Effectiveness and cost-effectiveness of diet advice for patients with type 2 Diabetes Mellitus

A systematic review

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Abstract

Diabetes Mellitus type 2 is a common chronic disease where the glucose metabolism is disturbed mostly because of insulin resistance. One of the available treatments is diet advice provided by a dietitian. However, unknown is the cost-effectiveness of this diet advice. The objective of this review is to show to what extent diet advice is cost-effective for diabetic patients. A search strategy was performed in PubMed and 20 articles corresponded with the inclusion criteria. The most common result was a significant reduction of HbA1c and FPG levels. Also BMI, weight, waist circumference, BP and lipid profiles reduced significantly. Less frequently measured effects were significant improvements for disability days lost, complications, quality of life, work days lost and health utilization. Results stated that costs can be reduced by a decrease in complications, but that even savings can occur with risk reduction and this lead to fewer inpatient admissions, hospitalization rates, primary care and specialty visits. A relation is visible between T2DM and quality of life. Especially, smoking, body weight (BMI) and physical activity are risk factors who can contribute to the level of quality of life of a patient and diet advice could help to reduce these risk factors. It is not possible to quantify diet advice provided by a dietitian as cost-effective for patients with T2DM, but further research could be conducted to investigated this, even as the relation between T2DM and care chains and the optimal amount of hours of diet advice.

Preface

This document is the final result of my master Health Economics, Policy and Law at the Erasmus University in Rotterdam. After almost seven months of intensively working on this project, this thesis has been finished. I really liked to investigate this subject about diet advice provided by dietitians for patients with T2DM because it is a very actual subject and there is almost no information available. However, on the other hand it was sometimes quiet difficult to find all the relevant articles.

When starting this research, the reimbursement for diet advice was excluded from the benefit package by the Minister of HWS. For me it was a challenge to investigate whether diet advice was indeed not cost-effective or maybe it was. During my research there was many commotion around this subject and finally the Minister determined to reimburse the costs for diet advice again within the basic benefit package. For me the purpose of my investigation did not change because the objective was still to investigate to what extent diet advice provided by a dietitian was cost-effective for patients with T2DM. However, the background changed because now I could investigate if the Minister made the right decision.

When starting, there was not a single review available about this subject. However, right before I had finished writing, another research was published which investigated almost the same subject as I did. This research also focuses specifically on the role of the dietitian, but looks not specifically at the treatment for patients with T2DM. All patients treated by a dietitian for all kinds of diseases are included in this research. The study was a cost-benefit analysis which includes also the effects, but was not a review. It was nice to read that study and to know that my results and their results matched. However, it was a pity that it was published right before I finished my thesis.

I could not have written this thesis without the help and support of my family and friends. I would like to thank you all very much. Especially, I want to thank my supervisor, Dr. Stolk for her opinions, comments and help. My thesis is now finished and with this final result I will also finish my period as a student.

Elise Boksebeld

Executive summary

Background:

Since 1 January 2012, diet advice for people with T2DM is excluded from the basic benefit package. Much attention is paid to this subject in the media and politics because different parties had different opinions about the importance and effects of the reimbursement of diet advice. About a half year later, the Minister of HWS decided to reimburse diet advice again. Since 1 January 2013, diet advice will be reimbursed for three hours per year, instead of four hours as it was before 2012. However, there is not much information about the cost-effectiveness of diet advice for patients with T2DM and thus it is not clear if it is necessary to reimburse diet advice or not.

Objective:

To review the literature and to show what is known about the effectiveness and cost-effectiveness of diet advice specifically for people with T2DM.

Research question:

To what extent is diet advice for diabetic patients cost-effective and under which conditions?

Data sources:

A search strategy is performed in PubMed. Central in this search were three keywords, namely 'diabetes mellitus type 2', 'diet advice', and 'cost-effectiveness' and around these words a search strategy is build.

Participants:

Patients with T2DM; age > 18 years.

Intervention:

Diet advice, MNT, diabetes/diet education or individual counseling sessions and all provided by a dietitian. Interventions are compared with usual care, group sessions, or a treatment provided by other health professionals.

Outcome measures:

HbA_{1C}, FPG level, BMI, BP, weight, waist circumference, lipid profiles, quality of life, costs, health care utilization, medication frequency, work days lost, disability days.

Study design:

RCTs, qualitative studies, non-controlled studies, descriptive studies.

Synthesis methods:

The search strategy was performed after an intense process of reading and searching for synonyms and words related to the three keywords. After this, the remaining articles were tested on inclusion and exclusion criteria. The characteristics of the articles who were finally selected, were synthesized through tables. Also the quality of the RCTs, the outcome measures, and the distinction between partial and complete economic evaluations, were synthesized through tables.

Search results:

The search strategy included 5335 items, but these items were limited by exclusion criteria. In total 5315 items were excluded, so a total of 20 articles were used during this research result. The used articles are published between 1995 and 2012, all of which have different study designs and contain both complete and partial economic evaluations.

Results:

Significant reduction of HbA_{1C} levels and FPG levels, significant lower BMI values, weight reduction, decreasing waist circumference levels, lower BP values, and better lipid profiles. Also significant improvements for disability days lost, complications, quality of life, work days lost and health utilization. Results stated that costs can be reduced, especially by a decrease in complications, but diet advice could even save money with risk reduction and thus fewer inpatient admissions, hospitalization rates, primary care visits and specialty visits.

