Opportunities for diabetes prevention

risk factors for diabetes and cost-effectiveness of interventions

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Mogelijkheden voor diabetespreventie

risicofactoren voor diabetes en kosteneffectiviteit van interventies

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ABSTRACT

Diabetes is already one of the most common chronic diseases in the Dutch population and a substantial further increase in the number of people with diabetes is expected in the near future. A large part of the burden of diabetes can be ascribed to the cardiovascular complications of diabetes which affect quality of life, as well as life expectancy of the patients. In this thesis we explore the opportunities to reduce the future burden of diabetes and cardiovascular diabetes complications in the Dutch population, through prevention. These opportunities depend on the existence of modifiable risk factors for diabetes and the availability of interventions aimed at reducing the incidence of diabetes or diabetes complications. In this thesis we consider the role of weight change, alcohol consumption and smoking as risk factors for diabetes and the cost-effectiveness of preventive interventions in different target populations.

Body Mass Index (BMI) is acknowledged as an important modifiable risk factor for diabetes but the role of weight change is not so clear. We showed that, conditional upon initial weight, people who gained weight, had an increased risk of diabetes, compared to persons with relatively stable weight. If adjusted for initial BMI, 5-years weight change was a significant risk factor for diabetes (OR 1.08, 95% CI: 1.04, 1.13 per kg weight change). There was no association between weight change and diabetes incidence, if the association was adjusted for attained BMI (OR 0.99, 95% CI 0.94, 1.04 per kg weight change). We concluded that weight change appears to have no effect on diabetes incidence, beyond its effect on attained BMI.

In previous studies, smoking has been reported to increase diabetes risk, while for alcohol consumption the lowest risk for diabetes is generally observed for people who drink moderately. We assessed the associations between these, potentially modifiable, risk factors and diabetes incidence in a Dutch population. We found a u-shaped association between alcohol consumption and diabetes incidence in Dutch women, with the lowest risk for moderate drinkers (1 or 2 drinks per day). We found no evidence for a significant association between alcohol consumption and diabetes incidence in Dutch men. Smoking more than 10 cigarettes per day tended to increase diabetes risk in both men and women, but the associations were not statistically significant.

There is substantial evidence that lifestyle interventions focused at improved diet and physical exercise are cost-effective in persons at high risk of developing diabetes. However, the cost-effectiveness of these interventions in other target populations was relatively unknown. We explored the potential long-term health effects and cost-effectiveness of two types of lifestyle interventions: a community-based intervention, targeted at the general Dutch population, and an individual-based intervention, targeted at obese Dutch adults. The long-term effects of these interventions were simulated with a computer-based model: the Chronic Diseases Model (CDM). We showed that the 20-year cumulative incidence of diabetes could be reduced by 0.5-2.4% through large-scale implementation of a community-based intervention, and by 0.4-1.6%, through an individual based intervention for obese adults. Both interventions were projected to reduce lifetime diabetes-related medical costs, but total health care costs increased. The cost-effectiveness ratios ranged from €3,100 to €3,900 per quality adjusted life year (QALY) for the community-based intervention, and from

€3,900 to €5,500 per QALY for the individual-based intervention, which means that both interventions are cost-effective according to general standards.

We also assessed the potential health effects and cost-effectiveness of seven selected lifestyle interventions for Dutch diabetes patients. Again, long-term effects were simulated with the CDM. There was a large variation in effectiveness between the seven interventions. The reductions in cumulative lifetime incidence of cardiovascular complications among participants ranged from 0.1% to 6.1%. The most effective intervention was a two year structured counseling program, aimed to increase physical activity in inactive diabetes patients. The intervention costs ranged from €124 to €584 per participant, and the cost-effectiveness ratios ranged from €10,000 to €39,000 per QALY. The impact of uncertainty in intervention costs, intervention effects, and long-term maintenance of effects, were quantified with probabilistic sensitivity analyses. These analyses revealed, that four out of seven interventions had a high probability to be very cost-effective.

Besides lifestyle, appropriate medication contributes to the prevention of complications in diabetes patients. Guidelines for cardiovascular management recommend lipid lowering treatment for nearly all patients with diabetes. However, in Dutch current practice (in 2007) 'only' about 1 out of 3 patients received this treatment. We modeled the long-term effects on cardiovascular complications in the Dutch diabetes population, under the assumption that all patient would use lipid-lowering medication (statins). We showed that treatment for all patients (compared to current care) reduced the life-time cumulative incidence of cardiovascular complications in the Dutch diabetic population by approximately seven percent. With more realistic assumptions about effectiveness and participation, the cumulative incidence of cardiovascular complications decreased by approximately two percent.

We conclude that lifestyle interventions can be cost-effective in divers target populations, including diabetes patients. Large-scale implementation of these interventions is justified, and required in order to reduce the future burden of diabetes. However, since the impact on population health, achieved through these interventions, is expected to be moderate, additional research should aim to improve currently available interventions. Simultaneously, opportunities for alternative approaches to the prevention of diabetes and its complications should be further explored.

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Chapter 1. General introduction

GENERAL INTRODUCTION

During the last decades, the prevalence of diabetes has increased worldwide, and a further increase is expected for the future [1]. In the Netherlands, the prevalence of diagnosed diabetes increased from just over 400,000 in 2000 to approximately 670,000 in 2007 [2]. Diabetes affected about 4% of the Dutch population in 2007, but is expected to affect about 8% in 2025 [2]. The enormous increase in diabetes prevalence is partly explained by demographic developments such as population growth, aging, and improved survival, as well as by improved early diagnoses. Another part results from unfavorable developments in lifestyle habits, such as a decrease in physical activity, poor diets, and an associated increase in the prevalence of obesity. The burden of diabetes is high due to the frequent, severe complications associated with diabetes, which strongly affect quality of life and life expectancy of the patients as well as the health care costs related to diabetes [3-9]. To gather more insight in what can be done to minimize the future burden of diabetes in the Dutch population, the opportunities to prevent diabetes and its complications should be further explored. Therefore, extensive knowledge is required about modifiable risk factors for diabetes and its complications, and the (cost)effectiveness of available interventions. The focus in this thesis is on prevention of *type 2* diabetes and its *cardiovascular* complications, because 85%-90% of diabetes patients have type 2 diabetes and cardiovascular complications are the main cause of increased mortality among diabetes patients (see textbox).

Diabetes prevention

In this thesis, diabetes prevention refers to the prevention of diabetes in persons who do not yet have the disease (universal, selective or indicated prevention) or to the prevention of complications in diabetes patients (care-related prevention, see textbox for definitions). Opportunities for diabetes prevention depend on the existence of risk factors and the extent to which these risk factors can be modified. The existence of risk factors is generally explored in observational cohort studies, while intervention studies are required to examine if risk factors can be modified and if risk factor modification is actually followed by a lower incidence of diabetes or diabetes complications. Prevention can be considered successful if, on a population or group level, the number of new diabetes cases or complications is lower than would have been expected if preventive measures would not have been applied. In addition, prevention can be considered successful if diabetes or complications are delayed, or if (quality adjusted) life-expectancy improves.

The next paragraphs provide a brief overview of the current knowledge of the opportunities to prevent diabetes and cardiovascular diabetes complications. Subsequently, the general aim and main research questions of this thesis will be defined and the content outlined. Background information about diabetes and its complications and the definitions of prevention as used in this thesis are given in the textbox on the next page.

Diabetes mellitus
Diabetes mellitus is a chronic disease which is characterized by a disturbance in the metabolism of glucose. The body needs insulin, a hormone produced by the pancreas, to absorb glucose from the blood and to convert it into energy. Persons with diabetes have increased levels of glucose in their blood as a result of either an absolute (type 1 diabetes) or relative (type 2 diabetes) deficiency of insulin. The absolute insulin deficiency in type 1 diabetes results from an inability of the pancreas to produce sufficient insulin. Type 1 diabetes is generally diagnosed before the age of 30 years. The relative deficiency in type 2 diabetes results from an impaired ability of body tissues to respond properly to insulin in combination with insufficient compensatory insulin production. Type 2 diabetes is the most common type of diabetes, about 85-90% of persons with diabetes has type 2 diabetes. This type is generally first diagnosed in adults. Diabetes is diagnosed based on measurement of the level of blood glucose. This level can be determined irrespective of the time of the last meal (random glucose), after 8 hours fasting (fasting glucose) or two hours after an oral glucose tolerance test (2-hour glucose). According to Dutch guidelines, measurement of blood glucose should be performed once every three years in persons > 45 years at increased risk for diabetes or if a person presents with diabetes-related symptoms such as excessive thirst, frequent urination, unintentional weight loss, blurred vision or fatigue. Because these symptoms can be mild, vague or even absent, diabetes may initially be undiagnosed for several years.

Impaired fasting glucose and impaired glucose tolerance
Persons with high glucose levels just below the threshold for diabetes have 'impaired fasting glucose' (IFG) if only fasting levels are high or 'impaired glucose tolerance' if 2-hour glucose levels are (also) high. Persons with IFG or IGT have increased risks for diabetes. In the Dutch Hoorn study, the 6-year progression rate to diabetes was 9%, 33% and 65% for persons with IFG, IGT or both respectively [10]. Due to their high risk, these persons constitute an important target group for preventive interventions.

Diabetes complications
Acute complications emerge if, at a certain moment, the level of blood glucose is extremely high (hyperglycemia) or too low (hypoglycemia). At the longer term, the continued high concentration of glucose in the blood causes damage to the blood vessels and the nerves, which may eventually lead to serious chronic complications. Complications that affect the eyes (retinopathy), kidneys (nephropathy) or nerves (neuropathy) are called the micro vascular complications. Coronary artery disease, peripheral arterial disease and stroke are known as the macro vascular or cardiovascular complications of diabetes. The risk to develop cardiovascular disease is about two times higher in persons with diabetes than in persons without diabetes [5, 6]. Cardiovascular complications are the main cause of increased mortality among diabetes patients [5].

Definitions of prevention as used in this thesis, based on definitions by CVZ [11]:
Universal prevention targets the general population without increased risk for diabetes and aims to reduce the risk to develop (risk factors) for diabetes.

Selective prevention targets (high) risk groups and aims to reduce the risk to develop (risk factors) for diabetes in these specific groups by conducting specific local, regional or national prevention programs (includes screening).

Indicated prevention targets individuals without diagnosed diabetes but with increased risk or symptoms of diabetes. Indicated prevention aims to reduce the risk of developing diabetes or further health damage by offering intervention or treatment.

Care-related prevention targets individuals with diagnosed diabetes and is an essential and integral part of high quality care. It aims to reduce the health burden of diabetes, and to reduce the risk of developing diabetes complications.

Opportunities for the prevention of diabetes

There are several potentially modifiable risk factors for diabetes. Observational studies have consistently shown strong associations between obesity measures and the incidence of diabetes [12-17]. Body Mass Index (BMI) is often used as a measure of overweight in epidemiological research. With every one unit increase in BMI, corresponding to an increase in body weight of approximately 3kg in adults of average height, the risk to develop diabetes increases with about 20% [18]. In addition, body fat situated around the waist increases diabetes risk [19]. Physical activity and a healthy diet are important to control and maintain a healthy weight but they are also independent determinants of diabetes [12;15;20-23]. Other potentially modifiable lifestyle factors that have been associated with diabetes are smoking, alcohol -, and coffee consumption [24-26].

There is substantial evidence that lifestyle interventions, targeted at obesity, physical activity and a healthy diet, can improve body weight and cardiovascular risk factors in overweight and obese persons [27], and that these interventions can successfully reduce diabetes incidence in persons with IGT [28-34], even at longer term follow-up [35;36]. Several studies have shown that these interventions are cost-effective compared to placebo or alternative (pharmacological) interventions [37-40]. Since lifestyle interventions are safe and at least equally effective as most preventive pharmacological treatments [41-43], lifestyle modification should be the main, preferred (first) strategy in the prevention of diabetes.

Although weight reduction appears to be the main determinant of the success of lifestyle interventions [44], the role of weight change as a risk factor for diabetes, independent from the level of body weight remains unclear [45;46]. It is also not clear if additional lifestyle habits such as smoking or alcohol consumption need to be considered in the prevention of diabetes. Another issue that remains to be addressed is how lifestyle interventions may affect long-term health outcomes such as cardiovascular disease incidence and quality adjusted life expectancy [36;47].

In contrast to the convincing evidence for efficacy and cost-effectiveness of indicated prevention of diabetes for persons at high risk, universal and selective prevention of diabetes, as well as lifestyle counseling to patients at low risk, have been conducted with varying results [48-53] and information about the cost-effectiveness of these interventions is limited [54;55]. Therefore, the cost-effectiveness of lifestyle interventions for persons at different levels of diabetes risk should be further explored.

Opportunities for the prevention of cardiovascular diabetes complications

Most risk factors for diabetes are also risk factors for cardiovascular disease (CVD). BMI [56;57], waist circumference [57], physical activity [58-61] and smoking [62-64] have all been associated with the incidence of CVD. It has been shown that about half of the excess risk for coronary heart disease related to overweight, is independent of blood pressure and the level of cholesterol [65]. The association between alcohol consumption and CVD seems to be J-shaped, with the lowest risk for persons with moderate alcohol consumption [66;67]. Moderate alcohol consumption, compared to not drinking, is also associated with a lower incidence of CHD and reduced mortality in diabetic populations [68]. Blood pressure, cholesterol- and blood glucose levels are all important risk factors for CVD and, together with age and smoking,

their contribution to CVD risk is quantified in several cardiovascular risk assessment scores [69,70].

Several trials in persons with diabetes have shown that CVD risk factors can be successfully modified through lifestyle interventions [71-74]. However, these trials are generally too short to show reductions in the incidence of CVD. On the contrary, trials that applied medical treatments have shown substantial reductions in he incidence of CVD and there is some evidence for improved survival [75]. Antihypertensive treatment and cholesterol lowering treatment can effectively reduce the incidence of CVD, both in persons with and without diabetes [76-78]. Intensive glucose lowering treatment in diabetes patients is generally associated with a moderate reduction in major CVD complications [79], although very strict glucose lowering may not to be beneficial in specific populations [80]. Antihypertensive, lipid-lowering and glucose lowering treatments for diabetic patients (care-related prevention) appear to be cost-effective [54;81].

Although self-management (including a healthy lifestyle) is considered to be an essential part of diabetes treatment, there is little information about which lifestyle modification strategies are the most effective. It is also unclear how short-term improvements in cardiovascular risk factors, achieved through lifestyle interventions, may translate into improved long-term outcomes for cardiovascular complications or survival. In addition, the cost-effectiveness of lifestyle interventions for diabetic patients is relatively unknown [82;83]. With respect to pharmaceutical treatments, it is unknown to what extent, on a population level, improved adherence to treatment guidelines could improve long-term health outcomes of Dutch diabetic patients.

Aim of this thesis

The general aim of this thesis is to explore opportunities to reduce the future burden of diabetes and its cardiovascular complications in the Dutch population through prevention. Therefore the three main questions addressed in this thesis are:

1) Are weight change, alcohol consumption and smoking associated with diabetes incidence in a Dutch population?

2) To what extent can preventive lifestyle interventions reduce the future incidence of diabetes in the Netherlands and are these interventions cost-effective?

3) To what extent can care-related preventive interventions reduce the future incidence of cardiovascular diabetes complications in the Netherlands and are these interventions cost-effective?

Methods

Information from three related Dutch observational studies, the Monitoring Project on Cardiovascular Disease Risk Factors (MP-CVDRF study), the Monitoring project on Chronic Diseases Risk Factors (MORGEN study) and the Doetinchem Cohort Study are used to assess research question 1. Although questions 2 and 3 could, theoretically, be examined with large long-term intervention studies, this would require tremendous efforts, budgets and many years of patience. Therefore, a computer-based simulation model, the Dutch Chronic Diseases Model (CDM) [84] is used instead. A brief general description of the observational studies and the Chronic Diseases Model is provided below.

Monitoring Projects

The MP-CVDRF study was conducted between 1987 and 2002 in order to monitor the prevalence of cardiovascular risk factors in the Dutch, general population. Participants were 20-59 yrs old men and women selected from three Dutch towns: Doetinchem, Amsterdam and Maastricht. About 12,000 participants from each town visited the municipal health service where they filled out questionnaires and underwent a physical examination. The MP-CVDRF study was followed by the MORGEN study, a quite similar but extended study conducted between 1993 and 1997. In Doetinchem only, a subset of participants from the MP-CVDRF study was re-invited to participate. These re-invited participants (N=7,769) were subsequently followed in the Doetinchem Cohort Study [85], a cohort with repeated measurements every five years. Repeated measurements are not available for MP-CVDRF participants from Amsterdam and Maastricht because MORGEN participants in these towns were selected from new random samples drawn from the general population. However, follow-up data is available for specific outcomes such as diabetes.

The Chronic Diseases Model

The CDM is a Markov-type state transition model, developed at the Dutch National Institute for Public Health and the Environment (RIVM) [84]. The CDM comprises different lifestyle and biomedical risk factors and many chronic diseases including diabetes and CVD. By combining relevant data from different sources in a consistent way, the model can simulate developments over time of demography, risk factor prevalence, disease incidence and mortality in the Dutch population. Simulations can also be confined to the Dutch diabetic population. The model is well suited to explore the potential consequences of different kinds of interventions if implemented in the Dutch (diabetic) population.

Due to the health care costs and utility weights incorporated in the CDM, the model can also be used to generate cost-effectiveness ratios of interventions. The cost-effectiveness analyses in the CDM are performed from a health care perspective; only health related effects, expressed in quality adjusted life years (QALYs) and costs incurred by the health care system are included. Health care costs are intervention costs and medical costs for the treatment of chronic diseases. The CDM includes costs for illnesses, such as dementia, which are unrelated to the risk factors targeted by the intervention, but for which expenditures may increase, especially if the intervention prolongs life [86]. A preventive intervention with a CER below €20.000 per QALY is generally considered to be (very) cost-effective [87, 88].

Outline of this thesis

The first main question of this thesis 'Are weight change, alcohol consumption and smoking associated with diabetes incidence in a Dutch population?' is addressed in Chapters 2 and 3. Chapter 2 explores the role of weight change as a risk factor for diabetes incidence, independent from the level of attained BMI and Chapter 3 explores the (joint) associations between alcohol, smoking and diabetes incidence. Chapter 4 deals with the second main question: 'To what extent can preventive lifestyle interventions reduce the future incidence of diabetes in the Netherlands and are these interventions cost-effective?'. It explores the potential health effects and the cost-effectiveness of large-scale implementation of two

lifestyle interventions aimed to prevent diabetes: a community-based intervention for the general population (universal prevention) and an intensive individual-based intervention for obese adults (indicated prevention). The final main question 'To what extent can care-related preventive interventions reduce the future incidence of cardiovascular diabetes complications in the Netherlands and are these interventions cost-effective?' is addressed in Chapters 5 and 6. Chapter 5 explores the (cost)effectiveness of seven lifestyle interventions for diabetic patients, if implemented in the Dutch population, as well as the impact of uncertainty in model input parameters on simulated outcomes. Chapter 6 quantifies the potential long-term health gains for the Dutch diabetic population, in terms of cardiovascular complications prevented and life years gained, if all patients would use lipid-lowering medication. Chapter 7 provides a general overview and discussion with recommendations for health policy and future research as well as a brief general conclusion.

References

1. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047-1053, 2004

2. Baan CA, van Baal PH, Jacobs-van der Bruggen MA, Verkley H, Poos MJ, Hoogenveen RT, Schoemaker CG: [Diabetes mellitus in the Netherlands: estimate of the current disease burden and prognosis for 2025]. *Ned Tijdschr Geneeskd* 153:1052-8, 2009

3. Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA: Mortality in people with type 2 diabetes in the UK. *Diabet Med* 23:516-21, 2006

4. Hansen LJ, Olivarius Nde F, Siersma V: 16-year excess all-cause mortality of newly diagnosed type 2 diabetic patients: a cohort study. *BMC Public Health* 9:400, 2009

5. Grauw WJCd, Lisdonk EHvd, Hoogen HJMvd, Weel Cv: Cardiovascular morbidity and mortality in type 2 diabetic patients: a 22-year historical cohort study in Dutch general practice. *Diabet Med* 12:117-122, 1995

6. Mulnier HE, Seaman HE, Raleigh VS, Soedamah-Muthu SS, Colhoun HM, Lawrenson RA, De Vries CS: Risk of stroke in people with type 2 diabetes in the UK: a study using the General Practice Research Database. *Diabetologia* 49:2859-65, 2006

7. Rubin RR, Peyrot M. Quality of life and diabetes. *Diabetes Metab Res Rev* 15:205-18, 1999.

8. Redekop WK, Koopmanschap MA, Rutten GE, Wolffenbuttel BH, Stolk RP, Niessen LW. Resource consumption and costs in Dutch patients with type 2 diabetes mellitus. Results from 29 general practices. *Diabet Med* 19:246-53, 2002.

9. O'Brien JA, Patrick AR, Caro J. Estimates of direct medical costs for micovascular and macro vascular complications resulting from type 2 diabetes mellitus in the United States in 2000. *Clin Ther* 25:1017-38, 2003.

10. Vegt Fd, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CDA, Nijpels G, Bouter LM, Heine RJ: Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: The Hoorn Study. *JAMA* 285:2109-2113, 2001

11. College voor Zorgverzekeingen 2007. Van Preventie Verzekerd. (www.cvz.nl).

12. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC: Diet, lifestyle, and

the risk of type 2 diabetes mellitus in women. *N Engl J Med* 345:790-797, 2001

13. 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* 17:961-9, 1994

14. Han TS, Feskens EJ, Lean ME, Seidell JC: Associations of body composition with type 2 diabetes mellitus. *Diabet Med* 15:129-35, 1998

15. Weinstein AR , Sesso HD, Lee IM, Cook NR, Manson JE, Buring JE, Gaziano JM: Relationship of physical activity vs body mass index with type 2 diabetes in women. *JAMA* 292:1188-1194, 2004

16. Field AE, Manson JE, Taylor CB, Willett WC, Colditz GA: Association of weight change, weight control practices, and weight cycling among women in the Nurses' Health Study II. *Int J Obes Relat Metab Disord* 28:1134-1142, 2004

17. Koh-Banerjee P, Wang Y, Hu FB, Spiegelman D, Willett WC, Rimm EB: Changes in body weight and body fat distribution as risk factors for clinical diabetes in US men. *Am J Epidemiol* 159:1150-1159, 2004

18. Hartemink N, Boshuizen HC, Nagelkerke NJ, Jacobs MA, van Houwelingen HC: Combining risk estimates from observational studies with different exposure cutpoints: a meta-analysis on body mass index and diabetes type 2. *Am J Epidemiol* 163:1042-52, 2006

19. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, Sellers TA, Lazovich D, Prineas RJ: Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. *Arch Intern Med* 160:2117-2128, 2000

20. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB: Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med* 161:1542-1548, 2001

21. Hu FB, Dam RMv, Liu S: Diet and risk of Type II diabetes: the role of types of fat and carbohydrate. *Diabetologia* 44:805-817, 2001

22. Folsom AR, Kushi LH, Hong CP: Physical activity and incident diabetes mellitus in postmenopausal women. *Am J Public Health* 90:134-138, 2000

23. Wannamethee SG, Shaper AG, Alberti KGMM: Physical activity, metabolic factors, and the incidence of coronary heart disease and type 2 diabetes. *Arch Intern Med* 160:2108-2116, 2000

24. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J: Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 298:2654-64, 2007

25. Carlsson S, Hammar N, Grill V: Alcohol consumption and type 2 diabetes Meta-analysis of epidemiological studies indicates a U-shaped relationship. *Diabetologia* 2005

26. Dam RMv, Hu FB: Coffee consumption and risk of type 2 diabetes: a systematic review. *JAMA* 294:97-104, 2005

27. Galani C, Schneider H: Prevention and treatment of obesity with lifestyle interventions: review and meta-analysis. *Int J Public Health* 52:348-59, 2007

28. Eriksson KF, Lindgarde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. *Diabetologia* 34:891-898, 1991

29. Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roque I Figuls M, Richter B, Mauricio D: Exercise

or exercise and diet for preventing type 2 diabetes mellitus. *Cochrane Database Syst Rev*CD003054, 2008

30. Roumen C, Corpeleijn E, Feskens EJ, Mensink M, Saris WH, Blaak EE: Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. *Diabet Med* 25:597-605, 2008

31. Lindstrom J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J, for the Finnish Diabetes Prevention Study Group.: The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 26:3230-3236, 2003

32. Diabetes Prevention Program Research Group , Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393-403, 2002

33. Tuomilehto J , Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343-1350, 2001

34. Lindahl B, Nilsson T, Borch-Johnsen K, Roder ME, Soderberg S, Widman L, Johnson O, Hallmans G, Jansson JH: A randomized lifestyle intervention with 5-year follow-up in subjects with impaired glucose tolerance: Pronounced short-term impact but long-term adherence problems. *Scand J Public Health* 2009

35. Lindstrom J, Peltonen M, Eriksson JG, Aunola S, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Uusitupa M, Tuomilehto J: Determinants for the effectiveness of lifestyle intervention in the Finnish Diabetes Prevention Study. *Diabetes Care* 2008

36. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, Li H, Li H, Jiang Y, An Y, Shuai Y, Zhang B, Zhang J, Thompson TJ, Gerzoff RB, Roglic G, Hu Y, Bennett PH: The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 371:1783-9, 2008

37. Galani C, Schneider H, Rutten FF: Modelling the lifetime costs and health effects of lifestyle intervention in the prevention and treatment of obesity in Switzerland. *Int J Public Health* 52:372-82, 2007

38. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, Hamman RF, Ackermann RT, Engelgau MM, Ratner RE, for the Diabetes Prevention Program Research Group: The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 142:323-332, 2005

39. Palmer ALS, Roze S, Valentine WJ, Spinas GA, Shaw JE, Zimmet PZ. Intensive lifestyle changes or metformin in patients with IGT: modeling the long-term health economic implications of the diabetes prevention program in Australia, France, Germany, Switzerland and the United Kingdom. *Clin Ther* 26:304-21, 2004.

40. Caro JJ, Getsios D, Caro I, Klittich WS, o'Bien JA. Economic evaluation of therapeutic interventions to prevent type 2 diabetes in Canada. *Diabet Med* 21:1229-36, 2004.

41. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, Khunti K: Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ* 334:299, 2007

42. Bosch J, Yusuf S, Gerstein HC, Pogue J, Sheridan P, Dagenais G, Diaz R, Avezum A, Lanas F,

Probstfield J, Fodor G, Holman RR: Effect of ramipril on the incidence of diabetes. *N Engl J Med* 355:1551-62, 2006

43. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 368:1096-105, 2006

44. Roumen C, Blaak EE, Corpeleijn E: Lifestyle intervention for prevention of diabetes: determinants of success for future implementation. *Nutr Rev* 67:132-46, 2009

45. Field AE, Manson JE, Laird N, Williamson DF, Willett WC, Colditz GA: Weight cycling and the risk of developing type 2 diabetes among adult women in the United States. *Obes Res* 12:267-74, 2004

46. Mishra GD, Carrigan G, Brown WJ, Barnett AG, Dobson AJ: Short-term weight change and the incidence of diabetes in midlife: results from the Australian Longitudinal Study on Women's Health. *Diabetes Care* 30:1418-24, 2007

47. Uusitupa M, Peltonen M, Lindstrom J, Aunola S, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Valle TT, Eriksson JG, Tuomilehto J: Ten-year mortality and cardiovascular morbidity in the Finnish Diabetes Prevention Study--secondary analysis of the randomized trial. *PLoS One* 4:e5656, 2009

48. Verheijden MW, Kok FJ: Public health impact of community-based nutrition and lifestyle interventions. *Eur J Clin Nutr* 59 Suppl 1:S66-75; discussion S76, 2005

49. Wendel-Vos GC, Dutman AE, Verschuren WM, Ronckers ET, Ament A, van Assema P, van Ree J, Ruland EC, Schuit AJ: Lifestyle factors of a five-year community-intervention program: the Hartslag Limburg intervention. *Am J Prev Med* 37:50-6, 2009

50. McTigue K, Hess R, Bryce CL, Fitzgerald K, Olshansky E, Sacco D, Fischer G: Perception of "healthy" body weight by patients with diabetes. *Diabetes Care* 29:695-697, 2006

51. Brownson RC, Smith CA, Pratt M, Mack NE, Jackson-Thompson J, Dean CG, Dabney S, Wilkerson JC: Preventing cardiovascular disease through community-based risk reduction: the Bootheel Heart Health Project. *Am J Public Health* 86:206-13, 1996

52. Taylor CB, Fortmann SP, Flora J, Kayman S, Barrett DC, Jatulis D, Farquhar JW: Effect of long-term community health education on body mass index. The Stanford Five-City Project. *Am J Epidemiol* 134:235-49, 1991

53. Fleming P, Godwin M: Lifestyle interventions in primary care: systematic review of randomized controlled trials. *Can Fam Physician* 54:1706-13, 2008

54. Vijgen SMC, Hoogendoorn M, Baan CA, Wit GAd, Limburg W, Feenstra TL: Cost effectiveness of preventive interventions in type 2 diabetes mellitus: a systematic literature review. *Pharmacoeconomics* 24:425-441, 2006

55. Segal L, Dalton AC, Richardson J: Cost-effectiveness of the primary prevention of non-insulin dependent diabetes mellitus. *Health Promotion International* 13:197-209, 1998

56. Wannamethee SG, Shaper AG, Walker M: Overweight and obesity and weight change in middle aged men: impact on cardiovascular disease and diabetes. *J Epidemiol Community Health* 59:134-139, 2005

57. van Dis I, Kromhout D, Geleijnse JM, Boer JM, Verschuren WM: Body mass index and waist circumference predict both 10-year nonfatal and fatal cardiovascular disease risk: study conducted in 20 000 Dutch men and women aged 20-65 years. *Eur J Cardiovasc Prev Rehabil* 2009

58. Prasad DS, Das BC: Physical inactivity: a cardiovascular risk factor. *Indian J Med Sci* 63:33-42, 2009

59. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB: Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation* 107:2435-2439, 2003

60. Weinstein AR, Sesso HD: Joint effects of physical activity and body weight on diabetes and cardiovascular disease. *Exerc Sport Sci Rev* 34:10-5, 2006

61. Wendel-Vos GC, Schuit AJ, Feskens EJ, Boshuizen HC, Verschuren WM, Saris WH, Kromhout D: Physical activity and stroke. A meta-analysis of observational data. *Int J Epidemiol* 33:787-98, 2004

62. Doll R, Peto R, Boreham J, Sutherland I: Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 328:1519, 2004

63. Mucha L, Stephenson J, Morandi N, Dirani R: Meta-analysis of disease risk associated with smoking, by gender and intensity of smoking. *Gend Med* 3:279-91, 2006

64. Lawlor DA, Song YM, Sung J, Ebrahim S, Smith GD: The association of smoking and cardiovascular disease in a population with low cholesterol levels: a study of 648,346 men from the Korean national health system prospective cohort study. *Stroke* 39:760-7, 2008

65. Bogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, Knekt P, van Dam RM, Hu FB, Visscher TL, Menotti A, Thorpe RJ Jr, Jamrozik K, Calling S, Strand BH, Shipley MJ: Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. *Arch Intern Med* 167:1720-8, 2007

66. Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K: Alcohol and coronary heart disease: a meta-analysis. *Addiction* 95:1505-23, 2000

67. Hill JA: In vino veritas: alcohol and heart disease. *Am J Med Sci* 329:124-35, 2005

68. Koppes LLJ, Dekker JM, Hendriks HFJ, Bouter LM, Heine RJ: Moderate Alcohol Consumption Lowers the Risk of Type 2 Diabetes: A meta-analysis of prospective observational studies. *Diabetes Care* 28:719-725, 2005

69. Chamnan P, Simmons RK, Sharp SJ, Griffin SJ, Wareham NJ. Cardiovascular risk assessment scores for people with diabetes: a systematic review. *Diabetologia* 52:2001-14, 2009.

70. Adler,AL. UKPDS-modeling of cardiovascular risk assessment and lifetime simulation of outcomes. *Diabet Med* 25 S2:41-6, 2008.

71. Deakin T, McShane CE, Cade JE, Williams RD: Group based training for self-management strategies in people with type 2 diabetes mellitus. *Cochrane Database Syst Rev* CD003417, 2005

72. Kavookjian J, Elswick BM, Whetsel T: Interventions for being active among individuals with diabetes: a systematic review of the literature. *Diabetes Educ* 33:962-88; discussion 989-90, 2007

73. Conn VS, Hafdahl AR, Mehr DR, LeMaster JW, Brown SA, Nielsen PJ: Metabolic effects of interventions to increase exercise in adults with type 2 diabetes. *Diabetologia* 50:913-21, 2007

74. Norris SL, Zhang X, Avenell A, Gregg E, Brown TJ, Schmid CH, Lau J: Long-term non-pharmacological weight loss interventions for adults with type 2 diabetes mellitus (Review). *The Cochrane Library*1-65, 2005

75. Zoungas S, de Galan BE, Ninomiya T, Grobbee D, Hamet P, Heller S, Macmahon S, Marre M, Neal B, Patel A, Woodward M, Chalmers J: The combined effects of routine blood pressure lowering and intensive glucose control on macro vascular and micro vascular outcomes in patients with type 2 diabetes; new results from ADVANCE. *Diabetes Care* 2009

76. Blood Pressure Lowering Treatment Trialists' Collaboration. , Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, Woodward M, MacMahon S: Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 165:1410-1419, 2005

77. Cholesterol Treatment Trialists' (CTT) Collaborators , Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 366:1267-1278, 2005

78. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C: Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 371:117-25, 2008

79. Huang ES, Meigs JB, Singer DE: The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. *Am J Med* 111:633-642, 2001

80. Akalin S, Berntorp K, Ceriello A et al.: Intensive glucose therapy and clinical implications of recent data: a consensus statement from the Global Task Force on Glycemic Control. *Int J Clin Pract* 63:1421-5, 2009

81. Jacobs-van der Bruggen, MAM, Engelfriet, PM, Bos, G, Hoogenveen, RT, Feenstra, TL, and Baan, CA. Opportunities for preventing diabetes and its cardiovascular complications. A modelling approach. 2007. Bilthoven, RIVM.

82. Herman WH, Urbanski P, Wolf AM : Cost effectiveness issues of diabetes prevention and diabetes treatment. *Newsflash* 29, 2008

83. Urbanski P, Wolf A, Herman WH: Cost-effectiveness of diabetes education. *J Am Diet Assoc* 108:S6-11, 2008

84. Hoogenveen RT, van Baal PH, Boshuizen HC: Chronic disease projections in heterogeneous ageing populations: approximating multi-state models of joint distributions by modelling marginal distributions. *Math Med Biol* 2009

85. Verschuren WM, Blokstra A, Picavet HS, Smit HA: Cohort profile: the Doetinchem Cohort Study. *Int J Epidemiol* 37:1236-41, 2008

86. Rappange DR, Brouwer WBF, Rutten FFH, van Baal PHM. Lifestye intervention: from cost savings to value for money. *J of Public Health* 2009.

87. Casparie AF, van Hout BA, Simoons ML. [Guidelineds and costs]. *Ned Tijdsch Geneesk* 142:2075-7, 1998.

88. Rawlings MD, Culyer AJ. National Institute for Clinical Excellence and its value judgements. *Br Med J* 329:224-7, 2004.

Chapter 2. Weight change and incident diabetes: addressing an unresolved issue

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Weight change and incident diabetes: addressing an unresolved issue

ABSTRACT

The impact of weight change on diabetes incidence remains unclear. To clarify the role of weight change as a risk factor for diabetes, the authors assessed the association between weight change and diabetes incidence conditional upon either initial or attained BMI. 7,837 Observations available from repeated measurements of 4,249 participants (men and women 20-59 years) of the Dutch population based Doetinchem Cohort Study were used to analyze the association between 5-years weight change and diabetes incidence (n=124) in the subsequent 5 years. If adjusted for initial BMI, 5-years weight change was a significant risk factor for diabetes (OR 1.08, 95% CI: 1.04, 1.13 per kg weight change). However, there was no significant association between weight change and diabetes if the association was adjusted for attained BMI (OR 0.99, 95% CI: 0.94, 1.04 per kg weight change). Our results suggest that weight change is associated with diabetes incidence because, conditional upon initial BMI, weight change determines attained BMI. This implies that lifestyle interventions can contribute to diabetes prevention because they affect attained BMI. Weight change appears to have no effect on diabetes incidence beyond its effect on attained BMI.

BACKGROUND

Obesity is acknowledged as an important risk factor for diabetes (1-8). The pooled 'average' relative risk for diabetes is approximately 1.18 per unit increase in body mass index (BMI) (4), but several studies have shown that the impact of BMI on diabetes incidence is larger for BMI measured more proximal to diabetes outcome, compared to earlier, remote measures (9-13). Therefore, it is important that weight attained at the end of the weight change period is taken into account if the impact of weight change on diabetes incidence is assessed. We identified fifteen prospective observational studies that explored the association between weight change and incident diabetes (9-23, Table 1). It appeared that only two studies (11,18) took account of attained BMI, while two studies adjusted for 'overall weight status' (19) or 'average weight' (22) during the weight change period. Most studies (12 out of 15) assessed the association with adjustment for initial BMI. Therefore, although many studies have found positive associations between weight change and diabetes, the impact of weight change on diabetes incidence, beyond its effect on attained weight, remains unclear.

In an attempt to clarify this unresolved issue, this paper starts with discussing the implications of using different analytic approaches. Subsequently we will use Dutch data to analyze the association between weight change and diabetes with adjustment for either initial or attained BMI and discuss the implications of the different results.

The methodological question of how to disentangle the impact of risk factor level versus risk factor change on disease incidence has been addressed by Hofman in 1983 (24). He pointed out that there are two different ways of looking at the impact of risk factor change on disease risk, that each way implies a specific data-analytic approach and that the obtained results have different implications. With respect to the impact of weight change on diabetes, the association can be explored from, what we will call, a 'prospective' or 'retrospective' point of view.

With the prospective approach we can explore whether, at a certain level of BMI, future weight change is important. For the data-analysis this means that the effect of weight change is assessed, conditional upon initial BMI (Figure 1A). From Figure 1A it is easy to imagine that, conditional upon initial BMI, weight change determines attained BMI. Persons who loose weight will have lower attained levels of BMI and persons who gain weight will attain higher levels of BMI. Since both weight loss and a low attained BMI are expected to be associated with a lower risk for diabetes, the coefficient for weight change in this analysis could reflect a positive association with diabetes, 'simply' because weight change determines attained BMI. Results from this approach do not reveal whether weight change is a risk factor for diabetes, independent of the level of attained BMI.

The retrospective approach explores whether, at a certain level of attained BMI, weight change history is important. In this analysis, the effect of weight change is assessed conditional upon attained BMI (Figure 1B). Figure 1B illustrates that, conditional upon attained weight, previous weight change determines initial BMI. Persons who lost weight started with higher initial levels of BMI and persons who gained weight started at lower levels. This means that the coefficient for weight change in this model reflects the joint presumably opposite (!) effects of weight change and initial BMI. A negative coefficient for

weight change in this model would imply that initial weight is more important than subsequent weight change while a positive coefficient would imply that weight change has a larger impact than initial weight and affects diabetes incidence beyond its effect on attained BMI.

