Netherlands, as in many other countries (73-77). As cardiovascular diseases are responsible for more than 60% of the deaths of diabetic subjects (5, 78, 79), changes in incidence and survival of cardiovascular diseases can be expected to have an effect on the diabetes prevalence and comorbidity. In Chapter 9, we examined whether the changes in epidemiology of coronary heart disease and stroke can explain the observed increase in diabetes prevalence.

In chapter 10, the effect of several intervention strategies for primary prevention of diabetes on the burden of cardiovascular diseases in the total population is estimated. As obesity and physical inactivity are major risk factors for the onset of diabetes mellitus, both were selected as targets for primary prevention of diabetes. In addition, the effect of secular trends in obesity and physical inactivity on diabetes related cardiovascular complications is estimated.

Finally, part VI contains a general discussion and summary of this thesis. Chapter 11 concludes this thesis with a general discussion on the methods used, the main results, the applications and suggestions for further research. In chapter 12 and 13, a summary of the thesis is given.

References

1. World Health Organization. *Diabetes mellitus: report of a study group*. Geneva: WHO, 1985.
2. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 22 (supplement 1):S5-S19, 1999

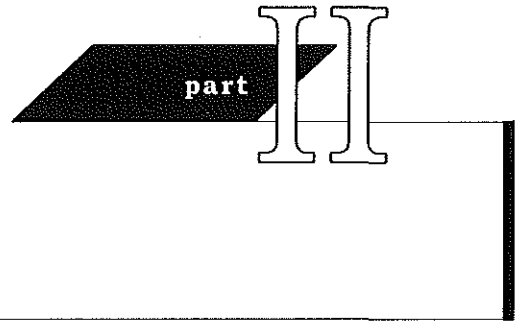
3. DECODE Study Group: Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. *Br Med J* 317:371-375, 1998
4. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Comparison of diabetes diagnostic categories in the US population according to 1997 American Diabetes Association and 1980-1985 World Health Organization diagnostic criteria. *Diabetes Care* 20:1859-1862, 1997
5. Panzram G: Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 30:123-131, 1987
6. Wingard DL, Barrett-Connor, ed. *Heart Disease and Diabetes*. 2 ed. Bethesda: NIH, 1995:429-448. (National Diabetes Data Group, ed. *Diabetes in America*;)
7. Bell DS: Stroke in the Diabetic patient. *Diabetes Care* 17:213-219, 1994
8. Benderly M, Behar S, Reicher-Reiss H, Boyko V, Goldbourt U: Long-term prognosis of women after myocardial infarction. *Am J Epidemiol* 146:153-160, 1997
9. Behar S, Boyko V, Reicher-Reiss H, Goldbourt U: Ten-year survival after acute myocardial infarction: comparison of patients with and without diabetes. *Am Heart J* 133:290-296, 1997
10. Currie CJ, Morgan CL, Gill L, Stott NCH, Peters JR: Epidemiology and costs of acute hospital care for cerebrovascular disease in diabetic and nondiabetic populations. *Stroke* 28:1142-1146, 1997
11. Barrett-Connor EL, Wingard DL: Sex differential in ischemic heart disease mortality in diabetics: a prospective population-based study. *Am J Epidemiol* 118:489-496, 1983
12. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SH: Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA* 265:627-631, 1991
13. Wingard DL, Barrett-Connor E, Criqui MH, Suarez L: Clustering of heart disease risk factors in diabetic compared to nondiabetic adults. *Am J Epidemiol* 117:19-26, 1983
14. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR: Diabetes, blood lipids and the role of obesity in coronary heart disease risk for women. The Framingham Study. *Ann Intern Med* 87:393-397, 1977
15. Baan CA, Bonneux L, Ruwaard D, Feskens EJM: The prevalence of diabetes mellitus in The Netherlands: a quantitative review. *Eur J Publ Health* 8:210-216, 1998
16. Helmrich SP, Ragland DD, Leung RW, Paffenbarger RS: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Eng J Med* 325:147-152, 1991
17. Elbein SC, Hoffman MD, Bragg KL, Mayorga RA: The genetics of NIDDM. *Diabetes Care* 17:1523-1533, 1994
18. Barrett-Connor EL: Epidemiology, obesity and non-insulin-dependent diabetes mellitus. *Epidemiol Rev* 11:172-181, 1989
19. Golay A, Felber JP: Evolution from obesity to diabetes. *Diabete Metab* 20:3-14, 1994
20. Haffner SM, Stern MP, Mitchell BD, Hazuda HP, Patterson JK: Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity and body-fat distribution. *Diabetes* 39:283-288, 1990

21. Morris RD, Rimm DL, Hartz AJ, Kalkhoff RK, Rimm AA: Obesity and heredity in the etiology of non-insulin-dependent diabetes mellitus in 32,662 adult white women. *Am J Epidemiol* 130:112-121, 1989
22. Turner RC: The role of obesity in diabetes. *Int J Obesity* 16:S43-S46, 1992
23. Mykkänen L, Laakso M, Uusitupa M, Pyörälä K: Prevalence of diabetes and impaired glucose tolerance in elderly subjects and their association with obesity and family history of diabetes. *Diabetes Care* 13:1099-1105, 1990
24. Everhart JE, Pettitt DJ, Bennett PH, Knowler WC: Duration of obesity increases the incidence of NIDDM. *Diabetes* 41:235-240, 1992
25. Sakurai Y, Teruya K, Shimada N, et al.: Association between duration of obesity and risk of non-insulin-dependent diabetes mellitus. The Sotetsu Study. *Am J Epidemiol* 149:256-260, 1999
26. Stern MP, Haffner SM: Body fat distribution and hyperinsulinemia as risk factors for diabetes and cardiovascular disease. *Atherosclerosis* 6:123-130, 1986
27. Qiao Q, Keinänen-Kiukaanniemi S, Kivela S: Association of waist to hip ratio with diabetes among middle-aged subjects with impaired glucose tolerance. *Eur J Publ Health* 7:106-108, 1997
28. Blair SN, Horton E, Leon AS, et al.: Physical activity, nutrition and chronic disease. *Med Sci Sports exerc* 28:335-349, 1996
29. Blair SN, Kohl HW, Gordon NF: How much physical activity is good for health? *Annu Rev Publ Health* 13:99-126, 1992
30. Pescatello LS, DiPietro L: Physical activity in older adults. An overview of health benefits. *Sports medicine* 15:353-364, 1993
31. Laws A, Reaven GM: Physical activity, glucose tolerance and diabetes in older adults. *Annals of Behavioural Medicine* 13:125-132, 1991
32. Horton ES: Role and management of exercise in diabetes mellitus. *Diabetes Care* 11:201-211, 1988
33. Rimm EB, Manson JE, Stampfer MJ, et al: Cigarette smoking and the risk of diabetes in women. *Am J Public Health* 83:211-214, 1993
34. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC: Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *Br Med J* 310:555-559, 1995
35. Feskens EJM, Kromhout D: Cardiovascular risk factors and the 25-year incidence of diabetes mellitus in middle-aged men. The Zutphen Study. *Am J Epidemiol* 130:1101-1108, 1989
36. Ford ES, Malarcher AM, Herman WH, Aubert RE: Diabetes Mellitus and cigarette smoking. Findings from the 1989 National Health Interview Survey. *Diabetes Care* 17:688-692, 1994
37. Stampfer MJ, Colditz GA, Willett WC, et al: A prospective study of moderate alcohol drinking and risk of diabetes in women. *Am J Epidemiol* 128:549-558, 1988
38. Holbrook TL, Barrett-Connor EL, Wingard DL: A prospective population-based study of alcohol use and non-insulin-dependent diabetes mellitus. *Am J Epidemiol* 132:902-909, 1990
39. Frati AC, Iniestra F, Ariza CR: Acute effect of cigarette smoking on glucose tolerance and other cardiovascular risk factors. *Diabetes Care* 19:112-118, 1996

40. Feskens E, van Dam R: Dietary fat and the etiology of type 2 diabetes: an epidemiological perspective. *Nutrition, Metabolism and Cardiovascular Diseases*, in press
41. King H, Rewers M: Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. *Diabetes Care* 16:157-177, 1993
42. Harris MI: Undiagnosed NIDDM: clinical and public health issues. *Diabetes Care* 16:642-653, 1993
43. Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Heine RJ: Prevalence and determinants of glucose intolerance in a Caucasian population. The Hoorn Study. *Diabetes Care* 18:1270-1273, 1995
44. Stolk RP, Pols HAP, Lamberts SWJ, Jong de PTVM, Hofman A, Grobbee DE: Diabetes mellitus, impaired glucose tolerance and hyperinsulinemia in an elderly population. The Rotterdam Study. *Am J Epidemiol* 145:24-32, 1997
45. Harris MI, Klein R, Welborn TA, Knuiman MW: Onset of NIDDM occurs at least 4-7 years before clinical diagnosis. *Diabetes Care* 15:815-819, 1992
46. Klein R: Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258-268, 1995
47. Eschwege E, Richard JL, Thibault N, et al.: Coronary heart disease mortality in relation with diabetes, blood glucose and plasma insulin levels. The Paris Prospective study, ten years later. *Hormone and Metab Res* 15 (Suppl):41-46, 1985
48. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263:2893-2898, 1990
49. King H, Aubert RE, Herman WH: Global burden of diabetes, 1995-2025. *Diabetes Care* 21:1414-1431, 1998
50. Steering Committee on Future Health Scenarios: *Chronische ziekten in het jaar 2005. Volume 1: scenario's van diabetes mellitus 1990-2005. (Chronic diseases in the year 2005. Volume 1: scenarios on diabetes mellitus 1990-2005)*. Dordrecht, Boston, London Kluwer Academic Publishers, 1991
51. van de Lisdonk EH, Bosch WJHM, Huygen FJA, Lagro-Jansen ALM, ed. *Ziekten in de huisartspraktijk (Diseases in the general practice)*. Utrecht: Wetenschappelijke uitgeverij Bunge, 1990:342.
52. Verhoeven S. *Behandeling, controle en metabole instelling van patienten met diabetes mellitus type II en de prevalentie van late complicaties bij deze patienten (Treatment, follow-up and metabolic regulation of patients with diabetes mellitus type II and the prevalence of late complications in this group of patients)*. Erasmus University Rotterdam, 1989
53. Cromme PHV, Eijk van JTM, Veen van der EA, Nauta JJP, Knottnerus JA: Glucose-intolerantie bij ouderen in Nederland; het Twello-onderzoek (Glucose tolerance in an elderly Dutch countryside population: the Twello Study). *Ned Tijdschr Geneesk* 139:2558-2563, 1995
54. Meyboom-de Jong B. *Bejaarde patiënten: een onderzoek in 12 huisartsenpraktijken (Elderly patients: a research in 12 general practices)*. University Groningen, 1989
55. Lamberts H, Brouwer HJ, Mohrs J. *Reasons for encounter- & episode- & process-oriented standard output from the Transition project. Part 1 and 2*. Amsterdam: Department of General Practice, 1991.

56. Central Bureau of Statistics. Gezondheidsenquêtes (Health interview surveys), 1989-1993.
57. Mackenbach JP, van de Mheen H, Stronks K: A prospective cohort investigating the explanation of socio-economic inequalities in health in The Netherlands. *Soc Sci Med* 38:299-308, 1994
58. Deeg DJH, Westendorp - de Serière M: *Autonomy and well being in the aging population I: report from the Longitudinal Aging Study Amsterdam 1992-1993*. Amsterdam VU University Press, 1994
59. Feskens EJM, Tuomilehto J, Stengard JH, Pekkanen J, Nissinen A, Kromhout D: Hypertension and overweight associated with hyperinsulinaemia and glucose tolerance: a longitudinal study of the Finnish and Dutch cohorts of the Seven Countries Study. *Diabetologia* 38:839-847, 1995
60. Lamberts H: *Morbidity in general practice. Diagnosis related information from the Monitoring Project*. Utrecht Huisartsenpers, 1984
61. van der Velden J, de Bakker DH, Claessens AAMC, Schellevis FG: *Een nationale studie naar ziekten en verrichtingen in de huisartspraktijk. Basisrapport: Morbiditeit in de huisartsenpraktijk (A national study for diseases and operations in the general practice. Morbidity in the general practice)*. Utrecht Netherlands Institute of Primary Health Care, 1991
62. Herman WH, Sincock P, Brenner E, et al: An epidemiologic model for diabetes mellitus: incidence, prevalence and mortality. *Diabetes Care* 7:367-371, 1984
63. Laakso M, Pyörälä K: Age of onset and type of diabetes. *Diabetes Care* 8:114-117, 1985
64. Rodriguez BL, Curb JD, Burchfield CM, et al.: Impaired glucose tolerance, diabetes and cardiovascular disease risk factor profiles in the elderly. *Diabetes Care* 19:587-590, 1996
65. Jouglé E, Papoz L, Balkau B, Maguin P, Hatton F: Death certificate coding practices related to diabetes in European countries - the EURODIAB subarea C study. *Int J Epidemiol* 21:343-351, 1992
66. Mackenbach JP, Snels IAK, Friden-Kill LM: Diabetes mellitus als doodsoorzaak (Diabetes as a cause of death). *Ned Tijdschr Geneesk* 135:1492-1496, 1991
67. Fuller JH: Mortality trends and causes of death in diabetic patients. *Diabetes Metab* 19:96-99, 1993
68. Schoen R: *Modeling Multigroup populations*. New York and London Plenum Press, 1987
69. Neil HAW, Gatling W, Mather HM, et al.: The Oxford Community Diabetes Study: Evidence for an increase in the prevalence of known diabetes in Great Britain. *Diabetic Med* 4:539-543, 1987
70. Wetterhall SF, Olson DR, DeStefano F, et al: Trends in diabetes and diabetic complications, 1980-1987. *Diabetes Care* 15:960-967, 1992
71. Kenny SJ, Aubert RE, Geiss LS, ed. *Prevalence and incidence of non-insulin-dependent diabetes*. 2 ed ed. Bethesda: NIH, 1995. (National Diabetes Data Group, ed. Diabetes in America;)
72. Leibson CL, O'Brien PCO, Atkinson E, Palumbo PJ, Melton III LJ: Relative contributions of incidence and survival to increasing prevalence of adult-onset diabetes mellitus: a population-based study. *Am J Epidemiol* 146:12-22, 1997

73. Sprafka JM, Burke GL, Folsom AR, Luepker RV, Blackburn H: Continued decline in cardiovascular disease risk factors: results of the Minnesota Heart Survey 1980-1982 and 1985-1987. *Am J Epidemiol* 132:489-500, 1990
74. Demirovic J, Blackburn H, McGovern P, Sprafka JM, Doliszny K: Sex differences in coronary heart disease mortality trends: the Minnesota Heart Survey, 1970-1988. *Epidemiology* 4:79-82, 1993
75. Kuller LH, ed. *Stroke and diabetes*. 2 ed. Bethesda: NIH, 1995:449-456. (Group NDD, ed. *Diabetes in America*;)
76. Sytkowski PA, Agostino RB, Belanger A, Kannel WB: Sex and time trends in cardiovascular disease incidence and mortality: The Framingham Heart Study, 1950-1989. *Am J Epidemiol* 143:338-350, 1996
77. Bonneux L, Barendregt JJ, Van der Maas PJ: The new old epidemic of coronary heart disease. *Am J Public Health* 89:379-382, 1999
78. Moss SE, Klein R, Klein BEK: Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 81:1158-1162, 1991
79. Geiss LS, Herman WH, Smith PJ, ed. *Mortality in non-insulin-dependent diabetes mellitus*. 2 ed. Bethesda: NIH, 1995:233-258. (National Diabetes Data Group, ed. *Diabetes in America*;)



RISK FACTORS

FOR DIABETES MELLITUS

Obesity and physical inactivity as risk factors for diabetes mellitus

In this chapter, two risk factors for diabetes mellitus will be discussed: obesity and physical inactivity. The discussion must be interpreted in the context of the diabetes model we have developed and described in this thesis. Input for the model are relative risks for obesity and physical inactivity in relation to incidence of diabetes mellitus as well as the prevalence of these risk factors in The Netherlands. With the model we will estimate the effect of different preventive strategies (Chapter 10), as well as the effect of trends in these risk factors. Therefore, also the observed trends in the prevalence of obesity and physical inactivity will be summarised as well as the results of the limited number of trials on primary prevention of the diabetes by reducing body weight and/or increasing physical activity.

OBESITY

Definition

Of the several ways of estimating the total amount of body fat, body mass index is most frequently used. It is calculated by dividing weight (in kilograms) by squared height (in meters). The World Health Organisation (WHO) recommended the following classification for overweight (1) based upon the body mass index:

18.5-24.9 kg/m ²	: acceptable weight
25.0-29.9 kg/m ²	: degree I overweight
30.0-39.9 kg/m ²	: degree II overweight or obesity
≥ 40 kg/m ²	: degree III overweight or morbid obesity

This classification can be used for adults only; for children and young adolescents another index has to be used, which will not be described in this paper. For the elderly (70 years and older) it is not clear whether the above classification is applicable (2).

Relationship between obesity and diabetes mellitus

The results of 15 cohort studies confirm that there is a strong association between presence of overweight or obesity and the development of NIDDM (Table 1) (3-18). The studies differ in the way information on body mass index was obtained (self-report or measured height and weight) as well as how diabetes mellitus was defined (self-report or OGTT). Also the categories of body mass index, as well as the reference category used to estimate the relative risks, were different in all studies. This makes comparison of the relative risks difficult.

Still, a number of conclusions can be drawn from this table. All studies show an increase in risk of diabetes with an increase in body mass index. The relative risk for diabetes associated with body mass index ranges from 1.1 to 50.7 for men and from 1.9 to 93.2 for women, with the highest risks observed for the highest body mass index. On average, the effect of body mass index seems to be stronger in women than in men, although Njolstad showed that after adjustment for other risk factors the association attenuated in women more than in men (14).

In Table 1 only the age-adjusted relative risks are shown. Most studies also reported relative risks after adjustment for confounders, such as family history of diabetes, hypertension and physical inactivity. After adjustment for additional risk factors, the relative risks for obesity decreased, but remained high, indi-

Table 1

Obesity as risk factor for diabetes mellitus: an overview of the age-adjusted relative risks reported for men and women separately

Study (reference)	N	Age (yr.)	Follow up	Measurement DM	Measurement obesity	Categories BMI	Cases	RR
Men								
Former college men Pennsylvania (3)	26,446	38-56	16-50	self report	self report	<23,2 vs >23,2	384	1,5
Israeli IHD Study (4)	9,462	>40	5	non fasting OGTT	measured	<24 vs >27	373	2,5
Paris Protective Study (5)	7,362	43-54	4.4	OGTT	measured	< 24,5 24,5-27 ≥ 27	174	\$ 2.2 6.2
NUHI (6)	761	20-50	6-17	registered by GP	registered by GP	<27 vs >27		5.2
Göteborg (7)	792	54	13.5	OGTT	measured	I V	47	\$ 21.7
Zutphen Study (8)	841	40-59	25	clinical diagnosis	measured	<22.2 vs >25.8	58	2.4
Rancho Bernardo (9)	747	40-79	12	OGTT	measured	< 23 vs > 23		2.4
Rancho Bernardo (10)	747	40-79	10-15	OGTT	measured	per 3.3 kg/m ² increase	102	1.3
Veterans (11)	1,972	20-80	18	OGTT	measured	<24.59 vs >26.88	226	1.9
Health Professional's Follow-up Study (12)	51,529	40-75	5	self report	self report	< 23 23-23.9 24-24.9 25-26.9 27-28.9 29-30.9 31-32.9 33-34.9 ≥ 35	17 13 20 55 57 38 27 21 24	\$ 1.0 1.6 2.3 4.8 8.1 13.8 26.9 50.7

British Regional Heart Study (13)	7,735	40-59	14.8	non fasting OGTT	measured	20-21.9	8	\$
						22-23.9	19	1.1
						24-25.9	44	1.8
						26-27.9	64	3.4
						28-29.9	47	5.0
						≥ 30	61	9.3
Finland (14)	6,098	35-52	12	self report	measured	< 27	27	\$
						27.1-28.9	16	3.2
						29.0-31.9	20	6.7
						32.0-34.9	13	20.0
						≥ 35.0	11	42.0
Women								
NUHI (6)	1,192	20-50	6-17	registered by GP	registered by GP	< 27 vs > 27		5.6
Göteborg (15)	1,462	38-60	12	OGTT	measured	1st quintile vs 5 th	43	8.0
Rancho Bernardo (9)	969	40-79	12	OGTT	measured	< 23 vs > 23		3.1
Rancho Bernardo (10)	969	40-79	10-15	OGTT	measured	Per 3.3 kg/m ² Increase	117	1.9
Iowa Women's Health Study (16)	41,837	55-69	2 *	self report	self report	< 24.7	55	\$
						24.7-29.2	98	1.9
						≥ 29.2	235	6.0
Nurses Health Study (17)	113,861	30-55	14	self report	self report	< 22	55	\$
						22-22.9	71	2.9
						23-23.9	88	4.3
						24-24.9	94	5.0
						25-26.9	227	8.1
						27-28.9	267	15.8
						29-30.9	329	27.6
						31-32.9	263	40.3
						33-34.9	224	54.0
≥ 35	579	93.2						

Table 1 – continued

Study (reference)	N	Age (yr.)	Follow up	Measurement DM	Measurement obesity	Categories BMI	Cases	RR
Nurses Health Study (18) followed from '86-'94	42,492	30-55	8	self report	self report	< 21	21	\$
						21-22.9	40	1.2
						23-24.9	82	3.1
						25-26.9	90	7.0
						27-28.9	96	9.6
						29-30.9	112	12.7
Finland (14)	5,556	35-52	12	self report	measured	≥ 31	264	18.1
						< 27	10	\$
						27.1-28.9	12	7.9
						29.0-31.9	24	18.9
						32.0-34.9	10	14.2
						≥ 35.0	19	36.6

DM: diabetes mellitus; BMI: Body mass index (kg/m²); RR: relative risk; CI: confidence interval; OGTT: Oral Glucose Tolerance Test; GP: general practitioner; \$: reference category; * nested case-control study

cating that obesity is a risk factor for diabetes, independent of other risk factors.

Duration of obesity and previous overweight seem to be more important than current overweight. (17, 19-21) Also weight gain was associated with an increased risk for developing diabetes (12, 17, 22-25). Using data of the NHANES I study it was estimated that for every kilogram of increase in weight, the risk for diabetes increased by 4.5 percent (24). French et al showed that a large weight gain (>10% weight gain) resulted in a relative risk for diabetes of 1.80 (25).

It is generally accepted that obesity is invariably accompanied by increased insulin resistance (26, 27). Insulin resistance induces high insulin levels, necessary to keep the plasma glucose levels within the normal range. When an obese subject has normal beta-cell function, the beta cells secrete sufficient insulin to overcome insulin resistance and prevent the development of diabetes. Diabetes is thought to develop when increased insulin resistance is accompanied by beta-cell dysfunction through exhaustion of the beta-cells or other internal and external causes (26, 27)

Prevalence

Body mass index increases with age, for both men and women. The mean BMI in The Netherlands varied between studies from 24.3 to 25.3 for adult men and from 23.9 to 24.7 kg/m² for adult women (28, 29).

Several studies in The Netherlands reported prevalence of overweight and/or obesity in The Netherlands (28, 30-35). Overweight ($25 \leq \text{BMI} < 30$ kg/m²) varies between 35-36% among men and 24-25 among women (28, 30, 31). The prevalence of severe overweight or obesity ($\text{BMI} \geq 30$ kg/m²) is higher among women than men and varies between 4-9% among men and 5-11% among women respectively in the age group 20-70 years (Table 2). The prevalence of obesity in older subjects, as measured in the Rotterdam study, is about 6.5 % for men and 17 % for women. On average, the studies with self-reported BMI reported lower prevalence rates of obesity (35). This is probably due to the fact that people tend to underreport their body weight (36).

Trends

Only a few studies report prevalence of body mass index over time. The Health Interview Survey showed an increase in the percentage of overweight men and women aged 20 years and over in the period 1985-1996 (30). Among men, the

Table 2
Prevalence of obesity in The Netherlands

Study (reference)	N	Measurement BMI	Age (year)	Prevalence (%)	
				M	F
Health interview Survey 1985-1996 (30)	76,560	self-report	> 20	5.1	7.5
Sentinel station 1990 (31)	6,961	measured	20-60	9	10.5
Morgen Study 1993 (32),	4,969	measured	20-59	8.2	10.2
Morgen Study 1994 (33)	3,952	measured	20-59	9.9	10.7
Morgen Study 1996 (34)	4,490	measured	20-59	9.1	10.3
Heart Foundation (28)	2,176	self-report	18-70	4	7
ERGO (35)	7,983	measured	55+	6.5	16.8

prevalence of overweight increased from 34% to 36% between 1985 and 1996, while obesity increased from 4 to 6%. In the same period, overweight among women increased from 22% to 28% while obesity rose from 7 to 9% (30). After adjustment for age-differences, the increase was 1.4 and 2.3% for men with overweight or obesity respectively and 2.9% and 1.6% for women with overweight or obesity respectively (30). Another study in a more age-restricted group (36-43 years) showed an increase in the mean BMI among men from 24.7 to 25.2 kg/m², but no increase among women in the period 1974-1980 (37). Data from the Sentinel Stations and MORGEN-study in the period 1987-1995 showed an increase in prevalence of obesity of 4.6% for men and 3.6% for women (35).

Implementing obesity in the model

Obesity is implemented in the model using a potential impact fraction (PIF) in which prevalence of obesity and relative risks for diabetes associated with body mass index were combined (chapter 10). As observed from Tables 1 and 2, the categories used for calculating the prevalence of overweight and obesity are different from the categories used for relative risks.

The studies reporting prevalence of overweight and/or obesity all used similar categories for overweight and obesity, and these categories were therefore used for the model. Considering the prospective studies on the association of body mass index and onset of diabetes mellitus, there were two studies that reported relative risks for the two categories we used in the model (5, 16). Four other studies used different categories, but reported for each category the number of person years lived, as well as the number of incident cases of diabetes mellitus (12, 13, 17, 18). For these four studies we have recalculated the rela-

Table 3
The six prospective studies with the relative risks used for implementing in the simulation model

Study (reference)	Age (yr.)	Category BMI	RR (95% CI)
Men			
Paris Prospective study (5)	43-54	<24.5	§
		24.5-27	2.2
		>27	6.2
Health professional's Follow-up Study (12)	40-75	< 25	§
		25-30.9	3.3 *
		≥ 31	17 *
British Regional Heart Study (13)	40-59	<25	§
		25-29.9	3.6 *
		≥ 30	7.7 *
Women			
Iowa Women's Health Study (16)	55-69	<24.7	§
		24.7-29.2	1.9
		>29.2	6.0
Nurses Health Study (17)	30-55	<25	§
		25-30.9	4.6 *
		≥ 31	26.8 *
Nurses Health Study, followed from '86-'94 (18)	30-55	<25	§
		25-30.9	5.0 *
		≥ 31	16.9 *

* Recalculated to two categories of body mass index on the basis of number of cases and person year's follow-up.

tive risks for the two BMI-categories we will use in the simulation model (Table 3). This might lead to an overestimation of relative risk as no adjustment is made for age. We have used a range of relative risks for estimating PIFs with a lower and upper boundary (see also chapter 10).

PHYSICAL INACTIVITY

Definition

Physical activity is a complex behaviour and therefore difficult to define operationally (38). The terms "physical activity", "exercise" and "physical fitness" are often used interchangeably in epidemiological research. Physical activity is defined as any bodily movement produced by the skeletal muscles that result in

Table 4

Relative risks of physical inactivity for developing diabetes mellitus: an overview of published prospective studies

	N	Age (yr.)	Follow-up	Definition DM	Classification physical activity	Relative Risk (95% CI)	Adjusted for
Men							
Pennsylvania Alumni Health Study (23, 49)	5,990	39-68	14	self-report	leisure time (kcal/week) for each decrease with 2000 kcal/week	1.31 (1.08-1.59)	age, BMI, family history diabetes mellitus, hypertension
Physicians Health Study (50)	22,071	40-84	5	self-report	vigorous exercise (frequency/week) < 1/wk vs. >1/wk	1.41 (1.09-1.78)	age, BMI
Honolulu Heart Program (51)	6,815	45-68	6	self-report	hours/day spent on activity multiplied with weighing factor for oxygen consumption low vs. high quintile	1.82 (1.33-2.43)	age, BMI
IHDRFS* (52)	897	42-60	4	OGTT	metabolic units (METS) based on 12 months physical activity history <5,5 METS and < 40 min/wk vs. >5,5 METS and > 40 min/wk	2.27 (1.14-4.55)	age, baseline glucose level, BMI, blood pressure, triglyceride, cholesterol, alcohol use
British regional heart study (53)	7,735	40-59	12.8	self-report	physical activity score based on frequency and intensity not active vs. moderate active	2.5 (1.4-5)	age, BMI
Finland (56)	1,340	35-63	10	self-report	energy expenditure (METS) low vs. high expenditure	1.54 (0.83-2.84)	age

Women

Nurses Health Study (55)	87,253	30-55	8	self-report	vigorous exercise (frequency/week) < 1/wk vs. >1/wk	1.19 (1.05-1.33)	age, BMI
Finland (56)	1,500	35-63	10	self-report	energy expenditure (METS) low vs. high expenditure	2.64 (1.28-5.44)	age

DM: diabetes mellitus; BMI: body mass index (kg/m²); CI: confidence interval; OGTT: oral glucose tolerance test; *: Ischaemic Heart Disease Risk Factor Study, Kuopio Finland

energy expenditure. Exercise is considered to be a subcategory of physical activity and is defined as any physical activity which is planned, structured, repetitive and results in improvements or maintenance of one or more facets of physical fitness. Thus physical activity and exercise are classified as behaviours, whereas physical fitness is classified as an outcome (38).

Physical activity can be described by type, frequency, duration and intensity of the activity for a defined period. It can be measured by questionnaires, keeping a diary, direct observations or by use of equipment such as mechanical or electronic movement meter. Several aspects of physical activity are related with different aspects of fitness and health. Because of this complex picture it is difficult to give a general definition of physical inactivity. As a guideline for sufficient physical activity in relation to fitness and health, the current advice for adults is to be moderately active for 30 minutes per day, on most days of the week, preferable all days of the week (39).

Relationship between physical inactivity and diabetes mellitus

Physical inactivity as a potential risk factor for diabetes mellitus gets more and more attention. In several cross-sectional studies, physical activity has been inversely associated with the prevalence of diabetes (40-48). Also the prevalence of impaired glucose tolerance is higher in inactive than in active subjects (42, 48). Odds ratio's reported in these studies varied between 2.0 and 2.9 for men and 1.7 to 3.1 for women, and the more vigorous the activity, the more strongly the association.

More evidence for a relationship between physical inactivity and diabetes mellitus can be obtained from prospective studies. Up to now (January 1999), seven prospective studies have been reported. These studies provide evidence that a high level of physical activity may prevent the development of non-insulin dependent diabetes mellitus compared with a low level of activity (Table 4) (23, 49-55).

Due to the large variation in measuring and definition of physical activity and in the choice of the reference category, it is difficult to compare the reported relative risks. They varied between 1.3 and 2.5. Again, as in cross sectional studies it appears that the more vigorous activities seem to be the most protective in relation to risk of NIDDM, although moderate or light activity may also give protection (23, 49, 53).

The mechanism by which physical activity affects the occurrence of diabetes mellitus has not yet been clearly understood. There is evidence that physical activity increases peripheral sensitivity to insulin, especially in skeletal muscle and adipose tissue (57-60). In a cross sectional study, performed in a non-diabetic population, it was shown that physical activity was related with the level of

fasting insulin and C-peptide: the more active, the lower these levels (61). Another study showed that there is an association between physical activity and 2-hr glucose tolerance, independent from obesity (62). Thus, physical activity itself has an effect on the onset of diabetes mellitus, through the mechanisms of insulin sensitivity and/or glucose concentration. Besides, physical activity may improve weight reduction by increasing the energy expenditure associated with exercise (63).

It is not clear whether physical activity throughout life is required for a reduced risk of NIDDM, or whether physical activity initiated at an older age is equally protective. Several studies have shown that the benefits of physical activity disappear within several days after exercise, which implies a need for regular exercise (64). Adults who have previously been sedentary require a period of training to increase their fitness to a level where they can perform the necessary duration and intensity of exercise that will be effective. Since this level of training may be difficult or impossible to achieve in older subjects, exercise should preferably be initiated at younger ages and continued throughout life.

Prevalence

Several studies have been performed in which data about prevalence of physical (in)activity in The Netherlands is collected (Table 5) (28, 31, 34, 65-67). Comparing the results of these studies is difficult since different populations were used, as well as different definitions for physical inactivity. When inactivity is defined as reporting no sporting activity or other vigorous activity, the prevalence of inactivity varied between 25-52% in men and between 26-52% in women in the age group 20-70 years. The prevalence of inactivity increased with age. On average, women showed a higher prevalence of physical inactivity compared with men. When also other physical activities are included, such as bicycling or walking, the prevalence of inactivity decreased.

Trends

Until now, data on measured trends in physical inactivity in The Netherlands are not consistent. The Dutch Sport Federations reported that the number of members of a sport club has increased from 13% to 32% in the period 1963 and 1989. However, all sports have been counted (including chess) and in addition people can be counted twice when they are members of two sport societies (68). In the Sentinel Station Project in the period 1987-1992 a significant increase in the percentage of physical inactivity is reported for men (0.5% per year). For women, no increase in percentage of physical inactivity was shown, although

Table 5
Prevalence of physical inactivity in The Netherlands

Study (reference)	N	Definition physical inactivity	Age	Prevalence inactive(%)	
				M	F
Health Interview Survey, 1990/1991 (65)	10,948	no sporting or other physical activity (walking, cycling, gardening)	16-24	23.8	27.0
			25-34	27.2	26.1
			35-44	30.5	27.7
			45-54	34.5	36.0
			55-64	36.2	39.2
			>65	48.5	61.9
			Total	34.6	35.4
Health Interview Survey, 1996 (66)	6,102	no sporting or other physical activity	16-24	27.4	29.6
			25-34	32	28.1
			35-44	29.7	29.8
			45-54	35.4	27.4
			55-64	40.2	33.7
			>65	48.3	62.4
			Total	32.2	36.0
Morgen Study 1994/1995 (67)		no sporting or at least 4 weeks/year vigorous activity	20-59	45	48
Morgen Study 1996 (34)	4,490	no sporting activities as well as no other vigorous activity in leisure time	20-24	42.5	32.1
			25-29	31	37.6
			30-34	29.6	45.7
			35-39	41	43.4
			40-44	40.6	49.6
			45-49	48.7	46.3
			50-54	55	48.5
			55-59	56.4	54.4
			Total	41.4	43.8
Heart Foundation (28)	2,176	no bicycling	18-70	22 *	22 *
		no sporting activity	18-70	52 *	52 *
Sentinel Station (31)	6,961	sedentary or standing work and no regular activity in leisure time	20-59	25.3	26.4

* For men and women together

the prevalence increased in younger women (20-29 years) and decreased in the women aged 50-59 years. (67). When comparing the two Health Interview Surveys, the prevalence of inactivity seems to have slightly increased in the period 1991-1996(65, 66).

Implementing physical inactivity in the model

As with obesity, the cut-off points used for both prevalence of inactivity in The Netherlands as well as for the relative risks of physical inactivity for developing

diabetes mellitus are different. However, no recalculation of the relative risks was possible, and thus the reported prevalence of physical inactivity and relative risks were combined in potential impact fractions. As the relative risks were reported for large age-groups only, the prevalence of physical inactivity of the total age-group was used (see chapter 10).

PREVENTION OF DIABETES MELLITUS BY REDUCING WEIGHT AND/OR INCREASING PHYSICAL ACTIVITY

Disease prevention can be considered at three levels: primary (avoiding disease occurrence), secondary (early detection and reversal) and tertiary (prevention or delay of complications). The diabetes model developed in this project, focussed on primary prevention interventions of diabetes. However, body weight and physical inactivity are important in secondary and tertiary prevention of diabetes as well. Several studies have shown that weight loss by patients with type II diabetes improves glycaemic control, insulin sensitivity and other cardiovascular risk factors (69-72). This suggests that the risk of developing long-term complications related to diabetes may be reduced when weight is lost. Also an increase in physical activity in subjects with diabetes can reduce the risk of developing complications (73, 74), although the outcomes of different studies are not consistent (58).

Treatment of obesity, especially among older individuals is difficult. Weight loss can be obtained by following a (strict) diet and/or performing exercise or by surgical interventions (75). Energy restriction is the most common method of weight loss. However, the long-term success rate of this method is low (76). In a trial in which the effect of energy restriction was estimated in subjects with IGT and/or a family history of diabetes mellitus it was shown that those who lost weight had a lower risk of developing diabetes (77). The subjects with the best compliance to the prescribed diet had the largest weight loss.

In most trials, both the effects of energy restriction and increasing physical activity are investigated (78-82). In a trial in Sweden, 181 subjects with impaired glucose tolerance (IGT) were stimulated to perform more exercise and/or to change their diet. After 6 years of follow-up the intervention group had decreased their weight with 2.3-3.7% and had an increased maximal oxygen intake (10-14%), while the control group had increased their weight with 0.5-1.7%

and decreased maximal oxygen intake (5-9%). The glucose tolerance was normalised in > 50% of the subjects with IGT (78).

The Oslo Diet and Exercise Study consisted of four randomised groups of 40-y old non-diabetic men and women (82). The two interventions consisted of diet and exercise. The largest reduction in BMI was seen in the group with the combined intervention (-3.7 kg/m²) followed by the diet group (-1.3 kg/m²). Fasting and 1-hr glucose levels were reduced correspondingly, as was fasting insulin, an indicator of insulin resistance in non-diabetics.

Wing et al. (81) performed a trial in which 154 obese non-diabetic subjects were randomised in one control and 3 treatment groups: diet only, exercise only, and diet plus exercise. All subjects had a family history of diabetes and/or IGT. After a follow-up period of 2 years, subjects with weight loss of 4.5 kg had a 30% reduction in risk of diabetes mellitus. However, the percentage of subjects who had lost weight at 2 years was low (24%); most subjects lost weight in the first 6 months of the study, but regained weight thereafter. The three life-style interventions differed in their initial effect, but not in their long-term impact. This is in contrast with another Chinese study where subjects with IGT, randomised over the same treatment groups as in the trial by Wing et al, showed differences in reduction in incidence of diabetes in the three intervention groups (80). Using a diet only resulted in a risk reduction of 31%, exercise resulted in a risk reduction of 46% while diet in combination with exercise resulted in a risk reduction of 42%. Whether these results are applicable to a Western setting remains to be questioned, since the baseline diet of the participants already contained the recommended proportion of carbohydrates and relative low energy percentage of fat (26%).

To conclude, weight reduction and an increased physical activity are important in primary prevention of diabetes mellitus, even in high risk individuals such as subjects with impaired glucose tolerance and/or a family history of diabetes mellitus. On the short-term, intervention programmes on energy restriction and increase of physical activity appear to be successful. However, it appears to be difficult for people to maintain an improved risk profile on the long term.

References

1. WHO Expert committee. *Physical status: the use and interpretation of anthropometry*. Geneva: World Health organization, 1995.

2. Berns M. *Over gewicht en hart- en vaatziekten*. Den Haag: Nederlandse Hartstichting, 1995:224.
3. Paffenbarger RS, Wing AL: Chronic disease in former college students. XII Early Predictors of adult onset diabetes mellitus. *Am J Epidemiol* 97:314-323, 1973
4. Medalie JH, Papier C, Herman JB, et al.: Diabetes mellitus among 10,000 adult men. Five-year incidence and associated variables. *Israel J Med* 10:681-697, 1974
5. Papoz L, Eschwege E, Warnet J-M, Richard J-L, Claude J-R, ed. *Incidence and risk factors of diabetes in the Paris Prospective Study (GREX)*. Amsterdam: Elsevier Biomedical Press, 1982:113-122. (Eschwege E, ed. *Advances in Diabetes Epidemiology*;)
6. Seidell JC, Bakx KC, Deurenberg P, van den Hoogen HJM, Hautvast JGAJ, Stijnen T: Overweight and chronic illness - a retrospective cohort study with a follow-up of 6-17 years, in men and women of initially 20-50 years of age. *J Chron Dis* 39:585-593, 1986
7. Ohlson LO, Larsson B, Björntorp P, et al: Risk factors for type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and on-half years of follow-up of the participants in a study of Swedish men born in 1913. *Diabetologia* 31:798-805, 1988
8. Feskens EJM, Kromhout D: Cardiovascular risk factors and the 25-year incidence of diabetes mellitus in middle-aged men. The Zutphen Study. *Am J Epidemiol* 130:1101-1108, 1989
9. Holbrook TL, Wingard DL, Barrett-Connor E: Sex-specified vs. unisex body mass indices as predictors of non-insulin dependent diabetes mellitus in older adults. *Int J Obesity* 14:803-807, 1990
10. Brown-McPhillips J, Barrett-Connor E, Wingard DL: Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non-insulin dependent diabetes mellitus in a community of older adults. *Am J Epidemiol* 131:443-453, 1990
11. Cassano PA, Rosner B, Vokonas PS, Weiss ST: Obesity and body fat distribution in relation to the incidence of non-insulin-dependent diabetes mellitus. *Am J Epidemiol* 136:1474-86, 1992
12. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC: Obesity, fat distribution and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 17:961-969, 1994
13. Shaper AG, Wannamethee SG, Walker M: Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men. *Br Med J* 314:1311-1317, 1997
14. Njolstad I, Arnesen E, Lund-Larsen PG: Sex differences in risk factors for clinical diabetes mellitus in a general population: a 12 year follow-up of the Finnmark Study. *Am J Epidemiol* 1998:49-58, 1998
15. Lundgren H, Bengtsson C, Blohme G, Lapidus L, Sjöström L: Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: results from a prospective population study in Gothenburg, Sweden. *Int J Obesity* 13:413-423, 1989
16. Kaye SA, Folsom AR, Sprafka JM, Prineas RJ, Wallace RB: Increased incidence of diabetes mellitus in relation to abdominal adiposity in older women. *J Clin Epidemiol* 44:329-334, 1991

17. Colditz GA, Willett WC, Rotnitzky A, Manson JE: Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 122:481-486, 1995
18. Carey VJ, Walters EE, Colditz GA, et al.: Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses Health study. *Am J Epidemiol* 145:614-619, 1997
19. Modan M, Karasik A, Halkin H, et al.: Effect of past and concurrent body mass index on prevalence of glucose intolerance and type 2 (non-insulin-dependent) diabetes and on insulin response. The Israel study of glucose intolerance, obesity and hypertension. *Diabetologia* 29:82-89, 1986
20. Barrett-Connor EL: Epidemiology, obesity and non-insulin-dependent diabetes mellitus. *Epidemiol Rev* 11:172-181, 1989
21. Everhart JE, Pettitt DJ, Bennett PH, Knowler WC: Duration of obesity increases the incidence of NIDDM. *Diabetes* 41:235-240, 1992
22. Colditz GA, Willett WC, Stampfer MJ, et al.: Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 132:501-513, 1990
23. Helmrigh SP, Ragland DD, Leung RW, Paffenbarger RS: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Eng J Med* 325:147-152, 1991
24. Ford ES, Williamson DF, Simin L: Weight change and diabetes incidence: Findings from a national cohort of US adults. *Am J Epidemiol* 146:214-222, 1997
25. French S, Folsom A, Jeffery R, Zheng W, Mink P, Baxter J: Weight variability and incident disease in older women: the Iowa Women's Health Study. *Int J Obesity* 21:217-223, 1997
26. Turner RC: The role of obesity in diabetes. *Int J Obesity* 16:S43-S46, 1992
27. Golay A, Felber JP: Evolution from obesity to diabetes. *Diabetes Metab* 20:3-14, 1994
28. Jansen MCJF, van Dis SJ, Kok FJ. *National inquiry lifestyle and riskfactors for cardiovascular disease*. (Landelijke enquête-onderzoek leefstijl en risicofactoren voor hart- en vaatziekten). Den Haag: Netherlands Heart Foundation, 1996.
29. Seidell JC, Verschuren WMM, Kromhout D: Prevalence and trends of obesity in the Netherlands 1987-1991. *Int J Obesity* 19:924-927, 1995
30. Verweij GCG: Health Interview Survey. Underweight and overweight, 1985-1996. *Mndber gezondheid* :4-13, 1998
31. Kromhout D, Obermann-de Boer GL, Blokstra A, Verschuren WMM. *Peilstationsproject Hart- en vaatziekten 1991*. Bilthoven: RIVM, 1991.
32. Smit H, Verschuren W, Bueno de Mesquita H, Seidell J. *Het project Monitoring Risicofactoren en Gezondheid Nederland (MORGEN-project)*. Jaarverslag 1993. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieuhygiene, 1994.
33. Seidell J, Smit H, Verschuren W, Bueno de Mesquita H, Blokstra A. *Het project Monitoring Risicofactoren en Gezondheid Nederland (MORGEN-project)*. Jaarverslag 1994. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieuhygiene, 1995.
34. Blokstra A, Seidell JC, Smit HA, Bueno de Mesquita HB, Verschuren WMM. *Het project Monitoring Risicofactoren en Gezondheid Nederland (MORGEN-project)*. Jaarverslag 1994. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieuhygiene, 1997.