Discussion:

Diet advice provided by a dietitian results in positive effects for patients with T2DM. This result is important for the political debate and decision making about reimbursement, especially now with the spending cuts and because of the lack of information about this subject. However, only twenty articles are used in a period of 17 years, so dated information

could have been used. Also the comparability is low, because of the differences in the designs of the studies, the interventions, and the quality. Nevertheless, this thesis has some strengths like the measurement of the quality of the articles, an extensive search strategy, focus on bias, but especially by focusing on the role of the dietitian instead of a multidisciplinary approach. There is no hard evidence about the cost-effectiveness of diet advice because of heterogeneity, however it is reliable to claim that the positive effects of diet advice will increase the quality of life of patients with T2DM.

Conclusion:

Diet advice provided by a dietitian is an effective tool for patients with T2DM. However, due to a lack of information it is not possible to quantify diet advice provided by a dietitian as cost-effective for patients with T2DM. Nevertheless, results show positive effects in outcome and there is also a relationship between T2DM and quality of life. Especially, smoking, body weight (BMI) and physical activity are the main risk factors who can contribute to the level of quality of life of a patient. Diet advice provided by a dietitian could help to reduce these risk factors. Further research should be conducted to investigate if dietitians really deliver a contribution to the health status of patients with T2DM (and the cost-effectiveness). Also the optimal amount of hours could be investigated even as the relation between T2DM and care chains and their cost-effectiveness.

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List of abbreviations

BMI	=	Body Mass Index
CMC	=	Coordinated Multidiscipline Care
CONSORT	=	Consolidated Standards of Reporting Trials
COPD	=	Chronic Obstructive Pulmonary Disease
CVR	=	Cardiovascular risks
DM	=	Diabetes Mellitus
FPG	=	Fasting Plasma Glucose
HbA_{1C}	=	Glycated Hemoglobin
IBS	=	Irritable Bowel Syndrome
IFG	=	Impaired Fasting Glucose
IGT	=	Impaired Glucose Tolerance
ITT (analysis)	=	Intention to Treat (analysis)
MeSH term	=	Medical Subject Headings
Minister of HWS	=	Minister of Health, Welfare and Sports
MNT	=	Medical Nutrition Therapy
NFK	=	Dutch Association of Organizations for Cancer Patients (Nederlandse Federatie voor Kankerpatiënten)
NGT	=	Normal Glucose Tolerance
NIDDM	=	Non-insulin-dependent Diabetes Mellitus
NVD	=	Dutch Organization of Dieticians (Nederlandse Vereniging voor Diëtisten)
OGTT	=	Oral Glucose Tolerance Test
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-ana Analyses
QALY	=	Quality-Adjusted Life Year
QoL (HRQoL)	=	Quality of Life (Health Related Quality of Life)
RCT	=	Randomized Controlled Trial
T1DM	=	Diabetes Mellitus Type 1
T2DM	=	Diabetes Mellitus Type 2
WHO	=	World Health Organization
Zvw	=	Dutch Law for Health Insurance (Zorgverzekeringswet)

1. Introduction

Since 1 January 2012, diet advice is excluded from the basic benefit package in the Netherlands. Diet care for patients with Diabetes Mellitus (DM), Chronic Obstructive Pulmonary Disease (COPD) and cardiovascular risks (CVR) are not excluded from the basic benefit package, however this care should be included in coordinated multidiscipline care (CMC) before reimbursement will take place (Rijksoverheid, 2011). The Dutch Organization of Dietitians (NVD) complained about this decision from the Dutch Minister for Health, Welfare and Sports (HWS), Mrs. Schippers. According to the NVD many patients need diet advice, but they are not involved in a coordinated multidiscipline care program. The NVD complained that the amount of consults decreased and according to the director of NVD, Anja Evers, no reimbursement results in higher health care costs instead of lower costs for the state and the society. Because patients who do not get an appropriate diet advice will go to the general practitioner more often, use more medicines and have a higher risk to be treated in a hospital, the health care costs will increase. The Minister thought that the insurance companies would have responded to this decision of excluding diet advice from the basic benefit package, by reimburse the costs for diet advising through supplementary insurance. However, this has happened rarely and when insurance companies did, the premiums were too high (NVD, 2012a).

The two parties mentioned earlier have different views about the cost-effectiveness of diet advice for chronically ill people. On one side, the Minister maintained that the costs for health care increase every year and more own payments (out-of-pocket) are necessary to control those costs. The Minister explained that the costs for diet advice is not that high compared to a high technology treatment, so people can pay it by themselves when they need it (ANP, 2011, December 3). On the other side, for 250.000 till 300.000 patients diet advice is necessary because of their chronic illnesses, like diabetes, cancer or irritable bowel syndrome (IBS) (Nederlandse Diabetes Federatie, 2011a). According to a survey of NVD conducted among 900 Dutch dietitians in March of 2012, 70% of them saw a decline of at least 40% of their consults since the beginning of 2012. This decline was a result of the decrease in the amount of references and the reimbursement cut-off. The consequence of the decline is an increase in the health care costs for the long term according to the NVD. Anja Evers stated that those patients will use more medicines, go to general practitioners more often, or even go

to a hospital in the future to treat their illnesses and therefore the long term health care costs for patients with T2DM will increase (NVD, 2012b).