In the analyses in this paper we explore the association between weight change and incident diabetes conditional upon either initial or attained BMI. We hypothesize that, conditional upon initial BMI, weight change affects diabetes incidence by affecting attained BMI, but that weight change in itself has some additional effect.

Table 1. Summary of previous observational studies that analyzed the association between weight change and incident diabetes.

Publication [a]	Cohort	Weight measurement	Incident diabetes at follow-up	Results
Waring 2010 (19)	1,476 adults 28-40 years at baseline in 1948-1952 Fram. Heart Study original cohort limited data-set	Measured during biennial visits from age 40 to age 50	217 incident cases during 35,359 person-years of follow-up after age 50 (until 2003). Cases determined from non-fasting glucose levels or medical treatment for diabetes	Hazard ratio for diabetes incidence after age 50 in relation to weight change pattern from age 40 to age 50 compared to adults with stable weight (quintile 2 on weight change function) crude analyses: Loss (quintile 1): 1.2 (0.8-1.9) Gain (quintile 3 or 4): 1.1 (0.7-1.5) When adjusted for overall weight status and weight cycling (age 40-50) and confounders: Loss (quintile 1): 1.1 (0.7-1.8) Gain (quintile 3 or 4): 1.2 (0.8-1.7) Additional adjustment for recent weight does not influence these estimates.
Mishra 2007 (16)	7,329 women 45-50 yrs in 1996 Australian Long. Study on Women's Health	Self-reported in 1996, 1998, 2001 and 2004	206 incident cases of self-reported, physician diagnosed diabetes	Odds ratio for diabetes incidence 1998-2001 in relation to weight change 1996-1998 or diabetes incidence 2001-2004 in relation to weight change 1998-2001 compared to women with stable weight (±1.5%). Adjusted for initial BMI in 1996: Loss (≥5%): 0.6 (0.2-1.4) Loss (2.5-5%): 1.3 (0.8-2.1) Loss (1.5-2.5%): 0.6 (0.3-1.2) Gain (1.5-2.5%): 1.2 (0.8-1.9) Gain (2.5-5%): 0.9 (0.6-1.4) Gain (≥5%): 1.5 (0.9-2.6) p for rend 0.08
Schien-kiewitz 2007 (20)	7,720 men and 10,371 women 40-65 years at baseline in 1994-1998 EPIC-Potsdam study	Retrospective self-reported weight at age 25 and age 40 Measured weight at baseline	390 men and 303 women with incident diabetes based on self-report and confirmed clinical diagnosis between	Relative risk for diabetes between baseline (1994-1998) and 2005 in relation to weight change from age 25 to 40 and from age 40 to age 55 (estimated from baseline weight) per unit change in BMI, adjusted for initial weight at age 25 and included in one model. Men: BMI change 25-40: 1.3 (1.2-1.3)

Publication [a]	Cohort	Weight measurement	Incident diabetes at follow-up	Results
			baseline and 7-year follow-up	BMI change 40-55: 1.1 (1.1-1.2) Women: BMI change 25-40: 1.2 (1.2-1.3) BMI change 40-55: 1.1 (1.1-1.2)
Oguma 2005 (9)	20,187 men mean age 46 years at baseline in 1962 or 1966	Measured at university entry (mean age 19) self-reported at baseline	1223 incident cases of self-reported diabetes on one of the several follow-up questionnaires from baseline until 1998 (mean duration 27 years)	Relative risk of incident diabetes from 1962/1966 until 1998 by categories of per decade change in BMI between university entry and baseline (1962/1966) adjusted for initial BMI at university entry compared to men with stable weight (±0.5 kg/m2 per decade): Loss ≥0.5: 0.9 (0.6-1.3) Gain 0.5-1.0: 1.3 (1.0-1.6) Gain 1.0-1.5: 2.1 (1.7-2.6) Gain 1.5-2.0: 2.7 (2.2-3.3) Gain 2.0-3.0: 4.7 (3.8-5.8) Gain ≥3.0: 7.0 (5.4-9.1)
Wanne-methee 2005 (17)	6,798 men 40-59 at baseline (1978-1980) British regional heart study	Measured at baseline (1978-1980) and self-reported at 5-year follow-up (1983-1985)	327 incident cases of self-reported and confirmed diabetes during follow-up from baseline (1983-1985) until 2000	Relative risk of incident type 2 diabetes (1983/1985-2000) by categories of 5-year weight change (between 1978/1980 and 1983/1985) adjusted for initial BMI in 1978-1980 compared to men with stable weight (±4%): Loss ≥4%: 0.6 (0.4-0.9) Gain 4-10%: 1.3 (1.0-1.6) Gain ≥10%: 1.8 (1.2-2.7)
Black 2005 (18)	484 men 'healthy' at final follow-up over-sampling of obese men	Measured at average age 20,33,44 and 51 year	46 newly diagnosed diabetes cases determined with OGTT at the final follow-up at average age 51	Odds ratio for type 2 diabetes diagnosed at age 51 vs. NGT (n=316) per unit BMI increase adjusted for attained BMI: BMI change (age 44-51): 0.9 (0.7-1.0) BMI change (age 33-44): 0.9 (0.8-1.1) BMI change (age 20-33): 1.1 (1.0-1.3)
Field 2004 (22)	46,634 women 25-43 years at baseline in 1989	Biennial self-reported weight from 1989 to 1995 'recent weight change': weight change in the 4 years prior to inc. diabetes or end of	418 incident cases of physician diagnosed diabetes during 6-years follow-up (1993-1999)	Relative risk of incident diabetes (1993-1999) by categories of weight change (1989-1993) and 'recent weight change' adjusted for average weight during the 'recent weight change' period compared to women with 'stable weight'(±5lb) included in one model: Weight gain 1989-1993 (5-14.9 lbs): 3.4 Recent weight gain (5-14.9 lbs): 1.3 Confidence limits and other estimates were not reported

Publication [a]	Cohort	Weight measurement	Incident diabetes at follow-up	Results
		follow-up.		
Koh-Banerjee 2004 (10)	22,171 men 40-75 years at baseline in 1986 Health prof. follow-up study	Self-reported weight at age 21, in 1986 and biennial thereafter	305 self-reported and confirmed incident diabetes cases between 1996 and 2000	Relative risk of incident diabetes (1996-2000) by categories of weight change from age 21 until 1996 adjusted for initial BMI at age 21 compared to men with stable weight (±2kg): Loss (≥3kg): 0.4 (0.2-1.1) Gain (3-6kg): 1.8 (1.0-3.2) Gain (7-11kg): 2.1 (1.2-3.6) Gain (12-18kg): 3.0 (1.8-5.2) Gain (≥19kg): 8.8 (5.2-14.70) =7% (6-8) increase in risk /kg weight gain Relative risk of incident diabetes (1996-2000) by categories of weight change (1986-1996) adjusted for initial BMI in 1986 compared to men with stable weight (±2kg): Loss (≥6kg): 0.5 (0.3-0.9) Loss (3-5kg): 1.0 (0.7-1.5) Gain (3-5kg): 1.4 (1.0-1.9) Gain (6-8kg): 1.6 (1.1-2.4) Gain (≥9kg): 2.1 (1.5-3.0)
Will 2002 (14)	73,745 men and 70,278 women with BMI> 25 from the First Cancer Prevention Study > 30 years at baseline 1959/1960	Self-reported weight history: (intentional) weight gain or (intentional) weight loss before baseline. Duration of weight change period unclear	Men 3857 and women 4290 with incident diabetes determined from self-report or death certificates from baseline until 1972.	Incidence density ratio for incident diabetes during follow-up (1959/1960-1972) for different classes of weight history at baseline, adjusted for initial, pre-baseline BMI, compared to those without weight change: Men: Unintentional gain: 1.3 (1.2-1.5) Unintentional loss: 0.9 (0.8-1.1) Intentional gain: 1.0 (0.7-1.5) Intentional loss: 0.8 (0.7-0.9) Women: Unintentional gain: 1.4 (1.3-1.5) Unintentional loss: 0.8 (0.7-0.9) Intentional gain: 1.2 (0.9-1.5) Intentional loss: 0.7 (0.7-0.8) Among those with intentional weight loss men decreased their rate of diabetes by 11% and women by 7% for every 20lb weight loss
Resnick 2000 (21)	1,929 over-weight adults 25-74 years at	Measured weight at baseline and 10-years	251 incident cases in the 10 years follow-up after the weight	Odds ratios for incident diabetes in the 10 years following the 10-years weight change period per kg weight change per year adjusted for initial, baseline BMI.

Publication [a]	Cohort	Weight measurement	Incident diabetes at follow-up	Results
	baseline in 1971-1975 (NHEFS)	follow-up examination	change period. Ascertained from self-report, hospital records and death certificates.	Weight change (per kg/y): 1.5 (1.3-1.7)
Brancati 1999 (11)	798 men (former) medical students	Measured at average age 20. Self-reported at average age 25, 35 and 45 year	35 self-reported, physician diagnosed incident diabetes cases during 1-30 (mean 16 year) follow-up after age 50.	Relative risk of incident diabetes during 1-30 year follow-up after age 50 per unit BMI change between age 25 and 45 adjusted for initial BMI at age 25: BMI change (age 25-45): 3.2 (1.4-7.4) Relative risk of incident diabetes during 1-30 year follow-up after age 50 per unit BMI change between age 25 and 45, adjusted for age and attained BMI at age 45: not significant (RR not reported)
Wanna-methee 1999 (23)	6,916 men 40-59 years at baseline 1978-1980 (Q1) British Regional Heart Study	Measured weight at baseline (1978-1980) and self-reported weight 5 years later (Q5)	237 cases of self-reported and confirmed diabetes during follow-up until 1995 Average follow-up 12 years	Relative risk for incident diabetes during 12 years follow-up after Q5 by categories of 5-years weight change between Q1 and Q5 adjusted for initial weight at Q1 compared to men with stable weight (±4%) Weight loss (>4%): 0.7 (0.5-1.1) Weight gain (4-10%): 1.2 (0.9-1.6) Weight gain (>10%): 1.6 (1.0-2.6) Test for trend p=0.0009
Ford 1997 (15)	8,545 adults ≥ 25 years at baseline (1971-175) NHANES	Measured at baseline (1971-1975) and at follow-up examination (1982-1984)	487 self-reported cases of incident diabetes from self-report or medical records during ±10 years follow-up (1982/1984-1992)	Hazard ratio for incident diabetes during ±10 years follow-up (1982/1984-1992) by categories of weight change between baseline (1971-1975) and follow-up (1982-1984) adjusted for initial BMI at baseline compared to men with stable weight (±5kg): Loss ≥11kg: 0.8 (0.5-1.4) Loss 5-11kg: 1.1 (0.7-1.8) Gain 5-8kg: 2.1 (1.4-3.2) Gain 8-11kg: 1.2 (0.8-1.9) Gain 11-20kg: 2.7 (1.8-3.9) Gain ≥20kg: 3.8 (2.0-7.2) 4.5% increase in diabetes risk per 1kg weight gain (over 10 years)
Colditz 1995 (12)	114,281 women 30-55 years at baseline in 1976 Nurses'	Self-reported at age 18 and in 1976 and 1986.	2204 self-reported (and confirmed) incident diabetes cases on biennial	Relative risk of incident diabetes (1976-1990) by categories of weight change from age 18 until 1976, adjusted for initial BMI at age 18 compared to women with stable weight (±5kg): Loss (11.0-19.9kg): 0.2 (0.1-0.4)

Publication [a]	Cohort	Weight measurement	Incident diabetes at follow-up	Results
	health study		questionnaires during 14 years of follow-up (1976-1990)	Loss (5.0-10.9kg): 0.5 (0.4-0.8) Gain (5.0-7.9kg): 1.9 (1.5-2.3) Gain (8.0-10.9kg): 2.7 (2.1-3.3) Gain (11.0-19.9kg): 5.5 (4.7-6.3) Gain (≥20.0kg): 12.3 (10.9-13.8)
			762 self-reported (and confirmed) incident diabetes cases during 4 years of follow-up (1986-1990)	Relative risk of incident diabetes (1986-1990) by categories of weight change (1976-1986) adjusted for initial BMI in 1976 compared to women with stable weight (±3kg): Loss (≥5kg): 0.6 (0.4-1.0) Loss (3.0-4.9kg): 1.0 (0.6-1.5) Gain (3.0-4.9kg): 1.5 (1.1-2.0) Gain (≥10kg): 1.8 (1.4-2.3)
Chan 1994 (13)	27,338 men 40-75 years at baseline in 1986 Health prof. follow-up study	Self-reported at age 21, in 1986 and biennial thereafter	266 self-reported and confirmed incident diabetes cases between 1987 and 1992	Relative risk of incident diabetes (1987-1992) by categories of weight change from age 21 until 1987 adjusted for initial BMI at age 21 compared to men with stable weight (±2kg): Loss (≥3kg): 0.3 (0.1-0.8) Gain (3-5kg): 0.9 (0.5-1.8) Gain (6-7kg): 1.9 (1.0-3.7) Gain (8-9kg): 3.5 (2.0-6.3) Gain (10-14kg): 3.4 (2.0-5.8) Gain (≥15kg): 8.9 (5.5-14.7) Relative risk of incident diabetes (1987-1992) by categories of weight change from 1981-1986 adjusted for initial BMI in 1981 compared to men with stable weight (±4.5kg): Loss (≥4.5kg): 0.8 (0.5-1.2) Gain (4.5-13.6kg): 1.7 (1.2-2.3) Gain (≥13.6kg): 4.5 (2.4-8.2)

[a] Prospective observational cohort studies, published after 1990, examining the association between weight change and incident diabetes in mainly Caucasian populations, identified through Pubmed search and reference tracking.

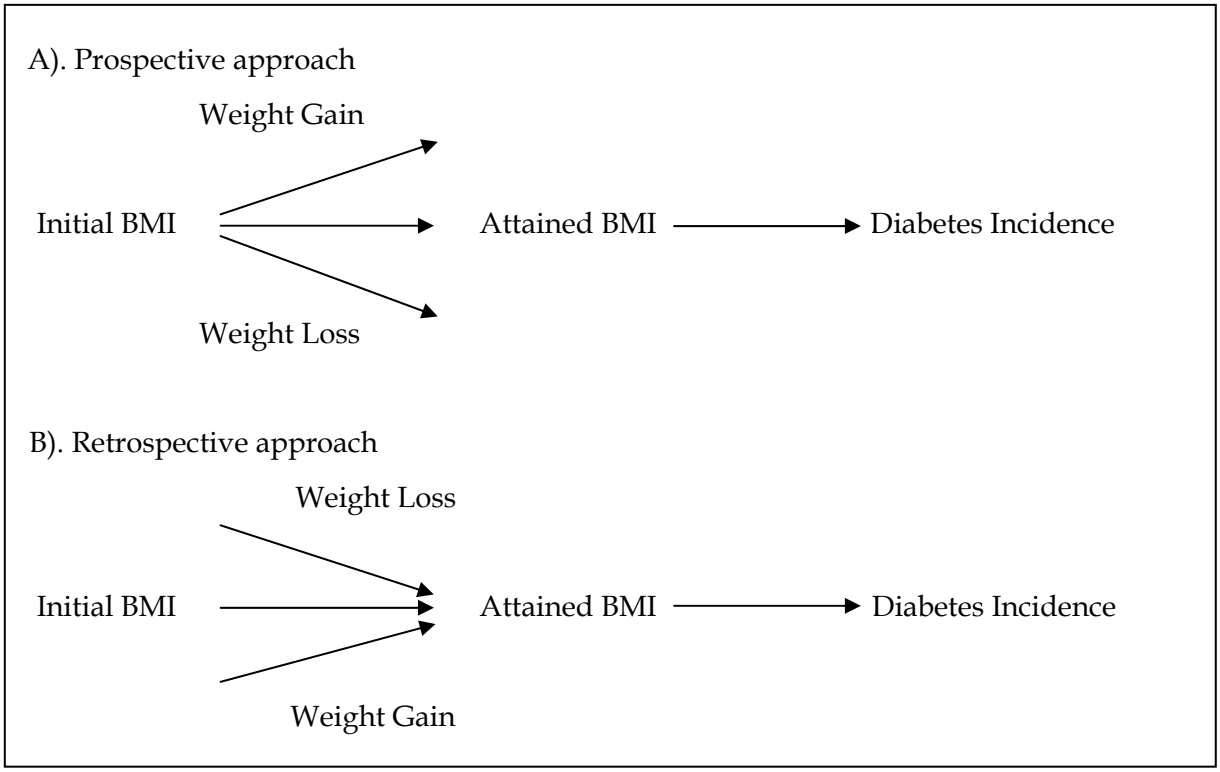

Figure 1: BMI, Body Mass Index; A) Prospective approach: Illustration of the data-analysis in which the association between Weight Change and Diabetes Incidence is assessed with adjustment for Initial BMI. The figure illustrates that, conditional upon Initial BMI, Weight Change determines Attained BMI. B) Retrospective approach: Illustration of the data-analysis in which the association between Weight Change and Diabetes Incidence is assessed with adjustment for Attained BMI. The figure illustrates that, conditional upon Attained BMI, previous Weight Change determines Initial BMI.

MATERIALS AND METHODS

Study population

The Doetinchem Cohort Study is a prospective observational population-based Dutch study with four measurement rounds (at 5-year intervals) completed between 1987 and 2007. The first measurements took place between 1987 and 1991. In that period 12,405 inhabitants of Doetinchem between 20 and 59 years old were examined as part of the 'Monitoring Project on Cardiovascular Disease Risk Factors'. From the participants of the first round (R1), a random sample of 7,769 was invited to participate in a second examination (R2: 1993-1997), and again five and ten years later for a third (R3: 1998-2002) and fourth examination (R4: 2003-2007). Measurements included questionnaires and a physical examination. Details on sampling and data collection procedures are described elsewhere (25). The study was approved according to the guidelines of the Helsinki Declaration by the external Medical Ethics Committee of the Netherlands Organization of Applied Scientific Research Institute. All participants gave written informed consent.

Assessment of weight and weight change

Body weight and height were measured during each examination. Weight change was calculated between R1 and R2 and R2 and R3. Although the actual time between measurements was approximately six years between R1 and R2, '5-years weight change' is used throughout this paper. To calculate 5-years weight change, weight change (absolute

change in kg, weight change relative to initial weight or absolute change in BMI) was divided by the actual time between measurements (in years) and multiplied by five. 5-Years weight change was modeled as a continuous risk factor (with weight loss having a negative value) and also considered in categories: 'weight loss' (> 2.0 kg), 'stable weight' (± 2.0 kg, = reference), 'small weight gain' (2.0-4.0 kg), 'moderate weight gain' (4.0-6.0 kg) and substantial weight gain (> 6.0 kg). These categories were based on a stable, sufficiently large reference group and a fair, relatively equal number of cases and observations in each of the remaining categories.

Other variables

Demographic and lifestyle characteristics were obtained from self-administered questionnaires filled out at home and checked during the examination visits. Biomedical outcomes were obtained from the physical examinations. Characteristics that were considered as potential confounders were age, gender, menopausal status (men, women with regular menstrual cycle or women without regular cycle), nationality (Dutch or other), prevalent cardiovascular disease (self-reported history of acute myocardial infarction or stroke) and education. Educational level was assessed as the highest level of completed education and classified into four categories: primary school or less, lower vocational or intermediate secondary education, intermediate vocational or higher secondary education, and higher vocational education or university. Lifestyle characteristics that were considered were leisure time physical activity (active or inactive), smoking (current, former or never), alcohol consumption (four categories) and coffee consumption (cups per day). Potential 'biomedical confounders' were systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension (SBP≥140, DBP≥ 90 or antihypertensive medication), high-density lipoprotein (HDL) cholesterol, total cholesterol and cholesterol ratio (total/HDL cholesterol). In addition, 5-years changes in blood pressure and cholesterol levels were considered as confounders in the retrospective analyses.

Outcome measurements

Cases were defined based on self-reported diabetes ('Do you have diabetes?' yes/no) only. However, most of the self-reported cases have been verified against information from the general practitioner or pharmacist. Of the 99 (out of 124) self-reported cases that could be verified, 88 were confirmed cases with incident type 2 diabetes, 5 were confirmed non-type 2 diabetics, 3 were prevalent type 2 diabetic cases and 3 were confirmed non-diabetics. 'Sensitivity' analyses were performed with 'confirmed incident type 2 diabetes' cases only. In these latter analyses, all self-reported diabetic cases that were not 'confirmed incident type 2' were excluded.

Statistical methods

We used generalized estimating equation analyses (proc GENMOD in SAS with link=logit, D=binomial and correlation structure =exchangeable) to assess the association between 5-years weight change and incident diabetes in the subsequent 5 years (Figure 2). Observations used in cluster 1 were initial BMI at R1, weight change between R1 and R2, attained BMI at

R2 and incident diabetes between R2 and R3. Observations used in cluster 2 were initial BMI at R2, weight change between R2 and R3, attained BMI at R3 and incident diabetes between R3 and R4. There was a significant, negative correlation between repeated weight change observations in cluster 1 and cluster 2 (r=-0.12) and we used the 'repeated' statement to control for this correlation.

We applied a 'prospective approach', with baseline data from R1 and R2 to asses the association between weight change and diabetes, conditional upon initial BMI (Figure 2A). A 'retrospective approach' with baseline data from R2 and R3 was used to assess the association between weight change and diabetes, conditional upon attained BMI (Figure 2B).

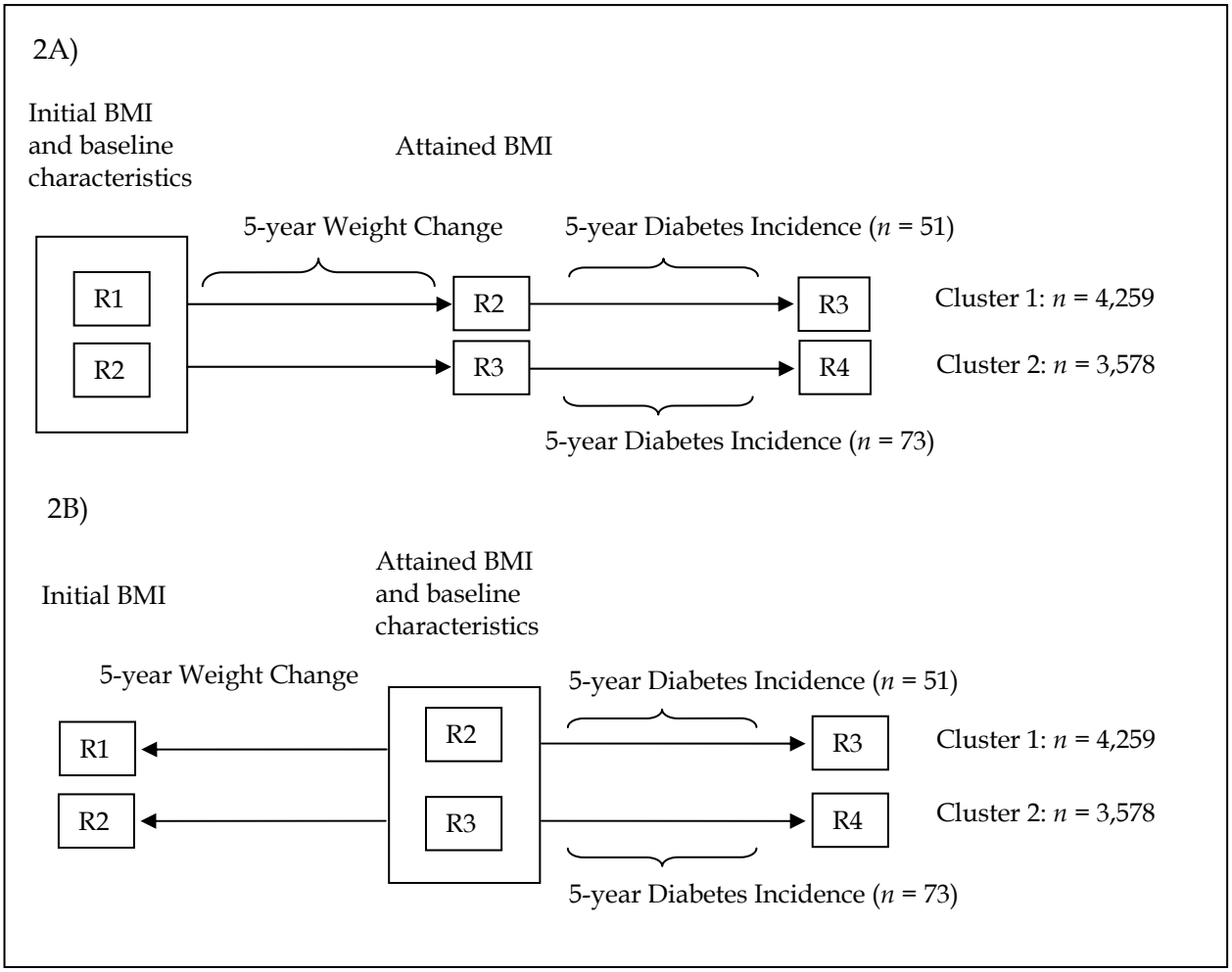

Figure 2. BMI, Body Mass Index; A) Prospective approach: Illustration of the data-analysis in which the association between Weight Change and Diabetes Incidence is assessed conditional upon Initial BMI and initial baseline characteristics. The figure illustrates how observations from four repeated measurements are combined and gives the number of participants (observations) and cases in each cluster. B) Retrospective approach: Illustration of the data-analysis in which the association between Weight Change and Diabetes Incidence is assessed conditional upon Attained BMI and attained baseline characteristics. The figure illustrates how the data from four repeated measurements are combined and gives the number of participants (observations) and cases in each cluster.

Persons with prevalent diabetes at R1 or R2 were completely excluded, while observations from persons with incident diabetes at R3 were excluded in cluster 2. We excluded observations from pregnant women at R1 or R2 from cluster 1 and observations from women who were pregnant at R2 or R3 from cluster 2. Observations from persons with cancer (R1, R2 or R3) or (R2, R3 or R4) were excluded from cluster 1 and 2 respectively. To adjust for confounders, we explored which individual confounders caused a > 5% change in the odds ratio (OR) for diabetes for any of the four weight change categories if they were included in the age and gender adjusted models. Subsequently, these confounders were included simultaneously in fully adjusted models but removed if leaving them out caused a less than 5% change. Initially 'cluster' was included in each model but finally removed since it did not confound nor modify the associations.

RESULTS

There were 7,837 observations available for the analyses; 4,259 participants had observations in cluster 1 and 3,578 of these participants had repeated observations in cluster 2 (Figure 2).
Mean initial BMI was 24.8 kg/m^2 (standard deviation (SD) 3.4). Mean 5-years weight change was a gain of 2.2 kg (SD 4.0) consistent with a 3.1% (SD 5.6) increase from initial weight. Among persons who gained weight (74% of the observations) mean 5-years weight gain was 3.9 kg (SD 3.1). Among persons in the substantial weight gain category, median weight gain was 8.0 kg (range 6-29 kg). Persons who lost weight (26% of the observations) lost 2.4 kg (SD 2.4) on average. Among persons in the weight loss category median weight loss was 3.5 kg (range 2-24 kg). The negative correlation between initial BMI and weight change was weak (r=-0.06) but significant. The positive correlation between weight change and attained BMI (r=0.35) was much stronger. Mean attained BMI was 25.6 kg/m^2 (SD 3.6).
During follow-up, 124 persons developed diabetes. The risk to develop diabetes within 5 years was 1.6% (Table 2). After adjustment for age and gender, initial BMI, 5-years weight change and attained BMI were all 'crudely' associated with diabetes incidence. The adjusted OR was 1.24, 95% confidence interval (CI): 1.20, 1.29 per kg/m^2 for initial BMI and 1.23, 95% CI: 1.19, 1.27 per kg/m^2 for attained BMI. The adjusted OR for 5-years weight change as a continuous variable was 1.08, 95% CI: 1.03, 1.14 per kg change.

Prospective approach

The crude association between weight change and diabetes remained essentially unchanged after adjustment for initial BMI and baseline characteristics (Table 3). The fully adjusted OR for 5-years weight change was 1.08, 95% CI: 1.04, 1.13 per kg change, 1.08, 95% CI 1.04, 1.12 per % change from initial weight and 1.27, 95% CI: 1.12, 1.44 per unit change in BMI. Persons with substantial weight gain had more than doubled risk for diabetes compared to persons with stable weight: adjusted OR 2.4, 95% CI: 1.4, 4.0.
It appears that the odds ratio for diabetes associated with 5-years weight change (OR 1.27, 95% CI: 1.12, 1.44 per unit of BMI) is not larger than the odds ratio for diabetes associated with a one unit difference in attained BMI (OR 1.23, 95% CI: 1.19, 1.27). This suggests that the association between weight change and diabetes might be explained by differences in the attained level of BMI (see also Figure 1A).

Table 2. Absolute and Relative Risks (Odds Ratios) for 5-Years Diabetes Incidence According to Baseline Characteristics and Weight Variables, Doetinchem Cohort Study, the Netherlands, 1987-2007.

	Observations [a]	Cases [b]	Cumulative diabetes incidence (%)	Odds ratio [c]	95% CI
All	7837	124	1.6		
Men	3831	71	1.9	1.0 ref	
Women	4006	53	1.3	0.7	0.5, 1.1
Age d					
age 25-49	4634	34	0.7	1.0 ref	
age 50-70	3203	90	2.8	3.9	2.6, 5.8
Initial BMI unit					
BMI< 25	4476	17	0.4	1.0	
BMI 25-30	2837	66	2.3	4.4	2.5, 7.6
BMI>30	520	41	7.9	15.7	8.7, 28.3
5-years weight change					
gain > 6.0 kg	1139	29	2.6	2.8	1.7, 4.5
gain 4.0 - 6.0 kg	1141	20	1.8	1.6	0.9, 2.7
gain 2.0 - 4.0 kg	1663	19	1.1	0.9	0.5, 1.6
stable ± 2.0 kg	2986	42	1.4	1.0	
loss > 2.0 kg	895	14	1.6	1.0	0.6, 1.9
Attained BMI unit					
BMI< 25	3665	11	0.3	1.0	
BMI 25-30	3324	57	1.7	4.2	2.2, 8.1
BMI>30	838	56	6.7	17.3	8.9, 33.5

[a] 3578 of 4259 participants contributed observations to both clusters (Figure 2)
[b] Incident cases (self-reported diabetes) in cluster 1 or cluster 2 (Figure 2)
[c] Adjusted for age, age*age and gender
[d] Attained age (after the 5-years weight change period, Figure 2)

Table 3. Prospective Approach: Adjusted Odds Ratio's for Diabetes Incidence in the 5 Years Following the Weight Change Period, According to 5-Years Weight Change, Adjusted for Initial BMI

	Model 1		Model 2	
	OR	95% CI	OR	95% CI
5-years weight change (per kg) [a]	1.07	1.02, 1.11	1.08	1.04, 1.13
5-years weight change (per %) [a]	1.06	1.02, 1.10	1.08	1.04, 1.12
5-years change in BMI (per unit) [a]	1.21	1.07, 1.36	1.27	1.12, 1.44
5-years weight change class [a]				
weight gain > 6.0 kg	2.0	1.2, 3.4	2.4	1.4, 4.0
weight gain 4.0 - 6.0 kg	1.3	0.8, 2.3	1.3	0.8, 2.3
weight gain 2.0 - 4.0 kg	0.9	0.5, 1.5	0.9	0.5, 1.6
stable weight ± 2.0 kg	1.0		1.0	
weight loss > 2.0 kg	0.8	0.4, 1.4	0.7	0.4, 1.3

[a] Each measure of weight change (per kg increase, per % increase from initial weight, per BMI unit or in weight change classes) is analyzed in a separate model
Model 1: adjusted for age, age*age, gender, and initial BMI
Model 2: adjusted for age, age*age, gender, initial BMI, initial hypertension and initial total/HDL cholesterol ratio

The impact of weight change (and attained BMI) on diabetes incidence was slightly modified by initial BMI (P = 0.12, for interaction). The adjusted OR for diabetes for persons with initial

BMI <30 was 1.38, 95% CI: 1.15, 1.65 per one unit change in BMI and 1.32, 95% CI: 1.22, 1.42, for a one unit difference in attained BMI. For persons with initial obesity the corresponding ORs were 1.14, 95% CI: 0.98, 1.34 and 1.11, 95% CI: 1.02, 1.20, respectively.

Retrospective approach

The crude association between 5-years weight change and diabetes disappeared completely after adjustment for attained BMI (Table 4). The fully adjusted OR for 5-years weight change was 0.99, 95% CI: 0.94, 1.04 per kg weight change, 0.99, 95% CI: 0.95, 1.03 per % change from initial weight and 0.97, 95% CI: 0.84, 1.12 per unit change in BMI. This association was not modified by the level of attained BMI: the association was similar for persons with attained BMI lower than 30 and persons with attained BMI higher than 30.

Sensitivity analyses

The results remained essentially similar when the analyses were based on cases with *confirmed* incident type 2 diabetes only: fully adjusted odds ratios were 1.12, 95% CI: 1.07, 1.17 per kg weight change in the prospective approach and 1.02, 95% CI: 0.96, 1.08 per kg change in the retrospective approach.

Table 4. Retrospective Approach: Adjusted Odds Ratio's for Diabetes Incidence in the 5 Years Following the Weight Change Period, According to 5-Years Weight Change, Adjusted for Attained BMI

	Model 1		Model 2	
	OR	95% CI	OR	95% CI
5-years weight change (per kg) [a]	1.00	0.95, 1.05	0.99	0.94, 1.04
5-years weight change (per %) [a]	1.00	0.96, 1.04	0.99	0.95, 1.03
5-years change in BMI (per unit) [a]	1.00	0.87, 1.14	0.97	0.84, 1.12
5-years weight change class [a]				
weight gain > 6.0 kg	1.1	0.7, 1.9	1.0	0.6, 1.7
weight gain 4.0 - 6.0 kg	0.9	0.5, 1.5	0.8	0.5, 1.4
weight gain 2.0 - 4.0 kg	0.7	0.4, 1.3	0.7	0.4, 1.2
stable weight ± 2.0 kg	1.0		1.0	
weight loss > 2.0 kg	1.1	0.6, 2.0	1.1	0.6, 2.1

[a] Each measure of weight change (per kg increase, per % increase from initial weight, per BMI unit or in weight change classes) is analyzed in a separate model
Model 1: adjusted for age, age*age, gender, and attained BMI
Model 2: adjusted for age, age*age, gender, attained BMI, attained diastolic blood pressure and 5-years change in total/HDL cholesterol ratio

DISCUSSION

Our study shows that short-term weight change is associated with diabetes incidence in crude analyses as well as after adjustment for initial BMI. However, weight change is not associated with diabetes incidence if attained BMI is taken into account. Taken together, our results seem to imply that weight change does not affect diabetes incidence beyond its effect on attained BMI.

A literature search yielded fifteen previous observational studies in which the association between weight change and diabetes was explicitly addressed (9-23, table 1). There were

large differences between these studies with respect to the duration of the weight change period (ranging from two to more then 20 years) as well as the duration of follow-up that ranged from 0 to more than 20 years. Eleven studies compared diabetes risk for different categories of weight change compared to a 'stable' reference group. Nine studies (also) assessed a continuous association between weight change and diabetes. Weight change was generally assessed as absolute change in kg or units BMI.

Most studies assessed the association between weight change and diabetes with adjustment for initial BMI and most of these studies reported positive associations. For example, Colditz et al. (12) showed that weight gain from young adulthood until early midlife increased diabetes risk among women in the Nurses' Health Study and stressed the importance of maintaining a constant weight throughout adult life. Oguma et al. (9) reported very similar findings for men and concluded that avoidance of weight gain is important even among those who are initially lean. Mishra et al. (16) did not find a continuous effect of short-term weight change on diabetes incidence after adjustment for initial BMI, but women with a high gain had a higher risk for diabetes than women with stable weight.

Only four studies examined the association between weight change and diabetes while taking account of attained (11,18) or 'average' weight (19,22). In one other study (23), attained BMI was used as stratification variable to assess the impact of duration of overweight and obesity on diabetes risk. Brancati et al. (11) reported that weight change between age 25 and 45 was crudely associated with diabetes incidence after age 50, but not after adjustment for attained weight at age 45. This suggests that long-term weight change does not affect diabetes incidence beyond its effect on attained BMI. However, Black et al. (18) found that the risk of diabetes at age 51 increased by weight gain from age 20 to age 31 but not by weight gain from age 33 to 44 or by recent weight gain from age 44 to 51, suggesting that the impact of weight change might differ between specific stages in life. In the study by Waring at al. (19), weight change between age 40 and 50 was not associated with diabetes incidence after age 50 in crude analyses, maybe due to the long duration of follow-up in this study (average 24 years), and this negative result remained after adjustment for either 'overall weight status' during the weight change period, or 'recent' weight. In the study by Field et al. (22), the impact of weight gain between 1989 and 1993 appeared to have a larger impact on diabetes incidence in the subsequent 6 years than 'recent' weight gain in the four years period prior to the development of diabetes, after adjustment for average weight during this latter period. Again, the findings suggest that the impact of weight change might be different during different periods of life.

We explored the impact of weight change on diabetes incidence from two different points of view. The results from the prospective analyses showed that substantial weight gain is associated with a higher risk for diabetes; persons who gain more than 6 kg over 5 years have more than doubled risk to develop diabetes in the subsequent five years compared to persons with stable weight. The significant, continuous association between weight change and diabetes also suggests that weight loss is associated with a lower risk for diabetes, and underscores the potential benefits of weight loss interventions. Weight loss over five years was also associated with a lower risk to develop diabetes in men in the British regional heart

study (17), but there was no evidence for weight loss to be associated with a lower risk for major cardiovascular disease (CVD) events. On the other hand, men who gained weight (> 10% in five years) had a higher risk for diabetes as well as for CVD. Based on these results it seems justified to conclude that weight loss appears beneficial in order to prevent diabetes, but at least (substantial) weight gain should be avoided.
The results from our retrospective analyses suggest that recent weight change history is not an independent risk factor for diabetes. This finding could be of interest for clinicians, who have to decide upon possible treatments, for epidemiologists who are engaged in risk prediction or for those who are interested in the causation of diabetes. We showed in our introduction (Figure 1b) that the results from a 'retrospective analysis' are difficult to interpret and that potential effects of initial BMI and weight change can not be separated. However, together with our results from the prospective approach, we showed that the impact of weight change on diabetes incidence can be explained through its effect on attained BMI. Our results imply that weight change history is not an independent risk factor for diabetes and not an important additional factor to consider in clinical or epidemiological prediction models (26-28). However, since only a few former studies have applied this 'retrospective approach', further research is required to explore the impact of short-term weight change, long-term weight change and weight change at different stages of life.

The Doetinchem Cohort Study is a population based study with repeated measurements for over four thousand Dutch men and women of different ages. The comprehensiveness of the study enabled us to adjust for many lifestyle variables such as physical activity, alcohol and smoking, as well as for biomedical factors such as blood pressure and cholesterol. Due to the physical examinations in each round, all our analyses were based on measured weight variables, in contrast to many other studies that have to rely on self-reported weight.
There were also some limitations. First, identification of cases was based on self-reported diabetes and we might have missed persons with undiagnosed diabetes. This potential misclassification could have caused an underestimation of the associations that were found. Self-reported diabetes in our study appeared to be quite accurate and our results remained essentially similar when the analyses were restricted to diabetic cases with confirmed incident type 2 diabetes. Second, we do not know the reasons for weight loss. (Intentional) weight loss could be advised by a physician to persons with unfavorable risk profiles and unintentional weight loss might be caused by pre-clinical disease. Although both reasons could cause weight loss to be associated with a higher risk for diabetes (14,17), our results suggest that weight loss is associated with a lower risk of diabetes. Finally, information about weight cycling during the 5-year periods was not available. However, although weight cycling appeared associated with diabetes incidence in both the Framingham Heart Study (19) and the Nurses' Health study II (22), the associations between weight cycling and diabetes disappeared in both studies after adjustment for respectively 'overall weight status' (19) or attained BMI (22).