35. Seidell JC, ed. *Lichaamsgewicht*. Bilthoven: RIVM, Elsevier/De Tijdstroom, 1997. (Maas IAM, Gijzen R, Lobbezoo IE, Poos MJJC, ed. Volksgezondheid Toekomst Verkenning 1997. De gezondheidstoestand: een actualisering; vol 1)
36. Rowland ML: Self-reported weight and height. *Am J Clin Nutr* 52:1125-1133, 1990
37. Blokstra A, Kromhout D: Trends in obesity in young adults in The Netherlands from 1974 to 1986. *Int J Obesity* 15:513-521, 1991
38. Caspersen CJ: Physical activity epidemiology: concepts, methods, and applications to exercise science. *Exercise Sport Sciences Reviews* 17:423-473, 1989
39. American college of sports medicine: The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness in healthy adults. *Med Science Sports Exercise* 22:265-275, 1990
40. Taylor R, Ram P, Zimmet P, Raper L, Ringrose H: Physical activity and prevalence of diabetes in Melanesian and Indian men in Fiji. *Diabetologia* 27:578-582, 1984
41. Frisch RE, Wyshak G, Albright TE, Schiff I: Lower prevalence of diabetes in female former college athletes compared with nonathletes. *Diabetes* 35:1101-1105, 1986
42. Dowse GK, Zimmet PZ, King H: Relationship between prevalence of impaired glucose tolerance and NIDDM in a population. *Diabetes Care* 14:968-974, 1991
43. Zimmet PZ, Collins VR, Dowse GK, et al.: The relation of physical activity to cardiovascular disease risk factors in Mauritians. *Am J Epidemiol* 134:862-875, 1991
44. Perry IJ, Wannamethee SG, Walker MK, Shaper AG: Sporting activity and hyperglycemia in middle-aged men. *Diabetes Care* 16:581-583, 1993
45. Schulz LO, Weidensee RC: Glucose tolerance and physical activity in a Mexican indigenous population. *Diabetes Care* 18:1274-1276, 1995
46. Mooy JM, Grootenhuys PA, de Vries H, Valkenburg HA, Bouter LM, Heine RJ: Prevalence and determinants of glucose intolerance in a Caucasian population. The Hoorn Study. *Diabetes Care* 18:1270-1273, 1995
47. Rodriguez BL, Curb JD, Burchfield CM, et al.: Impaired glucose tolerance, diabetes and cardiovascular disease risk factor profiles in the elderly. *Diabetes Care* 19:587-590, 1996
48. Baan CA, Stolk RP, Grobbee DE, Witteman JCM, Feskens EJM: Physical activity in elderly subjects with impaired glucose tolerance and newly diagnosed diabetes mellitus. *Am J Epidemiol* 149:219-227, 1999
49. Helmrigh SP, Ragland DR, Paffenbarger RS: Prevention of non-insulin-dependent diabetes mellitus with physical activity. *Med Sci Sports Exerc* 26:824-830, 1994
50. Manson HE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH: A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* 268:63-67, 1992
51. Burchfiel CM, Sharp DS, Curb JD, et al.: Physical activity and incidence of diabetes: The Honolulu Heart Program. *Am J Epidemiol* 141:360-368, 1995
52. Lynch J, Helmrigh SP, Lakka TA, et al.: Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Arch intern med* 156:1307-1314, 1996

53. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG: Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *Br Med J* 310:560-564, 1995
54. Haapanen N, Miilunpalo S, Vuori I, Pekka O, Pasanen M: Characteristics of Leisure time physical activity associated with decreased risk of premature all-cause and cardiovascular disease mortality in middle-aged men. *Am J Epidemiol* 143:870-880, 1996
55. Manson JR, Rimm EB, Stampfer MJ, et al: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774-778, 1991
56. Haapanen N, Miilunpalo S, Vuori I, Oja P, Pasanen M: Association of leisure time physical activity with the risk of coronary heart disease, hypertension and diabetes in middle-aged men and women. *Int J Epidemiol* 26:739-747, 1997
57. Horton ES: Exercise and decreased risk of NIDDM. *N Engl J Med* 325:196-197, 1991
58. King H, Kriska AM: Prevention of type II diabetes by physical training. Epidemiological considerations and study methods. *Diabetes Care* 15:1794-1799, 1992
59. Pescatello LS, DiPietro L: Physical activity in older adults. An overview of health benefits. *Sports medicine* 15:353-364, 1993
60. Feskens EJM, Loeber JG, Kromhout D: Diet and physical activity as determinants of hyperinsulinemia: the Zutphen Elderly Study. *Am J Epidemiol* 140:350-360, 1994
61. Regensteiner JG, Mayer EJ, Shetterly SM, et al: Relationship between habitual physical activity and insulin levels among nondiabetic men and women. *Diabetes Care* 14:1066-1074, 1991
62. Pereira MA, Kriska AM, Joswiak ML, et al.: Physical inactivity and glucose intolerance in the multiethnic island of Mauritius. *Med Sci Sports Exerc* 27:1626-1634, 1995
63. Horton ES: Role and management of exercise in diabetes mellitus. *Diabetes Care* 11:201-211, 1988
64. Laws A, Reaven GM: Physical activity, glucose tolerance and diabetes in older adults. *Annals of Behavioural Medicine* 13:125-132, 1991
65. Backx F, Swinkels H, Bol E: Health Interview Surveys. How physically (in)active are Dutch adults during their leisure time? *Mndber gezondheid (CBS)* :4-16, 1994
66. Hoeben J: Health Interview Survey. Leisure time physical activity. *Mndber gezondheid* :18-28, 1998
67. Bijnen FCH, Peeters PHM, Pols MA, Mosterd WL, ed. *Lichamelijke (in)activiteit*. Bilthoven: RIVM, Elsevier/De Tijdstroom, 1997. (Maas IAM, Gijzen R, Lobbezoo IE, Poos MJJC, ed. Volksgezondheid Toekomst Verkenning 1997. De gezondheidstoestand: een actualisering; vol 1)
68. Peeters PHM, Bijnen FCH, Pols MA, Kemmeren JM, Collette HJA, Mosterd WL, ed. *Lichamelijke (in)activiteit*. Den Haag: SDU-uitgeverij, 1994. (Ruwaard D, Kramers P, ed. Volksgezondheid Toekomstverkenningen: de gezondheidstoestand van de Nederlandse bevolking in de periode 1950-2010. 1993.)
69. Wing R, Blair EH, Bononi P, Marcus M, Watanabe R, Bergman RN: Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. *Diabetes Care* 17:30-36, 1994

70. Niskanen LK, Penttilä I, Parvainen M, Uusitupa MJ: Evolution, risk factors and prognostic implications of albuminuria in NIDDM. *Diabetes Care* 19:486-493, 1996
71. Bosello O, Armellini F, Zamboni M, Fichet M: The benefits of modest weight loss in type II diabetes. *Int J Epidemiol* 21 (suppl 1):S10-S13, 1997
72. Agurs-Collins TD, Kumanyika SK, Have ten TR, Adams-Campbell LL: A randomized controlled trial of weight reduction and exercise for diabetes management in older african-american subjects. *Diabetes Care* 20:1503-1511, 1997
73. Ligtienberg PC, Hoekstra JBL, Bol E, Zonderland ML, Erkelens DW: Effects of physical training on metabolic control in elderly type 2 diabetes mellitus patients. *Clinical Science* 93:127-135, 1997
74. Lehman R, Vokac A, Niedermann K, Agosti K, Spinaz GA: Loss of abdominal fat and improvement of the cardiovascular risk profile by regular moderate exercise training in patients with NIDDM. *Diabetologia* 38:1313-1319, 1995
75. Long SD, O'Brien K, MacDonald KG, et al: Weight loss in severely obese subjects prevents the progression of impaired glucose tolerance to type II diabetes. A longitudinal interventional study. *Diabetes Care* 17:372-375, 1994
76. Pasman W, Saris W, Westerterp-Plantenga M: Predictors of weight maintenance. *Obes Res* 7:43-50, 1999
77. Viswanathan M, Snehalatha C, Viswanathan V, Vidyavathi P, Indu J, Ramachandran A: Reduction in body weight helps to delay the onset of diabetes even in non-obese with strong family history of the disease. *Diab Res Clin Pract* 35:107-112, 1997
78. Eriksson KF, Lindgärde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. *Diabetologia* 34:891-898, 1991
79. Katzell LI, Bleecker ER, Colman EG, Rogus EM, Sorkin JD, P GA: Effects of weight loss vs Aerobic exercise training on Risk Factors for coronary disease in health, obese, middle-aged and older men. *JAMA* 274:1915-1921, 1995
80. Pan X, Li G, Wang J, Yang W, et al: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. *Diabetes Care* 20:537-544, 1997
81. Wing RR, Venditti E, Jakicic JM, Polley BA, Lang W: Lifestyle intervention in overweight individuals with a family history of diabetes. *Diabetes Care* 21:350-359, 1998
82. Torjesen P, Birkeland K, Anderssen S, Hjerman I, Holme I, Urdal P: Lifestyle changes may reverse development of the insulin resistance syndrome. *Diabetes Care* 20:26-31, 1997

Physical activity
in elderly subjects
with impaired glucose
tolerance and newly
diagnosed diabetes mellitus

ABSTRACT

The authors carried out a study to investigate the association between different indicators of physical activity and the prevalence of impaired glucose tolerance (IGT) and newly diagnosed diabetes (nDM) in a population-based cohort of elderly men and women in The Netherlands. A sample of participants of the Rotterdam study (n=1,016), aged 55-75 years, who were not known to have diabetes mellitus, underwent an oral glucose tolerance test. Physical activity was assessed by means of a self-administered questionnaire and expressed as time spent on activities per week. Associations with the prevalence of IGT and nDM were assessed by logistic regression analysis after adjustment for age, body mass index, waist-hip ratio, family history of diabetes and smoking. A total of 745 subjects had normal glucose tolerance, 153 IGT and 118 nDM. The total amount of time spent on physical activity decreased with increasing glucose intolerance. Adjusted for main confounders, vigorous activities such as bicycling (men: odds ratio (OR) = 0.26, 95% confidence interval (CI) 0.14-0.49; women: OR = 0.37, 95% CI 0.18-0.78) and sports (men: OR = 0.28, 95% CI 0.11-0.74) showed an inverse association with the presence of nDM. For IGT, the associations pointed in the same direction but did not reach statistical significance. These results indicate that physical inactivity and glucose intolerance are associated among older adults similar to the way they are associated among middle-aged adults.

Acknowledgements

This study is part of a research project supported by grants from the National Institute for Health Sciences (NIHES) and The Netherlands Diabetes Fund. The authors like to thank Dr. A.E.J.M. Cavelaars for her helpful comments and advice with regard to the statistical analysis.

INTRODUCTION

Cross-sectional studies have shown an inverse association of physical activity with the prevalence of clinically diagnosed diabetes mellitus and diabetes newly diagnosed by an oral glucose tolerance test (OGTT) (1, 2). In addition, the prevalence of impaired glucose tolerance is higher in inactive subjects than in active subjects (1). In prospective studies, physical inactivity was found to be a risk factor for the incidence of diabetes mellitus, independent of body weight (3-7).

These findings indicate that promotion of physical activity may be important in the prevention of diabetes mellitus. From a public health perspective, the health benefits that accrue from increased physical activity may be greater in older populations than among middle-aged subjects, given the higher prevalence of diabetes mellitus and lower levels of physical activity observed among older persons (8). Yet, most studies to date have focussed on the association between physical activity and diabetes in middle-aged populations. To our knowledge, thus far, only two studies have been conducted in elderly subjects (9, 10). However, in both studies physical activity was presented as a single index and no information was reported about specific types of physical activity or the intensity of the activity.

The present study was conducted in men and women aged 55 and older, diagnosed with impaired glucose tolerance, newly diagnosed diabetes or normal glucose tolerance. The aim of the study was to evaluate the association between different indicators of physical activity and the prevalence of newly diagnosed diabetes and impaired glucose tolerance.

MATERIAL AND METHODS

Selection of the study population

The selection of the study sample is given in figure 1. The present study was conducted among participants of the Rotterdam Study. The Rotterdam Study is a population-based cohort study that has been carried out in The Netherlands to assess the determinants of chronic disabling diseases in the elderly (11). The baseline examination was conducted from 1990 to 1993 and included 7,983 subjects, aged 55 and older (response rate 78%). Informed consent was obtained from all subjects and the study was approved by the medical ethics committee of Erasmus University Medical School.

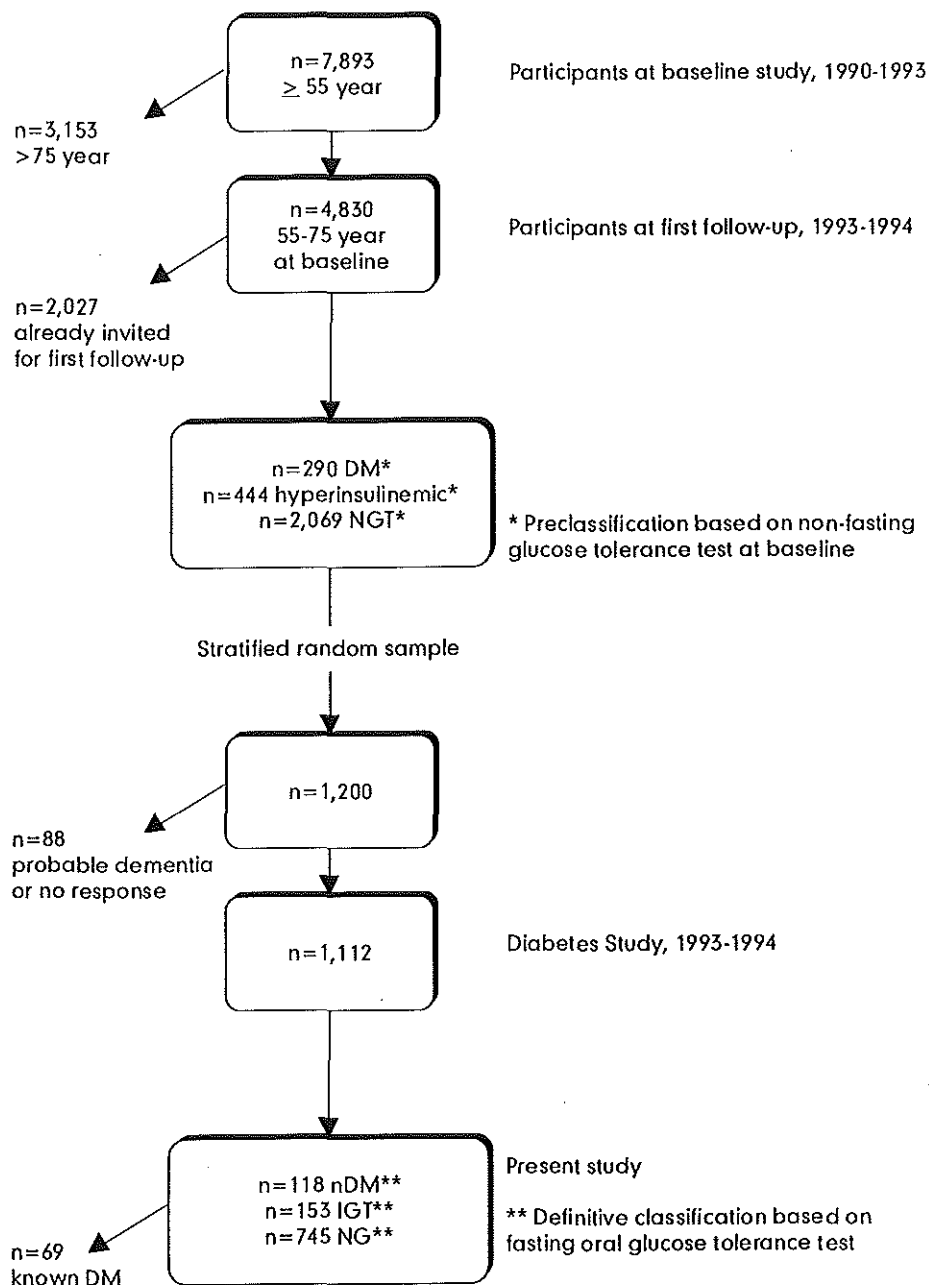


Figure 1
Selection of the study sample: the Rotterdam Study, 1990-1994

During the first follow-up examination in 1993-1994 of the 4,830 participants aged 55 to 75 years at the baseline examination, a sample was invited to participate in the diabetes study. Because the follow-up examination had already started and the invitations to participate in the present study were sent together with the invitation for the examination, only 2,803 subjects were available for sampling in the diabetes study. These subjects did not differ in the main characteristics from the subjects who had already been invited. The subjects were temporarily divided into diabetic (using medication or random or postload level ≥ 11.1 mmol/l), hyperinsulinemic (upper quintile of the gender-specific post-load insulin distribution in subjects without impaired glucose tolerance or diabetes mellitus) or normal glucose tolerant, based on a non-fasting glucose tolerance test at baseline. A random sample was taken from each glucose tolerance group, which resulted in 200 subjects with diabetes, 400 with hyperinsulinemia and 600 with normal glucose tolerance being invited for the diabetes study. Subjects with probable dementia were not invited. The overall response rate for the follow-up examination was 90%, and 1,112 subjects took part in the Rotterdam Diabetes Study. In this study a definitive classification of the glucose tolerance status was made, based on an oral glucose tolerance test (OGTT), which is described below.

As this paper proposes to examine the aetiology of the development of diabetes mellitus, the known clinically diagnosed diabetic patients (those using medication, $n=69$) were excluded from analysis. The analyses are thus based on the data of 1,016 participants.

Examinations

Information on medication use, medical history, smoking habits and family history (first degree) of diabetes was obtained by means of a self-administered questionnaire.

The participants came to the research center after an overnight fast (no food intake after 11.00 p.m.). Blood was drawn between 8.00 a.m. and 9.00 a.m. by venipuncture and subjects not using antidiabetes medication underwent an oral glucose tolerance test (75 grams glucose in 200 ml water). Fasting and two hour plasma levels were determined using the glucose hexokinase method. Diabetes mellitus was defined as the use of antidiabetes medication (insulin or oral hypoglycaemic medication), or a 2-hour plasma glucose concentration of ≥ 11.1 mmol/litre according to the World Health Organization (WHO) criteria (12). Subjects with a glucose level in the diabetic range and who did not use antidiabetes medication were classified as newly diagnosed cases of diabetes mellitus (nDM). Impaired glucose tolerance (IGT) was defined as a 2-hour

plasma glucose concentration of ≥ 7.8 mmol/litre, but < 11.1 mmol/litre, combined with a fasting plasma glucose concentration of < 7.8 mmol/litre.

Sitting blood pressure was measured with a random-zero sphygmomanometer, and the mean of two measurements, obtained at one occasion, was used in the analyses. Hypertension was defined as the use of antihypertensive medication or blood pressure of $\geq 160/95$ mmHg. Weight and height were measured with the participants wearing indoor clothes and no shoes. Waist circumference was measured midway between the lower rib margin and iliac crest; hip circumference was measured at the trochanter major. The body mass index was determined by dividing the weight by the height squared (kg/m^2) and body fat distribution was assessed by means of the waist-to-hip circumference ratio (waist-hip ratio).

Physical activity

Physical activity was estimated using a self-administered questionnaire derived from a validated questionnaire designed to measure physical activity in elderly men (13), modified for use in the current study. Modification comprised primarily of adding activities considered to be relevant for elderly women, which means including questions about housekeeping activities. The questionnaire consisted of questions about the average frequency (times/week) and duration (hours/day) of walking and bicycling in summer, winter and for transportation purposes; the average frequency (times/week) and length of time (hours/day) spent on work (paid or volunteer), hobbies, sports, gardening in both summer and winter, housekeeping and odd jobs. There was no defined time period queried.

Estimated times were converted to minutes per week for each type of activity and summed to obtain the total weekly duration of physical activity. If someone reported to perform an activity only during summer or winter, the amount of minutes/week were divided by two. Leisure time activity was calculated by summing the minutes per week for walking, bicycling, hobbies, odd jobs, gardening and sport.

If a subject did not report engaging in a particular activity, it was coded as zero. Activities were only included when they demanded a certain amount of physical effort expressed as an intensity code (13). The classification of household chores was based on the intensity codes proposed by Ainsworth et al (14). Mopping and window cleaning were classified as vigorous activities; all remaining household chores were classified as moderate activities. All activities with an intensity code ≤ 1.5 (such as doing puzzles, reading, and playing chess) were excluded from the calculations (15). Billiards, fishing, bowling and dancing was classified as hobbies. Activities were also grouped by level of intensity using the intensity codes and categories proposed by Caspersen et al (13): light (intensity

code ≥ 1.5 but < 2 ; e.g. tending animals), moderate (intensity code ≥ 2 but < 4 ; e.g. walking, odd jobs, billiards, fishing) and vigorous (intensity code > 4 ; e.g. sport, gardening, bicycling, dancing).

Data analysis

The SPSS computer package version 7.0 (SPSS Inc., Chicago, Illinois) was used for all statistical analyses. For each physical activity variable, the mean time spent on it and standard deviation was calculated, as well as the frequency of subjects reporting no activity. The difference in mean time spent on a physical activity was estimated according to category of glucose tolerance for physical activity variables in which 60 percent or more of the participants reported that they engaged. In this calculation, we used linear regression with physical activity as a dependent variable and presence or absence of nDM/IGT as an independent variable, adjusting for age. Because the distributions of these physical activity variables were skewed, the data were transformed by taking the square root. For the other variables, the difference in frequency of subjects reporting no activity was estimated with logistic regression, with physical activity (active/inactive) as a dependent variable and the presence or absence of nDM/IGT as an independent variable, adjusting for age.

Next, the variables of which more than 60 percent of the respondents reported some activity were divided into tertiles, with the lowest tertile as a reference category. All the other variables were divided into active (> 0 minutes/week) or inactive (0 minutes/week). Odds ratios were calculated using logistic regression with the presence or absence of nDM/IGT as a dependent variable and physical activity as an independent variable, adjusting for age, body mass index, waist-hip ratio, family history of diabetes mellitus and smoking.

The relation between continuous glucose levels (fasting and post-load) and physical activity was estimated using linear regression, adjusted for the main confounders age, body mass index, waist-hip ratio, family history of diabetes mellitus and smoking.

RESULTS

Table 1 gives the main characteristics of the study population. Both male and female subjects with normal glucose tolerance (NGT) were younger, had a lower body mass index and waist hip ratio, and a lower percentage of positive family history of diabetes, compared to the subjects with impaired glucose tolerance (IGT) or newly diagnosed diabetes mellitus (nDM). The percentage of smokers

Table 1

Selected characteristics of subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) or newly diagnosed diabetes (nDM): the Rotterdam Study, 1990-1994

Variables	NGT	IGT	nDM
Men	(n=357)	(=77)	(=69)
Age (years), mean (SD)†	66.2 (5.2)	67.1 (5.4)	67.9 (5.5)
BMI † (kg/m ²), mean (SD)	25.9 (2.8)	27.1 (2.9)**	26.9 (3.2)**
Waist-hip ratio, mean (SD)	0.95 (0.07)	0.97 (0.06)	0.97 (0.07)*
Smoking (% current)	29	25	25
Family history (% first-degree relatives with diabetes)	22	20	33**
Women	(=388)	(=76)	(=49)
Age (years), mean (SD)†	66.3 (5.7)	68.5 (5.6)	67.7 (5.9)
BMI † (kg/m ²), mean (SD)	26.2 (3.6)	28.7 (4.9)**	28.3 (4.6)**
Waist-hip ratio, mean (SD)	0.86 (0.08)	0.91 (0.09)**	0.89 (0.08)*
Smoking (% current)	19	22	14
Family history (% first-degree relatives with diabetes)	23	35*	36*

* $p < 0.10$; ** $p < 0.05$; different from NGT, adjusted for age

† SD, standard deviation; BMI, body mass index

was similar in all three groups for both for men and women. The differences between the subjects with IGT or nDM were small for most studied variables.

The physical activity patterns differed between men and women. Men reported spending 1,557 minutes/week on physical activity. Of these, 701 minutes/week were spent on leisure activities. On average, the most time was spent on house-keeping (25 percent), walking (18 percent), work (19 percent) and bicycling (13 percent), whereas much less was spent on sports (3 percent), hobbies (7 percent), odd jobs (9 percent) and gardening (5 percent). The percentage of men with nDM or IGT reporting no activity was higher for all parameters of physical activity compared to men with NGT (Table 2), and it was statistically significant for bicycling and sport in men with nDM (differences, 34 percent and 19 percent, respectively). Men with nDM or IGT reported spending less time on physical activity compared to men with NGT, a difference which was statistically significant for vigorously intense activities (differences, 83 minutes/week for nDM and 143 minutes/week for IGT).

Women spent an average of 1,721 minutes/week on physical activity. These included 416 minutes/week spent on leisure activities. The most time was spent on housekeeping (61 percent), walking (15 percent) and bicycling (7 per-

Table 2

Time spent on physical activity (minutes/week) and frequency of subjects reporting no activity in men with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) or newly diagnosed diabetes mellitus (nDM): the Rotterdam Study, 1990-1994.

Type of physical activity	Total (n=503)		NGT (n=357)		IGT (n=77)			nDM (n=69)		
	Time per PA* mean (SD*)	Freq* (%)	Time per PA mean (SD)	Freq (%)	Time per PA mean (SD)	Freq (%)	<i>p</i> value†	Time per PA mean (SD)	Freq (%)	<i>p</i> value†
Total activity	1,557 (1,280)	6	1,593 (1,212)	4	1,366 (1,217)	12	0.08	1,582 (1,640)	12	0.48
Leisure activity	701 (770)	11	708 (733)	8	682 (761)	16	0.50	684 (659)	19	0.21
Vigorous intensity	358 (454)	18	391 (454)	15	248 (298)	18	0.01	308 (561)	38	0.004
Moderate intensity	955 (925)	8	955 (874)	6	930 (1,046)	12	0.52	976 (1,046)	15	0.52
Light intensity	243 (691)	79	245 (704)	80	186 (577)	77	0.32	296 (739)	77	0.24
Housekeeping	396 (454)	16	398 (444)	14	377 (405)	16	0.62	405 (550)	22	0.23
Walking	282 (389)	22	284 (402)	20	238 (267)	25	0.55	319 (435)	28	0.81
Bicycling	197 (337)	37	216 (348)	31	131 (207)	39	0.21	172 (386)	65	< 0.001
Work	292 (787)	84	313 (812)	82	208 (698)	88	0.34	280 (750)	84	0.72
Hobbies	114 (323)	73	105 (298)	73	138 (352)	69	0.41	129 (403)	75	0.73
Odd jobs	136 (365)	50	125 (322)	48	170 (492)	51	0.83	157 (406)	57	0.32
Gardening	85 (200)	54	86 (189)	52	62 (137)	57	0.56	104 (293)	65	0.10
Sport	54 (160)	76	65 (181)	72	38 (102)	81	0.16	14 (54)	91	0.003

* PA, physical activity; Freq, frequency of subjects reporting no activity; SD, standard deviation. † For the activities in which > 60 % of the subjects reported engaging in, the difference in mean time spent between NGT and IGT/nDM was tested. For the other variables, the difference between NGT and IGT/nDM in frequency was tested. All Adjusted for age.

Table 3

Time spent on physical activity (minutes/week) and frequency of subjects reporting no activity in women with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) or newly diagnosed diabetes mellitus (nDM): the Rotterdam Study, 1990-1994.

Type of physical activity	Total (n=513)		NGT (n=388)		IGT (n=76)			NDM (n=49)		
	Time per PA* mean (SD*)	Freq * (%)	Time per PA mean (SD)	Freq (%)	Time per PA mean (SD)	Freq (%)	<i>p</i> value†	Time per PA mean (SD)	Freq (%)	<i>p</i> value†
Total activity	1,721 (1,024)	5	1,768 (1,039)	5	1,578 (1,104)	5	0.34	1,566 (958)	6	0.28
Leisure activity	416 (460)	16	449 (479)	14	356 (474)	20	0.15	242 (267)	20	0.005
Vigorous intensity	272 (313)	15	293 (318)	13	210 (299)	20	0.06	199 (267)	22	0.03
Moderate intensity	1,370 (853)	6	1,387 (840)	6	1,350 (967)	7	0.77	1,267 (1,046)	6	0.40
Light intensity	77 (296)	86	86 (310)	85	18 (66)	91	0.29	99 (388)	88	0.74
Housekeeping	1,058 (655)	9	1,064 (648)	9	1,029 (654)	11	0.71	1,055 (719)	12	0.71
Walking	256 (372)	24	257 (369)	24	266 (427)	26	0.93	230 (306)	27	0.59
Bicycling	122 (215)	50	134 (222)	44	89 (201)	67	0.003	77 (169)	67	0.007
Work	96 (350)	89	104 (353)	87	55 (311)	96	0.07	96 (386)	88	0.93
Hobbies	49 (150)	82	53 (150)	94	25 (85)	96	0.17	53 (155)	96	0.67
Odd jobs	47 (206)	84	53 (198)	82	45 (290)	88	0.42	5 (21)	92	0.14
Gardening	53 (134)	64	56 (138)	62	44 (110)	71	0.42	36 (131)	71	0.36
Sport	38 (98)	73	44 (108)	71	23 (57)	80	0.19	12 (29)	84	0.08

* PA, physical activity; Freq, frequency of subjects reporting no activity; SD, standard deviation. † For the activities in which >60 % of the subjects reported engaging in, the difference in mean time spent between NGT and IGT/nDM was tested. For the other variables, the difference between NGT and IGT/nDM in frequency was tested. All adjusted for age.

cent) while much less time was spent on work, sports (2 percent), hobbies (3 percent), odd jobs (3 percent) and gardening (3 percent). As was also the case in men, a decrease in the mean time spent on physical activity was observed with increasing glucose intolerance, accompanied by an increase in the percentage of women reporting no activity (Table 3). After adjusting for age differences, the mean time spent on leisure activity and vigorous activity was significantly lower in women with nDM compared to women with NGT (differences, 207 and 94 minutes/week, respectively). Again, a significantly higher percentage of women with IGT or nDM, reported that they did not cycle, compared with women with NGT (difference, 23 percent).

In Table 4, odds ratios are given for the summary variables of physical activity, adjusted for age, body mass index, waist-hip ratio, family history of diabetes and smoking. Men with physical activity in the middle or highest tertile had a lower risk of having undiagnosed diabetes compared with the men in the lowest tertile. The inverse association between physical activity and risk of nDM was significant for vigorous activity (p trend=0.005). The association between IGT and physical activity was less clear compared with nDM, yet for IGT too, vigorous intense activities also seems to be associated with a lower prevalence of IGT (p trend=0.12).

In women, vigorous activity was also inversely associated with nDM (p trend=0.01). In addition, increasing leisure activity was inversely associated with a reduced prevalence of nDM (p trend=0.04). For IGT, no clear associations with activity were observed.

When we considered the relation between specific types of activity and glucose intolerance, significant inverse associations with nDM were found in men after adjustment for the main confounders for sports (OR=0.28, 95 percent CI 0.11-0.74), bicycling (OR=0.26, 95 percent CI 0.14-0.49), and housekeeping (OR=0.42, 95 percent CI 0.19-0.96) (Table 5). Among women, bicycling was the activity which was most strongly associated with absence of nDM (OR=0.37, 95 percent CI 0.18-0.78). No such associations were found with IGT for either men or women.

In order to be able to compare the magnitude of the effect of physical activity on diabetes mellitus with other risk factors for diabetes mellitus, we estimated the associations of the main confounders (age, body mass index, waist-hip ratio and smoking) with the presence of IGT or nDM. A higher body mass index or waist-hip ratio was associated with a higher prevalence of IGT or nDM in both men and women, independent of the other confounders. The association with IGT was significant for the highest body mass index tertile among both men and women (men, OR=2.91, 95 percent CI 1.32-6.35; women, OR= 4.7, 95 percent CI 1.81-11.9) and for the highest waist-hip ratio tertile among women

Table 4

Odds ratios (OR) for presence of impaired glucose tolerance (IGT) and newly diagnosed diabetes mellitus (nDM) according to physical activity tertiles, adjusted for age, body mass index, waist-hip ratio, family history of diabetes and smoking: the Rotterdam Study 1990-1994

Type of physical activity	Men					Women				
	Values (minutes/week)	IGT		nDM		Values (minutes/week)	IGT		nDM	
		OR	95% CI *	OR	95% CI		OR	95 % CI	OR	95% CI
Total activity										
Low	<847	†		†		<1245	†		†	
Medium	847 to <1860	0.80	0.41-1.59	0.67	0.32-1.43	1245 to <2007	0.99	0.45-2.21	0.89	0.40-1.99
High	≥ 1860	0.68	0.33-1.40	0.74	0.34-1.59	≥ 2007	1.05	0.45-2.43	0.80	0.34-1.88
p-trend		0.29		0.41			0.91		0.61	
Leisure activity										
Low	<270	†		†		< 135	†		†	
Medium	270 to <780	1.26	0.62-2.56	0.86	0.41-1.81	135 to < 467	0.70	0.31-1.57	0.69	0.32-1.47
High	>780	1.07	0.52-2.19	0.72	0.34-1.52	≥ 467	0.83	0.36-1.88	0.39	0.15-0.97
p-trend		0.89		0.39			0.66		0.04	
Vigorous activity										
Low	< 90	†		†		< 90	†		†	
Medium	90 to < 390	0.97	0.48-1.94	0.27	0.12-0.59	90 to < 298	0.73	0.33-1.63	0.50	0.23-1.09
High	> 390	0.56	0.26-1.19	0.35	0.17-0.73	≥ 298	0.72	0.32-1.62	0.32	0.13-0.79
p-trend		0.12		0.005			0.42		0.01	
Moderate activity										
Low	<510	†		†		< 1,007	†		†	
Medium	510 to < 990	1.01	0.51-2.02	0.86	0.39-1.88	1,007 to < 1,520	1.56	0.69-3.55	1.05	0.46-2.40
High	> 990	0.77	0.38-1.57	0.95	0.45-1.99	≥ 1,520	1.18	0.50-2.79	0.95	0.1-2.19
p-trend		0.47		0.90			0.72		0.90	
Light intensity	active vs. inactive	1.23	0.61-2.45	1.34	0.64-2.80	active vs inactive	0.77	0.27-2.18	0.77	0.27-2.19

* CI, confidence interval; †, reference category

Table 5

Odds ratios (OR) for presence of impaired glucose tolerance (IGT) and newly diagnosed diabetes mellitus (nDM) according to specific physical activities, adjusted for age, body mass index, waist-hip ratio, family history of diabetes and smoking: the Rotterdam Study 1990-1994

Type of physical activity	Values (minutes/week)	Men				Women			
		IGT		nDM		IGT		nDM	
		OR	95% CI *	OR	95% CI	OR	95 % CI	OR	95% CI
Housekeeping									
Low	<165	†		†		†		†	
Medium	165 to <457	1.10	0.54-2.23	0.42	0.19-0.96	0.86	0.37-1.95	0.65	0.29-1.50
High	≥ 457	0.83	0.40-1.73	0.66	0.32-1.36	1.02	0.46-2.26	0.77	0.34-1.72
p-trend		0.59		0.29		0.95		0.52	
Walking‡									
Low	<60	†				†		†	
Medium	60 to <285	1.80	0.87-3.69	1.62	0.73-3.55	1.03	0.45-2.39	0.86	0.38-1.97
High	>285	1.24	0.57-2.70	1.45	0.63-3.32	1.40	0.63-3.15	1.05	0.47-2.36
p-trend		0.65		0.42		0.40		0.89	
Bicycling	inactive vs active	0.89	0.48-1.65	0.26	0.14-0.49	0.78	0.40-1.55	0.37	0.18-0.78
Work	inactive vs active	0.52	0.20-1.33	1.03	0.45-2.36	0.57	0.16-2.03	1.03	0.39-2.74
Hobbies	inactive vs active	1.62	0.88-2.99	0.89	0.45-1.80	0.77	0.31-1.90	0.68	0.26-1.75
Odd jobs	inactive vs active	1.12	0.63-2.00	0.65	0.35-1.20	0.97	0.40-2.33	0.53	0.18-1.58
Gardening	inactive vs active	1.16	0.64-2.10	0.56	0.29-1.06	0.86	0.43-1.74	0.46	0.21-1.01
Sport	inactive vs active	0.70	0.35-1.41	0.28	0.11-0.74	0.82	0.38-1.75	0.59	0.26-1.35

* CI, confidence interval; †, reference category

‡ By tertile of activity

(OR=3.4, 95 percent CI 1.4-8.1). Smoking showed no association with presence of IGT or nDM.

To see whether a dose-response-relation can be observed between physical activity and glucose intolerance, the effect of physical activity on glucose level as a continuous variable was estimated. All physical activities seem to be inversely associated with a lower glucose level (both fasting and post-load). Significant associations were found between lower glucose level and vigorous activity ($p<0.01$ for both men and women), bicycling ($p<0.01$ for both men and women) and sports ($p=0.03$ for men) after adjustment for the main confounders (data not shown).

DISCUSSION

Physical activity is known to reduce the risk of non-insulin-dependent diabetes mellitus (NIDDM) in younger and middle-aged populations (3, 7, 16). The purpose of this study was to estimate the association between physical activity and presence of glucose intolerance in elderly subjects. A significant inverse association between physical activity and presence of newly diagnosed diabetes was observed. For impaired glucose tolerance, the association was less clear. Of special note was the finding that more vigorous activity was inversely associated with the presence of nDM, independent of age, overweight, waist-hip ratio, family history of diabetes mellitus and smoking. This observation is in accordance with several prospective studies, performed among middle-aged subjects, in which vigorous exercise was shown to be effective in reducing the risk of NIDDM (3-5). The literature is less consistent (3, 7, 16) in regard to activities of moderate intensity. In the present study, moderate activities were not associated with presence of nDM or IGT. This might be a consequence of measurement error due to inaccurate recall. Several studies have demonstrated low accuracy in recalling low-intensity behaviours, but higher accuracy with vigorous-intensity activity (17).

The questionnaire we used was originally designed and validated for elderly men (13). However, for use in this study, the questionnaire was modified by including questions about housekeeping and work. The correlation between physical activity and resting heart rate may give an impression of the validity of the questionnaire used (18). Although the correlation in the present study was comparable with that obtained in the original questionnaire (15), the results must be interpreted with some caution because the correlation is generally quite low (-0.08 , $p=0.04$ for women and -0.04 , $p=0.39$ for men). The estimates obtained through the activity questionnaire are, however, valuable in relative

terms and can be used to rank individuals or groups within a population. By categorizing the variables into tertiles or as active/inactive, misclassification is reduced.

Physical activity behaviour can be biased by the diagnosis of diabetes. Therefore subjects with known diabetes mellitus were excluded from this study. Subjects with nDM or IGT were most likely unaware of the diagnosis at the time of examination, which makes it less likely that they have altered physical activity behaviour through treatment interventions or their own efforts to change life-style factors.

Because diabetes is a clear risk factor for cardiovascular disease and persons with cardiovascular disease may be less physically active because of their disease, some of the association between physical activity and diabetes might be artefactual. However, an analysis excluding subjects with known coronary heart disease or stroke yielded virtually the same findings. In other studies, the results similarly remained essentially unchanged following the exclusion of subjects with prevalent coronary heart disease, hypertension or stroke (3, 4, 6). Although this study is cross-sectional, which makes a definitive conclusion about cause and effect impossible, it seems that the observed association was not due to coexistent disease.

The mechanism by which physical activity affects the occurrence of diabetes mellitus has not yet been clearly established. There is evidence that physical activity increases peripheral sensitivity to insulin, especially in skeletal muscle and adipose tissue (19-21). Besides, physical activity may improve weight reduction by increasing the energy expenditure associated with exercise (22) and obesity is a risk factor for developing diabetes mellitus (23). Indeed, in the present study, body mass index was inversely associated with physical activity. However, the crude odds were very similar (data not shown) to the adjusted odds ratios. This would suggest that the effect of physical activity is at least partly independent of obesity.

Elderly persons, both men and women, who cycled had a lower risk of having undiagnosed diabetes mellitus, whereas walking, an activity ideally suited for older persons (24), showed no association with nDM or IGT in the present study. It may well be that elderly persons with a lower level of ADL (activities of daily living), are more willing to continue walking, instead of, for example, bicycling. As we stated earlier, the intensity of an activity seems to be related with the effectiveness in reducing the risk of NIDDM. Bicycling is more intense than walking, which might partly explain why it is more associated with the occurrence of nDM or IGT. Walking is certainly to be advocated, but, at least in this study, showed no effect on diabetes mellitus.

Sports were significantly associated with nDM among men, but not among women. While women reported spending less time on sporting activities, this

could also be explained by the differences in the type of sport practised; men participated in more vigorous sports. Because the numbers concerned were so small, no analysis was performed to estimate the effect of the different types of sports.

Two other studies reported associations between physical activity and diabetes mellitus in elderly subjects. In the Honolulu Heart Study, a single index for physical activity was used in 4,560 Japanese-American subjects, aged 71-93 years (9). The authors did not describe how this index was obtained nor which activities were included. Contrary to our results, no difference in physical activity between subjects with NGT and newly diagnosed diabetes was found. In the Dutch "Hoorn" Study (10), 1,029 men and women, aged 50-75 years, reported on their physical activity, using the same questionnaire we used in the present study. The level of the physical activity was expressed as a score, ranging from 0-9. As in our study, both men and women with nDM had a lower physical activity score than subjects with NGT, which was significant in women.

In addition to an association with nDM, vigorous physical activity seemed to be inversely associated with the presence of impaired glucose tolerance, although not significantly. A few other studies examined the association between IGT and physical activity, and the results are conflicting. In the Hoorn Study (10) significant differences in physical activity score were found between men and women with IGT and NGT. The number of subjects with IGT in this study was twice as high as in our study, which might explain the significance reached. Dowse et al. (1), reported equal relative risks for impaired glucose tolerance and diabetes mellitus, although the risks were not significant. In two other studies, no association was observed between physical activity and IGT (9, 25).

In our study, diagnosis of IGT was made by a single OGTT, which is prone to intra-individual variation (26, 27). Using two OGTTs to diagnose IGT is likely to yield a more homogeneous group and may reveal a clearer association of IGT with physical activity. Lending support for the association between IGT and physical activity is the fact that, at least for the more vigorous activities, a dose-response-relation was observed. The higher the vigorous activities, such as sports and bicycling, the lower the fasting or postload glucose levels.

Because this study is cross-sectional in design with no questions asked about physical activities in the past, we could not analyze whether physical activity throughout life is important or whether physical activity initiated at an older age is also protective. Several studies have shown that the benefits of physical activity disappear within several days after exercising, which implies a need for regular exercise (28). Adults who have previously been sedentary require a period of training to increase their fitness to a level where they can perform the necessary duration and intensity of exercise that will be effective. Because this level of training may be difficult or impossible to achieve in older

subjects, exercise optimally should be initiated at much younger ages and continued throughout life.

In conclusion, regular exercise may protect against diabetes mellitus in older adults as it does among middle-aged adults. This finding therefore serves to strengthen the ground for encouraging physical activity in elderly subjects.

References

1. Dowse GK, Zimmet PZ, King H: Relationship between prevalence of impaired glucose tolerance and NIDDM in a population. *Diabetes Care* 14:968-974, 1991
2. Taylor R, Ram P, Zimmet P, Raper L, Ringrose H: Physical activity and prevalence of diabetes in Melanesian and Indian men in Fiji. *Diabetologia* 27:578-582, 1984
3. Helmrigh SP, Ragland DD, Leung RW, Paffenbarger RS: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Eng J Med* 325:147-152, 1991
4. Burchfiel CM, Sharp DS, Curb JD, et al.: Physical activity and incidence of diabetes: The Honolulu Heart Program. *Am J Epidemiol* 141:360-368, 1995
5. Manson JR, Rimm EB, Stampfer MJ, et al: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774-778, 1991
6. Manson HE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH: A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* 268:63-67, 1992
7. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG: Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *Br Med J* 310:560-564, 1995
8. Clark DO: Physical activity efficacy and effectiveness among older adults and minorities. *Diabetes Care* 20:1176-1182, 1997
9. Rodriguez BL, Curb JD, Burchfield CM, et al.: Impaired glucose tolerance, diabetes and cardiovascular disease risk factor profiles in the elderly. *Diabetes Care* 19:587-590, 1996
10. Mooy JM, Grootenhuys PA, de Vries H, Valkenburg HA, Bouter LM, Heine RJ: Prevalence and determinants of glucose intolerance in a Caucasian population. The Hoorn Study. *Diabetes Care* 18:1270-1273, 1995
11. Hofman A, Grobbee DE, Jong de PVTM, Ouweland van de FA: Determinants of disease and disability in the elderly: the Rotterdam Elderly study. *Eur J Epidemiol* 7:403-22, 1991
12. World Health Organization. *Diabetes mellitus: report of a study group*. Geneva: WHO, 1985.
13. Caspersen CJ, Bloembergen BPM, Saris WHM, Merritt RK, Kromhout D: The prevalence of selected physical activities and their relation with coronary heart

- disease risk factors in Elderly men: the Zutphen Study 1985. *Am J Epidemiol* 133:1078-1092, 1991
14. Ainsworth BE, Haskell WL, Leon AS, et al.: Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 25:71-80, 1993
15. Bijnen FCH, Feskens EJM, Casperen CJ, et al.: Physical activity and cardiovascular risk factors among elderly men in Finland, Italy and The Netherlands. *Am J Epidemiol* 143:553-561, 1996
16. Lynch J, Helmrigh SP, Lakka TA, et al.: Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Arch intern med* 156:1307-1314, 1996
17. DiPietro L: Physical activity, body weight and adiposity: an epidemiologic perspective. *Exerc Sport Sci Rev* 23:275-303, 1995
18. Blair SN, Kohl HW, Gordon NF: How much physical activity is good for health? *Annu Rev Publ Health* 13:99-126, 1992
19. Horton ES: Exercise and decreased risk of NIDDM. *N Engl J Med* 325:196-197, 1991
20. Pescatello LS, DiPietro L: Physical activity in older adults. An overview of health benefits. *Sports medicine* 15:353-364, 1993
21. Feskens EJM, Loeber JG, Kromhout D: Diet and physical activity as determinants of hyperinsulinemia: the Zutphen Elderly Study. *Am J Epidemiol* 140:350-360, 1994
22. Horton ES: Role and management of exercise in diabetes mellitus. *Diabetes Care* 11:201-211, 1988
23. Barrett-Connor EL: Epidemiology, obesity and non-insulin-dependent diabetes mellitus. *Epidemiol Rev* 11:172-181, 1989
24. Harris SS, Caspersen CJ, DeFries GH, Estes EH: Physical activity counseling for healthy adults as a primary preventive intervention in the clinical setting: report from the US Preventive Services Task Force. *Journal of American Medical Association* 261:3590-3598, 1989
25. Schulz LO, Weidensee RC: Glucose tolerance and physical activity in a mexican indigenous population. *Diabetes Care* 18:1274-1276, 1995
26. Feskens EJM, Kromhout D: Glucose tolerance and the risk of cardiovascular diseases: the Zutphen Study. *J Clin Epidemiol* 45:1327-1334, 1992
27. Wiener K: The diagnosis of diabetes mellitus, including gestational diabetes. *Ann Clin Biochem* 29:481-493, 1992
28. Laws A, Reaven GM: Physical activity, glucose tolerance and diabetes in older adults. *Annals of Behavioural Medicine* 13:125-132, 1991

Performance of a
predictive model
to identify undiagnosed
diabetes mellitus
in a health care setting

ABSTRACT

The aim of this study was to develop a predictive model to identify individuals with an increased risk for undiagnosed diabetes allowing for the availability of the information within the health care system.

A sample of participants of the Rotterdam Study (n=1,016), aged 55 to 75, not known to have diabetes, completed a questionnaire on diabetes-related symptoms and risk factors and underwent a glucose tolerance test. Predictive models were developed using stepwise logistic regression analyses with absence or presence of newly diagnosed diabetes as the dependent variable and various items with a plausible connection to diabetes as the independent variables. The models were evaluated in another Dutch population-based study, the Hoorn Study (n=2,364), in which the participants were aged 50-74. Performances of the predictive models were compared by using receiver-operator characteristics (ROC) curves.

We developed three predictive models (PMs). PM1 contained information routinely collected by the general practitioner, while PM2 also contained variables obtainable by additional questions. The third predictive model, PM3, included variables that had to be obtained from a physical examination. These latter variables did not have additive predictive value, resulting in a PM3 similar to PM2. The area under the ROC-curve was higher for PM2 than for PM1, but the 95% confidence intervals overlapped (0.74 (95% CI: 0.70-0.78) and 0.68 (0.64-0.72) respectively).

Using only information normally present in the files of a general practitioner, a predictive model was developed that performed similarly to one supplemented by information obtained from additional questions. The simplicity of PM1 makes it easy to implement in the current health care setting.

Acknowledgements

This study is part of a research project supported by grants from the National Institute for Health Sciences (NIHES).

INTRODUCTION

Several studies have reported that up to 50% of all subjects with diabetes are undiagnosed (1-4). Although these subjects are not aware of their disease, they are at risk for the micro- and macrovascular complications of diabetes (5, 6). Early treatment of diabetes and the associated cardiovascular risk factors (hypertension, obesity, dyslipidemia) may reduce the occurrence of these complications (7). Therefore, early detection of the subjects with undiagnosed diabetes might be of importance in reducing the burden of complications of diabetes. Identifying people at increased risk for undiagnosed diabetes, followed by blood glucose testing to establish diagnosis, is considered to be an appropriate way of dealing with this problem (8). The American Diabetes Association (ADA) recommends screening for type 2 diabetes by using a verbal or written questionnaire to select high-risk individuals, to increase the cost-effectiveness of testing undiagnosed individuals (9).

A number of questionnaires have been developed to identify subjects with an increased risk of having undiagnosed diabetes (10-12). However, a tool based on information already available to a general practitioner would be more easily implemented in the current health care setting. In a sample of the Rotterdam Study in The Netherlands, we developed a predictive model to identify individuals at increased risk for undiagnosed diabetes, using information routinely collected by the general practitioner. In addition, we developed predictive models using information collected by simple questions or physical examination. These predictive models were tested in the Hoorn Study, another Dutch population based study (3), and their diagnostic value is evaluated in this study.

METHODS

Rotterdam Study

The present study was conducted among participants of the Rotterdam Study (13). The selection of the study sample is described in detail elsewhere (14). A baseline examination was conducted from 1990 to 1993 and included 7,983 subjects, aged 55 and older (response rate 78%). Based on the baseline non-fasting oral glucose tolerance test (OGTT), participants aged 55 to 75 years were temporarily classified as diabetic (using medication or random or postload level >11.1 mmol/l), hyperinsulinemic (upper quintile of the gender-specific post-load insulin distribution in subjects without impaired glucose tolerance or diabetes

mellitus) or normal glucose tolerant. A stratified random sample was taken from each group to participate in the Rotterdam Diabetes Study. The overall response rate in the follow-up examination was 90%, and 1,112 subjects took part in the diabetes study. In this study a definitive classification of the glucose tolerance status was made, based on a fasting OGTT.

The participants came to the research center after an overnight fast (no food intake after 11.00 P.M.), and had blood taken between 8.00 and 9.00 A.M. Subjects not using antidiabetic medication went on to have a standard 75-g oral glucose tolerance test (15). Fasting and two hour plasma glucose levels were determined using the glucose hexokinase method. Diabetes was defined as the use of antidiabetic medication (insulin or oral hypoglycemic medication) and/or a 2-hour plasma glucose concentration ≥ 11.1 mmol/l according to the World Health Organization (WHO) criteria (15). Subjects with a glucose level in the diabetic range, who did not use antidiabetic medication, were classified as newly diagnosed cases of diabetes mellitus. All known diabetic patients ($n=69$) were excluded from the present analysis.

Information on medication use, medical history (cardiovascular disease, stroke), smoking habits and family history (first degree) of diabetes was obtained from a self-administered questionnaire. The Rose questionnaire was used to assess angina pectoris and intermittent claudicatio (16). Physical activity was assessed by a self-administered questionnaire derived from one originally designed for retired men and described by Caspersen and others (17). This was modified for use in the current study by the addition of questions of household activities (14).

Sitting blood pressure was measured with a random-zero sphygmomanometer, and the mean of two measurements was used in the analyses. Weight and height were measured with the participants wearing indoor clothes and no shoes. Waist circumference was measured midway between the lower rib margin and iliac crest; hip circumference was measured at the trochanter major. The body mass index (BMI) was determined by dividing the weight by the height squared (kilograms per meter squared) and body fat distribution was assessed by means of the waist-to-hip circumference ratio (WHR).

Analysis

We used three levels of information, defined by the degree of effort needed by a general practitioner for their collection. Level 1 is normally present in routine general practitioner records, level 2 is obtainable by simple questions and level 3 requires additional measurements. Three predictive models were developed, based on these three levels of information. In Table 1 the variables used for the analysis are grouped according to the level of information.

Table 1
Characteristics of the Rotterdam Diabetes Study population ordered by level of information

Variables	Nondiabetic	Newly detected diabetes	OR (95% CI)
	n=898	n=118	
<i>Level 1: present in routine general practice records</i>			
Age (years)	66.2 ± 5.5	67.8 ± 5.7	–
Sex (% F)	51.7	41.5	–
Presence of obesity	13.2	20.3	1.75 (1.07-2.88)
Use of antihypertensive medication	24.6	35.6	1.57 (1.04-2.38)
Use of lipid lowering medication	5.3	6.8	1.29 (0.59-2.82)
Gestational diabetes (% of the women)	1	0	–
Prevalence of CVD	13.7	22.0	1.54 (0.95-2.51)
<i>Level 2: additional questions</i>			
BMI (kg/m ²)	26.1 ± 3.2	27.5 ± 3.9	1.10 (1.04-1.16)
Family history of diabetes	20.5	28.8	1.94 (1.25-30.1)
Smoking	23.2	20.3	0.88 (0.54-1.42)
Cardiovascular symptoms			
Chest pain	6.7	11.0	1.97 (1.04-3.75)
Pain during walking	4.0	7.6	2.30 (1.10-4.81)
Pain during walking with need to slow down	2.9	3.4	1.10 (0.38-3.19)
Pain in calf during walking	2.4	2.5	1.06 (0.31-3.59)
Shortness of breath when			
Washing/dressing	2.7	3.4	1.18 (0.40-3.49)
Walking with people of the same age	4.2	3.4	0.72 (0.25-2.08)
Not cycling	40.1	66.1	2.99 (1.97-4.55)
<i>Level 3: additional measurements</i>			
Diastolic blood pressure (mmHg)	76.3 ± 10.7	76.8 ± 11.4	1.00 (0.98-1.03)
Systolic blood pressure (mm Hg)	135.7 ± 19.7	143.6 ± 20.6	1.02 (1.00-1.03)
WHR	0.91 ± 0.09	0.94 ± 0.09	12.51 (1.04-150.8)

Data are means ± SD or %. Odds Ratios (OR) are adjusted for age and sex. Obesity is defined in this study as BMI ≥ 30 kg/m². Blood pressure measurements exclude those subjects using antihypertensive medication.