Because of all these reasons, but especially for the main reason that the patients benefit from the diet advices, the NVD went to Court to challenge the decision of the Minister. The NVD stated that diet advice should be reimbursed not only for patients with a coordinated multidiscipline care program, but for all patients who need diet advice. The verdict of the Court legally approved the decision of the Minister and this was a disappointment for the NVD and the Dutch Association of Organizations for Cancer patients (NFK), which supported the NVD. The Court argued that diet advice is temporary care with relatively low costs per patient and reimbursement is available through supplementary insurance. Also the Court stated that the law for health insurance (in Dutch: Zorgverzekeringswet (Zvw)) arranges the relation between patient and insurer and those definitions do not serve as the protection of economic interests for the dietitians. Namely, the NVD had complained for loss of income for dietitians because of the reimbursement cut-off and thus a smaller amount of patients (Evers, 2012; NVD & NFK v. the Netherlands, 2012).

So, the NVD lost their case, but they still disagreed with the Court and the Minister, because there are still patients who do not get the treatment they need. According to a survey from NIVEL, a decrease of 28% of patients occurred in 2012 and 17% of the patients get less time during the diet consult (Tol, Swinkels, Leemrijse, & Veenhof, 2012) . However, in the agreement different political parties made in the spring of 2012, to decrease the budgetary deficit (in Dutch called Lente akkoord), the Minister for HWS is intended to reimburse diet advice in 2013. The Minister expected that the amount of reimbursement would be different than for 2011 because a reduction of 25% of the health care costs should take place (NVD, 2012c). On June 21st, the Second Chamber agreed with an amendment for reinstalling the reimbursement for diet advice for three hours a year (NVD, 2012d). Due to this decision, diet advice will be part of the basic benefit package again, however the amount of reimbursement, three hours, is less than before (De Telegraaf, 2012, August 23; Rijksoverheid, 2012).

When reading this whole discussion about reimbursement of diet advice for chronically ill people, a central question is playing a role, namely: is diet advice effective and even cost-effective? Different parties in this discussion have different views. The answer on this question can be obtained with cost-effectiveness studies and this thesis will show what is known about cost-effectiveness of diet advice for chronically ill people.

2. Objective

The purpose of this thesis is to review the literature and to show what is known about cost-effectiveness of diet advice specifically for people with Diabetes Mellitus type 2. Diabetes Mellitus type 2 (T2DM) is a very common illness in the Netherlands. In 2003, 608.900 people had diabetes and almost 90% of these people suffered from T2DM (Poortvliet, Schrijvers, & Baan, 2007). In 2007, the amount of people with diabetes increased by more than 20% (Baan & Poos, 2011). In 2011, approximately 1 million people in the Netherlands suffered from diabetes and more than 3000 people die every year because of Diabetes (Diabetes Fonds, 2011). The amount of people suffering from diabetes is not stable and will increase every year. In 2025 approximately 1.4 million people will suffering from diabetes (Baan et al., 2009). Because many people suffer from diabetes, especially T2DM, this thesis will focus on this subgroup of chronic diseases.

Besides the growing group of patients suffering from T2DM, this disease is also a costly disease because of its chronic character, the complications and the means required to control T2DM (WHO, 2012). The costs of diabetes care in the Netherlands were more than 1 billion euros in 2007. This means that 1,4% of all health care costs in the Netherlands are spend on diabetes care (RIVM, 2012). However, besides the costs for diabetes care, other costs are also involved with diabetes and affects everyone. Indirect costs, such as productivity loss and disability days also affect the costs related to diabetes. What is also important is the quality of life of patients with T2DM which can be (negatively) influenced by pain and anxiety. Also personal relationships, leisure and mobility can influence the quality of life because of the diabetes treatment and complications (WHO, 2012).

T2DM is a costly disease which affects many people. To treat those people, diet advice is an important component (Nederlands Huisartsen Genootschap, 2006). However, it is important to know if diet advice is cost-effective. To investigate this, a research question is proposed:

To what extent is diet advice for diabetic patients cost-effective and under which conditions?

A systematic literature review will take place to investigate the cost-effectiveness of diet advice for patients with T2DM and to answer the research question at the end of this thesis. It is important that also the conditions are taken into account because there are some important factors that can influence the cost-effectiveness. For example the result can be different when diet advice is a part of a multidisciplinary approach or when diet advice is the only treatment for the patient. Other influencing factors are the patient population or complications. The factors can influence the cost-effectiveness and this will be taken into account when answering the research question. However, first the background of T2DM will be explained.

3. Background

This thesis is specified to one patient population, namely patients with T2DM. In this section the definition of T2DM will be given. Furthermore, this section will describe the disease and the functioning of glucose metabolism in patients with T2DM compared to individuals without T2DM. Besides the diagnose and influencing factors, the role of diet advice in the treatment of T2DM will also be explained. Last part of this section includes the currently use of cost-effectiveness of diet advice in the media.