In conclusion, weight change is associated with diabetes incidence because, conditional on initial BMI, weight change determines attained BMI. This implies that lifestyle interventions

can contribute to diabetes prevention because these interventions can influence attained BMI. Weight change history appears to have no effect on diabetes incidence beyond its effect on attained BMI.

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References

1. Weinstein AR, Sesso HD, Lee IM, et al. Relationship of physical activity vs body mass index with type 2 diabetes in women. *JAMA* 2004;292(10):1188-94.

2. Field AE, Coakley EH, Must A, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med* 2001;161(13):1581-6.

3. Folsom AR, Kushi LH, Anderson KE, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. *Arch Intern Med* 2000;160(14):2117-28.

4. Hartemink N, Boshuizen HC, Nagelkerke NJD, et al. Combining risk estimates from observational studies with different exposure cutpoints: a meta-analysis on body mass index and diabetes type 2. *Am J Epidemiol* 2006;163(11):1042-52.

5. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.

6. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344(18):1343-50.

7. Orozco LJ, Buchleitner AM, Gimenez-Perez G, et al. Exercise or exercise and diet for preventing type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2008;3;CD003054.

8. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 2006;29(9):2102-7.

9. Oguma Y, Sesso HD, Paffenbarger RS, et al. Weight change and risk of developing type 2 diabetes. *Obes Res* 2005;13(5):945-51.

10. Koh-Banerjee P, Wang Y, Hu FB, et al. Changes in body weight and body fat distribution as risk

factors for clinical diabetes in US men. *Am J Epidemiol* 2004;159(12):1150-9.

11. Brancati FL, Wang N, Mead LA, et al. Body weight patterns from 20 to 49 years of age and subsequent risk for diabetes mellitus: the Johns Hopkins Precursors Study. *Arch Intern Med* 1999;159:957-63.

12. Colditz GA, Willett WC, Rotnitzky A, et al. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 1995;122(7):481-6.

13. Chan JM, Rimm EB, Colditz GA, et al. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 1994;17(9):961-9.

14. Will JC, Williamson DF, Ford ES. Intentional weight loss and 13-year diabetes incidence in overweight adults. *Am J Public Health* 2002;92(8):1245-48.

15. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence. Findings from a national cohort of US adults. *Am J Epidemiol* 1997;146(3):214-22.

16. Mishra GD, Carrigan G, Brown WJ et al. Short-term weight change and the incidence of diabetes in midlife: results from the Australian Longitudinal Study on Women's Health. *Diabetes Care* 2007;30(6):1418-24.

17. Wannamethee SG, Shaper AG, Walker M. Overweight and obesity and weight change in middle aged men: impact on cardiovascular disease and diabetes. *J Epidemiol Community Health* 2005;59:134-9.

18. Black E, Holst C, Astrup A, et al. Long-term influences of body-weight changes, independent of the attained weight, on the risk of IGT and type 2 diabetes. *Diabetic Medicine* 2005; 22:1199-1205.

19. Waring ME, Eaton CB, Lasaer TM, et al. Incident diabetes in relation to weight patterns during middle age. *Am J of Epidemiol* 2010;171(5):550-556.

20. Schienkiewitz A, Schulze MB, Hoffman K, et al. Body mass index history and risk of type 2 diabetes: results from the European prospective investigation into cancer and nutrition (EPIC)-Potsdam study. *Am J Clinical Nutrition* 2006:84:427-33.

21. Resnick HE, Valsania P, Halter JB, et al. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. *J Epidemiol Community Health* 2000;54:596-602.

22. Field AE, Manson JE, Laird N, et al. Weight cycling and the risk of developing type 2 diabetes among adult women in the United States. *Obes Res* 2004;12(2):267-74.

23. Wannamethee SG, Shaper AG. Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. *Diabetes Care* 1999;22(8):1266-72.

24. Hofman A. Change viewed on the level. *Int J Epidemiol* 1983;12(4):391-2.

25. Verschuren WM, Blokstra A, Picavet HS, et al. Cohort profile: the Doetinchem Cohort Study. *Int J Epidemiol* 2008;37(6):1236-41.

26. Schwarz PE, Li J, Lindstrom J, et al. Tools for predicting the risk of type 2 diabetes in daily practice. *Horm Metab Res* 2009;41:86-97.

27. Hoogenveen RT, van Baal PH, Boshuizen HC. Chronic disease projections in heterogeneous ageing populations: approximating multi-state models of joint distributions by modelling marginal distributions. *Math Med Biol* 2010;27(1):1-19.

28. Jacobs-van der Bruggen MA, Bos G, Bemelmans WJ, et al. Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modeling study. *Diabetes Care* 2007;30(1):128-34.

Chapter 3. Alcohol use, cigarette smoking and the incidence of type 2 diabetes: findings from a prospective cohort study in the Netherlands

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Alcohol use, cigarette smoking and the incidence of type 2 diabetes: findings from a prospective cohort study in the Netherlands

ABSTRACT

Background: The potential roles of alcohol consumption and smoking in diabetes prevention are not entirely clear. Furthermore, only few studies explored the interaction between alcohol and smoking with respect to diabetes risk.

Methods: A prospective cohort study was conducted among 20 119 Dutch adults, aged 20-59 years at baseline, followed for 7.8 years on average. Adjusted hazard ratios (HR) were determined to quantify the associations between alcohol use, cigarette smoking and self-reported diabetes incidence.

Results: During 156 387 person-years 308 persons developed type 2 diabetes. A significant U-shaped association between alcohol consumption and diabetes incidence was observed in women. Compared to moderate drinkers, adjusted hazard ratios were 2.54 (1.26-5.13) for abstainers, 2.16 (1.09-4.31) for occasional drinkers, 1.69 (0.83-3.45) for light drinkers and 1.93 (0.73-5.10) for heavy drinkers. No significant association between alcohol consumption and diabetes risk was found in men. Compared to never smoking, current smoking of at least ten cigarettes per day tended to increase diabetes risk in both men and women. Interaction between smoking and alcohol consumption with respect to diabetes risk was found for men. Alcohol consumption tended to decrease diabetes risk only among former smokers. Current smoking increased diabetes risk among drinkers only.

Conclusions: In order to prevent diabetes, women who drink moderately and safely may not need to change their drinking habits, but smoking should be discouraged. In males, interaction between lifestyle risk factors, their mechanisms and potential implications for diabetes prevention should be further explored.

BACKGROUND

The prevalence of diabetes is growing steadily and is expected to have doubled by the year 2030 (1). Type 2 diabetes accounts for the majority of cases and is, besides hereditary factors, strongly associated with lifestyle-aspects such as being overweight and physically inactive (2). These lifestyle factors have become the main subject of prevention programs. However, other risk factors may also play a role, such as the consumption of alcohol and cigarette smoking, both modifiable aspects of behavior and potentially of added value in preventing diabetes.

Moderate alcohol consumption has been found to reduce diabetes risk in most (3-15), but not all studies (16). Two meta-analyses reported a U-shaped relationship where both low and high alcohol intake were associated with a higher diabetes risk compared to moderate alcohol intake (11,12). However, inconsistent results have been found with respect to high alcohol intake, both for men and for women (6,7,9,10,13,15,17).

Smoking has been reported to increase diabetes risk by almost all previous studies, but a lack of association has also been observed (16,29). Most studies found higher diabetes risks for heavy smokers as compared to light smokers or an increase in diabetes risk with the amount smoked (19,22,30). In general, results for men and women are not substantially different (19,20). The relative risk for active smokers to develop diabetes compared with nonsmokers is approximately 1.4, as estimated in a recent meta-analysis (31).

Although "unhealthy habits" such as smoking and drinking tend to cluster, few studies have explored the joint relationship of alcohol and smoking with diabetes. One study reported the absence of interaction between alcohol intake and cigarette smoking with respect to diabetes risk in women (7). In the British Regional Heart Study, the protective effect of alcohol was more prominent in smoking men compared to non-smoking men (6).

The aim of this study is to further examine the relationship between alcohol, smoking and diabetes, in a large Dutch population based cohort. In addition, the joint effect of alcohol and smoking on the incidence of type 2 diabetes will be explored.

RESEARCH DESIGN AND METHODS

Participants

Since 1987 two consecutive monitoring studies have been conducted to evaluate the health situation and occurrence of risk factors in the Netherlands: the Monitoring Project on Cardiovascular Disease Risk Factors and the Monitoring Project on Chronic Diseases Risk Factors (MORGEN-project). Prospective data was gathered on men and women aged 20 to 59 in the towns Doetinchem and Maastricht, in three rounds conducted between 1987 and 2002, as was described previously by van Dam and Feskens (32). Participants visited the municipal health service where they answered a questionnaire and underwent a physical examination. In Doetinchem baseline data were retrieved in the first round (1987 to 1991), while diabetes status was retrieved from the latest follow-up survey available (1993 to 1997 or 1998 to 2002).

In Maastricht, cross-sectional samples were drawn in the first and second round, while diabetes status was assessed with a short questionnaire that was sent to all participants in 1998. All participants gave written informed consent and approval was obtained from the local ethics committee.

Persons with self reported diabetes at baseline were excluded (n=241), as were pregnant women (n=193), subjects with a history of cardiovascular disease (n=418) and subjects with a nationality other than Dutch (n=748). Persons with missing values on any of the diabetes risk factors were also excluded (n=160). Finally, we excluded persons with missing diabetes status at follow-up (n=43) or who were considered probable type 1 diabetics, based on self-reported diabetes diagnosed before age 40 and treated with insulin within six months of diagnosis (n=17). The final study population totaled 20 119 persons (9236 men and 10 883 women), with a total follow-up of 156 387 person-years.

Assessment of variables and outcome

To assess alcohol habits, subjects were asked whether they consumed alcohol at the time and the amount of consumed glasses per week. The variable was divided into four categories based on the Dutch Institute for Health Promotion and Prevention of Diseases' guidelines on safe alcohol use; 1. never drinkers, 2. former drinkers, 3. occasional drinkers: less than 1 consumption per week, 2. light drinkers: 0 to 1.5 drinks/day (men) and 0 to 1.0 (women), 3. moderate drinkers: 1.5 to 3.0 drinks/day (men) and 1.0 to 2.0 (women) and 4. heavy drinkers: 3 or more drinks/day (men) and 2 or more (women). One standard drink contains 10 gram of alcohol on average. People were asked whether they currently smoked cigarettes and if so, the average number of cigarettes each day. Cigarette smoking was categorized into three levels: never, former or current smoker. In addition current smokers were classified into three categories (<10, 10 to 19 or ≥20 cigarettes/day).

Height and weight were measured and used to calculate BMI as weight in kilograms divided by the height in squared meters.

In contrast to all other variables used, the questions and response options for physical activity during leisure time differed between both monitoring projects. The variable was dichotomized into active or inactive. Active was defined as at least 4 hours of activity per week, with undefined intensity, in the Monitoring Project on Cardiovascular Disease Risk Factors, while active was defined as at least three hours of activity per week, with at least moderate intensity, in the Monitoring Project on Chronic Diseases Risk Factors. The different definitions were chosen in such a way that the proportion of people who were classified as active was more or less similar for both projects in consecutive years. Socio-economic status was classified into lower, intermediate and higher socio-economic status based on highest level of education and current employment. Questionnaires were also used to gather information on family history of diabetes in a first-degree relative (yes, no or unknown) and coffee consumption.

To assess diabetes status at baseline and follow-up subjects were asked whether they had ever been diagnosed with diabetes (yes or no) and if so, at what age. Also, treatment modality was asked for (diet, oral medication, insulin injections or none at all) and specifically the use of insulin in the first six months after diagnosis. Since subjects also reported the year of diagnosis, time between baseline and diagnosis of diabetes or time between baseline and end of follow-up for non-cases could be calculated (in years).

Statistical analysis

All analyses were conducted with SPSS version 12.0 (SPSS Inc., Chicago, Illinois). To assess the statistical significance of the differences between men and women with and without diabetes, t-tests and chi-square analyses were used. To verify whether relative risks were constant over time, Kaplan Meier survival curves were generated. After that, multivariate analyses using Cox's proportional-hazards were carried out. For alcohol moderate drinkers were the referent group, for smoking the never smokers were referent, because they were expected to have the lowest diabetes risk. Former drinkers were excluded from the analyses for alcohol.

Analyses were carried out in 4 steps. Model 1 adjusted for age and age squared. In model 2 the modifiable aspects of lifestyle (consumption of coffee, physical activity, alcohol and smoking) and familial diabetes were added. BMI and BMI squared were added in model 3 and socio-economic status was added in model 4. 95% Confidence intervals were calculated, the significance level was set at $p<0.05$ (two sided). Indications for interaction were assessed with the age adjusted model (model 1). Stratified analyses were conducted if the p value for the interaction term was lower than 0.10.

RESULTS

Baseline characteristics

Of 20 119 subjects, 308 developed diabetes (1.5%), during an average follow-up of 7.8 years; 168 men (1.7%) and 140 women (1.2%, table 1). Subjects that developed diabetes were more likely to be older and male and to have a higher BMI than subjects that did not. Also, they were more likely to be inactive, have a lower socio-economic status and to have a first degree relative with diabetes. Alcohol habits differed substantially between sexes, while smoking patterns for men and women were very similar.

Alcohol and type 2 diabetes

There was some indication for interaction between alcohol and gender with respect to diabetes risk (p for interaction 0.06) and thus analyses were conducted for men and women separately (table 2).

In men, non drinkers (ex-drinkers excluded) had the highest diabetes risk but no significant associations between alcohol consumption and diabetes risk were observed.

In women the risk pattern for diabetes was U-shaped. Not drinking or occasional drinking were significant risk factors when compared to moderate drinking, with fully adjusted hazard ratios of 2.54 (1.26-5.13) and 2.16 (1.09-4.31) respectively. The HRs for light and heavy drinking compared to moderate drinking were 1.69 (0.83-3.45) and 1.93 (0.73-5.10) respectively.

Smoking and type 2 diabetes

There was some interaction between smoking and gender with respect to diabetes risk (p for interaction 0.07) and therefore gender specific analyses were conducted.

In men, former smoking and smoking of at least ten cigarettes per day tended to increase diabetes risk, although not significant (table 3). Also in women, smoking of at least ten

cigarettes per day increased diabetes risk with a significantly increased risk in women smoking 10 to 19 cigarettes per day, HR 1.66 (1.04-2.66). There was no evidence for an increased diabetes risk for female ex-smokers.
After adjustment for confounders, no significant dose-response associations between smoking and diabetes risk were observed within current smokers.

Table 1. Baseline characteristics by gender and diabetes status

Variable	Men			Women		
	Diabetes Yes (n=168)	No (n=9068)	p	Diabetes Yes (n=140)	No (n=10 743)	p
Mean±SD for age (years)	48.5±7.3	40.9±10.4	<0.01	48.7±8.0	40.7±10.7	<0.01
Mean±SD for BMI (kg/m²)	29.4±3.9	25.3±3.2	<0.01	29.9±5.1	24.4±3.8	<0.01
Mean±SD coffee (cups/day)	5.5±3.3	5.4±3.0	0.60	4.8±3.0	4.5±2.8	0.30
Alcohol, n(%)‡			0.14			<0.01
Former drinker	3 (1.8)	128 (1.4)		3 (2.1)	95 (0.9)	
Non drinker	13 (7.7)	408 (4.5)		42 (30.0)	1846 (17.2)	
Occasional drinker	15 (8.9)	1186 (13.1)		46 (32.9)	3420 (31.8)	
Light	73 (43.5)	3583 (39.5)		32 (22.9)	3006 (28.0)	
Moderate	39 (23.2)	2243 (24.7)		10 (7.1)	1708 (15.9)	
Heavy	25 (14.9)	1520 (16.8)		7 (5.0)	668 (6.2)	
Smoking, n(%)			<0.01			0.19
Never	34 (20.2)	2821 (31.1)		66 (47.1)	4318 (40.2)	
Former	81 (48.2)	3095 (34.1)		22 (15.7)	2484 (23.1)	
<10/day	5 (3.0)	691 (7.6)		10 (7.1)	990 (9.2)	
10-19/day	19 (11.3)	1238 (13.7)		26 (18.6)	1710 (15.9)	
≥20/day	28 (16.7)	1222 (13.5)		16 (11.4)	1234 (11.5)	
Family history dm, n(%)			<0.01			<0.01
Positive	63 (37.5)	1411 (15.6)		63 (45.0)	1950 (18.2)	
Negative	87 (51.8)	6985 (77.0)		59 (42.1)	8039 (74.8)	
Unknown	18 (10.7)	672 (7.4)		18 (12.9)	754 (7.0)	
SES, n(%)			<0.01			<0.01
Lower	111 (66.1)	4712 (52.0)		119 (85.0)	6878 (64.0)	
Intermediate	29 (17.3)	2274 (25.1)		14 (10.0)	2208 (20.6)	
Higher	26 (15.5)	2066 (22.8)		7 (5.0)	1624 (15.1)	
Physically inactive, n(%)	70 (41.7)	2728 (30.1)	<0.01	62 (44.3)	3829 (35.6)	0.03

SD standard deviation, SES socio-economic status. ‡ Occasional < 1 drink/week, light > 1 drink/week – 1.5 drinks/day (men), > 1 drink/week – 1.0 drinks/day (women), moderate 1.5 – 3.0 drinks/day (men), 1.0 – 2.0 drinks/day (women), heavy ≥3.0 drinks/day (men), ≥2.0 drinks/day (women).

Alcohol and smoking combined

Alcohol consumption was dichotomized into more or less than one consumption per week (non drinkers and occasional drinkers combined) to assess a possible clustering of lifestyle habits and to assess whether there is interaction between alcohol consumption and smoking status with respect to diabetes risk.

Alcohol consumption and smoking habits appeared to cluster. Among never smoking men, 25% drink less than one alcohol consumption per week, as compared to only 15% in current smokers and 14% in former smokers. The corresponding figures for women are 59% versus 45% and 41%. Correspondingly, among men and women who drink less than one alcohol

consumption per week, 44% and 48% are never smokers compared to 28% and 33% among men and women drinking more than one consumption per week.

There was some interaction between alcohol consumption and smoking with respect to diabetes risk in men (p=0.06), but not in women (p=0.69). The hazard ratio's for diabetes for drinking more versus less than one consumption per week in men were 1.89 (0.68-5.24), 0.60 (0.35-1.04) and 1.65 (0.70-3.93) among current, former and never smokers, respectively. The hazard ratios for smoking more than 10 cigarettes per day versus never-smoking were 0.71 (0.17-2.90) and 1.44 (0.87-2.37) among men who consume less or more than one alcohol consumption per week, respectively. For men, new categories based on both alcohol consumption and smoking status were constructed with never smokers who consumed more than one alcohol consumption per week as the referent category. Former smokers who consumed less than one alcohol consumption per week had the highest diabetes risk: HR 1.91 (1.03-3.53, table 4).

Table 2. Hazard ratios (95% CI) for type 2 diabetes by alcohol categories in different models†

Alcohol categories‡	Non drinkers	Occasional	Light	Moderate	Heavy	p§
Men						
cases / py	13 / 3242	15 / 9166	73 / 29 403	39 / 17 897	25 / 11 788	
Model 1	1.83 (0.98-3.43)	0.79 (0.43-1.43)	1.16 (0.78-1.70)	1.0 (ref.)	0.97 (0.59-1.61)	0.36
Model 2	1.50 (0.78-2.89)	0.79 (0.44-1.44)	1.17 (0.79-1.72)	1.0 (ref.)	0.92 (0.56-1.53)	0.60
Model 3	1.38 (0.72-2.67)	0.93 (0.51-1.69)	1.25 (0.84-1.84)	1.0 (ref.)	0.95 (0.58-1.58)	0.35
Model 4	1.38 (0.71-2.68)	0.94 (0.51-1.70)	1.23 (0.83-1.82)	1.0 (ref.)	0.92 (0.55-1.53)	0.32
Women						
cases / py	45 / 14 484	46 / 26 360	32 / 23 939	10 / 13 224	7 / 5080	
Model 1	3.61 (1.81-7.21)	2.78 (1.40-5.52)	1.92 (0.94-3.90)	1.0 (ref.)	1.79 (0.68-4.71)	<0.01
Model 2	3.27 (1.63-6.57)	2.62 (1.32-5.22)	1.88 (0.92-3.84)	1.0 (ref.)	1.75 (0.66-4.61)	<0.01
Model 3	2.58 (1.28-5.19)	2.19 (1.10-4.37)	1.71 (0.84-3.49)	1.0 (ref.)	1.94 (0.73-5.12)	0.05
Model 4	2.54 (1.26-5.13)	2.16 (1.09-4.31)	1.69 (0.83-3.45)	1.0 (ref.)	1.93 (0.73-5.10)	0.05

† Model 1 adjusted for age, model 2 adjusted for model 1 + coffee, physical activity, smoking and familial diabetes, model 3 adjusted for model 2 + BMI, model 4 adjusted for model 3 + socio-economic status. ‡ Occasional < 1 drink/week, light > 1 drink/week – 1.5 drinks/day (men), > 1 drink/week – 1.0 drinks/day (women), moderate 1.5 – 3.0 drinks/day (men), 1.0 – 2.0 drinks/day (women), heavy ≥3.0 drinks/day (men), ≥2.0 drinks/day (women). § p-value for exponential trend (drinks/day squared); py: person years

Table 3. Hazard ratios (95% CI) for type 2 diabetes by smoking categories for different models†

Smoking categories						p #
	Never	Former	<10/day	10-19/day	≥20/day	
Men						
cases /py	34 / 22 246	81 / 24 866	5 / 5 284	19 / 10 121	28 / 9 987	
Model 1	1.0 (ref.)	1.34 (0.89-2.00)	0.53 (0.21-1.34)	1.05 (0.60-1.84)	1.32 (0.80-2.18)	0.05
Model 2	1.0 (ref.)	1.37 (0.91-2.06)	0.57 (0.22-1.45)	1.04 (0.59-1.84)	1.24 (0.73-2.13)	0.06
Model 3	1.0 (ref.)	1.40 (0.93-2.10)	0.59 (0.23-1.51)	1.39 (0.79-2.46)	1.40 (0.82-2.38)	0.10
Model 4	1.0 (ref.)	1.37 (0.91-2.06)	0.59 (0.23-1.51)	1.43 (0.80-2.53)	1.44 (0.84-2.45)	0.10
Women						
cases /py	66 / 34 039	22 / 19 001	10 / 7 573	26 / 13 599	16 / 9 634	
Model 1	1.0 (ref.)	0.68 (0.42-1.11)	0.83 (0.43-1.62)	1.20 (0.76-1.90)	1.00 (0.58-1.74)	0.75
Model 2	1.0 (ref.)	0.82 (0.50-1.34)	0.96 (0.49-1.88)	1.31 (0.82-2.11)	1.13 (0.63-2.01)	0.99
Model 3	1.0 (ref.)	0.83 (0.51-1.35)	1.08 (0.55-2.12)	1.66 (1.04-2.66)	1.39 (0.78-2.46)	0.96
Model 4	1.0 (ref.)	0.84 (0.51-1.37)	1.08 (0.55-2.12)	1.64 (1.02-2.64)	1.39 (0.78-2.46)	0.96

† Model 1 adjusted for age, model 2 adjusted for model 1 + coffee, physical activity, alcohol consumption and familial diabetes, model 3 adjusted for model 2 + BMI, model 4 adjusted for model 3 + socio-economic status. # p for linear trend within current smokers: py: person years

Table 4. Hazard ratios (95% CI) for the joint effect of alcohol and smoking on diabetes incidence among men*

Smoking categories	Alcohol categories	
	Less than one alcohol consumption per week †	At least one consumption per week
Never		
Cases / person-years	7 / 5 454	27 / 20 438
Hazard ratio	0.72 (0.31-1.66)	1.0 (ref.)
Former		
Cases / person-years	17 / 3 365	61 / 21 084
Hazard ratio	1.91 (1.03-3.53)	1.11 (0.70-1.76)
Current		
Cases / person-years	4 / 3 594	49 / 21 391
Hazard ratio	0.64 (0.22-1.86)	1.23 (0.76-1.98)

* adjusted for age, coffee, physical activity, familial diabetes, BMI and SES (model 4).
† non drinkers and occasional drinkers combined, ex-drinkers excluded.

CONCLUSIONS

We evaluated the associations between alcohol consumption, smoking and the incidence of type 2 diabetes in a Dutch population. For women the relationship between alcohol and diabetes risk was U-shaped with the lowest risk for women consuming one to two drinks per day. In men, no significant association between alcohol consumption and diabetes risk was observed. Current smoking of at least 10 cigarettes per day tended to increase the risk of diabetes in both men and women, but a clear dose-response association was not found.

All analyses were adjusted for confounders in a stepwise manner, in order to observe the additional effect of adjusting for each factor. In women, adding BMI to the model attenuated the increased risk for non-, and occasional drinkers, but did not alter statistical significance. Additional adjustment for BMI increased the hazard ratios for diabetes for moderate and heavy smokers. The effect of additional adjustment for SES was ignorable.

Our results for alcohol consumption are partly consistent with previous findings. In 2005 Koppes et al. conducted a meta-analysis on the association between alcohol consumption and incidence of type 2 diabetes and concluded that moderate alcohol consumption reduces diabetes risk by ~30%, in an U-shaped manner (12). The systematic review by Howard et al. also reported a U-shaped relationship, with moderate alcohol consumption reducing diabetes risk by 33 – 56% (13). Both studies present their results for men and women combined. The U-shaped association has also been found for women specifically (3). Carlsson et al. reported results for men and women more similar to ours; abstaining increased the risk in both sexes and heavy alcohol intake increased the risk in women, but not in men (10).

Our finding for an increased diabetes risk among current smokers (although not significant) is concordant with findings from most previous studies (30). We did not find a significant dose-response association between smoking and diabetes risk, in contrast to some other studies that did report such association (22,24,25).

In men there appeared to be some interaction between alcohol and smoking status. Alcohol consumption reduced diabetes risk only among former smokers, while current smoking appeared to be a risk factor only for men drinking more than one alcohol consumption per week. However, the number of diabetes cases in some subgroups was very low and confidence intervals very wide. Overall, non-drinking, former smokers had the highest risk which may point at a 'sick quitter effect', where men stop drinking and smoking because of disease related complaints. However, former drinkers were already excluded from the analyses, as were men with a cardiovascular history at baseline, making it less likely that such an effect was present.

With respect to a possible interaction, Wannamethee et al. (6) found a more prominent risk reduction of light and moderate alcohol consumption (compared to non or occasional drinking) in currently smoking men as compared to non-smoking men. As Wannamethee included former smokers in the non smoking group, these result seem inconsistent with our findings. In 2003, the same researchers found no significant interaction, between smoking and drinking in younger women (7), which is consistent with our results.

Several potential limitations of our study need to be addressed. Like all epidemiological research into behavior and diabetes our study knew two major difficulties: obtaining accurate information on exposure and identifying all cases of diabetes. In this study, information on alcohol and smoking habits was based on subjects' self-report and was not validated. The reported amounts of alcohol and cigarettes were most probably underreported; the observed associations could in reality belong to a higher consumed amount of alcohol or number of cigarettes smoked.
Diabetes status was also self-reported and since many patients are unaware of the disease, this too was likely to have been underreported. However, assuming that the observed associations between alcohol and smoking and the incidence of diabetes are true, underreporting of diabetes would have attenuated the association. Authors who investigated the validity of self-reported diabetes report high levels of agreement between self-reported diabetes and medical records with κ-values for agreement varying from 0.67 (33), to 0.76 (34) and up to 0.84 (35). This suggests that the use of self-reported diabetes as an endpoint is justified. In order to evaluate the effect of potentially having included subjects with only impaired glucose tolerance, we repeated the analyses, restricted to diabetes subjects who used diabetes medication and the results remained essentially the same.

In conclusion, the results of this study support the evidence that alcohol and type 2 diabetes are related in a non-linear, U-shaped pattern in women, in which moderate alcohol use generates the lowest risk. It also supports previous findings that moderate and heavy smoking increase the risk of type 2 diabetes in both men and women. These findings suggest that, with respect to diabetes prevention, women who drink moderately and safely may not need to change their drinking habits, and should be encouraged to stop smoking. Our results also suggest that the association between alcohol consumption and diabetes risk in men may be modified by smoking habits (and vice versa). However, it seems preliminary to infer any subgroup recommendations such as for example discouraging moderate alcohol consumption in currently smoking or never smoking men. At least in males, further studies should explore the possible interaction between alcohol and smoking with respect to diabetes risk, what mechanisms are involved and what the potential consequences for diabetes prevention could be.

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References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004, 27:1047-53
2. Weinstein AR, Sesso HD, Lee IM, Cook NR, Manson JE, Buring JE, Gaziano JM. Relationship of physical activity vs body mass index with type 2 diabetes in women. JAMA 2004, 292:1188-94
3. Beulens JW, Stolk RP, van der Schouw YT, Grobbee DE, Hendriks HF, Bots ML. Alcohol consumption and risk of type 2 diabetes among older women. Diabetes Care 2005, 28:2933-8
4. Hu G, Jousilahti P, Peltonen M, Bidel S, Tuomilehto J. Joint association of coffee consumption and other factors to the risk of type 2 diabetes: a prospective study in Finland. Int J Obes (Lond) 2006, 30:1742-9
5. Djousse L, Biggs ML, Mukamal KJ, Siscovick DS. Alcohol consumption and type 2 diabetes among older adults: the cardiovascular health study. Obesity (Silver Spring) 2007, 15:1758-65
6. Wannamethee SG, Shaper AG, Perry IJ, Alberti KGMM. Alcohol consumption and the incidence of type II diabetes. J Epidemiol Community Health 2002, 56:542-8
7. Wannamethee SG, Camargo CA Jr, Manson JE, Willett WC, Rimm EB. Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. Arch Intern Med 2003, 163:1329-36
8. Kao WHL, Puddey IB, Boland LL, Watson RL, Brancati FL. Alcohol consumption and the risk of type 2 diabetes mellitus: atherosclerosis risk in communities study. Am J Epidemiol 2001, 154:748-57
9. Conigrave KM, Hu BF, Camargo CA Jr, Stampfer MJ, Willett WC, Rimm EB. A prospective study of drinking patterns in relation to risk of type 2 diabetes among men. Diabetes 2001, 50:2390-5
10. Carlsson S, Hammar N, Grill V, Kaprio J. Alcohol consumption and the incidence of type 2 diabetes: a 20-year follow-up of the Finnish twin cohort study. Diabetes Care 2003, 26:2785-90
11. Carlsson S, Hammar N, Grill V. Alcohol consumption and type 2 diabetes Meta-analysis of epidemiological studies indicates a U-shaped relationship. Diabetologia 2005, 48 (6):1051-4.
12. Koppes LLJ, Dekker JM, Hendriks HFJ, Bouter LM, Heine RJ. Moderate Alcohol Consumption Lowers the Risk of Type 2 Diabetes: A meta-analysis of prospective observational studies. Diabetes Care 2005, 28:719-25
13. Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on diabetes mellitus: a systematic review. Ann Intern Med 2004, 140:211-9
14. Schulze MB, Hu FB. Primary prevention of diabetes: what can be done and how much can be prevented? Annu Rev Public Health 2005, 26:445-67
15. Lapidus L, Bengtsson C, Bergfors E, Bjorkelund C, Spak F, Lissner L. Alcohol intake among women and its relationship to diabetes incidence and all-cause mortality: the 32-year follow-up of a population study of women in Gothenburg, Sweden. Diabetes Care 2005, 28:2230-5
16. Kumari M, Head J, Marmot M. Prospective study of social and other risk factors for incidence of type 2 diabetes in the Whitehall II study. Arch Intern Med 2004, 164:1873-80
17. Meisinger C, Thorand B, Schneider A, Stieber J, Doring A, Lowel H. Sex differences in risk factors for incident type 2 diabetes mellitus: the MONICA Augsburg cohort study. Arch Intern Med 2002, 162:82-9
18. Foy CG, Bell RA, Farmer DF, Goff DC Jr, Wagenknecht LE. Smoking and incidence of diabetes among U.S. adults: findings from the Insulin Resistance Atherosclerosis Study. Diabetes Care 2005, 28:2501-7

19. Patja K, Jousilahti P, Hu G, Valle T, Qiao Q, Tuomilehto J. Effects of smoking, obesity and physical activity on the risk of type 2 diabetes in middle-aged Finnish men and women. J Intern Med 2005, 258:356-62

20. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. Int J Epidemiol 2001, 30:540-6

21. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001, 345:790-7

22. Rimm EB, Manson JE, Stampfer MJ, et al. Cigarette smoking and the risk of diabetes in women. Am J Public Health 1993, 83:211-4

23. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. BMJ 1995, 310:555-9

24. Manson JE, Ajani UA, Liu S, Nathan DM, Hennekens CH. A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. Am J Med 2000, 109:538-42

25. Wannamethee SG, Shaper AG, Perry IJ. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. Diabetes Care 2001, 24:1590-5

26. 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. BMJ 1995, 310:560-4

27. Carlsson S, Midthjell K, Grill V. Smoking is associated with an increased risk of type 2 diabetes but a decreased risk of autoimmune diabetes in adults: an 11-year follow-up of incidence of diabetes in the Nord-Trondelag study. Diabetologia 2004, 47:1953-6

28. Feskens EJ, Kromhout D. Cardiovascular risk factors and the 25-year incidence of diabetes mellitus in middle-aged men. The Zutphen Study. Am J Epidemiol 1989, 130:1101-8

29. 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: 147(1)49-58

30. Meisinger C, Doring A, Thorand B, Lowel H. Association of cigarette smoking and tar and nicotine intake with development of type 2 diabetes mellitus in men and women from the general population: the MONICA/KORA Augsburg Cohort Study. Diabetologia 2006, 49:1770-6

31. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2007, 298(22):2654-64

32. van Dam RM, Feskens EJ. Coffee consumption and risk of type 2 diabetes mellitus. Lancet 2002, 360:1477-8

33. Robinson JR, Young TK, Roos LL, Gelskey DE. Estimating the burden of disease. Comparing administrative data and self-reports. Med Care 1997, 35:932-47

34. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. J Clin Epidemiol 2004, 57:1096-103

35. Skinner KM, Miller DR, Lincoln E, Lee A, Kazis LE. Concordance between respondent self-reports and medical records for chronic conditions: experience from the Veterans Health Study. J Ambul Care Manage 2005, 28:102-10

Chapter 4. Lifestyle interventions are cost-effective in people with different levels of diabetes risk

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Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modeling study

ABSTRACT

Objective: The current study explores the long-term health benefits and cost-effectiveness of both a community-based lifestyle program for the general population (community intervention) and an intensive lifestyle intervention for obese adults, implemented in a health care setting (health care intervention).

Research design and methods: Short-term intervention effects on Body Mass Index and physical activity were estimated from the international literature. The RIVM Chronic Diseases Model was used to project lifetime health effects and effects on health care costs for minimum and maximum estimates of short-term intervention effects. Cost-effectiveness was evaluated from a health care perspective and included intervention costs and related and unrelated medical costs. Effects and costs were discounted at 1.5% and 4.0% annually.

Results: One new case of diabetes per 20 years was prevented for every 7 to 30 participants in the health care intervention and for every 300 to 1500 adults in the community intervention. Intervention costs needed to prevent one new case of diabetes (per 20 years) were lower for the community intervention (€2000 to €9000) than for the health care intervention (€5000 to €21,000). The cost-effectiveness ratios were €3100 to €3900 per quality-adjusted life-year (QALY) for the community intervention and €3900 to €5500 per QALY for the health care intervention.

Conclusions: Health care interventions for high-risk groups and community-based lifestyle interventions targeted at the general population (low risk) are both cost-effective ways of curbing the growing burden of diabetes.

BACKGROUND

Risk factors for developing type 2 diabetes include a high body weight, physical inactivity, and smoking, while moderate consumption of alcohol or coffee appears to be protective (1-9). The most serious of these factors is being overweight. With every one-unit increase in body mass index (BMI), the risk of developing type 2 diabetes increases by approximately 10% to 30% (10). There is substantial evidence that lifestyle interventions focused at diet and physical exercise can reduce diabetes incidence in persons at high risk of developing diabetes (11-14). Although the direct effect of lifestyle interventions on diabetes incidence in other target populations is relatively unknown, it is suggested that a relatively small shift of the entire general population towards more healthy behavior could lead to a reduction in the incidence of diabetes (15).

Modeling can be used to assess the potential long-term impact of lifestyle programs on future health and health care costs. Such information is interesting to policy makers who have to decide on optimal allocation of limited budgets. Models have been used to demonstrate that intensive lifestyle modification programs are cost-effective for persons at high risk of developing diabetes (16,17). However the cost-effectiveness of such interventions for persons at lower risk of developing diabetes is relatively unknown (15,16,18-20). Only a few lifestyle intervention studies have directly assessed the incidence of diabetes in persons without a high risk of developing this disease (18,21). However, effects on the most important diabetes risk factors, BMI and physical inactivity, have been evaluated for different kinds of lifestyle interventions, in different target populations. The long-term impact of lifestyle interventions can be modeled through modifying risk factor levels, with the advantage that effects of risk factor modification on all cause mortality and diseases other than type 2 diabetes can be taken into account (22).

Therefore, the aim of this study is to explore and compare the cost-effectiveness of lifestyle interventions for persons at different levels of diabetes risk, using the RIVM Chronic Diseases Model (CDM). The CDM is a Markov type, dynamic population model which describes transitions between risk factors, chronic diseases and mortality (23). This allows the effects of risk factor modification on mortality and the incidence and prevalence of several diseases. A second aim is to explore the potential health benefits for large-scale implementation of lifestyle interventions in the Netherlands.

RESEARCH DESIGN AND METHODS

A large amount of data is available about the long-term effects of two types of interventions, namely community-based lifestyle programs and intensive lifestyle programs for high risk groups (24-27). Typically, community programs comprise mass media campaigns, and a range of activities in various settings aimed at changing risk factor behavior in the general population. Lifestyle interventions for high-risk groups are typically implemented in a health care setting and comprise dietary advice, exercise programs and/or behavior modification therapy for individuals or groups. The current study explores the lifetime health effects and cost-effectiveness of a once-only implementation of the following interventions:

1. A community-based program with a duration of 5 years, focusing on nutrition and exercise and targeted at the general population; further referred to as 'community intervention'.
2. An intensive lifestyle intervention with a duration of 3 years, focusing on diet and exercise, for adults with moderate risks of developing diabetes (obese adults 30-70 years), implemented in a health care setting; referred to as 'health care intervention'.

Short-term effects on BMI and physical (in)activity are estimated from published studies, which are representative for the aforementioned interventions. In general, community programs have modest effects on body weight and physical inactivity (25,28-32), while on average, the effects of health care interventions are larger (11,13,26,33). In the current study, potential intervention effects are expressed within a range that reflects the diversity of positive intervention effects that we found in the international literature.