Within each level of information a stepwise logistic regression analysis was used with the absence or presence of newly detected diabetes as the dependent variable and the variables of the predictive model as independent variables. Any symptom or risk factor associated with newly detected diabetes at a significance

level of $p < 0.05$ was included in the first predictive model. This model was extended to include the variables of the second model and, subsequently, those of the third model as well. The regression coefficients of the predictive models were transformed into scores (multiplied by 10 and rounded off to the nearest integer) that were added up to obtain an aggregated score. All analyses were performed with the SPSS-PC software package, version 7.0.

Validation of the predictive models

The derived predictive models were tested in the Hoorn Study. A random sample of 50 to 74 year-old subjects was taken from the population register of the town of Hoorn in The Netherlands. The final Hoorn cohort consisted of 2,484 subjects, as described previously (3). All subjects who reported having diabetes ($n=104$) were excluded from the present analysis. Participants completed a detailed questionnaire on symptoms and risk factors for diabetes before visiting the center. All participants underwent a 75-g OGTT and were classified according to the WHO criteria (15). Height and weight of the subjects were also measured without shoes and outer garments during the visit.

To compare the performance of the different risk functions, receiver-operator characteristic (ROC) curves were constructed. ROC curves characterise the relationship between sensitivity and 1-specificity. The sensitivity of a test is the probability (0-100%) that the test is positive for subjects with diabetes. The specificity is the probability that a test is negative for subjects without diabetes. The area under the ROC-curve quantifies how well the test correctly distinguishes a subject with diabetes from a subject without diabetes; the larger the area under the curve, the better the performance of the risk function. The Epistat package was used to construct the ROC-curves and their 95% confidence intervals (CI).

At different cut-off points of the predictive models, the number of subjects who would need to be referred for further testing to diagnose diabetes was calculated, as was the number of subjects with undiagnosed diabetes mellitus who will be missed. In order to be able to compare the performance of the three predictive models with previously reported studies (10-12), we used cut-off values yielding a specificity of 55%.

Table 2
Results of stepwise logistic regression analyses, predicting newly diagnosed diabetes mellitus - the content of two predictive models (Rotterdam Diabetes Study)

Variables	Unit	PM1				PM2			
		LRC	Score	OR (95% CI)	p-value	LRC	Score	OR (95% CI)	p-value
Constant		-3.02				-5.42			
Age	per 5-year increment from 55 yr	0.19	2	1.21 (1.02-1.44)	0.03	0.13	1	1.13 (0.95-1.36)	0.17
Sex	0: female, 1: male	0.46	5	1.59 (1.07-2.36)	0.02	0.66	7	1.94 (1.28-2.93)	0.02
Use of antihypertensive medication	0: no, 1: yes	0.42	4	1.53 (1.00-2.32)	0.04	0.27	3	1.31 (0.85-2.03)	0.22
Presence of obesity	0: not obese, 1: obese	0.51	5	1.68 (1.02-2.76)	0.05				
Physical inactivity	0: cycling, 1: not cycling					1.04	10	2.83 (1.85-4.33)	<0.001
Family history of DM	0: no, 1: yes					0.70	7	2.01 (1.28-3.18)	0.003
BMI	continuous					0.07	1	1.07 (1.02-1.13)	0.01

Scores were obtained by multiplying the regression coefficient with 10 and rounding to the nearest integer. Obesity is defined as ≥ 30 kg/m² for both sexes. The actual BMI of a subject has to be multiplied by 1 and added to the total sum of scores. LCR: logistic regression coefficient; OR odds ratio.

RESULTS

Selection of the predictive models

Compared to the non-diabetic subjects, the group of individuals with newly detected diabetes mellitus ($n=118$) were more likely to be men and to have a higher BMI, WHR and systolic blood pressure, to use more antihypertensive medication, and to have a family history of diabetes mellitus (Table 1). Chest pain was more prevalent among subjects with newly detected diabetes mellitus, as was pain during walking. Two-thirds of the subjects with nDM reported that they did not cycle compared to 40% of the nondiabetic subjects.

In the first predictive model (PM1) age, sex, presence of obesity and use of antihypertensive medication were selected (Table 2). The second predictive model (PM2) also included family history of diabetes, BMI (continuous), and physical activity (operationalised as cycling). The variables obtained from physical examination (blood pressure and WHR) did not have an additive predictive value, resulting in a third predictive model (PM3) that was identical to the second one. The regression coefficients were transformed into scores. The age score showed that from age 55 onward, every increment of 5 years corresponded with an additional score of 2 points for PM1 and 1 point for PM2. The aggregated score ranged from 0 to a maximum of 22 for PM1 and from 19 to 60 for PM2.

Table 3

Percentage of newly diagnosed diabetes mellitus in both studies, according to strata of the aggregated score of the two predictive models.

Predictive model 1			Predictive model 2		
Score	Prevalence		Score	Prevalence	
	Rotterdam Diabetes Study	Hoorn Study		Rotterdam Diabetes Study	Hoorn Study
< 4	18/227 (8.6)	10/606 (1.7)	<33	10/239 (4.4)	14/869 (1.6)
4 - 6	22/268 (8.9)	27/803 (3.5)	33 - 36	17/188 (9.9)	20/497 (4.1)
7 - 8	23/180 (12.7)	9/269 (3.5)	37 - 41	16/175 (10.1)	21/458 (5.0)
9 - 10	24/140 (20.7)	20/336 (6.4)	42 - 47	30/216 (16.1)	20/343 (6.2)
≥ 11	31/174 (20.9)	44/350 (14.4)	≥ 48	45/171 (35.7)	34/197 (21.0)
Total	118/989 (13.5)	110/2364 (4.9)	Total	118/989 (13.5)	110/2364 (4.9)

Data are number of subjects with newly detected diabetes/total n (%)

Validation of the predictive models

Both predictive models were evaluated in the Hoorn Study. In this study, 110 out of 2,364 subjects had newly diagnosed diabetes mellitus. The characteristics of the Hoorn population differed slightly from the Rotterdam Diabetes Study. The mean age of subjects with or without nDM was lower (66.2 and 60.5 years). The proportion of women among the two groups was 47%. The proportion of subjects with obesity among newly diagnosed diabetics and non-diabetic subjects was higher as compared to the Rotterdam Diabetes Study (36.4 and 14.0 respectively). The proportion of subjects using antihypertensive drugs was lower in the Hoorn Study (28.7 (newly detected diabetes) and 13.3% (non-diabetic)), as was the percentage of subjects reporting that they did not cycle (41.3% and 23.6%).

In Table 3, the percentage of newly diagnosed diabetes mellitus in the Rotterdam Diabetes Study and in the Hoorn Study is given according to strata of the aggregated score of the two predictive models. The percentage of nDM increased with a higher score in both models. In the Rotterdam Study 20% of the subjects with a score ≥ 9 in PM1 and ≥ 42 in PM2 had newly diagnosed diabe-

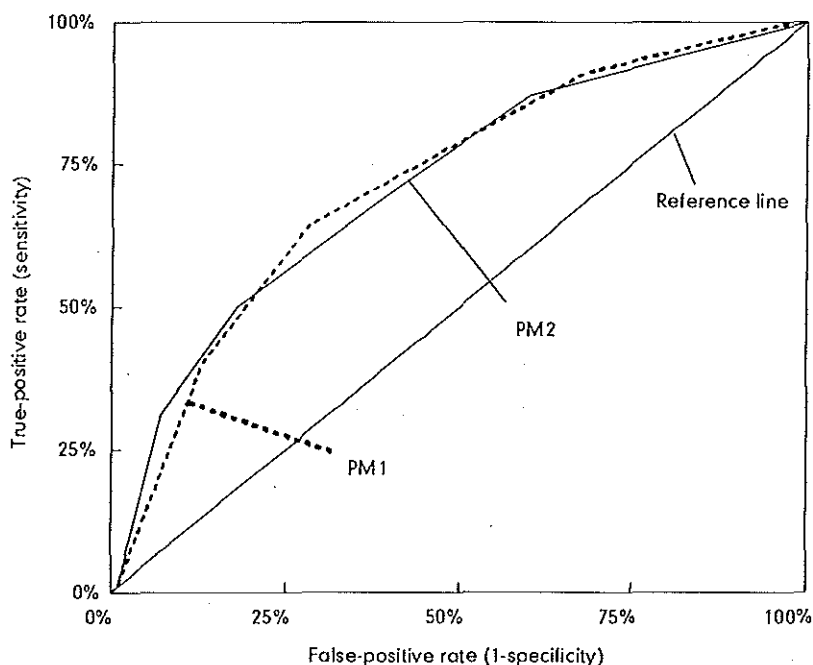


Figure 1
ROC-curves for PM1 and PM2 (Hoorn Study).

Table 4
Performance of PM1 and PM2 (Hoorn Study)

	PM1	PM2
Cut-off point	Score >6	Score >36
<i>Performance of the predictive model</i>		
Specificity	55	55
Sensitivity	78	72
Positive predictive value	8	7.2
Negative predictive value	98	98
<i>Characteristics of the false positives</i>		
% of subjects with IGT (n)	14.7 (130 of the 882)	14.4 (133 of the 923)

tes. In the Hoorn study, the optimal cut-off point was ≥ 11 in PM1 and ≥ 48 in PM2.

The area under the ROC-curve was larger for PM2 (0.74; 95% CI: 0.70-0.78) compared with PM1 (0.68; 95%CI 0.64-0.72), but the confidence intervals overlap (Figure 1). Of the 110 subjects (63.6%) with newly detected diabetes, 70 had positive scores on both PM1 as PM2 when using the cut-off point of ≥ 6 for PM1 and ≥ 36 for PM2.

With a specificity of 55%, the positive predictive value (PPV) of PM1 was 8% and of PM2 7.2%. When characterising the false positive subjects, 14.4% had impaired glucose tolerance in PM1 and 13.9% in PM2 (Table 4).

The predictive models select subjects who should undergo further testing for diagnosing diabetes mellitus. In Figure 2, the number of subjects required to undergo blood glucose testing (e.g. an OGTT) to find one diabetic subject is plotted against different cut-off points of the predictive models. When no predictive model is used to select subjects with a higher risk of undiagnosed diabetes, 20.5 subjects would have to undergo an OGTT to find one diabetic subject (assuming a prevalence of undiagnosed diabetes of 5%, as in the Hoorn Study). At higher cut-off points, fewer subjects have to be referred for further testing. However, the percentage of diabetic subjects missed will increase (Figure 3).

DISCUSSION

We developed three predictive models for selecting subjects with an increased risk of having undiagnosed diabetes mellitus. In the first predictive model, we

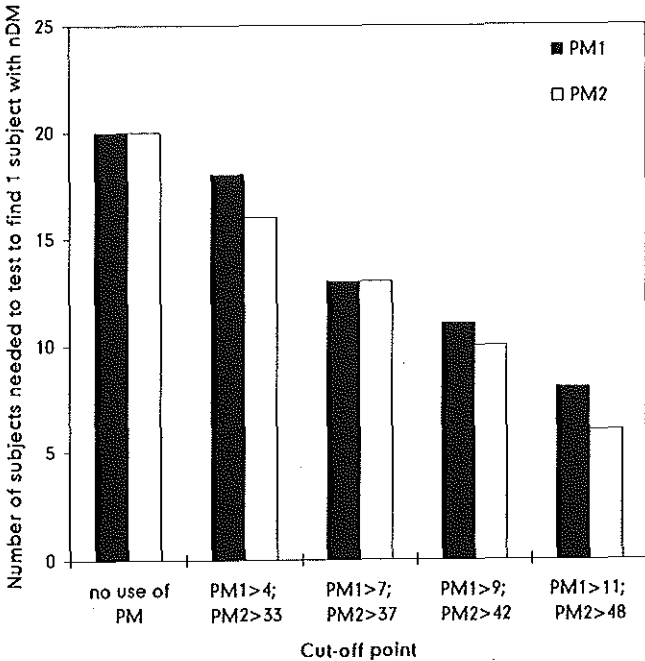


Figure 2
Effect of selecting subjects with a high risk of having undiagnosed diabetes mellitus, expressed as the number of subjects which has to be referred for further testing to diagnose one diabetic subject.

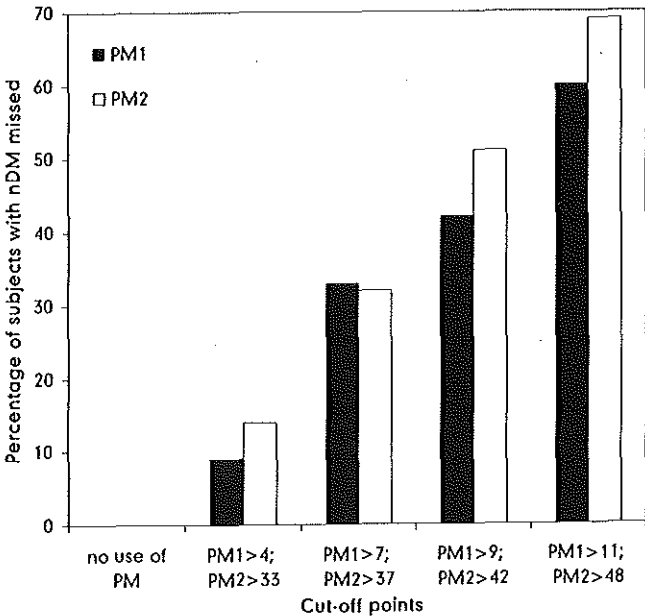


Figure 3
The percentage of undiagnosed diabetic subjects that will be missed when using the PM1 or PM2.

included only information readily available to the general practitioner. The variables age, gender, use of antihypertensive medication and presence of obesity appeared to be predictive. In the second predictive model items that could easily be obtained by simple additional questions were included. A family history of diabetes and physical inactivity (in this Dutch study operationalised as bicycling) was included as risk factor in this model, of which the variables of the first model were also part. The third predictive model (PM3) was rejected, since the items obtainable by non-invasive measurements (blood pressure or WHR) had no additive predictive value in this study population, resulting in a PM3 similar to PM2. To gain more insight into the performance of the two predictive models, both were evaluated in another study population. The differences between the two models were rather small.

In the Rotterdam Study 20% of the subjects with a score ≥ 9 in PM1 and ≥ 42 in PM2 had newly diagnosed diabetes. In the Hoorn study, the optimal cut-off point was ≥ 11 in PM1 and ≥ 48 in PM2. This is probably due to the fact that the differences in characteristics between newly diagnosed diabetic subjects and the non-diabetic subjects are larger in the Hoorn Study as compared with the Rotterdam study. For example the mean age in the Rotterdam study is 66.2 years for non-diabetic subjects and 67.8 years for diabetic subjects, whereas in the Hoorn study the mean age is 60.2 and 66.5 years respectively.

In the first predictive model obesity was defined as BMI ≥ 30 kg/m², whereas in the second predictive model BMI was included as a continuous variable. Assuming that in reality a general practitioner can not exactly estimate whether a person has a BMI below or above 30 kg/m², the predictive value of this variable will be lower in clinical practice. The performance of PM1 is thus slightly overestimated. However, the BMI used in PM2 will usually be based on self-reported height and weight instead of taking these measurements, as was the case in this study. It has been shown that self-reported height and weight lead to an underestimation of the BMI (18, 19), and this underestimation tends to be higher in more obese subjects than in lean ones (20). It is not clear whether this will influence the predictive value of PM2, but the performance of PM2 is likely to be slightly overestimated. When using the categorical variable obesity instead of the continuous variable in the PM2, the performance of this model did not change (data not shown).

Physical activity was a highly discriminative variable between subjects with and without diabetes, an observation also reported in other studies (9, 11). As has been shown in a previous study (14), cycling was the variable that contributes most to the discrimination in The Netherlands. We have chosen to use cycling as a variable in the PM2, since now the subject only has to answer one simple question, whereas when using the more broad and vague variable "physical activity", a number of questions have to be answered to arrive at a

score. Obviously, in other countries different activities will contribute to total activity.

Considering the small differences between the two predictive models in performance, and the simplicity of the first one, PM1 seems to be the most appropriate predictive model to use in the current health care setting. The variables selected for PM1 are very logical from a clinical point of view and, as most general practices are computerised, it will be easy to identify the subjects with a positive score on PM1 by the computer.

Several other tools for screening undiagnosed diabetes mellitus have been developed in earlier studies. The American Diabetes Association (ADA) suggests that everyone with more than one risk factor for diabetes (family history of diabetes, obesity, an at risk race, hypertension, significant hyperlipidemia and a history of gestational diabetes or delivery of heavy babies) should be referred to the general practitioner and tested for diabetes (9). Herman et al. (11) developed a classification tree in which age, physical inactivity, family history of diabetes and having given birth to a heavy baby were predictive variables. In the Hoorn Study (12) a questionnaire was developed which included age, gender, obesity, physical inactivity, frequent thirst and some cardiovascular symptoms. The questionnaires differ in the number of risk factors, but all include age, gender and family history of diabetes. In our study, no obstetrical questions were asked, and thus the variable 'delivery of heavy babies' could not be included in the analysis.

The performance of the reported tools has been compared by Ruige et al (12) in yet another Dutch population-based study with a prevalence of newly detected diabetes similar to that of the Hoorn Study. The positive predictive values (PPV) ranged from 5% to 7%, which is comparable to the PPVs of our PM1 (8%) and PM2 (7.2%). The choice of the cut-off values ensured that the specificity was ~55% for all tools to facilitate a comparison between the PPVs. These low PPVs place into question the usefulness of a tool for selection of subjects with high risk for undiagnosed diabetes. On the one hand, they are simple and easy to use. Without much effort, the population to be tested for diabetes (using a blood glucose measurement) can be reduced. They are, moreover, useful in making the general practitioner and the patients more attentive to the problem of undiagnosed diabetes mellitus. For example, the possibility of having undiagnosed diabetes seems to be underestimated in men, considering the high score of this variable in both predictive models (score=5 in PM1 and 7 in PM2). After selection of a high-risk group, a large number of people will nonetheless turn out not to have diabetes, depending on the cut-off point used. In addition, a number of subjects with undiagnosed diabetes mellitus will be missed, since they will have a score below the cut-off point.

In the development and evaluation of the questionnaires, attention has only been paid to screening of undiagnosed diabetes mellitus. However, there will also be a number of subjects with IGT. In the Hoorn Study 15% of the subjects who scored positively on the first predictive model had IGT, using a cut-off point of 6. These subjects have been shown to have an increased risk for developing diabetes (21), as well as an increased risk for (macrovascular) complications (22-24). Intervention strategies in people with IGT or other high-risk characteristics may prevent or delay NIDDM (25, 26). More insight into this question will be obtained from the Diabetes Primary Prevention Trial, in which treatment of people with high risk characteristics such as IGT will be tested (27).

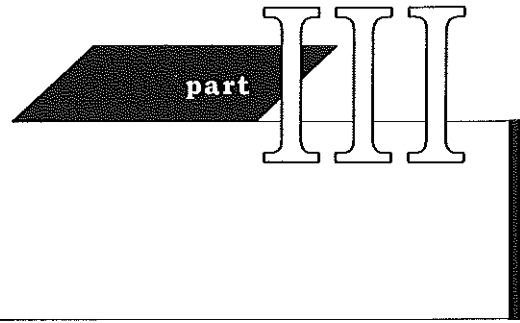
To conclude, the predictive models can be used to identify subjects with a higher risk for having undiagnosed diabetes mellitus. Both the predictive models we developed may easily be used in the current health care setting. However, from a pragmatic point of view PM1 seems to be the most appropriate predictive model. Until the discussion is solved about who, when and how to screen for undiagnosed diabetes on a community-wide basis, general practitioners can use PM1 to check which of their patients have a higher probability of having undiagnosed diabetes mellitus.

References

1. King H, Rewers M: Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. *Diabetes Care* 16:157-177, 1993
2. Harris MI: Undiagnosed NIDDM: clinical and public health issues. *Diabetes Care* 16:642-653, 1993
3. Mooy JM, Grootenhuys PA, de Vries H, Valkenburg HA, Bouter LM, Heine RJ: Prevalence and determinants of glucose intolerance in a Caucasian population. The Hoorn Study. *Diabetes Care* 18:1270-1273, 1995
4. Stolk RP, Pols HAP, Lamberts SWJ, Jong de PTVM, Hofman A, Grobbee DE: Diabetes mellitus, impaired glucose tolerance and hyperinsulinemia in an elderly population. The Rotterdam Study. *Am J Epidemiol* 145:24-32, 1997
5. Balkau B, Eschwege E, Papoz L, et al.: Risk factors for early death in non-insulin-dependent diabetes and men with known glucose tolerance status. *Br Med J* 307:295-299, 1993
6. Klein R: Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258-268, 1995
7. Harris MI, Modan M: Screening for NIDDM. Why is there no national program? *Diabetes Care* 17:440-444, 1994
8. Paterson KR: Population screening for diabetes mellitus. *Diabetic Medicine* 10: 777-781, 1993

9. American Diabetes Association: Screening for type 2 Diabetes. Position Statement. *Diabetes Care* 21:supplement 1 S20-S22, 1998
10. American Diabetes Association: American diabetes alert. *Diabetes Forecast* 46: 54-55, 1993
11. Herman WH, Smith PJ, Thompson TJ, Engelgau MM, Aubert RE: A new and simple questionnaire to identify people at increased risk for undiagnosed diabetes. *Diabetes Care* 18:382-387, 1995
12. Ruige JB, Neeling de JND, Kostense PJ, Bouter LM, Heine RJ: Performance of an NIDDM Screening questionnaire based on symptoms and risk factors. *Diabetes Care* 20:491-496, 1997
13. Hofman A, Grobbee DE, Jong de PVTM, Ouweland van de FA: Determinants of disease and disability in the elderly: the Rotterdam Elderly study. *Eur J Epidemiol* 7:403-22, 1991
14. Baan CA, Stolk RP, Grobbee DE, Witteman JCM, Feskens EJM: Physical activity in elderly subjects with impaired glucose tolerance and newly diagnosed diabetes mellitus. *Am J Epidemiol* 149:219-227, 1999
15. World Health Organization. *Diabetes mellitus: report of a study group*. Geneva: WHO, 1985.
16. Rose G, Blackburn H: *Cardiovascular Survey Methods*. Geneva WHO Monogr. Ser., 1968
17. Caspersen CJ, Bloemberg BPM, Saris WHM, Merritt RK, Kromhout D: The prevalence of selected physical activities and their relation with coronary heart disease risk factors in Elderly men: the Zutphen Study 1985. *Am J Epidemiol* 133:1078-1092, 1991
18. Roberts RJ: Can self-reported data accurately describe the prevalence of overweight? *Public Health* 109:275-284, 1995
19. Crawley HF, Portides G: Self-reported versus measured height, weight and body mass index amongst 16-17 year old teenagers. *Int J Obes Relat Metab Disord* 19:579-584, 1995
20. Jeffery RW: Bias in reported body weight as a function of education, occupation, height and weight concern. *Addict Behav* 21:217-222, 1996
21. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, Bennett PH: A two-step model for development of non-insulin-dependent diabetes. *Am J Med* 90: 229-235, 1991
22. Fuller JH: Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall Study. *Lancet* 1(8131):1372-1376, 1980
23. Rewers M, Shetterly SM, Baxter J, Marshall JA, Hamman RF: Prevalence of coronary heart disease in subjects with normal and impaired glucose tolerance and non-insulin-dependent diabetes mellitus in a biethnic Colorado population. The San Luis Valley Diabetes Study. *Am J Epidemiol* 135:1321-30, 1992
24. Nijpels G, Popp-Snijders C, Kostense PJ, Bouter LM, Heine RJ: Cardiovascular Risk factors prior to the development of non-insulin-dependent diabetes mellitus in persons with impaired glucose tolerance: the Hoorn Study. *J Clin Epidemiol* 50:1003-1009, 1997
25. Eriksson KF, Lindgärde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. *Diabetologia* 34:891-898, 1991
26. Tuomilehto J, Knowler WC, Zimmet P: Primary prevention of non-insulin dependent diabetes mellitus. *Diabetes Metab Rev* 8:339-353, 1992

27. Knowler WC: Screening for NIDDM. Opportunities for detection, treatment, and prevention. *Diabetes Care* 17:445-450, 1994



BASIC ELEMENTS

OF DIABETES EPIDEMIOLOGY:
INCIDENCE, PREVALENCE,
MORTALITY OF DIABETES MELLITUS
IN THE NETHERLANDS

Prevalence of diabetes mellitus in The Netherlands: a quantitative review

ABSTRACT

The prevalence of diabetes above the age of 30 years in The Netherlands was estimated and the influence of methodological variables on the reported prevalence rates was quantified. Fifteen Dutch studies performed since 1970 were entered in logistic regression models with the presence or absence of known diabetes above the age of 30 years as a dependent variable. In order to quantify the variability among studies, the study methodology and population characteristics were chosen as independent variables. The age-standardized prevalence of known diabetes varied between the studies. The total prevalence of known diabetes above the age of 30 years in 1993 can be estimated at 2.7% on the basis of the cases reported by general practitioners and at 3.2% based on self-reported cases in surveys. The prevalence according to age increased by 7.1% per life year for men and by 7.7% for women. These associations were essentially similar in all studies. Systematic screening, performed with an oral glucose tolerance test, revealed a prevalence which was 1.5-2 times higher. Depending on the method used, the number of subjects with known diabetes in the Netherlands in 1993 varied between 235,000 and 285,000. After systematic screening, this prevalence will be 1.5-2 times higher. These estimates may serve various goals. The prevalence rates based on self-reports or reports by general practitioners are important for estimating health care use. Prevalence rates based on screening are relevant for preventive strategies and latent health care needs.

Acknowledgements

The authors are grateful to P.J. van der Maas, D. Kromhout, P.J. van de Mheen, J. Barendregt, R.P. Stolk and R. Gijsen for their helpful comments and E.H. van de Lisdonk and the staff of the department of General Practice in Nijmegen, R.P. Stolk and D.J.H. Deeg for generously providing data.

INTRODUCTION

Diabetes mellitus is a major cause of morbidity and mortality in the world. Non-insulin-dependent diabetes mellitus (NIDDM) is by far the most common form and thus causes the most comorbidity (1, 2). As prevalence increases sharply with age, it is an important determinant of health care needs in an ageing society. To assess future needs for health care, policy makers need more information on the number of patients and changes in prevalence over time. This requires reliable estimates of age- and sex-specific prevalence rates. However, prevalence studies are hard to interpret. Reported prevalence rates may vary due to various population characteristics or differences in methodology. Populations may vary by composition (age and sex) or by other characteristics such as obesity and other determinants of diabetes. Methodological diversity is caused by selection of the study population, case definition and case ascertainment. The study population may, for instance, be a random sample of the general population (survey) or have been selected on the basis of health care use (population in a general practice). Case definitions have changed over time. In 1965, diagnostic criteria were first formulated by the World Health Organization (WHO) and revised and standardized in 1980 and 1985 (3, 4). Moreover, cases can be ascertained from self-reports, general practitioners reports or by screening with an oral glucose tolerance test (OGTT). Obviously, systematic screening for an often asymptomatic disease will yield much higher prevalence rates.

To obtain a best possible estimate of the prevalence of diabetes in the adult population in The Netherlands, we compared all the studies performed since 1970 and tried to account for differences in methodological characteristics by using logistic regression models. The estimated prevalence rates will be judged according to their relevance to health policy.

METHODS

Data sources

The data were collected from all studies on the prevalence of diabetes mellitus in the adult population in The Netherlands conducted since 1970. Few were published in peer reviewed papers and most were identified through the snow-ball method (checking references in all the publications found) and expert advice. We turned up 22 studies reporting the prevalence of diabetes mellitus in

The Netherlands. For inclusion in our analyses, the studies were required to report, for men and women separately, age-specific prevalences for age groups which differed by a maximum of 20 years. This excluded 5 studies (5-9). One study was excluded from analysis because of its highly selective study population (patients in nursing homes and homes for the elderly) (10). Another study was excluded from analysis because all the diabetic patients who visited the general practitioner were registered during a 3-month period. This period was too short to estimate the prevalence of diabetes reliably (11).

Fifteen studies qualified for analysis. Table 1 gives an overview of the characteristics of these studies (12-26). They were performed either in general practices or as surveys. Cases of known diabetic patients were ascertained by means

Table 1
Characteristics of the 15 studies on the prevalence of diabetes mellitus in The Netherlands used in the analysis

Name of the study	Period	Sample size	Age (years)	Case ascertainment
<i>General Practice (GP)</i>				
Sentinel Station (12)	1980-1983 1990-1991	162,626	0-65+ 0-80+	report by GP
CMR-Nijmegen (13)	1971-1993	12,000	0-75+	report by GP
Twello Study (14)	1985	516	65-80+	report by GP and fasting OGTT
Autonomy Project (15)	1986	5,163	65-74	report by GP
Transition Project (16)	1987	40,796	0-75+	report by GP
Heerde study (17)	1987	11,800	0-80+	report by GP
<i>Survey</i>				
EPOZ (18)	1975-1978	10,616	0-95	self-report
LSO (19)	1983+1986	7,968	18-75	self-report
CFRM (20)	1987-1991	36,000	20-59	self-report
Health Survey (21)	1989-1993	41,450	0-85	self-report
GLOBE (22)	1991	18,973	14-78	self-report
LASA (23)	1992-1993	3,108	55-85	self-report
Hoorn Study (41)	1989-1991	2,484	50-75	self-report and fasting OGTT
Zutphen Study (25)	1990	492	70-90	self-report and fasting OGTT
Rotterdam Study (26)	1991-1993	7,983	55-85+	self-report and non-fasting OGTT

CMR: Continuous Morbidity Registration;

EPOZ: Epidemiologic Preventive Research Zoetermeer;

LSO: Living-Situation Study;

CFRM: Cardiovascular Risk Factors Monitorings Project;

GLOBE: Health and living Conditions of the population of Eindhoven and surroundings

LASA: Longitudinal Ageing Study Amsterdam

OGTT: oral glucose tolerance test

of reports from general practitioners or self-reports in a questionnaire. Two studies measured the prevalence of diabetes at several points in time (12, 13). Four studies identified, next to all known cases of diabetes, unknown cases of diabetes by systematic screening of the remaining population with an OGTT. These 4 studies differed from each other in type of OGTT (fasting or non-fasting) and study population (survey or population from a general practice) (14, 24-26).

Analyses of prevalence

The data were analysed using a logistic regression model with the presence or absence of diabetes mellitus as a dependent variable. The same method was used for estimating the prevalence of hypertension on the basis of a number of studies (27). The statistical package EGRET was used in all the analyses. We restricted the analyses to ages 30 years and above. All the analyses were performed for men and women separately. Age was always specified as an independent variable; the median age of each age group was used. When open-ended, age groups were excluded from the analyses, as the median age in such open-ended age groups may differ strongly between studies. The numbers in each age and sex group were used as weights. Two studies (12, 17) reported only aggregated sample sizes. However the distribution by age and sex of these studies was equal to the Dutch population during that period, which made it possible to calculate the number in each age and sex group.

In the first analysis, the study was chosen as an independent (dummy) variables in order to identify the differences between the studies, adjusted for different age structures. The Sentinel Station study performed in 1980-1983 was taken as a reference, because this study has the largest sample size. Because 4 studies also measured asymptomatic diabetes by screening with an OGTT, we performed the analysis twice. First, the reported prevalence rates of known diabetes were entered as a dependent variable in the model, while for the second analysis for these 4 studies (14, 24-26) we used the sum of known and newly diagnosed diabetes.

Next, we tried to find an explanation for the difference in the prevalence rates of known diabetes between studies by estimating the influence of methodological variation on the prevalence of diabetes. Report by general practitioner and self-report in a survey were chosen as independent variables, adjusted for age and calendar year. Because the 4 studies using an OGTT used a different test and methodology, a pooled estimate of the effect of systematic screening on the prevalence rate could not be calculated. The regression equations, used for the 2 analyses are given in the appendix.

The coefficients from the logistic regression models were used to estimate the prevalence of diabetes in The Netherlands.

RESULTS

The surveys reported higher prevalences as compared with the Sentinel Station, with the exception of the Epidemiologic Preventive Research Zoetermeer (EPOZ) study (Table 2). Within the studies performed in a general practice, the Continuous Morbidity Registration (CMR)-Nijmegen and the Twello study reported significant higher prevalences than the reference study. The 2 studies which measured the prevalence at several points in time (12, 13) showed contradictory results. The Sentinel Stations reported a lower prevalence in 1989-1990 as compared with 1980-1983. CMR-Nijmegen study showed a slight increase in prevalence over time, for both men and women.

Table 2

Variation in the prevalence of diabetes mellitus in The Netherlands expressed as odds ratios (95% confidence intervals) adjusted for age

Variable	Period	Known diabetes		Known and newly diagnosed diabetes	
		Men	Women	Men	Women
<i>General practice</i>					
Sentinel Station	1980-1983	1.00	1.00	1.00	1.00
	1989-1990	0.82 (0.72-0.94)	0.74 (0.66-0.84)	°	°
CMR-Nijmegen	1971-1975	1.19 (0.88-1.59)	1.08 (0.84-1.40)	°	°
	1976-1980	1.43 (1.08-1.87)	1.22 (0.95-1.56)	°	°
	1981-1985	1.56 (1.20-2.01)	1.27 (1.00-1.62)	°	°
	1986-1990	1.48 (1.15-1.90)	1.33 (1.06-1.67)	°	°
	1991-1993	1.48 (1.16-1.89)	1.44 (1.14-1.77)	°	°
Twello Study		1.76 (1.02-3.04)	1.70 (1.11-2.61)	7.08 (4.90-10.24)	5.59 (4.08-7.66)
Autonomy Study		0.93 (0.71-1.23)	1.04 (0.83-1.29)	°	°
Transition Study		1.04 (0.87-1.24)	0.97 (0.83-1.13)		
Heerde Study		1.12 (0.85-1.48)	1.08 (0.86-1.36)		
<i>Survey</i>					
EPOZ		0.83 (0.59-1.16)	0.74 (0.56-0.97)	°	°
LSO		1.23 (0.92-1.65)	1.15 (0.89-1.49)	°	°
CFRM		1.32 (1.11-1.58)	0.92 (0.78-1.10)	°	°
Health Survey		1.30 (1.11-1.52)	1.11 (0.96-1.28)	°	°
GLOBE		1.71 (1.45-2.03)	1.17 (0.99-1.37)	°	°
LASA		1.39 (1.09-1.76)	1.05 (0.84-1.31)	°	°
Hoorn Study		1.05 (0.74-1.50)	0.98 (0.73-1.32)	2.93 (2.30-3.74)	2.32 (1.87-2.88)
Zutphen Study		1.59 (1.12-2.25)	-	3.10 (2.36-4.09)	-
Rotterdam Study		2.08 (1.75-2.47)	0.94 (0.79-1.10)	2.84 (2.40-3.36)	1.77 (1.53-2.05)

° No newly diagnosed diabetes available.

The 4 studies which identified unknown cases of diabetes in addition to all known cases of diabetes by systematically screening the remaining population with an OGTT, reported higher prevalence estimates compared with the studies identifying only the known cases of diabetes. The number of known diabetic patients could be separated from the newly diagnosed patients in these studies, enabling us to compare the prevalence estimates of known versus known and newly diagnosed within the 4 studies. Three of the 4 studies reported prevalences 1.5-2 times as high as their own prevalence rate of known diabetes. The fourth study (14) reported prevalences 6 times as high as its own prevalence rate of known diabetes and can be considered as an outlier.

Some of the differences between the studies may be explained by methodological variation. Measuring known diabetes in a survey using self-reported cases resulted in higher prevalence rates than those based on reports made by general practitioners (Table 3). These differences were somewhat larger for men than for women but did not differ significantly: an odds ratio of 1.47 (95% CI 1.35-1.60) for men versus 1.14 (95% CI: 1.06-1.23) for women. The prevalence of known diabetes mellitus increased for men by 7.1% (95% CI 6.8-7.4) for each year of age and by 7.7% (95% CI 7.4-8.0) for women. When estimating the increase in prevalence by age for each of the studies separately, we found that the pooled estimate of the increase by age fell within the confidence intervals of each individual study (data not shown). No effect of calendar year could be observed.

The coefficients estimated from the logistic model were used to estimate the prevalence of known diabetes in The Netherlands in 1993 (Figures 1 and 2). The best possible estimate of the age-specific prevalence varied with the methodology used. In The Netherlands, the total number of diabetic patients above the age of 30 years in 1993 was 235,000 (2.7%) based on cases reported by general practitioners and 285,000 (3.2%) based on self-reported cases in a survey. The prevalence is higher for women of all ages. Systematic screening with an OGTT will yield prevalence rates 1.5-2 times as high. Assuming this increase in the prevalence rate is similar in all age groups, the total number of subjects with

Table 3
Influence of methodological variation on the reported prevalence estimates expressed as odds ratios (95% confidence intervals) adjusted for age and calendar year.

Variable	Men	Women
Age (continuous)	1.071 (1.068-1.074)	1.077 (1.074-1.080)
Calendar year (continuous)	1.00 (0.99-1.01)	0.99 (0.98-1.00)
Self-report in a survey versus report by GP	1.47 (1.35-1.60)	1.14 (1.06-1.23)

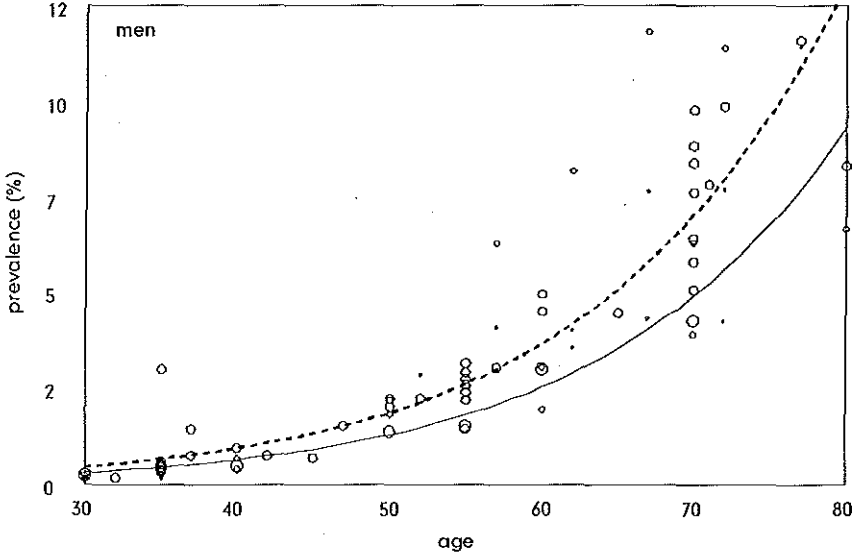


Figure 1
Prevalence of diabetes for men according to a survey with self-reported data (—) or a report by a general practitioner (- - -). The study prevalences are plotted with the size of the ball as an indicator for the sample size.

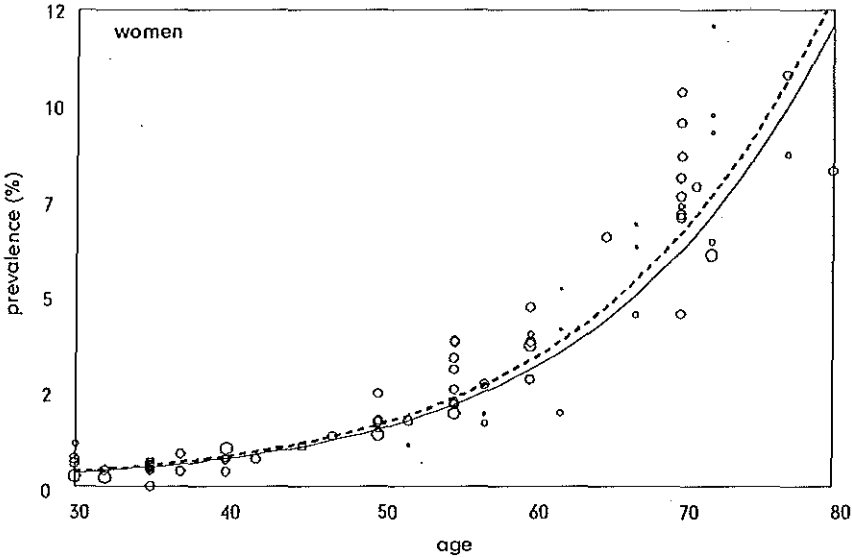


Figure 2
Prevalence of diabetes for women according to a survey with self-reported data (—) or a report by a general practitioner (- - -). The study prevalences are plotted with the size of the ball as an indicator for the sample size.

diabetes after a systematic screening of the total population will amount to 460,000 (5.2%) based on the reports of general practitioners or 560,000 (6.4%) based on self-reports in a survey. These estimates should be interpreted as an upper limit, as they are based on systematic screening with a single glucose tolerance test. The use of repeated measurements will result in a lower prevalence of diabetes (28).

DISCUSSION

We evaluated all the studies published in The Netherlands in order to obtain a tentative estimate of the prevalence of diabetes. The age-standardized prevalence of known diabetes varied considerably among the studies, with a higher prevalence in surveys using self-reported data. The prevalence increase by age is clear-cut. When systematic screening with an OGTT was performed, the prevalence rates were 1.5-2 times higher.

Pooling the data from heterogeneous studies to arrive at a single estimate might be considered a scientifically unsound undertaking. However, it seemed the only way to overcome the shortcomings of each individual study and to minimize the loss of information. If only selected data sources are considered, the selection might be guided by the (often unconscious) wishes of the reviewer and yield biased results. Furthermore, pooling offers an insight into the effect of methodological variations on the estimates of the prevalence of diabetes. Obviously, the results need to be interpreted with caution, but it is also important to realise that the studies are not heterogeneous in all aspects. For instance, the prevalence increase by age, estimated from the pooled analysis, was more or less similar in all studies.

The analyses started from age 30 years. The incidence and prevalence of NIDDM are by far the greatest (29, 30) at older ages. Almost 85% of all diabetic patients, registered in 19 general practices, have the non-insulin-dependent form of diabetes (31). The percentage of insulin-dependent diabetes (IDDM) patients diagnosed before age 30 years, but who were older than 30 years when the studies were carried out, is expected to be low and decreases with age. In the Heerde study in which a discrimination could be made between NIDDM and IDDM based on age of diagnosis and treatment with insulin, the percentage of IDDM patients decreased from 30% at age 30 years to less than 10% at age 80 years (17). Therefore, the results of our analyses mainly concern NIDDM patients.

A changing case definition over time is a major problem in the interpretation of the different studies and in the interpretation of time series. As the definition

becomes more and more specific, it may be assumed that the number of wrongly classified cases will drop and that, moreover, the prevalence of diabetes was relatively overestimated in the past. Part of the differences in prevalence rates observed between the studies might be explained by these changes in case definition. In several studies it was checked whether the diagnostic criteria had changed and how this might have influenced the prevalences reported (17, 32). The effect of changed criteria on the reported prevalence differed among these studies. The CMR-Nijmegen study reported that 13% of the diabetic patients did not have diabetes according to the WHO criteria of 1985. Moreover, the CMR-Nijmegen study also reported that for 14% of the subjects, the diagnostic criteria could not be traced anymore (32). The Heerde study found that in 12.8% of the previously diagnosed diabetic patients the diagnosis could not be reconfirmed with an OGTT when the WHO criteria of 1985 were applied. In general, patients diagnosed by a single glucose tolerance test and/or treated with a diet were shown to be non-diabetic according to the WHO criteria of 1985 (17). For the surveys which used self-reported data, it is impossible to judge if and how case definition influenced the reported prevalence. In studies using a screening with an OGTT, newly diagnosed diabetes was defined according to the WHO criteria of 1985 (3).

Another explanation for the observed differences in the prevalence rates between the studies could be the differences in the prevailing interest of general practitioners in NIDDM. Since the presence of NIDDM is not always clinically manifest, some of the subjects with diabetes are undiagnosed as such (33, 34). Some general practitioners will be more aware of this phenomenon and may be more attentive to diagnosing diabetes.

Surveys using self-reported data resulted in higher prevalence estimates as compared with those based on reports made by general practitioners. A possible explanation is that those responding to a survey may state that they are diabetic but are no longer registered in general practice as diabetic patients (because of, for example, changed diagnostic criteria or repeated measurements). On the other hand, in registering the cases in a general practice diabetic patients can be missed due to administration problems (hospital visits fail to be reported to the general practitioner) or the approach to registration (only patients who visit the general practitioner in a certain period are counted) (35). In particular, those patients who are treated with a diet only may cause a discrepancy between self-reported data and those reported by general practitioners.

As neither the general practitioners nor the surveys took into account persons who are institutionalized in nursing homes or rest homes (only the Longitudinal Ageing Study Amsterdam (LASA) included the institutionalized population) underestimation of the prevalence is likely. A study in nursing homes and rest-homes, (10) which was excluded from our analysis for reasons of compara-

bility, reported a higher prevalence of diabetes than the estimated prevalences of our analysis: 13% (95% CI 10-16) for men aged 75-79 years and 21% (95% CI 19-23) for women of this age, compared with our estimated prevalences of 5.7 and 8.4% for men and women respectively. In The Netherlands, 4.3% of all men and 7.9% of all women aged 75-79 years are institutionalized (10).

Comparing the prevalence estimates with other countries, The Netherlands appears to be low in the hierarchy. In other European countries, surveys reveal an age-adjusted prevalence of known diabetes between 30 and 64 years of age, which varies from 1.8% in Russia to 10.7% in Italy (1). In American surveys, the age-standardized prevalences of known diabetes in the White population vary between 3 and 8% (1, 33). This is comparable to our estimate of known diabetes of 1.7% between the ages of 30 and 64 years.

The effect of systematic screening on the prevalence rates can best be estimated by comparing studies measuring known and unknown diabetes. Three studies that systematically screened for unknown diabetes reported 1.5-2 times higher prevalence estimates (24-26). The Twello study reported prevalence rates 6 times as high and is considered to be an outlier. Although it is unclear why this study reported such extreme prevalence rates, a few comments are in order. The study population of this study was relatively small ($n = 560$) and was based on a general practice in a rural village. The almost doubled prevalence found when systematic screening with an OGTT was carried out corresponds with studies which found that approximately 50% or more of the subjects with NIDDM are undiagnosed (33, 34). The 3 screening studies used a single glucose tolerance test, which is known to be prone to intra individual variation (36, 37). This may explain part of the different prevalence estimates among the 4 studies using an OGTT. The Hoorn Study assessed the prevalence of diabetes in a sample using 2 OGTTs, repeated during a period of 2-6 weeks. The prevalence of newly diagnosed diabetes after 2 OGTTs was lower compared with a single test (3.4 versus 4.3%), probably due to regression towards the mean (28). Repeated measurements are advisable to avoid possible misclassification and to obtain a more valid estimate of the prevalence of diabetes.

In our analysis, we included studies conducted in the period 1970-1993. However, trends in time were difficult to interpret. As noted before, case definitions became more specific, inducing an artificial decrease by minimizing false positives. The 2 studies that measured prevalence at several points in time were contradictory. The Sentinel Station showed a decrease in prevalence, but only measured the diabetes prevalence at 2 points in time. The decreased prevalence is probably due to a clearance of the diabetic register in general practice (38). The only study with a continuous registration of diabetes since 1970, the CMR-Nijmegen study, showed a slight increase in prevalence. However, these estimates were based on small numbers. In other populations too, little is

known about secular time trends. Two studies reported an increase in prevalence in the US over the past decades (39, 40). This issue also merits further study in The Netherlands.

In this study, the prevalence of known diabetes increased for men by 7.1% for each year of age and by 7.7% for women. Age appears to be a reliable predictor for the future numbers of patients in an ageing society. The number of patients aged 30 years and up will increase by 36% (95% CI 19-41%) between 1993 and 2010 based on age-specific prevalence rates.

For health policy makers, it is important to realise that, depending on the way prevalence rates are measured, the prevalence of known diabetes in The Netherlands varies between 235,000 and 285,000 known diabetic patients or is 2.7-3.2% of the total population. Systematic screening with an OGTT yields prevalences that are twice as high. Depending on the intended application, different estimates can be of use. Prevalence rates based on self-reported data may be used when estimating total health care use, while the prevalence based on cases reported by general practitioners may be of use for that specific aspect of the health care system. Prevalence rates of diabetes based on screening are relevant for preventive strategies and latent health care needs.