3.1 Definition of diabetes mellitus type 2

Before Christ was even born, T2DM was already known as 'a disease of elevated blood sugar levels associated with obesity' (Timper & Donath, 2012). The World Health Organization (WHO) describes diabetes mellitus as:

'a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both' (Alberti & Zimmet, 1998).

So, actually T2DM is a chronic disease with a disturbed glucose metabolism and mostly because of insulin resistance (Diabetes Fonds, 2012). The main difference with type 1 diabetes (T1DM) is that the beta cells in the pancreas of a person with T1DM are destroyed. Thus, the body does not produce insulin, while a person with T2DM does produce insulin, but not enough, and/or is not responding properly to the insulin (Nordqvist, 2009).

3.2 Functioning of glucose metabolism

Individuals with a normal glucose metabolism, also called a normal glucose tolerance (NGT), have a specific insulin, glucose and glucagon profile in plasma as a response after the ingestion of a meal. After ingestion, plasma glucose levels increase and also the insulin response to dispose the ingested glucose. At the same time, glucagon secretion is discontinued and thus plasma levels of glucagon decrease. These processes together promote storage and disposal of glucose. This process is different at patients with T2DM because the metabolic response to ingested glucose changes with the development of impaired glucose tolerance

(IGT) (Müller, Faloona, Aguilar-Parada, & Unger, 1970). IGT is a pre-diabetic state and associated with insulin resistance and may precede T2DM (Barr et al., 2007).

Insulin resistance occurs due to inactivity and over-nutrition. Individuals can cope with this increased demand of insulin by enhancing the releasing activity of the beta-cells of the pancreas and prevent these individuals from developing T2DM. However, within the bodies of some individuals the releasing capacity of beta-cells fails and that results in consequent insulin deficiency and resistance to insulin action. This results in failure to control blood glucose levels (Kahn, Hull, & Utzschneider, 2006). Thus, abnormalities of carbohydrate, protein and fat metabolism occur (Alberti & Zimmet, 1998).

There is a decline in pancreatic islet cell function in patients with T2DM. That results in reduced insulin secretion and an inadequate suppression of glucagon secretion. Consequence of insulin resistance is a decrease of metabolic responses to insulin (Weyer, Bogardus, Mott, & Pratley, 1999). The beta-cells of the pancreas produce insulin to control blood glucose levels and the alpha-cells secrete glucagon to decrease plasma glucose levels. The interaction between these two mechanisms is the main component in the understanding of T2DM (Spellman, 2010). Pre-diabetes, also called impaired fasting glucose (IFG) is associated with high fasting blood glucose levels, but not high enough to be diagnosed as T2DM (Nathan et al., 2007).

3.3 Diagnose

Diabetes can be diagnosed by measuring plasma glucose in the fasting state or at two hours with the 75 g oral glucose tolerance test (OGTT) or randomly. Nowadays another diagnostic tool for the diagnosis of diabetes is used, namely the level of HbA_{1C} (Timper & Donath, 2012). When one of the following criteria, seen in table 1, is met, T2DM is diagnosed.

Table 1: diagnose of T2DM (American Diabetes Association, 2011)
When one of the following criteria is met, T2DM is diagnosed:
Level of HbA_{1C} > 6,5%
Fasting plasma glucose > 7.0 mmol/L
2-hours plasma glucose > 11.1 mmol/L during 75-g OGTT
Random plasma glucose > 11.1 mmol/L incl. symptoms of hyperglycaemia (high blood sugar)

The newest test for diabetes, plasma haemoglobin A1c or also called glycated hemoglobin (HbA_{1C}), reflects the mean blood glucose levels over the previous two to three months of an individual (Davidson & Schriger, 2010). HbA_{1C} is formed by a slow and irreversible reaction

that is occurring in the erythrocyte by exposure of hemoglobin to plasma glucose (glycation of valine and lysine residues in the haemoglobin molecule) (O'Sullivan et al., 2006). Normally, glucose levels produce a normal amount of glycated hemoglobin. However, if the average plasma glucose increases, the level of glycated hemoglobin does too (American Diabetes Association, 2011). So, higher amounts of glycated hemoglobin levels, indicate a poorer control of blood glucose levels (Larsen, Hørder, & Mogensen, 1990) . HbA_{1C} can always be performed and does not require a special preparation or condition like fasting is with a OGTT (WHO, 2011).

3.4 Influencing factors and complications

The development of T2DM is associated with genetic and environmental factors. Inactivity, mostly through a sedentary lifestyle, and overweight or even obesity contribute to insulin resistance and thus the development of T2DM (Horton, 2009). Complications of diabetes create a health burden for patients, for example cardiovascular diseases which are the major causes of mortality for patients with T2DM (Hogan, Dall, Nikolov, & ADA, 2003). Other complications are development of atherosclerosis, retinopathy (damage to retina and potential blindness), nephropathy (damage to kidneys), neuropathy (damage to nerves) and infections of feet and legs (with risk of foot ulcers and amputation) (Alberti & Zimmet, 1998; Leids Universitair Medisch Centrum, 2011). In the literature, different treatments are available, like dietary interventions, physical activity programs, drugs supply, education sessions, self-management education, and many combination interventions (American Diabetes Association, 2011; Clar et al., 2010).