Effects of the community intervention are defined as:
Minimum effect: Average BMI decreases by 0.05 kg/m2 and physical (in)activity is unchanged.
Maximum effect: Average BMI decreases by 0.25 kg/m2 and 15% of inactive persons increase their level of physical activity (to moderately active).
Effects are assumed for adults 20─80 years.

Effects of the 'health care intervention' are defined as:
Minimum effect: Average BMI decreases by 0.3 kg/m2 and 50% of inactive persons increase their level of physical activity (to moderately active).
Maximum effect: Average BMI decreases by 1.5 kg/m2, 75% of inactive persons become moderately active and 20% of moderately active persons increase their level of physical activity (to active).

In the current study, intervention costs are based on two Dutch projects. The community-based program entitled 'Hartslag Limburg' (Heart Health Limburg) aimed at decreasing the prevalence of cardiovascular diseases in the general population (34). Total intervention costs for activities focusing on nutrition and physical activity for 5 years were approximately €4.50 per inhabitant (or €6 per 20+ adult) in the target area (35).
The "Study on Lifestyle intervention and Impaired glucose tolerance Maastricht (SLIM)" is an intensive lifestyle intervention that aims to improve lifestyle in overweight subjects with impaired glucose tolerance by means of a 3-year dietary advice and an exercise program (36,37). The cost calculations for this intervention are briefly outlined in Appendix A. The costs for large-scale implementation are estimated at approximately €700 per participant, based on the assumption that 50% of the participants will participate in the exercise program.
Health effects, intervention costs and effects on health care costs are assumed to be proportional to the number of intervention participants (which implies that the cost-effectiveness ratios are independent on the reach of the interventions).

For each intervention, the CDM computes lifetime health effects, effects on health care costs, and costs per QALY resulting from the minimum and maximum estimated intervention effect. In the model each intervention is compared to a reference scenario which describes developments in the Dutch population when no interventions are applied.

The RIVM Chronic Diseases Model (CDM)

The CDM is a Markov-type, multistate transition model, developed at the Dutch National Institute for Public Health and the Environment (RIVM) (38-42). An extensive description of the CDM structure and the relevant input data used is given in Appendix B. The model was updated for diabetes in 2005 (43). In short, the model describes the development over time of demography, risk factor prevalence, disease incidence and mortality in the Dutch population. In the CDM, BMI and physical activity are each modeled in three classes: normal weight (BMI <25, class 1), overweight (BMI 25-30, class 2) and obesity (BMI ≥30, class 3), active (30 minutes of activity of moderate intensity on at least 5 days of the week, class 1), moderately active (30 minutes of activity of moderate intensity on 1-4 days of the week, class 2) and inactive (30 minutes of activity of moderate intensity on less than 1 day a week, class 3). BMI and physical activity are linked to all cause mortality, diabetes, cardiovascular diseases, musculoskeletal disorders and cancers through relative risks on disease incidence (43,44). Relative risks are based on international literature, while incidence, prevalence, transition rates and mortality rates in the model apply to the Dutch population. All data are age- and sex specific. Health care costs are based on the Costs of Illness study in the Netherlands (45,46). The Global and Dutch Burden of Disease studies are used to compute health effects in terms of quality-adjusted life-years (QALYs) (46-50). Recently the RIVM model was extended with a module for cost-effectiveness analyses (46). The cohort in the start year of the simulation resembles the total Dutch population at the end of 2004 (n=16.3 million). Newborns or migrants are not included in the analysis. The time step used for modeling is 1 year. A lifetime horizon (70 years) is applied.

Translation of intervention effects into model parameters

The intervention effects on BMI and physical activity were translated into altered prevalence rates in each risk factor class in the model. For example, we assumed that all adults in the Netherlands had been reached by the community intervention. At the end of year 5, the prevalence of normal weight (BMI class 1) in the 'community scenario' (maximum effect) was 2.4%-points higher compared to the reference scenario (52.4% versus 50%). The differences in BMI classes 1 to 3 and physical activity classes 1 to 3 (in %-points) were: +2.4, -1.1, -1.3, no change, +1.2 and -1.2, respectively. For the health care intervention, we assumed that 200,000 obese adults participated. In the "maximum effect scenario", differences between the intervention and reference scenario after 3 years in BMI classes 1 to 3 and physical activity classes 1 to 3 (in %-points) were: no change, +1.7, -1.7, +0.2, +0.1 and -0.3, respectively. After the interventions, yearly age- and gender specific transition probabilities between risk factor classes (for example the chance to gain weight with ageing) were equal for the intervention and reference scenarios. As a result of extinction of the intervention

'cohorts', the differences between intervention and reference scenarios gradually declined to zero.

Cost-effectiveness analysis

The cost-effectiveness analysis was performed from a health care perspective, meaning that only health-related effects and costs incurred by the health care system were included. A distinction was made between related and unrelated medical costs. Related medical costs are intervention costs and (prevented) medical costs for diseases linked to BMI or physical activity within the CDM. Unrelated medical costs are costs for illnesses, for example dementia, that may develop in life years gained as a result of the intervention. Costs and effects were discounted by 4% and 1.5% per year according to recent Dutch guidelines (51). A cost-effectiveness ratio below €20,000 per QALY gained was considered cost-effective (52,53).

Outcome measures

Intervention effects in terms of life-years and QALYs per person were estimated by dividing the total gain in life-years or QALYs resulting from the interventions (minimum and maximum estimate) by the number of assumed intervention participants in each intervention (12 million for the community intervention and 200,000 for the health care intervention). The same applied to effects on health care costs per person. The number needed to treat (NNT) to prevent one new case of diabetes or cardiovascular disease (in 20 years) was calculated by dividing the number of intervention participants by the cumulative number of incident cases prevented in 20 years. Cost-effectiveness ratios were determined for intervention costs per prevented diabetes case (in 20 years), intervention costs per QALY gained (lifetime), related costs per QALY gained (lifetime) and total costs per QALY gained (lifetime).

Sensitivity analysis

Analyses were performed in which intervention costs and discount rates were varied. Costs for the interventions were varied between €4 and €8 per adult for the community intervention and between €400, €1000 and €2000 (comparable to the intervention costs found in the DPP (54) per participant for the health care intervention. Both costs and effects were discounted by 0% or 4% per year. Discount rates of 3% on both costs and effects were calculated to enhance comparability with a former study (16).

RESULTS

Health effects

Outcomes for both interventions compared to the reference scenario (no intervention) are displayed in Table 1. On average health benefits per participant are larger for the health care intervention compared to the community intervention: 1.17 versus 0.04 QALYs based on the maximum estimated intervention effects. This can be interpreted as an average individual gain of 15 days versus 14 months of living in good health. The number needed to treat (NNT) is lower for the health care intervention: 7 to 30 obese adults should participate in a

health care intervention to prevent 1 new case of diabetes in 20 years, while a community program should reach 300 to 1500 adults to obtain the same result.

Table 1. Effects on health, health care costs and cost-effectiveness of lifestyle interventions

Outcome	Community intervention	Health care intervention
Health effects		
Life years *	0.007 to 0.043	0.32 to 1.35
	2 to 16 days	4 to 16 months
QALYs *	0.006 to 0.039	0.27 to 1.17
	2 to 15 days	3 to 14 months
NNT to prevent 1 case of diabetes in 20 years	1500 to 300	30 to 7
NNT to prevent 1 case of CVD in 20 years †	3700 to 400	60 to 18
Costs ‡		
Intervention costs	5.55	675
Δ Lifetime related medical costs	-10 to -70	-500 to -1700
Δ Lifetime unrelated medical costs	30 to 180	1300 to 5600
Δ Lifetime total medical costs	20 to 110	800 to 3900
Cost-effectiveness		
Intervention costs per QALY	900 to 140	2500 to 600
Related costs per QALY §	-500 to -1500	800 to -900
Total costs per QALY ‖	3900 to 3100	5500 to 3900

All ranges correspond to result when "minimum intervention effect" is assumed to result when "maximum intervention effect" is assumed; * effect per intervention participant; life-years and QALYs discounted by 1.5% per year; NNT: number needed to treat; † CVD: cardiovascular disease; ‡ costs per adult or intervention participant in 2005 in Euros, discounted by 4% per year; § intervention costs and lifetime related medical costs; ‖ intervention costs and lifetime total medical costs

Costs

Both interventions reduce cumulative lifetime medical costs for diabetes, cardiovascular diseases and other intervention-related diseases (related costs, Table 1). Unrelated and total medical costs increase because people live longer as a result of the interventions. For participants in the health care intervention, lifetime-related medical costs per person may be reduced by up to €1700. On the other hand, unrelated health care costs increase by €5600. Average lifetime total health care costs therefore increase by €3900 for participants in the health care intervention.

Cost-effectiveness

Intervention costs needed to prevent disease are lower for the community intervention; €1800 to €9000 (300 to 1500 *€6) to prevent one new case of diabetes in 20 years versus €4900 to €21,000 (7 to 30* €700) for the health care intervention (intervention costs not discounted). Related costs per QALY in the community intervention are negative because over a patient's lifetime, savings in related health care costs are larger than initial intervention costs. Whether the high costs of health care intervention are counterbalanced by savings in related health care costs depends on the intervention effect achieved. Cost-effectiveness ratios in which unrelated medical costs are accounted for are €3100 to €3900 per QALY for the community intervention and €3900 to €5500 for the health care intervention.

Sensitivity analyses

The results of the sensitivity analyses on QALYs and cost-effectiveness ratios are given in Table 2. Discounting health effects by 4% (versus 1.5% in the base-case analyses) reduces health benefits by approximately 50%. For both interventions, all cost-effectiveness ratios remain below €20,000 per QALY.

Table 2. Quality-adjusted life-years (QALYs) and cost-effectiveness of both interventions; sensitivity analyses

	QALYs	Related costs (€) / QALY	Total costs (€) / QALY
Community intervention			
Base-case analysis *	0.006 to 0.04	-500 to -1500	3900 to 3100
Intervention costs 4 /adult		-800 to -1600	3600 to 3100
Intervention costs 8 /adult		-200 to -1500	4200 to 3200
D.R. 0% costs and effects †	0.01 to 0.06	-1300 to -2300	10,000 to 9400
D.R. 3% costs and effects	0.004 to 0.03	-1100 to -2700	7700 to 6500
D.R. 4% costs and effects	0.003 to 0.02	-1000 to -2800	7200 to 5800
Health care intervention			
Base-case analysis ‡	0.27 to 1.17	800 to -900	5500 to 3900
Intervention costs 400 pp		-200 to -1100	4500 to 3600
Intervention costs 1000 pp		1900 to -600	6600 to 4100
Intervention costs 2000 pp		5400 to 200	10,100 to 4900
DR 0% costs and effects	0.41 to 1.75	-300 to -1300	12,000 to 11,200
DR 3% costs and effects	0.19 to 0.82	800 to -1600	10,000 to 7800
DR 4% costs and effects	0.15 to 0.66	1500 to -1600	10,000 to 6900

All ranges correspond to result when "minimum intervention effect" is assumed to result when "maximum intervention effect" is assumed; * intervention costs €6 per adult and discount rates 4% for costs and 1.5% for effects; † DR: discount rates; ‡ intervention costs €700 per participant and discount rates 4% for costs and 1.5% for effects

Large-scale implementation in the Netherlands

The Netherlands has approximately 12 million adults aged 20-80 years and 1 million obese adults aged 30-70 years. Potential effects of large-scale implementation of the lifestyle intervention in the Netherlands are illustrated in Table 3. Theoretically, a community intervention reaching all adults might prevent 2.4% of the new diabetes cases in 20 years. A health care intervention including 200,000 (20%) of the obese adults in the Netherlands may reduce 20-year diabetes incidence by 1.6% but intervention costs are high.

CONCLUSIONS

By modeling the effect of risk factor modification on long-term disease incidence, mortality and health care costs we demonstrated that lifestyle interventions can be cost-effective in persons with low or moderate risks of developing diabetes.

Community-based lifestyle interventions have been conducted with varying results (25,31).

In general, effects on weight are modest. The largest effect on weight, the maximum effect of the community intervention in our study (-0.25 kg/m2) was based on this, was found in the Stanford Five City Project (28). This study found that after 5 years, weight increase was 0.7 kg less in intervention communities compared to control regions. Most community-based

Table 3. Effects of large-scale implementation of lifestyle interventions in the Netherlands

	Reach of the intervention low estimate	Reach of the intervention high estimate
Community intervention		
# adults reached	2.4 million (20%)	12 million (100%)
Δ Life-years	16,000 to 104,000	81,000 to 522,000
Δ QALYs	15,000 to 95,000	76,000 to 477,000
prevented DM in 20 years	1600 to 8600 (0.1% to 0.5%)	8000 to 43,000 (0.4% to 2.4%)
prevented CVD in 20 years	600 to 6200 (0.0% to 0.1%)	3000 to 31,000 (0.1% to 0.7%)
intervention costs	€13 million	€66 million
Δ related medical costs	savings: 20 to 160 million	savings: 100 to 800 million
Δ total medical costs	40 to 280 million	200 to 1400 million
Health care intervention		
# obese participants	50,000 (5%)	200,000 (20%)
Δ Life-years	16,000 to 68,000	64,000 to 271,000
Δ QALYs	14,000 to 59,000	56,000 to 234,000
prevented DM in 20 years	1500 to 7000 (0.1% to 0.4%)	6000 to 28,000 (0.3% to 1.6%)
prevented CVD in 20 years	1000 to 2800 (0.0% to 0.1%)	4000 to 11,000 (0.1% to 0.3%)
intervention costs	€34 million	€135 million
Δ related medical costs	savings 20 to 70 million	savings 100 to 300 million
Δ total medical costs	40 to 200 million	200 to 800 million

All ranges correspond to result when "minimum intervention effect" is assumed to result when "maximum intervention effect" is assumed; discount rates 4% for costs and 1.5% for effects; DM: Diabetes Mellitus; CVD: cardiovascular disease

programs fail to achieve substantial effects on physical activity, but the prevalence of physical inactivity may be reduced. In contrast, effects of 'health care interventions' on mean body weight can be substantial, especially within the first year (21). A recent review revealed that a weight loss of 5% can be achieved within 1 year (27). However, the effect tends to decrease at longer term follow-up (11-13,21,26,33,55). After three years, as we simulated in our study, the maximum effect is about 4.5 kg (or 1.5 kg/m2) (11,13). With regard to physical activity, intensive programs have been shown to improve maximum oxygen uptake (13), increase time spent on physical activities (11,12) and reduce physical inactivity (12). As intervention effects differ considerably between studies, we explored the cost-effectiveness for a range of potential intervention effects. Despite methodological differences, average individual health benefits for participants in the health care intervention in our study were in the same order of magnitude as those projected for participants in the Diabetes Prevention Program (0.19 to 0.82 QALYs versus 0.56 in the DPP, all discounted at 3% (11). Both studies concluded that intensive lifestyle interventions for persons at increased risk for diabetes are cost-effective.

The literature on cost-effectiveness of interventions aimed at primary prevention of diabetes is scarce (20). Only one earlier study assessed the cost-effectiveness of a community-based program aimed at diabetes prevention (56). Several preventive interventions for different target groups were compared in this study. In general, the cost-effectiveness of (theoretical) interventions was more favorable in IGT groups compared to "mixed populations". However, lifestyle interventions appeared to be highly cost-effective in all target groups and were more effective than surgery for the severely obese. Lifestyle interventions have also

been shown to be more cost-effective than metformin treatment for the primary prevention of diabetes (57).

With respect to the potential impact of community-based lifestyle programs, a recent study showed that, theoretically, diabetes incidence could fall by 20% if the entire (UK) population were able to meet one more of the five predefined "diabetes healthy behavior prevention goals" related to BMI, diet and physical activity (15). BMI and physical activity had the largest impact on diabetes incidence and the authors suggested that even small shifts of the entire population towards more healthy behavior (through population-level interventions) would reduce diabetes incidence. Based on more realistic assumptions about potential effects on just BMI and physical inactivity, the community program in our study would prevent between 0.4% and 2.4% of the diabetes incidence in 20 years, if the entire Dutch population were to be reached by the intervention. Although the average lifetime health benefits per person were relatively low (a gain of a few days in good health), health benefits may be substantial for persons whose risk factor levels are actually changed.

Several comments need to be made with respect to the generalizability of the results obtained from our study. First, cost-effectiveness of lifestyle interventions differs between countries due to country-specific intervention- and health care costs (17). Although the per person intervention costs of the health care intervention in our study (€700) were much lower then the intervention costs calculated for the US Diabetes Prevention Program (approximately €2000 if screening costs for IGT are not considered), they compare well to the costs of other lifestyle interventions within health care as reported in a recent review (27). Costs of diabetes care in the Netherlands appear to be relatively low compared to other (European) countries (58). Second, the potential impact of large-scale implementation of interventions depends on risk factor distributions. For example, one out of four US adults is considered obese, and so there is a large potential target population for health care interventions. Third, the efficiency of lifestyle interventions may also differ due to country-specific risk factor prevalence; a community-based program aimed at increasing physical activity might be more cost-effective in for example the US, where the prevalence of physical inactivity is three times as high as the Netherlands (59).

In conclusion, both an intensive lifestyle intervention implemented in a health care setting and targeted at persons at increased risk of developing diabetes as well as a community-based lifestyle intervention for the general population are effective in reducing diabetes incidence. Although the average lifetime health benefit per person for the community intervention is relatively low, health gains on a population level may be substantial when the intervention is implemented on a large scale. Both kinds of lifestyle interventions are cost-effective ways to curb the growing burden of diabetes.

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References

1. Field AE, Manson JE, Laird N, Williamson DF, Willett WC, Colditz GA: Weight cycling and the risk of developing type 2 diabetes among adult women in the United States. *Obes Res* 12:267-74, 2004
2. Koh-Banerjee P, Wang Y, Hu FB, Spiegelman D, Willett WC, Rimm EB: Changes in body weight and body fat distribution as risk factors for clinical diabetes in US men. Am J Epidemiol 159:1150-1159, 2004
3. Weinstein AR, Sesso HD, Lee IM, Cook NR, Manson JE, Buring JE, Gaziano JM: Relationship of physical activity vs body mass index with type 2 diabetes in women. JAMA 292:1188-1194, 2004
4. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC: Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 345:790-797, 2001
5. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB: Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. Arch Intern Med 161:1542-1548, 2001
6. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE: Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. Int J Epidemiol 30:540-546, 2001
7. Koppes LLJ, Dekker JM, Hendriks HFJ, Bouter LM, Heine RJ: Moderate Alcohol Consumption Lowers the Risk of Type 2 Diabetes: A meta-analysis of prospective observational studies. Diabetes Care 28:719-725, 2005
8. Carlsson S, Hammar N, Grill V: Alcohol consumption and type 2 diabetes Meta-analysis of epidemiological studies indicates a U-shaped relationship. Diabetologia 48:1051-4, 2005
9. Dam RM van, Hu FB: Coffee consumption and risk of type 2 diabetes: a systematic review. JAMA 294:97-104, 2005
10. Hartemink N, Boshuizen HC, Nagelkerke NJ, Jacobs MA, van Houwelingen HC: Combining risk estimates from observational studies with different exposure cutpoints: a meta-analysis on body mass index and diabetes type 2. Am J Epidemiol 163:1042-52, 2006
11. Diabetes Prevention Program Research Group , Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393-403, 2002
12. Lindstrom J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J, for the Finnish Diabetes Prevention Study Group.: The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 26:3230-3236, 2003
13. Eriksson KF, Lindgärde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. Diabetologia 34:891-898, 1991
14. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 20:537-44, 1997
15. Simmons RK, Harding AH, Jakes RW, Welch A, Wareham NJ, Griffin SJ: How much might achievement of diabetes prevention behaviour goals reduce the incidence of diabetes if implemented at the population level? Diabetologia 49:905-911, 2006
16. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P , Hamman RF, Ackermann RT, Engelgau MM, Ratner RE, for the Diabetes Prevention Program Research Group.: The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med 142:323-332, 2005
17. Palmer AJ, Roze S, Valentine WJ, Spinas GA, Shaw JE, Zimmet PZ: Intensive lifestyle changes or

metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the diabetes prevention program in Australia, France, Germany, Switzerland, and the United Kingdom. Clin Ther 26:304-321, 2004

18. Davey Smith G, Bracha Y, Svendsen KH, Neaton JD, Haffner SM, Kuller LH, for the Multiple Risk Factor Intervention Trial Research Group.: Incidence of type 2 diabetes in the randomized multiple risk factor intervention trial. Ann Intern Med 142:313-322, 2005

19. Zimmet P, Shaw J, Alberti KG: Preventing Type 2 diabetes and the dysmetabolic syndrome in the real world: a realistic view. Diabet Med 20:693-702, 2003

20. Vijgen SM, Hoogendoorn M, Baan CA, de Wit GA, Limburg W, Feenstra TL: Cost effectiveness of preventive interventions in type 2 diabetes mellitus: a systematic literature review. Pharmacoeconomics 24:425-41, 2006

21. 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

22. Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, Smith WC, Jung RT, Campbell MK, Grant AM: Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. Health Technol Assess 8:iii-iv, 1-182, 2004

23. Hoogenveen RT, Feenstra TL, van Baal PHM, Baan CA. A conceptual framework for budget allocation in the RIVM Chronic Disease Model - A case study of Diabetes Mellitus. 2005. Bilthoven, RIVM.

24. Kahn EB, Ramsey LT, Brownson RC, Heath GW, Howze EH, Powell KE, Stone EJ, Rajab MW, Corso P: The effectiveness of interventions to increase physical activity. A systematic review. Am J Prev Med 22:73-107, 2002

25. Verheijden MW, Kok FJ: Public health impact of community-based nutrition and lifestyle interventions. Eur J Clin Nutr 59 Suppl 1:S66-75; discussion S76, 2005

26. McTigue KM, Harris R, Hemphill B, Lux L, Sutton S, Bunton AJ, Lohr KN: Screening and interventions for obesity in adults: summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 139:933-49, 2003

27. Bogers RP, Vijgen SMC, and Bemelmans WJE. Costs of lifestyle interventions within health care and the amount of weight loss achieved. 2006. Bilthoven, RIVM.

28. Taylor CB, Fortmann SP, Flora J, Kayman S, Barrett DC, Jatulis D, Farquhar JW: Effect of long-term community health education on body mass index. The Stanford Five-City Project. Am J Epidemiol 134:235-49, 1991

29. Brownson RC, Smith CA, Pratt M, Mack NE, Jackson-Thompson J, Dean CG, Dabney S, Wilkerson JC: Preventing cardiovascular disease through community-based risk reduction: the Bootheel Heart Health Project. Am J Public Health 86:206-13, 1996

30. Goodman RM, Wheeler FC, Lee PR: Evaluation of the Heart To Heart Project: lessons from a community-based chronic disease prevention project. Am J Health Promot 9:443-55, 1995

31. Bemelmans WJE, Wendel-Vos GCW, Bos G, Schuit AJ, and Tijhuis MAR. Interventions to prevent overweight in a community setting, at school, at work or in a health care setting; exploring the results [in Dutch] . 2004. Bilthoven, RIVM.

32. O'Loughlin JL, Paradis G, Gray-Donald K, Renaud L: The impact of a community-based heart disease prevention program in a low-income, inner-city neighborhood. Am J Public Health 89:1819-26, 1999

33. Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J: Long-term non-pharmacological weight loss interventions for adults with prediabetes. Cochrane Database Syst Rev 2005

34. Schuit AJ, Wendel-Vos GC, Verschuren WM, Ronckers ET, Ament A, van Assema P, van Ree J, Ruland EC: Effect of 5-year community intervention hartslag limburg on cardiovascular risk

factors. Am J Prev Med 30:237-42, 2006

35. Ronckers ET, Groot W, Steenbakkers M, Ruland E, Ament A: Costs of the 'Hartslag Limburg' community heart health intervention. BMC Public Health 6:51, 2006

36. Mensink M, Feskens EJM, Saris WHM, de Bruin TWA, Blaak EE: Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht (SLIM): preliminary results after one year. Int J Obes Relat Metab Disord 27:377-384, 2003

37. Mensink M, Blaak EE, Corpeleijn E, Saris WH, de Bruin TW, Feskens EJ: Lifestyle intervention according to general recommendations improves glucose tolerance. Obes Res 11:1588-1596, 2003

38. Feenstra TL, Hamberg-van Reenen HH, Hoogenveen RT, Rutten-van Molken MP: Cost-effectiveness of face-to-face smoking cessation interventions: a dynamic modeling study. Value Health 8:178-90, 2005

39. Hoogenveen RT, Feenstra TL, van Baal PHM , and Baan CA. A conceptual framework for budget allocation in the RIVM chronic disease model. A case study of diabetes mellitus. 2005. Bilthoven, RIVM.

40. Feenstra TL, van Genugten ML, Hoogenveen RT, Wouters EF, Rutten-van Molken MP: The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. Am J Respir Crit Care Med 164:590-6, 2001

41. Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, van Genugten ML, Buist AS, Wouters EF, Feenstra TL: A dynamic population model of disease progression in COPD. Eur Respir J 26:223-33, 2005

42. Struijs JN, van Genugten MLL, Evers SMAA, Ament AJHA, Baan CA, van de Bos GAM: Modeling the future burden of stroke in The Netherlands: impact of aging, smoking, and hypertension. Stroke 36 :1648-1655, 2005

43. Baan CA, Bos G, and Jacobs-van der Bruggen MAM. Modeling chronic disease: the diabetes module. 2005. Bilthoven, RIVM.

44. Kreijl CF van, Knaap AGAC, van Raaij JMA. Our food, our health. Healthy diet and safe food in the Netherlands. 2006. Bilthoven, RIVM.

45. Polder JJ, Takken J, Meerding WJ, Kommer GJ, and Stokx LJ. Costs of illness study in the Netherlands [in Dutch]. 2002. Bilthoven, RIVM.

46. Baal PHM van, Feenstra TL, Hoogenveen RT, and de Wit GA. Cost effectiveness analysis with the RIVM Chronic Disease Model. 2005. Bilthoven, RIVM.

47. Melse JM, Essink-Bot ML, Kramers PGN, Hoeymans N, on behalf of the Dutch Burden of Disease Group : A national burden of disease calculation: Dutch disability-adjusted life-years. Am J Public Health 90:1241-1247, 2000

48. Stouthard M, Essink-Bot M, Bonsel G, Group. obotDDWD: Disability weights for diseases - a modified protocol and results for a Western European region. European Journal of Public Health24-30, 2000

49. Lopez AD, Murray CC: The global burden of disease, 1990-2020. Nat Med 4:1241-3, 1998

50. Baal PH van, Hoeymans N, Hoogenveen RT, de Wit GA, Westert GP: Disability weights for comorbidity and their influence on health-adjusted life expectancy. Popul Health Metr 4:1, 2006

51. College voor zorgverzekeringen. Guidelines for farmaco-economic evaluations, actualised version [in Dutch]. 2006. Diemen, the Netherlands, College voor zorgverzekeringen.

52. Casparie AF, van Hout BA, Simoons ML: [Guidelines and costs]. Ned Tijdschr Geneeskd 142:2075-7, 1998

53. Simoons ML, Casparie AF: [Therapy and prevention of coronary heart diseases through lowering of the serum cholesterol levels; third consensus 'Cholesterol'. Consensus Working Group, CBO]. Ned Tijdschr Geneeskd 142:2096-101, 1998

54. Hernan WH, Brandle M, Zhang P, Williamson DF, Matulik MJ, Ratner RE, Lachin JM, Engelgau MM, The Diabetes Prevention Program Research Group: Costs associated with the primary prevention of type 2 diabetes mellitus in the diabetes prevention program. Diabetes Care 26:36-47, 2003

55. Stevens VJ, Obarzanek E, Cook NR, Lee IM, Appel LJ, Smith West D, Milas NC, Mattfeldt-Beman M, Belden L, Bragg C, Millstone M, Raczynski J, Brewer A, Singh B, Cohen J: Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. Ann Intern Med 134:1-11, 2001

56. Segal L, Dalton AC, Richardson J: Cost-effectiveness of the primary prevention of non-insulin dependent diabetes mellitus. Health Promotion International 13:197-209, 1998

57. The Diabetes Prevention Program Research Group.: Within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes. Diabetes Care 26:2518-2523, 2003

58. Jönsson B: Revealing the cost of Type II diabetes in Europe. Diabetologia 45:S5-S12, 2002

59. Centers for Disease Control and Prevention (CDC): Trends in leisure-time physical activity by age, sex and race/ethnicity--United States, 1994-2004. MMWR Morb Mortal Wkly Rep 54:991-4, 2005

Appendix Chapter 4

A. Calculation of costs of the SLIM-intervention (health care intervention)

Short description of the SLIM-project

SLIM is the abbreviation of 'Study on lifestyle-intervention and impaired glucose tolerance Maastricht' (1,2). The intervention consisted of counseling sessions with a nutritional component, based on conventional dietary guidelines, and information about the benefits of being physically active (according to the standard of at least half an hour a day on 5 days in the week). In overweight persons the intervention consisted of individual dietary counseling aiming at weight loss. In addition to the counseling sessions, participants were encouraged to participate in an organized fitness program. This program consisted of a combination of increasing strength and aerobic training.

Assessment of costs

Fixed costs, for example the training of personnel, and costs for developing and starting up the intervention were not included. Only the costs for executing the intervention (real resource use) were considered. The first step was to identify the different costs parts of the intervention, e.g. primarily material and personnel. Thereafter the consumption frequency and duration of these costs parts were assessed. For instance, the frequency and average length of a counseling session. The usage is multiplied by the costs per unit.

Costs for personnel

Personnel costs were calculated by using the method as described in the Dutch guidelines for cost calculations within pharmaco-economic research (3). Firstly, the monthly mean gross salary per professional category was determined by using the middle number plus 1 within the specific salary scale. A surcharge of 35% was calculated for holiday allowance, social security etc. Thereafter, a surcharge of 35% was calculated for institutional overhead costs. A further surcharge of 10% was calculated for housing costs. Finally the amount of working hours in one year was calculated, 1540 for a 36-hour working week and 1632 for a 38-hour working week. The unit cost per hour was calculated assuming a productivity of 70 percent.

The cost calculation of the SLIM intervention is shown in Table 1:

Table 1. Costs of the SLIM intervention

Intervention component	content	units per person	costs per unit	costs per person
Nutrition	Year 1			
	4 individual sessions with a dietician	4*45 = 180 min	€ 0.84 /min	€ 151
	1 group session with a dietician	90 min / 15 persons = 6 min / person	€ 0.84 /min	€ 5
	1 handbook nutrition	1	€ 13	€ 13
	Year 2 and 3			
	3 individual sessions with a dietician	3*45 = 180 min	€ 0.84 /min	€ 114
	1 group session with a dietician	90 min / 15 persons = 6 min / person	€ 0.84 /min	€ 5
	Total nutrition			€ 407 (A)
Exercise	Year 1			
	1 individual advice by a researcher	45 min	€ 1.02	€ 46 (B)
	Fitness program	52*60 min / 15 persons = 208 min / person	€ 0.70	€ 146
	Year 2 and 3			
	Fitness program	52*60 min / 15 persons = 208 min / person	€ 0.70	€ 146
	Total exercise			€ 484 (C)
Total	for participants of the fitness program		A+C	891
	for non participants		A+B	453
	(rounded) average costs used for the analyses*			700

*Based on the intervention results it was known that 50% of the participants participated in the fitness program. This participation rate can be anticipated in planning large-scale implementation of the program.

1. Mensink M, Feskens EJM, Saris WHM, Bruin TWAd, Blaak EE: Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht (SLIM): preliminary results after one year. *Int J Obes Relat Metab Disord* 27:377-384, 2003

2. Mensink M, Blaak EE, Corpeleijn E, Saris WH, de Bruin TW, Feskens EJ: Lifestyle intervention according to general recommendations improves glucose tolerance. *Obes Res* 11:1588-1596, 2003

3. Oostenbrink JB, Koopmanschap MA, Rutten FFH: Handleiding voor kostenonderzoek. Methoden voor economische evaluaties in de gezondheidszorg [Guideline for cost research. Methods for economic evaluations in the health care]. *Amstelveen: College voor zorgverzekeringen* 2000

B: Description of the Chronic Diseases Model (CDM) and relevant input data with respect to diabetes prevention

Introduction

The RIVM Chronic Disease Model is a multistate Markov-type simulation model. It describes how morbidity and mortality rates for several chronic diseases change over time in the Dutch population as a result of changes in epidemiological risk factors (1,2). In general, the state transition model is a suitable and accepted model to describe demographic / epidemiological processes (3). Disease experts and modelers have cooperated in building and testing of the CDM. Several studies with different applications of the model have already been published (4-7). The model states defined are classes for the risk factors (i.e. normal weight: BMI<25; overweight: BMI 25-30; obesity: BMI ≥ 30) and states for the diseases included in the model (diabetes; yes or no). In the starting year of the simulation period all persons are distributed over these states. Then for each 1-year simulation step persons move from one state to another. These transitions are governed by so-called transition rates. E.g., class transition rates between the BMI states 'normal weight' and 'overweight' govern the change of the BMI distribution in the population, incidence rates between the states 'without diabetes' and 'with diabetes' govern the disease prevalence rates, and mortality rates from the state 'alive' to 'deceased' govern the surviving population numbers. The transition rate is assumed independent from the preceding states and depends only on the present state defined by risk factor class, disease state, sex and age. All dependencies in the Chronic Diseases Model relevant to diabetes prevention are illustrated in figure 1.

The disease incidence rates depend on the risk factor class, using relative risk values. E.g., 'overweight' persons have higher diabetes risks than persons with 'normal weight'. For non diseased, the mortality rates depend on risk factor class, e.g., obese persons have higher mortality risks than persons with a normal weight. The mortality rates also depend on the disease states, but are conditional hereon independent on the risk factor values. E.g., the excess mortality risks of people with diabetes compared to people without diabetes are equal for all weight states.

As depicted in figure 1, interventions that affect BMI directly influence the incidence of diabetes, cardiovascular diseases, musculoskeletal disorders, (six forms of) cancer and total mortality (see tables 4 and 5 for relative risks). Physical activity is related to diabetes, coronary heart disease, (two forms of) cancer and total mortality (tables 4 and 6). Diabetes is related to increased incidence of cardiovascular disease (table 7). All patients have higher mortality risks as compared to disease free persons.

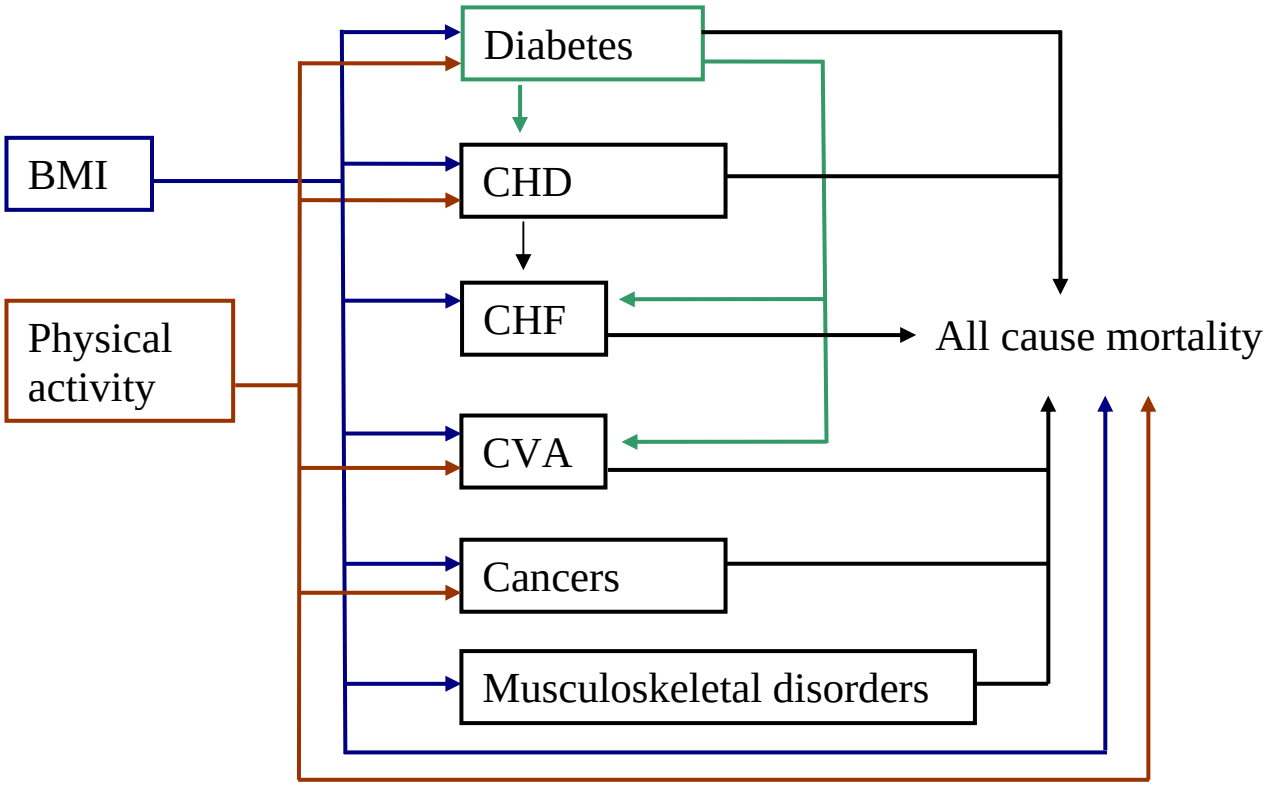

Figure 1. Dependency relations between risk factors, diabetes mellitus, cardiovascular diseases, other (related) diseases and mortality

Data on risk factors were obtained from representative national or regional surveys, disease incidence and prevalence data were obtained from national registries in general practice (nearly all non-institutionalized people in the Netherlands are registered by a general practitioner) and cancer registries. Relative risks were obtained from international epidemiological literature. Sources and references for input data are given in table 1. The higher mortality risks of patients compared to disease-free persons were calculated from published relative survival proportions for types of cancer, and from incidence and prevalence figures for other chronic diseases, using an Incidence, Prevalence, Mortality (IPM) model (8). All input data were specified by gender and age (2).

We assumed that all risk factors that are distinguished are independently distributed, e.g. we assumed that the distribution of physical inactivity is independent from BMI. All disease incidence risks were made dependent on these risk factors by multiplying the baseline risk with relative risk values specified by risk factor class. Adjusted relative risks were used (i.e. the relative risk for physical inactivity on diabetes was adjusted for BMI). Moreover, we assumed for some disease pairs independent effects of one disease on the other. E.g., people with diabetes have higher risks of myocardial infarction compared to people without diabetes, independently from overweight and the other risk factors.

Data used

Table 1. Input data for the model and the sources.

Input data	Source
Population numbers	Statistics Netherlands
Total mortality in population	Statistics Netherlands
Prevalence rates of risk factors	National representative data sources
- body weight and physical activity	- lifestyle monitoring surveys from Statistics Netherlands
Transition rates for risk factors (e.g. body weight increases when ageing)	Derived from prevalence rates (9)
Disease incidence and prevalence rates	General practice registrations, cancer registration (8)
Relative risks	Literature reviews (2,10)
- risk factor / disease combinations	
- risk factor / mortality combinations	
- disease / disease combinations	
Weights for quality of life (DALYs)	Burden of Disease Studies (11-14)
Costs of diseases	Dutch Costs of illness study (15,16)

Table 2. Incidence and prevalence rates for diabetes and health care costs for diabetes treatment for men (M) and women (F) in the Netherlands.