References

1. King H, Rewers M: Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. *Diabetes Care* 16:157-177, 1993
2. Alberti KGMM: Problems related to definitions and epidemiology of type 2 (non-insulin-dependent) diabetes mellitus: studies throughout the world. *Diabetologia* 36:978-984, 1993
3. World Health Organization. Diabetes mellitus: report of a study group. Geneva: WHO, 1985.
4. World Health Organization. World Health Organization Expert Committee on Diabetes mellitus. Second report. Geneva: WHO, 1980.
5. May JF. *Epidemiologic cardiology: ischaemic heart disease study Vlagtwedde, 1970*. University of Groningen, 1974
6. Schellevis FG, van de Lisdonk E, van der Velden J, van Eijk JTM, van Weel C: Validity of diagnoses of chronic disease in general practice. The application of diagnostic criteria. *J Clin Epidemiol* 46:461-468, 1993
7. Reenders K, de Nobel E, van Weel C: Diabetes mellitus in een groepspraktijk. 1. Diagnostiek, controle en behandeling. (Diabetes in a general practice. 1. Diagnosis, control and treatment). *Huisarts en wetenschap* 31:327-330, 1988

8. Metsemakers JFM, Höppener P, Knottnerus JA, Limonard CBG. *Health problems and diagnoses in family practice*. Maastricht: Registration Network Family Practices University of Limburg, 1992.
9. Lamberts H: *Morbidity in general practice. Diagnosis related information from the Monitoring Project*. Utrecht Huisartsenpers, 1984
10. van de Mheen PJ. *Prevalentie van diabetes mellitus in verzorgingstehuizen (Prevalence of diabetes mellitus in nursing homes)*. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieuhygiëne, 1989.
11. van der Velden J, de Bakker DH, Claessens AAMC, Schellevis FG: *Een nationale studie naar ziekten en verrichtingen in de huisartspraktijk. Basisrapport: Morbiditeit in de huisartsenpraktijk (A national study for diseases and operations in the general practice. Morbidity in the general practice)*. Utrecht Netherlands Institute of Primary Health Care, 1991
12. Steering Committee on Future Health Scenarios: *Chronische ziekten in het jaar 2005. Volume 1: scenario's van diabetes mellitus 1990-2005. (Chronic diseases in the year 2005. Volume 1: scenarios on diabetes mellitus 1990-2005)*. Dordrecht, Boston, London Kluwer Academic Publishers, 1991
13. van de Lisdonk EH, Bosch WJHM, Huygen FJA, Lagro-Jansen ALM, ed. *Ziekten in de huisartspraktijk (Diseases in the general practice)*. Utrecht: Wetenschappelijke uitgeverij Bunge, 1990:342.
14. Cromme PHV, Eijk van JTM, Veen van der EA, Nauta JJP, Knottnerus JA: Glucose-intolerantie bij ouderen in Nederland; het Twello-onderzoek (Glucose tolerance in an elderly Dutch countryside population: the Twello Study). *Ned Tijdschr Geneesk* 139:2558-2563, 1995
15. Meyboom-de Jong B. *Bejaarde patiënten: een onderzoek in 12 huisartsenpraktijken (Elderly patients: a research in 12 general practices)*. University Groningen, 1989
16. Lamberts H, Brouwer HJ, Mohrs J. *Reasons for encounter- & episode- & process-oriented standard output from the Transition project*. Part 1 and 2. Amsterdam: Department of General Practice, 1991.
17. Verhoeven S. *Behandeling, controle en metabole instelling van patienten met diabetes mellitus type II en de prevalentie van late complicaties bij deze patienten (Treatment, follow-up and metabolic regulation of patients with diabetes mellitus type II and the prevalence of late complications in this group of patients)*. Erasmus University Rotterdam, 1989
18. Valkenburg HA, Hofman A, Klein F, Groustra FN: Een epidemiologisch onderzoek naar risico-indicatoren voor hart- en vaatziekten (EPOZ). I. Bloeddruk, serumcholesterolgehalte, Quetelet index en rookgewoonten in een open bevolking van vijf jaar en ouder (An epidemiological study of cardiovascular risk factors (EPOZ). 1. Blood pressure, serum cholesterol level, quetelet index and smoking habits in an open population aged five years and over). *Ned Tijdschr Geneesk* 124:183-189, 1980
19. van den Berg J, van den Bos GAM: Gezondheidsenquetes. Het (meten van het) voorkomen van chronische aandoeningen. 1974-1987 (Health interview surveys. The (measurement of the) prevalence of chronic conditions, 1974-1987). *Mndber Gezondheid (CBS)* 3:4-21, 1989
20. Verschuren M, Kromhout D: Total cholesterol concentration and mortality at a relatively young age: do men and women differ? The Netherlands Consultation Bureau Project on Cardiovascular Diseases. *Br Med J* 311:779-783, 1995

21. Central Bureau of Statistics. Gezondheidsenquêtes (Health interview surveys), 1989-1993.
22. Mackenbach JP, van de Mheen H, Stronks K: A prospective cohort investigating the explanation of socio-economic inequalities in health in the Netherlands. *Soc Sci Med* 38:299-308, 1994
23. Deeg DJH, Westendorp - de Serière M: *Autonomy and well being in the aging population I: report from the Longitudinal Aging Study Amsterdam 1992-1993*. Amsterdam VU University Press, 1994
24. Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Heine RJ: Prevalence and determinants of glucose intolerance in a Caucasian population. The Hoorn Study. *Diabetes Care* 18:1270-1273, 1995
25. Feskens EJM, Tuomilehto J, Stengard JH, Pekkanen J, Nissinen A, Kromhout D: Hypertension and overweight associated with hyperinsulinaemia and glucose tolerance: a longitudinal study of the Finnish and Dutch cohorts of the Seven Countries Study. *Diabetologia* 38:839-847, 1995
26. Stolk RP, Pols HAP, Lamberts SWJ, Jong de PTVM, Hofman A, Grobbee DE: Diabetes mellitus, impaired glucose tolerance and hyperinsulinemia in an elderly population. The Rotterdam Study. *Am J Epidemiol* 145:24-32, 1997
27. van de Mheen PJ, Bonneux L, Gunning-Schepers LJ: Variation in reported prevalences of hypertension in the Netherlands: the impact of methodological variables. *J Epidemiol Community Health* 49:277-280, 1995
28. Mooy JM, Grootenhuis PA, Vries d, H, et al.: Intra-individual variation of glucose, specific insulin and pro-insulin concentrations measured by two oral glucose tolerance tests in a general caucasian population: the Hoorn Study. *Diabetologia* 39:298-305, 1996
29. Herman WH, Sincock P, Brenner E, et al: An epidemiologic model for diabetes mellitus: incidence, prevalence and mortality. *Diabetes Care* 7:367-371, 1984
30. Laakso M, Pyörälä K: Age of onset and type of diabetes. *Diabetes Care* 8:114-117, 1985
31. Reenders K, de Nobel E, van den Hoogen HJM, Rutten GEHM, van Weel C: Diabetes and its long-term complications in general practice: a survey in a well-defined population. *Family Practice* 10:169-172, 1993
32. de Grauw WJC, van de Lisdonk E, van den Hoogen HJM. *Longitudinale evaluatie van morbiditeitsgegevens van patienten met diabetes mellitus in de huisartspraktijk (Longitudinal evaluation of morbidity data of patients with diabetes mellitus in a general practice)*. Nijmegen: Katholieke Universiteit Nijmegen, Vakgroep huisartsgeneeskunde, 1991.
33. Harris MI, Hadden WC, Knowler WC, Bennet PH: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20-74 Yr. *Diabetes* 36:523-534, 1987
34. Harris MI: Undiagnosed NIDDM: clinical and public health issues. *Diabetes Care* 16:642-653, 1993
35. Meyboom-de Jong B: Morbidity registration in general practice in the Netherlands. *Huisarts Wet* 36:S49-53, 1993
36. Feskens EJM, Kromhout D: Glucose tolerance and the risk of cardiovascular diseases: the Zutphen Study. *J Clin Epidemiol* 45:1327-1334, 1992
37. Wiener K: The diagnosis of diabetes mellitus, including gestational diabetes. *Ann Clin Biochem* 29:481-493, 1992

38. Ruwaard D. *Diabetes mellitus: from epidemiology to health policy* . Erasmus University Rotterdam, 1996
39. Harris MI, Hamman RF. Diabetes in America: NIH, Washington DC, 1985.
40. Wetterhall SF, Olson DR, DeStefano F, et al: Trends in diabetes and diabetic complications, 1980-1987. *Diabetes Care* 15:960-967, 1992
41. Mooy JM, Grootenhuys PA, Vries de H, Heine RJ, Bouter LM: The Hoorn Study: disorders of glucose tolerance in a general caucasian population. *Neth J Med* 41:A29-30, 1992

Appendix

In the first analysis, the differences in prevalence estimates between the studies were identified adjusted for different age structures, by using the following regression equation:

$$\text{logit (y)}_{\text{sex}} = \text{logit } (\alpha + \beta_1 \times \text{age} + \beta_2 \times \text{study})$$

where age is a continuous variable and the study is a dummy variable.

In the second analysis, the influence of methodological variation on the prevalence of diabetes was estimated by using the following regression equation:

$$\text{logit (y)}_{\text{sex}} = \text{logit } (\alpha + \beta_1 \times \text{age} + \beta_2 \times \text{calendar year} + \beta_3 \times M_r)$$

where age and calendar year are continuous variables and M_r is the methodology used: *0* is a report by a general practitioner and *1* is a self-report in a survey.

The burden of mortality of diabetes mellitus in The Netherlands

ABSTRACT

Our objective was to estimate the excess mortality and the reduction in life expectancy related to diabetes mellitus. We developed a life table to describe the Dutch population in two states, diabetic and non-diabetic, using age and sex specific prevalence of diabetes mellitus and risks of dying for diabetic subjects. We compared the calculated excess deaths with registered deaths. The cause-of-death registration practice underestimates diabetes-related mortality. The method used in this study, combining mortality data with data from epidemiologic studies, provides an assessment of the impact of diabetes on the Dutch population.

Acknowledgements

This study is part of a research project supported by grants from the National Institute for Health Sciences (NIHES). We are grateful to Daan Kromhout and Paul J. van der Maas for their helpful comments.

INTRODUCTION

To gain insight into the burden of diabetes mellitus, data on incidence, prevalence and mortality are essential. In this paper we attempt to estimate the excess mortality associated with diabetes. Since a valid estimate of diabetic mortality can not be derived from cause-of-death statistics (1, 2), we combined data from epidemiologic studies on the prevalence of diabetes mellitus and the relative risks for mortality of diabetes with mortality data from the municipal population register. We then estimated the excess mortality related to diabetes and the loss of life expectancy attributable to diabetes for the total and for the diabetic population.

DATA AND METHODS

Data

We obtained sex and age specific data on total and cause-specific mortality rates as well as on the population distribution for the period 1990 to 1992 in The Netherlands from Statistics Netherlands (3). Several studies have reported sex- and age-specific relative mortality risks for diabetes mellitus (Table 1) (4-15). For our analysis we used a recent population-based study, the Verona Study (15). We linearly interpolated the relative risks for 1-year age groups to avoid discontinuities. Within the open-ended age group of 75 years and over, the relative risk as reported by the Verona study was kept constant over age. We assessed the sex- and age specific prevalence of diabetes from Dutch studies performed since 1970 (16).

Mortality analysis

We estimated sex and age specific mortality rates for diabetic and non-diabetic subjects using:

$$M = pM_1 + (1 - p)M_0 \quad (1)$$

and:

$$M_1 = M_0R \quad (2)$$

where: M is the average total mortality rate of the Dutch population; M_1 is the total mortality rate for diabetic subjects; M_0 for non-diabetic subjects; p is the

Table 1
Studies reporting mortality ratios for diabetes mellitus, for men and women separately

Country (Name of the study)	Period	Follow- up (in years)	Number of diabetic subjects	Reference population	Age	Mortality ratio	
						Men	Women
USA (Joslin Clinic) (4)	1990-1930	30	21,447	gen pop	40-49	2.48	2.99
					50-59	1.81	2.62
					60-69	1.63	2.44
					70-79	1.49	2.02
					≥ 80	1.18	1.45
Germany (5)	1966-1976	10	2,381	gen pop	45-49	1.82	1.99
					50-54	1.26	1.82
					55-59	1.56	1.88
					60-64	1.49	1.48
					65-69	1.37	1.33
					70-74	1.21	1.26
England+Wales (6)	1966-1992	22	5,783	gen pop	75-79	0.96	1.04
					40-59	1.62	2.55
England (7)	1967-1979	11-14	5,971	gen pop	60-84	1.45	2.15
					45-64	1.98	2.72
Scotland (8)	1968-1975	8	3,113	gen pop	≥ 65	1.38	1.97
					40-49	2.44	4.55
					50-59	2.39	2.81
					60-69	1.65	3.03
					70-79	1.35	1.98
USA (NHANES I) (9)	1971-1984	10	407	non-dm pop	≥ 80	1.01	1.16
					40-64	2.78	2.32
					65-69	1.86	1.60
The Netherlands (10)	1974-1980	13-19	420	non-dm pop	70-77	2.56	2.54
The Netherlands (11)	1974-1993	6.8	265	non-dm pop	45-55	0.83	1.48
West Australia (12)	1978-1986	6.7	888	gen pop		1.61	1.47
					50-59	1.27	2.87
					60-69	1.48	1.79
UK (13)	1979-1990	11	717	gen pop	≥ 70	1.42	0.92
					45-64	1.47	3.08
					65-74	1.32	2.09
					≥ 75	1.12	1.43
UK (14)	1985-1989	5	4,186	gen pop	45-64	2.83	3.01
					65-74	1.20	2.21
					≥ 75	0.81	0.92
Verona (15)	1986-1991	5	5,996	non-dm pop	45-54	2.33	3.43
					55-64	2.13	2.33
					65-74	1.50	2.27
					≥ 75	1.13	1.32

gen pop: general population; non-dm pop: non-diabetes population

prevalence of diabetes; R is the relative risk for total mortality, given exposure to diabetes. Age indexes are suppressed. Substituting 2 into 1 yields the mortality of the non-diabetic subjects:

$$M_0 = \frac{M}{pR + (1 - p)} \quad (3)$$

In Table 2 an example of the calculations for two one-year age groups is presented.

Life expectancy analysis

We calculated life tables for diabetic and non-diabetic men and women (17, 18). The life expectancy of the non-diabetic population can be interpreted as the life expectancy after elimination of the excess diabetes mortality. The gain in life expectancy for the total population is the difference between the life expectancies of the total and non-diabetic population. We performed a sensitivity analysis by recalculating all estimates with a range of relative risks, guided by the 95% confidence intervals reported in the Verona Study. We called the thus obtained lower and upper estimates uncertainty limits (UL).

RESULTS

Based on our mortality analyses, we calculated deaths among 7,918 male diabetics age 45 and older (UL: 2,978 to 8,908) and 11,433 among female diabetics (UL: 10,423 to 12,481) age 45 and older each year in the period 1990-1992 (Table 3). Of these, the number of excess deaths related to diabetes was, for men, 1,576 (UL: 596 to 2,704) and for women 3,325 (UL: 2,125 to 4,562). By comparison, the annual number of deaths in 1990-1992 with diabetes coded by Statistics Netherlands as the underlying cause of death was, on average, 1,194 for men and 2,168 for women of age 45 and over. The number of deaths increased to 2,009 men and 3,240 women if both underlying and contributory causes were used.

The life expectancy analyses showed that if the excess mortality in diabetic patients is eliminated, the gain in life expectancy at age 45 for the total population is 0.25 years (UL: 0.11 to 0.41) for men and 0.44 (UL: 0.27 to 0.64) for women. The loss in life expectancy for diabetics age 45 or over is 4.65 years (UL: 2.47 to 6.99) for men and 6.31 years (UL: 3.41 to 9.72) for women (Figure 1).

Table 2

Example of the calculations of the number of diabetic deaths in The Netherlands in the period 1990-1992.

Age	Population	M	Prevalence of diabetes	Relative risk	M ₀	M ₁	Total number of diabetic deaths	Number of deaths attributable to diabetes
<i>Males</i>								
59	70,874	0.0115	0.0328	2.13	0.011	0.0236	55	29
60	68,885	0.0129	0.0351	2.13	0.0125	0.0266	64	34
<i>Females</i>								
59	73,632	0.0061	0.0296	2.33	0.00584	0.00136	25	15
60	72,637	0.0070	0.0317	2.33	0.0067	0.0156	30	17

M=average total mortality rate for the Dutch population; M₀=average mortality rate of non-diabetic subjects; M₁=average total mortality rate of subjects with diabetes mellitus.

Table 3

Registered number of deaths with diabetes mellitus as underlying cause of death and calculated number of deaths in diabetic patients in The Netherlands per year in the period 1990-1992, by sex.

Age	Population	M *	Prevalence of diabetes	RR	Estimated number of diabetic deathst† (95% uncertainty limits)		Diabetes registered as cause of death	
					Total	Excess	Underlying	Total‡
<i>Males</i>								
45-54	887,490	0.0043	0.0177	2.33	151 (96-226)	85 (36-162)	72	110
55-64	684,935	0.0130	0.0345	2.13	607 (503-728)	304 (196-429)	194	398
65-74	490,145	0.0374	0.0662	1.5	1,698 (1,487-1,925)	559 (334-804)	321	385
75+	280,492	0.1732	0.1724	1.13	5,462 (892-6,029)	628 (0-1,309)	607	1,116
Total					7,918 (2,978-8,908)	1,576 (596-2,704)	1,194	2,009
% §					11.9 (4.5-13.4)	2.4 (0.9-4.1)	1.8	3.0
<i>Females</i>								
45-54	850,031	0.0027	0.0153	3.43	110 (51-201)	76 (17-168)	41	67
55-64	719,855	0.0066	0.0312	2.33	351 (254-471)	203 (103-328)	157	321
65-74	622,369	0.0171	0.0628	2.27	1,381 (1,146-1,535)	710 (510-927)	417	782
75+	539,980	0.0214	0.1735	1.32	9,638 (8,972-10,274)	22,336 (1,495-3,139)	1,553	2,070
Total					11,433 (10,423-12,481)	3,325 (2,125-4,562)	2,168	3,240
% §					18.1 (16.5-19.8)	5.3 (3.4-7.2)	3.4	5.1

* M: average total mortality rate of Dutch population.

†: The estimated numbers of deaths are calculated in a life table for one-year age groups and summarised to the ten-year age groups presented. Due to the strongly increasing mortality risks with age, the numbers of diabetic deaths will differ when using the average mortality, diabetes prevalence and population size for the ten-year age groups

‡All deaths with diabetes registered as underlying or contributory cause of death;

§: Percentage of the total number of deaths in 1990-1992 in The Netherlands

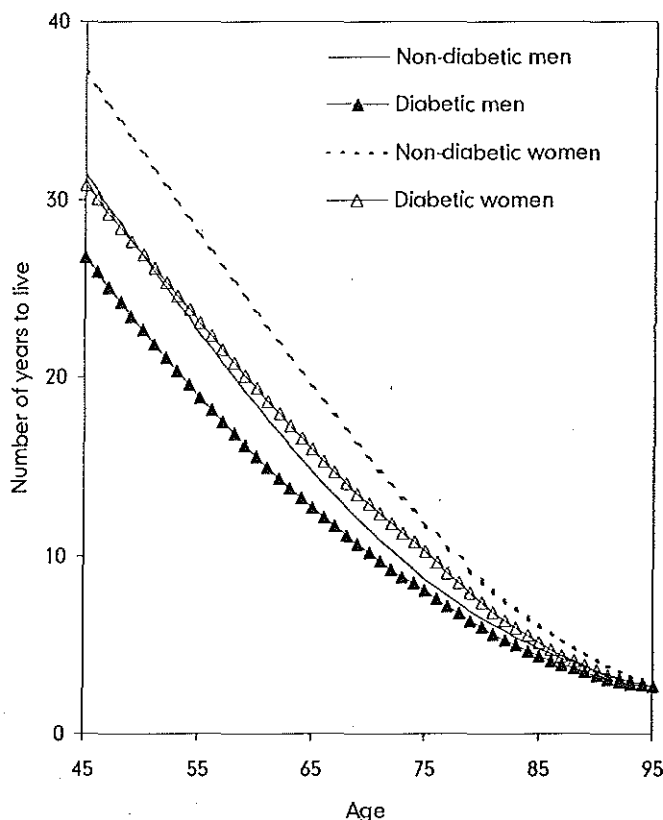


Figure 1
Life expectancy from age 45 and up for diabetics and non-diabetics.

DISCUSSION

Diabetes mellitus mortality based on cause-of-death registration is difficult to interpret. Cause-of-death statistics are based on the concept of a single cause, the underlying cause of death. People with diabetes often have multiple medical conditions, making the actual cause of death difficult to define. Coding practices may differ between countries and over time, which enhances difficulties in interpretation (19). In The Netherlands, diabetes is more often selected as underlying cause of death (1), which may explain the relatively small differences in our estimates and vital statistics.

Although many death certificates have more than one condition listed, the underlying cause of death is often the only information retained from the coding procedure (19). Multiple cause analyses (analysing all conditions mentioned on the death certificate) may reduce the underregistration of diabetes as a cause of

death. For the purpose of cause-elimination analyses, however, multiple cause data are difficult to interpret, as one subject can have more contributory causes of death. Eliminating one contributory cause of death, therefore, does not mean the elimination of one death.

In our method we take into account competing risks, making it possible to partition total mortality into excess mortality due to diabetes and the remaining mortality. When the excess mortality is eliminated, the remaining mortality is unaffected, the number of deaths from the other causes will increase, because a lower mortality risk in one age group will result in more people alive in the next. The unchanged mortality risks will result in a higher number of deaths. The advantage of our method is that we use the mortality hazards for excess mortality and a mortality hazard for the non-diabetic subjects to calculate the number of deaths per year in the Dutch population, and the gain in life expectancy when eliminating the excess mortality. For the latter, taking into account the force of mortality from other causes of death is indispensable.

The standard method for estimating mortality attributable to a risk factor is the population attributable risk (PAR) (20). The disadvantage of the PAR is that it does not take into account the increased mortality of substituting other causes of death when the risk factor is eliminated. A solution would be to use a combination of the PAR and a cause elimination life table (17). The method used in this paper yields exactly the same result as such a combination, but we think it is more transparent.

Although the various studies that reported age-specific relative mortality risks for diabetes differed in design, population and time, the relative risks were similar, taking into account the different ages. We chose the Verona study for several reasons: it is recent, it is large, it used the non-diabetic population as the reference population, and it reported relative risks by sex for several age groups. We also performed the analyses using the relative risks from seven other studies presented in Table 1 (4-6, 8, 9, 13, 14) to test the sensitivity of the results to these relative risks. The results of these analyses fell within the uncertainty limits, using the 95% confidence intervals of the relative risks published by the Verona Study (data not shown). Only the Erfurt relative risks (5) resulted in lower estimates for all age groups. We did not use the other studies presented in Table 1.

Our estimated gain in life expectancy at age 45 was comparable with the results of several studies that showed that NIDDM reduces life expectancy by 5-10 years in middle aged persons (21, 22).

References

1. Jouglu E, Papoz L, Balkau B, Maguin P, Hatton F: Death certificate coding practices related to diabetes in European countries - the EURODIAB subarea C study. *Int J Epidemiol* 21:343-351, 1992
2. Mackenbach JP, Snels IAK, Friden-Kill LM: Diabetes mellitus als doodsoorzaak (Diabetes as a cause of death). *Ned Tijdschr Geneeskde* 135:1492-1496, 1991
3. Centraal Bureau voor de Statistiek. Overledenen naar doodsoorzaak, leeftijd en geslacht in 1990, Serie A1. Voorburg, 1990.
4. Kessler II: Mortality experience of diabetic patients. A twenty-six year follow-up study. *Am J Med* 51:715-724, 1971
5. Panzram G, Zabel-Langhennig R: Prognosis of diabetes mellitus in a geographically defined population. *Diabetologia* 20:587-591, 1981
6. Swerdlow AJ, Jones ME: Mortality during 25 years of follow-up of a cohort with diabetes. *Int J Epidemiol* 25:1250-1261, 1996
7. Fuller JH, Elford J, Goldblatt P, Adelstein AM: Diabetes mortality: new light on an underestimated public health problem. *Diabetologia* 24:336-341, 1983
8. Shenfield GM, Elton RA, Bhalla IP, Duncan LJP: Diabetic mortality in Edinburgh. *Diab Metab* 5:149-158, 1979
9. Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB: Mortality among diabetics in a national sample. *Am J Epidemiol* 128:389-401, 1988
10. Verschuren M, Kromhout D: Total cholesterol concentration and mortality at a relatively young age: do men and women differ? The Netherlands Consultation Bureau Project on Cardiovascular Diseases. *Br Med J* 311:779-783, 1995
11. de Grauw WJC, van de Lisdonk EH, van den Hoogen HJM, van Weel C: Cardiovascular morbidity and mortality in type 2 diabetic patients: a 22-year historical cohort study in Dutch general practice. *Diab Med* 12:117-122, 1995
12. Knuiman MW, Welborn TA, Whittall DE: An analysis of excess mortality rates for persons with non-insulin-dependent diabetes mellitus in Western Australia using the Cox Proportional Hazards Regression Model. *Am J Epidemiol* 135:638-648, 1992
13. Walters DP, Gatling W, Houston AC, Mullee MA, Julious SA, Hill RD: Mortality in Diabetic subjects: an eleven-year follow-up of a community-based population. *Diab Med* 11:968-973, 1994
14. Wong JSK, Pearson DWM, Murchison LE, Williams MJ, Narayan V: Mortality in diabetes mellitus: experience of a geographically defined population. *Diab Med* 8:135-139, 1991
15. Muggeo M, Verlato G, Bresson F, et al: The Verona diabetes study: a population-based survey on known diabetes prevalence and 5-year all-cause mortality. *Diabetologia* 38:318-325, 1995
16. Baan CA, Bonneux L, Ruwaard D, Feskens EJM: The prevalence of diabetes mellitus in The Netherlands: a quantitative review. *Eur J Publ Health* 8:210-216, 1998
17. Namboodiri K, Sunchindran CM: *Life table techniques and their applications*. Orlando Academic Press, 1987

18. Manton KG, Stallard E: *Chronic disease modelling: measurement and evaluation of the risks of chronic disease processes*. New York Oxford University Press, 1988
19. Fuller JH: Mortality trends and causes of death in diabetic patients. *Diabetes Metab* 19:96-99, 1993
20. Rothman K: *Modern epidemiology*. Boston/Toronto Little, Brown and company, 1986
21. Geiss LS, Herman WH, Smith PJ, ed. *Mortality in non-insulin-dependent diabetes mellitus*. 2 ed. Bethesda: NIH, 1995:233-258. (National Diabetes Data Group, ed. Diabetes in America;)
22. Schneider H, Lischinski M, Jutzi E: Survival time after onset of diabetes: 29-year follow-up mortality study in a diabetes cohort from a rural district. *Diabetes Metab* 19:152-158, 1993

An indirect estimate of NIDDM incidence

ABSTRACT

The objective of this study was to estimate NIDDM incidence in The Netherlands in the absence of consistent empirical data. Incidence can be expressed as a function of age, sex, prevalence, and mortality. Prevalence data were obtained from a study that pooled existing prevalence estimates. Diabetes-related mortality was calculated using relative risks on all cause mortality. Sensitivity for the rate of excess mortality was determined using the 95% confidence bounds of the relative risks. The estimated incidence increases exponentially with age, with a doubling time of 10 years for men and 9 years for women. The rate increases from 8.1 per 10,000 (7.7-8.8) for men aged 40-44, and 7.0 (6.8-8.0) for women, to 79.7 per 10,000 (69.5-90.9) for men aged 75-79, and 85.8 (80.6-91.0) for women. When empirical estimates of incidence are largely lacking, the methodology described offers a useful alternative, in particular for the assessment of potential intervention effects.

Acknowledgements

The authors are indebted to Paul J. van der Maas (Department of Public Health, Erasmus University) and Edith J. Feskens (National Institute for Public Health and the Environment) for their helpful comments on an earlier draft. This research was funded by The Netherlands Heart Foundation and The Netherlands Institute of Health Sciences (NIHES).

INTRODUCTION

Non-Insulin Dependent Diabetes Mellitus (NIDDM) is a common condition among the elderly, and with the ageing of populations is bound to increase. Describing the burden of disease caused by diabetes can help to assess the potential gains in population health status that could be made by a better control of risk factors for diabetes, and of diabetes itself. Assessing such gains requires a consistent means of measuring incidence, prevalence, and mortality rates, which can be used as input in a causal epidemiological model that describes the natural history of the disease and its complications (1, 2). The impact of changes in incidence, for example through weight control, on diabetes prevalence and diabetes related mortality can be estimated with such a model.

Describing the epidemiology of NIDDM is surprisingly difficult. The onset of NIDDM is a gradual process. Initially the patient experiences few if any symptoms, and therefore a large part of all NIDDM patients is presumed to be undiagnosed: some estimates are as high as 50% (3).

In such a situation of difficult case definition and a high prevalence of occult disease the observed incidence and prevalence become highly dependent on factors other than the true occurrence of disease such as patient and doctor awareness and level of case finding. The results are highly variable estimates of incidence and prevalence. Studies of prevalence and incidence in The Netherlands show a variation in estimates by a factor of about 3 (4-8)

Also mortality, for most diseases the best recorded epidemiological aspect, can in the case of diabetes not reliably be obtained from cause of death registration. Cause-of-death statistics are based on the concept of a single cause, termed the underlying cause of death. Diabetes is associated at the time of death with other conditions, such as cardiovascular diseases. It is often difficult to determine the role played by diabetes mellitus in the death process. But the coding may also promote difficulties in interpretation (9, 10).

In a previous study an estimate of diabetes prevalence in The Netherlands was presented, based on a pooled analysis of existing studies (4). Mortality of diabetes was estimated by combining data from epidemiological studies on the prevalence of diabetes and the relative risks for mortality of diabetes with mortality data from Statistics Netherlands (11).

The purpose of the present study is to obtain an age and sex specific estimate of NIDDM incidence that is consistent with the previously estimated prevalence and mortality. By combining both the prevalence estimate and the mortality estimate in an incidence-prevalence-mortality (IPM) model, an estimate of the incidence of diabetes can be obtained. We compare the estimates with the few observations available, and discuss results and the method used.

DATA AND METHODS

Incidence-prevalence-mortality (IPM) models of disease processes are not new to epidemiologic research (12-14). 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. 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, however shortly. Jointly estimated incidence, prevalence and mortality rates, using a causal model, are therefore internally consistent (12).

We constructed a diabetes-related mortality (m^d), independent from the cause-of-death statistics. The method is described in a previous study (11). This diabetes-related mortality equals all excess mortality caused by diabetes, however coded in death statistics. Total mortality for people with and without diabetes is estimated from the average population total mortality, the relative risk on mortality for diabetics, and diabetes prevalence using:

$$m = p m^1 + (1 - p) m^0 \quad (1)$$

and:

$$m^1 = m^0 R \quad (2)$$

Substituting eq (2) in (1) we can write the mortality of the non-diabetics as (11):

$$m^0 = \frac{m}{pR + 1 - p} \quad (3)$$

The diabetes related mortality rate (m^d) in a population with a diabetes prevalence of p then becomes:

$$m^d = p m^0 (R - 1) = \frac{p(R - 1)m}{pR + 1 - p} \quad (4)$$

where:

p : prevalence of diabetes; R : relative risk on total mortality, given exposure to diabetes; m : average total mortality rate; m^0 : total mortality rate of non-diabetics; m^1 : total mortality rate of diabetics; m^d : diabetes related mortality rate of the mixed population with. Age and sex indexes are suppressed. Note that equation (4) is the same as the population attributable risk (PAR) times total mortality.

Given this mortality rate in the population and the prevalence of diabetes we can now write incidence at age a as a function of prevalence at a and $a+1$, and mortality at a :

$$i_a = \frac{p_{a+1}(1-m_a^d) - p_a + m_a^d}{1 - p_a} \quad (5)$$

Equation 5 is based on the description of the disease process as a continuous time Markov process, and is derived elsewhere (15). A moving average is applied to the resulting age-specific incidences to smooth the discontinuities that are caused by the age group subdivision of the relative risks used (see Table 1).

Data

Prevalence of diabetes is obtained from a previous study in which a pooled estimate was made based on 15 studies performed since 1970 (4). The studies largely fall into two groups: one based on registrations by general practitioners, and one based on self report in a survey. For each group we fitted an exponential curve on age-specific prevalence using logistic regression. The fit based on the survey group of studies yielded a somewhat higher pooled prevalence than the one on the general practice (GP) studies. The fitted curve of the survey studies forms the basis of the current analysis. Because of data limitations the pooled prevalence estimate is restricted to the age range of 30-80 years, and therefore the prevalence estimate concerns mainly NIDDM patients. Figure 1 shows the resulting prevalence rates by age of men and women. More details on the pooled estimate have been published elsewhere (4).

The relative risks for the calculations in this analysis are based on the Verona study (Table 1) (16). This decision was based on an earlier study, in which we have compared several studies reporting relative risks on all cause mortality for diabetes (11).

Table 1
Relative risk (95% confidence interval) on total mortality for diabetics from the Verona study.

Age (years)	Men	Women
0-44	4.69 (1.71-10.2)	3.03 (0.03-16.86)
45-54	2.33 (1.38-3.69)	3.43 (1.43-6.77)
55-64	2.13 (1.76-2.56)	2.33 (1.63-3.22)
65-74	1.50 (1.30-1.72)	2.27 (1.92-2.66)
75+	1.13 (1.00-1.28)	1.32 (1.20-1.44)

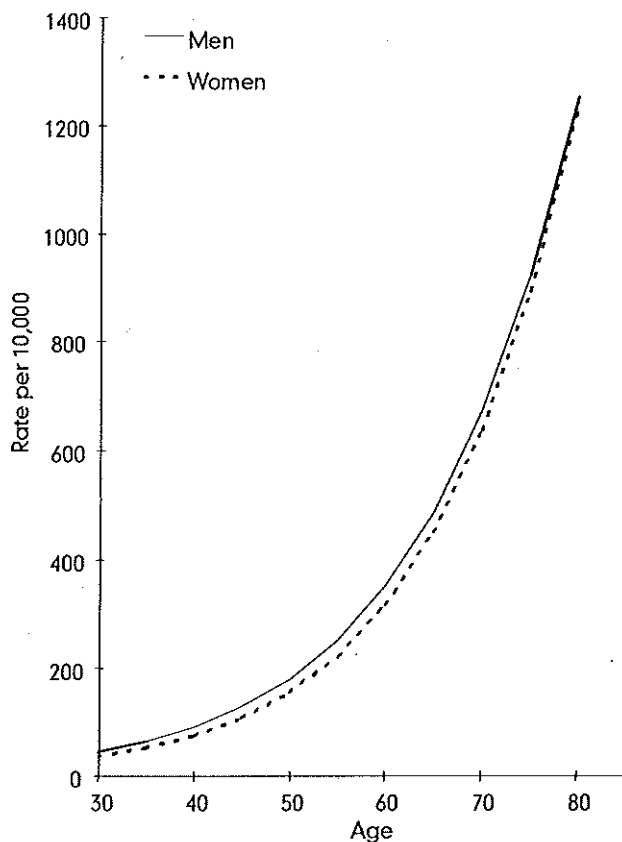


Figure 1
Prevalence of diabetes in The Netherlands by age and sex, pooled estimates of 15 studies (4).

We are aware of four studies in The Netherlands that have reported incidence of diabetes mellitus (5-8) (Table 2), and these will be compared with our estimation of diabetes incidence.

Table 2
Characteristics of the studies of incidence of diabetes mellitus in The Netherlands.

Name of the study	Period	Sample size	Age	Case-ascertainment
Sentinel Stations (5)	1980-1983	162,626	0-65+	report general practitioner
Sentinel Stations (6)	1990-1991	160,000	0-80+	report general practitioner
CMR*-Nijmegen (7)	1971-1993	12,000	0-75+	report general practitioner
National Study (8)	1987-1988	335,000	0-75+	report general practitioner in 3 months period

*CMR: Continuous Morbidity Registration

RESULTS

Figures 2 (men) and 3 (women) present a central incidence estimate by age and a lower and upper bound, based on the estimates of relative risks and their 95% confidence intervals from the Verona study. The central estimates are very similar for men and women, increasing over the whole age range, and reaching an incidence of about 1% per year at age 80 (see also Table 3). The lower bound relative risks result in an incidence estimate below the central estimate, the higher bound in one above: with lower mortality selection a lower incidence will be needed to reproduce the prevalence and vice versa. The difference between the lower and upper estimate is greater for men than for women. This is due to a relatively wider confidence interval of the relative risk (see also Table 1) and a higher absolute mortality risk.

In the Figures 2 and 3 also the observations from four Dutch incidence studies (Table 2) are presented. The data points are plotted in the middle of the (wide) age intervals, for the open ended highest age groups we used the average age of these groups as calculated with a life table. The four incidence studies give rather similar results for younger ages, but diverge at higher, with the CMR Nijmegen 1982-1993 estimate tending to be the highest, and the National Study the lowest. Comparing our results with the four studies, our estimates seem to be more or less in the middle of the observations for all age groups, except for the (usually open-ended) oldest where only the CMR observation is within the estimated range, while the other studies report (sometimes much) lower rates.

DISCUSSION

To estimate incidence and prevalence of NIDDM, sufficiently large empirical studies with adequate follow-up are preferred. To conduct such a study is difficult and expensive, and consequently most studies are too small to yield reliable estimates. This is true in particular for incidence estimates, of which there are only a few, and they are of limited use because of small numbers when age specific rates are required. As a result the estimates vary widely.

As an alternative to direct observation, this paper describes an indirect method to estimate the incidence of NIDDM. It is based on the prevalence estimate from a previous study, a pooled analysis of 15 empirical studies. Added to that is information about the excess mortality of diabetics as compared to non-diabetics (16), and theoretical knowledge about the relation between incidence, prevalence and mortality.

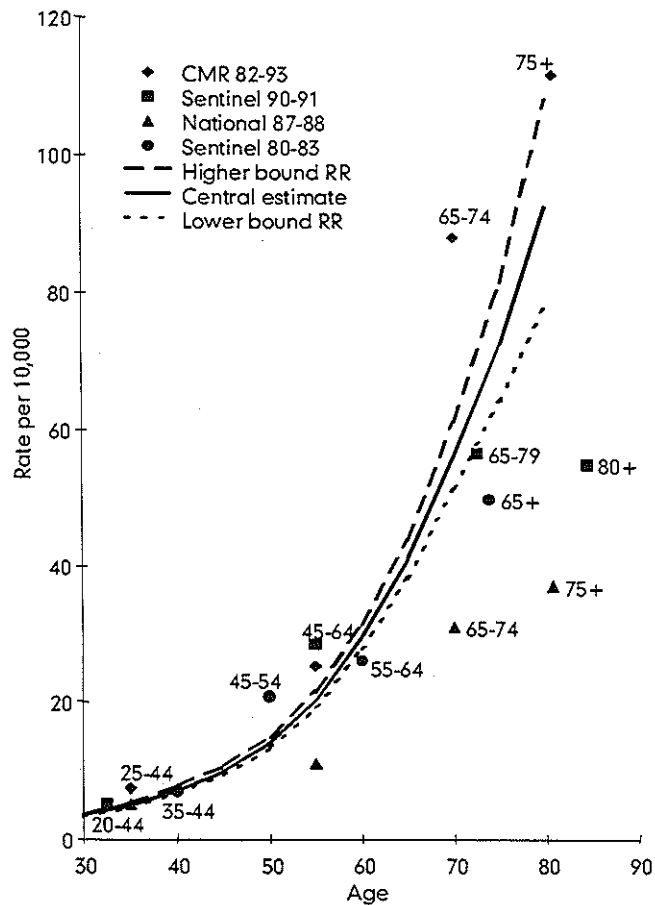


Figure 2
Incidence of NIDDM in The Netherlands by age, Men,
estimates based on IPM model, compared with age-
specific observations from 4 empirical studies.

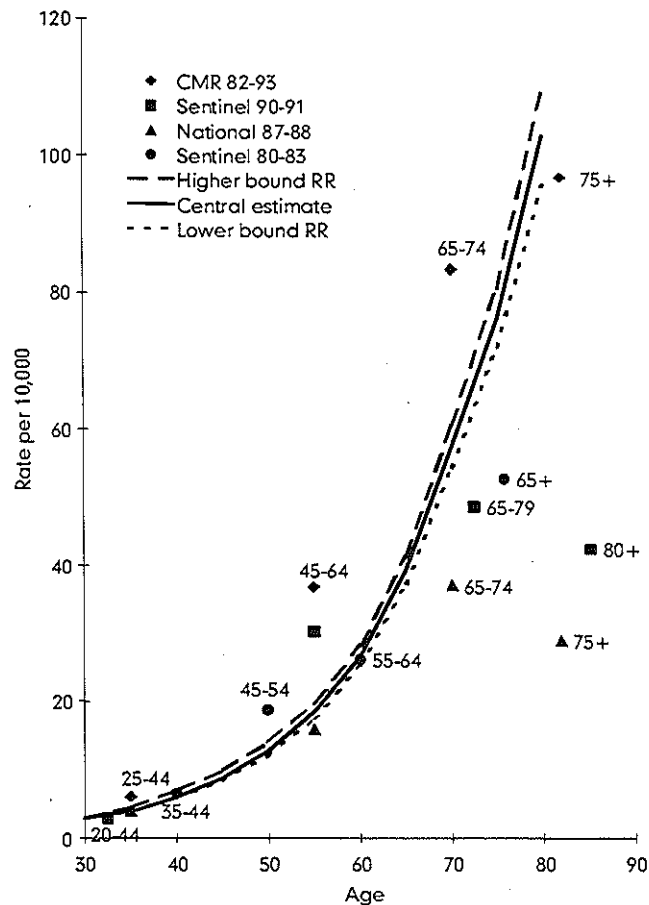


Figure 3
Incidence of NIDDM in The Netherlands by age, Women,
estimates based on IPM model, compared with age-specific
observations from 4 empirical studies.

Table 3
NIDDM incidence estimates per 1000, from the Cremona and the present study, by age group and sex.

Age	Cremona		This study	
	Men	Women	Men	Women
30-39	5	3	5	4
40-49	15	15	10	9
50-59	43	30	21	19
60-69	70	78	42	41
70-79	58	67	74	79
80-89	31	50	93*	103*

* At age 80

The relationship between epidemiological variables is not simple. The oft-cited relationship prevalence equals incidence times duration is an oversimplification (17). With rising age, true duration is lower because of increasing general mortality and thus declining life expectancy, whereas duration estimated by age-specific prevalence divided by incidence is increasing because of the accumulation of prevalence cases.

The most convenient way to model a disease process is to assume independence from all

other causes of death. Under that assumption the mortality rate of the disease can be obtained from the disease specific mortality as reported by the national statistics bureau, and an 'all other causes' mortality rate can easily be calculated (18). An independence assumption, though convenient, is not appropriate in the case of diabetes mellitus: in addition to being coded as a cause of death itself (ICD-9 250), diabetes also acts as a risk factor for a range of causes of death, such as cardiovascular diseases. We therefore constructed a diabetes-related mortality rate with relative risks for mortality of diabetics, as well as the prevalence of diabetes. Because the diabetes-related mortality rate includes all excess mortality for diabetics, it is independent from 'all other' mortality. Therefore it can be used, unlike the specific mortality restricted to diabetes mellitus (ICD 250), in an incidence-prevalence-mortality (IPM) model that assumes independence from the non-diabetes-related mortality.

The incidence estimates comply well with the available empirical incidence estimates from four Dutch incidence studies, but have upper and lower bounds that are considerably more narrow than the observed range of values. Three of the four empirical studies reported for the open ended (oldest) age groups a (much) lower incidence as compared with our estimates. This may be due in part to the calculation of the average age for the oldest age groups employing a life table. Institutionalized people, who, on average, will be older than non-institutionalized, were not included in the empirical studies, but are in the life table. The calculated average age will therefore tend to be higher than the actual one in the studies, causing the data points to be plotted too far to the right.

The incidence is jointly determined by the shape of the prevalence curve and the rate of mortality selection. From Figures 2 and 3 it can be deduced that

the former is by far the most important: the 95% confidence intervals on the relative risk for total mortality, which determine the rate of mortality selection, result in very narrow range. The rate of mortality selection is determined by the excess absolute risk, which for most of the age range involved, remains rather small. Only for the higher ages among men this absolute risk becomes big enough to have a sizeable impact. Therefore the incidence estimate is most sensitive to the prevalence used.

An assumption implicit in using cross-sectional data is that there are no time trends in incidence and survival. With strong recent time trends in incidence or survival currently observed cross-sectional prevalence will not be at their equilibrium values. For example, if incidence has recently increased, it will take several years for prevalence to reach the new higher equilibrium value. Since the incidence estimate is based on prevalence, it will reflect conditions prevailing in the past, so our estimates may diverge from current incidence.

The IPM model used in this study ignores remission: an extra parameter would be required, whose value is uncertain. One study evaluated the diabetic status of patients after 8 years of follow-up, and reported a remission of 14% (19). However, there are reasons to suspect misclassification at baseline to be responsible for at least some of these cases. We assumed remission to be mostly temporary and too small to affect the incidence estimates substantially.

A weak point is the lack of an estimate for ages over 80. It would be desirable to extend the age range of the analysis beyond 80: NIDDM is a disease of the elderly, and based on current mortality rates over half of the women and more than a third of the men survive to at least that age. Since the estimates will be used to assess the burden of disease and potentials for prevention for NIDDM, we feel that such large parts of the population ought not to be excluded. However, without a reliable prevalence estimate the procedure to estimate incidence breaks down. The message here is that better data, in particular on the oldest old, are badly needed.

The resulting incidence estimates are internally consistent with the prevalence and mortality estimates, which is not necessarily a property of empirical estimates, even when done in the same population. For example, the huge increases in prevalence (+40%) simultaneous with large decreases in incidence (-20%), as reported for Manitoba between 1986 and 1991, are difficult to explain (20, 21).

In a recent study Garancini *et al* estimated NIDDM incidence from data on prevalence of known diabetes and disease duration using data from the Cremona study (22). In Table 3 their results are compared with the present study. Their results are rather different: for ages between 40 and 70 their estimates are much higher, and they reach a peak of 70 (men) and 78 (women) per ten thousand for the 60-69 age group (our estimate is about 40 per 10,000), and subse-

quently slump down to about 30 (men) and 50 (women) per 10,000 for the 80-89 group.

This result strikes us as rather implausible: the declining incidence suggests a pool of susceptibles that is being drained. But NIDDM is a senescent disease, glucose tolerance keeps declining with age for most people, and not just for a limited group (23, 24). When among the middle-aged groups the proportion of known cases is higher than among the elderly, the prevalence of known diabetes will be relatively higher at those middle ages. An IPM-based incidence estimate will then initially show a steeper increase in incidence at the younger and middle ages as the prevalence build up is faster, and subsequently flatten out or even decline as the prevalence build-up slows at higher ages. Thus it is possible to obtain such a peaked incidence curve of known diabetes, but the usefulness as a description of diabetes epidemiology seems limited.

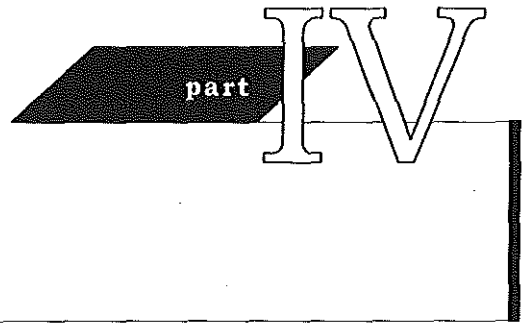
The estimate is the incidence necessary to explain observed prevalence and estimated diabetes-related mortality. This allows assessing the impact on diabetes prevalence and excess mortality of interventions or trends that influence diabetes incidence, even if diabetes incidence itself is difficult to observe. The method is general enough to be employed for other diseases where incidence assessment is a problem, such as dementia. It can also be applied for specific ethnic groups with high prevalences of NIDDM, for example to assess the potential effectiveness of interventions in such groups. It is in this field of intervention impact assessment where the method may prove most useful.

References

1. Eastman RC, Javitt JC, Herman WH, et al.: Model of complications of NIDDM. I. Model constructions and assumptions. *Diabetes Care* 20:725-734, 1997
2. Eastman RC, Javitt JC, Herman WH, et al.: Model of complications of NIDDM. II. Analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. *Diabetes Care* 20:735-744, 1997
3. King H, Rewers M: Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. *Diabetes Care* 16:157-177, 1993
4. Baan CA, Bonneux L, Ruwaard D, Feskens EJM: The prevalence of diabetes mellitus in The Netherlands: a quantitative review. *Eur J Publ Health* 8:210-216, 1998
5. Steering Committee on Future Health Scenarios: *Chronische ziekten in het jaar 2005. Volume 1: scenario's van diabetes mellitus 1990-2005. (Chronic diseases in the year 2005. Volume 1: scenarios on diabetes mellitus 1990-2005)*. Dordrecht, Boston, London Kluwer Academic Publishers, 1991

6. Ruwaard D, Gijsen R, Bartelds AIM, Hirasing RA, Verkleij H, Kromhout D: Is the incidence of diabetes increasing in all age-groups in The Netherlands. Results of the second study in the Dutch Sentinel Practice Network. *Diabetes Care* 19:214-218, 1996
7. van de Lisdonk EH, Bosch WJHM, Huygen FJA, Lagro-Jansen ALM, ed. *Ziekten in de huisartspraktijk (Diseases in the general practice)*. Utrecht: Wetenschappelijke uitgeverij Bunge, 1990:342.
8. van der Velden J, de Bakker DH, Claessens AAMC, Schellevis FG: *Een nationale studie naar ziekten en verrichtingen in de huisartspraktijk. Basisrapport: Morbidity in de huisartsenpraktijk (A national study for diseases and operations in the general practice. Morbidity in the general practice)*. Utrecht Netherlands Institute of Primary Health Care, 1991
9. Mackenbach JP, Snels IAK, Friden-Kill LM: Diabetes mellitus als doodsoorzaak (Diabetes as a cause of death). *Ned Tijdschr Geneesk* 135:1492-1496, 1991
10. Jouglé E, Papoz L, Balkau B, Maguin P, Hatton F: Death certificate coding practices related to diabetes in European countries - the EURODIAB subarea C study. *Int J Epidemiol* 21:343-351, 1992
11. Baan CA, Nusselder WJ, Barendregt JJ, Ruwaard D, Bonneux L, Feskens EJM: The burden of mortality of diabetes mellitus in The Netherlands. *Epidemiology* 10:184-187, 1999
12. Murray C, Lopez A: Quantifying disability: data, methods and results. *Bull World Health Organ* 72 (3):481-94, 1994
13. Bonneux L, Barendregt J, Looman C, van der Maas P: Diverging trends in colorectal cancer morbidity and mortality: earlier diagnosis comes at a price. *Eur J Cancer* 31 A(10):1665-1671, 1995
14. Niessen LW, Barendregt JJ, Bonneux L, Koudstaal P: Stroke trends in an ageing population. *Stroke* 24:931-939, 1993
15. Barendregt JJ, Oortmarssen GJ, van, Hout BA, van, Bosch JM, van den, Bonneux L: Coping with multiple morbidity in a life table. *Mathematical Population Studies* 7:29-49, 1998
16. Muggeo M, Verlato G, Bresson F, et al: The Verona diabetes study: a population-based survey on known diabetes prevalence and 5-year all-cause mortality. *Diabetologia* 38:318-325, 1995
17. Murray C, Lopez A. *Global comparative assessments in the health sector. Disease burden, expenditures and intervention package*. Geneva: WHO, 1994.
18. Manton KG, Stallard E: *Chronic disease modelling: measurement and evaluation of the risks of chronic disease processes*. New York Oxford University Press, 1988
19. Stern MP, Valdez RA, Haffner SM, Mitchell BD, Hazuda HP: Stability over time of modern diagnostic criteria for type II diabetes. *Diabetes Care* 16:978-983, 1993
20. Blanchard JF, Ludwig S, Wadja A, et al.: Incidence and prevalence of diabetes in Manitoba, 1986-1991. *Diabetes Care* 19:807-811, 1996
21. Leibson CL, O'Brien PCO, Atkinson E, Palumbo PJ, Melton III LJ: Relative contributions of incidence and survival to increasing prevalence of adult-onset diabetes mellitus: a population-based study. *Am J Epidemiol* 146:12-22, 1997
22. Garancini MP, Gobbi C, Errera A, Sergi A, Gallus G: Age-specific incidence and duration of known diabetes. The Cremona study. *Diabetes Care* 19:1279-1282, 1996

23. West KM: *Epidemiology of diabetes and its vascular lesions*. New York Elsevier, 1978
24. King H, Dowd JE: Primary prevention of type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 33:3-8, 1990



THE DIABETES—

CARDIOVASCULAR DISEASE MODEL

Estimating the age-specific cardiovascular morbidity and mortality of diabetes mellitus in The Netherlands

INTRODUCTION

Cardiovascular diseases (CVD) are the most common complications of non-insulin-dependent diabetes mellitus (NIDDM). People with diabetes have a risk of dying of CVD 2-5 times higher than that of non-diabetic individuals (1-3). The relation between diabetes and its cardiovascular co-morbidity and -mortality is complex. To gain insight in the burden of the diabetes and its cardiovascular complications and to estimate the potential effect of preventive strategies for diabetes or its complications, a disease model can be of use.