3.5 Role of diet advice in the treatment

The treatment of T2DM in the Netherlands has two goals. The first goal is to prevent patients from complications and second to fight against complaints (Leids Universitair Medisch Centrum, 2011). To reach these goals, the treatment is focused on the decrease of blood glucose level and also on the regulation of blood glucose to decrease the chance of complaints and further problems to kidneys, eyes, nerves, feet, heart and blood vessels (Diabetesvereniging Nederland, 2013; NVD, 2010). The basis of the treatment consists of diet advice and physical exercise. Overweight plays an important role because 80% of the patients with T2DM have overweight. Diet advice and physical activity reduce insulin resistance and

improve glucose tolerance, decrease body weight and change the fat distribution (Nederlandse Diabetes Federatie, 2000; Nederlandse Diabetes Federatie, 2010).

Besides a healthy food pattern and sufficient exercise, self control and self regulation and in some particular cases medicines or insulin use, are also important parts of the treatment of T2DM. Overweight is an important cause of the development of T2DM and therefore weight reduction is also an important part of the treatment via diet advice and physical exercise (Diabetesvereniging Nederland, 2013). It is also important to pay attention to other risk factors like smoking, high blood pressure and high cholesterol level. The influence of the last two risk factors can be reduced by using medicines, however, also with a healthy life and food pattern alone these two risk factors can be reduced (Nederlands Huisartsen Genootschap, 2011).

Diabetes is a chronic disease and a whole team of professionals is involved with the care of a diabetes patient. Professionals of different sectors and organizations try to adjust their activities to each other so a coherent and coordinated plan exist with a focus on the individual needs of the patient with a specific disease, like T2DM. This is called integrated care or multidisciplinary care (Huijben, 2011; Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP), n.a.). This team is per patient different because every person has different needs. Mostly, a team consists of a physician, diabetes nurse or practice supporter and a dietitian with collaboration agreements with a physiotherapist, social worker, psychologist, podiatrist and a pharmacist (Nederlandse Diabetes Federatie, 2011b). However, diabetes care delivery is specifically focused on the individual needs of the patient. The dietitian has an important role in this because the basis treatment consists of diet advice and physical activity. A care standard is available for the treatment of diabetes, made by the Netherlands Diabetes Federation (NDF). This NDF Care Standard plays a central role in the delivery of good diabetes care and is a guide for all professionals involved in diabetes care delivery (Netherlands Diabetes Federation, 2007).

However, not for every diabetes patient a multidisciplinary approach or integrated care program is available due to lacks of cooperation between different professionals (Ketelaars, Reulings, & Zwietering, 2012). According to dietitian Jolande van Teeffelen, in practice much agreements and cooperation exist between different professionals, but the integrated care is not formalized everywhere (Kassa, 2012).

3.6. Cost-effectiveness of diet advice

Diet advice is an effective tool in the treatment of T2DM (Voedingscentrum, n.a.). According to the NVD (2012a), no reimbursement results in an increase of the health care costs because patients will go to a general practitioner more often and use more medicines. In the future, cost savings on diet advices will lead to an increase of health care costs, according to Anja Evers (Nicolasen & Schipper, 2012). Diet advice prevent patients from health complaints with expensive treatments and medication. Also the Board for Health Insurances (CVZ) advised the Minister of HWS in 2010 that reimbursement of diet advice can prevent higher health costs in the future (Nederlandse Diabetes Federatie, 2011a; Van der Meer, Couwenbergh, Enzing, Ligtenberg, & Staal, 2010).

Different parties agree that diet advice is one of the main components in the treatment of T2DM and that it is effective. They also agree that without diet advice, costs of diabetes care will increase in the long term, especially due to complications in the long term. Without reimbursement, the amount of patients participating in a diet program will decrease and costs will increase. The different parties do not claim directly that diet advice is cost-effective, but they implicate the cost-effectiveness indirectly because of the positive effects and low costs. However, not one single survey is done who investigate the actual cost-effectiveness. The claims about the reimbursement of diet advice are not based on evidence from cost-effectiveness analysis or cost-utility analysis. It is unclear on which evidence those claims are based. This thesis will review if those claims are justified.

Cost-effectiveness analysis use both costs and effects and measure if the costs are in proportion to the effects. Mostly these outcomes do have one outcome measure. For example costs are measured in euros and the preferred outcome measure for effects is QALY because then the cost-effectiveness of different interventions can be compared to each other. When an intervention costs beneath 20.000 euros per QALY, in the Netherlands it is called cost-effective (Hamberg-van Reenen, 2011).

3.7 Summary of background

In summary, the development of T2DM depends on genetic and environmental factors and insulin resistance is an important factor. The health burden for the patients is huge, because of the complications of T2DM. Already mentioned in the beginning of this thesis is the increasing prevalence of patients with T2DM and together with the implications of the disease, it will influence the health care costs. The cause of T2DM is now known and also the

importance of treatments, especially the role of diet advice and the dietitian in the treatment of T2DM. Multiple parties claim the positive effects and low costs of diet advice, but it is unclear on which evidence those claims are based and if they are justified. Therefore, it is now important to review the cost-effectiveness of diet advice provided by a dietitian.