Age	incidence per 1000 per year		prevalence %		costs in 2004 € per patient per year (15)
	M	F	M	F	M /F
20-25	0.5	0.5	0.3	0.3	1840
25-30	0.6	0.8	0.3	0.4	1700
30-35	1.2	0.7	0.6	0.6	1580
35-40	1.4	1.6	1.0	0.7	1480
40-45	2.7	2.1	1.2	1.1	1400
45-50	5.1	2.7	2.1	1.9	1330
50-55	9.0	4.3	4.4	2.9	1290
55-60	9.2	7.9	7.0	4.7	1280
60-65	13.1	12.2	9.4	7.4	1290
65-70	13.6	13.0	11.4	11.1	1320
70-75	18.8	16.1	13.0	12.8	1390
75-80	12.4	17.0	14.8	15.0	1480
80-85	12.3	14.2	14.4	15.7	1600
85+	15.4	12.9	13.0	15.9	1750

Table 3. Prevalence rates (%) for overweight and activity for men (M) and women (F) in the Netherlands.

Age	Overweight (%)						Activity (%)					
	Normal		Overweight		Obesity		Norm active		Medium active		Inactive	
	M	F	M	F	M	F	M	F	M	F	M	F
20-25	79	80	18	16	3	4	46	42	42	43	12	15
25-30	59	70	32	21	8	9	49	49	42	44	9	7
30-35	55	64	35	25	10	12	48	52	44	43	8	5
35-40	51	62	38	25	11	14	48	55	43	40	9	5
40-45	44	58	43	28	13	14	47	56	44	37	9	7
45-50	39	56	46	32	15	13	45	55	45	37	10	8
50-55	34	44	48	38	18	18	43	55	45	37	12	8
55-60	36	43	45	37	19	20	65	67	27	25	8	8
60-65	37	44	49	39	14	18	75	72	18	19	7	9
65-70	41	38	45	43	14	19	75	69	16	20	9	11
70-75	37	35	50	45	14	21	71	59	16	24	13	17
75-80	48	40	41	43	11	17	65	46	16	26	19	28
80-85	53	44	38	39	9	17	54	31	21	25	25	44
85+	55	53	39	36	6	11	40	16	27	21	33	63

Statistics Netherlands: Overweight 2000-2002 (adjusted for self reporting); Activity 2001-2003

Table 4. Relative risks for diabetes mellitus for men (M) and women (F) for overweight and activity (2)

	Overweight						Activity					
	Normal		Overweight		Obesity		Norm active		Medium		Inactive	
	M	F	M	F	M	F	M	F	M	F	M	F
20-25	1.0	1.0	4.9	3.7	21.1	23.7	1.0	1.0	1.1	1.2	1.5	1.4
25-30	1.0	1.0	3.7	3.7	17.4	19.3	1.0	1.0	1.1	1.2	1.5	1.4
30-35	1.0	1.0	3.6	3.3	16.2	13.3	1.0	1.0	1.1	1.2	1.5	1.4
35-40	1.0	1.0	3.2	3.1	15.6	13.8	1.0	1.0	1.1	1.2	1.5	1.4
40-45	1.0	1.0	2.8	2.9	11.8	12.3	1.0	1.0	1.1	1.2	1.5	1.4
45-50	1.0	1.0	2.6	2.6	9.7	9.5	1.0	1.0	1.1	1.2	1.5	1.4
50-55	1.0	1.0	2.4	2.5	7.8	8.8	1.0	1.0	1.1	1.2	1.5	1.4
55-60	1.0	1.0	2.2	2.3	5.9	7.0	1.0	1.0	1.1	1.2	1.5	1.4
60-65	1.0	1.0	1.9	2.0	4.6	5.2	1.0	1.0	1.1	1.2	1.5	1.4
65-70	1.0	1.0	1.8	1.9	3.1	3.8	1.0	1.0	1.1	1.2	1.5	1.4
70-75	1.0	1.0	1.6	1.6	2.5	2.9	1.0	1.0	1.1	1.2	1.5	1.4
75-80	1.0	1.0	1.4	1.4	1.9	2.1	1.0	1.0	1.1	1.2	1.5	1.4
80-85	1.0	1.0	1.2	1.2	1.5	1.6	1.0	1.0	1.1	1.2	1.5	1.4
85+	1.0	1.0	1.1	1.1	1.1	1.2	1.0	1.0	1.1	1.2	1.5	1.4

Table 5. Relative risks for mortality and diseases (other than diabetes) for overweight and obesity, as compared to normal body weight (reference class; RR=1.0). The relative risks are ranges, because of variation by age. In general, the risks decline in older ages (10).

Risk factor class	Overweight		Obesity	
	M	F	M	F
Total mortality	1.0-1.2	1.0-1.2	1.2 -1.9	1.2- 2.1
Coronary heart disease	1.0-1.4	1.0-1.5	1.0 -2.2	1.0-2.5
Heart failure	1.2	1.2	1.4 -1.5	1.5
Cerebro vascular disease	1.0-1.1	1.0-1.2	1.0 -1.4	1.0 -1.4
Artrosis – knee	1.1-2.3	1.1-2.3	1.2 -6.4	1.2 -6.4
Artrosis – hip	1.2-1.3	1.2-1.3	1.5 -1.6	1.5 -1.6
Low back pain	1.0 -1.2	1.0 -1.2	1.1 -1.6	1.1 -1.6
Cancer – rectum	1.1	1.1	1.2 -1.3	1.3
Cancer – colon	1.2	1.2	1.4 -1.6	1.5 -1.7
Cancer – breast	-	1.1 -1.2	-	1.0 -1.7
Cancer – prostate	1.0 -1.1	-	1.1 -1.3	-
Cancer – kidney	1.0 -1.8	1.0 -1.8	1.0 -3.6	1.0 -3.6
Cancer – cervical	-	1.6	-	2.5

Table 6. Relative risks for mortality and diseases other than diabetes for medium activity and inactivity as compared to norm activity (reference category; RR=1.0) (10).

Class of activity	Medium active				Inactive			
Age category	< 60 yrs		≥ 60 yrs		< 60 yrs		≥ 60 yrs	
	M	F	M	F	M	F	M	F
Total mortality	1.1	1.1	1.1	1.1	1.4	1.4	1.4	1.4
Coronary heart disease	1.2	1.2	1.2	1.2	1.8	1.8	2.0	2.0
Cerebro vascular disease	1.2	1.2	1.3	1.3	2.0	2.0	2.2	2.2
Colon cancer	1.1	1.7	1.1	1.7	1.1	1.7	1.1	1.7
Breast cancer	-	1.1	-	1.1	-	1.3	-	1.3

Table 7. Relative risks for cardiovascular diseases for people with diabetes as compared to people without diabetes (reference category; RR=1.0). The relative risks are ranges, because of variation by age. In general, the risks decline in older ages (2).

	M	F
Chronic heart failure	1.1 - 10.0	1.1 - 10.0
Coronary heart disease	1.5 - 2.1	1.8 - 3.2
Cerebro vascular disease	1.0 - 3.1	1.0 - 3.1

Table 8. DALY weights derived in the Global Burden of Disease 1990 study for relevant diseases. Some DALY weights are expressed in ranges because of variation by age (11).

	M	F
Diabetes	0.03	0.03
Acute myocardial infarction	0.40	0.40
Other coronary heart disease	0.17	0.17
Heart failure	0.17	0.17
Cerebrovascular disease	0.26	0.26
Artrosis hip / knee	0.16	0.16
Low back pain	0.07	0.07
Cancer – rectum / colon	0.24-0.25	0.24-0.25
Cancer – breast	0.09-0.11	0.09-0.11
Cancer – prostate	0.14-0.15	-
Cancer – kidney	0.19-0.27	0.28-0.44
Cancer – cervical	-	0.09-0.14

References

1. Hoogenveen RT, Feenstra TL, Baal PHM van, and Baan CA. A conceptual framework for budget allocation in the RIVM Chronic Disease Model - A case study of Diabetes Mellitus *Bilthoven: National Institute of Public Health and the Environment (RIVM)* 2005

2. Baan CA, Bos G, and Jacobs-van der Bruggen MAM. Modeling chronic disease: the diabetes module. *Bilthoven: National Institute of Public Health and the Environment (RIVM)* 2005

3. Manton KG, Stallard E: *Chronic disease modelling: measurement and evaluation of the risks of chronic disease processes*. New York, Oxford University Press, 1988

4. Feenstra TL, van Genugten ML, Hoogenveen RT, Wouters EF, Rutten-van Molken MP: The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. *Am J Respir Crit Care Med* 164:590-6, 2001

5. Feenstra TL, Hamberg-van Reenen HH, Hoogenveen RT, Rutten-van Molken MP: Cost-effectiveness of face-to-face smoking cessation interventions: a dynamic modeling study. *Value Health* 8:178-90, 2005

6. Struijs JN, Genugten MLLv, Evers SMAA, Ament AJHA, Baan CA, Bos GAMvd: Modeling the future burden of stroke in The Netherlands: impact of aging, smoking, and hypertension. *Stroke* 36 :1648-1655, 2005

7. Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, van Genugten ML, Buist AS, Wouters EF, Feenstra TL: A dynamic population model of disease progression in COPD. *Eur Respir J* 26:223-33, 2005

8. Hoogenveen RT, Gijsen R, van Genugten MLL, Kommer GJ, Schouten JSAG, de Hollander AEM: Dutch DisMod. Constructing a set of consistent data for chronic disease modelling. *Bilthoven: National Institute of Public Health and the Environment (RIVM)* 2000

9. Hoogenveen RT, van der Lucht F, Willemsen M: Starters, stoppers en herstarters. Veranderingen van rook-status in de algemene bevolking [Starters, quitters and restarters. Changes in smoking status in the general population]. *Bilthoven: National Institute of Public Health and the Environment (RIVM)* 2000

10. Kreijl, van CF, Knaap AGAC, and Raaij, van JMA. Our food, our health. Healthy diet and safe food in the Netherlands. *Bilthoven: National Institute of Public Health and the Environment (RIVM)* 2006

11. Lopez AD, Murray CC: The global burden of disease, 1990-2020. *Nat Med* 4:1241-3, 1998

12. van Baal PH, Hoeymans N, Hoogenveen RT, de Wit GA, Westert GP: Disability weights for comorbidity and their influence on health-adjusted life expectancy. *Popul Health Metr* 4:1, 2006

13. Melse JM, Essink-Bot ML, Kramers PGN, Hoeymans N, on behalf of the Dutch Burden of Disease Group : A national burden of disease calculation: Dutch disability-adjusted life-years. *Am J Public Health* 90:1241-1247, 2000

14. Stouthard M, Essink-Bot M, Bonsel G, Group. obotDDWD: Disability weights for diseases - a modified protocol and results for a Western European region. *European Journal of Public Health* 24-30, 2000

15. Polder JJ, Takken J, Meerding WJ, Kommer GJ, and Stokx LJ. Costs of illness study in the Netherlands [in Dutch]. *Bilthoven: National Institute of Public Health and the Environment (RIVM)* 2002

16. van Baal PHM, Feenstra TL, Hoogenveen RT, and de Wit GA. Cost effectiveness analysis with the RIVM Chronic Disease Model. *Bilthoven: National Institute of Public Health and the Environment (RIVM)* 2005

Chapter 5. Cost-effectiveness of lifestyle modification in diabetes patients

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Cost-effectiveness of lifestyle modification in diabetes patients

ABSTRACT

Objective - To explore the potential long-term health and economic consequences of lifestyle interventions for diabetes patients.

Research Design and Methods - A literature search was performed to identify interventions for diabetes patients in which lifestyle issues were addressed. We selected recent (2003-2008), randomized controlled trials with a minimum follow-up of 12 months. The long-term outcomes for these interventions, if implemented in the Dutch diabetes population, were simulated with a computer-based model. Costs and effects were discounted at respectively 4% and 1.5% annually. A life-long time horizon was applied. Probabilistic sensitivity analyses were carried out, taking account of variability in intervention costs and (long-term) treatment effects.

Results - Seven trials with 147 to 5,145 participants, met our pre-defined criteria. All interventions improved cardiovascular risk factors at ≥ one year follow-up and were projected to reduce cardiovascular morbidity over lifetime. The interventions resulted in an average gain of 0.01 to 0.14 quality adjusted life-years (QALYs) per participant. Health benefits were generally achieved at reasonable costs (≤ €50,000/QALY). A self-management education program (X-PERT) and physical activity counseling achieved the best results with ≥ 0.10 QALYs gained and ≥ 99% probability to be very cost-effective (≤ €20.000/QALY).

Conclusions - Implementation of lifestyle interventions would probably yield important health benefits at reasonable costs. However, essential evidence for long-term maintenance of health benefits was limited. Future research should focus on long-term effectiveness and should compare multiple treatment strategies to determine incremental costs and benefits of one over the other.

BACKGROUND

Compared to lifestyle interventions for persons at high risk for diabetes, the long-term health and economic consequences of lifestyle interventions for diabetes patients are relatively unknown (1). This is noteworthy, since diabetes patients have a high risk for (cardiovascular) complications and therefore, improving lifestyle is also worthwhile in this population. Furthermore, optimal management of lifestyle issues, often addressed within the context of self-management programs, is increasingly acknowledged as an essential part of diabetes treatment, and incorporated in most national standards of care (2). Additional knowledge about long-term effects of these interventions is required to be able to identify the most successful strategies. Since the common aim of self-management, education, diets, lifestyle- and exercise interventions is to reduce cardiovascular risk through lifestyle modification, we will refer to all of them as lifestyle interventions.

Trials are generally too short to capture the long-term benefits of an intervention, and epidemiological modeling can be used to fill this gap. By combining available evidence from different sources, modeling enables predictions of future outcomes and can be regarded as a valuable tool in addition to long-term trials. However, there is an important difference between modeling pharmaceutical and lifestyle interventions. With pharmaceutical interventions, the assumption is that if you keep taking the drug, you keep getting the benefits. If you stop taking the drug, you lose the benefits but the costs of the intervention cease. With lifestyle interventions, the costs are up front costs and long-term outcomes are substantially affected by the extent to which health benefits are sustained after the intervention has stopped. Therefore, modeling lifestyle interventions requires explicit assumptions about how lifestyle changes are sustained over time (3;4).

The aim of our study is to explore the long-term outcomes of lifestyle interventions for diabetes patients. We use a computer-based simulation model to project long-term health benefits and cost-effectiveness, assuming implementation in the Dutch diabetes population.

RESEARCH DESIGN AND METHODS

Selection of trials

A literature search was performed to identify randomized controlled trials of patient-centered interventions, in persons with type 2 diabetes, in which lifestyle issues (at least nutrition and/or exercise) were addressed. Inclusion criteria were: recent publication (2003-2008), large trial (n >150), a minimum follow-up of 12 months, mainly Caucasian population, risk factor outcomes reported (weight, BMI, physical activity, smoking, diet, glycemic control, lipids and/or blood pressure) and sufficient information to be able to calculate intervention costs. In addition we searched for studies that provided quantitative information about long-term maintenance of health benefits achieved through lifestyle interventions. Selection criteria for these studies as well as the methods for determining long-term maintenance estimates are described in the online Appendix.

Model input

Intervention effect was defined as a significant change in risk factor outcome for intervention participants compared to controls, at the latest follow-up. Long-term maintenance for each

risk factor was defined as the proportion of the intervention effect that could be expected to sustain over lifetime. For each risk factor, intervention effect was multiplied with long-term maintenance to estimate the average intervention effect over lifetime. Calculations of intervention costs were based on publications and additional information provided by authors. We assumed that the interventions would be implemented as described, but with a minimum of two patient contacts during the first two years (to enhance long-term maintenance). We accounted for additional intervention costs if these requirements were not met in the original intervention.

The Chronic Diseases Model

The CDM is a Markov type simulation model, developed at the Dutch National Institute for Public Health and the Environment (RIVM). The model simulates developments for the Dutch diabetes population and is well suited to explore long-term consequences of lifestyle changes. The model combines epidemiological data to quantify the associations between multiple risk factors and chronic diseases, such as cardiovascular diseases and cancers (Appendix, Figure A1 and Table A1). The model does not include micro vascular complications. Starting from base-line distributions over risk factor classes and diseases, one-year state transitions determine future developments. State transition probability values depend on a persons risk level, determined by age, gender, risk factor class and prevalent disease. Estimates of the strengths of the associations between risk factors and diseases are based on international, observational studies. The CDM has previously been used to evaluate long-term outcomes for diabetes prevention and diabetes treatment and to explore the impact of lifestyle risk factors on healthy life expectancy and life-time medical costs (5-8).

Long-term health benefits

We explored the long-term health benefits of the interventions by comparing simulated outcomes for a reference cohort and an intervention cohort. Both cohorts represented Dutch diabetes patients eligible for each specific intervention. The intervention cohort differed from the reference cohort (usual care) by an altered risk factor distribution at the start of the simulation, based upon the trials results. For example, participants in the ICAN trial lost 2.4 kg of baseline weight compared to a weight gain of 0.6 kg in controls; a difference of 3 kg, or 2.8% of baseline weight (BMI). The long-term maintenance estimate for BMI was 35% (see results) and consequently, ICAN participants were assumed to have an average 2.8%*35%=1.0% lower BMI over lifetime, compared to patients receiving usual care. We used a large Dutch diabetes data-base to determine how this difference affected BMI risk factor class distributions at the start of the simulation.

Once the simulation had started, the same state-specific transition probabilities were applied to both reference and intervention cohorts. Cumulative life-time incidence of cardiovascular disease (CVD = AMI + CHD + CHF + stroke) and (quality adjusted) life years, were simulated for these cohorts as well as for 60-year old participants.

Cost-effectiveness

Economic analyses were performed from a health care perspective. Participants were eligible Dutch diabetes patients. Intervention costs were determined by multiplying resource use with Dutch unit costs in 2007. The incremental effects on the costs of care were calculated from the model simulations as follows: All model states in the CDM were associated with health care costs, depending on age, gender and disease state. These costs represent total medical costs, including costs for 'unrelated' diseases such as dementia and mental illness (9). For each intervention net present values of incremental costs were calculated by summing the discounted costs over all simulation years and taking the difference with the reference scenario (usual care). Cost-effectiveness ratios (CER) were calculated as (Δ intervention costs + Δ lifetime medical costs) / Δ quality adjusted life-years (QALYs) for each intervention. In the base-case analyses, clinical benefits and costs were discounted at 1.5% and 4% annually, in accordance with Dutch guidelines. The simulations were run for closed cohorts, with a lifelong time horizon.

Sensitivity analyses

One way sensitivity analyses were performed to explore the impact of discount rates, time horizon and additional long-term intervention costs on the cost-effectiveness of the interventions. Probabilistic sensitivity analyses were performed, taking account of uncertainty in intervention effects, long-term maintenance and intervention costs. For each intervention 200 random, independent drawings were taken from the distributions for effect, maintenance and costs. Intervention effect and maintenance estimates were multiplied to generate 'long-term effect' estimates. We took into account that changes in lifestyle risk factors may be correlated. For example, participants with the largest increase in physical activity may also achieve the largest weight loss (10-12). Since quantitative information about all possible combinations of risk factor outcomes is limited (and sometimes inconsistent) we assumed respectively 0% and 100% correlation between the long-term effect estimates of all risk factors affected. To do so, the 'long-term effect estimates' for each risk factor were ordered, before they were combined. Consequently, a low (high) effect estimate for one risk factor was combined with low (high) estimates for all other risk factors affected. For intervention costs we considered variation in total contact time of the interventions and we varied the number of participants in group activities.

RESULTS

Selected trials

Seven trials fulfilled all pre-defined criteria. The interventions differed by scope, focus, content, intensity and target population. Intervention duration ranged from six hours to 24 months. The included trials were:

- DESMOND: a 6-hour self-management education program for newly diagnosed patients (n=824) evaluated at 12 months (13)
- Beyond Good Intentions (BGI): a 12-week self-management course for screen-detected patients (n=196) evaluated at 12 months (14)

- Look AHEAD: a one-year intensive lifestyle intervention for overweight patients (n=5145) evaluated at 12 months (15)
- Mediterranean lifestyle program (MLP): a 6-month lifestyle program for postmenopausal women with diabetes (n=279) followed by two different maintenance programs, evaluated at 24 months (16)
- X-PERT: a 6-week, structured self-management education program for diabetes patients (n=314) evaluated at 14 months (17)
- Improving Control with Activity and Nutrition (ICAN): a one-year moderate intensity lifestyle intervention for overweight patients (n=147) evaluated at 12 months (18)
- Counseling for physical activity (CPA): a two-year structured counseling intervention to promote physical activity (n=340) evaluated at 24 months (10)

The selected trials, calculations of intervention costs and characteristics of the simulated cohorts are described in Appendix, Tables A2 to A5.

Model input

Significant reductions in risk factors were obtained in all trials (Table 1). Based on the long-term results from five other trials (see Appendix) we assumed that on average, respectively 85%, 55% and 35% of the initial effects for HbA1c, physical activity and BMI (and all other risk factors) could be sustained over life-time. We assumed slightly better maintenance for MLP and CPA, since 'initial effects' in these trials were measured at 24 months follow-up. Total intervention costs, incurred over two years, ranged from €124 to €584 per participant (Table 1).

Table 1. Model input: intervention costs and intervention effects

Total per participant costs for the interventions *	BMI % decrease	HbA1c decrease	Physical activity increase	SBP decrease	Smokers % who quit	Fruit / vegetables increase	Saturated fat % decrease
DESMOND € 206	1.1	0.3 ns	% active: -1 ns	0 mmHg ns	15	NA	NA
BGI € 248	2.6	0 ns	NA	6 mmHg	NA	NA	NA
Look AHEAD € 503	7.9	0.5	NA ‡	4 mmHg	NA	NA	NA
MLP € 584	2.5 ns †	0.1 ns	45 MET min/wk	1 mmHg ns	NA	0.1 portion (80g) fruit	2%
X-PERT € 124	2.0	0.7	20 min/wk	3 mmHg ns	NA	1 portion (80g) each	0.4% ns
ICAN € 373	2.8	0.2 ns	NA	NA	NA	NA	NA
CPA € 345	3.4	0.5	24 MET h/wk	NA	NA	NA	NA

ns: not significant; NA: not available

* Details are provided in Table A2 in the online appendix

† This was the only non significant effect that was included in the simulations.

‡ Significant increase in fitness

Long-term health benefits

The interventions were projected to reduce lifetime cumulative incidence of cardiovascular complications by 1 to 54 per 1000 participants (Table 2). In other words, the number needed to treat to prevent one new cardiovascular complication over lifetime was 19 to 1000. The relative reduction in expected lifetime CVD incidence ranged from 0.1 to 6.1%. The interventions increased life expectancy by 0.02 to 0.34 years and (discounted) QALYs by 0.01 to 0.14. For 60-year old participants (Appendix, Table A6) life-expectancy increased by 0.02 to 0.42 years and (discounted) QALYs by 0.01 to 0.18. The physical activity intervention (CPA) had the largest simulated health gains. This intervention increased life expectancy of 60-year old participants by 0.42 years, while average time spent with CVD complications decreased by 0.06 and 0.07 years for stroke and CHD respectively (data not shown).

Table 2. Clinical benefits and health care costs for intervention participants compared to usual care

	Incident CVD prevented *	Life years gained per participant	QALYs gained per participant †	Increase in total health care costs € per participant ‡
DESMOND	1 of 761 (0.1%)	0.02	0.01	63
BGI	12 of 835 (1.4%)	0.09	0.04	215
Look AHEAD	33 of 828 (4.0%)	0.18	0.08	475
MLP	7 of 776 (0.9%)	0.05	0.02	125
X-PERT	38 of 768 (5.0%)	0.21	0.09	718
ICAN	2 of 888 (0.2%)	0.02	0.01	30
CPA	54 of 881 (6.1%)	0.34	0.14	1128

* absolute reduction in cumulative lifetime incidence of new CVD complications per 1000 participants, expected cumulative number of new CVD complications without intervention (per 1000 patients in the reference cohort) and between brackets, relative reduction achieved through the intervention
† discounted with 1.5% annually; ‡ discounted with 4% annually

Cost-effectiveness

Despite prevented costs for complications, all interventions were projected to increase health care costs over lifetime, due to increased survival (Table 2). The base-case CERs ranged from 10,000 to 39,000 €/QALY (Table 3). Four interventions (BGI, X-PERT, Look AHEAD and CPA) had average CER below €20,000/QALY even with equal discounting of costs and effects, a 20-year time-horizon or additional lifetime intervention costs. In the probabilistic sensitivity analyses (for which details are provided in Appendix Tables A7 to A9), these interventions had > 85% probability to remain below €20,000/QALY (Table 3).

As expected, assuming 100% correlation between risk factor outcomes increased the variability of the simulated outcomes (Appendix, Table A10). For example for Look AHEAD, QALYs increased by 0.03-0.12 if outcomes were assumed to be independent and by 0.01-0.15 with 100% correlation. Similarly, the variability in simulated health care costs and CERs was higher if outcomes were assumed to be correlated (data not shown). The cost-effectiveness acceptability curves for the interventions, assuming correlated outcomes, are displayed in Figure 1.

In the base-case analyses, immediate cost-savings through reduced medication use (reported for X-PERT, Look AHEAD and ICAN) were not taken into account and additional analyses were performed to explore the potential impact of these additional intervention benefits

(Table 3). Although economic outcomes for the three interventions improved, the main results as summarized above were not substantially changed.

Table 3. Results for cost-effectiveness (€/QALY): base-case and sensitivity analyses

	lifetime DC 1.5-4 base-case	lifetime DC 0-0	lifetime DC 3-3	20 years DC 1.5-4	additional costs *	% below €20.000
DESMOND	32,000	35,000	43,000	39,000	62,000	5.0† / 9.0‡
BGI	12,000	18,000	17,000	9000	19,000	91.5/86.0
Look AHEAD	12,000	19,000	18,000	11,000	16,000	98.5/90.5
MLP	33,000	35,000	43,000	38,000	46,000	1.0/ 2.5
X-PERT	10,000	17,000	15,000	8000	13,000	100/100
ICAN	39,000	38,000	52,000	52,000	68,000	4.0/NA
CPA	10,000	18,000	15,000	8000	12,000	100/ 99.5
Look AHEAD §	11,000	18,000	16,000	9000	15,000	99.5/95
X-PERT §	9000	16,000	13,000	6000	12,000	100/100
ICAN §	30,000	30,000	39,000	38,000	59,000	16.0/ NA

DC: annual discount rates for effects and costs
NA: not available, just one risk factor affected
* assuming one additional 30 minutes individual contact (€27) per year for the remaining lifetime, starting from year three
† independent intervention effects for affected risk factors
‡ dependent intervention effects for affected risk factors (100% correlation)
§ assuming an average €100 per patient reduction in life-time health care costs due to reduced medication use

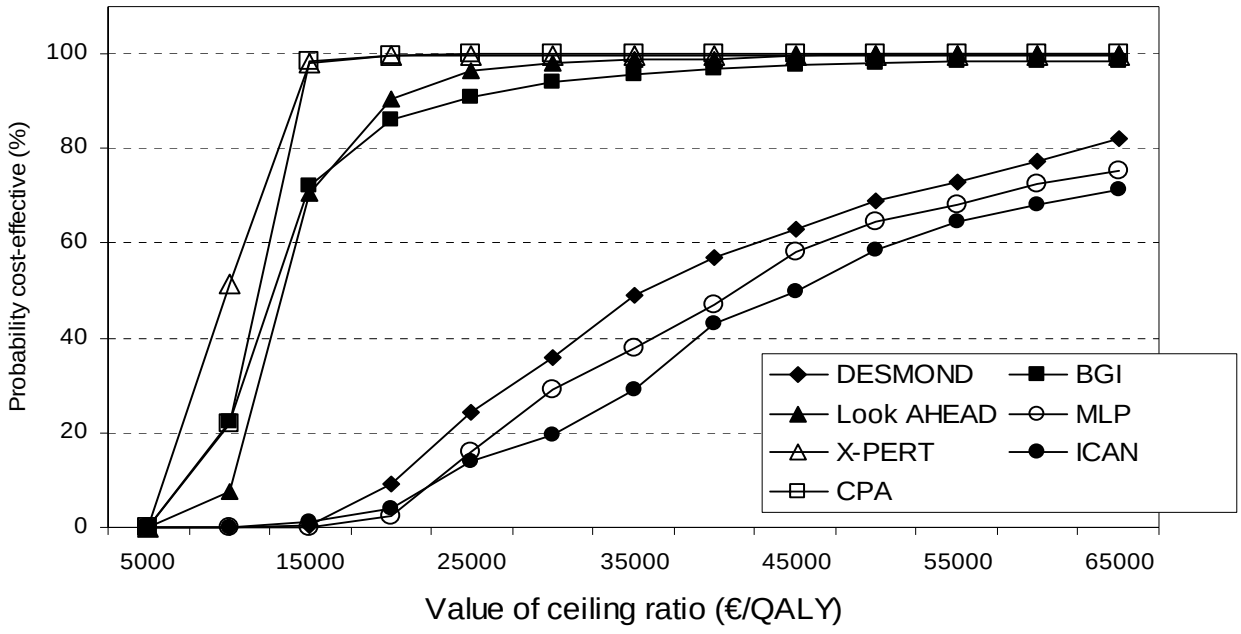

Figure 1. Cost-effectiveness acceptability curves for each intervention

CONCLUSIONS

We showed that it is feasible to simulate long-term outcomes for different kinds of lifestyle interventions for diabetes patients. However, due to limited information about long-term maintenance of health benefits, there was substantial variability (uncertainty) in the expected long-term outcomes for each intervention. Large differences in health outcomes were also observed between interventions (0.01 to 0.14 QALYs gained). However, despite this variability, health gains were generally achieved at reasonable costs (≤ €50,000/QALY). Self-management education (X-PERT) and physical activity counseling (CPA) achieved the most promising results with ≥ 0.10 QALYs gained per person and a very high probability to be cost-effective.

Overall, the results of the selected trials were consistent with results from several meta-analyses that generally showed 0.3-0.8% improvements in HbA1c and modest (1.5 kg) reductions in weight achieved through non-pharmacological diabetes interventions (2;19;20). However, we want to highlight some interesting results. First, substantial weight loss was achieved in the Look AHEAD trial. This intervention focused on weight loss, mainly through caloric restriction, and included meal replacement products and weight loss medication (12). Although substantial short-term weight loss with caloric restriction has been reported previously (21), long-term results of Look AHEAD must be awaited to see whether these weight losses are sustained long-term. Second, the major increase in voluntary physical activity in the CPA trial (23 MET hours per week, corresponding to one addition hour of brisk walking per day) was much larger than the average 20 to 60 minutes of additional physical activity *per week* generally seen in other studies (22). Although the CPA intervention combined multiple evidence-based treatment strategies to enhance physical activity, it remains to be seen whether its findings can be replicated in other settings. Finally, three trials reported a decrease in medication use which is an important, relatively new finding, since health care utilization outcomes were not assessed in any of 21 diabetes self-management trials included in a previous review (23).

Our study has several important strengths. The large number of participants in each of the studies indicates that implementation in regular care is probably feasible. To ensure that health benefits were sustained for a reasonable period of time, we only used intervention effects that were measured at least 12 months after the start of the intervention. In addition, we required interventions to be continued (with at least two counseling sessions) in the second year. Long-term maintenance estimates were based on the best evidence available, and the impact of uncertainty in these estimates was explored in extensive sensitivity analyses. Finally, since changes in various lifestyle habits may go together we considered the impact of correlated outcomes (10;11).

Some methodological issues should be considered. Our simulations were based upon randomized trial results and it may be difficult to replicate these findings in daily practice. On the other hand, there are some reasons to believe that our health benefits might be underestimated. First, only risk factors included in the model could be used and consequently reported improvements in waist circumference, diastolic blood pressure, lipids, fitness and psycho-social outcomes were not taken into account. Second, our model does not include micro vascular complications. Although long-term health outcomes and

health care costs are mainly determined by macro vascular diabetes complications, excluding micro vascular disease results in an under-estimation of health benefits, especially in case of improved glycemic control. Finally, enhanced standard care was provided to controls in three trials (13;15;17) and for these interventions we may have underestimated the effects in relation to the assumed resources used. On the other hand, large variation also exists in the extent to which lifestyle issues are currently addressed in Dutch usual care.

Since promotion of a healthy lifestyle is already acknowledged as an essential part of diabetes treatment the question is no longer *if* lifestyle issues should be addressed, but how to find the most (cost)effective strategies for specific groups of patients. For example, Look AHEAD and ICAN were both directed at overweight diabetes patients. Although Look AHEAD seemed to dominate ICAN (larger health benefits and lower CER), these trials used different inclusion criteria and outcome measures and therefore, results could not be properly compared. In addition, favorable efficacy and cost-effectiveness are not sufficient and potential Reach, Effectiveness, Adoption, Implementation and Maintenance issues (RE-AIM) of interventions should also be addressed (24). Since numerous factors influence the effectiveness of lifestyle interventions, standardized descriptions of intervention components are required to identify successful strategies and to enhance replication and implementation in regular care (23;25).

We showed that lifestyle interventions can probably improve long-term health of diabetes patients at reasonable costs. Future research should focus on long-term maintenance of health benefits achieved through lifestyle interventions and should directly compare multiple treatment strategies to determine incremental costs and benefits of one over the other. Since the potential benefits of successful lifestyle interventions are huge, we should be investing much more in gathering this valuable information.

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References

1. Urbanski P, Wolf AM, Herman WH. Cost effectiveness issues of diabetes prevention and treatment. Newsflash 29: 2008. Available from: http://www.dce.org/pub_resources/files/ cost-effective.
2. Deakin T, McShane CE, Cade JE, Williams RD: Group based training for self-management strategies in people with type 2 diabetes mellitus. Cochrane Database Syst Rev CD003417, 2005
3. Dalziel K, Segal L: Time to give nutrition interventions a higher profile: cost-effectiveness of 10 nutrition interventions. Health Promot Int 22:271-83, 2007
4. Roux L, Pratt M, Tengs TO, Yore MM, Yanagawa TL, Van Den Bos J, Rutt C, Brownson RC, Powell KE, Heath G, Kohl HW 3rd, Teutsch S, Cawley J, Lee IM, West L, Buchner DM: Cost effectiveness of community-based physical activity interventions. Am J Prev Med 35:578-88, 2008
5. Jacobs-van der Bruggen MA, Bos G, Bemelmans WJ, Hoogenveen RT, Vijgen SM, Baan CA: Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modeling study. Diabetes Care 30:128-34, 2007
6. Jacobs-van der Bruggen MA, Engelfriet PM, Hoogenveen RT, van Baal PH, Struijs JN, Verschuren

WM, Smit HA, Baan CA: Lipid-lowering treatment for all could substantially reduce the burden of macro vascular complications of diabetes patients in the Netherlands. Eur J Cardiovasc Prev Rehabil 15:521-5, 2008

7. van Baal PH, Hoogenveen RT, de Wit GA, Boshuizen HC: Estimating health-adjusted life expectancy conditional on risk factors: results for smoking and obesity. Popul Health Metr 4:14, 2006

8. van Baal PH, Polder JJ, de Wit GA, Hoogenveen RT, Feenstra TL, Boshuizen HC, Engelfriet PM, Brouwer WB: Lifetime Medical Costs of Obesity: Prevention No Cure for Increasing Health Expenditure. PLoS Med 5:e29, 2008

9. van Baal PH, Feenstra TL, Hoogenveen RT, de Wit GA, Brouwer WB: Unrelated medical care in life years gained and the cost utility of primary prevention: in search of a 'perfect' cost-utility ratio. Health Econ 16:421-33, 2007

10. Di Loreto C, Fanelli C, Lucidi P, Murdolo G, De Cicco A, Parlanti N, Santeusanio F, Brunetti P, De Feo P: Validation of a counseling strategy to promote the adoption and the maintenance of physical activity by type 2 diabetic subjects. Diabetes Care 26:404-8, 2003

11. Marcus BH, Dubbert PM, Forsyth LH, McKenzie TL, Stone EJ, Dunn AL, Blair SN: Physical activity behavior change: issues in adoption and maintenance. Health Psychol 19:32-41, 2000

12. Wadden TA, West DS, Neiberg RH, Wing RR, Ryan DH, Johnson KC, Foreyt JP, Hill JO, Trence DL, Vitolins MZ: One-year Weight Losses in the Look AHEAD Study: Factors Associated With Success. Obesity 17:713-22, 2009

13. Davies MJ, Heller S, Skinner TC, Campbell MJ, Carey ME et al.: Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. BMJ 336:491-5, 2008

14. Thoolen B, De Ridder D, Bensing J, Maas C, Griffin S, Gorter K, Rutten G: Effectiveness of a self-management intervention in patients with screen-detected type 2 diabetes. Diabetes Care 30:2832-7, 2007

15. Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R et al. : Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care 30:1374-83, 2007

16. Toobert DJ, Glasgow RE, Strycker LA, Barrera M Jr, Ritzwoller DP, Weidner G: Long-term effects of the Mediterranean lifestyle program: a randomized clinical trial for postmenopausal women with type 2 diabetes. Int J Behav Nutr Phys Act 4:1, 2007

17. Deakin TA, Cade JE, Williams R, Greenwood DC: Structured patient education: the diabetes X-PERT Programme makes a difference. Diabet Med 23:944-54, 2006

18. Wolf AM, Conaway MR, Crowther JQ, Hazen KY, L Nadler J, Oneida B, Bovbjerg VE: Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving Control with Activity and Nutrition (ICAN) study. Diabetes Care 27:1570-6, 2004

19. Conn VS, Hafdahl AR, Mehr DR, LeMaster JW, Brown SA, Nielsen PJ: Metabolic effects of interventions to increase exercise in adults with type 2 diabetes. Diabetologia 50:913-21, 2007

20. Norris SL, Zhang X, Avenell A, Gregg E, Brown TJ, Schmid CH, Lau J: Long-term non-pharmacological weight loss interventions for adults with type 2 diabetes mellitus (Review). The Cochrane Library 1-65, 2005

21. Anderson JW, Kendall CWC, Jenkins DJA: Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr 22:331-339, 2003

22. Ogilvie D, Foster CE, Rothnie H, Cavill N, Hamilton V, Fitzsimons CF, Mutrie N: Interventions to promote walking: systematic review. BMJ 334:1204, 2007

23. Newman S, Steed L, Mulligan K. Self-management interventions for chronic illness. Lancet

364:1523-37, 2004

24. Glasgow RE: Translating research to practice: lessons learned, areas for improvement, and future directions. Diabetes Care 26:2451-6, 2003

25. Abraham C, Michie S. A taxonomy of behavior change techniques used in interventions. Health Psychol. 27:379-87, 2008.