One of the basic data used in a disease model is cause-specific mortality. However, a valid estimate of diabetes mortality can not be obtained from the cause-of-death registration, since it is based upon a single cause of death, the underlying cause of death (4). A diabetic subject who dies of a heart attack will either be registered with myocardial infarction or diabetes as the underlying cause of death. This not only leads to an under registration of the diabetes mortality, but it also precludes a valid estimate of the cardiovascular mortality rate among diabetic subjects.

Data on CVD incidence, prevalence and mortality rates among diabetic subjects are scarce and, probably due to small numbers, published on an aggregated level. As age is an important variable in the association diabetes-cardiovascular disease, it is necessary to have age-specific incidence and prevalence and mortality rates. In addition, attention has to be paid to the consistency of the data, i.e. cardiovascular mortality rates among diabetics have to fit the CVD incidence and prevalence rates.

We therefore calculated the cardiovascular morbidity and mortality among diabetic subjects by combining data from epidemiological studies with mortality data from vital statistics in a multi-state life table. The method used is described and the results are validated with data from epidemiological studies.

METHODS

The study consists of two parts (Figure 1). In the first part, the total cardiovascular mortality rate (ICD-9 390-458) of the diabetic population is estimated. In the second part the total cardiovascular mortality rate is divided into coronary heart disease (ICD-9 410-414), stroke (ICD-9 430-439) and other cardiovascular diseases mortality, and estimated together with the coronary heart disease and stroke incidence and prevalence rates. The definition and description of the several mortality rates used in this study are given in Table 1.

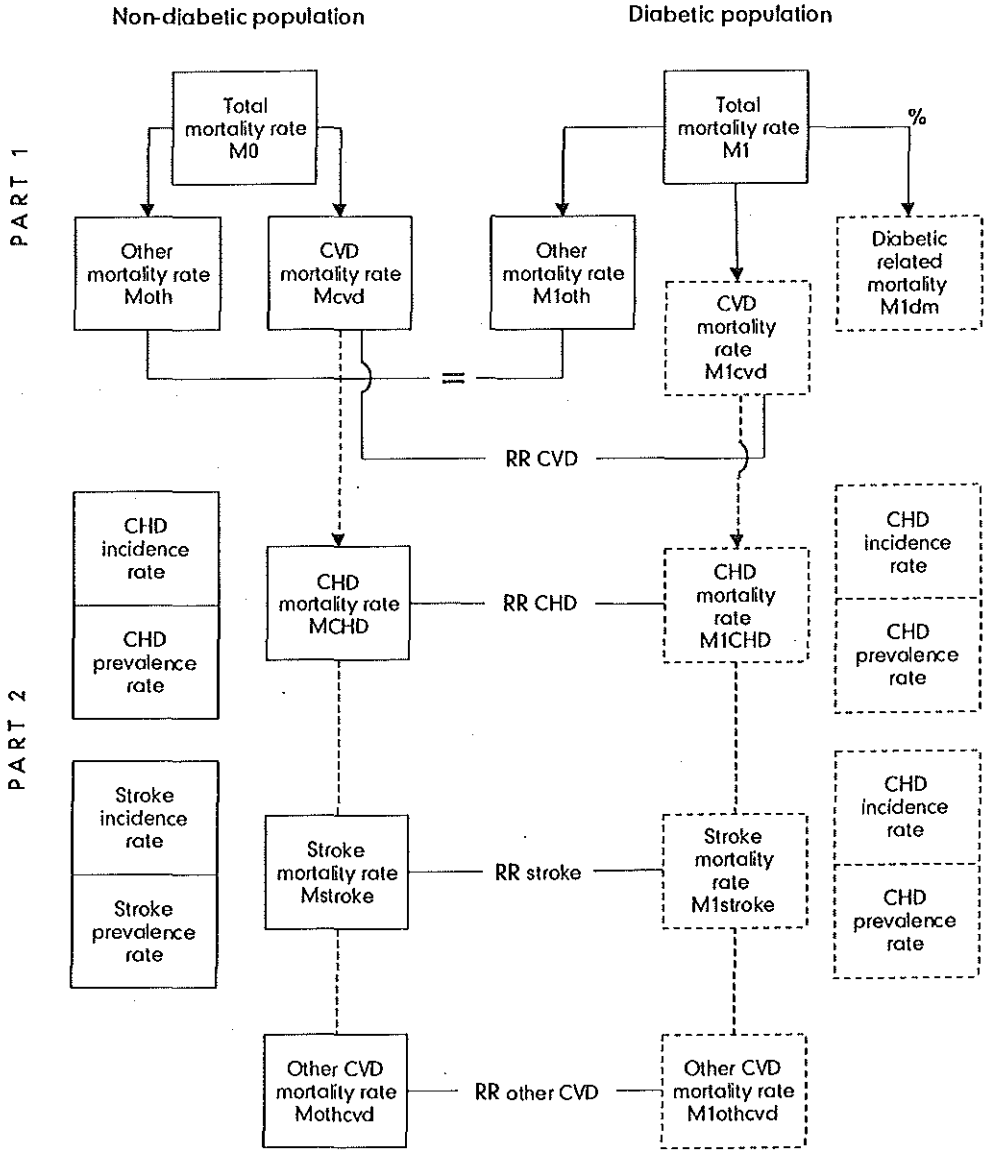


Figure 1

The top-down structure of the estimations of the cause-specific mortality of the diabetic population. The boxes with solid borders indicating those variables that are known, the boxes with dashed borders indicating the variables to be estimated in this study.

Table 1

The abbreviations and definitions of the mortality rates used.

Abbreviation	Description	Formula	Assumptions	Source
<i>Total population</i>				
M	Total mortality rate			(9)
M _{CVD}	Cardiovascular mortality rate, ICD-9 394-459			(9)
M _{CHD}	Coronary mortality rate, ICD-9 410-414			(9)
M _{stroke}	Stroke mortality rate, ICD-9 430-438			(9)
M _{othCVD}	Other cardiovascular mortality rate			(9)
M _{dm}	Diabetes mortality rate, ICD-9 250			(9)
M _{oth}	Other mortality rate	$M_{oth} = M - (M_{CVD} + M_{dm})$		
M _{casefatCHD}	Case fatality rate for coronary heart disease			(14)
M _{casefatstroke}	Case fatality rate for stroke			(15)
<i>Non-diabetic population</i>				
M ₀	Total mortality rate	$M_0 = \frac{M}{pR + (1-p)}$ *		previous study (8)
M _{0CVD}	Cardiovascular mortality rate	Idem, with R _{CVD} instead of R		
M _{0CHD}	Coronary mortality rate	Idem, with R _{CHD} instead of R		
M _{0stroke}	Stroke mortality rate	Idem, with R _{stroke} instead of R		
M _{0casefatCHD}	Case fatality rate for coronary heart disease	Idem, with R _{casefatCHD} instead of R		
M _{0casefatstroke}	Case fatality rate for stroke	Idem, with R _{casefatstroke} instead of R		

Table 1 – continued

Abbreviation	Description	Formula	Assumptions	Source
<i>Diabetic population</i>				
M_1	Total mortality rate	$M_1 = M_0 \times R^*$		previous study (8)
M_{1CVD}	Cardiovascular mortality rate	$M_{1CVD} = M_{0CVD} \times R_{CVD}$	$M_{1CVD} = w M_1$	
M_{1CHD}	Coronary mortality rate	$M_{1CHD} = M_{0CHD} \times R_{CHD}$	$M_{1IHD} = y M_{1CVD}$	
$M_{1stroke}$	Stroke mortality rate	$M_{1stroke} = M_{0stroke} \times R_{stroke}$	$M_{1stroke} = z M_{1CVD}$	
$M_{1othCVD}$	Other cardiovascular mortality rate	$M_{1othCVD} = M_{0othCVD} \times R_{othCVD}$	$M_{1othCVD} = 1 - y - z M_{1CVD}$	
M_{1dm}	Diabetes specific mortality rate **	$M_{1dm} = M_{dm} \times F_{dm}$	$M_{1dm} = x M_1$	
M_{1oth}	Other mortality rate	M_{oth}	= equal to M_{oth} of total population	
$M_{1casefatCHD}$	Case fatality rate for coronary heart disease	$M_{1casefatCHD} = M_{0casefatCHD} \times R_{casefatCHD}$	mean $R_{casefatCHD}$ for age-group 30-80 = 1.3***	
$M_{1casefatstroke}$	Case fatality rate for stroke	$M_{1casefatstroke} = M_{0casefatstroke} \times RR_{casefatstroke}$	mean $R_{casefatstroke}$ for age-group 30-80 = 1.3***	

*: p is the prevalence of diabetes, R is the relative risk for total mortality, given exposure to diabetes. **: mortality rate among diabetics caused by glycemic coma or nephropathy; w,x,y,z: proportion, based on literature in Table 2 ***: based upon literature (16-19).

Table 2
Distribution of causes of death (%) in persons with diabetes mellitus.

Study (reference)		WHO-multinational Study of Vascular Disease in Diabetics (5)	Wisconsin Study (6)	England + Wales (7)
Age (year)		35-54	55 ± 12.6	40-85
Men	CVD	57	62	52
	CHD*	89	71	71
	Stroke*	7	11	17
	Other CVD*	4	18	12
	DM	10	12	20
	Other causes	33	24	28
Women	CVD	54	58	52
	CHD*	85	57	62
	Stroke*	9	21	21
	Other CVD*	4	22	17
	DM	10	18	22
	Other causes	36	24	26

*: Percentage of total number of cardiovascular deaths

CVD: cardiovascular disease; CHD: coronary heart disease; DM: diabetes mellitus

The basic method to arrive at age-specific cardiovascular mortality and morbidity rates is to link diabetes and cardiovascular morbidity and mortality in the causal chain of a model. This puts restrictions on the values the variables can take on. Further restrictions are obtained by making the results from the model comply with empirical observations as obtained from the literature. In Table 2, three studies are presented which reported distributions of causes of death in subjects with diabetes mellitus (5-7). These distributions have been used as constraint as will be explained below. In the appendix the calculations are described in more detail.

Part 1 – Estimating the age-specific total cardiovascular mortality rate of diabetic subjects (see also appendix)

To arrive at the total cardiovascular mortality rate of diabetic subjects, the total mortality rate of the diabetic population is divided into three mortality rates: the cardiovascular mortality rate, the diabetic specific mortality rate and all other mortality. Total mortality rates for diabetic and non-diabetic population were derived from a previous study (8). From the cause-of-death registration of Statistics Netherlands, cause-specific mortality rates were obtained for the total popula-

tion (9). Prevalence of diabetes in the Netherlands was derived from a pooled analysis of all studies performed since 1970 (10).

The higher mortality rate of diabetic subjects compared to non-diabetic subjects is mostly due to the excess risk for diabetic subjects to die of cardiovascular complications or complications such as nephropathy and hyperglycaemic coma. The risk of dying due to other causes is not significantly higher among diabetic subjects (6, 11, 12). Therefore, we assumed that the mortality rate for other causes in the diabetic population (M_{10th}) is equal to the mortality rate for other causes in the total population (M_{0th}).

The diabetic specific mortality rate is defined as the mortality rate due to diabetes itself (hyperglycaemic coma) or diabetic complications such as nephropathy. As reported in the literature (Table 2), between 10-22% of the diabetic deaths is due to diabetes specific complications. Dividing the ICD-250 mortality rate (ICD 250 is the code of diabetes in the cause of death registration) of the total population by the prevalence rate of diabetes, yields a mortality rate for the diabetic population. However, diabetic subjects who die due to cardiovascular complications can also be registered with the code ICD-250. When using this rate, far too many deaths will be attributed to diabetic specific causes. Therefore, we multiplied the ICD-250 mortality rate of the total population with a factor to obtain the diabetes specific mortality rate of the diabetic population. The factor is chosen such that the M_{1dm} multiplied with the number of life-years lived yields the percentage of deaths due to diabetes specific complications as reported in the studies of Table 2.

To obtain the age-specific cardiovascular mortality rate for diabetic subjects, the cardiovascular mortality rate of the non-diabetic subjects (M_{0cvd}) is multiplied with an age-specific relative risk of cardiovascular mortality for diabetic subjects. In a life-table, the age-specific relative risk for cardiovascular mortality is estimated, such that the total number of deaths, obtained by using the distribution of deaths, is equal to the total number of deaths when using the estimated age-specific relative risk. With an optimisation method, the diabetes factor as well as the age-specific relative risk for cardiovascular mortality are estimated such that conditions are fulfilled. The estimates of the age-specific relative risks for the cardiovascular disease mortality rates were judged by the residuals as well as the sum of squares of the optimisation method. In addition the mean relative risks for the age-group 45-74 years were compared with relative risks reported in literature.

A sensitivity analysis was performed: the sensitivity for the diabetes factor was estimated. We have two variants: one for which the factor is constant with age, and one for which the factor is assumed to decline with age.

Part 2 – *Estimating the age-specific coronary heart disease, stroke and other cardiovascular disease morbidity and mortality rates of the diabetic population (see also appendix)*

In this part, coronary heart disease, stroke and other cardiovascular morbidity and mortality rates were estimated, by use of a multi-state life table approach. A multi-state life table is an extension of the standard life table that distinguishes not just between 'alive' and 'dead', but allows for additional states like 'alive, healthy', 'alive, with heart disease', etc (13). In addition to cause-specific mortality rates, the multi-state life table comprises also incidence, prevalence and case-fatality rates.

The mortality rates of coronary heart disease, stroke and other cardiovascular mortality for the total population as well as the survival rate for coronary heart disease and stroke were obtained from previous studies (14, 15). These mortality rates were converted to mortality rates for the non-diabetic population, using the same method as for the total mortality rate (8) (see also Table 1). Multiplying these rates for the non-diabetic population with age-specific relative risks of coronary heart disease, stroke or other cardiovascular mortality for diabetic subjects yields the mortality rates for the diabetes population.

The number of deaths due to stroke or coronary heart disease when using the M_{stroke} or M_{CHD} in the life-table, must be equal to the number of deaths obtained by multiplying the percentages of deaths due to stroke or coronary heart disease with the total number of cardiovascular deaths among diabetic subjects.

The survival rate for coronary heart disease and stroke for the diabetic population were obtained by multiplying the case-fatality rates of the non-diabetic population with an age-specific relative risk (R_{survCHD} or $R_{\text{survstroke}}$). A few studies have reported a relative risk for case fatality, and these estimates are rather similar (16-19). We assumed the mean relative risk for the age group 30-80 to be about 1.3 for diabetic patients with cardiovascular diseases.

We added the condition that incidence for coronary heart disease or stroke of the diabetic population has to be higher at all ages than the incidence rates for the non-diabetic population. Also the prevalence of coronary heart disease or stroke have to be equal or higher in the diabetic population.

The different morbidity and mortality rates were simultaneously estimated, such that they are consistent with each other as well as consistent with what is known in literature. As in the first part, the estimates of the age-specific rates for the cardiovascular disease morbidity and mortality rates were judged by the residuals as well as the sum of squares of the optimisation method. In addition, the mean relative risks for the age-group 45-74 years were compared with relative risks reported in literature.

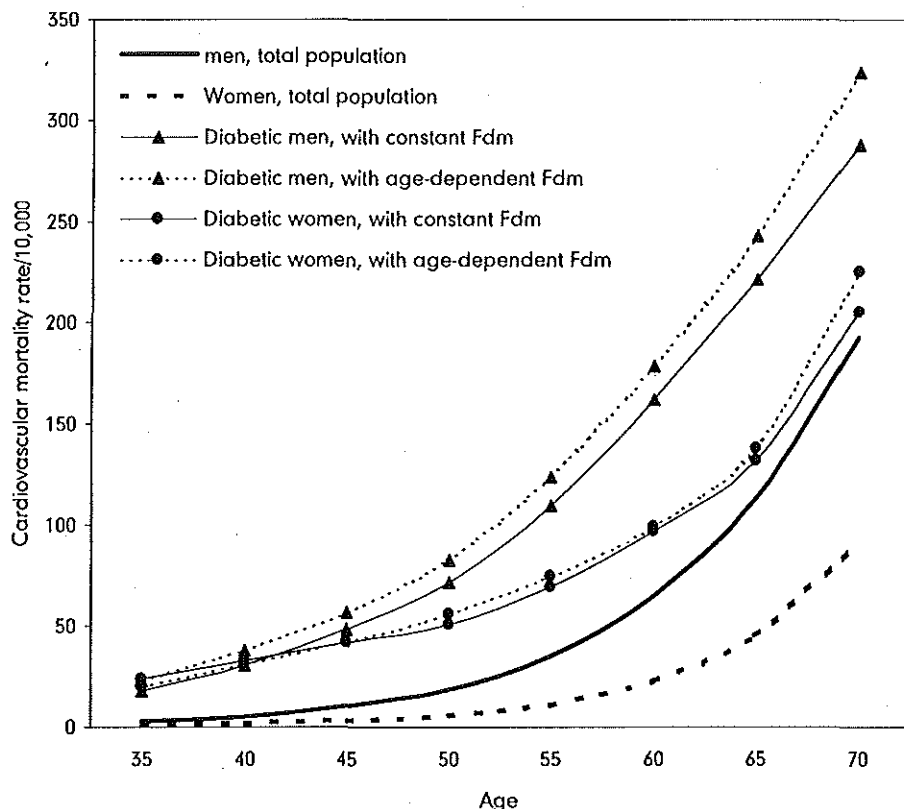


Figure 2

Age-specific cardiovascular mortality rates among men and women in total Dutch population and for diabetic men and women, estimated with two variants of the diabetes factor (F_{dm}).

RESULTS

Part 1 – Only the estimates are shown as obtained using the Wisconsin Study data (6). When using the two other studies (5, 7), the results were very similar. In Figure 2, the age-specific cardiovascular mortality rates in the total population as well as in diabetic subjects are shown for men and women. The mean relative risks for the age group 45-74 for men was 2.6 and for women 4.8, which is in accordance with the literature (Table 3).

Two variants of cardiovascular mortality rate among diabetics were estimated in the sensitivity analysis (Figure 2). Although the differences between

Table 3

Mean relative risks of cardiovascular diseases (CVD), coronary heart disease (CHD), stroke or other cardiovascular diseases mortality (other CVD) for diabetic subjects.

	Age group (yr)	Men				Women			
		CVD	CHD	Stroke	other CVD	CVD	CHD	Stroke	other CVD
Our estimate	45-74	2.6	3.0	3.0	1.7	4.8	4.5	3.0	2.6
Literature									
Framingham (23)	45-74	2.1				4.9			
NHANES (12)	40-77	2.6	2.8			2.4	2.6		
Finland (24)	40-70	2.5				2.9			
Tecumseh Study (25)	40-70		3.0				3.0		
Finland (26)	40-69	2.6				3.9			
Finland (27)	30-74	3.0	3.0	3.5	2.3	4.5	5.2	3.9	3.4
Monica Study (28)	35-74			4.4				5.1	
Wisconsin Study (6)	55.5 ± 12.6		2.4	1.8	1.7		2.2	2.2	2.4
Gothenburg (20)	51-59	3.8	4.1	3.9					
Chicago Heart Association (29)	35-64		4.0				5.9		
England + Wales (7)	40-59		2.0				3.6		
Aberdeen (30)	45-64		3.8	3.3			5.4	2.2	
Finland (31, 32)	45-64		3.5	2.4			9.2	5.5	
Ohao, HI (26)	45-68	2.6							
Whitehall Study (33)	40-64		2.4						
Nurses Health Study (34)	30-55					6.3	6.7	5.0	
Mr Fit (35)	30-57		3.9	2.8					
Finland (36)	30-59			3.8				6.0	

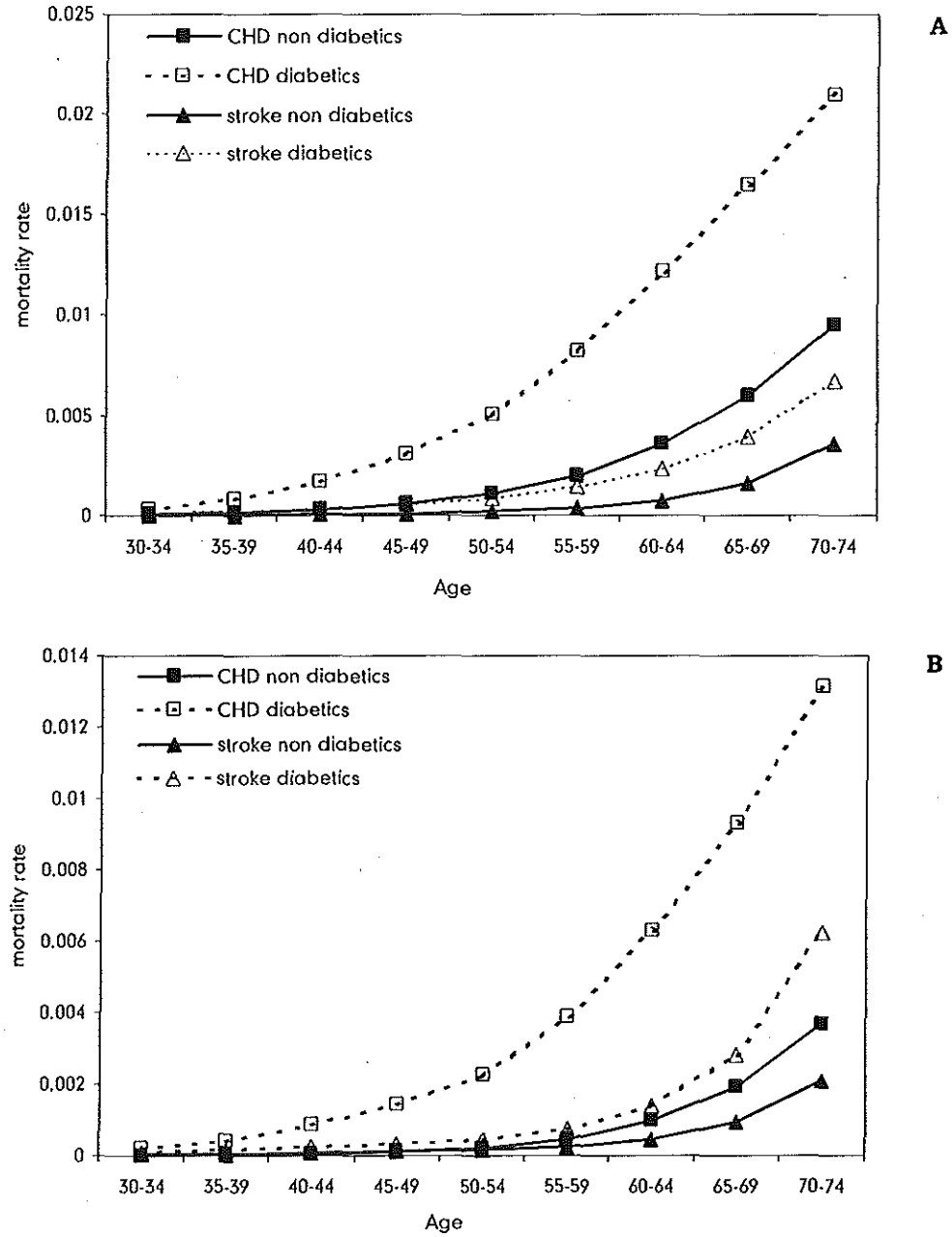


Figure 3
Coronary heart disease and stroke mortality rates in The Netherlands for diabetic and non-diabetic subjects. A: men, B: women.

the two methods are not large, the CVD mortality rate for a constant F_{dm} is lower compared with the CVD mortality rate estimate using the age-dependent F_{dm} . The sum of squares and the residuals of the two estimates showed that when using an age-dependent diabetes factor the cardiovascular mortality rate among diabetics fitted slightly better.

Part 2 – Again, only the results for the Wisconsin Study data are presented. In Table 3, the mean relative risks for coronary heart disease, stroke and other cardiovascular mortality are shown for men and women. The estimated relative risks are in accordance with those reported in the literature. When using the England and Wales study (7), the mean relative risks for coronary heart disease, stroke and other cardiovascular mortality are very similar. The WHO-multinational Study showed different results, probably due to their different distribution in causes of death compared with the other two studies (Table 2).

In Figure 3 the coronary and stroke mortality rates for diabetic and non-diabetic men and women are plotted in the age-group 45-74 years. The differences between diabetic and non-diabetic subjects were larger among women than among men. The prevalence rates of coronary heart disease and stroke for diabetic and non-diabetic subjects are presented in figure 4, the incidence rates are presented in figure 5.

DISCUSSION

In this paper we have, based on several data-sources, arrived at estimates of the age-specific total cardiovascular mortality rate, as well as the coronary, stroke and other cardiovascular morbidity and mortality rates of diabetic subjects.

To estimate the total cardiovascular mortality rate in the first part of this study, we assumed that a diabetic subject does not have an excess risk for dying due to other causes. As reported in the Joslin Study, the risk of dying due to, for example, cancer or accidents is not significantly raised among diabetic subjects (11). They reported standardised mortality ratio (SMR) for all causes of death of 1.6 for men and 2.2 for women. After exclusion of cardiovascular complications and diabetes as causes of death, the SMR decreased to 1 for both men and women. Also other studies reported no significant excess mortality for causes of death other than cardiovascular or diabetes itself (6, 12, 20).

We defined the diabetic specific mortality rate (M_{ldm}) as 'the mortality rate among diabetics due to diabetes specific complications', such as hyperglycaemic coma or nephropathy. The mortality rate of the ICD-250 is a cause specific mortality rate for the total population. By dividing this mortality rate by the

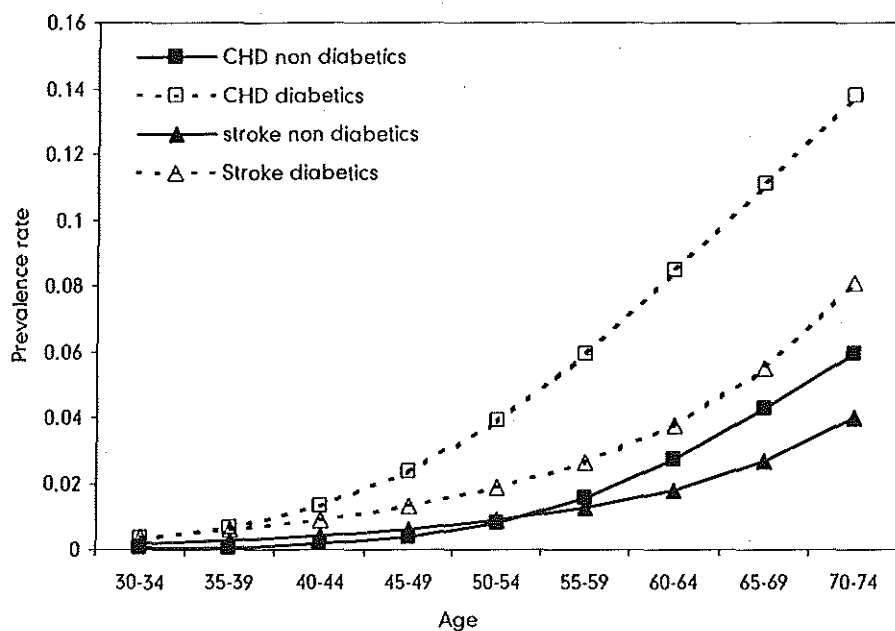
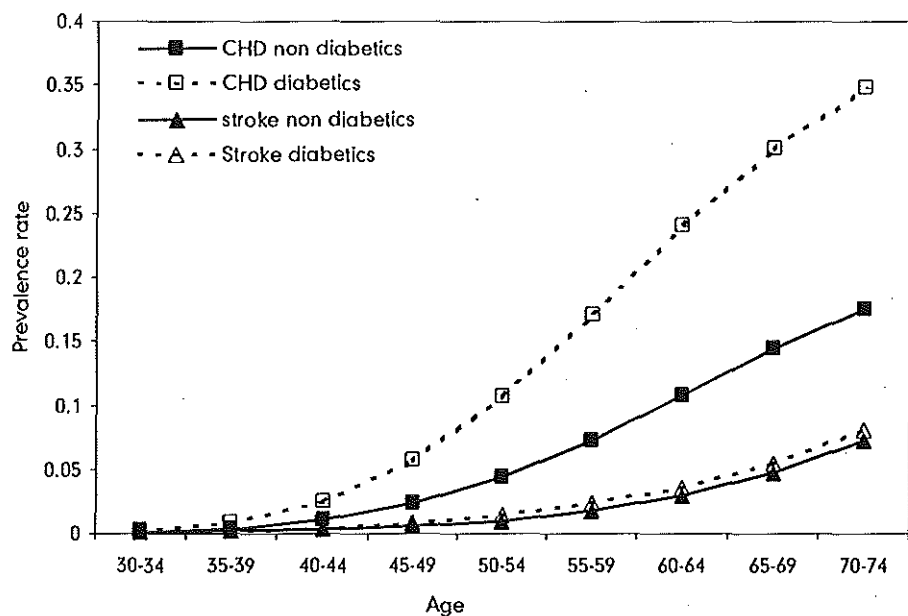


Figure 4
Coronary heart disease and stroke prevalence rates in The Netherlands for diabetic and non-diabetic subjects. A: men, B: women.

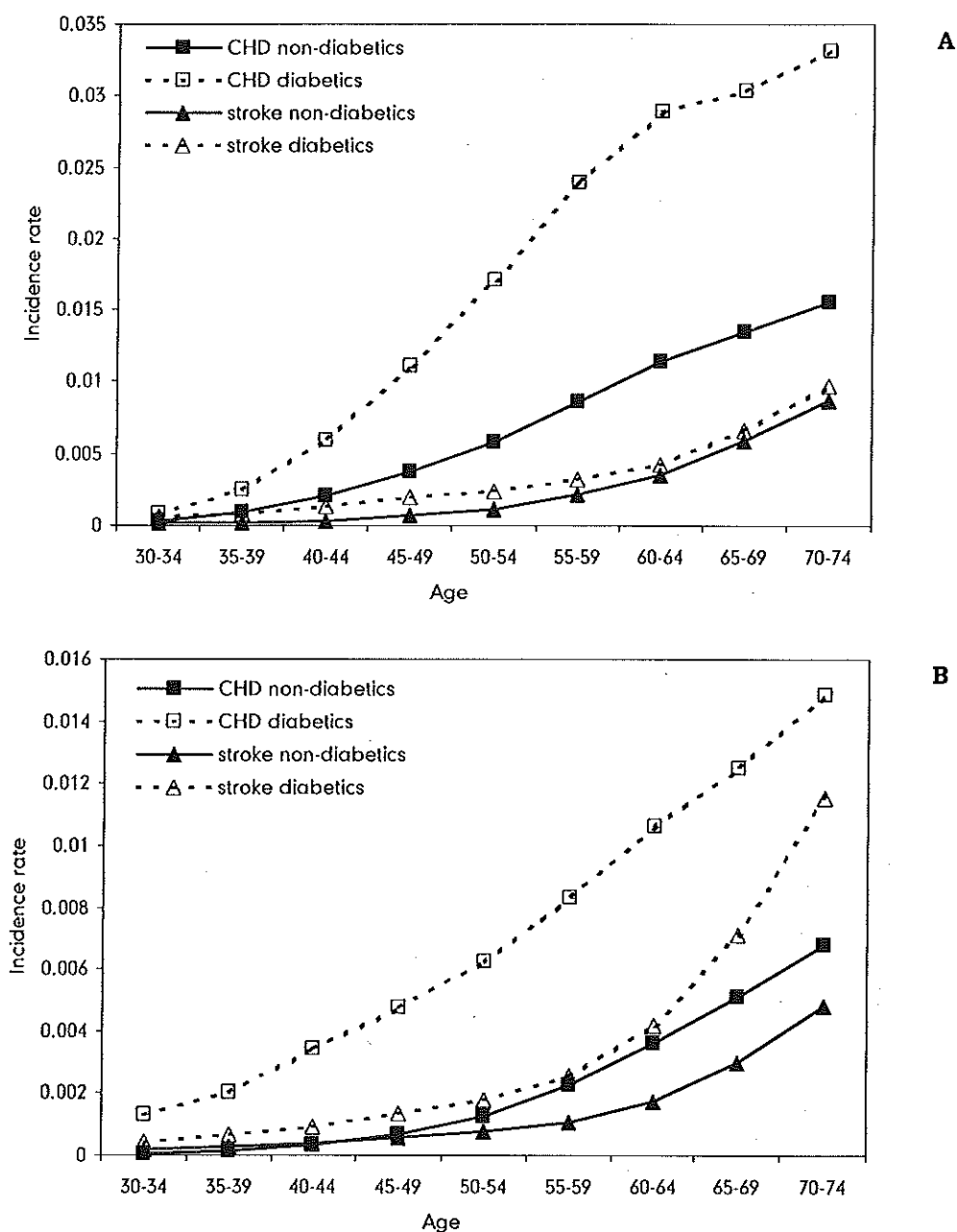


Figure 5
Coronary heart disease and stroke incidence rates in The Netherlands for diabetic and non-diabetic subjects. A: men, B: women.

prevalence rate of diabetes, the mortality rate ICD-250 of the diabetic population is obtained. This rate is much higher as our estimate of the diabetic specific mortality rate (data not shown). However, the concept of ICD-250 is difficult to interpret. We assumed that if a hyperglycaemic coma or nephropathy is diagnosed in a deceased diabetic patient, the code ICD-250 is given as the cause of death. But diabetic subjects who died due to/with cardiovascular complications might also be registered in the cause of death registration with the code ICD-250. As reported in the three studies stated in Table 2, between 10-20% of male diabetic deaths and 10-22% of the female diabetic deaths is due to diabetes specific complications. These numbers of diabetic specific deaths have to be distributed over the ages. If we use the ICD-250 mortality rate of the diabetic population as the diabetic specific mortality rate, far too many deaths will be contributed to diabetic specific causes. Therefore we multiplied the diabetes mortality rate of the total population with a factor to obtain the diabetes specific mortality rate of the diabetic population. The factor is chosen such that the M_{ldm} multiplied with the number of life-years lived yields the percentage of deaths due to diabetes specific complications reported in literature.

In the second part of this study, age-specific morbidity and mortality rates of coronary heart disease, stroke and other cardiovascular disease morbidity and mortality were estimated. One of the main data sources used as a restrictive condition were the distributions of causes of death as reported in literature. However, the coding practice for causes of death differs between countries and over time. Using distributions of causes of death of foreign countries might introduce bias. Especially for the second part of the study, where we estimated three different types of cardiovascular mortality rates, this coding difference might influence the results. But we added more limiting conditions, such as that the incidence for coronary heart disease or stroke of the diabetic population had to be higher at all ages than those for the non-diabetic population. Also the prevalence of coronary heart disease or stroke had to be equal or higher in the diabetic population.

As there were no data available on cardiovascular morbidity and mortality rates among diabetics in The Netherlands, we could not validate our estimates directly. However, it was possible to compare the outcomes on a more aggregated level, such as mean relative risk for cardiovascular mortality. Despite the possible bias it appeared that within all limiting conditions, very few solutions were possible and all solutions resulted in the same mean relative risk for mortality. Only using the WHO multinational Study of Vascular disease in Diabetics (5) resulted in different mean relative risks and odd age-patterns of coronary and stroke morbidity and mortality rates. Using these percentages resulted in far too high relative risks for coronary heart disease, which were not in accordance with the mean relative risks for CHD reported by different studies (Table

3). This is probably due to the fact that they reported a high percentage of deaths due to coronary heart disease (89% for men, 85% for women and a rather low percentage of deaths due to stroke (7% and 9% for men and women respectively).

The age pattern of the relative risks of the three specific cardiovascular mortality rates was somewhat different for men and women, especially for stroke mortality. The relative risk was decreasing more sharply with age in men as in women. Based on the current knowledge, this finding can not be verified, although one review article suggests that the age-pattern of the relative risks for stroke is different for diabetic women compared to diabetic men (21). The Framingham risk function, where incidence of stroke (both fatal and non-fatal) is included, shows a constant relative risk of incidence of stroke among women (22). It is, however, interesting to observe whether this age-pattern indeed differs in reality and if so, what is the cause of this difference.

To conclude, the estimates of the different cardiovascular morbidity and mortality rates presented here might serve several goals. The results can be used to generate new hypotheses that should be tested in epidemiological studies. One example is the difference found in the age-pattern of stroke mortality between diabetic men and women. The second goal of this exercise is to identify the gap in the current knowledge on certain aspects of the relationship between diabetes and cardiovascular diseases. For example data about cardiovascular diseases in the elderly are lacking. Although most western societies are ageing, and diabetes as well as cardiovascular disease is increasing with age, we still have very little data about the elderly. Finally, we have tried to come to an internally consistent estimate of the different mortality and morbidity rates for diabetic subjects. These rates will be used in a multi-state life table in which we can examine the influence of demographic trends or changes in cardiovascular mortality on the diabetes prevalence or mortality (chapter 9).

References

1. Panzram G: Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 30:123-131, 1987
2. Nathan DM: Long-term complications of diabetes mellitus. *New Eng J Med* 328:1676-1685, 1993
3. Wingard DL, Barrett-Connor, ed. *Heart Disease and Diabetes*. 2 ed. Bethesda: NIH, 1995:429-448. (National Diabetes Data Group, ed. Diabetes in America;)

4. Jouglia E, Papoz L, Balkau B, Maguin P, Hatton F: Death certificate coding practices related to diabetes in European countries - the EURODIAB subarea C study. *Int J Epidemiol* 21:343-351, 1992
5. Morrish NJ, Stevens LK, Head J, Fuller JH, Jarrett RJ, Keen H: A prospective study of mortality among middle-aged diabetic patient (the London cohort of the WHO Multinational Study of Vascular Disease in Diabetics)I: causes and death rates. *Diabetologia* 33:538-541, 1990
6. Moss SE, Klein R, Klein BEK: Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 81:1158-1162, 1991
7. Swerdlow AJ, Jones ME: Mortality during 25 years of follow-up of a cohort with diabetes. *Int J Epidemiol* 25:1250-1261, 1996
8. Baan CA, Nusselder WJ, Barendregt JJ, Ruwaard D, Bonneux L, Feskens EJM: The burden of mortality of diabetes mellitus in The Netherlands. *Epidemiology* 10:184-187, 1999
9. Centraal Bureau voor de Statistiek. *Overledenen naar doodsoorzaak, leeftijd en geslacht in 1990*, Serie A1. Voorburg, 1990.
10. Baan CA, Bonneux L, Ruwaard D, Feskens EJM: The prevalence of diabetes mellitus in The Netherlands: a quantitative review. *Eur J Publ Health* 8:210-216, 1998
11. Kessler II: Mortality experience of diabetic patients. A twenty-six year follow-up study. *Am J Med* 51:715-724, 1971
12. Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB: Mortality among diabetics in a national sample. *Am J Epidemiol* 128:389-401, 1988
13. Schoen R: *Modeling Multigroup populations*. New York and London Plenum Press, 1987
14. Bonneux L, Barendregt JJ, Van der Maas PJ: The new old epidemic of coronary heart disease. *Am J Public Health* 89:379-382, 1999
15. Niessen LW, Barendregt JJ, Bonneux L, Koudstaal P: Stroke trends in an ageing population. *Stroke* 24:931-939, 1993
16. Abbud ZA, Shindler DM, Wilson AC, Kostis JB: Effect of diabetes mellitus on short- and long-term mortality rates of patients with acute myocardial infarction: a statewide study. *Am Heart J* 130:51-57, 1995
17. Herlitz J, Brandrup Wognsen G, Emanuelsson H, et al.: Mortality and morbidity in diabetic and nondiabetic patients during a 2-year period after coronary artery bypass grafting. *Diabetes Care* 19:698-703, 1996
18. Currie CJ, Morgan CL, Gill L, Stott NCH, Peters JR: Epidemiology and costs of acute hospital care for cerebrovascular disease in diabetic and nondiabetic populations. *Stroke* 28:1142-1146, 1997
19. Behar S, Boyko V, Reicher-Reiss H, Goldbourt U: Ten-year survival after acute myocardial infarction: comparison of patients with and without diabetes. *Am Heart J* 133:290-296, 1997
20. Adlerberth AM, Rosengren A, Wilhelmsen L: Diabetes and long-term risk of mortality from coronary and other causes in middle-aged swedish men. A general population study. *Diabetes Care* 21:539-545, 1998
21. Bell DS: Stroke in the Diabetic patient. *Diabetes Care* 17:213-219, 1994

22. Anderson KM, Odell PM, Wilson PWF, Kannel WB: Cardiovascular disease risk profiles. *Am Heart J* 121:293-298, 1990
23. Kannel WB, McGee DL: Diabetes and glucose tolerance as risk factors for cardiovascular disease: The Framingham Study. *Diabetes Care* 2:120-126, 1979
24. Reunanen A: Mortality in type 2 diabetes. *Ann Clin Res* 15 suppl 37:26-8, 1983
25. Butler WJ, Ostrander LD, Carman WJ, Lamphiear DE: Mortality from coronary heart disease in the Tecumseh Study. Long term effect of diabetes mellitus, glucose tolerance and other risk factors. *Am J Epidemiol* 121:541-547, 1985
26. Geiss LS, Herman WH, Smith PJ, ed. *Mortality in non-insulin-dependent diabetes mellitus*. 2 ed. Bethesda: NIH, 1995:233-258. (National Diabetes Data Group, ed. Diabetes in America;)
27. Koskinen SVP, Reunanen ARS, Martelin TP, Valkonen T: Mortality in a large population-based cohort of patients with drug-treated diabetes mellitus. *Am J Public Health* 88:765-770, 1998
28. Stegmayr B, Asplund K: Diabetes as a risk factor for stroke. A population perspective. *Diabetologia* 38:1061-1068, 1995
29. Pan W, Cedres LB, Liu K, et al: Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. *Am J Epidemiol* 123:504-516, 1986
30. Wong JSK, Pearson DWM, Murchison LE, Williams MJ, Narayan V: Mortality in diabetes mellitus: experience of a geographically defined population. *Diab Med* 8:135-139, 1991
31. Laakso M, Rönnekaa T, Letho S, Puukka P, Kallio V, Pyörälä K: Does NIDDM increase the risk for coronary heart disease similarly in both low and high-risk populations? *Diabetologia* 38:487-493, 1995
32. Lehto S, Rönnekaa T, Pyörälä K, Laakso M: Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. *Stroke* 27:63-68, 1996
33. Fuller JH: Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall Study. *Lancet* 1(8131):1372-1376, 1980
34. Manson JE, Colditz GA, Stampfer MJ, et al: A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 151:1141-1147, 1991
35. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434-444, 1993
36. Tuomilehto J, Rastenyte D, Jousilahti P, Sarti C, Vartiainen E: Diabetes mellitus as a risk factor for death from stroke. Prospective study of the middle-aged Finnish population. *Stroke* 27:210-215, 1996
37. Mantol KG, Stallard E: *Chronic disease modelling: measurement and evaluation of the risks of chronic disease processes*. New York Oxford University Press, 1988
38. Barendregt JJ, Oortmarssen GJ, van, Hout BA, van, Bosch JM, van den, Bonneux L: Coping with multiple morbidity in a life table. *Mathematical Population Studies* 7:29-49, 1998
39. Barendregt JJ, Baan CA, Bonneux L: An indirect estimate of NIDDM incidence. submitted

Appendix

Part 1:

In a life table we calculated the number of diabetic deaths (D) for the age-group 45-74 years:

$$D = \sum_{45}^{74} q_1^A * l^A \quad (1)$$

Where l is the number of diabetic persons in a 1-year age group and q_1 is the probability of death, obtained by converting the mortality rate M_1 (37).

This total diabetic mortality is split up into three parts, based upon the distribution of causes of death reported for diabetic subjects (Table 2):

$$\text{CVD mortality: } d_{cvd} = w * D \quad (2)$$

$$\text{Diabetic related mortality: } d_{dm} = x * D \quad (3)$$

$$\text{Other mortality: } d_{oth} = D - d_{cvd} - d_{dm} \quad (4)$$

Where w and x are the proportions of death due to the specific cause, obtained from Table 2.

We assume that the M_{oth} is equal to the M_{1oth} and thus we can calculate the age-specific as well as the total number of deaths due to other causes in another way as in formula 2-4, using:

$$d'_{oth} = \sum_{45}^{74} M_{oth}^A \times L^A \quad (5)$$

Where L is the number of life-years lived in an age group.

The age-specific deaths due to cardiovascular mortality or diabetic mortality are:

$$d'_{CVD} = \sum_{45}^{74} M_{CVD}^A \times R_{CVD}^A \times L^A \quad (6)$$

$$d'_{dm} = \sum M_{dm}^A \times F_{dm} \times L^A \quad (7)$$

With R_{CVD} is the relative risk for a diabetic subject to die due to cardiovascular complications. The F_{dm} is a factor by which the M_{dm} of the total population is multiplied to obtain the M_{Idm} .

The outcomes of the formulas 2, 3 and 4 have to be equal to 5, 6 and 7. With this limiting condition, we can estimate the age-specific relative risk R_{CVD} and the F_{dm} using the Solver function of Excel97.

It has been shown that the relative risk of dying of cardiovascular diseases decreases with age. We have used the simplest best-fitted function:

$$R^A_{CVD} = a + b \cdot A + c \cdot A^2 \quad (8)$$

With A is age. For the diabetes factor two variances were used. First the factor is held constant with age and secondly we estimated an age-specific factor using the linear function:

$$F^A_{dm} = d + e \cdot A \quad (9)$$

With the Solver, the parameters a , b , c , d and e were chosen such that the total sum of squared error (SS) is minimised:

$$SS(a, b, c, d, e) = \sum_{45}^{74} (d'_{oth}{}^A - d_{oth}{}^A)^2 + \sum_{45}^{74} (d'_{CVD}{}^A - d_{CVD}{}^A)^2 + \sum_{45}^{74} (d'_{dm}{}^A - d_{dm}{}^A)^2 \quad (10)$$

Part 2:

The total number of cardiovascular deaths among diabetic population d_{CVD} is split up into three parts, based upon the distribution of causes of deaths (Table 2):

$$\text{Coronary heart disease mortality: } d_{CHD} = y \cdot d_{CVD} \quad (11)$$

$$\text{Stroke mortality: } d_{stroke} = z \cdot d_{CVD} \quad (12)$$

$$\text{Other heart disease mortality: } d_{othCVD} = (1 - y - z) \cdot d_{CVD} \quad (13)$$

Where y and z are proportions, based upon Table 2.

The age-specific deaths due to the three heart mortality rates are:

$$d'_{CHD} = \sum_{45}^{74} M_{CHD}{}^A \times R_{CHD}{}^A \times L^A \quad (14)$$

$$d'_{stroke} = \sum_{45}^{74} M_{stroke}{}^A \times R_{stroke}{}^A \times L^A \quad (15)$$

$$d'_{othCVD} = \sum_{45}^{74} M_{othCVD}^A \times R_{othCVD}^A \times L^A \quad (16)$$

and:

$$d'_{CVD} = d'_{CHD} + d'_{stroke} + d'_{othCHD} \quad (17)$$

The outcomes of the formulas 11, 12 and 13 have to be equal to 14, 15 and 16, as well as the outcome of 17 has to be equal to the d_{CVD} estimated in part 1.

The case fatality rate of coronary heart disease of the non-diabetic population $M_{0casefatCHD}$ combined with the coronary heart disease mortality rate of the non-diabetic population M_{0CHD} yields the prevalence of coronary heart disease in the non-diabetic population P_{0CHD} :

$$P_{0CHD}^A = \frac{M_{0CHD}^A}{M_{0casefatCHD}^A} \quad (18)$$

Next, the incidence of coronary heart disease in the non-diabetic population I_{0CHD} at age x can be calculated: (38, 39)

$$I_{0CHD}^A = \frac{(P_{0CHD}^A + 1 \times (1 - M_{0CHD}^A) - P_{0CHD}^A + M_{0CHD}^A)}{P_{0CHD}^A} \quad (19)$$

For diabetic subjects the case fatality of coronary heart disease is:

$$M_{1casefatCHD}^A = M_{0casefatCHD}^A \times R_{casefatCHD}^A \quad (20)$$

When using the formulas 18 and 19 with the rates $M_{1survCHD}$ and M_{1CHD} , the prevalence and incidence of coronary heart disease of the diabetic population can be calculated.

Furthermore, we assume

$$I_{1CHD}^A > I_{0CHD}^A, \text{ for all } A \text{ 30-79 year} \quad (21)$$

$$P_{1CHD}^A > P_{0CHD}^A, \text{ for all } A \text{ 30-79 year} \quad (22)$$

The mean $R_{casefatCHD}$ for age 30-80 has to be about 1.3

The same approach for stroke.

With these constraints, we can estimate the age-specific relative risks for coronary heart disease, stroke and other cardiovascular disease mortality.