4. Methods

This methods section is divided into several parts. First the eligibility criteria are mentioned, after which the search is described. In the third part, the data items, quality and data collection process are described. In the fourth part the summary measures and synthesis of results are described and in the last part something will be said about bias.

4.1 Eligibility criteria

The eligibility criteria include the study characteristics and can be divided into inclusion criteria and exclusion criteria. In table 2, the criteria for determining study eligibility are shown. When searching for articles, these inclusion criteria are used to determine whether an article should be included or excluded from the search strategy.

Table 2: criteria for determining study eligibility.

Subject	***Criteria***
Patient population	Participants with T2DM and older than 18 years.
Intervention	Diet advice, Medical Nutrition Therapy (MNT), diabetes/diet education, individual counseling sessions. All provided by a dietitian.
Comparator	Usual care, group sessions, or provision by other health professionals, like GPs or nurses.
Outcome measures	HbA_{1C}, BMI, weight, FPG level, lipid profiles, quality of life, costs, or other outcomes mentioned in the articles.
Publication type	English, about humans, whole papers.
Study design	RCTs, qualitative studies, non controlled studies, descriptive studies.

Some studies fit these inclusion criteria, but should not be selected because of other reasons. These reasons are called exclusion criteria. In this review, studies in which diet advice is provided by a group of health professionals, for example dietitians and nurses, physicians and general diabetes educators, are excluded, because the research goal is to determine the impact of diet advice provided by a dietitian only.

When diet advice is combined with other treatments like medication, physical activity programs and weight loss programs, a multidisciplinary approach is given. Those studies with combination treatments are excluded, because the research goal is to focus on diet advice only. Studies are also excluded when diet advice is not given face-to-face, but via telephone counseling or when the sessions are not individually but given in groups. When specific forms

of diets are compared in a study, like the Mediterranean diet or fruit diet, those studies are also excluded. The objective is not to find the most effective type of diet, but to show what is known about the cost-effectiveness of diet advice. Another reason to exclude some studies is when participants have other huge complications or diseases, like heart failure. In this case these complications can influence the effect of giving diet advice for patients with T2DM.

The last reason to exclude articles is the type of study design. Study designs which are excluded are reviews, meta-analyses, comments and editorials. Reviews were excluded because every review have their own eligibility criteria and methods. Also reviews show only the existing evidence and do not add new information. The individual studies the reviews used can be valuable for this thesis, but not the review itself. With the research strategy those individual studies will be found and the chance of bias is then lower than using the reviews. In table 3 all these reasons are presented briefly.

Table 3: reasons to exclude studies who fit the eligibility criteria
Exclusion criteria:
When diet advice is provided by a group of health professionals (including dietitian).
When diet advice is a part of a multidisciplinary approach.
When diet advice is not given individually or face-to-face (group sessions or telephone counseling).
When diet advice includes the advice of specific forms of diets.
When participants have also other huge complications or diseases (e.g. heart failure).
When the study design is a review, meta-analysis, comment or editorial.

4.2 Search

This literature review is done by using the search program of PubMed. The three keywords were “diabetes mellitus type 2”, “diet advice”, and “cost-effectiveness”. A search strategy was determined to find all related articles to these keywords. First, synonyms and related words to these three search items were defined. Then, a quick search was performed with these three keywords. The results were read and corresponding MeSH terms were added to the search strategy to find other articles. Also the process of ‘snowballing’ was used and refers to locating, tracking and chasing down references in articles already read (Greenfield & Braithwaite, 2008). Actually, with every search the search strategy became larger and better than the last search.

The final search strategy combined three searches, namely one about diabetes mellitus type 2 with synonyms. The second search included words like “diet advice” and “dietitian” and other words related to these words. The last search included all words about cost-effectiveness and related words. With the combined search strategy, a total of 5335 items were found. However, these items were limited to the English language and to humans only. Also the articles with a review design were excluded from the strategy and this resulted in a total of 3730 remaining articles.

In the first instance, there was no limit in publication year, because all information available could be relevant for the review. However, results from a decade ago could be misleading because of dated facts and information, technology developments and a changing society. Therefore, the publication year was taken into account when interpreting and evaluating the results. Other specific details of the search strategies are given in appendix 1.

After the real strategy search, the process of selecting articles started. The articles were screened manually by title and/or abstract. The inclusion and exclusion criteria were used to check whether the article could be selected. After this screening, the second round of selecting articles started by reading the remaining articles entirely or partially. The relevance and usability of the articles was again determined by using the inclusion and exclusion criteria.

4.3 Data and quality

The remaining articles were again read and the characteristics of the studies were described. It depended on the study design which characteristics were described. However, from all the studies their objectives, participants, interventions, outcomes, methods and quality and, eventually, their inclusion criteria and follow-up were noted. Not every article was of the same high quality. Therefore, the quality of the different articles is evaluated and the overall quality of each article is taken into account, when using the costs and effects measured in that article. The quality of the RCTs were measured using the Consolidated Standards of Reporting Trials (CONSORT Statement) (Schulz, Altman, & Moher, 2010). This guideline contains 25 items in the checklist, but this thesis summarized these items in ten criteria for the consideration of study quality (Clar et al., 2010). These items are shown in table 4.