Appendix Chapter 5

Estimating long-term maintenance

Selection of trials

To determine long-term maintenance of treatment effect we searched for studies that met the following criteria:

- controlled lifestyle intervention trial with at least 100 participants (intervention (I) + controls (C))
- with either impaired glucose tolerance or diabetes
- at least three measurements of BMI, HbA1c, physical activity, smoking, SBP or nutrition
- t1=baseline measurement
- t2= measurement after active / intensive intervention phase
- t3= measurement after maintenance / less intensive / follow-up phase
- t1-t2 and t2-t3 at least 12 months
- significant intervention effect between t1 and t2

Maintenance (%) was defined as: (Δ t3-t1 (I) - Δ t3-t1(C)) / (Δ t2-t1 (I) - Δ t2-t1(C))
For example:

BMI (kg/m2)	t1	t2	t3	t2-t1	t3-t1
I	30.0	28.5	29.5	-1.5	-0.5
C	30.5	30.5	31.0	0	+0.5
Δ				1.5	1.0

maintenance=1.0/1.5=67%

Results

Five trials (six publication) met our criteria:

- Diabetes Prevention Program (DPP) [1]
- Diabetes Prevention Study (DPS) [2,3]
- China Da Qing Diabetes Prevention Study [4]
- An educational intervention for diabetes patients [5]
- A one-month residential lifestyle intervention [6]

The results of these trials are plotted in figures 1 (BMI), 2 (glycemic control) and 3 (physical activity). We fitted a trend line by using the logarithmic equation (y=clnx+b) for each intervention. Lifetime average maintenance was estimated from the figures as the average of the trials at six years of follow-up (the average expected lifetime of participants in the trials was almost 15 years). Estimated long-term maintenance was 35% for BMI, 85% for glyceamic control and 55% for physical activity.
Only two studies provided information for systolic blood pressure with respectively >100% sustained after two years [7] and 35% sustained after four years [6]. We found ≤ one study with information about maintenance for other risk factors. For these risk factors (SBP, nutrition and smoking) we assumed that maintenance would be similar to maintenance for BMI (35%). The assumed distributions for long-term maintenance are given in Table A8 in this appendix.

Figure 1. Long-term maintenance for BMI

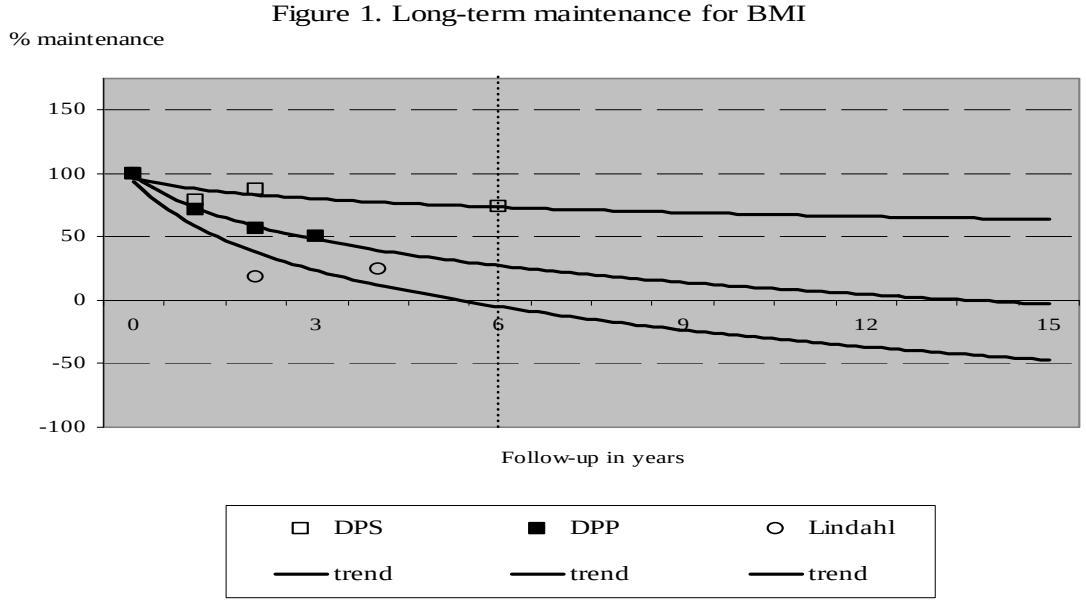


Figure 2. Long-term maintenance for glycemic control

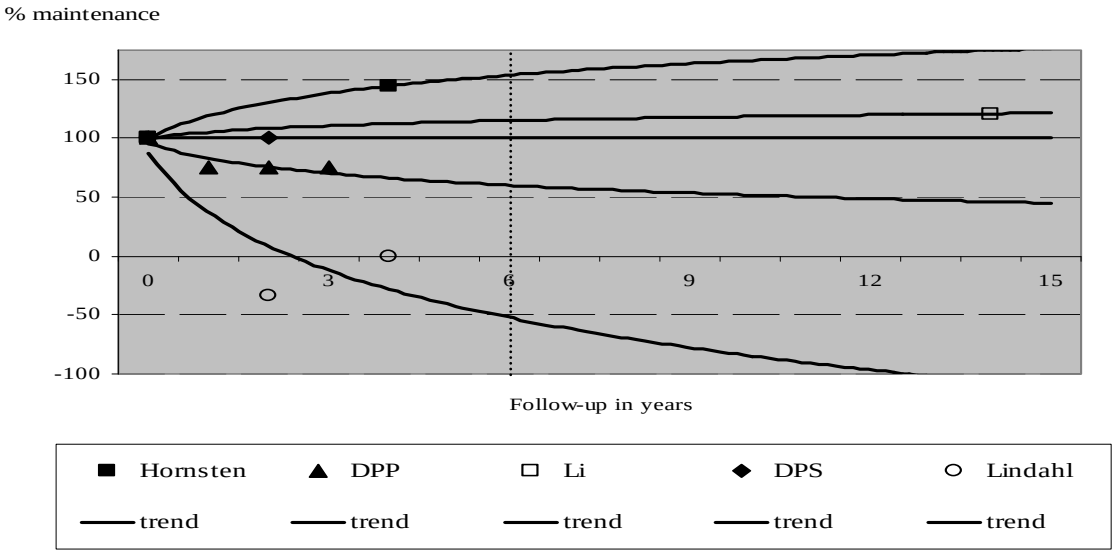
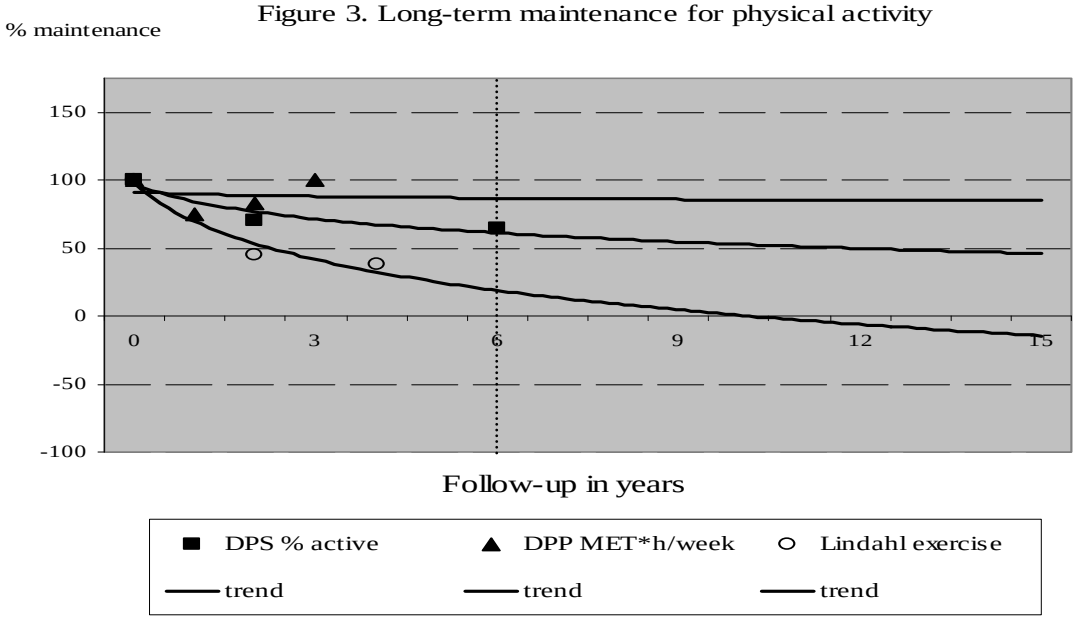


Figure 3. Long-term maintenance for physical activity



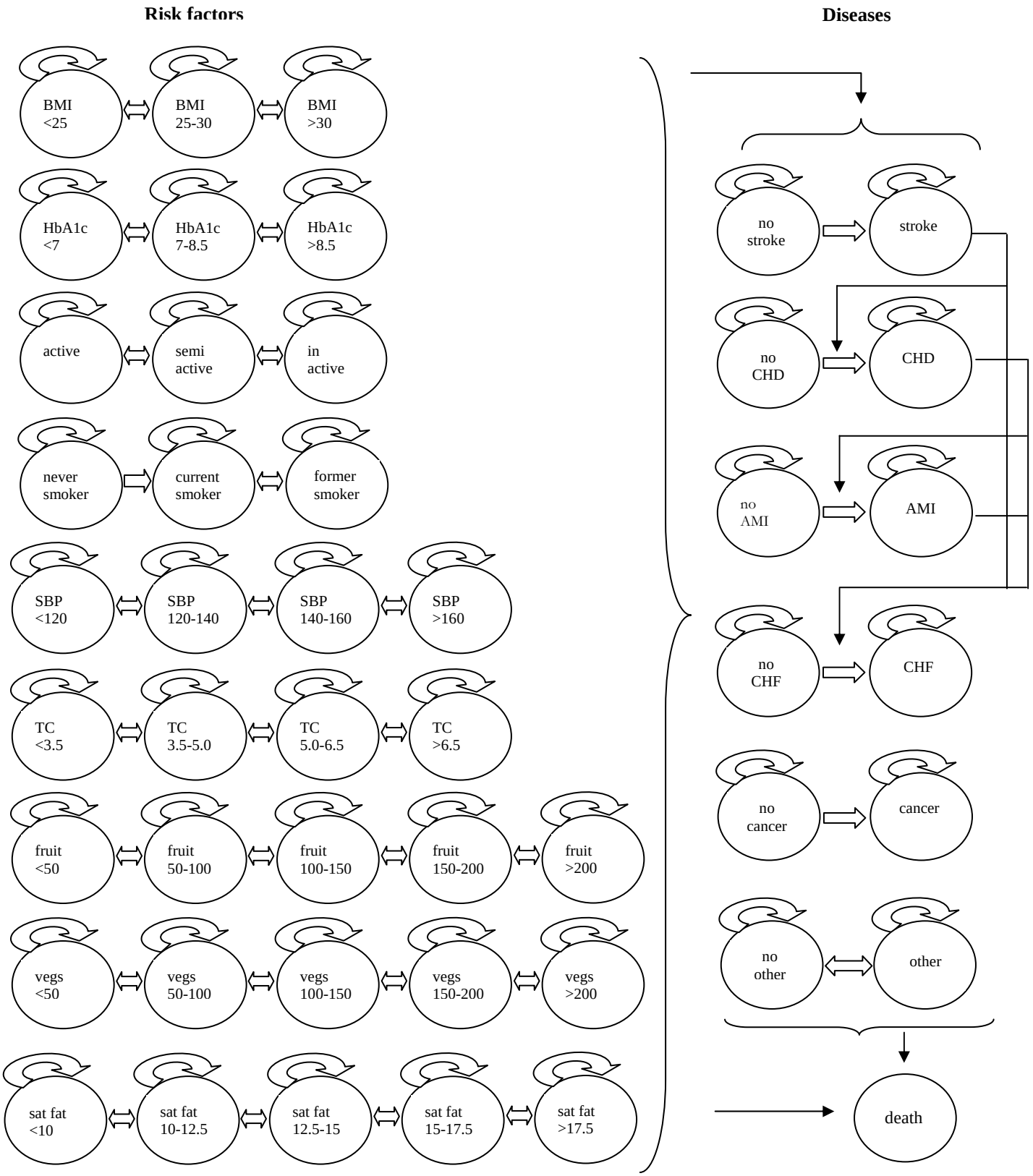


Figure A1. Schematic representation of the Dutch Chronic Diseases Model

⇨ potential transitions → states influence transition rates

BMI: Body Mass Index (kg/m2); HbA1c: glycemic control (%); SBP: systolic blood pressure (mmHg); TC: total cholesterol (mmol/l); fruit (g); vegs: vegetables (g); sat fat: saturated fat (%)

CHD: coronary heart disease (angina pectoris); AMI: acute myocardial infarction; CHF: chronic heart failure

Cancer: 15 subtypes; other diseases: asthma, COPD, dementia, musculoskeletal disorders (5 types)

Disease state = (history) of disease (event), recurrent events not possible

Model starts with Dutch (diabetes) population specified by age gender, risk factor distribution and disease prevalence

Model simulates yearly transitions and tracks population numbers in each state for each risk factors and disease, not for joint states

Qalys and health care costs are calculated; Closed cohort simulation until extinction

Table A1. Associations between risk factors, diseases and mortality in the Chronic Diseases Model

	Diseases						
Risk factor	Stroke	CHD	AMI	CHF	Cancer(s)	Other	Mortality
BMI	X	X	X	X	X	X	X
HbA1c	X	X	X				
Physical activity	X	X	X		X		X
Smoking	X	X	X	X	X	X	X
SBP	X	X	X	X			X
Total cholesterol		X	X				X
Fruit	X	X	X		X		
Vegetables		X	X		X		
Saturated fat		X	X				
Stroke		X	X	X			X
CHD			X	X			X
AMI				X			X
CHF							X
Cancers							X
Others							

BMI: Body Mass Index; HbA1c: glycemic control; SBP: systolic blood pressure (mmHg)
CHD: coronary heart disease (angina pectoris); AMI: acute myocardial infarction; CHF: chronic heart failure
Cancers: 15 subtypes; Other: asthma, COPD, dementia, musculoskeletal disorders (5 types)
Patients in unfavorable risk factor classes (for example BMI 25-30 or BMI>30) have higher relative risks for all X-marked outcomes compared to patients in the reference class (BMI<25).

Table A2. Characteristics and results of the selected trials

Reference	Study characteristics	Intervention Control	Outcome	Comments
Davies 2008 [8] DESMOND program	Multi-center RCT (UK) 824 newly diagnosed diabetes patients mean age 60 range 28-87 mean weight 91.8 (19.2) mean Hba1c 8.3 (2.2)	6 hour structured group education based on psychological theories of learning enhanced usual care	Treatment differences at 12 months: weight reduction: 1.0 (0.1-1.9) kg % smokers from 14% to 11% (intervention group) stable (16%) in controls 10-year CVD risk from 19% to 11% (intervention group) from 18% to 14% in controls	greater improvements in CHD risk score, depression score and knowledge. no effect on HbA1c (nor with adjustment for oral medication) or quality of life response 12-monts questionnaire 75% large improvements in HbA1c in both groups, financial rewards for good CVD control in UK, difficult to have additional improvements in newly diagnosed
Thoolen 2007 [9] Beyond Good Intentions (BGI)	RCT (Netherlands) 196 screen-detected diabetes patients from the Dutch arm of the ADDITION study, mean age 62 range 50-70 mean BMI 29.6 mean HbA1c 6.2	12 week self-management course based on theories of proactive coping and self-regulation individual and group meetings enhanced usual care	Intervention effect-size at 12 months: BMI decrease: 0.8 kg/m2 SBP decrease: 6 mmHg	no effect on HbA1c
Pi-Sunyer 2007 [10] Look-AHEAD	Multi-center RCT (USA) 5145 overweight diabetes patients (±35% from ethnic / racial minority groups) mean age 59 range 45-74 mean BMI 36.3 (6.2) women 35.3 (5.7) men mean HbA1c 7.3	ongoing intensive lifestyle intervention (planned duration 4 years / follow-up 11 years): prescribed diets (caloric restriction, liquid meal replacement and structured meal plans) and home-based exercise group and individual meetings main focus: weight loss enhanced usual care	Change from baseline at 12 months for intervention participants versus controls: BMI decrease: 8.6% (6.9) versus 0.7% (4.8) % achieving weight loss > 7%: 55% versus 7% A1c decrease: 0.64 (0.02) versus 0.14 (0.02) SBP decrease: 6.8 (0.4) versus 2.8 (0.3)	significant improvements in waist, fasting glucose, diastolic blood pressure, HDL, triglycerides, albumine to creatine ratio, fitness and % with metabolic syndrome reduced diabetic, antihypertensive and lipid-lowering medicine use 97% attended 1-year examination

Reference	Study characteristics	Intervention Control	Outcome	Comments
Toobert 2007 [11] Mediterranean lifestyle program	RCT (USA) 279 postmenopausal women with diabetes mean age 60.7 (7.8) mean BMI: 35.6 (8.8) mean HbA1c 7.4 (1.3)	6 months of group education focused on Mediterranean diet, exercise and stress management 18 months maintenance condition using social-cognitive strategies and peer support (social support, stress management, graded goals, self-monitoring, rewards, videotapes) usual care	Change from baseline at 24 months for intervention participants versus controls: reduction in % calories from saturated fat: 3% versus 1% (24 months sign) Change in physical activity in MET min/week: 44 versus -1 (24 months sign) Change in BMI: -0.55 versus +0.39 (6 months, sign) -0.32 versus +0.56 (24 months not sign) Decrease in HB: 0.37 versus 0.01 (6 months, sign) 0.34 versus 0.27 (24 months not sign) Increase in fruit intake 0.36 versus 0.25 (24 months sign)	improved problem solving and self-efficacy no difference in maintenance of treatment effects between two strategies used between 6 and 24 months no effect on medication
Deakin 2006 [12] Diabetes X-PERT program	RCT (UK) 314 diabetes patients mean age 61.3 (9.7) mean BMI 30.8 (5.3) mean Hba1c 7.7 (1.6)	6-week group-based self-management education based on theoretical models of empowerment and discovery learning enhanced usual care	Post-intervention difference between groups at 14 months / effect-size: BMI decrease: 0.4 (-1.0-1.7) / 0.6 HbA1c decrease: 0.7 (0.3-1.0) / 0.7	improvements in waist, physical activity, knowledge, diet, total cholesterol and less medication
Wolf 2004 [13] ICAN	RCT (USA) 147 diabetes patients mean age 53.4 (8.0) BMI>27 mean BMI 37.5 (6.4) mean Hba1c 7.5 (1.5)	one year lifestyle intervention case-management approach to lifestyle change usual care	Intervention effect-size at 12 months: weight: 3.0 (0.6-5.4) (5.0 at 8 months but weight regain in last 4 months) HbA1c difference at 4 months (0.6%) but not significant at 12 months (0.2%) (adjusted for change in medication) medication: -0.8/day	Improved waist Change in weight did not predict change in HbA1c improved quality of life (7 of 9 SF-36 domains) 26% of intervention group dropped out
Di Loretto 2003 [14]	RCT (Italy) one outpatient diabetes center 340 diabetes patients mean age 62 (SE 0.7) mean BMI 29.3 (SE 0.2) mean Hb 7.6 (SE 0.1)	Brief, two year structured counseling recommending physical activity usual care	Intervention effect-size at 24 months: BMI decrease: 1.0 (0.7-1.3) HbA1c decrease: 0.5 (0.37-0.63) physical activity increase: 23 (21-25) METs*h/week	equal diets for both groups drop out 3/182 intervention based on SG report recommendations ΔLA correlates with ΔBMI r=0.55 ΔLA correlates with ΔHB r=0.63

Table A3. Intervention costs

Intervention	Intervention components	Calculations	Total costs
DESMOND [8]			
intervention	1* 6-hour group session with 2 dietitians with 5 participants	6*60* € 0.88 *2 /5	
	3 * 30 min with individual counseling with dietician †	3*30* € 0.88	€ 206
control	practices resourced to enable equivalent contact-time with healthcare professionals		
BGI [9]			
intervention	2 one-hour individual session with nurse	2*60* € 0.90	
	4 two-hour group session with nurse with 6-8 participants	4*2*60* € 0.90 /7	
	3 * 30 min with individual counseling with dietician †	3*30* € 0.88	€ 248
control	self-management brochure	€ 3.20	€ 3
LookAHEAD [10]			
intervention	1 one-hour group session with 'interventionist' with 15 participants	60* € 0.88 /15	
	12 20-30 min individual sessions with 'interventionist'	12*25* € 0.88	
	30 group sessions (60-75 minutes) with 'interventionist' with 10-20 participants	30*67.5* € 0.88 /15	
	orlistat: 20% of participants, average use 16.8 weeks	0.2*€18*16.8	
	brochure	€ 3.20	
	2 * 30 min with individual counseling with dietician †	2*30* € 0.88	€ 503
control	1 one-hour group session with interventionist * with 15 participants	60* € 0.88 /15	
	3 group sessions (60-90 minutes) with interventionist with 15 participants	3*75* € 0.88 / 15	
	brochure	€ 3.20	€ 20
MLP [11]			
intervention	1 20-hour (2.5 days) group sessions with professional and assistant	20*60* (€ 0.88 + € 0.66)/40	
	23 4-hour group meetings:		
	1-hour with physical activity leader + assistant	23*€ 483/ 40	
	1-hour with stress management leader	60* (€ 0.90+€ 0.66)	
	1-hour potluck dinner with meeting leader	60* € 0.90	
	1-hour with 3 professional leaders and 3 assistants	60* € 0.90	
	39 or 4 (mean 21.5) 4-hour group meetings	60*3*((€ 0.90+€ 0.66) 21.5*€ 483 / 40	€ 584
control	-		
X-PERT [12]			
intervention	6 two-hour group sessions with dietitian with 16 participants	6*2*60* € 0.88 /16	
	manual	€ 5.10	
	3 * 30 min with individual counseling with dietician †	3*30* € 0.88	€ 124
control	1 individual 30-minutes session with dietitian	30* € 0.88	
	1 individual 15-minutes session with nurse	15* € 0.90	
	1 individual 15-minutes session with GP	15* € 2.13	
	manual	€ 5.10	€ 77
ICAN [13]			
intervention	6 individual sessions with dietitian (totaling 4 hour)	4*60* € 0.88	
	6 one-hour small group sessions with dietitian	6*60* € 0.88/6	
	monthly phone contacts	12*5* € 0.88	
	written information	€ 3,20	
	2 * 30 min with individual counseling with dietician †		€373
control	written information	€ 3,20	€ 3
CPA [14]			
intervention	1 30-min sessions with physician	30* € 2.13	
	7 15-min sessions with physician	7*15* € 2.13	

Intervention	Intervention components	Calculations	Total costs
	1 15-30 min telephone call	22* € 2.13	
	brochures and diary	3* € 3.20	€345
control	brochures and diary	3* € 3.20	€10

* dietician, psychologist, exercise specialist

† these counseling sessions were added to the original intervention as described in order to have the required minimum of two annual contacts during the first two years

Table A4. Baseline characteristics of Dutch diabetes patients (30-75 years)

	Diabetes cohort
N	398 016
Men (%)	53
BMI 25 - 30 kg/m² (%)	41
BMI ≥ 30 kg/m² (%)	40
Current smokers (%)	25
Former smokers (%)	48
Moderately active (%)	27
Inactive (%)	14
Total cholesterol ≥ 6.5 mmol/l (%)	37
Systolic blood pressure ≥ 140 mmHg (%)	67
Coronary Heart Disease (%)	21
Stroke (%)	4
Hemoglobin A1c 7-8.5% (%)	45
Hemoglobin A1c ≥ 8.5% (%)	15

Table A5. Eligible patients for each intervention

Intervention	Characteristics of the cohorts used for the simulations
DESMOND	Dutch diabetes population, 30-85 years.
BGI	Dutch diabetes population, 50-70 years. HbA1c < 7%
Look AHEAD	Dutch diabetes population, 45-75 years. BMI > 25 kg/m2 and SBP < 160 mmHg
MLP	Dutch diabetes population, 45-75 years. Women
X-PERT	Dutch diabetes population, 30-85 years.
ICAN	Dutch diabetes population, 35-75 years. BMI > 25
CPA	Dutch diabetes population, 40-80 years. Inactive (28%) or moderately active (72%)

Table A6. Clinical benefits, health care costs and cost-effectiveness ratio's for 60-year old participants

	Incident CVD prevented *	Life years gained per participant	QALYs gained per participant †	Increase in total health care costs per participant ‡	CER
DESMOND	2 / 918	0.03 of 16.6	0.01	67	24,000
BGI	12 / 855	0.09 of 16.8	0.04	209	12,000
LOOK A.	35 / 885	0.20 of 16.8	0.09	485	11,000
MLP	7 / 841	0.05 of 16.8	0.02	126	29,000
X-PERT	46 / 923	0.25 of 16.5	0.11	723	8000
ICAN	2 / 930	0.02 of 16.4	0.01	27	39,000
CPA	64 / 1007	0.42 of 15.9	0.18	1107	8000

* prevented per 1000 participants over lifetime; † discounted with 1.5% annually; ‡ discounted with 4% annually

Details for the probabilistic sensitivity analyses (PSA)

Intervention effect

Table A7. Distributions of intervention effects used for PSA

	BMI % decrease	HbA1c decrease	Physical activity	SBP decrease	Smokers who quit (%)	Fruit and vegs	Sat fat % decrease
DESMOND	N(1.1,0.45)				N(15, 7)		
BGI	N(2.6,0.8)			N(6,2.5)			
L. AHEAD	N(7.9,0.17)	N(0.5,0.028)		N(4, 0.5)			
MLP	N(2.6,1.5)		N(45,7) Met*min/wk			N(0.1,0.05) fruit	N (2.0,0.4)
X-PERT	N(2,0.75)	N(0.7,0.18)	N(20,10) min/week			N(1,0.25) fruit / vegs	
ICAN	N(2.8,1.1)						
CPA	N(3.4,0.53)	N(0.5,0.065)	N(23,2) Met*h/wk				

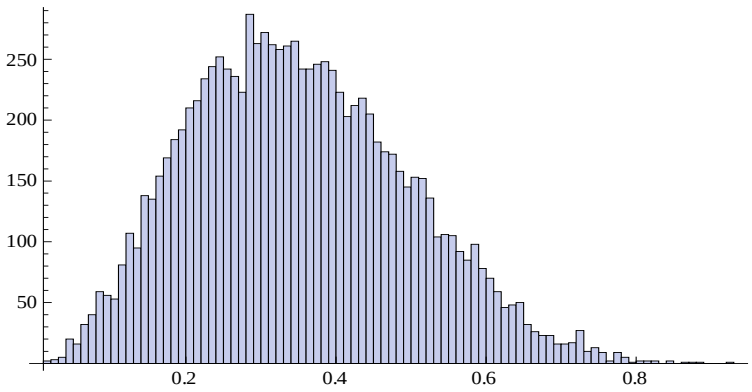
N: Normal distribution; wk: week; vegs: vegetables

Long-term maintenance

Table A8. Distribution of long-term maintenance of intervention effects used for PSA

Risk factor	Average proportion of effect maintained over lifetime	Distribution	References on which the estimated effect is based
BMI and other risk factors	35 45 MLP/CPA	B(3.5, 6.5) B(4.5, 5.5) MLP/CPA	1,3,6
Physical activity	55 65 MLP/CPA	N(55, 20) N(65, 20) MLP/CPA	1-3,6
HbA1c	85 85 CPA	N(85, 30) N(85, 25) CPA	1,2,4-6

B: beta distribution (used to avoid negative maintenance); N: Normal distribution



Beta-distribution B(3.5,6.5) (with 10.000 drawings) used to reflect (uncertainty in) long-term maintenance for BMI, SBP, nutrition and smoking

Intervention costs

Table A9. Distributions for intervention costs used for PSA

	Individual contact time	Contact time in groups	Number of participants in groups	Other variable costs
DESMOND		N(360,80)	N(5,1)	
BGI	N(120,15)	N(480,60)	N(7,1)	
LOOK AHEAD	N(300,38)	N(2085,261)	N(15,2.5)	N(23, 10)*
MLP		N(11760,1470)† N(5340,668) ‡	N(35,5)	
X-PERT		N(720,90)	N(16,3)	
ICAN	N (240,30)	N(360,45)	N(6,1)	N(60,15)§
CPA	N(135,17)			N(22,5) §

* use of weight loss medication (average number of days with orlistat per participant)
† total contact time with one professional + one assistant
‡ total contact time with one professional
§ telephone time

References

1. Diabetes Prevention Program Research Group , Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393-403, 2002

2. Lindstrom J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J, for the Finnish Diabetes Prevention Study Group.: The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 26:3230-3236, 2003

3. Lindstrom J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemio K, Hamalainen H, Harkonen P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Paturi M, Sundvall J, Valle TT, Uusitupa M, Tuomilehto J: Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 368:1673-9, 2006

4. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, Li H, Li H, Jiang Y, An Y, Shuai Y, Zhang B, Zhang J, Thompson TJ, Gerzoff RB, Roglic G, Hu Y, Bennett PH: The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 371:1783-9, 2008

5. Hornsten A, Stenlund H, Lundman B, Sandstrom H: Improvements in HbA1c remain after 5 years--a follow up of an educational intervention focusing on patients' personal understandings of type 2 diabetes. *Diabetes Res Clin Pract* 81:50-5, 2008

6. Lindahl B, Nilsson T, Borch-Johnsen K, Roder ME, Soderberg S, Widman L, Johnson O, Hallmans G, Jansson JH: A randomized lifestyle intervention with 5-year follow-up in subjects with impaired glucose tolerance: Pronounced short-term impact but long-term adherence problems. *Scand J Public Health* 2009

7. The Diabetes Prevention Program Research Group. , Ratner R, Goldberg R, Haffner S, Marcovina S, Orchard T, Fowler S, Temprosa M: Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care* 28:888-894, 2005

8. Davies MJ, Heller S, Skinner TC, Campbell MJ, Carey ME, Cradock S, Dallosso HM, Daly H, Doherty Y, Eaton S, Fox C, Oliver L, Rantell K, Rayman G, Khunti K: Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. *BMJ* 336:491-5, 2008

9. Thoolen B, De Ridder D, Bensing J, Maas C, Griffin S, Gorter K, Rutten G: Effectiveness of a self-management intervention in patients with screen-detected type 2 diabetes. *Diabetes Care* 30:2832-7, 2007

10. Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, Curtis JM, Espeland MA, Foreyt JP, Graves K, Haffner SM, Harrison B, Hill JO, Horton ES, Jakicic J, Jeffery RW, Johnson KC, Kahn S, Kelley DE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montgomery B, Nathan DM, Patricio J, Peters A, Redmon JB, Reeves RS, Ryan DH, Safford M, Van Dorsten B, Wadden TA, Wagenknecht L, Wesche-Thobaben J, Wing RR, Yanovski SZ: Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care* 30:1374-83, 2007

11. Toobert DJ, Glasgow RE, Strycker LA, Barrera M Jr, Ritzwoller DP, Weidner G: Long-term effects of the Mediterranean lifestyle program: a randomized clinical trial for postmenopausal women with type 2 diabetes. *Int J Behav Nutr Phys Act* 4:1, 2007

12. Deakin TA, Cade JE, Williams R, Greenwood DC: Structured patient education: the diabetes X-PERT Programme makes a difference. *Diabet Med* 23:944-54, 2006

13. Wolf AM, Conaway MR, Crowther JQ, Hazen KY, L Nadler J, Oneida B, Bovbjerg VE: Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving Control with Activity and Nutrition (ICAN) study. *Diabetes Care* 27:1570-6, 2004

14. Di Loreto C, Fanelli C, Lucidi P, Murdolo G, De Cicco A, Parlanti N, Santeusanio F, Brunetti P, De Feo P: Validation of a counseling strategy to promote the adoption and the maintenance of physical activity by type 2 diabetic subjects. *Diabetes Care* 26:404-8, 2003

Chapter 6. Lipid lowering treatment for all could substantially reduce the burden of macro vascular complications of diabetes patients in the Netherlands

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Lipid lowering treatment for all could substantially reduce the burden of macro vascular complications of diabetes patients in the Netherlands

ABSTRACT

Background We aimed to quantify the potential health benefits of increased use of lipid lowering treatment (LLT), according to current guidelines, for the Dutch diabetes population.
Design Simulation study.
Methods We compared the long-term health outcomes for a scenario in which all diabetes patients received LLT to those in a 'current practice' scenario, in which 28% received LLT. The model reflected the Dutch diabetes population 40 to 80 years of age, in 2003. Sensitivity analyses were performed, using more conservative assumptions.
Results Over the lifetime, LLT for all diabetes patients reduced the expected cumulative incidences of coronary heart disease (CHD) and stroke by respectively six and nine percent. Average life expectancy of Dutch diabetes patients would increase by 0.33 years, ranging from 0.14 years for patients aged 70-79 years, to 0.84 years for patients aged 40-49 years at the start of the simulation. Life-long treatment for patients aged 50-59 contributed most to the life-years gained (55,000 out of 146,000). With reduced effectiveness of LLT and fewer patients starting LLT, the cumulative incidences of both CHD and stroke would decrease by approximately two percent. The number needed to treat (NNT) in order to prevent one incident case of cardiovascular disease over lifetime was 20 for CHD and 44 for stroke.
Conclusions This simulation study shows that increased use of LLT can substantially reduce the expected future burden of CHD and stroke in the Dutch diabetes population.

BACKGROUND

What would the health impact be for a population if lipid lowering treatment (LLT) was actually prescribed to all diabetes patients? This is an interesting question as most of the recent guidelines recommend LLT for virtually all persons with diabetes [1;2], while prescription rates in daily practice are still far below that target.

There is a wealth of evidence that persons with diabetes are at increased risk for cardiovascular disease (CVD) while excess mortality in diabetes patients is mainly due to CVD [3:4]. Consequently, cardiovascular prevention should be undertaken more rigorously in diabetes patients than in the general population. Several studies have shown that LLT can substantially reduce the occurrence of major cardiovascular events in persons with diabetes [5-9]. The proportional reductions in CVD incidence due to LLT are almost similar for persons with and without diabetes, with or without coronary disease, and independent of the baseline level of cholesterol [5;6;9]. Furthermore, in persons with diabetes, relative treatment benefits appear to be independent of diabetes duration and glycemic control [9].

However, the long-term health benefits that could be gained on a population level when all diabetes patients would be treated according to recent guidelines, are unknown. So far, all reports of observed health outcomes are from clinical trials, conducted in selected populations with a follow-up duration of at most five years [5]. Previous modeling studies were confined to newly diagnosed patients and patients with dyslipidemia [10;11].

In this study we assess the potential long-term health benefits of lipid-lowering treatment, for the Dutch diabetes population.

METHODS

The Chronic Diseases Model

The Chronic Diseases Model (CDM) is a Markov type state transition model [12;13]. In this study, the CDM simulation starts with a cohort resembling the Dutch diabetes population. The states specified in the CDM are risk factor classes, presence or absence of chronic diseases and vital status. The current state determines the probability to change to another state in the next one year time-step. The risk factors included in the simulations in this study are total cholesterol (TC), body mass index (BMI), systolic blood pressure (SBP), and glycemic control (HbA1c). The cardiovascular complications of diabetes modeled are coronary heart disease (CHD) and stroke.

With every time-step, patients have a risk to change risk factor class, disease state or to die. The probability to develop CHD or stroke depends on age, gender and risk factor class. For example, the risk for stroke is higher for higher levels of SBP. Subsequently, the probability to die is higher for patients with CHD or stroke than for patients without cardiovascular complications. In addition, stroke increases the risk for CHD independently from all risk factors.

We used a closed cohort approach, meaning that persons leave the cohort due to mortality, but there are no new persons entering the cohort. With every time-step the simulated cohort becomes smaller, until finally all persons have died.

The CDM has been used previously to evaluate cost-effectiveness of diabetes prevention and smoking cessation [12;14] to explore the impact of lifestyle risk factors on healthy life expectancy [15] and life-time health care costs [16], and to estimate the future burden of stroke and COPD [17;18].

Input data

Age-specific prevalence rates for diabetes derive from Dutch general practitioners' registrations [13]. The risks for CHD and stroke in the diabetes group are calculated from two different input parameters: 1) age-specific CHD and stroke incidence rates in the general population (from general practitioners registrations) and 2) relative risks for CHD and stroke for persons with diabetes compared to persons without diabetes. A similar approach is used to calculate age-specific mortality rates for persons with diabetes. Distributions of cholesterol levels derive from Dutch health monitoring studies conducted between 1998-2001 [19-21] The strengths of the associations (relative risks) between risk factors and diseases (CHD and stroke) are based on international observational studies, and we assume that these associations are similar in persons with and without diabetes. All data in the CDM are age and sex-specific.

Treatment effect

In the CDM, total cholesterol (TC) is modeled in four classes, with cut-off points at 5.0, 6.5 and 8.0 mmol/L. In the model, these classes are linked to coronary heart disease (CHD) through relative risks of disease incidence [13]. The level of TC has no effect on the incidence of stroke [22]. To simulate the effect of LLT, each cholesterol class is stratified by treatment status (treated or untreated). Estimates for cardiovascular risk reductions for treated patients as compared to untreated patients derive from a meta-analysis of statin treatment [6]. We used the following estimates, independent of the pre-treatment level of TC: a 26% risk reduction for CHD incidence in persons younger than 65 years, and a 19% risk reduction for persons over 65. For stroke, a 17% risk reduction for all ages. These estimates correspond to treatment effects obtained with an average LDL reduction of 1.0 mmol/L [6].

Current practice scenario

At the start of the simulation (2003), the cohort comprised 445,200 diabetes patients aged 40-80 years, with a mean age of 65 years. The prevalence of known CHD was 24% and that of stroke 5%. In this cohort, 86% had TC levels >5.0 mmol/L and 28% (123,600 patients) were treated with lipid-lowering medication. We assumed that treated patients continued treatment for the rest of their lives. Similarly, we assumed that untreated patients remained untreated, while TC levels stayed stable (no transitions between cholesterol classes).

Guideline scenario

In this scenario we assumed treatment for all patients, while keeping all other risk factors unchanged. This means that we assumed life-time treatment for an additional 321,600 patients.

Sensitivity analysis

The effect of LLT may be lower in daily practice than in well-controlled trials. Furthermore, some patients may refuse treatment or discontinue within a few years. Therefore, we defined and run the following alternative scenarios (AS):

AS 1. the relative risk reductions for CHD and stroke, due to LLT, were set equal to the lower boundaries of the confidence intervals as reported by Baigent et al. [6]: 21% for persons under 65 years and 12% for persons over 65 for CHD; 12% for stroke

AS 2. reduced effect (AS 1) + the assumption that additional treatment is confined to 50% of currently untreated patients

AS 3. reduced effect (AS 1) + additional treatment is confined to 50% of currently untreated patients with TC >5.0 mmol/L

AS 4. reduced effect (AS 1) + additional treatment is confined to 50% of currently untreated patients with TC >5.0 mmol/L and age ≤ 70 years.

RESULTS

CHD and stroke incidence

Cumulative CHD and stroke incidence were consistently lower in the guideline scenario than in the current practice scenario, although the proportional reductions declined with increased treatment duration (table 1). With life-long treatment, cumulative numbers of incident cases of CHD and stroke were 16,100 (5.6%) respectively 7,300 (8.8%) lower in the guideline scenario. Life-long treatment started at age 50-59 years contributed most to the reduction in CHD (5,247 cases, table 2) and treatment started at age 60-69 years contributed most to the reduction in strokes (2,304 cases).