The following age-specific functions are used:

$$R_{CHD} = \frac{N}{1 + a \times \exp-(b \times (c - A))} \quad (23)$$

$$R_{stroke} = \frac{O}{1 + d \times \exp-(f \times (g - A))} \quad (24)$$

$$R_{othCVD} = \frac{Q}{1 + h \times \exp-(i \times (j - A))} \quad (25)$$

$$R_{casefatCHD} = y0 + k \times \exp(-l \times (A - 20)) \quad (26)$$

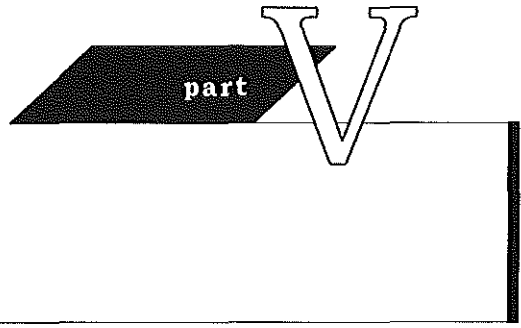
$$R_{casefatstroke} = y0 + m \times \exp(-n \times (A - 20)) \quad (27)$$

The formulas 23-27 make sure that the relative risk will decline with age, but not become < 1.

With the Solver, all parameters were chosen such that the total sum of squared errors (SS') is minimised:

$$SS'(a, b, c, d, f, g, h, i, j, k, l, m, n) = \quad (28)$$

$$\begin{aligned} & \sum_{45}^{74} (d'_{CHD}^A - d_{CHD}^A)^2 + \sum_{45}^{74} (d'_{stroke}^A - d_{stroke}^A)^2 + \sum_{45}^{74} (d'_{othCVD}^A - d_{othCVD}^A)^2 \\ & + (\overline{R_{casefatCHD}} - 1.3)^2 + \sum_{45}^{74} (I'_{0CHD}^A - I_{1CHD}^A)^2 + \sum_{45}^{74} (P'_{0CHD}^A - P_{1CHD}^A)^2 + (\overline{RR_{casefatstroke}} - 1.3)^2 \\ & + \sum_{45}^{74} (I'_{0stroke}^A - I_{1stroke}^A)^2 + \sum_{45}^{74} (P'_{0stroke}^A - P_{1stroke}^A)^2 \end{aligned}$$



APPLICATIONS



Increasing cardiovascular morbidity among diabetic subjects

ABSTRACT

Over the past decades, the survival rates for cardiovascular diseases (CVD) have shown a marked improvement. Since diabetes is associated with CVD, an improved CVD survival affects the prevalence of diabetes and comorbidity. We have examined the impact of these changes.

We used a multi-state life table including three disease processes: coronary heart disease, stroke and diabetes, which were modelled as continuous time Markov processes. The changes in coronary heart disease and stroke hospital admission rates and mortality rates between 1980-83 and 1990-93 in the Netherlands were used to estimate the impact on diabetes prevalence of the decline in mortality selection.

The improved CVD survival resulted in an age related increase in diabetes prevalence rates by a maximum in old age of 3% (women) or 5% (men). The comorbidity of coronary heart disease and diabetes showed age-related increases of 50 to 70% at older age (both sexes). Comorbidity of stroke and diabetes increased for women at all ages, but for men only after the age of 60.

While the changes in cardiovascular mortality and survival are unlikely to be a major source of increasing diabetes prevalence, they do raise the comorbidity of cardiovascular diseases and diabetes to a considerable extent.

Acknowledgement

This study is part of a research project supported by grants from the National Institute for Health Sciences (NIHES).

INTRODUCTION

Recent studies from various countries have reported that the prevalence of diabetes is on the rise (1-4). Understanding the causes of the increase in the prevalence of diabetes is essential for the development of effective interventions. The increase in prevalence over time is partly due to the ageing of the population in the developed countries, as age is a strong determinant of diabetes mellitus. After age standardization, however, the rates were still seen to rise. This may be due to an increasing incidence or decreasing mortality of diabetes.

Incidence may rise through case finding or due to the increasing prevalence of risk factors for diabetes. Several studies have shown that about half of all NIDDM patients are unaware of their disease and thus undiagnosed (5-8). With such a large pool of undiagnosed patients, even a minor enhancement in case finding practice will have a major impact on reported prevalence. The increase in incidence may also be due to an increase in the prevalence of risk factors for diabetes, such as obesity and physical inactivity, over the past decades (9-11).

Another reason for the increase in prevalence over time may be an improved survival of persons with diabetes. Since the early 1970s mortality from cardiovascular diseases for the total population has plummeted (9, 12-15). Between 1970 and 1990 age-standardized mortality from ischaemic heart disease and stroke halved, which can be attributed to a combination of lower incidence and improved survival (15-18). As cardiovascular diseases are the cause of death in more than 60% of the diabetic subjects (19-21), changes in incidence and survival of cardiovascular diseases will affect the prevalence of diabetes and cardiovascular comorbidity.

In this study, we will estimate the effect of changes in epidemiology of coronary heart disease and stroke on the prevalence of diabetes, using data on events and mortality rates of coronary heart disease and stroke from two periods (1980-1983 to 1990-1993) which are combined with the incidence and prevalence of diabetes with the help of life table techniques. We will estimate the change in prevalence of diabetes and in the prevalence of comorbidity of diabetes, coronary heart disease and stroke as a consequence of the change in incidence and survival of coronary heart disease and stroke between 1980 and 1993.

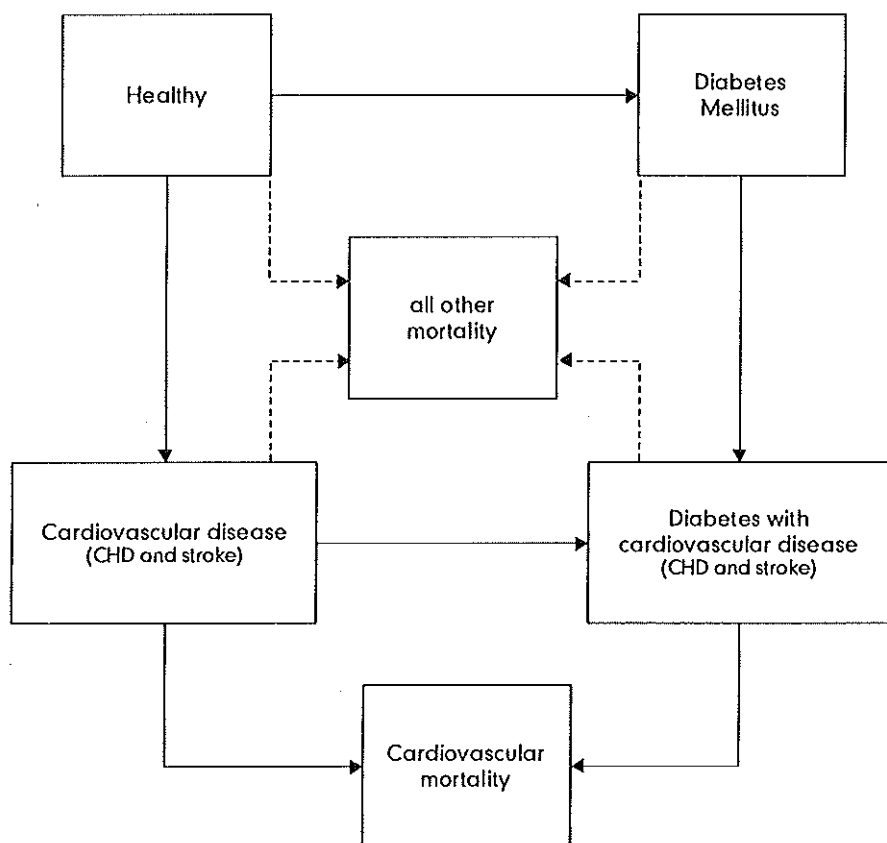


Figure 1
Diabetes and cardiovascular diseases multi-state life table model. All transition probabilities are age and sex specific.

METHODS

Model

To model the diabetes and cardiovascular heart disease processes, we used an extension of the standard life table, the multi-state life table, which not only distinguishes between 'alive' and 'dead', but allows for additional states like 'alive, healthy', 'alive, with heart disease', etc (22).

In Figure 1, the model is schematically presented. Our model includes three diseases: coronary heart disease (CHD), stroke and diabetes, which are modelled as continuous time Markov processes (23). The population is divided over two life tables: one for diabetic subjects, and one for non-diabetic subjects.

Diabetes incidence is used to link the two life tables: at each age, incidence rates determine the new cases of diabetes.

Each life table distinguishes a state with and without coronary heart disease or stroke. The CHD and stroke incidence rates of the diabetic and non-diabetics are determined by rate ratios. In each state, the life table cohort is subjected to 'all other mortality' probabilities. In the coronary heart disease or stroke state, the life table cohort is also subjected to a CHD or stroke mortality probability, which we assume to be higher for diabetic subjects. Therefore, subjects with diabetes have a higher incidence of cardiovascular diseases and a worse survival than subjects without diabetes.

Data

Sex and age specific data on total and cause-specific mortality rates, as well as on the population distribution for the two periods 1980-1983 and 1990-1993 in The Netherlands were obtained from Statistics Netherlands (24).

Incidence and survival of coronary heart disease for the total population is based on a nation-wide hospital register by age, sex and outcome (fatal or non-fatal), and numbers of deaths were obtained from vital statistics by age and sex for the two periods 1980-1983 and 1990-1993. In a previous study, these data were integrated into multi-state life tables (15). The life table estimated an incidence of coronary heart disease by calculating back from the observed attack and mortality rates and from the estimated probabilities of recurrence (15). For stroke, incidence and survival figures for the period 1980-1983 were obtained from a previous study (25) in which epidemiological data were combined in a state-event transition model. The same approach was used again for the period 1990-1993.

The sex and age specific prevalence of diabetes was assessed from 15 Dutch studies performed since 1970 (26). Mortality rates, by age and sex, for diabetic and non-diabetic subjects were calculated combining epidemiological data with vital statistics (27). Diabetes incidence was backcalculated from the excess mortality and prevalence, using the same continuous time Markov process technique (28).

The incidence and survival of coronary heart disease and stroke in the diabetes population was obtained from a previous study (29). In that study we arrived, based on several data-sources which formed the limiting conditions, at estimates of the age-specific mortality rates for coronary heart disease and stroke, as well as the case-fatality rates for the diabetic population. A full description of the method of this study is available at our Internet website (www.eur.nl/fgg/mgz/). A spreadsheet sample of the multi-state life table is available on request.

Table 1A

Coronary heart disease in non-diabetic and diabetic population in The Netherlands, 1980-83 and 1990-93, men

	1980-1983		1990-1993		Change %	
	No.	Rates *	No.	Rates *	No.	Rates
Non-diabetic population						
Mortality						
40-59 y	9 885	1.6	6 583	0.9	-33	-46
60-74 y	24 423	8.4	19 630	5.9	-20	-29
Prevalence						
40-59 y	221 029	36.1	251 021	33.1	14	-8
60-74 y	339 561	116.9	455 860	138.0	34	17.9
Incidence						
40-59 y	32 925	5.4	34 839	4.6	6	-14
60-74 y	35 609	12.3	43 649	13.2	23	8
Diabetic population						
Mortality						
40-59 y	1 033	9.3	677	5.1	-34	-45
60-74 y	3 758	23.7	3 033	16.8	-19	-29
Prevalence						
40-59 y	12 034	108.4	13 335	101.1	11	-7
60-74 y	40 059	252.2	54 646	301.8	36	20
Incidence						
40-59 y	2 180	20.0	2 099	15.9	-4	-19
60-74 y	4 713	30.0	5 620	31.0	19	5

* Rate per 1000

To estimate the influence of changes in coronary heart disease and stroke on diabetes epidemiology, the calculations were performed twice. First, the coronary heart disease and stroke incidence and survival rates for the period 1980-1983 were used, after which use was made of the incidence and survival rates for the period 1990-1993. The diabetes incidence and excess mortality risk were assumed to be constant for the two periods. Age- and sex- specific rates were calculated by using the midyear population of the Netherlands as person-years.

RESULTS

In Table 1, the age-standardized rates of coronary heart disease incidence, prevalence and mortality are shown for the non-diabetic and diabetic population

Table 1B

Coronary heart disease in non-diabetic and diabetic population in The Netherlands, 1980-83 and 1990-93, women

	1980-1983		1990-1993		Change %	
	No.	Rates *	No.	Rates *	No.	Rates
Non-diabetic population						
Mortality						
40-59 y	1 809	0.3	1 361	0.2	-25	-37
60-74 y	10 539	2.9	8 289	2.1	-21	-29
Prevalence						
40-59 y	34 022	5.6	47 692	6.5	40	17
60-74 y	104 886	29.3	166 542	42.3	59	44
Incidence						
40-59 y	5 891	1.0	7 400	1.0	26	5
60-74 y	16 285	4.6	19 940	5.1	22	11
Diabetic population						
Mortality						
40-59 y	421	4.3	320	2.9	-24	-33
60-74 y	1 988	10.6	1 567	7.5	-21	-29
Prevalence						
40-59 y	3 085	31.5	4 268	38.4	38	22
60-74 y	15 083	80.5	24 157	116.4	60	45
Incidence						
40-59 y	661	6.7	685	6.2	4	-9
60-74 y	2 475	13.2	2 711	13.1	10	-1

* Rate per 1000

and the two periods. The mortality rate of coronary heart disease declined during the period from the early 1980s to the early 1990s, for both non-diabetics and diabetics. This decline was even more pronounced among the younger age groups (46% versus 29% and 37% versus 29% for non-diabetic men and women respectively). The prevalence rate of coronary heart disease in men increased only among the older age groups, whereas in women, the prevalence rate had climbed for all age groups. The changes in the incidence rate of coronary heart disease followed the same pattern as the changes seen in prevalence rates.

The age-standardized rates of incidence, prevalence and mortality for stroke are shown in Table 2. The same pattern in changes of incidence, prevalence and mortality rates over the period 1980-1983 to 1990-1993 can be observed as for coronary heart disease, although the changes are somewhat smaller.

Figures 2 A and B show the effect of changes in coronary heart disease and stroke on diabetes prevalence and on the comorbidity of diabetes and coronary

Table 2A
Stroke in non-diabetic and diabetic population in The Netherlands, 1980-83 and 1990-93, men

	1980-1983		1990-1993		Change %	
	No.	Rates *	No.	Rates *	No.	Rates
Non-diabetic population						
Mortality						
40-59 y	1 448	0.2	1 239	0.2	-14	-31
60-74 y	6 925	2.4	5 950	1.8	-14	-25
Prevalence						
40-59 y	56 328	9.2	61 705	8.2	10	-11
60-74 y	127 270	43.8	154 119	46.6	21	6
Incidence						
40-59 y	6 751	1.1	7 406	1.0	10	-11
60-74 y	16 085	5.5	18 822	5.7	17	3
Diabetic population						
Mortality						
40-59 y	146	1.3	127	0.9	-13	-27
60-74 y	572	3.6	492	2.7	-14	-25
Prevalence						
40-59 y	1 706	15.4	1 831	13.9	7	-10
60-74 y	8 694	54.7	10 634	58.7	22	7
Incidence						
40-59 y	304	2.7	307	2.3	1	-15
60-74 y	1 120	7.1	1 289	7.1	15	1

* Rate per 1000

heart disease or stroke. The effect is expressed as indices, with 1980-83=100. The effect on the diabetes prevalence rate is small; this is because both the denominator and the nominator rise, as a consequence of the increased survival. The increase in the diabetes prevalence rate does not exceed 5% for men in old ages, and is even less (3%) for women. More pronounced is the increase of diabetes prevalence expressed in numbers: improved survival with coronary heart disease and stroke causes an age-dependent rise of over 10% for men, and 5% for women at age 80. This is a consequence of ageing, due to declining mortality.

The comorbidity of coronary heart disease and diabetes increased between 1980-83 and 1990-93 for both men and women. Both rates and numbers demonstrate an age-dependent increase that reaches a maximum of 50 to 70% in the oldest age groups. A notable difference between men and women is that comorbidity of CHD and diabetes rose considerably in the latter among those under sixty-five. The increase in the younger age groups for males was far less striking, and even decreased for ages under 55.

Table 2B

Stroke in non-diabetic and diabetic population in The Netherlands, 1980-83 and 1990-93, women

	1980-1983		1990-1993		Change %	
	No.	Rates *	No.	Rates *	No.	Rates
Non-diabetic population						
Mortality						
40-59 y	1 104	0.2	999	0.1	-9	-24
60-74 y	5 268	1.5	4 359	1.1	-17	-25
Prevalence						
40-59 y	42 117	6.9	54 607	7.5	30	8
60-74 y	87 861	24.6	108 548	27.6	24	12
Incidence						
40-59 y	4 125	0.7	4 723	0.6	14	-4
60-74 y	10 967	3.1	12 157	3.1	11	1
Diabetic population						
Mortality						
40-59 y	64	0.6	54	0.5	-15	-25
60-74 y	938	5.0	780	3.8	-17	-25
Prevalence						
40-59 y	1 811	18.5	2 222	20.0	22	8
60-74 y	11 113	59.0	13 860	66.8	25	13
Incidence						
40-59 y	192	1.9	202	1.8	5	-7
60-74 y	1595	8.5	1 729	8.3	8	-2

* Rate per 1000

The comorbidity of stroke and diabetes for women increased at all ages by about 20%. For men, the comorbidity of stroke and diabetes seems to have shifted to the oldest age groups in both rates and numbers. Comorbidity at younger ages dropped with 20%, and only increased by 10% in the oldest age groups.

DISCUSSION

We studied the impact of diminishing mortality hazards of coronary heart disease and stroke observed over the past decade, on the prevalence of diabetes. We have shown that if these changes apply equally to the diabetic population, a modest increase in the prevalence of diabetes in the life table population will result in both rates and in numbers. An increase in the number of elderly diabetic men can be observed between 1980-83 and 1990-93, although due to the

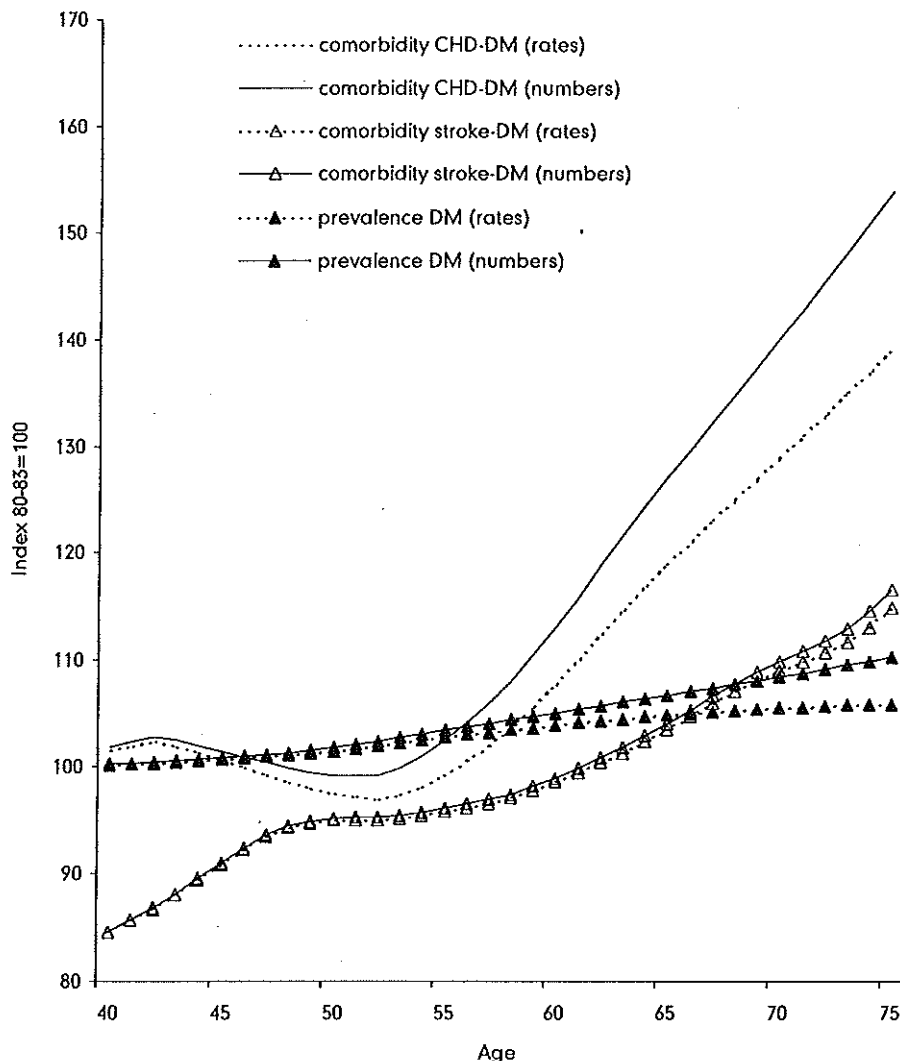


Figure 2A

Prevalence of diabetes and comorbidity of coronary heart disease or stroke with diabetes in the Netherlands, men. Indices of 1990-93 estimates with 1980-83=100.

growing number of similarly aged non-diabetic men, the diabetes prevalence rates hardly budged.

Due to the much smaller role of cardiovascular heart disease, the impact in women is even less. This difference in increase of prevalence of diabetes by age between men and women is in accordance with reports from earlier studies (4)

The increase in the prevalence of diabetes is negligible for the younger age groups, but rises with age. This age pattern is caused by selection as a result of

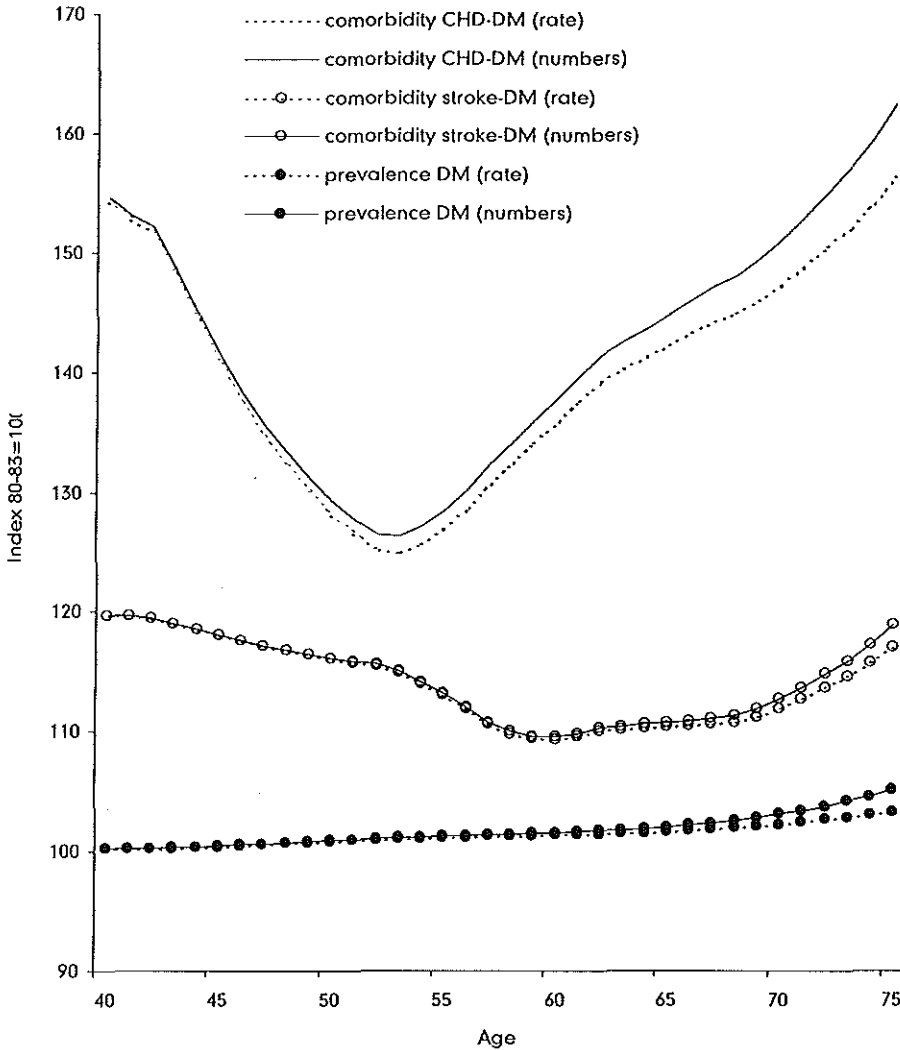


Figure 2B
Prevalence of diabetes and comorbidity of coronary heart disease or stroke with diabetes in The Netherlands, women. Indices of 1990-93 estimates with 1980-83=100.

the diminished mortality from cardiovascular diseases; it operates more in the age groups where cardiovascular diseases mortality is substantial.

Although the impact of changes in the epidemiology of coronary heart disease and stroke on the diabetes prevalence is small, the comorbidity rate has increased substantially. The comorbidity rate is the sum of the proportional increase in cardiovascular prevalence and the diabetes prevalence. As the cardiovascular diseases rate underwent marked changes in the period 1980-1993, the

comorbidity rate was also subject to considerable change in that this was seen to increase enormously.

The pattern of changes in comorbidity rates is different between men and women. The comorbidity rate declined or remained more or less the same in recent years, for younger men, whereas comorbidity rates increased for women at all ages. As stated above, the comorbidity pattern is wholly attributable due to the changes in the epidemiology of coronary heart disease and stroke. Although it is difficult to disentangle the age, period and cohort yielding the observed rates, the following explanations may be hazarded. The increased comorbidity seen at older ages is probably a consequence of ageing. Ageing occurs both in men as in women, which explains the increase in comorbidity rates for both sexes.

The substantial increase in comorbidity rates of coronary heart disease and stroke for women of the younger ages may be due in part to a post-World War II female cohort effect. This cohort took up smoking in large numbers and has now reached an age at which cardiovascular diseases strikes. As coronary heart disease rates are higher than those for stroke at these ages, the effect is greater for the comorbidity rate of coronary heart disease. Comorbidity rates rose more in diabetic women than in men.

The increased awareness of the fact that women are also at risk for cardiovascular diseases may well partially be attributable to this increase (30). In addition, the incidence of coronary heart disease and stroke in the younger male cohorts decreased due to lower smoking prevalence and improving hypertension control. This explains the decreased comorbidity rates at younger ages, shown in figure 2A.

The improvement in coronary heart disease or stroke survival rates, observed for the general population, was assumed to be equal in the diabetic population. A longitudinal study revealed that the survival of women with diabetes failed to keep pace with the improved rates seen in non-diabetic women. In men, however, the survival rates for diabetic subjects improved just as much as that for non-diabetic men (4). Sniderman reviewed several studies reporting mortality rates (in- and out-hospital) in diabetic subjects who suffered an acute myocardial infarction and concluded that diabetics have also benefited from the new therapies (31). In addition, it has been reported that diabetic patients with acute myocardial infarction receive thrombolytic therapy less often than patients without diabetes, mostly due to late arrival at the hospital (32). As the improved survival rate for heart disease in the general population is probably partly determined by new medical interventions, differences in treatment of diabetic versus non-diabetic patients will influence the difference in survival trends. Although the changes in the survival rates of coronary heart disease and stroke over time in the diabetic population are beyond debate, we might have

overestimated the impact of improved cardiovascular diseases survival on the prevalence of diabetes.

Another reason for overestimation is due to the nature of life table calculations. Life table analysis produces an estimate that reflects the full impact of the changed incidence and survival, while in reality it takes time for this impact to develop. Due to these dynamic effects, the increase in the prevalence of coronary heart disease and stroke between 1980-83 and 1990-93 will actually have been smaller, which applies equally to the impact on the prevalence of diabetes. On the other hand, underestimation may also have occurred. The coronary heart disease epidemic peaked in the early seventies, which means that the decline in mortality has been going on for a longer time (33). As the prevalence of coronary heart disease is a stock variable, its increase during the period between 1980-83 and 1990-93 will have consequently been larger and hence also the impact on the prevalence of diabetes.

In any case, the comorbidity increase which we calculated is in accordance with the empirical observations reported. The Minnesota Heart Survey reported an increased prevalence of diabetes in cardiovascular patients during the period 1970 and 1985 (34, 35). Other studies also have reported an increase in comorbidity of diabetes and cardiovascular complications during that same period (2), especially in the oldest age groups (36). The increase in the comorbidity of cardiovascular diseases and diabetes mellitus results in more extensive health care needs (36).

There is a striking lack of data about cardiovascular mortality in the elderly and we could only validate our estimates up to the age of 74. However, in today's ageing society, the pattern of comorbidity in the oldest age groups is of great importance for public health policies. More data are required for reliable estimates, especially on women, in whom the bulk of cardiovascular deaths occur after the age of 70.

On balance, we can conclude that the dwindling mortality of cardiovascular diseases does not cause a marked increase in the prevalence of diabetes, but may well cause a sizeable increase in the comorbidity of cardiovascular diseases and diabetes. This increasing comorbidity will have a major impact on the health care needs.

References

1. Neil HAW, Gatling W, Mather HM, et al.: The Oxford Community Diabetes Study: Evidence for an increase in the prevalence of known diabetes in Great Britain. *Diabetic Med* 4:539-543, 1987

2. Wetterhall SF, Olson DR, DeStefano F, et al: Trends in diabetes and diabetic complications, 1980-1987. *Diabetes Care* 15:960-967, 1992
3. Kenny SJ, Aubert RE, Geiss LS, ed. *Prevalence and incidence of non-insulin-dependent diabetes*. 2 ed ed. Bethesda: NIH, 1995. (National Diabetes Data Group, ed. Diabetes in America;)
4. Leibson CL, O'Brien PCO, Atkinson E, Palumbo PJ, Melton III LJ: Relative contributions of incidence and survival to increasing prevalence of adult-onset diabetes mellitus: a population-based study. *Am J Epidemiol* 146:12-22, 1997
5. Harris MI, Hadden WC, Knowler WC, Bennet PH: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20-74 Yr. *Diabetes* 36:523-534, 1987
6. King H, Zimmet P: Trends in the prevalence and incidence of diabetes non-insulin-dependent diabetes mellitus. *Rapp trimest statist sanit mond* 41:190-194, 1988
7. Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Heine RJ: Prevalence and determinants of glucose intolerance in a Caucasian population. The Hoorn Study. *Diabetes Care* 18:1270-1273, 1995
8. Stolk RP, Pols HAP, Lamberts SWJ, Jong de PTVM, Hofman A, Grobbee DE: Diabetes mellitus, impaired glucose tolerance and hyperinsulinemia in an elderly population. The Rotterdam Study. *Am J Epidemiol* 145:24-32, 1997
9. Sprafka JM, Burke GL, Folsom AR, Luepker RV, Blackburn H: Continued decline in cardiovascular disease risk factors: results of the Minnesota Heart Survey 1980-1982 and 1985-1987. *Am J Epidemiol* 132:489-500, 1990
10. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL: Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960-1991. *JAMA* 272:205-211, 1994
11. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P: Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. *J Pediatr* 128:608-615, 1996
12. Demirovic J, Blackburn H, McGovern P, Sprafka JM, Doliszny K: Sex differences in coronary heart disease mortality trends: the Minnesota Heart Survey, 1970-1988. *Epidemiology* 4:79-82, 1993
13. Kuller LH, ed. *Stroke and diabetes*. 2 ed. Bethesda: NIH, 1995:449-456. (Group NDD, ed. Diabetes in America;)
14. Sytkowski PA, Agostino RB, Belanger A, Kannel WB: Sex and time trends in cardiovascular disease incidence and mortality: The Framingham Heart Study, 1950-1989. *Am J Epidemiol* 143:338-350, 1996
15. Bonneux L, Barendregt JJ, Van der Maas PJ: The new old epidemic of coronary heart disease. *Am J Public Health* 89:379-382, 1999
16. McGovern PG, Burke GL, Sprafka M, Xue S, Folsom AR, Blackburn H: Trends in mortality, morbidity and risk factor levels for stroke. From 1960 through 1990. The Minnesota Heart Survey. *JAMA* 268:753-759, 1992
17. Bonita R: Epidemiology of stroke. *Lancet* 339:342-347, 1992
18. Bonneux L, Barendregt JJM, Meeter K, Bonsel GJ, Maas van der PJ: Estimating clinical morbidity due to ischemic heart disease and congestive heart failure: the future rise of heart failure. *Am J Public Health* 84:20-28, 1994
19. Pänzram G: Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 30:123-131, 1987

20. Moss SE, Klein R, Klein BEK: Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 81:1158-1162, 1991
21. Geiss LS, Herman WH, Smith PJ, ed. *Mortality in non-insulin-dependent diabetes mellitus*. 2 ed. Bethesda: NIH, 1995:233-258. (National Diabetes Data Group, ed. Diabetes in America;)
22. Schoen R: *Modeling Multigroup populations*. New York and London Plenum Press, 1987
23. Barendregt JJ, Oortmarssen GJ, van, Hout BA, van, Bosch JM, van den, Bonneux L: Coping with multiple morbidity in a life table. *Mathematical Population Studies* 7:29-49, 1998
24. Statistics Netherlands. *Deaths by causes of death, age and gender*. Voorburg: Central Bureau of Statistics, 1994.
25. Niessen LW, Barendregt JJ, Bonneux L, Koudstaal P: Stroke trends in an ageing population. *Stroke* 24:931-939, 1993
26. Baan CA, Bonneux L, Ruwaard D, Feskens EJM: The prevalence of diabetes mellitus in The Netherlands: a quantitative review. *Eur J Publ Health* 8:210-216, 1998
27. Baan CA, Nusselder WJ, Barendregt JJ, Ruwaard D, Bonneux L, Feskens EJM: The burden of mortality of diabetes mellitus in The Netherlands. *Epidemiology* 10:184-187, 1999
28. Barendregt JJ, Baan CA, Bonneux L: An indirect estimate of NIDDM incidence. submitted
29. Baan C, Barendregt J, Bonneux L: Estimating the age-specific cardiovascular morbidity and mortality of diabetes mellitus in The Netherlands. submitted
30. Healy B: The Yentl syndrome. *N Engl J Med* 325:274-276, 1991
31. Sniderman A, Michel C, Racine N: Heart disease in patients with diabetes mellitus. *J Clin Epidemiol* 24:1257-1370, 1992
32. Hansen HT, Kjaergaard SC, Bulow I, Fog L, Christensen PD: Trombolytic therapy in diabetic patients with acute myocardial infarction. *Diabetes Care* 19:1135-1137, 1996
33. Bonneux L, Looman CW, Barendregt JJ, Van der Maas PJ: Regression analysis of recent changes in cardiovascular mortality and morbidity in the Netherlands. *Br Med J* 314:789-792, 1997
34. Sprafka JM, Burke GL, Folsom AR, Mc Govern PG, Hahn LP: Trends in prevalence of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival. The Minnesota Heart Survey. *Diabetes Care* 14:537-543, 1991
35. Sprafka J, Virnig B, Shahar E, McGovern P: Trends in diabetes prevalence among stroke patients and the effect of diabetes on stroke survival: the Minnesota Heart Survey. *Diabet Med* 11:678-684, 1994
36. Rosenthal MJ, Fajardo M, Gilmore S, Morley JE, Naliboff BD: Hospitalization and mortality of diabetes in older adults. *Diabetes Care* 21:231-235, 1998

Effect of primary prevention
of diabetes mellitus
on cardiovascular morbidity
and mortality

ABSTRACT

We estimated the effects of several prevention strategies as well as the effect of secular trends in obesity and physical inactivity on diabetes and related cardiovascular complications. We used a multi-state life table, which included three disease processes: coronary heart disease (CHD), stroke and diabetes, which are modelled as continuous time Markov processes. Effects of the scenarios were estimated by using potential impact fractions (PIF). We defined five scenarios. Three hypothetical intervention scenarios were defined in which overweight and obesity were eliminated, physical inactivity was eliminated or a combination of the two. The fourth scenario assumed a realistic intervention and the last scenario estimated the effect of secular trends on prevalence of both risk factors. The results of the scenarios have been compared with the effect of obesity and physical inactivity on all-cause mortality. The three hypothetical elimination scenarios showed a large impact on diabetes incidence. Eliminating overweight and obesity resulted in a PIF of 54% for men (68% for women). CHD mortality in the total population was then reduced by 4% in men (9% in women) in the age-group 30-79 years. The realistic scenario showed a 6% reduction in the incidence of diabetes in men (7% in women), while diabetes-related cardiovascular complications were reduced by less than 1%. Secular increases in both risk factors, as observed in The Netherlands, yielded an increase in the incidence of diabetes of 2.4% in men (3.5 % for women) and of less than 1% in diabetes related cardiovascular complications. The effect of both risk factors on diabetes and its cardiovascular complications only explained a small part of the excess risk on all-cause mortality. Based on current knowledge, the realistic scenario showed a low impact on diabetes and related cardiovascular disease, although in absolute numbers the result is still substantial.

INTRODUCTION

Diabetes mellitus is one of the major chronic diseases in Western societies, causing considerable comorbidity of cardiovascular diseases (CVD) and premature death. The increasing health care needs makes the search for preventive strategies more relevant. Obesity and physical inactivity are important risk factors for the onset of non-insulin dependent diabetes mellitus (NIDDM). There is a strong association between the presence of overweight or obesity and the development of NIDDM (1-7). The evidence in respect of physical inactivity is growing. Up to now, 7 prospective studies have been performed, all indicating that physical activity may prevent the onset of NIDDM (8-15). Promoting weight loss and/or physical activity is therefore an important way to prevent NIDDM and associated cardiovascular comorbidity. In this study we will estimate the potential effect of such preventive strategies.

There is evidence that the prevalence of overweight and obesity has increased over the past years and will continue to increase (16, 17). As far as physical inactivity is concerned, the picture is by no means as clear-cut. Physical activity at work has decreased, probably due to technological developments, but it is less clear how physical activity during leisure time has developed. Duration of obesity is related to an increased risk for diabetes or cardiovascular diseases (18-21). This implies that the consequences of the increase in prevalence of obesity may only become apparent after many years.

We have developed a simulation model for diabetes and its cardiovascular complications in a previous study (22). Using this model, we have now estimated the effect of primary prevention of diabetes on cardiovascular comorbidity and mortality. In addition, the effect of secular trends in obesity and physical inactivity on diabetes related cardiovascular comorbidity and mortality is estimated. The effects of the scenarios have been compared with the effect of both obesity and physical inactivity on all-cause mortality.

METHODS

Model

The simulation model for diabetes and cardiovascular disease processes was described in a previous study (22). Here, we used a multi-state life table (23), which included three disease processes: coronary heart disease (CHD), stroke and diabetes, which are modelled as continuous time Markov processes (24).

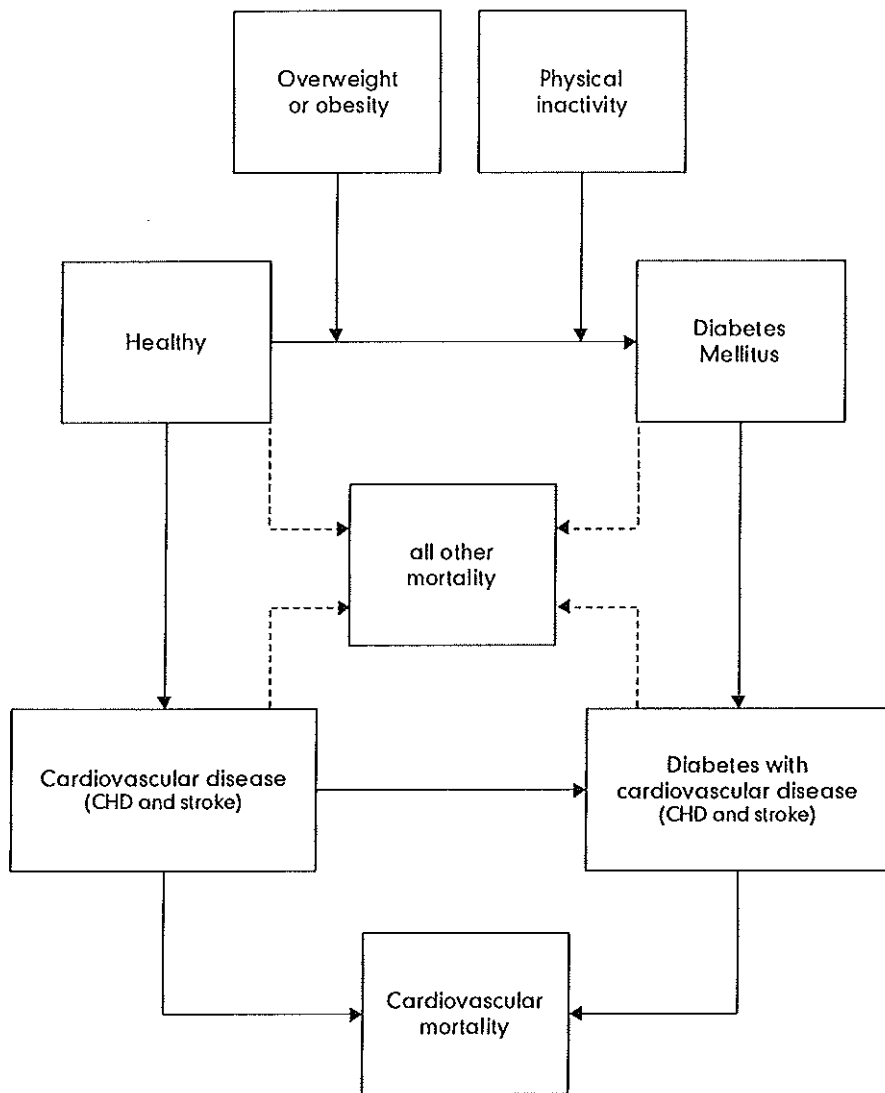


Figure 1
Diabetes and cardiovascular diseases multi-state life table model with overweight, obesity and physical inactivity as risk factors for onset of diabetes. All transition probabilities are age- and sex specific.

The population is divided over two life tables: one for diabetic subjects, and one for non-diabetic subjects. Incidence of diabetes is used to link the two life tables: at each age, incidence rates determine the new diabetes cases.

In Figure 1, the model is schematically presented. Both populations are at risk from coronary heart disease and stroke. Each life table distinguishes a state with and without coronary heart disease or stroke. The CHD and stroke

incidence rates of the diabetic and non-diabetic subjects are determined by rate ratios. In each state, the life table cohort is subjected to 'all other mortality' probabilities. In the coronary heart disease or stroke state, the life table cohort is also subjected to a CHD or stroke mortality probability, which we assume to be higher for diabetic subjects. Therefore, subjects with diabetes have a higher incidence of cardiovascular diseases and a worse survival than subjects without diabetes.

The effect of a scenario is estimated by using the potential impact fraction (PIF). A PIF is defined as "the proportional reduction in the total number of new (incident) cases of a certain disease, resulting from a specific change in the distribution of a risk factor in the population at risk" (25). This can be summarised as:

$$PIF = \frac{(P - P')(R - 1)}{P(R - 1) + 1}$$

where P is the estimated proportion of the population exposed before the planned intervention, P' is the estimated proportion of the candidate population exposed after the intervention and R is the relative risk. Multiplying $(1-PIF)$ by the incidence rate of diabetes, yields a new incidence of diabetes and subsequently also new incidence, prevalence and mortality rates for cardiovascular diseases.

Data

The data for the basic model of the diabetes and cardiovascular mortality have been described in more detail in a previous study (22). Sex and age specific total and cause-specific mortality rates as well as the population distribution for the period 1990-1993 in The Netherlands were obtained from Statistics Netherlands (26). Incidence and survival of coronary heart disease for the total population is based on a nation-wide hospital register by age, sex and outcome (fatal or non-fatal), and numbers of death were obtained from vital statistics by age and sex for the period 1990-1993 which were integrated into multi-state life tables. The life table estimated an incidence of coronary heart disease by calculating back from the observed attack and mortality rates and from the estimated probabilities of recurrence (27). For stroke, the same approach was used. The age and sex specific prevalence of diabetes was assessed from 15 Dutch studies performed since 1970 (28) and the rates per 5-year age groups are presented in Figure 2. Mortality rates, by age and sex, for diabetic and non-diabetic subjects were calculated combining epidemiological data with vital statistics (29). Diabetes incidence was backcalculated from the excess mortality and prevalence, using the

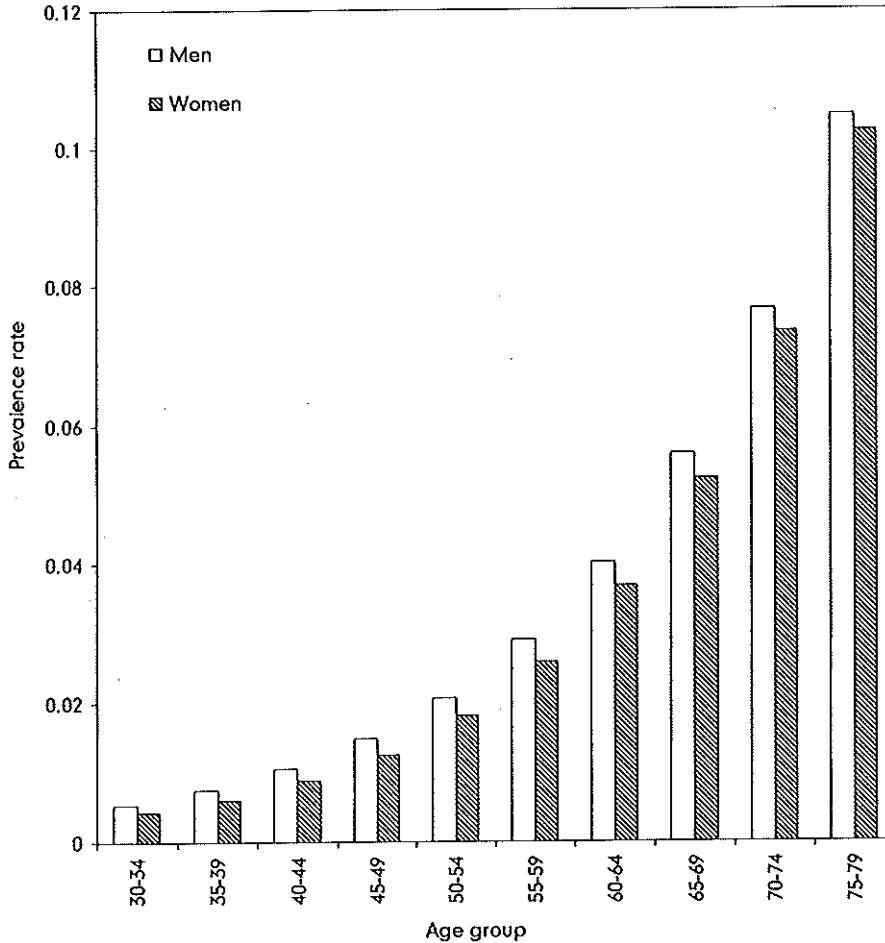


Figure 2
Prevalence of diabetes mellitus in The Netherlands (28).

same continuous time Markov process technique (30). The incidence, prevalence and survival of coronary heart disease and stroke in the diabetes population was obtained from a previous study (31). In this study we arrived at estimates of the age-specific mortality and morbidity rates for coronary heart disease and stroke, as well as the case-fatality rates for the diabetic population, based on several data sources. A full description of the method of this study is available at our Internet website (www.eur.nl/fgg/mgz/). A spreadsheet sample of the multi-state life table is available on request.

We used two cut-off points for overweight, based upon the body mass index (BMI): overweight (BMI 25.0-29.9 kg/m²) and obesity (BMI ≥ 30.0 kg/m²). These

Table 1

Range of prevalence (%) of overweight, obesity and physical inactivity and relative risk of these risk factors for onset of diabetes, used in the analysis.

	Men		Women	
	Prevalence (range)	RR (range)	Prevalence (range)	RR (range)
Overweight and obesity	(33-39)	(5, 6, 42)	(33-39)	(7, 20, 47)
25 < BMI < 30	0.36 (0.17-0.36)	3.3 (2.2-3.6)	0.24 (0.12-0.25)	4.6 (1.9-5.0)
BMI > 30	0.05 (0.04-0.09)	7.7 (6.2-17.0)	0.08 (0.05-0.11)	16.9 (6.0-26.8)
Physical inactivity	(34, 37, 38, 48-50)	(10-14)	(34, 37, 38, 48-50)	(14, 15)
No sporting activity or other physical activity	0.35 (0.25-0.45)	1.8 (1.5-2.5)	0.36 (0.26-0.48)	1.8 (1.5-2.5)

criteria are in accordance with the World Health Organisation (WHO) classification for different degrees of overweight (32). Physical inactivity was defined as "performing no sporting activity or other heavy activity". Both prevalence data on obesity and physical inactivity as well as relative risks of both risk factors are not easily comparable due to different definitions and cut-off points. We have dealt with this problem by taking a range in the prevalence of the risk factor, as well as a range in relative risks. Table 1 gives the ranges in prevalence and relative risks.

The range in prevalence of the two categories of overweight is based upon several Dutch studies (33-39). Many studies have reported relative risks for overweight and the onset of diabetes mellitus (1-7, 20, 40-47) and the results varied considerably. This is due to method by which the body mass index (BMI) was determined (self-report or measuring height and weight), the choice of categories of the BMI, as well as the choice of the reference category to estimate relative risks. Considering all prospective studies, two studies reported relative risks for the two categories we used in the model (BMI 25.0-29.9 kg/m² or BMI $\geq$ 30.0 kg/m²) (42, 47). Four other studies used different categories, but reported for each category the number of person years lived, as well as the number of incident cases of diabetes mellitus (5-7, 20). This enabled us to calculate relative risks for the two BMI-categories we used in the simulation model.

The range of prevalence of physical inactivity is based upon several Dutch studies (34, 37, 38, 48-50). As with obesity, the relative risks for physical inactivity and the onset of diabetes mellitus varied between studies, due to the large variation in measuring of physical activity and in the choice of the reference category (8-15). We used a range of relative risks, based on prospective studies that reported age-adjusted relative risk for men and women separately.

Table 2

Potential impact fraction (lower and upper boundary) on diabetes mellitus incidence for the five scenarios for age-group 30-79 years.