Table 4: criteria for the consideration of the quality of RCTs (summarized from the CONSORT Statement).	
Quality criteria	***Answer***
Was there an adequate description of the trial design and the participants?	Yes/No
Was the method of randomization described?	Yes/No
Was there allocation concealment?	Yes/No
Was the outcome assessment blinded?	Yes/No
Was there adequate power?	Yes/No
Were the number of randomized participants, excluded participants, and lost to follow-up reported?	Yes/No
Was the intention-to-treat analysis performed?	Yes/No
Was the statistical analysis appropriate?	Yes/No
Were the baseline characteristics similar?	Yes/No
Was the funding of the study reported?	Yes/No

Not all articles were RCTs. For the other articles there is no general quality measurement used because there is not an overall standard available for each study design used in this thesis. However, there is special attention paid to these articles and their quality. Special attention is paid to the availability of bias in the study, the way of selecting the subjects, the control group, follow-up and the randomization procedure.

Besides the quality of the articles and the characteristics of the studies the outcome measures of the articles were also evaluated. Not every article has the same outcome measures. In general, T2DM will be measured by determining the level of HbA_{1C}. In this review, the level of HbA_{1C} is the most important outcome measure because it is easy to compare these levels between different articles. However, other variables are also associated with T2DM, like weight, BMI, BP, blood lipids, FPG level, complications (e.g. retinopathy or nephropathy), and quality of life (QoL). Not only effects, but also the costs are important for this thesis. Therefore, direct costs, but also indirect costs such as productivity days lost and disability days, are measured. All these outcomes are evaluated in this review, despite the fact that not every article mentioned all outcome measures.

So, much data was collected during this process. All data was collected and put onto special extraction forms. These forms included data regarding objectives, study design, participant characteristics, follow-up, methods, treatment, intervention, outcomes and quality. The study results of each article are not mentioned in these extraction forms. These results are displayed in tables and divided into different categories to give an comprehensive overview.

4.4 Summary measures and synthesis of results

So, data were synthesized through tables. One table is made to show whether the studies measured costs or effects or both. The other table is made to show which outcome measures are used in the different articles. Not all studies measure the cost-effectiveness of diet advice. An economic evaluation can compare the costs and consequences of the alternatives. An economic evaluation is defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005).

Some articles only evaluate the effects of diet advice, while other articles have focused on the costs. When a study only analyzed the costs or effects of diet advice, the study is called a partial economic evaluation. When both costs and effects are analyzed, the study is a complete economic evaluation (U.S. National Library of Medicine, 2011). These partially cost or effectiveness studies are also included in this review. The results of all partial economic evaluations are divided into results containing only effects and results containing only costs.

The goal of this review is to use all the outcome measures from the different studies to give an overall conclusion. However, there are differences in quality and study design. A meta analysis can be performed to pool the results from individual studies to generate an estimate. When the methodology is comparable and of high quality, the participant characteristics are almost homogeneous and the reported bias is explainable, a meta-analysis can be used (Nordmann, Kasenda, & Briel, 2012). However, this would be very difficult in this thesis because of different study designs and because of bias. The results of the studies have to be expressed in a general and standardized outcome measure to allow for comparison between the individual studies (Egger, Smith, & Phillips, 1997). So, in the discussion section extra attention will be paid to this subject.

4.5 Risk of bias

In general, an RCT is considered as the study type, which is least subject to bias and has the highest level of evidence. Other studies like observational studies are considered to be more biased (Oxford Centre for Evidence-based Medicine, 2009). When determining the quality of the individual studies, the level of bias was one of the aspects related to the level of quality of an article and therefore mentioned in the extraction forms. However, bias is not always mentioned in the articles or discovered by authors of the articles. Also by writing this thesis and making the decisions necessary in this process, bias can occur. Bias defines a disposition

of study designs to produce results better or worse than other study designs (Bandolier, 2007). There are different types of biases between studies or within individual studies. Four of these types will be further explained.

First, publication bias is one example of bias which occurs often within systematic reviews, but it is difficult to know which influence this bias has. According to Higgins and Green (2011), publication bias is: "the publication or non-publication of research findings, depending on the nature and direction of the results". It is possible that negative trials are not published and thus the results could be overestimated when only published studies are included. Also heterogeneity is a term which is important in this thesis because it describes any kind of variability among studies. There are different types of heterogeneity, for example clinical heterogeneity which describes the variability in the participants, interventions and outcome measures between studies. Another type is methodological heterogeneity, which describes the variability in study design and risk of bias.

However, bias can also be present in individual studies. Bias can influence the quality of the study and therefore in this review the quality of the RCTs are measured with a quality checklist, which includes also bias. A high qualitative study meets several requirements such as allocation concealment, blinding of participants, and blinding of outcome assessment. When these requirements are not met, three other types of bias can influence the outcomes (Higgins & Green, 2011). Selection bias refers to differences in baseline characteristics between the two groups that are compared. Selection bias can be prevented with randomization and allocation concealment. Another example of bias, which is often present in a study, is performance bias. This type of bias refers to differences in care between groups and it could be prevented by blinding the participants. The last most known type of bias is detection bias. This type of bias refers to differences between groups in how outcomes are determined. By blinding the outcome assessors, this type of bias can be prevented (Bandolier, 2007; Higgins & Green, 2011).