Table 1. Expected health outcomes for the 'current practice' and 'guideline' scenario, for the total diabetes cohort

	Current practice scenario	Guideline scenario	Difference n (%)	Number Needed to Treat
n	445,200	445,200		
n with LLT(%)	123,600 (27.8)	445,200 (100)	321,600 (72.2)	
5-year incidence (n)				
CHD	95,461	86,520	-8,941 (9.4)	36
Stroke	27,173	23,917	-3,256 (12.0)	99
10-year incidence (n)				
CHD	160,168	146,556	-13,612 (8.5)	24
Stroke	45,696	40,569	-5,128 (11.2)	63
Lifetime incidence (n)				
CHD	284,344	268,294	-16,050 (5.6)	20
Stroke	82,097	74,840	-7,258 (8.8)	44
Life years	6.42 million	6.57 million	146,200 (2.3)	
Life expectancy (yrs)	14.42	14.75	+ 0.33 (2.3)	

LLT, Lipid Lowering Treatment: CHD, Coronary Heart Disease

Life years and life expectancy

The guideline scenario resulted in 146,200 life years gained, meaning that LE increased by 0.33 years (146,200/445,200) in the total diabetes cohort and by 0.45 years (146,200/321,600) in additionally treated patients (table 1). The largest contribution to the life years gained derived from life-long treatment for all patients aged 50-59 years at the start of the simulation. Increase in average LE ranged from 0.14 years in patients aged 70 to 79 years to 0.84 years in patients aged 40-49 years (table 2).

Numbers needed to treat

The NNT in order to prevent one incident case of CHD or stroke declined with increased treatment duration (table 1). The NNT for CHD declined from 36 to prevent one event in five years to 20 to prevent one event over the life-time. The corresponding numbers needed to treat for stroke were 99 and 44, respectively.

Table 2. Expected health outcomes for the 'current practice' and 'guideline' scenario

age group	Current practice scenario	Guideline scenario	Difference n (%)
40-49 years			
With LLT n (%)	8,148 (20.2)	40,280 (100)	32,132 (79.8)
CHD / NNT [a]	34,045	31,713	2,332 (6.8) / 14
Stroke / NNT [b]	9,906	9,119	787 (7.9) / 41
Life years (millions)	1.073	1.107	0.034 (3.1)
Life expectancy (years)	26.67	27.51	0.84 (3.1)
50-59 years			
With LLT n (%)	31,541 (29.8)	106,015 (100)	74,474 (70.2)
CHD / NNT [a]	85,057	79,809	5,247 (6.2) / 14
Stroke / NNT [b]	24,192	22,325	1,867 (7.7) / 40
Life years (millions)	2.049	2.104	0.055 (2.7)
Life expectancy (years)	19.34	19.86	0.52 (2.7)
60-69 years			
With LLT n (%)	47,106 (32.7)	143,978 (100)	96,872 (67.3)
CHD / NNT [a]	92,876	88,065	4,811 (5.2) / 20
Stroke / NNT [b]	26,316	24,012	2,304 (8.8) / 42
Life years (millions)	2.010	2.046	0.036 (1.8)
Life expectancy (years)	13.95	14.21	0.25 (1.8)
70-79 years			
With LLT n (%)	35,172 (24.6)	143,157 (100)	107,985 (75.4)
CHD / NNT [a]	68,305	64,848	3,457 (5.1) / 31
Stroke / NNT [b]	20,390	18,243	2,147 (10.5) / 50
Life years (million)	1.220	1.240	0.020 (1.6)
Life expectancy (years)	8.52	8.66	0.14 (1.6)

LLT, Lipid Lowering Treatment: CHD, Coronary Heart Disease : [a] Life-time cumulative incidence of coronary heart disease and number needed to treat to prevent one incident case of CHD over lifetime. [b] Life-time cumulative incidence of stroke and number needed to treat to prevent one incident case of stroke over lifetime.

Sensitivity analysis

With more conservative estimates for treatment effect and additional treatment confined to 50% of untreated patients with TC>5.0 mmol/L (AS 3), the proportional

reductions in CHD and stroke incidence declined to respectively 1.6% and 2.6%. Life years gained declined from 146,200 to 45,200 (table 3).

Table 3: Results for the sensitivity analysis: proportional reductions in life-time cumulative incidence of coronary heart disease and stroke and total life years gained

	Additionally treated patients (n)	CHD [a] prevented (%)	Stroke [b] prevented (%)	Total life years gained
Guideline scenario	321,600	5.6	8.8	146,200
Alternative scenario 1	321,600	3.8	6.3	110,800
Alternative scenario 2	160,800	1.9	3.1	55,100
Alternative scenario 3	132,800	1.6	2.6	45,200
Alternative scenario 4	87,900	1.3	1.8	39,800

CHD, Coronary Heart Disease: [a] Life-time cumulative incidence of coronary heart disease: [b] Life-time cumulative incidence of stroke

DISCUSSION

Our simulation study showed that six, respectively nine percent of the expected cumulative CHD and stroke incidence in the Dutch diabetes population could be prevented if all patients (instead of 28% in current practice) would use life-long lipid lowering medication. Average LE of the diabetes population would increase by 0.33 years. The NNT in order to prevent cardiovascular disease over lifetime was 20 for CHD and 44 for stroke.

Our study is not the first to model diabetes treatment. Palmer [23] evaluated the impact of theoretical 10% improvements in several cardiovascular risk factors. Life expectancy values for a typical US diabetes cohort increased by 1.0 due to improved glycemic control (HbA1c), 0.7 due to improved blood pressure control and 0.3 with improvements in cholesterol, from which the authors concluded that reducing HbA1c has the greatest impact on long-term health. However, although a ten percent reduction in HbA1c seems feasible [24], mean improvements in blood pressure are generally smaller [24;25]. On the other hand, average reductions in cholesterol due to lipid lowering treatment are generally much larger, in the range 15-20% [5]. Consequently, Palmer et al. underestimated the potential impact of LLT by assuming equal reductions in all cardiovascular risk factors.

Other simulation studies that examined the long-term health impact of LLT in diabetes patients reported increases in life expectancy ranging from 0.2 years for patients with CHD to 5.4 years in young patients with dyslipidemia [10] , showing the large variation in outcome depending on population characteristics and methods used [11]. In addition, the CDC study [10] showed that life-long treatment reduced lifetime cumulative incidence for CHD but not for stroke, probably because the CDC model did not include an effect of statin treatment on stroke. However, despite the absence of an independent positive association of cholesterol with stroke mortality as found in observational studies, there is conclusive evidence from randomized trials that statins substantially reduce stroke rates [22].

We found that in our diabetes cohort in which the majority had no vascular disease the NNT in order to prevent one case of CHD over a five-year period was 36. This is

consistent with previous findings. Costa et al. [5] showed that the NNT in order to prevent a coronary event was 37 in persons (with or without diabetes) without cardiovascular disease, for an average follow-up of five years. A recent meta-analysis [26] confined to persons with diabetes reported 36 fewer people with major vascular events after 5 years, per 1000 patients without vascular disease at baseline, corresponding to a NNT of 28. This is very close to the NNT of 26 to prevent one cardiovascular event over five years in our study, which can be calculated by adding the coronary and stroke events prevented as displayed in table 1.

There are several limitations with respect to the input data and assumptions used in our model. First, the input parameters in our model derived from well designed and controlled intervention studies, while for example treatment dose and adherence are probably lower in day-to-day realistic conditions. Although a Dutch study [27] showed that less than half of the patients were still taking their medication two years after initiating statin treatment, compliance might be better in persons with diabetes [28]. Our sensitivity analysis showed the impact of assuming lower treatment effect and compliance. Secondly, our estimates for treatment effect were based on a meta-analysis of trials including both persons with and without diabetes. Results of a recently published meta-analysis [26] confirmed that our model estimates are valid for persons with diabetes, because the impact of statin treatment on the incidence of major coronary events and strokes appeared similar for persons with and without diabetes. Finally, we assumed that untreated patients remained untreated, although treatment rates appear to increases with advancing age (table 2). If increased use of LLT in current practice would have been taken into account, the calculated health gains in our study would have been lower. On the other hand, we assumed that cholesterol levels did not increase with advancing age. If deterioration of cholesterol levels in untreated patients in the current practice scenario would have been included, the calculated health gains would have been larger.
Although our study provides meaningful insight into the possible long-term effects of LLT, our study did not address potential drug-induced adverse events [6;29], or the impact of drug use on quality of life [30]. On the other hand, our model ignores potential beneficial effects of statin treatment on micro vascular complications [29].

In conclusion, better adherence to current guidelines for LLT would substantially reduce the occurrence of cardiovascular complications in the Dutch diabetes population. With respect to future improvements, more efforts should be devoted to maximizing the potential for decreasing cardiovascular risk in diabetes patients. Strategies should be developed to increase adherence to guidelines by health care providers, and to increase patient compliance to pharmacological treatment as well as lifestyle recommendations.

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References

1. IDF Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: International Diabetes Federation, 2005.
2. Anonymous. Standards of medical care in diabetes--2007. Diabetes Care 2007; 30 (S1): 4-41.
3. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339: 229-234.
4. Laing SP, Swerdlow AJ, Slater SD, et al: Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia 2003; 46: 760-765.
5. Costa J, Borges M, David C, Carneiro AV: Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. BMJ 2006; 332:1115-24.
6. Cholesterol Treatment Trialists' (CTT) Collaborators , Baigent C, Keech A, et al: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366: 1267-1278.
7. Armitage J, Bowman L: Cardiovascular outcomes among participants with diabetes in the recent large statin trials. Curr Opin Lipidol 2004; 15: 439-446.
8. Vijan S, Hayward RA: Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. Ann Intern Med 2004; 140: 650-658.
9. Collins R, Armitage J, Parish S, Sleigh P, Peto R, Heart Protection Study Collaborative Group.: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003; 361: 2005-2016.
10. The CDC Diabetes Cost-effectiveness Group: Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA 2002; 287: 2542-2551.
11. Grover SA, Coupal L, Zowall H, Alexander CM, Weiss TW, Gomes DRJ: How cost-effective is the treatment of dyslipidemia in patients with diabetes but without cardiovascular disease? Diabetes Care 2001; 24: 45-50.
12. Hoogenveen, R. T., Feenstra, T. L., Baal, P. H. M. van, and Baan, C. A. A conceptual framework for budget allocation in the RIVM chronic disease model. A case study of diabetes mellitus. Bilthoven, 2005.
13. Baan, C. A., Bos, G., and Jacobs-van der Bruggen, M. A. M. Modeling chronic disease: the diabetes module - Justifaction of (new) input data. Bilthoven, 2005.
14. Jacobs-van der Bruggen MA, Bos G, Bemelmans WJ, Hoogenveen RT, Vijgen SM, Baan CA: Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modeling study. Diabetes Care 2007; 30: 128-34.
15. van Baal PH, Hoogenveen RT, de Wit GA, Boshuizen HC: Estimating health-adjusted life expectancy conditional on risk factors: results for smoking and obesity. Popul Health Metr 2006; 4: 14.
16. van Baal PH, Polder JJ, de Wit GA, et al: Lifetime Medical Costs of Obesity: Prevention No Cure for Increasing Health Expenditure. PLoS Med 2008; 5: e29.

17. Struijs JN, Genugten MLLv, Evers SMAA, Ament AJHA, Baan CA, Bos GAMvd: Modeling the future burden of stroke in The Netherlands: impact of aging, smoking, and hypertension. Stroke 2005; 36: 1648-55.

18. Feenstra TL, van Genugten ML, Hoogenveen RT, Wouters EF, Rutten-van Molken MP: The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease: a model analysis in the Netherlands. Am J Respir Crit Care Med 2001; 164: 590-6.

19. Houterman S, Verschuren WM, Oomen CM, Boersma-Cobbaert CM, Kromhout D: Trends in total and high density lipoprotein cholesterol and their determinants in The Netherlands between 1993 and 1997. Int J Epidemiol 2001; 30: 1063-70.

20. Westert GP, Schellevis FG, de Bakker DH, Groenewegen PP, Bensing JM, van der Zee J: Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice. Eur J Public Health 2005; 15: 59-65.

21. Hofman A, Boerlage PA, Bots ML, et al: Prevalence of chronic diseases in the elderly; the ERGO [in Dutch]. Ned Tijdschr Geneeskd 1995; 139: 1975-1978.

22. Lewington S, Whitlock G, Clarke R, et al: Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007; 370: 1829-39.

23. Palmer AJ, Roze S, Valentine WJ, et al: Impact of changes in HbA1c, lipids and blood pressure on long-term outcomes in type 2 diabetes patients: an analysis using the CORE Diabetes Model. Curr Med Res Opin 2004; 20 (Suppl 1): 53-58.

24. Huang ES, Meigs JB, Singer DE: The effect of interventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. Am J Med 2001; 111: 633-642.

25. Blood Pressure Lowering Treatment Trialists' Collaboration. , Turnbull F, Neal B, et al: Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med 2005; 165: 1410-1419.

26. Kearney PM, Blackwell L, Collins R, et al: Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008; 371: 117-25.

27. Mantel-Teeuwisse AK, Goettsch WG, Klungel OH, de Boer A, Herings RM: Long term persistence with statin treatment in daily medical practice. Heart 2004; 90: 1065-6.

28. Ho PM, Rumsfeld JS, Masoudi FA, et al: Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med 2006; 166: 1836-41.

29. Ludwig S, Shen GX: Statins for diabetic cardiovascular complications. Curr Vasc Pharmacol 2006; 4: 245-51.

30. Golomb BA, Criqui MH, White HL, Dimsdale JE: The UCSD Statin Study: a randomized controlled trial assessing the impact of statins on selected noncardiac outcomes. Control Clin Trials 2004; 25: 178-202.

Chapter 7. General Discussion

GENERAL DISCUSSION

The general aim of this thesis was to explore opportunities to reduce the future burden of diabetes and cardiovascular diabetes complications in the Dutch population through prevention. The three main questions addressed in this thesis were:
1) Are weight change, alcohol consumption and smoking associated with diabetes incidence in a Dutch population?
2) To what extent can preventive lifestyle interventions reduce the future incidence of diabetes in the Netherlands and are these interventions cost-effective?
3) To what extent can care-related preventive interventions reduce the future incidence of cardiovascular complications in Dutch diabetic patients and are these interventions cost-effective?

We used Dutch observational cohort studies to answer research question 1 and a computer-based simulation model, the Dutch Chronic Diseases Model (CDM) to answer questions 2 and 3 *.
In the following, the three research questions are addressed. Subsequently, methodological issues with respect to observational studies, intervention studies, simulation studies and health-economic evaluations are discussed. Finally, implications for future research and health policy are outlined and a general conclusion is drawn.

Are weight change, alcohol consumption and smoking associated with diabetes incidence in a Dutch population?

We showed in Chapter 2 that weight change was associated with diabetes incidence in a Dutch population, but that this association was explained by the level of body weight attained after the weight change period. There was a continuous association between 5-years weight change and diabetes incidence in the subsequent five years, if the association was adjusted for initial BMI (OR 1.08, 95% CI 1.04-1.13 for each kilogram of weight change). However, the association between weight change and diabetes incidence disappeared if we adjusted for attained BMI (OR 0.99, 95% CI 0.94-1.04).
In Chapter 3, we showed that alcohol consumption was associated with diabetes incidence in Dutch women, but we found no evidence for a significant association between alcohol consumption and diabetes incidence in Dutch men. Women with an average alcohol consumption of 1 or 2 drinks per day (moderate drinkers) had the lowest risk to develop diabetes. Non-drinking women had the highest risk with a hazard ratio (HR) of 2.5 (95% CI 1.3-5.1) compared to moderate drinkers. The HR for women drinking more than 2 drinks per day was 1.9 (95% CI 0.7-5.1). We found no

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* Due to the health care costs and quality of life weights - a value between 0 (death) and 1 (for perfect health) - incorporated in the model, we could calculate cost-effectiveness ratios for the interventions. An intervention was considered to be cost-effective if the (incremental) cost-effectiveness ratio (ICER) was below €20,000 per quality adjusted life year (QALY; a life year multiplied by its quality of life weight).

significant associations between smoking and diabetes incidence in a Dutch population, but smoking more than 10 cigarettes per day tended to increase diabetes risk in both men and women (HR compared to non-smokers approximately 1.4 both for men and for women).

Weight loss appears to be the main determinant for the success of lifestyle interventions in terms of the risk reduction for incident diabetes that is achieved [1,2]. Weight loss can improve insulin sensitivity, thereby lowering the risk of diabetes [1]. However, the role of weight change as an independent risk factor for diabetes and determinant of intervention success has not been entirely clear [3-5]. Our results from Chapter 2 suggest that weight loss interventions affect diabetes incidence by influencing attained weight, but that weigh loss in itself does not contribute to diabetes prevention. A healthy diet and sufficient physical activity are the main tools to achieve and sustain weight loss. In addition improvements in diet, physical activity and fitness have been shown to contribute to diabetes prevention, independent of associated changes in body weight [6-8]. Since body weight, dietary composition and physical activity are also risk factors for other chronic diseases, such as cardiovascular diseases and cancer [9-13], lifestyle interventions could contribute to the prevention of these diseases as well.

There is some discussion whether the lower (cardiovascular) disease risk for moderate compared to non-drinkers, often found in observational studies, is entirely explained by a causal, protective effect of alcohol consumption, or whether this observation is partly due to systematic error in observational studies [14]. It is suggested that the higher risks for unfavorable outcomes in non-drinkers can be partly explained by inclusion of former drinkers in the non-drinkers category, while former drinkers might have stopped drinking because of health problems. Since alcohol consumption has also been associated with unfavorable developments in cardiovascular risk factors (triglycerides, body weight and blood pressure [15]), recommending moderate alcohol consumption to non-drinkers in order to reduce diabetes risk is probably not desirable. On the other hand, it seems obvious that heavy, irregular drinking and binge drinking should be discouraged in order to reduce, at least, the risk for cardiovascular disease [16;17].

Smoking cessation will probably not reduce diabetes incidence in the Dutch population but, since smoking is acknowledged as an important risk factor for multiple, adverse health outcomes [18], it should be considered as an important target in lifestyle interventions. A moderate increase in the risk for diabetes for current smokers compared to non smokers has been reported in many studies [19]. The pooled relative risks of 1.6 (1.4-1.8) for heavy smokers, 1.3 (1.1-1.5) for light smokers and 1.2 (1.1-1.3) for former smokers are consistent with a dose-response phenomenon [19]. Despite this association, counseling for smoking cessation (alone) does not contribute to diabetes prevention [20,21]. Smoking cessation may even increase short-term risk for diabetes, due to weight gain which is often observed in smokers who quit [21]. Therefore, with respect to diabetes prevention, special attention is required for weight control in smokers who quit.

In conclusion, 5-years weight change does not affect diabetes incidence in a Dutch population, beyond its effect on attained weight. Alcohol consumption is associated with diabetes incidence in Dutch women but not in men. Smoking of at least 10 cigarettes per day tends to increase the risk for diabetes in Dutch men and women. Although lifestyle advice about alcohol consumption and smoking will not contribute to reducing the future burden of diabetes, these behaviors should be addressed as integral parts of interventions to improve public health.

The main results of the simulation studies in Chapters 4 to 6 that addressed research questions 2 and 3 are summarized in table 1.

Table 1: Intervention costs, health effects and cost-effectiveness of preventive diabetes interventions if implemented in different target groups of the Dutch population

Intervention and target population	Intervention costs per participant	Increase in LE per participant	NNT	Effect on disease incidence	CER €/QALY
Chapter 4: Community intervention for adults, 20-80 year	6	0.01-0.06	300-1500 # to prevent one incident case of diabetes in 20 years	Maximal decrease in diabetes incidence 2.4% with 100% implementation	3,100-3,900 #
Chapter 4: 'health care intervention' for obese adults, 30-70 years	700	0.4-1.8	7-30 # to prevent one incident case of diabetes in 20 years	Maximum decrease in diabetes incidence of 1.6% with 20% participation	3,900-5,500 #
Chapter 5: Lifestyle intervention for adult, diabetic patients	124-584 ‡	0.02-0.34 ‡	19-1000 ‡ to prevent one incident case of CVD over lifetime	Maximum decrease of 6% in CVD incidence for participants	9,000-39,000 ‡
Chapter 6: Statins for adult, diabetic patients, 40-80 years	371 per year *	0.45	14 to prevent one incident case of CVD over lifetime	Maximum decrease in CVD incidence 6-9% if all diabetic patients receive statins	14,000*

LE: life expectancy, CER: cost-effectiveness ratio, NNT: number needed to treat
Effects with assumed minimum and maximum effectiveness of the interventions
‡ Effect range for seven interventions * Data from RIVM report Jacobs-van der Bruggen et al [22]

To what extent can preventive lifestyle interventions reduce the future incidence of diabetes in the Netherlands and are these interventions cost-effective?

In Chapter 4 we used a computer simulation model to explore the potential long-term health effects and cost-effectiveness of lifestyle interventions. It was shown, that a community-based lifestyle intervention, targeted at the Dutch general population, could reduce the 20-year cumulative incidence of diabetes by 0.4% to 2.4% if such intervention would reach all Dutch adults (table 1). It was also shown that the 20-year cumulative incidence of diabetes could be reduced by 0.3% to 1.6%, if one out of five obese Dutch adults would participate in an intensive individual-based lifestyle intervention. Both interventions appeared to be cost-effective with ICERs ranging from 3,000 to 5,000 €/QALY in base-case analyses. The interventions remained cost-effective (with ICERs < 12,000 €/QALY) even with higher estimates for intervention costs or equal discounting of health effects and health care costs.

Our results suggest, that large-scale implementation of both the community-based and the individual-based lifestyle intervention could reduce 20-years incidence of diabetes in the Dutch population by approximately 1% to 4%, if the effects of the interventions would be additive. This result is moderate compared to a previously estimated 43% reduction in 20-years diabetes incidence in Dutch adults, if they would all have a normal weight [22] , or an estimated 20% fall in diabetes incidence estimated for the UK population, if *everybody* would meet one more of five predefined healthy behavior goals related to BMI, diet and physical activity [23]. A main reason for this moderate impact of lifestyle interventions on a population level, is that the population-based average change in lifestyle risk factors, achieved through the lifestyle interventions, is small due to either low effectiveness and/or a limited reach of the interventions. Body weight was assumed to be reduced by less than 1 kg per person through the community-based intervention and although effects were larger for participants of the intensive individual intervention (weight reduction of up to 4.5 kg), we assumed that 'only' 200,000 obese Dutch adults would participate in such program.

The impact of lifestyle interventions on a population level would increase, if the 200,000 participants in the intensive intervention would be persons at higher baseline risk for diabetes, for example (obese) adults with IGT *. Another way to increase the population impact, could be to extend the target population, for (moderately) intensive lifestyle counseling, to all persons who are overweight. Both intensive lifestyle interventions for persons with IGT and lifestyle counseling for overweight persons have been shown to be cost-effective [24-28]. In a recent report 'Diabetes until 2025' we estimated that implementation of a 'realistic set of interventions' in the Dutch population, including moderately intensive lifestyle counseling for overweight persons, could reduce diabetes incidence (from 2010 to 2025) by approximately 2.3% (1.2% to 3.9%) [29].

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* since persons with IGT can not be identified from the CDM model, our analyses were 'restricted' to persons with obesity.

It should be noted, that the 'relative reduction in cumulative diabetes incidence' does not capture the total health effect of the interventions. The outcome does not reflect that diabetes incidence in intervention participants can be delayed, and it does not show the potential health benefits associated with prevention and delay of other chronic diseases, such as cardiovascular diseases and cancers. The relative reduction in the annual risk to develop diabetes (often reported in trials) is always larger than the associated relative reduction in the cumulative incidence since, even among intervention participants, many persons will eventually develop diabetes. The annual risk to develop diabetes during the 20 year follow-up period in the China da Qing study was 7% for intervention participants, and 11% for controls; a relative risk reduction of 40% [30]. Since most persons developed diabetes in those 20 years (80% of intervention participants and 93% of the controls), the relative reduction in cumulative incidence was 'only' 14%. However, intervention participants spent an average 3.6 years less with diabetes compared to the controls. The total health effects of the interventions are better represented by improvements in quality adjusted life years (QALYs). In our study, the community-based intervention resulted in a modest projected average gain of 0.01 to 0.04 QALY per person. The projected increase of 0.3 to 1.2 QALY, for participants of the individual-based lifestyle intervention was large, compared to results obtained with other lifestyle [31,32] or pharmacological [24,33] interventions, but consistent with results from other studies that modeled similar interventions [24,31].
Although the (cost)effectiveness of universal diabetes prevention appears to be more uncertain compared to the (cost)effectiveness of indicated prevention [31], and the (cost)effectiveness of indicated prevention more uncertain, if targeted at moderately overweight persons, compared to obese persons [34], there seems to be sufficient evidence that preventive lifestyle interventions are generally cost-effective in different target groups of the population [24-28,31,32].

In conclusion, large-scale implementation of lifestyle interventions could reduce the future incidence of diabetes in the Netherlands by approximately 1% to 4%. Preventive lifestyle interventions are cost-effective in different target groups of the population.

To what extent can care-related preventive interventions reduce the future incidence of cardiovascular complications in Dutch diabetic patients and are these interventions cost-effective?
In Chapter 5 we showed that, despite a large variety in the projected long-term health effects of lifestyle interventions for Dutch diabetic patients, these health benefits were generally achieved at reasonable costs. The relative reductions in the cumulative lifetime incidence of cardiovascular complications, achieved through seven simulated interventions, ranged from 0.1% to 6.1%, for intervention participants. The cost-effectiveness ratios ranged from 10,000 to 39,000 €/QALY (table 1).
Chapter 6 revealed that the life-time cumulative incidence of coronary heart disease (CHD) and stroke could be reduced by 6% and 9% respectively, if all Dutch diabetic

patients would receive lipid lowering treatment (table 1). With more realistic assumptions about effectiveness and participation, the cumulative incidence of both CHD and stroke would decrease by approximately 2%.

Although promotion of a healthy lifestyle, as a part of self-management education, is acknowledged as an integral part of diabetes treatment, knowledge on the (cost)effectiveness of lifestyle interventions for diabetes patients has been relatively scarce [35]. We showed that there is a large variety in the efficacy and cost-effectiveness of available interventions (table 1). A two-year structured counseling program to promote physical activity [36], a six-week structured self-management education program called X-Pert [37] and a one-year intensive lifestyle intervention for overweight patients, called LOOK-AHEAD [38], obtained promising results; these interventions reduced lifetime CVD incidence among participants by respectively 6.1%, 5.0% and 4.0% and they had >90% probability to be very cost-effective (ICER ≤ 20,000 €/QALY) even when uncertainty in intervention costs, intervention effects and long-term maintenance of these effects were taken into account.
The average individual health gain of respectively 0.14, 0.09 and 0.08 QALY, obtained through the aforementioned interventions, is smaller than the health gain of 0.3 to 1.2 QALY, projected for the individual-based lifestyle intervention in Chapter 4. It should be noted, that the assumptions about long-term maintenance of intervention effects such as weight loss and increased physical activity, were more conservative in the simulations in Chapter 5. It is noteworthy, that the increase in life-expectancy of 0.34 years, associated with the most successful lifestyle intervention for diabetic patients, is not much lower than the projected increase by 0.45 years, associated with lifelong treatment with lipid lowering medication in the same population.
The extent to which increased use of preventive treatments can improve future health depends on the amount of people eligible for a specific intervention, and the extent to which treatments are already applied in current care. A recent simulation study [39] estimated that myocardial infarctions and strokes in the US population could be reduced by 36% and 20%, respectively, if everyone received each of 11 nationally recommended preventive activities for which they were eligible, if aggressive but feasible levels of performance and compliance of these treatments were assumed. Three of the interventions considered were blood glucose -, lipid lowering - and blood pressure lowering treatments for diabetic patients. Conform to the results in this US study, larger health benefits for the Dutch diabetic population can probably be achieved through adequate lipid-lowering and antihypertensive treatment, than through intensified treatment of blood glucose, partly because these interventions have a larger impact on CVD incidence and partly because more patients are eligible. We have previously shown that, with realistic treatment scenarios, lipid lowering, antihypertensive and blood glucose treatment can reduce the 20-year incidence of cardiovascular complications in the Dutch diabetic population by approximately 5%, 5% and 1% respectively [22]. The estimated cost-effectiveness ratios of these interventions were 14,000 €/QALY, 10,000 €/QALY and 22,000 €/QALY. The largest health benefits

are probably achieved in multifactor interventions in which self-management education (including lifestyle advise) and pharmacological treatments are combined [29,40]. We have estimated that implementation of a 'realistic set of interventions' in Dutch diabetes patients could reduce the incidence of cardiovascular complications (from 2010 to 2025) by approximately 3.4% (0.9% to 6.5%) [29].

In conclusion, there are several successful lifestyle interventions that could reduce lifetime incidence of cardiovascular complications, among Dutch diabetic participants, by up to 6%. A similar reduction could, in theory, be obtained in the whole Dutch diabetic population, if all patients would use lipid lowering medication. Although most care-related preventive interventions are cost-effective, the cost-effectiveness of some of the available lifestyle interventions is not so favorable and, based on current evidence, quite uncertain. Diabetes treatment should combine the most promising, cost-effective lifestyle interventions with optimal pharmacological treatment, in order to reduce the future incidence of cardiovascular complications in the Dutch diabetic population.

Methodological issues

Different kinds of studies were used in this thesis to explore opportunities for diabetes prevention. The results of *observational cohort studies* were used in Chapters 2 and 3 to examine associations between lifestyle risk factors and incident diabetes. Results of *intervention studies* were used to estimate (long-term) effectiveness of lifestyle- and lipid lowering interventions in Chapter 4, 5 and 6 and consecutively, *simulation studies* with the Chronic Diseases Model were used to explore the potential long-term health benefits of these interventions, if applied in the Dutch population. *Health-economic evaluation studies* were used in Chapters 4 and 5 to determine the *cost-effectiveness* of lifestyle interventions.

Observational studies

Observational studies are well suited to identify risk factors for specific outcomes. An observed association between a risk factor (the exposure variable) and the outcome of interest, indicates that the risk factor could be a target for preventive activities. If, for example, diabetes develops more frequently among persons with a high body weight than among lean persons, this suggests that weight loss interventions could be effective in order to prevent diabetes. There are many methodological issues to consider in observational studies. Some issues are especially relevant with respect to examining associations between lifestyle risk factors and diabetes, as done in this thesis.

First, lifestyle habits change over time and this could influence the strength of observed associations, especially in studies in which baseline exposure data is associated with outcome data at long-term follow-up. Changes in body weight over time could explain why the strength of the association between BMI and diabetes appears inversely associated with the follow-up duration of the study [41]. If possible, updated exposure data from repeated measurements should be used to account for these changes, for

example by using GEE analysis (Chapter 2). The association between BMI and diabetes incidence within 5 years in our analysis in Chapter 2 (OR 1.23, 95%CI 1.19-1.27) was indeed higher than the pooled relative risk (RR 1.18, 95%CI 1.16-1.20), derived from many observational studies with a median follow-up of 8 years [41]. Second, the reasons why people change their lifestyle habits are generally unknown. If changes to a healthier lifestyle are made in order to reduce health related problems, this could cause for example, weight loss, former alcohol consumption, or former smoking, to be associated with a higher incidence of diabetes, instead of an expected lower risk (sick quitter effect). This phenomenon could explain some of our findings in Chapter 3, such as the high risk for diabetes observed in never drinking, formerly smoking men. Another potential reason for weight loss to be associated with unfavorable prognosis, is if weight loss is unintentional.

The last issue relates to misclassification of exposure (for example body weight) or outcome (diabetic cases). Many observational studies have to rely on self-reported weight, which is known to be underestimated. The advantage of our study (Chapter 2) was that weight was repeatedly measured in participants in the Doetinchem Cohort Study. Similarly, many observational studies (including our studies in Chapter 2 and 3) have to rely on self-reported diabetes. Consequently, since many persons have undiagnosed diabetes, many diabetic cases are unidentified and in fact misclassified. If this misclassification is independent from the exposure, this will cause a dilution of the association of interest. However, with respect to body weight, it could be that diabetes is more often undiagnosed among lean persons, than among obese persons, and this could result in an observed association between body weight and diabetes which is stronger than the actual association. Although, ideally, formal diagnostic tests (blood glucose measurements) should be used to identify diabetic cases, this is generally not feasible in large observational studies.

Intervention studies

Although an association, identified from observational studies, is an important first step to identify targets for prevention, it is by no means sufficient. Whether a risk factor can be a valuable target also depends on the causality of the association and the extent to which the risk factor can be modified. Intervention studies, preferably randomized controlled trials, are needed to assess these requirements. However, intervention studies have limitations too. Due to the strict criteria for including participants, and the specified intervention protocols applied in a clinical trial setting, it is questionable whether results can be generalized to real-life settings. Long-term randomized trials require tremendous effort, patience and budgets, while evaluation of long-term effects is frequently hindered by (selective) drop out, and intervention activities which are eventually offered to the original control population as well. Therefore, most trials are relatively short; effects are frequently reported for intermediate outcomes such as lifestyle- and cardiovascular risk factors, but not for final outcomes such as disease incidence or mortality. In addition, essential information about long-term maintenance of lifestyle changes remains limited. The ability to provide relatively fast estimates of

long-term outcomes, while taking account of uncertainty around population characteristics, potential reach and (long-term) effects and costs of interventions is one of the main advantages of using simulation studies.

Simulation studies

A major strength of epidemiological models is that information from different sources can be used and combined in a consistent way. Besides information from observational- and intervention studies, a model can include demographic and epidemiological information of interest, such as population numbers, risk factor prevalence, disease incidence, and mortality rates. In addition, a model can include utility measures and disease- or age-related (health care) costs. This combination of data enables us to explore the (long-term) effects of multiple, sometimes theoretical scenario's. For example, the long-term health impact for the Dutch population, if lipid-lowering treatment would be given to all diabetic patients, (Chapter 6 of this thesis) could easily be explored with the Chronic Diseases Model, while it would otherwise be impossible to assess. Another advantage is that models can be used to calculate generic outcome measures such as life expectancy (LE) or quality adjusted life years (QALYs).

Inevitable, there are also limitations with respect to the use of simulation models. Models have to rely on simplifications and assumptions. For example, in the CDM, risk factors are modeled in (broad) classes, and diseases are either absent or present, meaning that severity is not taken into account. With respect to diabetes, the CDM does not (yet) include micro vascular complications. Transition probabilities in the CDM depend on being in a specific state or not, but are independent of the time spent in the specific state. This means, that the risk to develop cardiovascular disease depends on having diabetes or not, but is independent of diabetes duration. One of the assumptions in the CDM is that risk factor distributions are independent, meaning for example that the prevalence of inactivity is assumed to be equal among persons in different classes of body weight. The results of simulation studies depend on the validity of model assumptions, as well as the quality and accuracy of input data. Combining information from different sources in one model, implies that the limitations of each source affect the outcomes. On the other hand, enforcing a model structure on different data sources, enables the creation of epidemiological consistency meaning, for example, that there is consistency between disease incidence, prevalence and mortality.

Reports about simulation studies should be as clear as possible (about model structure, model assumptions and input data) and the impact of uncertainty of model parameters (such as relative risks and intervention effects) should be quantified and reported. Guidelines for reporting of simulation studies and methods of quantifying uncertainty are increasingly developed and applied [42]. In this thesis, probabilistic sensitivity analysis was used in Chapter 5 to explore the impact of intervention costs, intervention effects and long-term maintenance of these effects. Three out of seven interventions had at least 90% probability to remain below a cost-effectiveness threshold of 20.000

€/QALY, while on the other hand, three interventions had more than 20% probability of a ICER higher than 70.000 €/QALY.

Health-economic evaluation studies

In this thesis we addressed the cost-effectiveness of lifestyle interventions in different target populations. All analyses were performed from a health care perspective, meaning that only health-related effects and health care costs were included. In the CDM all health care costs, including costs for diseases that are not related to the intervention (so-called 'unrelated costs'), are accounted for [43,44]. These unrelated costs are especially high in elderly people because they include, for example, costs for dementia. Therefore, although health care costs are initially reduced through the interventions, due to prevention and delay of lifestyle-related diseases, these initial reductions are generally outweighed by the health care costs that are made in life years gained. It appeared that the interventions in this thesis were generally cost-effective, even if these costs were included.

Besides cost-effectiveness information, additional information for policy makers can be obtained from 'value of information analyses' and so-called 'budget allocation models'. In 'value of information analyses' one tries to quantify how much money should be spent on additional research, to reduce uncertainty in some of the model parameters. A recent study revealed that there is some uncertainty regarding the choice between lifestyle intervention and standard care in overweight persons in Switzerland, and that the uncertainty is larger in moderately overweight persons than in obese persons [33]. By using 'value of information analyses' it was demonstrated that further research should focus on the effect of lifestyle interventions on (cardiovascular) risk factors and utilities (quality of life values), rather than intervention- and treatment costs. 'Budget-allocation models' can be used to calculate how a given budget can be optimally distributed over different interventions, in order for maximal health gains to be achieved, while taking account of specific constraints (such as the number of eligible people, expected participation and/or availability of facilities). A Dutch budget allocation study [45] revealed that if budgets are either low (<€9 per person) or high (>€100 per person), larger health gains could be obtained by investing in cardiovascular prevention in the general population, than in preventive measures targeting diabetic patients, while moderate budgets (€9-€100 per person) were more optimally spent on interventions targeting diabetes patients.

Most health economists agree that public preferences should play a role in decisions about the distribution of scarce resources [46]. Factors that are considered to be important to the public in health-care resource allocation relate to characteristics of eligible patients (i.e. age, social role, health-related lifestyle), characteristics of the health effects of the interventions (start point, end point, size, duration and direction of the health effects) and to distributional rules [46]. For example, it appears that most persons are willing to trade efficiency for a more equal distribution of resources [47]. Although public preferences can be incorporated in health-economic evaluation methods, this is not commonly done (yet) and difficult to achieve because preferences differ between

people and preferences can be context-specific. Due to public preferences, decisions about how to invest in human health are generally not based on results from health-economic studies alone.

Implications for future research

More evidence is required for the (cost)effectiveness of universal and selective prevention. Successful strategies (for specific target groups) should be identified or developed and besides lifestyle, there should be more emphasis on the physical and social environment as important determinants of health. Additional research is required to explore potential effective measures, such as reductions in fat or sugar in frequently used products, or more time for physical activity at schools. Advantages of such measures could be that they are structural and that they reach many people, including those who are generally hard to reach with individual-based interventions (such as persons with a low socioeconomic status).

The efficacy and favorable cost-effectiveness of indicated prevention appear to be established for overweight persons and persons with IGT. Future studies should study participant- and intervention characteristics as determinants of the (cost)effectiveness of the interventions. Implementation studies are required to confirm whether results achieved in clinical trials can be reproduced in real-life settings [48,49] and to explore promoting and constraining factors for implementation [1].

With respect to care-related prevention, it is obvious that self-management education (including lifestyle advice) and pharmacological treatment should be combined. Research should aim to compare the (cost)effectiveness of different multi-component treatments, as well as individual preferences, and reasons why patients and health care providers do not comply to recommended treatments.

In general, future research should focus on a broad range of intervention effects, including effects on micro- and macro vascular diabetes complications, quality of life, health care costs and potential harms of the interventions (side effects of medication). In addition, effects of interventions on absenteeism and productivity could be included in future evaluations, in order to explore the (cost)effectiveness of preventive interventions from a societal perspective. Finally, the impact of multi-morbidity on quality of life values and health care costs should be established in order to improve the accuracy of simulation studies.