Scenario	Description	PIF (%)	
		Men	Women
1	Elimination of prevalence of overweight and obesity	54 (29-70)	68 (26-79)
2	Elimination of prevalence of physical inactivity	22 (11-40)	22 (12-42)
3	Elimination of prevalence of overweight, obesity and physical inactivity	64 (37-82)	75 (35-88)
4	Decrease of prevalence of overweight and obesity with 5% and increase of prevalence of physical activity with 20%	6 (3-11)	7 (3-12)
5	Increase in 10 years of prevalence of overweight with 1.5% for men and 3% for women, prevalence of obesity with 5% for men and 4% for women and prevalence of physical inactivity with 5% for both men and women.	-2.4 (-1.5- -4.5)	-3.5 (-1.5- -5.2)

Note: A decrease of prevalence of obesity with for example 5% is estimated by:
 $0.95 \times \text{prevalence obesity} = \text{new prevalence of obesity}$.

Multiplying $(1 - \text{PIF}/100)$ with age-dependent incidence of diabetes yields the new incidence of diabetes due to the scenario.

Scenarios

We formulated five scenarios (Table 2). A potential impact fraction (PIF) was calculated for all scenarios with a lower and upper boundary. The range of the prevalence percentages and the relative risks as given in Table 1 were used for calculating the boundaries. The lower boundary was calculated by using the lowest prevalence range with the lowest relative risk, and vice versa for the upper boundary, thus overestimating upper and lower ranges (as prevalence and risk are generally inversely related).

The first three scenarios yielded the maximum effect that can be obtained by primary intervention of the risk factors physical inactivity and obesity, separately or combined. The fourth scenario estimates the effect of a more realistic scenario: reducing the prevalence of overweight and obesity by 5% in a population, and increasing the prevalence of physical activity by 20%. These percentages are based three trials (51-53). The fifth scenario estimated the effect of secular trends in prevalence of the risk factors. Only a few studies reported trends in prevalence of body mass index and physical inactivity (17, 33, 48-50, 54, 55), with different results. Based on these studies, we formulated a trend in

the prevalence of overweight and obesity as well as in the prevalence of physical inactivity (see Table 2).

Obesity and physical inactivity also have a direct, non diabetes-related, effect on the incidence of cardiovascular diseases, as well as on other chronic diseases such as different types of cancer (56-59). To compare diabetes related and non diabetes-related mortality, we estimated a PIF on total mortality for obesity and physical inactivity for all scenarios. Based on the literature we assumed a relative risk of 1.1 for overweight and 2.0 for obesity on all-cause mortality and a relative risk of 1.4 for physical inactivity for both men and women (58-63). The change in number of life years (L_{cx}) after each intervention was estimated for the pathway diabetes-CHD and for total mortality in the following way:

$$L_{cx} = (d_x^i - d_x) e_x$$

where L_{cx} is the change in total number of life years for age x ; d_x^i is total number of deaths after intervention at age x ; d_x is total number of deaths before intervention at age x ; e_x is life expectancy at age x . The sex index is suppressed. We estimated the percentage of change in the number of life-years due to diabetes and CHD out of the total change in number of life-years lost for the age group 30-79 years.

RESULTS

In Table 2, the potential impact fractions are shown with the lower and upper boundaries. A potential impact fraction of, for example 54%, means that the incidence rate of diabetes is reduced by 54 percent. Subsequently, the prevalence of diabetes and mortality rate of diabetes also decreases by 54 percent. The hypothetical elimination scenarios had a major impact on the incidence of diabetes. Eliminating overweight and obesity together with physical inactivity resulted in potential impact fractions of 64% (uncertainty limits (UL): 29%-70%) for men and 75% (UL: 26%-79%) for women. The realistic prevention scenario reduced the incidence of diabetes by 6% (UL: 3%-11%) in men and 7% (UL: 3%-12%) in women. The secular trend scenario showed an increase in the incidence of diabetes of 2.4% (UL: 1.5%-4.5%) in men and 3.5% (1.5%-5.2%) in women.

The effect (both in numbers and in percentage) of primary prevention of diabetes mellitus on coronary heart disease and stroke incidence, prevalence and mortality in the total population is shown in Tables 3 and 4. Eliminating overweight and yielded a reduction in diabetes-related mortality of coronary heart disease in the total population of 4% in men and 9% in women in the age-

Table 3

Effect of five scenarios on diabetes related coronary heart disease mortality, prevalence and incidence of total population, for age-group 30-79 years, in period 1990-1993.

	MEN		
	Difference between reference and intervention population (upper and lower boundary)		
	Mortality	Prevalence	Incidence
<i>Baseline</i>	52,340	1,141,760	119,700
<i>Scenario 1: eliminating overweight and obesity</i>			
numbers	-2,150	-28,690	-2,610
percentage	-4.1 (-2.2- -5.4)	-2.5 (-1.2- -3.3)	-2.2 (-1.1- -2.9)
<i>Scenario 2: eliminating physical inactivity</i>			
numbers	-860	-10,180	-1,010
percentage	-1.7 (-0.8- -3.0)	-0.9 (-0.3- -1.8)	-0.8 (-0.4- -1.6)
<i>Scenario 3: eliminating both overweight and physical inactivity</i>			
numbers	-2,560	-34,636	-3,126
percentage	-4.9 (-2.8- -6.3)	-3.0 (-1.6- -4.0)	-2.6 (-1.5- -3.4)
<i>Scenario 4: reducing overweight and physical inactivity</i>			
numbers	-230	-1,040	-215
percentage	-0.4 (-0.2- -0.8)	-0.1 (-0.05- -0.3)	-0.2 (-0.1- -0.4)
<i>Scenario 5: secular trend</i>			
numbers	90	3,650	190
percentage	0.2 (0.1-0.3)	0.3 (0.3-0.4)	0.2 (0.1-0.3)
	WOMEN		
	Difference between reference and intervention population (upper and lower boundary)		
	Mortality	Prevalence	Incidence
<i>Baseline</i>	23,410	386,990	47,230
<i>Scenario 1: eliminating overweight and obesity</i>			
numbers	-2,080	-18,200	-1,650
percentage	-8.9 (-3.3- -10.4)	-6.7 (-1.8- -5.5)	-3.5 (-1.3- -4.1)
<i>Scenario 2: eliminating physical inactivity</i>			
numbers	-660	-5,790	-530
percentage	-2.8 (-1.5- -5.4)	-1.5 (-0.8- -2.9)	-1.1 (-0.6- -2.1)
<i>Scenario 3: eliminating both overweight and physical inactivity</i>			
numbers	-2,310	-20,130	-1,830
percentage	-9.9 (-4.5- -11.6)	-5.2 (-2.4- -6.1)	-3.87 (-1.8- -4.5)
<i>Scenario 4: reducing overweight and physical inactivity</i>			
numbers	-200	-1,800	-160
percentage	-0.9 (-0.4- -1.5)	-0.5 (-0.2- -0.8)	-0.4 (-0.2- -0.6)
<i>Scenario 5: secular trends</i>			
numbers	100	900	80
percentage	0.5 (0.2-0.7)	0.2 (0.1-0.4)	0.2 (0.1-0.3)

Table 4

Effect of five scenarios on diabetes related stroke mortality, prevalence and incidence of total population, for age-group 30-79 years, in period 1990-1993.

	MEN		
	Difference between reference and intervention population (upper and lower boundary)		
	Mortality	Prevalence	Incidence
<i>Baseline</i>	17,150	376,770	45,460
<i>Scenario 1: eliminating overweight and obesity</i>			
numbers	-560	-6,880	-320
percentage	-3.3 (-1.7 - -4.3)	-1.8 (-1.0 - -2.4)	-0.7 (-0.4 - -0.9)
<i>Scenario 2: eliminating physical inactivity</i>			
numbers	-220	-2,770	-130
percentage	-1.3 (-0.7 - -2.4)	-0.7 (-0.4 - -1.4)	-0.3 (-0.1 - -0.5)
<i>Scenario 3: eliminating both overweight and physical inactivity</i>			
numbers	-670	-8,200	-380
percentage	-3.9 (-2.2 - -5.0)	-2.2 (-1.2 - -2.8)	-0.8 (-0.5 - -1.1)
<i>Scenario 4: reducing overweight and physical inactivity</i>			
numbers	-60	-740	-30
percentage	-0.4 (-0.2 - -0.6)	-0.2 (-0.1 - -0.4)	0.1 (-0.04 - -0.1)
<i>Scenario 5: secular trend</i>			
numbers	20	300	10
percentage	0.1 (0.1-0.3)	0.1 (0.1-0.2)	0.03 (0.02-0.1)
	WOMEN		
	Difference between reference and intervention population (upper and lower boundary)		
	Mortality	Prevalence	Incidence
<i>Baseline</i>	14,710	293,140	33,440
<i>Scenario 1: eliminating overweight and obesity</i>			
numbers	-1,050	-10,940	-1,600
percentage	-7.2 (-2.7 - -8.4)	-3.7 (-1.4 - -4.4)	-4.8 (-1.8 - -5.6)
<i>Scenario 2: eliminating physical inactivity</i>			
numbers	-330	-3,460	-500
percentage	-2.3 (-1.2 - -4.4)	-1.2 (-0.6 - -2.3)	-1.5 (-0.8 - -2.9)
<i>Scenario 3: eliminating both overweight and physical inactivity</i>			
numbers	-1,170	-12,110	-1,770
percentage	-7.9 (-3.6 - -9.4)	-4.1 (-1.9 - -4.9)	-5.3 (-2.4 - -6.2)
<i>Scenario 4: reducing overweight and physical inactivity</i>			
numbers	-100	-1,070	-160
percentage	-0.7 (-0.3 - -1.2)	-0.4 (-0.2 - -0.6)	-0.5 (-0.2 - -0.8)
<i>Scenario 5: secular trends</i>			
numbers	50	550	80
percentage	0.4 (0.2-0.5)	0.2 (0.1-0.3)	0.2 (0.1-0.4)

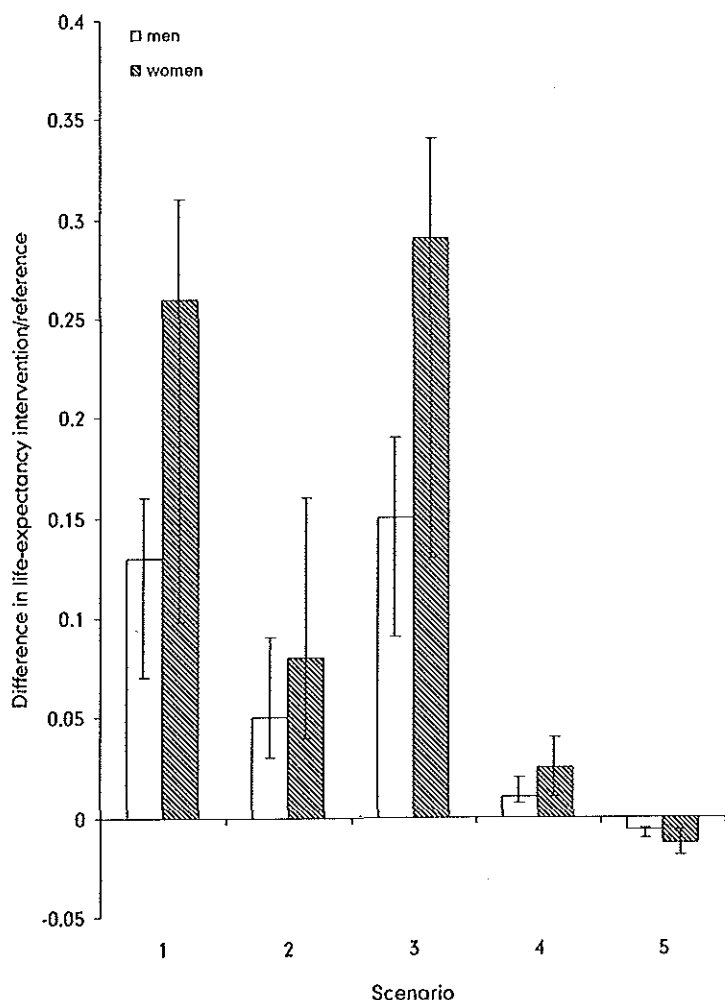


Figure 3
Differences in life expectancy for the total population for the five scenarios with a lower and upper boundary.

group 30-79 years. Translating this into absolute numbers, this would mean that 2,150 men and 2,080 women with coronary heart disease death would be avoided during the period 1990-1993.

In all scenarios, the largest effect is on mortality (in scenario 1 for example, the CHD mortality among men decreased 4%, prevalence and incidence decreased by 2.5 and 2.2% respectively). This is due to the fact that diabetic patients not only have a high risk of developing cardiovascular complications, but also have a higher case-fatality. Reducing the incidence of diabetes has a larger impact on coronary heart disease compared with stroke in both absolute numbers and percentages.

Table 5

Effect of primary prevention scenarios in total population, expressed as the percentage of number of life years changed due to a change in diabetes related cardiovascular mortality out of the total number of life years gained due to a reduction in total mortality.

Scenario	Percentage of number life years changed due to a change in diabetes related cardiovascular mortality (upper and lower boundary)	
	Men	Women
Elimination of O&O	17 (9-22)	38 (14-44)
Elimination of physical inactivity	4 (2-8)	8 (4-15)
Elimination of both O&O and physical inactivity	8 (5-10)	17 (8-20)
Reducing O&O and physical inactivity	6 (3-11)	11 (5-18)
Secular trend in both O&O and physical inactivity	7 (4-13)	17 (7-25)

O&O: overweight and obesity.

In Figure 3, the change in life expectancy is shown for the five scenarios with a lower and upper boundary. The change in life expectancy is rather low. When overweight and obesity are eliminated and the whole population engages in physical activity at least once a week (scenario 3), the gain in life expectancy is 0.15 year for men and 0.29 year for women.

Table 5 shows for each scenario the percentage of life years lost via the pathway diabetes-CVD out of the total number of life years lost. On eliminating overweight and obesity, 17% (men) and 38% (women) of the life years gained is related to the pathway of diabetes to cardiovascular mortality. When physical inactivity is eliminated in the total population, the life years gained via the pathway diabetes to CVD proved to be 4% for men and 8% for women,

DISCUSSION

In this study, we estimated the effect of changes in the two major risk factors for diabetes on cardiovascular morbidity and mortality in the total population during the period 1990-1993. The hypothetical elimination scenarios showed a substantial impact on the incidence of diabetes in the group aged 30-79: eliminating the prevalence of both overweight and physical inactivity caused the incidence of diabetes to drop 64% in men and 75% in women. Considering the incidence, prevalence and mortality of cardiovascular diseases, this impact is modest. For example, the decrease in CHD mortality was 5% for men and 10%

for women. In absolute numbers, however, this reduction is quite substantial: about 2,500 CHD deaths among men and 2,300 CHD deaths among women would be avoided per year in The Netherlands. The realistic scenario resulted in a 6-7% reduction of the incidence of diabetes and a decrease in CHD and stroke incidence, prevalence and mortality of less than 1%. Translating the latter into absolute numbers means that some 230 CHD deaths in men (200 for women) and 60 stroke deaths (100 for women) would be avoided. By comparison: the breast cancer screening programme in The Netherlands has been estimated to ward off approximately 600 female deaths per year (64). It should be noted that in this realistic scenario, the estimated effect is highly dependent of the assumed decrease in prevalence of the two risk factors. For the secular trend scenario we implemented a suspected increase in the prevalence of both risk factors. Since the few earlier studies reporting on this subject were inconsistent (33, 39, 50, 54), we used "extreme" values for prevalence increase (Table 2). This resulted in an increase in the incidence of diabetes of 2.4% in men and 3.5% in women in 10 years. Again, it should be noted that this result depends on the assumed increase in prevalence of the two risk factors. In the USA, for example, overweight was seen to increase by more than 8% between the 1976 to 1980 and 1988 to 1991 surveys (16), which is twice as high as the most extreme increase observed in our country. The effect on diabetes incidence and related CVD complications in the USA will thus be more striking.

We used potential impact fractions (PIF) to estimate the effect of preventive strategies in which the prevalence of the risk factors and the association between these risk factors and the onset of diabetes are combined. However, the literature shows a variation in relative risk estimates for body mass index as well as for physical inactivity in relation to the onset of diabetes. Also, the categories used for estimating the relative risks in those studies were not in accordance with the categories used in studies reporting prevalence of the risk factors. As far as body mass index was concerned, we were able to calculate relative risks for the same categories as applied in prevalence studies, which might have overestimated the relative risks, as age could not be adjusted for. All things considered, our results should be interpreted with caution. In compensation, however, we used a range of relative risks as well as a prevalence range of both risk factors. By multiplying the lowest relative risk with the lowest prevalence and subsequently the highest relative risk with the highest prevalence, we calculated the widest possible upper and lower boundaries of the PIFs. In this way, some indication of the uncertainty surrounding the obtained results is provided.

Besides this, the effect of the primary prevention strategies on cardiovascular morbidity and mortality of the total population is partly determined by the prevalence of diabetes. As the cardiovascular diseases rates for the total popu-

lation are weighted means of the CVD rates of both the diabetic and non-diabetic population, a low prevalence of diabetes will weigh less on CVD rates in the total population. The prevalence of diabetes increases by age, as shown in Figure 2, which means that the impact of primary prevention of diabetes on CVD in the total population will be heavier at older ages.

The effect of obesity and physical inactivity was assumed to be independent, which is obviously not the case. Part of the effect of physical inactivity on the onset of NIDDM is attributable to increasing obesity (65), although after adjustment for obesity, the risk is still significantly higher (66). By assuming independence, we might have overestimated the effect of an intervention involving both weight reduction and increased physical activity. On the other hand, we also might have overestimated the effect of a secular trend in both risk factors. The rather wide lower and upper boundaries of potential impact fractions tender it very likely that the true effect of our strategies will fall within these limits.

We estimated the effect of obesity and physical inactivity resulting from diabetes on cardiovascular morbidity and mortality. However, obesity and physical inactivity also have a direct effect, unrelated to diabetes, on the incidence of cardiovascular disease, as well as on other chronic diseases such as different types of cancer (56-59). Using a relative risk of 1.1 for overweight and 2.0 of obesity on all cause mortality, we estimated that 83% (men) and 62% (women) of the life years lost due to obesity were independent of diabetes. Using a relative risk of 1.4 for physical inactivity on excess mortality, 96% (men) and 92% (women) of the life years lost were independent of diabetes. These figures indicate that the effect of obesity and physical inactivity on diabetes and diabetes-related cardiovascular diseases explains a small part of the excess risk on all-cause mortality of both risk factors. Other pathways, such as independent cardiovascular diseases or the increased risk of different types of cancer explain the large effects of body mass index and physical inactivity on health status. However, it should be noted that studies on the relationship between body mass index and physical inactivity on overall and cause-specific mortality showed inconsistencies (67) and these inconsistencies can not fully be explained by differences in study design, misclassification bias or confounding (68). The association between body mass index and excess mortality seemed to be more pronounced in obese subjects ($BMI > 30 \text{ kg/m}^2$) compared to overweight subjects (58, 59, 61, 62, 69). The evidence is less clear with respect to physical inactivity, probably due to the difficulties existing in defining and measuring the variable. Studies with more precise definitions and better study designs were more likely to report a protective effect (56, 70). In addition to this, little or no information was available on age-specific prevalence of obesity or physical activity nor on age-specific relative risks for the two risk factors. Therefore, in our cal-

culations, we used potential impact fractions independent of age. It is likely, however, that the relative risks for the two risk factors for both the onset of diabetes and for all-cause mortality decrease by age. Prevalence of the two risk factors, on the other hand, is likely to increase by age. How these different responses to age influence the potential impact fractions is unclear, but it may well be that the effect of the scenarios are overestimated because of the use of these constant PIFs. If so, the overestimation of all-cause mortality will be larger than the overestimation of the diabetes incidence and the related cardiovascular complications. This might partly explain the low fraction of life-years gained due to diabetes-related CVD mortality compared to a reduction in all cause mortality.

In the present study, we used body mass index as an indicator for body fatness, as this is presently used in literature. However, it is known that there are other indicators for body fatness referring to the location of body fat, such as waist-to-hip ratio or skinfold thickness. Using one of these indicators might have changed the estimated effects of the different scenarios. Also, physical inactivity is difficult to measure. Most studies use questionnaires in which different types of activity are made operational in a different way. However, the validity of these questionnaires for measuring the true association between physical inactivity and diabetes is questionable. It may well be that, when using more precise methods for estimating physical inactivity, the association between this risk factor and onset of diabetes will change. This will cause the effects of the intervention scenarios to change as well. In further research, it will be necessary to focus more on the effects of using different indicators of both risk factors in relation to the strength of the association with the onset of diabetes.

Promoting weight loss and physical activity is difficult to achieve. Several trials have been performed so far and they all report a decreasing incidence of diabetes mellitus in the subjects who had lost weight and/or increased physical activity (51-53, 71). However, not all subjects were able to lose weight and it appeared to be difficult to maintain the lower weight and higher activity level over longer periods. Further research is necessary to evaluate whether the effort it takes to reduce weight and to maintain the achieved lower weight and increased activity level outweighs the benefits for the subject.

In conclusion, the effect of overweight and physical inactivity on the primary prevention of diabetes mellitus depends strongly on the extent to which these two risk factors can be reduced. The three hypothetical elimination scenarios showed the boundaries within which the health benefits from an intervention scenario on obesity and/or physical inactivity will lie. The more realistic scenario had a small impact on diabetes related cardiovascular disease, although in absolute numbers, the reduction is still substantial. However, the health policy issue of whether or not to promote weight loss and to increase

physical activity should not depend solely on the effects on diabetes-related morbidity and mortality.

References

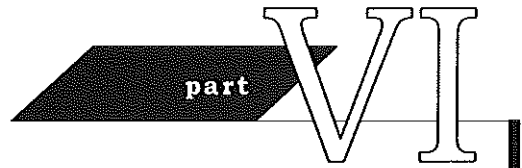
1. Feskens EJM, Kromhout D: Cardiovascular risk factors and the 25-year incidence of diabetes mellitus in middle-aged men. The Zutphen Study. *Am J Epidemiol* 130:1101-1108, 1989
2. Holbrook TL, Wingard DL, Barrett-Connor E: Sex-specified vs. unisex body mass indices as predictors of non-insulin dependent diabetes mellitus in older adults. *Int J Obesity* 14:803-807, 1990
3. Brown-McPhillips J, Barrett-Connor E, Wingard DL: Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non-insulin dependent diabetes mellitus in a community of older adults. *Am J Epidemiol* 131: 443-453, 1990
4. Cassano PA, Rosner B, Vokonas PS, Weiss ST: Obesity and body fat distribution in relation to the incidence of non-insulin-dependent diabetes mellitus. *Am J Epidemiol* 136:1474-86, 1992
5. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC: Obesity, fat distribution and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 17:961-969, 1994
6. Shaper AG, Wannamethee SG, Walker M: Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men. *Br Med J* 314:1311-1317, 1997
7. Carey VJ, Walters EE, Colditz GA, et al.: Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses Health study. *Am J Epidemiol* 145:614-619, 1997
8. Helmrigh SP, Ragland DD, Leung RW, Paffenbarger RS: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Eng J Med* 325:147-152, 1991
9. Helmrigh SP, Ragland DR, Paffenbarger RS: Prevention of non-insulin-dependent diabetes mellitus with physical activity. *Med Sci Sports Exerc* 26:824-830, 1994
10. Manson HE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH: A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* 268:63-67, 1992
11. Burchfiel CM, Sharp DS, Curb JD, et al.: Physical activity and incidence of diabetes: The Honolulu Heart Program. *Am J Epidemiol* 141:360-368, 1995
12. Lynch J, Helmrigh SP, Lakka TA, et al.: Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Arch intern med* 156:1307-1314, 1996

13. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG: Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *Br Med J* 310:560-564, 1995
14. Haapanen N, Miilunpalo S, Vuori I, Pekka O, Pasanen M: Characteristics of Leisure time physical activity associated with decreased risk of premature all-cause and cardiovascular disease mortality in middle-aged men. *Am J Epidemiol* 143: 870-880, 1996
15. Manson JR, Rimm EB, Stampfer MJ, et al: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774-778, 1991
16. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL: Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960-1991. *JAMA* 272:205-211, 1994
17. Seidell JC: Time trends in obesity: an epidemiological perspective. *Horm Metab Res* 29:155-158, 1997
18. Modan M, Karasik A, Halkin H, et al.: Effect of past and concurrent body mass index on prevalence of glucose intolerance and type 2 (non-insulin-dependent) diabetes and on insulin response. The Israel study of glucose intolerance, obesity and hypertension. *Diabetologia* 29:82-89, 1986
19. Barrett-Connor EL: Epidemiology, obesity and non-insulin-dependent diabetes mellitus. *Epidemiol Rev* 11:172-181, 1989
20. Colditz GA, Willett WC, Rotnitzky A, Manson JE: Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 122:481-486, 1995
21. Everhart JE, Pettitt DJ, Bennett PH, Knowler WC: Duration of obesity increases the incidence of NIDDM. *Diabetes* 41:235-240, 1992
22. Baan C, Barendregt J, Bonneux L: Increasing cardiovascular comorbidity among diabetic subjects. submitted
23. Schoen R: *Modeling Multigroup populations*. New York and London Plenum Press, 1987
24. Barendregt JJ, Oortmarssen GJ, van, Hout BA, van, Bosch JM, van den, Bonneux L: Coping with multiple morbidity in a life table. *Mathematical Population Studies* 7:29-49, 1998
25. Kleinbaum DG, Kupper LL, Morgenstern H: *Epidemiologic research. Principles and quantitative methods*. London, Singapore Lifetime Learning Publications, 1982
26. Statistics Netherlands. *Deaths by causes of death, age and gender*. Voorburg: Central Bureau of Statistics, 1994.
27. Bonneux L, Barendregt JJ, Van der Maas PJ: The new old epidemic of coronary heart disease. *Am J Public Health* 89:379-382, 1999
28. Baan CA, Bonneux L, Ruwaard D, Feskens EJM: The prevalence of diabetes mellitus in The Netherlands: a quantitative review. *Eur J Publ Health* 8:210-216, 1998
29. Baan CA, Nusselder WJ, Barendregt JJ, Ruwaard D, Bonneux L, Feskens EJM: The burden of mortality of diabetes mellitus in The Netherlands. *Epidemiology* 10:184-187, 1999
30. Barendregt JJ, Baan CA, Bonneux L: An indirect estimate of NIDDM incidence. submitted

31. Baan C, Barendregt J, Bonneux L: Estimating the age-specific cardiovascular morbidity and mortality of diabetes mellitus in The Netherlands. submitted
32. WHO Expert committee. *Physical status: the use and interpretation of anthropometry*. Geneva: World Health organization, 1995.
33. Verweij GCG: Health Interview Survey. Underweight and overweight, 1985-1996. *Mndber gezondheid* :4-13, 1998
34. Kromhout D, Obermann-de Boer GL, Blokstra A, Verschuren WMM. *Peilstationsproject Hart- en vaatziekten 1991*. Bilthoven: RIVM, 1991.
35. Smit H, Verschuren W, Bueno de Mesquita H, Seidell J. *Het project Monitoring Risicofactoren en Gezondheid Nederland (MORGEN-project)*. Jaarverslag 1993. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieuhygiene, 1994.
36. Seidell J, Smit H, Verschuren W, Bueno de Mesquita H, Blokstra A. *Het project Monitoring Risicofactoren en Gezondheid Nederland (MORGEN-project)*. Jaarverslag 1994. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieuhygiene, 1995.
37. Blokstra A, Seidell JC, Smit HA, Bueno de Mesquita HB, Verschuren WMM. *Het project Monitoring Risicofactoren en Gezondheid Nederland (MORGEN-project)*. Jaarverslag 1994. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieuhygiene, 1997.
38. Jansen MCJF, van Dis SJ, Kok FJ. *National inquiry lifestyle and risk factors for cardiovascular disease. (Landelijke enquête-onderzoek leefstijl en risicofactoren voor hart- en vaatziekten)*. Den Haag: Netherlands Heart Foundation, 1996.
39. Seidell JC, ed. *Lichaamsgewicht*. Bilthoven: RIVM, Elsevier/De Tijdstroom, 1997. (Maas IAM, Gijzen R, Lobbezoo IE, Poos MJJC, ed. Volksgezondheid Toekomst Verkenning 1997. De gezondheidstoestand: een actualisering; vol 1)
40. Paffenbarger RS, Wing AL: Chronic disease in former college students. XII Early Predictors of adult onset diabetes mellitus. *Am J Epidemiol* 97:314-323, 1973
41. Medalie JH, Papier C, Herman JB, et al.: Diabetes mellitus among 10,000 adult men. Five-year incidence and associated variables. *Israel J Med* 10:681-697, 1974
42. Papoz L, Eschwege E, Warnet J-M, Richard J-L, Claude J-R, ed. *Incidence and risk factors of diabetes in the Paris Prospective Study (GREX)*. Amsterdam: Elsevier Biomedical Press, 1982:113-122. (Eschwege E, ed. *Advances in Diabetes Epidemiology*;)
43. Seidell JC, Bakx KC, Deurenberg P, van den Hoogen HJM, Hautvast JGAJ, Stijnen T: Overweight and chronic illness - a retrospective cohort study with a follow-up of 6-17 years, in men and women of initially 20-50 years of age. *J Chron Dis* 39:585-593, 1986
44. Ohlson LO, Larsson B, Björntorp P, et al: Risk factors for type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and on-half years of follow-up of the participants in a study of Swedish men born in 1913. *Diabetologia* 31:798-805, 1988
45. Njolstad I, Arnesen E, Lund-Larsen PG: Sex differences in risk factors for clinical diabetes mellitus in a general population: a 12 year follow-up of the Finnmark Study. *Am J Epidemiol* 1998:49-58, 1998
46. Lundgren H, Bengtsson C, Blohme G, Lapidus L, Sjöström L: Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: results

- from a prospective population study in Gothenburg, Sweden. *Int J Obesity* 13: 413-423, 1989
47. Kaye SA, Folsom AR, Sprafka JM, Prineas RJ, Wallace RB: Increased incidence of diabetes mellitus in relation to abdominal adiposity in older women. *J Clin Epidemiol* 44:329-334, 1991
 48. Backx F, Swinkels H, Bol E: Health Interview Surveys. How physically (in)active are Dutch adults during their leisure time? *Mndber gezondheid (CBS)* :4-16, 1994
 49. Hoeben J: Health Interview Survey. Leisure time physical activity. *Mndber gezondheid* :18-28, 1998
 50. Bijnen FCH, Peeters PHM, Pols MA, Mosterd WL, ed. *Lichamelijke (in)activiteit*. Bilthoven: RIVM, Elsevier/De Tijdstroom, 1997. (Maas IAM, Gijsen R, Lobbezoo IE, Poos MJJC, ed. Volksgezondheid Toekomst Verkenning 1997. De gezondheidstoestand: een actualisering; vol 1)
 51. Katznel LI, Bleecker ER, Colman EG, Rogus EM, Sorkin JD, P GA: Effects of weight loss vs Aerobic exercise training on Risk Factors for coronary disease in health, obese, middle-aged and older men. *JAMA* 274:1915-1921, 1995
 52. Eriksson KF, Lindgärde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. *Diabetologia* 34:891-898, 1991
 53. Pan X, Li G, Wang J, Yang W, et al: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. *Diabetes Care* 20:537-544, 1997
 54. Blokstra A, Kromhout D: Trends in obesity in young adults in The Netherlands from 1974 to 1986. *Int J Obesity* 15:513-521, 1991
 55. Peeters PHM, Bijnen FCH, Pols MA, Kemmeren JM, Collette HJA, Mosterd WL, ed. *Lichamelijke (in) activiteit*. Den Haag: SDU-uitgeverij, 1994. (Ruwaard D, Kramers P, ed. Volksgezondheid Toekomstverkenningen: de gezondheidstoestand van de Nederlandse bevolking in de periode 1950-2010. 1993.;)
 56. Powell KE, Caspersen CJ, Koplan JP, Ford ES: Physical activity and chronic diseases. *Am J Clin Nutr* 49:999-1006, 1989
 57. Blair SN, Horton E, Leon AS, et al.: Physical activity, nutrition and chronic disease. *Med Sci Sports exerc* 28:335-349, 1996
 58. Bender R, Trautner C, Spraul M, Berger M: Assessment of excess mortality in obesity. *Am J Epidem* 147:42-48, 1998
 59. Manson JE, Willet WC, Stampfer MJ, et al.: Body weight and mortality among women. *N Eng J Med* 333:677-685, 1995
 60. Garfinkel L: Overweight and mortality. *Cancer* 58 (suppl 8):1826-1829, 1986
 61. Higgins M, Kannel W, Garisson R, Pinsky J, Stokes J: Hazards of obesity - the Framingham Experience. *Acta Med Scand* 723:23-36, 1988
 62. Seidell JC, Verschuren WMM, Van Leer EM, Kromhout D: Overweight, underweight and mortality. *Arch Intern Med* 156:958-963, 1996
 63. Rosengren A, Wilhelmsen L: Physical activity protects against coronary death and deaths from all causes in middle-aged men. Evidence from a 20-year follow-up of the primary prevention study in Goteburg. *Ann Epidemiol* 7:69-75, 1997
 64. de Koning H, Fracheboud J, Boer R, et al.: Nation-wide breast cancer screening in The Netherlands: support for breast cancer mortality reduction. National

- Evaluation Team for Breast Cancer Screening (NETB). *Int J Cancer* 60:777-780, 1995
65. Horton ES: Role and management of exercise in diabetes mellitus. *Diabetes Care* 11:201-211, 1988
66. Pereira MA, Kriska AM, Joswiak ML, et al.: Physical inactivity and glucose intolerance in the multiethnic island of Mauritius. *Med Sci Sports Exerc* 27:1626-1634, 1995
67. Manson JE, Stampfer MJ, Hennekens CH, Willett WC: Body weight and longevity. A reassessment. *JAMA* 257:353-358, 1987
68. Barrett-Connor EL: Obesity, atherosclerosis and coronary artery disease. *Ann Intern Med* 103:1010-1019, 1985
69. Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C: Prospective study of intentional weight loss and mortality in never-smoking overweight US white women aged 40-64 years. *Am J Epidemiol* 141:1128-1141, 1995
70. Berlin JA, Colditz GA: A meta-analysis of physical activity in the prevention of coronary heart disease. *Am J Epidemiol* 132:612-628, 1990
71. Wing RR, Venditti E, Jakicic JM, Polley BA, Lang W: Lifestyle intervention in overweight individuals with a family history of diabetes. *Diabetes Care* 21:350-359, 1998



DISCUSSION AND SUMMARY

General discussion

INTRODUCTION

The objectives of this thesis were twofold. First, we sought to describe the incidence, prevalence and mortality of diabetes mellitus, and the relation with its risk factors and its cardiovascular complications. The second objective was to study the effects of trends in cardiovascular diseases on the occurrence of diabetes and the effects of preventive strategies for diabetes mellitus on these cardiovascular complications. We addressed the first objective in parts II-IV of this thesis. The second objective is dealt with in part V.

We used a simulation model to investigate the answer to these two research questions. A simulation model has several advantages. First, it can be helpful in combining the many sources of information about the occurrence of diabetes effectively by demanding consistency in the various data and assumptions used. Secondly, a simulation model allows the boundaries to be estimated within which health benefits from intervention scenarios will lie. It provides answers to "what if" questions, even if the intervention should in fact be unrealistic. Finally, a disease model was felt to be a helpful tool for testing hypotheses.

This chapter will discuss per objective the available data, the methods used for data preparation and implementation in the model, and the main results. Finally the model is put in perspective, applications of the model are discussed and issues for future research are addressed.

OBJECTIVE 1

To describe the incidence, prevalence and mortality of diabetes mellitus, and the relation with its risk factors and cardiovascular complications.

Basic epidemiological elements of diabetes mellitus

Available data

The onset of non-insulin-dependent diabetes is a gradual process. At a certain point in time, a clinically defined threshold is reached and the patient has become a case. Few symptoms are present at the onset, implying that many subjects develop diabetes without their knowledge (1). The gradual onset makes it difficult to estimate the incidence and prevalence of diabetes. Changes in case-detection and in doctor and patient awareness also influence the incidence and prevalence estimate. As a result, Dutch studies on the incidence and prevalence

of diabetes have variously reported estimates differing almost by up to a factor of three (2-18).

Diabetes mortality could not validly be estimated from cause-of-death registrations (19), mainly because these use the concept of a single, underlying cause of death. As diabetes is accompanied by considerable comorbidity, especially at older ages, it is difficult to determine which condition should be identified as the underlying cause of death. Coding rules may also cause difficulties in interpretation. Coding practices differ between countries and over time, and explain 35% of the variation in the published diabetes mortality rates (20).

Methods used for data preparation and implementation

To arrive at valid estimates of the prevalence, mortality and incidence of diabetes, we used different methods based on the type of available data.

Fifteen studies, performed after 1970 and reporting the prevalence rates of diabetes mellitus in The Netherlands were used to obtain a summary estimate of the prevalence of diabetes (chapter 5). The studies largely fell into two groups: either they were based on registrations by general practitioners, or on self-report in a survey. We fitted an exponential curve of age-specific prevalence for ages 30-80 in both groups, using logistic regression analysis. Pooling data from heterogeneous studies to arrive at a single estimate might be considered a scientifically unsound undertaking. However, it seemed the only way to overcome the shortcomings of each individual study and to minimize the loss of information. Obviously the results should be interpreted with caution, although it should be pointed out that the studies were not heterogeneous in all respects. The prevalence increase by age, for example, was similar in all studies.

To estimate the mortality rate of diabetic subjects, another approach was used, based on the standard method for estimating mortality attributable to a risk factor: the population attributable risk (PAR) (21). We used the age-specific relative risks for mortality among diabetics together with the above estimated prevalence rate to divide the total mortality rate of the Dutch population into a diabetic and non-diabetic mortality rate (chapter 6). To end lacking relevant Dutch figures, we made use of the age-specific relative risks on total mortality from the Verona study (22). We used a sensitivity analysis with relative risks from seven other studies (23-29) to evaluate the robustness of the mortality estimate.

A pooled analysis as used to obtain the prevalence estimate, could not be performed to obtain the diabetes incidence, as too few studies reported incidence rates. Therefore we backcalculated the incidence from the prevalence and mortality rate of diabetes as previously estimated, by using an incidence-prevalence-mortality (IPM) model (chapter 7). It may seem trivial to estimate a third unknown variable from two known variables, but the oft-cited relationship

' $\text{prevalence} = \text{incidence} \times \text{disease duration}$ ' is an oversimplification (30). With increasing age, true duration is lower because of increasing general mortality and thus declining life expectancy, whereas duration estimated by age-specific prevalence divided by incidence will increase because of the accumulation of prevalent cases. This problem was dealt with by using an IPM-model and resulted in consistent estimates of incidence, prevalence and mortality rates.

Main results

The group of survey studies yielded a somewhat higher pooled prevalence of diabetes than the general practice studies. The total number of patients between 30 and 80 years of age in 1993 in The Netherlands was estimated to be 285,000 (survey) or 235,000 (general practice), or 3.2% or 2.7% of the total population respectively. The expected mortality was 12% among male diabetics and 18% among female diabetics in 1990-1992, of which 2.5% and 5% respectively were attributable to diabetes. When these mortality and prevalence rates were combined in the incidence-prevalence-mortality model an estimated incidence of diabetes was obtained which ranged from 8.1 per 10,000 for men aged 40-44 (7.0 for women), upward to 79.7 per 10,000 for men aged 75-79 (85.8 for women). These estimates of incidence, prevalence and mortality of diabetes are internally consistent and, in accordance with what is known from the literature (2, 3, 17, 18, 31-33).

Modifiable lifestyle related risk factors for diabetes

Obesity

The available empirical data on obesity as a risk factor for diabetes are difficult to interpret. The cut-off points used for prevalence of overweight and obesity are different from the cut-off points used for estimating relative risks. As we have used potential impact fractions (PIF) for estimating the effect of preventive strategies, we had to combine both the prevalence and relative risks of obesity for diabetes. To this end, we recalculated the relative risks corresponding to the case-definition used for the prevalence of obesity, by using person years lived and number of cases reported (chapter 2). It should be noted that these recalculated relative risks are rather crude, as no adjustment for age could be made. This has probably yielded an overestimation of the relative risk. However, we were unable to devise any other way of obtaining consistent relative risks for the cut-off points used in the model.

Physical inactivity

It also proved difficult to compare the various relative risks of physical inactivity for diabetes and to combine these with the physical inactivity prevalence estimates. Unlike obesity, the differences between the studies were not so much in choice of cut-off point, but more in the definition and measurement of physical activity. It was therefore not possible to recalculate relative risks at other thresholds, which forced us to use the data as published. Since most studies only reported relative risks for physical inactivity and diabetes for the middle-aged population, we have estimated the association between physical inactivity and presence of newly diagnosed diabetes mellitus in an elderly population (chapter 3).

Main results

Overweight was defined as overweight ($BMI > 25$ and $< 30 \text{ kg/m}^2$) and obesity ($BMI > 30 \text{ kg/m}^2$), in conformity with the WHO-standard (34). The prevalence of overweight in the Netherlands was about 36% among men and 23% among women, while the prevalence of obesity ranged between 4%-11% for men and women (35-41). Relative risks for diabetes associated with overweight and obesity ranged from 1.5 to 51.0 for men and from 2.0 to 93.0 for women, depending on the category of BMI used. The prevalence of inactivity (defined as reporting no sports activity or other vigorous activity) varied between 44-52% (36, 39, 40, 42-44). Risk ratios for diabetes associated with physical inactivity in middle aged subjects varied between 2.0 and 2.9 for men and 1.7 to 3.1 for women. In a sample taken from the Rotterdam Study (45), we estimated an odds ratio of 2.8 (men) and 3.1 (women) for no vigorous physical activity and the presence of newly diagnosed diabetes in elderly subjects. The foregoing ranges of prevalence of the two risk factors and relative risks for the onset of diabetes were the input for chapter 10, in which we estimated the health gains by changing the prevalence of both obesity and physical inactivity.

Diabetes as a risk factor for cardiovascular diseases

Available data

Considering the difficulties in estimating incidence, prevalence and mortality of diabetes, it should come as no surprise that it is even more complicated to obtain a valid estimate of the incidence, prevalence and mortality rates of cardiovascular diseases (CVD) among diabetic subjects. For example, the underlying cause of death in a diabetic subject who dies of a heart attack will either be registered as cardiovascular disease or diabetes. This not only leads to an un-

derregistration of diabetes mortality, it also precludes a valid estimate of the cardiovascular mortality rate among diabetic subjects. In addition, data on CVD incidence and prevalence rates among diabetic subjects are scarce and published on an aggregated level, probably due to the small numbers concerned.

Since age is an important variable in the association between diabetes and cardiovascular diseases, the diabetes model would lose much of its relevance without it. Changes in incidence and survival at younger ages affect disease prevalence and mortality at older ages. These changes in the age pattern can be described and analysed in a model. We therefore devoted much effort to estimating the age-dimension of the diabetes and CVD in connection with which we had to define age-dimension assumptions, as most empirical data were assimilated for large age groups. In addition, the consistency of the input of the model had to be safeguarded, i.e. cardiovascular mortality rates among diabetics had to fit the CVD incidence and prevalence rates.

Method of data preparation and implementation

With the available data, we estimated age-specific cardiovascular morbidity and mortality rates for diabetic and non-diabetic subjects simultaneously using a multi-state life table (chapter 8). This is an extension of the standard life table that distinguishes not only between 'alive' and 'dead', but allows for additional states like 'alive, healthy', 'alive, with heart disease', etc (46). In addition to cause-specific mortality rates, the multi-state life table also comprises incidence, prevalence and case-fatality rates.

In previous studies, a cardiovascular diseases model was developed for the total population (47-49). This model was combined with the diabetes IPM model. Several studies reported distributions of causes of death in subjects with diabetes mellitus (25, 50, 51). We used these distributions as constraints when combining the cardiovascular diseases model with the diabetes model. Furthermore, we made (trivial though necessary) assumptions that incidence and prevalence rates for CHD and stroke have to be higher at all ages for diabetic subjects compared to non-diabetic subjects. For all studies that reported a distribution of causes of death among subjects with diabetes mellitus we estimated age-specific cardiovascular morbidity and mortality rates and these outcomes were compared to published relative risks for cardiovascular diseases among diabetics.

Main results

While the mean relative risks for coronary heart disease, stroke and other cardiovascular mortality were similar in all solutions, the age-pattern of the various solutions differed somewhat. Taking the fit of the results into account, one pos-

sible solution was chosen for implementation of the age-specific morbidity and mortality rates of CVD in diabetic subjects in the model. The other possible solutions were used in sensitivity analyses. As there were no data available on cardiovascular morbidity and mortality rates among diabetics in the Netherlands, we could not validate our estimates. However, comparing these outcomes on a more aggregated level, such as mean relative risk for cardiovascular mortality, we found they were comparable with the literature.

To summarise

We have arrived at internally consistent estimates of incidence, prevalence and mortality rates for diabetic subjects, using various statistical and modelling techniques which could best overcome the mentioned limitations/inadequacies of the available data. These estimates enabled us to answer the second objective of this thesis.

OBJECTIVE 2

To study the effects of trends in cardiovascular diseases on the occurrence of diabetes and the effects of preventive strategies for diabetes mellitus on its cardiovascular complications.

Possible cause of secular trend in diabetes prevalence

Since the early 1970s the age-adjusted mortality rates from cardiovascular diseases for the total population plummeted (49, 52-55). This decline can be attributed to a combination of lower incidence and improved survival (48, 49, 56, 57). As cardiovascular diseases are the cause of death in more than 60% of diabetics, changes in incidence and survival of cardiovascular diseases will affect diabetes prevalence and cardiovascular comorbidity. We have used the diabetes-cardiovascular diseases model to study the effect of declining mortality hazards of coronary heart disease (CHD) and stroke on the prevalence of diabetes (chapter 9)

Methods and assumptions

The initial assumption was that the improvement in survival of CHD and stroke, observed for the general population was also applicable to the diabetic population. We thus may have overestimated the impact of improved cardiovascular diseases survival on diabetes prevalence. However, the way in which the sur-

vival of CHD and stroke has changed in the diabetic population is still open to discussion.

Another assumption related to the time dimension. Time is not included in the diabetes model, as we use multi-state life table techniques. The life table only describes steady states. This is important when interpreting the results; life table analysis produces estimates that reflect the full impact of the changed incidence and survival, while in reality these take time to develop.

Main results and discussion

We have shown that if the changes in CHD and stroke in the total population are similarly applicable to the diabetic population, this would only result in a small increase in the prevalence of diabetes, both in rates and in absolute numbers. The comorbidity rate of cardiovascular diseases and diabetes increased substantially, especially above the age of 60.

These results discredited the hypothesis that the observed increase in the prevalence of diabetes was largely caused by the decline in cardiovascular diseases mortality. We believe that the decline in CVD mortality seen in the total population rather than causing a sizeable increase in the prevalence of diabetes, may cause a marked increase in the cardiovascular comorbidity of diabetes. This conclusion can have major consequences with respect to the public health, and would make the need for intervention strategies even greater. One aspect of this issue will be addressed in the next paragraph.

Forecasting health gains by changing the prevalence of risk factor for diabetes

Increasing health care needs make the search for preventive strategies more relevant. In addition, for health care planning, it is important to know what burden of disease can be expected in the near future. Obesity and physical inactivity are important risk factors for the onset of diabetes mellitus, and thus will play an important role in the primary prevention of diabetes mellitus. There is evidence that prevalence of the overweight and obesity has risen over the past years with no end to this trend coming yet insight (58, 59). Regarding physical inactivity, the picture is less clear. In chapter 10, we estimated the effect of primary prevention strategies on diabetes and related cardiovascular complications as well as the effect of secular trends in obesity and physical inactivity on diabetes-related cardiovascular complications, using the model previously developed.

Methods and assumptions

The effect of a scenario was estimated by using the potential impact fraction (PIF). A PIF is defined as "the proportional reduction in the total number of new (incident) cases of a certain disease, resulting from a specific change in the distribution of a risk factor in the population at risk" (60). The range of prevalence of obesity and physical inactivity, as defined in chapter 2, as well as the range in relative risks of the two risk factors for the onset of diabetes were used to assess a PIF with a lower and upper boundary. We assumed that the two risk factors affected diabetes mellitus independently, both expressed by a separate potential impact fraction. However, part of the effect of physical activity on the onset of diabetes mellitus is due to losing weight (61), although after adjustment for body mass index, the risk of physical inactivity is still significantly higher (62). By assuming independence, we may have overestimated the effect of an intervention through which weight is lost and physical activity increased. However, by using rather wide lower and upper boundaries of the PIFs, the true effect of an intervention is nonetheless likely to fall within these limits.

We have defined five scenarios. Three hypothetical intervention scenarios have been defined in which either the presence of overweight and obesity or of physical inactivity or the presence of both risk factors was eliminated. The fourth intervention assumed a more realistic intervention (i.e. a 5% decrease in prevalence of overweight/obesity and a 20% decrease in prevalence of physical inactivity) and the last scenario estimated the effect of secular trends in prevalence of obesity and physical inactivity (i.e. a 1.5% increase in prevalence of overweight in 10 years for men (3% for women) and a 5% increase in prevalence of obesity in 10 years for men (4% for women) and an increase of 5% in 10 years of prevalence of physical inactivity for both men and women).

Main results and discussion

The hypothetical elimination scenarios showed a substantial impact on the incidence of diabetes. Eliminating the presence of overweight/obesity resulted in a reduction of the incidence of diabetes by 54% for men and 68% for women. Compared to the effect on diabetes incidence, the effect on cardiovascular morbidity and mortality of the total population was rather small (the cardiovascular mortality in the total population decreased by 4% in men and 9% in women). In absolute numbers though, the reduction was quite substantial (about 2,500 CHD deaths among men and 2,300 CHD deaths among women would be avoided). The fourth scenario showed a reduction in diabetes incidence of 6% for men and 7% for women. The effect on cardiovascular mortality in total population in this scenario was less than 1% for both men and women. The in-

crease in diabetes incidence due to the reported secular trend in the prevalence of both risk factors was 2% for men and 3% for women.