Implications for health policy

In view of the predicted increase in the future burden of diabetes and diabetes complications in the Netherlands, large-scale implementation of preventive diabetes interventions is required. The current state of knowledge justifies implementation of interventions, such as addressed in this thesis. Simultaneously, further research as proposed above should be facilitated and supported. With respect to universal prevention, at least information about a healthy lifestyle and the risks associated with unhealthy habits should be made available to all. Lifestyle counseling for high risk individuals (indicated prevention) could be made available through basic health care

insurance, while promising lifestyle counseling programs for diabetic patients (care-related prevention) should have a structural, prominent place in future standards of diabetes care. Finally, continuous collection of high quality, national survey and registry data on (determinants of) population health and health care use should be enhanced, since this information is essential to monitor, predict, and prepare, for future developments in the Dutch population.

General conclusions

Body weight appears to be the most important, modifiable risk factor for diabetes and target for preventive interventions. Lifestyle interventions which focus on weight loss, a healthy diet and increased physical activity appear to be (cost)effective in divers target populations. Large-scale implementation of these interventions is justified, and required to reduce the future burden of diabetes and its complications. However, the impact on population health, achieved through these interventions, is expected to be moderate. Additional research is required to improve currently available interventions while simultaneously, opportunities for alternative approaches to diabetes prevention should be further explored. In diabetic patients, promising lifestyle modification programs should be integrated in individual-based treatment strategies, aimed to reduce overall cardiovascular risk. Improved diabetes treatment could reduce the future burden of cardiovascular diabetes complications in the Netherlands.

References

1. Roumen C, Blaak EE, Corpeleijn E: Lifestyle intervention for prevention of diabetes: determinants of success for future implementation. *Nutr Rev* 67:132-46, 2009

2. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, Hoskin M, Kriska AM, Mayer-Davis EJ, Pi-Sunyer X, Regensteiner J, Venditti B, Wylie-Rosett J: Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 29:2102-7, 2006

3 Field AE, Manson JE, Laird N, Williamson DF, Willett WC, Colditz GA: Weight cycling and the risk of developing type 2 diabetes among adult women in the United States. *Obes Res* 12:267-74, 2004

4. Mishra GD, Carrigan G, Brown WJ, Barnett AG, Dobson AJ: Short-term weight change and the incidence of diabetes in midlife: results from the Australian Longitudinal Study on Women's Health. *Diabetes Care* 30:1418-24, 2007

5. Hofman A. Change viewed on the level. *Int J Epidemiol* 1983;12:391-2.

6. Finnish Diabetes Prevention Study Group: Physical activity in the prevention of type 2 diabetes: the finnish diabetes prevention study. *Diabetes* 54:158-165, 2005

7. Carnethon MR, Prineas RJ, Temprosa M, Zhang ZM, Uwaifo G, Molitch ME: The association among autonomic nervous system function, incident diabetes, and intervention arm in the Diabetes Prevention Program. *Diabetes Care* 29:914-9, 2006

8. Lindstrom J, Peltonen M, Eriksson JG, Louheranta A, Fogelholm M, Uusitupa M, Tuomilehto J: High-fibre, low-fat diet predicts long-term weight loss and decreased type 2 diabetes risk: the Finnish Diabetes Prevention Study. *Diabetologia* 49:912-20, 2006

9. van Dis I, Kromhout D, Geleijnse JM, Boer JM, Verschuren WM: Body mass index and waist circumference predict both 10-year nonfatal and fatal cardiovascular disease risk: study conducted in 20 000 Dutch men and women aged 20-65 years. *Eur J Cardiovasc Prev Rehabil* 2009

10. La Vecchia C: Association between Mediterranean dietary patterns and cancer risk. *Nutr Rev* 67 Suppl 1:S126-9, 2009

11. Tourlouki E, Matalas AL, Panagiotakos DB: Dietary habits and cardiovascular disease risk in middle-aged and elderly populations: a review of evidence. *Clin Interv Aging* 4:319-30, 2009

12. Weinstein AR, Sesso HD: Joint effects of physical activity and body weight on diabetes and cardiovascular disease. *Exerc Sport Sci Rev* 34:10-5, 2006

13. Wendel-Vos GC, Schuit AJ, Feskens EJ, Boshuizen HC, Verschuren WM, Saris WH, Kromhout D: Physical activity and stroke. A meta-analysis of observational data. *Int J Epidemiol* 33:787-98, 2004

14. Fillmore KM, Stockwell T, Chikritzhs T, Bostrom A, Kerr W: Moderate alcohol use and reduced mortality risk: systematic error in prospective studies and new hypotheses. *Ann Epidemiol* 17:S16-23, 2007

15. Koppes LLJ, Dekker JM, Hendriks HFJ, Bouter LM, Heine RJ: Moderate Alcohol Consumption Lowers the Risk of Type 2 Diabetes: A meta-analysis of prospective observational studies. *Diabetes Care* 28:719-725, 2005

16. Bagnardi V, Zatonski W, Scotti L, La Vecchia C, Corrao G: Does drinking pattern modify the effect of alcohol on the risk of coronary heart disease? Evidence from a meta-analysis. *J Epidemiol Community Health* 62:615-9, 2008

17. Rehm J, Sempos CT, Trevisan M: Alcohol and cardiovascular disease--more than one paradox to consider. Average volume of alcohol consumption, patterns of drinking and risk of coronary heart disease--a review. *J Cardiovasc Risk* 10:15-20, 2003

18. Mucha L, Stephenson J, Morandi N, Dirani R: Meta-analysis of disease risk associated with smoking, by gender and intensity of smoking. *Gend Med* 3:279-91, 2006

19. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J: Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 298:2654-64, 2007

20. Davey Smith G, Bracha Y, Svendsen KH, Neaton JD, Haffner SM, Kuller LH, for the Multiple Risk Factor Intervention Trial Research Group.: Incidence of type 2 diabetes in the randomized multiple risk factor intervention trial. *Ann Intern Med* 142:313-322, 2005

21. Yeh H, Duncan BB, Schmidt MI, Wang N, Brancati FL.Smoking, smoking cessation, and risk for type 2 diabetes mellitus. *Ann Intern Med* 152:1-44, 2010.

22. Jacobs-van der Bruggen, MAM, Engelfriet, PM, Bos, G, Hoogenveen, RT, Feenstra, TL, and Baan, CA. Opportunities for preventing diabetes and its cardiovascular complications. A modelling approach, 2007. Bilthoven, RIVM.

23. Simmons RK, Harding AH, Jakes RW, Welch A, Wareham NJ, Griffin SJ: How much might achievement of diabetes prevention behaviour goals reduce the incidence of diabetes if implemented at the population level? *Diabetologia* 49:905-911, 2006

24. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, Hamman RF, Ackermann RT, Engelgau MM, Ratner RE, for the Diabetes Prevention Program Research Group: The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 142:323-332, 2005

25. Palmer ALS, Roze S, Valentine WJ, Spinas GA, Shaw JE, Zimmet PZ. Intensive lifestyle changes or metformin in patients with IGT: modeling the long-term health economic implications of the diabetes prevention program in Australia, France, Germany, Switzerland and the United Kingdom. *Clin Ther* 26:304-21, 2004.

26. Galani C, Schneider H, Rutten FF: Modelling the lifetime costs and health effects of lifestyle intervention in the prevention and treatment of obesity in Switzerland. *Int J Public Health* 52:372-82, 2007

27. Caro JJ, Getsios D, Caro I, Klittich WS, o'Bien JA. Economic evaluation of therapeutic interventions to prevent type 2 diabetes in Canada. *Diabet Med* 21:1229-36, 2004.

28. Bemelmans, WJE, Wendel-Vos, GCW, Bogers, RP, Milder, IEJ, Hollander, EL, Barte, JCM, Tariq, L, and Jacobs-van der Bruggen, MAM. Cost-effectiveness of activity and nutrition advise for persons with (high risk of) type 2 diabetes mellitus [in Dutch]. 2008. Bilthoven, the Netherlands, RIVM.

29. Baan CA, Schoemaker CG, Jacobs-van der Bruggen MAM, Hamberg-van Rheenen, Verkleij H et al. Diabetes until 2025 [in Dutch]. 2009. Bilthoven, the Netherlands, RIVM.

30. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, Li H, Li H, Jiang Y, An Y, Shuai Y, Zhang B, Zhang J, Thompson TJ, Gerzoff RB, Roglic G, Hu Y, Bennett PH: The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 371:1783-9, 2008

31. Dalziel K, Segal L: Time to give nutrition interventions a higher profile: cost-effectiveness of 10 nutrition interventions. *Health Promot Int* 22:271-83, 2007

32. Roux L, Pratt M, Tengs TO, Yore MM, Yanagawa TL, Van Den Bos J, Rutt C, Brownson RC, Powell KE, Heath G, Kohl HW 3rd, Teutsch S, Cawley J, Lee IM, West L, Buchner DM: Cost effectiveness of community-based physical activity interventions. *Am J Prev Med* 35:578-88, 2008

33. Baal PHM van, Berg M van den, Hoogenveen RT, Vijgen, SMC, Engelfriet PM. Cost-effectiveness of a low calorie diet and orlistat for obese persons. Modeling long-term health gains through prevention of obesity related chronic diseases. *Value in Health* 11: 1033-40, 2008.

34. Galani C, Al M, Schneider H, Rutten F. Uncertainty in decision-making: Value of additional information in the cost-effectiveness of lifestyle intervention in overweight and obese people. *Value in Health* 11:424-34, 2008.

35. Urbanski P, Wolf AM, Herman WH. Cost effectiveness issues of diabetes prevention and treatment. Newsflash 29:2008. Available from: http://www.dce.org/pub_resources/files /cost-effective.

36. Di Loretto C, Fanelli C, Lucidi P, Murdolo G et al. Validation of a counseling strategy to promote the adoptionand the maintenance of physical activity by type 2 diabetic subjects. *Diabetes Care* 2:404-8, 2003.

37. Deakin TA, Cade JE, Williams R, Greenwood DC. Structured patient education: the

diabetes X-PERT programme makes a difference. *Diabet Med* 23:944-54, 2006

38. Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care* 30:1374-83,2007.

39. Kahn R, Robertson RM, Smith R, Eddy D: The impact of prevention on reducing the burden of cardiovascular disease. *Diabetes Care* 31:1686-96, 2008

40. Janssen PG, Gorter KJ, Stolk RP, Rutten GE. Randomised controlled trial of intensive multifactorial treatmentfor cardiovascular risk in patients with screen-detected type 2 diabetes: 1-year data from the ADDITION Netherlands study. *Br J Gen Prac* 59: 43-8, 2009.

41. Hartemink N, Boshuizen HC, Nagelkerke NJ, Jacobs MA, van Houwelingen HC: Combining risk estimates from observational studies with different exposure cutpoints: a meta-analysis on body mass index and diabetes type 2. *Am J Epidemiol* 163:1042-52, 2006.

42. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). *Lancet* 360:711-15, 2002.

43. Baal, PH van, Feenstra TL, Hoogenveen RT, Wit GA de. Brouwer WB. Unrelated medical care in life years gainedand the cost utility of primary prevention: in search of a 'perfect'cost-utility ratio. *Health Econ* 16:421-33, 2007.

44. Rappange DR, Brouwer WBF, Rutten FFH, Baal PHM van. Lifestyle interevention:from cost saving to value for money. *Journal of Public Health*, 2009.

45. Feenstra T et al. Targeted versus universal prevention. A resource allocation model to reduce diabetes mellitus and its cardiovascular complications (submitted 2010).

46. Schwappach DLB. Resource allocation, social values and the QALY: a review of the debate and empirical evidence. *Health expectations* 5:210-222, 2002.

47. Schwappach DL: Does it matter who you are or what you gain? An experimental study of preferences for resource allocation. *Health Econ* 12:255-67, 2003.

48. Absetz P, Oldenburg B, Hankonen N, Valve R, Heinonen H, Nissinen A, Fogelholm M, Talja M, Uutela A: Type 2 diabetes prevention in the real world: three-year results of the GOAL lifestyle implementation trial. *Diabetes Care* 32:1418-20, 2009

49. Seidel MC, Powell RO, Zgibor JC, Siminerio LM, Piatt GA: Translating the Diabetes Prevention Program into an urban medically underserved community: a nonrandomized prospective intervention study. *Diabetes Care* 31:684-9, 2008.

Summary

SUMMARY

Type 2 diabetes is a chronic disease with a high prevalence, especially at advancing age. At the moment, diabetes (with nearly 700.000 diagnosed patients in 2007) is one of the most common chronic diseases in the Dutch population. Due to population ageing, and the high prevalence of overweight, a substantial increase in the number of people with diabetes is expected in the near future. For the Netherlands, it has been predicted that approximately 1 out of 12 persons will be diagnosed with diabetes in 2025. The future increase in the burden of diabetes could be reduced by (large-scale) implementation of interventions aimed to prevent the incidence of diabetes. However, a large part of the burden of diabetes can be ascribed to the cardiovascular complications of diabetes. These complications affect quality of life, as well as life expectancy of the patients. Therefore, in order to reduce the future burden of diabetes, it is important to prevent or delay diabetes incidence as well as the occurrence of cardiovascular complications in diabetes patients.

The general aim of this thesis was to explore the opportunities to reduce the future burden of diabetes and cardiovascular diabetes complications in the Dutch population, through prevention. These opportunities depend on the existence of modifiable risk factors for diabetes and the (costs)effectiveness of currently available preventive interventions. In this thesis we consider the role of weight change, alcohol consumption and smoking as risk factors for diabetes and the (cost)effectiveness of interventions aimed to prevent diabetes incidence (universal-, selective and indicated prevention) or cardiovascular complications in diabetes patients (care-related prevention).

The three main questions addressed in this thesis were:
1) Are weight change, alcohol consumption and smoking associated with diabetes incidence in a Dutch population? (Chapters 2 and 3)
2) To what extent can preventive lifestyle interventions reduce the future incidence of diabetes in the Netherlands and are these interventions cost-effective? (Chapter 4)
3) To what extent can care-related preventive interventions reduce the future incidence of cardiovascular complications in Dutch diabetic patients and are these interventions cost-effective? (Chapters 5 and 6)

We used Dutch observational cohort studies to explore the associations between weight change, alcohol consumption, smoking and diabetes incidence in the Dutch population in Chapters 2 and 3 and the RIVM Chronic Diseases Model (CDM) to study the potential long-term health gains and cost-effectiveness of preventive interventions in Chapters 4 to 6. The results, methodological issues, and implications for future research and health policy were discussed in Chapter 7.

Weight change appears to have no effect on diabetes incidence, beyond its effect on attained BMI.

In chapter 2 we explored the role of weight change as a risk factor for diabetes incidence in a Dutch population. Conditional upon initial weight, people who gained more than 6 kg in five years, had an increased risk of diabetes, compared to persons with relatively stable weight (OR 2.4, 95%CI 1.4-4.0). If adjusted for initial BMI, 5-years weight change was a significant, continuous risk factor for diabetes (OR 1.08, 95% CI: 1.04, 1.13 per kg weight change). However, it appeared that the association between weight change and diabetes could be explained by attained weight (the level of BMI attained at the end of the weight change period). There was no association between weight change and diabetes incidence, if the association was adjusted for attained BMI (OR 0.99, 95% CI 0.94, 1.04 per kg weight change). We concluded that weight change affects diabetes incidence because, conditional upon initial BMI, weight change determines attained BMI.

Women who drink less than one alcohol consumption per week, have a higher risk for diabetes than women who drink moderately.

The associations between alcohol consumption, smoking and diabetes incidence were assessed in chapter 3. We found a u-shaped association between alcohol consumption and diabetes incidence in Dutch women, with the lowest risk for moderate drinkers (1 or 2 drinks per day). The HR for non-drinking, drinking less than 1 consumption per week, drinking 1-7 consumptions per week and drinking more than 2 consumptions per day were respectively 2.5 (95% CI 1.3-5.1), 2.2 (95% CI 1.1-4.3), 1.7 (95% CI 0.8-3.5) and 1.9 (95% CI 0.7-5.1). We found no evidence for a significant association between alcohol consumption and diabetes incidence in Dutch men. Smoking more than 10 cigarettes per day tended to increase diabetes risk in both men and women, but the associations were not significant.

Preventive lifestyle interventions can reduce the future incidence of diabetes in the Dutch population by approximately 1-4%.

In Chapter 4 we explored the potential long-term health effects and cost-effectiveness of two types of lifestyle interventions, if implemented in the Dutch population: a community-based intervention, targeted at the general Dutch population, and an individual-based intensive intervention, targeted at obese Dutch adults. From the literature, we first determined the minimum and maximum effects of these interventions on short-term changes in body weight and physical activity. The maximum effect on weight for example, was a 0.7 kg reduction for the community intervention and a 4.5 kg reduction for the intervention for obese adults. The long-term effects on diabetes incidence and health care costs of these interventions were simulated with the CDM. These simulations revealed that the 20-year cumulative incidence of diabetes could be reduced by 0.5-2.4% through implementation of a community-based intervention, if such intervention would reach all Dutch adults, and

by 0.4-1.6%, if one out of five obese Dutch adults would participate in an intensive intervention.

A community-based intervention and an intensive intervention for obese adults are both cost-effective.
Intervention costs were approximately €6 per adult inhabitant in the target area for the community-based intervention, and €700 per participant for the intervention targeted at obese adults. Both interventions were projected to reduce lifetime diabetes-related medical costs, but total health care costs increased. The cost-effectiveness ratios ranged from €3,100 to €3,900 per quality adjusted life year (QALY) for the community-based intervention and from €3,900 to €5,500 per QALY for the intervention for obese adults. Both interventions remained cost-effective in the sensitivity analyses, in which higher intervention costs were assumed, and other discount rates were applied.

In participating diabetes patients, lifestyle interventions can reduce the future incidence of cardiovascular complications by up to 6%.
In Chapter 5 we assessed the potential health effects and cost-effectiveness of lifestyle interventions for Dutch diabetes patients. A literature search was conducted to search for randomized, controlled trials that assessed the effects of lifestyle interventions for diabetes patients. Inclusion criteria were at least 150 persons in the study, and a follow-up of at least one year. For seven identified interventions, long-term effects on cardiovascular complications and health care costs were simulated with the CDM. In the simulations, we took account of 'unfavorable' long-term maintenance of short-term intervention effects. Based on limited available evidence we assumed, for example, that lifetime effect on weight would be approximately 35% of the effect achieved after one year of intervention. There was a large variation in effectiveness between the seven interventions, with reductions in cumulative lifetime incidence of cardiovascular complications ranging from 0.1% to 6.1%. The most effective intervention was a two year structured counseling program, aimed to increase physical activity in inactive diabetes patients.

Also in diabetes patients, many lifestyle interventions appear to be cost-effective.
There was a large variation in intervention costs, and cost-effectiveness between the seven interventions that were modeled. The intervention costs ranged from €124 to €584 per participant, and the cost-effectiveness ratios from €10,000 to €39,000 per QALY. The impact of uncertainty in intervention costs, intervention effects, and long-term maintenance of effects, were quantified with probabilistic sensitivity analyses. These analyses revealed that 4 out of 7 interventions had a high probability to be very cost-effective.

If all Dutch diabetes patients would use lipid-lowering medication, the future incidence of cardiovascular complications could be reduced by approximately 7%.
Guidelines for cardiovascular management recommend lipid lowering treatment for nearly all patients with diabetes. However, in current Dutch practice (in 2007) 'only' about 1 out of 3 patients received this treatment. The potential long-term health benefits for the Dutch diabetes population, if all patients would use lipid-lowering medication (statins), were modeled in Chapter 6. The simulations revealed that the life-time cumulative incidence of coronary heart disease (CHD) and stroke could be reduced by six and nine percent respectively, if all Dutch diabetic patients would use lipid lowering medication. With more realistic assumptions about effectiveness and participation, the cumulative incidence of both CHD and stroke would decrease by approximately two percent.

Large-scale implementation of preventive interventions is justified and required.
We showed that lifestyle interventions can be cost-effective in divers target populations, including diabetes patients. Large-scale implementation of these interventions is justified, and required in order to reduce the future burden of diabetes. However, since the impact on population health, achieved through these interventions, is expected to be moderate, additional research should aim to improve currently available interventions. Simultaneously, opportunities for alternative approaches to the prevention of diabetes and its complications should be further explored.

Samenvatting

SAMENVATTING

Diabetes type 2 is een chronische ziekte die vooral op oudere leeftijd veel voorkomt. Anno 2010 is diabetes (met grofweg 700.000 gediagnosticeerde patiënten in 2007) zelfs een van de meest voorkomende chronische aandoeningen in de Nederlandse bevolking. Door de vergrijzing en de hoge prevalentie van overgewicht zal het percentage mensen met diabetes de komende decennia verder toenemen. Het RIVM voorspelt, dat in 2025 ongeveer 8% van de Nederlanders diabetes zal hebben. Preventieve maatregelen kunnen de toekomstige ziektelast van diabetes mogelijk beperken, doordat zij de instroom van nieuwe patiënten verminderen. Echter, ook de cardiovasculaire complicaties van diabetes zijn in belangrijke mate bepalend voor de ziektelast van diabetes. Complicaties, zoals hart- en vaatziekten, beïnvloeden zowel de kwaliteit van leven als de levensverwachting van mensen met diabetes. Om de toekomstige ziektelast van diabetes terug te dringen, is het daarom van belang om zowel het ontstaan van diabetes als het optreden van complicaties bij mensen met diabetes zoveel mogelijk uit te stellen of te voorkomen.
In dit proefschrift onderzoeken we de mogelijkheden om de toekomstige ziektelast van diabetes en cardiovasculaire diabetes complicaties in Nederland terug te dringen door middel van preventie. Of preventie mogelijk is, hangt af van het bestaan van beïnvloedbare risicofactoren voor diabetes en van (kosten)effectieve preventieve interventies. In dit proefschrift onderzoeken we de invloed van gewichtsverandering, alcoholconsumptie en roken op het ontstaan van diabetes. Vervolgens onderzoeken we de kosteneffectiviteit van leefstijlinterventies die het ontstaan van diabetes beogen te voorkomen (universele, selectieve en geïndiceerde preventie). Tenslotte bestuderen we de (kosten)effectiviteit van interventies die tot doel hebben om cardiovasculaire complicaties bij mensen met diabetes te voorkomen (zorggerelateerde preventie).

In dit proefschrift staan drie onderzoeksvragen centraal:
1) Zijn gewichtsverandering, alcoholconsumptie en roken geassocieerd met diabetes incidentie in een Nederlandse populatie? (Hoofdstuk 2 en 3)
2) In hoeverre kunnen preventieve leefstijlinterventies de toekomstige diabetes incidentie in Nederland verminderen en zijn deze interventies kosteneffectief? (Hoofdstuk 4)
3) In hoeverre kunnen zorggerelateerde preventieve interventies de incidentie van cardiovasculaire complicaties bij mensen met diabetes in Nederland verminderen en zijn deze interventies kosteneffectief? (Hoofdstuk 5 en 6)

Om de invloed van risicofactoren op het ontstaan van diabetes te onderzoeken, hebben we in hoofdstuk 2 en 3 gebruik gemaakt van gegevens van Nederlandse cohortstudies. In hoofdstuk 4 tot en met 6 is gebruik gemaakt van een simulatiemodel, het Chronische Ziekten Model (CZM), om de kosteneffectiviteit van interventies te onderzoeken. De resultaten, methoden en de implicaties van de bevindingen voor toekomstig onderzoek en gezondheidsbeleid werden bediscussieerd in hoofdstuk 7.

De relatie tussen gewichtsverandering en diabetesincidentie wordt geheel verklaard door het bereikte gewicht.

In *hoofdstuk 2* onderzochten we de rol van gewichtsverandering in een periode van 5 jaar op het ontstaan van diabetes in de 5 jaar daarna. In analyses met correctie voor uitgangsgewicht, bleek dat mensen die meer dan 6 kilo waren aangekomen een veel grotere kans hadden om diabetes te krijgen dan mensen van wie het gewicht stabiel was gebleven (OR 2,4; 95%BI 1,4-4,0). Er was een continue, significant verband tussen gewichtsverandering en de kans op diabetes (OR 1,08; 95% BI 1,04-1,13 per kg gewichtsverandering). Uit aanvullende analyses bleek, dat de associatie tussen gewichtverandering en diabetes geheel verklaard werd door het bereikte gewicht na de periode van gewichtsverandering. Er was geen significante associatie tussen gewichtsverandering en het ontstaan van diabetes in analyses waarbij voor het effect van bereikt gewicht op diabetes werd gecorrigeerd (OR 0,99; 95% BI 0,94-1,04 per kg gewichtsverandering). We concludeerden dat gewichtsverandering invloed heeft op het ontstaan van diabetes omdat, uitgaande van het initiële gewicht, gewichts-verandering het nieuwe, bereikte gewicht bepaalt.

Vrouwen die minder dan een glas alcohol per dag drinken, hebben een hoger risico op diabetes dan vrouwen die matig drinken.

In *hoofdstuk 3* werden de associaties tussen alcohol, roken en diabetesincidentie onderzocht. Bij vrouwen was er sprake van een significant verband tussen alcoholgebruik en diabetes. Het laagste risico hadden vrouwen met een gemiddeld alcoholgebruik van 1 tot 2 consumpties per dag. De hazard ratio's (HR) voor diabetes voor vrouwen met '0 consumpties per jaar', 'minder dan 1 consumptie per week', '1-7 consumpties per week', en 'meer dan 2 consumpties per dag' waren respectievelijk 2,5 (95% BI 1,3-5,1), 2,2 (95% BI 1,1-4,3), 1,7 (95% BI 0,8-3,5) en 1,9 (95% BI 0,7-5,1). Bij mannen vonden we geen bewijs voor een significante associatie tussen alcoholconsumptie en de incidentie van diabetes. Nederlandse mannen en vrouwen die meer rookten dan 10 sigaretten per dag, hadden een hoger risico op diabetes dan mannen en vrouwen die nooit rookten. Het effect van roken op diabetesincidentie was in deze studie echter niet statistisch significant.

Preventieve leefstijlinterventies kunnen de toekomstige diabetesincidentie in Nederland met 1 tot 4% verminderen.

In *hoofdstuk 4* onderzochten we de mogelijk te behalen gezondheidswinst voor de Nederlandse populatie bij grootschalige implementatie van twee leefstijlinterventies: een wijkgerichte leefstijlbevorderende interventie voor de algemene populatie (wijkinterventie) en een intensieve leefstijlinterventie voor volwassenen met ernstig overgewicht. Op basis van literatuur werd voor beide interventies het minimaal en maximaal te verwachten kortetermijn effect op gewicht en lichamelijke activiteit bepaald. Het maximale effect op gewicht bijvoorbeeld was 0,7 kg voor de wijkinterventie en 4,5 kg voor de interventie voor volwassenen met obesitas. De langetermijn effecten van beide interventies werden gesimuleerd met het CZM. Uit de

simulaties bleek dat implementatie van de wijkinterventie in heel Nederland (bij 100% bereik) 0,5-2,4% van de verwachte diabetesincidentie in 20 jaar kan voorkomen. Deelname van 1 op de 5 Nederlandse volwassenen met ernstig overgewicht aan de intensieve leefstijlinterventie zou 0,4-1,6% van de verwachte diabetesincidentie voorkomen.

Een wijkgerichte interventie en een intensieve leefstijlinterventie voor volwassenen met obesitas zijn beiden kosteneffectief.
Het uitvoeren van de wijkgerichte interventie kost ongeveer €6 per volwassen inwoner. De intensieve interventie voor mensen met obesitas kost ongeveer €700 per deelnemer. Volgens de projecties zouden met beide interventies de diabetesgerelateerde medische kosten worden teruggedrongen, maar de totale medische kosten zouden toenemen. De interventies waren beiden kosteneffectief met kosteneffectiviteitsratio's variërend van €3.100 tot €3.900 per (voor kwaliteit gecorrigeerd) levensjaar (QALY) voor de wijkinterventie en van €3.900 tot €5.500 per QALY voor de interventie voor volwassenen met obesitas. Beide interventies bleven kosteneffectief in sensitiviteitsanalyses waarin hogere interventiekosten werden verondersteld.

Deelname aan leefstijlinterventies kan de kans op cardiovasculaire complicaties bij mensen met diabetes met 6% verminderen.
In *hoofdstuk 5* onderzochten we de mogelijke gezondheidswinst en de kosten-effectiviteit van leefstijlinterventies voor mensen met diabetes. In de literatuur zochten we recente gerandomiseerde, gecontroleerde studies naar de effectiviteit van leefstijlinterventies voor mensen met diabetes. Deze interventies moesten voldoen aan een aantal criteria zoals minimaal 150 deelnemers en een minimale follow-up duur van een jaar. Voor zeven geselecteerde interventies werden de langetermijneffecten op cardiovasculaire complicaties en medische kosten gesimuleerd met het CZM. Hierbij hielden we expliciet rekening met terugval in leefstijlveranderingen. Op basis van (beperkt beschikbare) gegevens van langdurige studies werd bijvoorbeeld aangenomen dat van het bereikte effect op gewicht na 1 jaar ongeveer 35% behouden blijft op lange termijn. Er was veel verschil in effectiviteit tussen de zeven interventies. De reductie van het risico op cardiovasculaire complicaties varieerde van 0,1% tot 6,1%. De meest effectieve interventie was een programma waarin artsen gedurende twee jaar op een gestructureerde manier probeerden om de lichamelijke activiteit van inactieve diabetespatiënten te verhogen.

Ook bij mensen met diabetes zijn veel leefstijlinterventies kosteneffectief.
De interventiekosten en de kosteneffectiviteitsratio's varieerden sterk tussen de zeven geselecteerde interventies. De kosten varieerden van €124 tot €584 per deelnemer en de kosteneffectiviteitsratio's van €10.000 tot €39.000 per QALY. De invloed van variatie in interventiekosten, interventie effecten en de mate van behoud van effecten op langetermijn op de modeluitkomsten werd gekwantificeerd met probabilistische

sensitiviteitsanalyses. Uit deze analyses bleek, dat 4 van de 7 interventies zeer waarschijnlijk kosteneffectief zullen zijn.

Meer gebruik van cholesterolverlagende medicatie zou maximaal 7% van de cardiovasculaire complicaties kunnen voorkomen.
Richtlijnen voor cardiovasculair risicomanagement bevelen aan om statines voor te schrijven aan nagenoeg alle mensen met diabetes. Echter, in de Nederlandse praktijk (2007) gebruikt 'slechts' een op de drie diabetespatiënten deze cholesterolverlagende medicatie. In *hoofdstuk 6* onderzochten we de mogelijke gezondheidswinst voor de Nederlandse diabetespopulatie als alle patiënten cholesterolverlagende medicatie (statines) zouden krijgen. Uit de modelsimulaties bleek, dat medicatie voor alle patiënten, in vergelijking tot behandeling volgens de huidige praktijk, maximaal 6% van de te verwachten cumulatieve incidentie van coronaire hartziekten en 9% van de cerebrovasculaire aandoeningen bij de Nederlandse diabetespopulatie zou kunnen voorkomen. Bij een scenario met realistischere veronderstellingen over de effectiviteit van de medicatie en uitbreiding van medicijngebruik, zou ongeveer 2% van de cardiovasculaire complicaties kunnen worden voorkomen.

Grootschalige inzet van preventieve maatregelen is gerechtvaardigd en nodig.
Leefstijlinterventies blijken, zowel voor mensen met als voor mensen zonder diabetes, kosteneffectief te zijn. Grootschalige inzet van leefstijladvisering is gerechtvaardigd en noodzakelijk om de toekomstige ziektelast van diabetes te beperken. Echter, de invloed van deze interventies op de volksgezondheid is relatief beperkt. Er zal gezocht moeten worden naar manieren om de mogelijkheden voor de preventie van diabetes en diabetescomplicaties verder uit te breiden en te verbeteren.

Dankwoord

DANKWOORD

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About the author

ABOUT THE AUTHOR

Monique Antoinette Maria Jacobs-van der Bruggen was born on May 01 1971 in 's-Hertogenbosch, the Netherlands. Directly after completing secondary school (at 'Rodenborch college' in 1989) she started studying 'Human movement science' at the VU University in Amsterdam. She graduated in 1994 with a major in 'psychology with respect to human movement'. From 1994 to 1997 she studied for physical therapist (at 'Hogeschool Utrecht') and she completed this in 1997. During her first job in 'Heliomare', Wijk aan Zee, she assisted in a study into hip problems in persons with cerebral palsy. During her second job, at the VU Medical Center, Amsterdam, she participated in a research program concerning early prognosis of newly diagnosed patients with Multiple Sclerosis.

At the end of 2000, she started working as a researcher at the Dutch National Institute for Public Health and the Environment (RIVM). She worked on different subjects and meanwhile, she successfully completed the program of Master of Science in Epidemiology at Erasmus University Rotterdam (in 2003). From 2005 onward, most of her work at RIVM concerned diabetes. After publication of several papers, she combined her findings into the current thesis 'opportunities for diabetes prevention', that she finished in 2010. From December 2009 onward she started a new job at the 'GGD Hart voor Brabant', in 's-Hertogenbosch, where she works as an epidemiologist. At the GGD, she and her colleagues bring together scientific evidence, health policy, and daily practice, thereby trying to contribute to improved public health.

Published papers

Jacobs-van der Bruggen MAM, Spijkerman A, Baal PHM van, Baan CA, Feskens EJM, Picavet HSJ, A DL van der, Verschuren WMM. Weight change and incident diabetes. Addressing an unresolved issue. *Am J Epidemiology 2010; 172(3): 263-270*.

Baan C, Baal P van, Jacobs-van der Bruggen M, Verkleij H, Poos M, Schoemaker C. Diabetes Mellitus in Nederland: heden, verleden en toekomst. Prevalentie en incidentie in 2007, trends over de periode 1990-2007 en prognose voor 2025. *Ned Tijdschr Geneeskd 2009; 153(22): 1052-1058*.

Ujcic-Voortman J, Schram MT, Jacobs-van der Bruggen MA, Verhoeff AP, Baan CA. Diabetes prevalence and risk factors among ethnic minorities. *European Journal of Public Health 2009; 19(5): 511-515*.

MA Jacobs-van der Bruggen, PH van Baal, RT Hoogenveen, TL Feenstra, AH Briggs, K Lawson, EJ Feskens, CA Baan. Cost-effectiveness of lifestyle modification in diabetes patients. *Diabetes Care 2009; 32(8): 1453-1458.*

L Kok, P Engelfriet, MA Jacobs-van der Bruggen, RT. Hoogenveen, HC. Boshuizen, WM Verschuren. The cost-effectiveness of implementing a new guideline for cardiovascular risk management in primary care. *Eur J Cardiovasc Prev Rehabil 2009; 16(3): 371-376*.

MA Jacobs-van der Bruggen, PM Engelfriet, RT Hoogenveen, PH van Baal, JN Struijs, WM Verschuren, HA Smit, CA Baan. Lipid-lowering treatment for all could substantially reduce the burden of macrovascular complications of diabetes patients in the Netherlands. *Eur J Cardiovasc Prev Rehabil. 2008; 15(5): 521-525.*

MA Jacobs-van der Bruggen, G Bos, Wanda J Bemelmans, Rudolf T Hoogenveen, Sylvia M Vijgen, Caroline A Baan. Lifestyle interventions are cost-effective in persons with different levels of diabetes risk; results from a modeling study. *Diabetes Care 2007; 30(1): 128-134.*

Boldingh EJ, Jacobs-van der Bruggen MA, Bos CF, Lankhorst GJ, Bouter, LM. Radiographic hip disorders and associated complications in severe cerebral palsy. *J Pediatr Orthop B. 2007; 16(1): 31-34.*

M. Jacobs-van der Bruggen, G. Donker, H. Verkley en C Baan. Stoppen met roken; samen lossen we het op. *Huisarts en Wetenschap 2007: 50(5).*

M Jacobs-van der Bruggen, A Wijga, J de Jongste, B Brunekreef, M Kerkhof, C Baan, H Smit. Do smoking parents underutilize health care services for their children? Result from the PIAMA study. *BMC Health Services Research 2007:12(7):83.*

Nienke Hartemink, Hendriek C. Boshuizen, Nico J.D. Nagelkerke, Monique A.M. Jacobs, Hans C. van Houwelingen. Combining risk estimates from observational studies with different exposure cut-off points: a meta-analysis on BMI and diabetes type II. *American Journal of Epidemiology 2006; 163(11): 1042-1052.*

E. Boldingh, M. Jacobs-van der Bruggen, C. Bos, G. Lankhorst, L. Bouter. Determinants of hip pain in adult patients with severe cerebral palsy. *Journal of Pediatric Orthopaedics B 2005; 14: 120-125.*

E.J. Boldingh, M.A. Jacobs- van der Bruggen, G.J. Lankhorst, L.M. Bouter. Assessing pain in patients with severe cerebral palsy. Development, reliability and validity of a pain assessment instrument for cerebral palsy. *Arch. Phys. Rehabil 2004; 85: 758-766.*

M. van der Bruggen, H. Huisman, H. Beckerman, F. Bertelsmann, C. Polman, G. Lankhorst. Randomized trial of 4-Aminopyridine in patients with chronic, incomplete spinal cord injury. *Journal of Neurology 2001: 8 (248); 665-671.*

Reports

C Baan, C Schoemaker, M Jacobs-van der Bruggen, H Hamberg-van Rheenen, H Verkleij, S heus, J Melse. Diabetes tot 2025; Preventie en zorg in samenhang. RIVM rapport 260322004/2009.

W Bemelmans, G Wendel-Vos, R Bogers, I Milder, E Hollander, J Barte, L Tariq, M Jacobs-van der Bruggen. Kosteneffectiviteit beweeg- en dieetadvisering bij mensen met (hoog risico op) diabetes mellitus type 2. RIVM rapport 260401005/2008

M Jacobs-van der Bruggen, P Engelfriet, G Bos, R Hoogenveen, T Feenstra. Opportunities for preventing diabetes and its cardiovascular complications. RIVM rapport 260801004/2007

G Bos, MAM Jacobs-van der Bruggen, JK Ujcic-Voortman, DG Uitenbroek, CA Baan
Etnische verschillen in diabetes, risicofactoren voor hart- en vaatziekten en zorggebruik
Resultaten van de Amsterdamse Gezondheidsmonitor 2004. RIVM rapport 260801002/2007

P van Baal, G de Wit, T Feenstra, H Boshuizen, W Bemelmans, M Jacobs-van der Bruggen, R Hoogenveen. Bouwstenen voor keuzes rondom preventie in Nederland. RIVM rapport 260901001/2006

C Baan, G Bos, M Jacobs-van der Bruggen (red). Modeling chronic diseases: the diabetes module. RIVM rapport 260801001/2005

C Baan, J Hutten, P Rijken. Afstemming in de zorg. Een achtergrondstudie naar de zorg voor mensen met een chronische aandoening. RIVM rapport 282701005/2003:
Hst 6. COPD. M. Jacobs, M. Bennema / Hst. 13. Dorsopathieen. M. Bennema, M. Jacobs
Hst 19. Autisme. M. Jacobs, C. Ghundy / Hst. 20. Dementie. A. Jansse, M. Jacobs

M. Jacobs, R. Welte, M. Koopmanschap, J. Jager. Aan roken toe te schrijven productiviteitskosten voor Nederlandse werkgevers in 1999. RIVM Bilthoven. Rapport 403505008/2002

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