Considering these results, it should first be noted that the data used for estimating the PIFs largely determine the validity of the results. However, there is a large variation in relative risk estimates for both body mass index as well as physical inactivity in relation to diabetes and CVD complications. We have used wide range of relative risks and prevalences and thus have calculated the widest possible upper and lower boundary of the PIFs. This gives an indication of the uncertainty existing in the obtained results. Secondly, we only took into account the effect of reducing overweight and inactivity on the incidence of diabetes and subsequently on diabetes-related cardiovascular diseases. However, obesity and physical inactivity have also a direct effect on the incidence of cardiovascular diseases. Finally, the effort it takes to lose weight, to maintain the achieved lower weight and to increase the level of physical activity should be balanced against the benefits to the subject. A decreased risk for onset of diabetes and its complications is one of those benefits, but, based on the current figures, is not a major one.

DIABETES MODEL IN PERSPECTIVE

Prior to interpreting the results of the diabetes model described above, these must first be considered in the light of the limitations of the input and of the assumptions made. This requires a clear description of how the data are prepared and implemented in the model, together with all the relevant assumptions. With this end in view, we described each step of the modelling process separately and validated the results.

Initial validation was performed by comparing our results with the literature whenever possible. Our estimates of the incidence and prevalence rates, two basic components of the diabetes model, were directly validated by observed incidence and prevalence rates. For CVD rates among diabetics, validation was only possible on a more aggregated level, such as mean relative risks for CVD mortality.

Another method for validating the output of the model involved performing sensitivity analyses on the input of the model. A sensitivity analysis was performed at every step in the development of the model, as presented in the corresponding chapters. Despite the, sometimes high, degree of uncertainty about the input of the model, the outcomes of the model were only slightly varied. For example, the estimate of the incidence of diabetes mellitus (chapter 7) was based on the prevalence as well as the mortality of diabetes. Varying the mortality of

diabetes by a factor of 2 did not affect the estimated incidence to any great extent (Figure 2 and 3, chapter 7).

A third method of validating the model is to compare the results with other comparable diabetes models. In the field of diabetes epidemiology, the use of modelling techniques is not common. For non-insulin-dependent diabetes mellitus, only Eastman et al (63-65) have published a model. They have developed a micro-simulation model in which various complications of diabetes as well as various risk factors and populations have been defined. This has resulted in a complex model in which it is not clear which input or assumptions have been used, which makes it difficult to compare their results with ours. Despite these difficulties, we could compare one outcome variable. Eastman et al. estimated a reduction in life expectancy for a middle-aged diabetic subject of 10 years, whereas our model yielded a reduction of 5-6 years, which corresponds to the literature (32, 33). Although comparison of the two different models with different designs and underlying research questions is difficult, it may give more insight in the association of diabetes and cardiovascular diseases. Furthermore, insight in the effect of the different approaches and data used for implementation in the model can be obtained. At present, no direct comparison can be made with the published results of the Eastman model, and would require a major effort of both research groups.

APPLICATIONS OF THE DIABETES MODEL

The diabetes-cardiovascular model can be used to estimate the impact on population health given the application of different intervention scenarios for modification of risk factors (e.g. physical inactivity and overweight). As described in chapter 10, we found that an elimination of presence of overweight and physical inactivity had a sizeable impact on diabetes related cardiovascular diseases. This hypothetical scenario showed the boundaries within which the health benefits from an intervention scenario on obesity and/or physical inactivity will lie. However once again, it is important to realize the limitations of the model for such applications. In particular, the quality of the available data on the strength of the association between both risk factors and onset of diabetes. In addition, the model only estimates the effect of eliminating obesity or physical inactivity on diabetes related morbidity and mortality, while obviously both risk factors also influence other diseases.

A second application is that the disease model can be a helpful tool for evaluating hypotheses. In our study, for example, this led to our rejecting the hypothesis that the increase in cardiovascular survival in the total population

had given rise to the increase in diabetes prevalence. We believe it more likely that the observed increase in prevalence of diabetes is caused by other processes.

FUTURE RESEARCH

This thesis demonstrates that combining epidemiological data from different sources can produce more insight into the complex nature of diabetes and its complications. However, as usual in scientific research, this has at the same time lead to new questions and served to pinpoint the gaps in the current knowledge base. For example, the prevalence of diabetes in this model is in fact the prevalence of known diabetes, whereas some 50% of all diabetic subjects are unaware of their disease and hence are undiagnosed (1). In addition, more information about the risk of CVD in these subjects is essential. Studies to date have reported contradictory results in this: various studies reported that the risk of complications in undiagnosed diabetic subjects is not different from that in diagnosed subjects, while others reported a lower risk for complications (66-69). If these figures are all taken into account, the prevalence estimate will be much higher and thus cause considerable changes in the input and output of the model. Future research must provide more information on these patients with a view to further adjusting and optimising the diabetes model to enhance prediction about the burden of diabetes and its complications.

Related to this is the strongly debated issue of whether or not to screen for undiagnosed diabetes. As we showed in chapter 4 of this thesis, the subjects with a high risk of having undiagnosed diabetes mellitus can be identified relatively easily within general practice, although the positive predictive value is rather low (8%). In the most recent version of the official Dutch protocol for general practitioners ("NHG-standard"), screening for undiagnosed diabetes mellitus is advised in persons aged 45 and older. The standard recommends that subjects with several risk indicators for diabetes (family history of diabetes, hypertension, CHD, obesity, gestational diabetes, etc) should have their blood glucose level tested every three years. Surprisingly, this recommendation is not accompanied by a cost-effectiveness evaluation. Future research should focus on the cost-effectiveness of a screening programme for undiagnosed diabetes, in which the diabetes model is highly useful.

Given the current definition problems in diabetes and the fact that the risk of complications of diabetes is steadily increasing as glucose levels continue to rise, it might be interesting to model glucose tolerance continuously rather than modelling diabetes as being present or absent. Several validation problems

would then be solved. Future research should focus on the possibilities of directly modelling glucose tolerance and cardiovascular complications. This may assist in forecasting the burden of diabetes and its complications.

Because of the striking lack of data about cardiovascular mortality in the elderly, the diabetes model in this thesis mainly included data on subjects up to the age of 74 year. However, the pattern of comorbidity of diabetes in the oldest age groups is of great importance for public health policy. More data are especially needed on women, in whom the bulk of cardiovascular deaths occur above the age of 70, in order to generate reliable estimates (70). Future research could yield the data needed to refine our diabetes model in order that these age groups too can be included. This is of particular relevance in view of the ageing of the population in the near future.

References

1. Harris MI: Undiagnosed NIDDM: clinical and public health issues. *Diabetes Care* 16:642-653, 1993
2. Steering Committee on Future Health Scenarios: *Chronische ziekten in het jaar 2005. Volume 1: scenario's van diabetes mellitus 1990-2005. (Chronic diseases in the year 2005. Volume 1: scenarios on diabetes mellitus 1990-2005)*. Dordrecht, Boston, London Kluwer Academic Publishers, 1991
3. van de Lisdonk EH, Bosch WJHM, Huygen FJA, Lagro-Jansen ALM, ed. *Ziekten in de huisartspraktijk (Diseases in the general practice)*. Utrecht: Wetenschappelijke uitgeverij Bunge, 1990:342.
4. Cromme PHV, Eijk van JTM, Veen van der EA, Nauta JJP, Knottnerus JA: Glucose-intolerantie bij ouderen in Nederland; het Twello-onderzoek (Glucose tolerance in an elderly Dutch countryside population: the Twello Study). *Ned Tijdschr Geneeskd* 139:2558-2563, 1995
5. Meyboom-de Jong B. *Bejaarde patiënten: een onderzoek in 12 huisartsenpraktijken (Elderly patients: a research in 12 general practices)*. University Groningen, 1989
6. Lamberts H, Brouwer HJ, Mohrs J. *Reasons for encounter- & episode- & process-oriented standard output from the Transition project. Part 1 and 2*. Amsterdam: Department of General Practice, 1991.
7. Verhoeven S. *Behandeling, controle en metabole instelling van patienten met diabetes mellitus type II en de prevalentie van late complicaties bij deze patienten (Treatment, follow-up and metabolic regulation of patients with diabetes mellitus type II and the prevalence of late complications in this group of patients)*. Erasmus University Rotterdam, 1989
8. Valkenburg HA, Hofman A, Klein F, Groustra FN: Een epidemiologisch onderzoek naar risico-indicatoren voor hart- en vaatziekten (EPOZ). I. Bloeddruk, serumcholesterolgehalte, Quetelet index en rookgewoonten in een open bevolking

- van vijf jaar en ouder (An epidemiological study of cardiovascular risk factors (EPOZ). 1. Blood pressure, serum cholesterol level, quetelet index and smoking habits in an open population aged five years and over). *Ned Tijdschr Geneesk* 124:183-189, 1980
9. van den Berg J, van den Bos GAM: Gezondheidsenquêtes. Het (meten van het) voorkomen van chronische aandoeningen. 1974-1987 (Health interview surveys. The (measurement of the) prevalence of chronic conditions, 1974-1987). *Mndber Gezondheid (CBS)* 3:4-21, 1989
 10. Verschuren M, Kromhout D: Total cholesterol concentration and mortality at a relatively young age: do men and women differ? The Netherlands Consultation Bureau Project on Cardiovascular Diseases. *Br Med J* 311:779-783, 1995
 11. Central Bureau of Statistics. *Gezondheidsenquêtes (Health interview surveys)*, 1989-1993.
 12. Mackenbach JP, van de Mheen H, Stronks K: A prospective cohort investigating the explanation of socio-economic inequalities in health in the Netherlands. *Soc Sci Med* 38:299-308, 1994
 13. Deeg DJH, Westendorp - de Serière M: *Autonomy and well being in the aging population I: report from the Longitudinal Aging Study Amsterdam 1992-1993*. Amsterdam VU University Press, 1994
 14. Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Heine RJ: Prevalence and determinants of glucose intolerance in a Caucasian population. The Hoorn Study. *Diabetes Care* 18:1270-1273, 1995
 15. Feskens EJM, Tuomilehto J, Stengard JH, Pekkanen J, Nissinen A, Kromhout D: Hypertension and overweight associated with hyperinsulinaemia and glucose tolerance: a longitudinal study of the Finnish and Dutch cohorts of the Seven Countries Study. *Diabetologia* 38:839-847, 1995
 16. Stolk RP, Pols HAP, Lamberts SWJ, Jong de PTVM, Hofman A, Grobbee DE: Diabetes mellitus, impaired glucose tolerance and hyperinsulinemia in an elderly population. The Rotterdam Study. *Am J Epidemiol* 145:24-32, 1997
 17. Ruwaard D, Gijzen R, Bartelds AIM, Hirasig RA, Verkleij H, Kromhout D: Is the incidence of diabetes increasing in all age-groups in The Netherlands. Results of the second study in the Dutch Sentinel Practice Network. *Diabetes Care* 19:214-218, 1996
 18. van der Velden J, de Bakker DH, Claessens AAMC, Schellevis FG: *Een nationale studie naar ziekten en verrichtingen in de huisartspraktijk. Basisrapport: Morbiditeit in de huisartsenpraktijk (A national study for diseases and operations in the general practice. Morbidity in the general practice)*. Utrecht Netherlands Institute of Primary Health Care, 1991
 19. Mackenbach JP, Snels IAK, Friden-Kill LM: Diabetes mellitus als doodsoorzaak (Diabetes as a cause of death). *Ned Tijdschr Geneesk* 135:1492-1496, 1991
 20. Jougl E, Papoz L, Balkau B, Maguin P, Hatton F: Death certificate coding practices related to diabetes in European countries - the EURODIAB subarea C study. *Int J Epidemiol* 21:343-351, 1992
 21. Rothman K: *Modern epidemiology*. Boston/Toronto Little, Brown and company, 1986
 22. Muggeo M, Verlato G, Bresson F, et al: The Verona diabetes study: a population-based survey on known diabetes prevalence and 5-year all-cause mortality. *Diabetologia* 38:318-325, 1995

23. Kessler II: Mortality experience of diabetic patients. A twenty-six year follow-up study. *Am J Med* 51:715-724, 1971
24. Panzram G, Zabel-Langhennig R: Prognosis of diabetes mellitus in a geographically defined population. *Diabetologia* 20:587-591, 1981
25. Swerdlow AJ, Jones ME: Mortality during 25 years of follow-up of a cohort with diabetes. *Int J Epidemiol* 25:1250-1261, 1996
26. Shenfield GM, Elton RA, Bhalla IP, Duncan LJP: Diabetic mortality in Edinburgh. *Diab Metab* 5:149-158, 1979
27. Kleinman JC, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB: Mortality among diabetics in a national sample. *Am J Epidemiol* 128:389-401, 1988
28. Walters DP, Gatling W, Houston AC, Mullee MA, Julious SA, Hill RD: Mortality in Diabetic subjects: an eleven-year follow-up of a community-based population. *Diab Med* 11:968-973, 1994
29. Wong JSK, Pearson DWM, Murchison LE, Williams MJ, Narayan V: Mortality in diabetes mellitus: experience of a geographically defined population. *Diab Med* 8:135-139, 1991
30. Murray C, Lopez A. *Global comparative assessments in the health sector. Disease burden, expenditures and intervention package*. Geneva: WHO, 1994.
31. King H, Rewers M: Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. *Diabetes Care* 16:157-177, 1993
32. Geiss LS, Herman WH, Smith PJ, ed. *Mortality in non-insulin-dependent diabetes mellitus*. 2 ed. Bethesda: NIH, 1995:233-258. (National Diabetes Data Group, ed. Diabetes in America;)
33. Schneider H, Lischinski M, Jutzi E: Survival time after onset of diabetes: 29-year follow-up mortality study in a diabetes cohort from a rural district. *Diabetes Metab* 19:152-158, 1993
34. WHO Expert committee. *Physical status: the use and interpretation of anthropometry*. Geneva: World Health organization, 1995.
35. Verweij GCG: Health Interview Survey. Underweight and overweight, 1985-1996. *Mndber gezondheid* :4-13, 1998
36. Kromhout D, Obermann-de Boer GL, Blokstra A, Verschuren WMM. *Peilstationsproject Hart- en vaatziekten 1991*. Bilthoven: RIVM, 1991.
37. Smit H, Verschuren W, Bueno de Mesquita H, Seidell J. *Het project Monitoring Risicofactoren en Gezondheid Nederland (MORGEN-project)*. Jaarverslag 1993. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieuhygiene, 1994.
38. Seidell J, Smit H, Verschuren W, Bueno de Mesquita H, Blokstra A. *Het project Monitoring Risicofactoren en Gezondheid Nederland (MORGEN-project)*. Jaarverslag 1994. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieuhygiene, 1995.
39. Blokstra A, Seidell JC, Smit HA, Bueno de Mesquito HB, Verschuren WMM. *Het project Monitoring Risicofactoren en Gezondheid Nederland (MORGEN-project)*. Jaarverslag 1994. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieuhygiene, 1997.
40. Jansen MCJF, van Dis SJ, Kok FJ. *National inquiry lifestyle and riskfactors for cardiovascular disease. (Landelijke enquête-onderzoek leefstijl en risicofactoren voor hart- en vaatziekten)*. Den Haag: Netherlands Heart Foundation, 1996.

41. Seidell JC, ed. *Lichaamsgewicht*. Bilthoven: RIVM, Elsevier/De Tijdstroom, 1997. (Maas IAM, Gijsen R, Lobbezoo IE, Poos MJJC, ed. Volksgezondheid Toekomst Verkenning 1997. De gezondheidstoestand: een actualisering; vol 1)
42. Backx F, Swinkels H, Bol E: Health Interview Surveys. How physically (in)active are Dutch adults during their leisure time? *Mndber gezondheid (CBS)* :4-16, 1994
43. Hoeben J: Health Interview Survey. Leisure time physical activity. *Mndber gezondheid* :18-28, 1998
44. Bijnen FCH, Peeters PHM, Pols MA, Mosterd WL, ed. *Lichamelijke (in)activiteit*. Bilthoven: RIVM, Elsevier/De Tijdstroom, 1997. (Maas IAM, Gijsen R, Lobbezoo IE, Poos MJJC, ed. Volksgezondheid Toekomst Verkenning 1997. De gezondheidstoestand: een actualisering; vol 1)
45. Hofman A, Grobbee DE, Jong de PVTM, Ouweland van de FA: Determinants of disease and disability in the elderly: the Rotterdam Elderly study. *Eur J Epidemiol* 7:403-22, 1991
46. Schoen R: *Modeling Multigroup populations*. New York and London Plenum Press, 1987
47. Niessen LW, Barendregt JJ, Bonneux L, Koudstaal P: Stroke trends in an ageing population. *Stroke* 24:931-939, 1993
48. Bonneux L, Barendregt JJM, Meeter K, Bonsel GJ, Maas van der PJ: Estimating clinical morbidity due to ischemic heart disease and congestive heart failure: the future rise of heart failure. *Am J Public Health* 84:20-28, 1994
49. Bonneux L, Barendregt JJ, Van der Maas PJ: The new old epidemic of coronary heart disease. *Am J Public Health* 89:379-382, 1999
50. Morrish NJ, Stevens LK, Head J, Fuller JH, Jarrett RJ, Keen H: A prospective study of mortality among middle-aged diabetic patient (the London cohort of the WHO Multinational Study of Vascular Disease in Diabetics): causes and death rates. *Diabetologia* 33:538-541, 1990
51. Moss SE, Klein R, Klein BEK: Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 81:1158-1162, 1991
52. Sprafka JM, Burke GL, Folsom AR, Luepker RV, Blackburn H: Continued decline in cardiovascular disease risk factors: results of the Minnesota Heart Survey 1980-1982 and 1985-1987. *Am J Epidemiol* 132:489-500, 1990
53. Demirovic J, Blackburn H, McGovern P, Sprafka JM, Doliszny K: Sex differences in coronary heart disease mortality trends: the Minnesota Heart Survey, 1970-1988. *Epidemiology* 4:79-82, 1993
54. Kuller LH, ed. *Stroke and diabetes*. 2 ed. Bethesda: NIH, 1995:449-456. (Group NDD, ed. Diabetes in America;)
55. Sytkowski PA, Agostino RB, Belanger A, Kannel WB: Sex and time trends in cardiovascular disease incidence and mortality: The Framingham Heart Study, 1950-1989. *Am J Epidemiol* 143:338-350, 1996
56. McGovern PG, Burke GL, Sprafka M, Xue S, Folsom AR, Blackburn H: Trends in mortality, morbidity and risk factor levels for stroke. From 1960 through 1990. The Minnesota Heart Survey. *JAMA* 268:753-759, 1992
57. Bonita R: Epidemiology of stroke. *Lancet* 339:342-347, 1992
58. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL: Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960-1991. *JAMA* 272:205-211, 1994

59. Seidell JC: Time trends in obesity: an epidemiological perspective. *Horm Metab Res* 29:155-158, 1997
60. Kleinbaum DG, Kupper LL, Morgenstern H: *Epidemiologic research. Principles and quantitative methods*. London, Singapore Lifetime Learning Publications, 1982
61. Horton ES: Role and management of exercise in diabetes mellitus. *Diabetes Care* 11:201-211, 1988
62. Pereira MA, Kriska AM, Joswiak ML, et al.: Physical inactivity and glucose intolerance in the multiethnic island of Mauritius. *Med Sci Sports Exerc* 27:1626-1634, 1995
63. Eastman RC, Javitt JC, Herman WH, et al.: Model of complications of NIDDM. I. Model constructions and assumptions. *Diabetes Care* 20:725-734, 1997
64. Eastman RC, Javitt JC, Herman WH, et al.: Model of complications of NIDDM. II Analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. *Diabetes Care* 20:735-744, 1997
65. Eastman RC, Keen H: The impact of cardiovascular disease on people with diabetes: the potentials for prevention. *Lancet* 350:S1.29-S1.32, 1997
66. Balkau B, Eschwege E, Papoz L, et al.: Risk factors for early death in non-insulin-dependent diabetes and men with known glucose tolerance status. *Br Med J* 307:295-299, 1993
67. Klein R: Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258-268, 1995
68. Jarrett RJ, Deen H, McCartney P: the Whitehall Study: ten year follow-up report on men with impaired glucose tolerance with reference to worsening to diabetes and predictors of death. *Diab Med* 1:279-283, 1984
69. Jarrett RJ, McCartney P, Keen H: The Bedford Survey: ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycaemic controls and risk indices for coronary heart disease in borderline diabetics. *Diabetologia* 22:79-84, 1982
70. King H, Aubert RE, Herman WH: Global burden of diabetes, 1995-2025. *Diabetes Care* 21:1414-1431, 1998

Summary

Given the complexity of the onset of non-insulin-dependent diabetes mellitus and its complications, it is difficult to estimate the burden of the disease. Comprehensive information on basic epidemiological elements, such as incidence, prevalence and mortality of diabetes are scarce, incomplete or inconsistent with other studies. The combination of changes in life style variables (such as obesity and physical inactivity) and changes in the natural history of complications of diabetes (such as cardiovascular disease) through medical interventions produces a variety of possible changes in diabetes incidence, prevalence and mortality. The objectives of this thesis were, first, to describe the incidence, prevalence and mortality of diabetes mellitus and the relation with its risk factors and its cardiovascular complications. Secondly, we aimed to study the effects of trends in cardiovascular diseases on the occurrence of diabetes and to estimate the effects of preventive strategies for diabetes mellitus. The first objective was addressed in parts II-IV of this thesis; the second objective is dealt with in part V.

In part II, the two main modifiable risk factors for onset of diabetes mellitus, obesity and physical activity are discussed. First, an overview of the literature was given (chapter 2). Relative risks for diabetes associated with obesity varied between studies and ranged from 1.5 to 50.7 for men and from 1.9 to 93.2 for women, with the highest risks observed for the most overweight subjects. Prevalence of overweight in The Netherlands (defined as $25 \text{ kg/m}^2 \leq \text{body mass index (BMI)} < 30 \text{ kg/m}^2$) was about 36% among men and 23% among women. The prevalence of obesity ($\text{BMI} > 30 \text{ kg/m}^2$) ranged between 4%-11% for men and women. Risk ratio's for diabetes associated with physical inactivity vary between 2.0 and 2.9 for men and 1.7 to 3.1 for women, and the more vigorous the activity, the more stronger the association. The prevalence of inactivity (defined as reporting no sporting activity) varied between 44-52%. Most studies to date have focussed on the association between physical inactivity and diabetes in middle-aged populations.

In Chapter 3, we estimated the association between physical inactivity and diabetes mellitus in an elderly population. A sample of participants of the Rotterdam Study ($n=1,016$), aged 55-75 years, not known to have diabetes mellitus, underwent an oral glucose tolerance test. Physical activity was assessed by means of a self-administered questionnaire and expressed as time spent on activities per week. Associations with the prevalence of impaired glucose tolerance (IGT) and newly diagnosed diabetes (nDM) were assessed by logistic regression analysis after adjustment for age, body mass index, waist-hip ratio, family history of diabetes, and smoking. The total amount of time spent on physical activity decreased with increasing glucose intolerance. Adjusted for main confounders, vigorous activities such as bicycling and sports showed an inverse as-

sociation with the presence of nDM. For IGT, the associations pointed in the same direction but did not reach statistical significance. These results indicate that physical inactivity and glucose intolerance are associated among older adults similar to the way they are associated among middle-aged adults.

In chapter 4, we have shown that risk factors for diabetes mellitus can be used to identify subjects who are at risk of having undiagnosed diabetes mellitus. In a subsample of the Rotterdam Study, three predictive models (PM) have been developed to identify individuals with an increased risk for undiagnosed diabetes. A sample of participants of the Rotterdam Study ($n=1,016$), aged 55 to 75 year, not known to have diabetes, completed a questionnaire on diabetes-related symptoms and risk factors and underwent a glucose tolerance test. Predictive models were developed using stepwise logistic regression analyses with absence or presence of newly diagnosed diabetes as the dependent variable and various items with a plausible connection to diabetes as the independent variables. The models were evaluated in another Dutch population-based study, the Hoorn Study ($n=2,364$), in which the participants were aged 50-74 years. Performances of the predictive models were compared by using ROC-curves. The first predictive model, PM1, contained information routinely collected by the general practitioner, while PM2 also contained variables obtainable by additional questions. The third predictive model, PM3, included variables which had to be obtained from a physical examination. Using only information normally available in the files of a general practitioner, a predictive model was developed that performed equally well to a model based on information obtained from additional questions. The simplicity of PM1 makes it easy to implement in the current health care setting.

The third part of this thesis describes how the basic elements of the diabetes epidemiology were estimated. In chapter 5, the prevalence of diabetes in The Netherlands is presented. We evaluated all the studies published in The Netherlands in order to obtain a tentative estimate of the prevalence of diabetes. Data from fifteen Dutch studies performed since 1970 were entered in logistic regression models with the presence or absence of known diabetes above the age of 30 years as a dependent variable. In order to quantify the variability among studies, the study methodology and population characteristics were chosen as independent variables. The age-standardised prevalence of known diabetes varied considerably among the studies, with a higher prevalence in surveys using self-reported data (2.7% versus 3.2%).

In chapter 6, the burden of mortality carried by diabetes mellitus in The Netherlands is quantified. A multi-state life table described the Dutch population in two states, diabetic and non-diabetic, using age and sex specific prevalence of diabetes mellitus and risks of dying for diabetic subjects. The obtained

numbers of excess deaths were compared to the number of deaths in which diabetes is registered as underlying cause of death. Uncertainty limits (UL) are based on 95% confidence limits of the published relative risks of dying. The expected mortality has been 12% among male diabetics and 18% among female diabetics, of which 2.5% and 5% respectively were attributable to diabetes. Cause of death registrations have registered diabetes as underlying cause of death in 1.8% among men and 3.4% among women. Elimination of excess mortality related to diabetes increased life expectancy at age 45 among diabetic subjects increased by 4.7 year for men and 6.3 year for women. We concluded that combining mortality data from the municipal population register with data based on epidemiological studies allows to assess the impact of diabetes. The loss in life expectancy among diabetic subjects is considerable.

Chapter 7 integrates the estimated prevalence and mortality rates in an incidence-prevalence and mortality (IPM) model to assess the incidence rate of diabetes mellitus. In condition of a steady state, incidence can be expressed as a function of age, sex, prevalence, and mortality. Prevalence and mortality data were obtained from our previous studies. Incidence increases exponentially by age, with a doubling time of 10 years for men and 9 years for women. The rate increases from 8 per 10,000 for males aged 40-44 (7 for females), to 80 per 10,000 for males aged 75-79 (85.8 for females).

In Part IV (chapter 8), the incidence-prevalence-mortality model is integrated in a cardiovascular model previously developed at the Department of Public Health of the Erasmus University Rotterdam. The basic method to arrive at age-specific cardiovascular mortality and morbidity rates was to link diabetes and cardiovascular morbidity and mortality in the causal chain of a model. This puts restrictions on the values the variables can take on. Further restrictions were obtained by making the results from the model comply with empirical observations as obtained from the literature. We have arrived at consistent estimates of the age-specific total cardiovascular morbidity and mortality rates. These estimates enabled us to answer the second objective of this thesis, which is addressed in part V (chapters 9 and 10).

In chapter 9, the impact of observed changes in cardiovascular diseases (CVD) survival on diabetes prevalence was estimated. We used the diabetes-cardiovascular model with the changes in coronary heart disease and stroke mortality and survival between 1980-83 and 1990-93 in The Netherlands for estimating the impact on diabetes epidemiology. The improved CVD survival resulted in an age-related increase in diabetes prevalence rates by a maximum in old age of 3% (women) or 5% (men). The comorbidity of coronary heart disease and diabetes showed age-related increases of 50 to 70% at older age (both sexes). Comor-

bidity of stroke and diabetes increased for women at all ages, but for men only after the age of 60. We thus concluded that while the changes in cardiovascular mortality and survival are unlikely to be a major source of increasing diabetes prevalence, but they do raise the comorbidity of cardiovascular diseases and diabetes to a considerable extent.

In chapter 10, we have estimated effects of various primary prevention scenarios on diabetes and related cardiovascular complications as well as the effect of secular trends in obesity and physical inactivity on diabetes and related cardiovascular complications. The effects of the scenarios were estimated using potential impact fractions (PIF). We defined five scenarios. Three hypothetical intervention scenarios were defined in which overweight and obesity were eliminated, physical inactivity was eliminated, or a combination of the two. The fourth scenario assumes a more realistic intervention and the last scenario estimates effect of secular trends in prevalence of obesity and physical inactivity. The three hypothetical elimination scenarios showed a large impact on diabetes incidence. Eliminating overweight and obesity resulted in a PIF of 54% for men (68% for women). CHD mortality in the total population was then reduced by 4% in men (9% in women) in the age-group 30-79 years. Translated this into absolute numbers means that some 2,500 CHD deaths in men and 2,300 CHD deaths in women would be avoided per year. The realistic scenario showed a 6% reduction in the incidence of diabetes in men (7% in women), while diabetes-related cardiovascular complications were reduced by less than 1%. In absolute numbers however, this reduction is quite substantial: about 230 CHD deaths in men and 200 in women would be avoided per year. Secular increases in both risk factors, as observed in The Netherlands, yielded an increase in the incidence of diabetes of 2.4% in men (3.5 % for women) in 10 years and of less than 1% in diabetes-related cardiovascular complications. Based on current knowledge, the realistic scenario showed a low impact on diabetes and related cardiovascular disease, although in absolute numbers the result is still substantial. However, it is clear that the question of whether or not to promote weight loss and to increase physical activity should not depend only on their effects on diabetes-related morbidity and mortality.

In summary, using modelling techniques for combining and integrating data from several sources has resulted in consistent estimates of the different morbidity and mortality rates for diabetic subjects. With this diabetes-cardiovascular model the impact on population health can be estimated for different intervention scenarios. As a second application, the disease model can be a helpful tool for evaluating hypotheses. However, it is of importance that the results of a model should always be interpreted in the light of the limitations of the data used and the assumptions made. Further research on diabetes in respect to

cardiovascular mortality, especially among elderly subjects, is necessary to further optimise the diabetes model to enhance forecasting the burden of diabetes and its complications.

Samenvatting

Diabetes mellitus is een chronische ziekte met een complexe aard door het sluipende ontstaan en de renale en andere cardiovasculaire complicaties die kunnen optreden. Verschillende risicofactoren voor diabetes die met elkaar verband houden zijn te identificeren, zoals leeftijd, overgewicht en lichamelijke inactiviteit. Door deze complexiteit is het moeilijk om de ziektelast van diabetes te schatten. Informatie over basale epidemiologische elementen zoals incidentie, prevalentie en sterfte van diabetes is schaars, incompleet of inconsistent met andere studies. Veranderingen in leefstijlfactoren, zoals obesitas en lichamelijke inactiviteit, en veranderingen in het natuurlijk beloop van complicaties van diabetes, door medische interventies bij hart- en vaatziekten, hebben een slecht te voorspellen effect op de diabetes epidemiologie.

Het doel van dit proefschrift is tweeledig: ten eerste wordt de epidemiologie van diabetes mellitus beschreven in samenhang met belangrijke risicofactoren voor diabetes en cardiovasculaire complicaties. Ten tweede bestuderen we de effecten van trends in de tijd in hart- en vaatziekten op het vóórkomen van diabetes en het effect van preventie van diabetes mellitus op de cardiovasculaire complicaties. Doelstelling 1 is behandeld in deel II tot en met IV, de tweede doelstelling wordt beantwoord in deel V.

Deel II bespreekt de twee belangrijkste beïnvloedbare risicofactoren (overgewicht en lichamelijke inactiviteit) voor het ontstaan van diabetes mellitus. Hoofdstuk 2 bevat een literatuuroverzicht. Verschillende studies rapporteren relatieve risico's voor overgewicht op het ontstaan van diabetes. De relatieve risico's varieerden van 1,5 tot 50,7 voor mannen en 1,9 tot 93,2 voor vrouwen, mede afhankelijk van de mate van overgewicht. In Nederland heeft ongeveer 36% van de mannen en 23% van de vrouwen overgewicht (gedefinieerd als een quetelet index tussen de 25 en 30 kg/m²). Obesitas (gedefinieerd als een quetelet index boven de 30 kg/m²) komt voor onder 4-11% van zowel mannen als vrouwen. De studies naar de relatie lichamelijke inactiviteit en het ontstaan van diabetes mellitus rapporteerden relatieve risico's variërend tussen 2,0 en 2,9 voor mannen en tussen 1,7 en 3,1 voor vrouwen. Hoe zwaarder de lichamelijke activiteit, des te minder kans op het ontstaan van diabetes. De prevalentie van lichamelijke inactiviteit in Nederland (gedefinieerd als het niet beoefenen van sport) varieerde tussen de diverse studies van 44 tot 52%.

Bijna alle studies naar lichamelijke inactiviteit en diabetes zijn uitgevoerd onder personen tot en met 50 jaar. In hoofdstuk 3 hebben we het effect van lichamelijke inactiviteit op het ontstaan van diabetes bij personen bestudeerd boven de 50 jaar in een steekproef uit de ERGO populatie. In onze studie hebben 1,016 personen tussen de 55 en 74 jaar, zonder diagnose "diabetes" voor aanvang van de studie, een glucose tolerantie test ondergaan. Lichamelijke

activiteit, uitgedrukt in tijd per week besteed aan lichamelijke activiteit, is gemeten door middel van een vragenlijst. Met behulp van logistische regressie technieken hebben we het verband tussen gestoorde glucose tolerantie (IGT) en net gediagnosticeerde diabetes (nDM) geschat, waarbij gecorrigeerd is voor de versturende variabelen leeftijd, quetelet index, middel-heup omtrek, het hebben van familieleden met diabetes en roken. De analyse liet zien dat de totale tijd gespendeerd aan lichamelijke activiteit af nam bij personen met glucose intolerantie. Met name de zwaardere lichamelijke activiteiten zoals fietsen en sporten lieten een verband zien met een lagere kans op het hebben van nDM. Deze studie onderbouwt de hypothese dat het verband tussen lichamelijke inactiviteit en glucose intolerantie eveneens geldt bij mensen van middelbare en oudere leeftijd.

Hoofdstuk 4 toont hoe risicofactoren voor diabetes kunnen worden gebruikt bij het identificeren van personen met een hoog risico op diabetes zonder diagnose. Daartoe hebben we in dezelfde steekproef uit de ERGO studiebevolking drie predictiemodellen ontwikkeld om personen met een hoog risico op nog niet bekende diabetes op te sporen. Alle 1,016 participanten hebben een vragenlijst ingevuld over met diabetes gerelateerde symptomen en risicofactoren en hebben een glucose tolerantie test ondergaan. De predictiemodellen zijn vervolgens getest in een andere Nederlandse studie populatie, de Hoorn Studie. De testkarakteristieken van de modellen zijn vergeleken met behulp van ROC-curves. Het eerste predictiemodel bevatte alleen informatie die routinematig door de huisarts verzameld wordt, het tweede predictiemodel bevatte daarnaast informatie verkregen door aanvullende vragen aan de patiënt, het derde predictiemodel bevatte ook informatie verkregen door middel van lichamelijk onderzoek. Uit de analyse bleek dat het eerste model even goed voorspelde als de anderen. Door zijn eenvoud, zou bij implementatie in de huidige gezondheidszorg setting de voorkeur gegeven moeten worden aan predictiemodel 1.

In het derde deel van dit proefschrift wordt beschreven hoe de drie basis-elementen van diabetes epidemiologie zijn geschat. Hoofdstuk 5 presenteert de prevalentie van diabetes mellitus in Nederland. Hiertoe evalueerden we alle studies over de prevalentie van diabetes die na 1970 zijn uitgevoerd. Gegevens van 15 studies zijn gebruikt in een logistisch regressie model waarbij aanwezigheid van diabetes de afhankelijke variabele is. Methodologie van de studie en karakteristieken van de populatie zijn de onafhankelijke variabelen. De studies waren grofweg onder te verdelen in twee groepen: een groep waarbij de prevalentie van diabetes is bepaald in huisartsenpraktijken en een groep waarbij de diabetes prevalentie bepaald is in een survey door zelfrapportage. De prevalentie van diabetes in Nederland in de leeftijdsgroep 30-80 jaar is op basis van deze huisartsenstudies 2,7% en op basis van de surveys wat hoger: 3,2%.

In hoofdstuk 6 is de sterfte van diabetes in Nederland geschat door bevolkingsstatistieken te combineren met gegevens uit epidemiologische studies. Hiertoe is gebruik gemaakt van sterftetafeltechnieken. De (meerdimensionale) sterftetafel gebruikt in deze studie, bestaat uit twee delen: een diabetes en een niet-diabetes sterftetafel. Deze opsplitsing is verkregen met behulp van de leeftijdsspecifieke prevalentie van diabetes zoals geschat in hoofdstuk 5 en relatieve risico's op sterfte door diabetes, afkomstig uit de literatuur. De berekende sterfte onder diabeten bedraagt 12% bij de mannen en 18% bij de vrouwen, waarbij respectievelijk 2,5% en 5% door diabetes zelf zou zijn veroorzaakt. In de doodsoorzakenstatistiek wordt diabetes bij 1,8% van de mannen en 3,4% van de vrouwen geregistreerd als doodsoorzaak. Indien de oversterfte van diabetes zou worden geëlimineerd zou de levensverwachting van mannen met diabetes op leeftijd 45 toenemen met 4,7 jaar en voor vrouwen zou de levensverwachting stijgen met 6,3 jaar.

In hoofdstuk 7 zijn de geschatte prevalentie- en sterftecijfers geïntegreerd in een incidentie-prevalentie-sterfte (IPM) model om de incidentie van diabetes te schatten. Aannemende dat de prevalentie en sterfte niet veranderen met de tijd (stationair zijn), kan de incidentie uitgedrukt worden als een functie van leeftijd, prevalentie en sterfte. De aldus berekende incidentie stijgt van 8 per 10.000 mannen (7 voor vrouwen) in de leeftijd 40-44 jaar tot 80 per 10.000 mannen (86 voor vrouwen) in de leeftijd 75-79 jaar.

In deel IV (hoofdstuk 8) is het incidentie-prevalentie-sterfte model van diabetes geïntegreerd met een al eerder op het instituut ontwikkeld hart- en vaatziekten model. We hebben randvoorwaarden opgelegd door de uitkomsten van het model te laten overeenstemmen met waarnemingen verkregen uit de literatuur. Aldus hebben we een consistente schatting kunnen maken van de leeftijds-specifieke cardiovasculaire morbiditeit en sterfte onder diabeten. Deze schattingen maakten het mogelijk om doelstelling 2 van dit proefschrift te beantwoorden. Dit is beschreven in het vijfde deel (hoofdstuk 9 en 10).

Hoofdstuk 9 schat het effect van geobserveerde veranderingen in sterfte aan hart- en vaatziekten in de bevolking op de prevalentie van diabetes. Het gebruikt het hierboven ontwikkelde diabetes-cardiovasculaire model, waarbij de veranderingen in sterfte aan coronaire hartziekte en beroerte in de periode 1980-1983 en 1990-1993 in Nederland de veranderingen in diabetes prevalentie en co-morbiditeit bepaalt. De dalende sterfte aan hart- en vaatziekten leidt in ons model tot een stijging in diabetes prevalentie met een maximum van 3% voor vrouwen op oudere leeftijd en 5% voor mannen. De co-morbiditeit van diabetes en coronaire hartziekte toont een stijging van 50-70% op oudere leeftijd voor zowel mannen als vrouwen. Co-morbiditeit van diabetes met beroerte stijgt op

alle leeftijden voor vrouwen, voor mannen is alleen een stijging te zien boven de 60 jaar. Op basis van deze analyses concluderen we dat de veranderingen in hart- en vaatziekten geen belangrijke bron zijn voor een stijging in diabetes prevalentie, maar wel een belangrijke stijging in de co-morbiditeit van hart- en vaatziekten en diabetes veroorzaken.

Hoofdstuk 10 schat het effect van primaire preventie scenario's op diabetes en aan diabetes gerelateerde hart- en vaatziekten. Daarnaast is ook het effect geschat van een toenemende prevalentie van overgewicht en lichamelijke inactiviteit op diabetes en aan diabetes gerelateerde hart- en vaatziekten. De effecten van de verschillende scenario's zijn berekend met behulp van potentiële impact fracties (PIF). We hebben 5 scenario's gedefinieerd. Drie, hypothetische, interventiescenario's zijn gedefinieerd waarbij het voorkomen van overgewicht is geëlimineerd in de bevolking, het voorkomen van lichamelijke inactiviteit ofwel beiden tegelijkertijd. Een vierde scenario omvat een meer realistische reductie in de prevalentie van beide risicofactoren en het vijfde scenario schat het effect van een toename in de prevalentie van zowel overgewicht als lichamelijk inactiviteit. De drie hypothetische scenario's geven een grote reductie in diabetes incidentie te zien. Het elimineren van overgewicht bijvoorbeeld, zal de incidentie van diabetes met 54% voor mannen en 68% voor de vrouwen reduceren. Hart- en vaatziekten (HVZ) sterfte in de totale populatie zou in dit scenario afnemen met 4% voor mannen en 9% voor vrouwen. In absolute aantallen betekent dit 2,500 HVZ-doden onder mannen en 2,300 HVZ-doden onder vrouwen minder per jaar. Het realistische interventie scenario laat de diabetes incidentie met 6% mannen (7% voor vrouwen). De aan diabetes gerelateerde HVZ-sterfte daalt dan met minder dan 1%. In absolute aantallen is dit nog steeds substantieel: per jaar zullen ongeveer 230 HVZ-doden onder de mannen en 200 HVZ-doden onder de vrouwen worden voorkomen. De stijging in prevalentie van de twee risicofactoren, zoals beschreven in de literatuur, veroorzaakt een toename in de incidentie van diabetes met 2,4% voor mannen en 3,5% voor vrouwen per 10 jaar. We besluiten dat het effect van een realistisch scenario dat overgewicht en lichamelijke inactiviteit doet dalen, klein is, alhoewel in absolute aantallen nog steeds een substantieel aantal sterfgevallen voorkomen zouden worden. De vraag of de overheid wel of niet moet investeren in het stimuleren van gewichtsverlies en toenemen van lichamelijk activiteit moet echter niet alleen afhangen van het effect op diabetes gerelateerde ziekte en sterfte.

Samenvattend stellen we dat consistente schattingen van de variabelen die de epidemiologie van diabetes mellitus beschrijven, kunnen worden verkregen met behulp van statische en modelmatige technieken die data van verschillende bronnen combineren. Het aldus verkregen model dat diabetes mellitus en HVZ beschrijft, kan vervolgens de effecten van verschillende interventiescenario's

schatten (hoofdstuk 10) of hypothesen toetsen (hoofdstuk 9). Onzekerheden omtrent gegevens en aannames beperken de interpretatie van de resultaten. Verder onderzoek naar diabetes in samenhang met hart- en vaatziekten, met name onder ouderen, is noodzakelijk om het diabetesmodel verder te verbeteren en de voorspellingen omtrent de ziektelast van diabetes te toetsen.

DANKWOORD

Zoals zo velen al terecht hebben opgemerkt, een proefschrift schrijven doe je nooit alleen (al kan je je af en toe gedurende het onderzoeksproces best eenzaam en verlaten voelen). Gedurende mijn onderzoekstijd ben ik door diverse mensen op de rails gezet of gehouden.

Allereerst wil ik mijn promotores noemen, Paul van der Maas en Daan Kromhout. Beste Paul, als drukbezet man heb je niet altijd zoveel tijd als je zou willen, maar je gawe om in die beperkte tijd toch een relevante bijdrage aan het onderzoek te leveren, maakt veel goed. Daarnaast kon ik altijd bij je terecht voor een persoonlijk woord, wat ik erg gewaardeerd heb. Beste Daan, fysiek was je een promotor op afstand, maar voor de begeleiding was dat gelukkig niet het geval. Bedankt voor het lezen van alle concepten. Zelfs tot het allerlaatst heb je tijd voor me vrijgemaakt.

Mijn co-promotores Edith Feskens en Jan Barendregt hebben de belangrijkste bijdrage geleverd in alle mogelijke fasen van het onderzoek en zijn dan ook terecht co-promotor. Beste Edith, ik ben ontzettend blij dat ik met je heb kunnen samenwerken. Als geen ander heb je me gestimuleerd om te blijven geloven in het onderzoek en je kennis over de diabetes epidemiologie was onontbeerlijk. Daarnaast wist je het aangename goed met het minder aangename te combineren. Hopelijk kunnen we na mijn promotie weer een keer op een terrasje zitten met een wit-biertje. Zonder Jan Barendregt was dit proefschrift in deze vorm niet geschreven. Beste Jan, je hebt grotendeels het modeltechnische deel van dit proefschrift vormgegeven en met je kritische blik vele tussentijdse resultaten terecht als ongeloofwaardig bestempeld. De keren dat ik bij je langs ben geweest voor, wat ik noemde een "domme vraag", zijn niet te tellen, maar je gaf elke keer geduldig antwoord. Daarnaast wist je me heel vaak op te monteren als ik weer eens in zak en as zat over het model.

Je zou denken dat ik met twee promotoren en twee copromotoren wel genoeg begeleiders had. Toch kan ik nog een vijfde begeleider opnoemen van wie ik veel geleerd heb: Luc Bonneux. Beste Luc, soms werd ik door wanhoop gedreven door de commentaren die je gaf op het onderzoek, maar het is er in alle gevallen beter van geworden. Samen met Jan waren jullie wat je noemt "een stel apart" en ik heb dan ook heel wat met jullie te stellen gehad. Maar, zonder jullie bijdrage was ik nooit gepromoveerd.

Een begeleider van het eerste uur was Dirk Ruwaard, toen zelf druk bezig met het schrijven van een proefschrift en het VTV. Ondanks die drukte heb je toch tijd gevonden om me in te wijden in de diabetes epidemiologie, mijn dank

hiervoor. Een ander die me ingewijd heeft binnen "de wereld van het diabetes-onderzoek" is Ronald Stolk. Beste Ronald, ik heb met veel plezier met je samengewerkt. De twee artikelen zijn daar een mooi resultaat van.

Naast al die slimme mannen en die ene slimme vrouw, zijn er nog twee slimme vrouwen geweest die me geholpen hebben bij het onderzoek: Wilma Nusselder en Perla Marang-van der Mheen. Beste Wilma, bedankt voor al je lessen in de sterftetafelmethodologie. Beste Perla, ik heb de vele gesprekken over het onderzoek in al zijn facetten erg fijn gevonden en de herkenning die we bij elkaar vonden was vaak een troost in moeilijke tijden.

Mooie herinneringen heb ik aan de vele internationale diabetes congressen en niet te vergeten de diabetes cursus in Cambridge. Dear Nick Wareham, Desmond Williams, Amanda Adler, Paivi Lempianen and Tor Claudi, thanks for all the good moments we shared. I still hope we can practise our synchronised swimming exercise one more time.

Werken op het instituut Maatschappelijke Gezondheidszorg (iMGZ) kan ik iedereen aanraden. Ik heb er een prachtige tijd gehad (en wie weet wat er nog gaat komen). Naast een wetenschappelijk klimaat, was er altijd veel ruimte voor sociale contacten en betrokkenheid onderling. Ook de creatieve expressie kwam aan bod op MGZ middels de vele stukjes die bedacht en geoefend moesten worden voor eenieder die promoveerde, met als hoogtepunt het cabaret tijdens het jubileum van MGZ. Ik ben trots dat ik hieraan een bijdrage heb mogen leveren. Ik kan niet iedereen noemen, maar een paar mensen wil ik echt wel even vermelden: Barry de Wit en Jolande te Griffel: met name jullie hulp bij het regelen van de financiën bij de vele congresbezoeken was onontbeerlijk. Voor de secretariële ondersteuning wil ik Else van den Engel en Nellie van der Hoeven bedanken. Ook mijn kamergenoten verdienen hier wel een aparte vernoeming. Kennelijk ben ik een moeilijke kamergenoot want ik heb vele kamergenoten "versleten": Bowine Michel, Loes Pijnenborg, Adrienne Cavelaars, Joke ter Harmsel en Arjen van Esch. In de laatste moeilijke loodjes waren mijn huidige kamergenoten Veerle Coupé en Johan de Koning toch voornamelijk slachtoffer van mijn gestress. Veerle, je kan nu weer terugkomen uit Denemarken, het is voorbij. En Johan, vanaf nu zal ik proberen met meer dan 1 ding tegelijk bezig te zijn. Een fenomeen op MGZ waren toch de zogenaamde "mutsen" en ik ben er trots op één van hen te zijn. Lieve Elles, Feikje, Adrienne, Xandra en Petra, jullie zijn heerlijke vriendinnen en ik moet zeggen: ik mis jullie op MGZ.

De inhoud van het boekje is een ding, de omslag is toch net zo belangrijk. Gelukkig heeft Christine Hooft daar haar hoofd over gebogen. Lieve Chris, het is prachtig geworden!

Lieve Xandra en Aletta, mijn paranimfen, fijn dat jullie me willen ondersteunen bij het echte allerlaatste loodje.

Rest mij nu nog de drie belangrijkste personen uit mijn leven te bedanken. Lieve papa en mama: dank jullie wel voor het feit dat ik heb kunnen studeren, maar vooral dat jullie er altijd voor me zijn! Lieve, lieve Carl: wat ben ik blij met jou!

CURRICULUM VITAE

Caroline Baan was born on September 2, 1969 in Delft. She graduated in 1987 at the Scholengemeenschap Hugo Grotius in Delft (secondary school). In the same year she started to study at the University of Utrecht. In 1993 she graduated in Biology and started to work at the Gewestelijke Gezondheidsdienst Brabant-Noordoost in Oss. During this period she wrote the report "Gezondheidsprofiel Streekgewest Brabant-Noordoost". In 1994 she started to work at the Department of Public Health at the Erasmus University Rotterdam and at the National Institute of Public Health and the Environment in Bilthoven. During this period, besides working at the studies described in this thesis, she was active in all PhD committies (the MAIOR, IFAR and the LAIOO). In 1995 she obtained her MSc-degree in Health Services Research of the Netherlands Institute of Health Sciences (NIHES). She obtained specific knowledge in diabetes epidemiology by participating in the "Sixth Cambridge Seminar on the Epidemiology and Public Health Aspects of Diabetes mellitus" and in the "Advanced course of epidemiology of diabetes mellitus" in Driebergen. In the period November 1998 to May 1999, beside finishing her thesis, she worked at the Department of Social Medicine at the University of Amsterdam. During this period, she was involved in the final phase of the Biomed-project "Public Health models" (under supervision of prof. dr. LJ Gunning-Schepers). Since may 1999 she is working on a project on the evaluation of screening programmes at the Department of Public Health.