Nevertheless, not only the influence of bias is important to take into account when interpreting the results. A cost-effectiveness analysis always consists of a comparison of two interventions. The choice of a good comparator is thus important because it can influence the outcome of the cost-effectiveness ratio (Rutten, 2000). In this review, diet advice provided by a dietitian is compared to usual care, group sessions and diet advice provided by other health professionals. A table of these comparators with the corresponding results can be find in the next section. Also the discussion section will pay attention to this subject.

5. Results of the individual studies

This section includes the results of the individual studies and is also divided in parts. The first part is about the study selection in which the amounts of screened and included articles are given even as the reasons of exclusion. In the second part, the results of the study characteristics are given, after which the outcome measures of the individual studies are discussed. The risk of bias of individual studies and across studies is explained in the fourth part and in the last part something is said about the results of the individual studies.

5.1 Study selection

The search strategy included 5335 items, but these items were limited to the English language and to humans. Also articles with a review as study design were excluded and then in total 3730 articles remained. Details of the search strategies are shown in appendix 1. After the first screening by title and/or abstract, a total of 3467 articles were excluded. The remaining 263 articles were read entirely and the second selection excluded another 243 articles. The trial flow of this process is described in appendix 2.

There were several reasons to explain the exclusion of the in total 3710 articles. The most common reason in the first screening was that the intervention did not contain diet advice. Many articles contained drug treatment or insulin therapy. Another reason was the focus on specific diets and food instead of merely diet advice. Also the focus on other complications besides T2DM and self-management were reasons to exclude articles. These reasons mentioned are not the only reasons for exclusion. The whole list of exclusion criteria with corresponding numbers of articles can be found in appendix 3a.

During the second screening, 243 articles were excluded. One of the most common reasons during this screening round includes the absence of a dietitian. Studies in which diet advice was given by other health professionals than dietitians were excluded. Another reason for exclusion was that different diet advice strategies were compared instead of the (cost-) effectiveness of diet advice in general. Also the multidisciplinary approach, where diet advice was a part of a larger treatment protocol with other professionals and interventions, like physical activity, weight loss and education, was a reason to exclude articles. The last two most common reasons were the focus on other complications besides T2DM and the involvement of group sessions instead of individual counseling. A list of exclusion criteria regarding the second screening is presented in appendix 3b.

After determining the relevance of all articles and the exclusion of the non-relevant articles, a total of 20 articles remained to use in this review to evaluate the cost-effectiveness of diet advice for T2DM patients. A list of approved articles is shown in appendix 4. These articles contain different types of studies and trials.

5.2 Study characteristics

The approved articles are compared to each other by using multiple matrices to show the characteristics of each study. These characteristics and quality measures of the RCT studies are shown in appendix 5. The quality is determined by using the CONSORT Statement. The overall quality of these studies was rated as 'high' if at least nine items were clearly fulfilled. If two or three of the criteria were not clearly fulfilled, the quality was rated as 'moderate' and it was rated 'poor' if more than three quality criteria were not fulfilled. The characteristics of the other articles, which did not have an RCT design, are shown in appendix 6. There is no quality measure for these articles, but that has been be taken into account when using the results of these studies.

In total, there are eleven RCTs, two cost analyses, two cross sectional studies, two retrospective studies, one historical cohort study, one comparative study, and one prospective non controlled descriptive study. The articles were published between 1995 and 2012. The amount of participants across studies varies from 21 to 26.531. All the studies with an intervention have more or less the same intervention, namely diet advice, but sometimes with some small differences. Some studies include individual education as intervention in comparison with the control group who receives usual education. Another example is a study who compares the results of diet advice guided by a dietitian or provided by other professionals like GPs. In addition, some studies compare individual tailored diet education with group sessions.

There are also differences in outcome measures. Most studies used HbA_{1C} as the main outcome measure, but also FPG level, weight and lipid profiles are frequently used as outcome measures. Less used, non-biological, outcome measures are health care utilization, medication frequency, work days lost, disability days and quality of life. Furthermore, there are also outcome measures related to costs and savings.

5.3 Outcome measures of the individual studies

Not all articles found within the search strategy have measured the cost-effectiveness of diet advice provided by dietitians. Both complete and partial economic evaluations are analyzed. In table 5 the studies are given with a number and the table shows if the study is a complete economic evaluation or a partial economic evaluation.

Table 5: Studies allocated with a number and aspects of focus.

		Economic evaluations		
		Partial		*Complete*
Articles	*Number*	*Effects only*	*Costs only*	*Costs & effects*
Gagliardino et al., 2012	1	X **		
Al-Shookri, Khor, Chan, Loke, & Al-Maskari, 2012	2	X		
Sperl-Hillen et al., 2011	3	X **		
Coppell et al., 2010	4	X		
Huang, Hsu, Wang, & Shin, 2010	5	X		
Wolf et al., 2009	6	X **		
Sinorita, Saádah, & Jazakillah, 2008	7	X		
Wolf et al., 2007	8		X *	
Gaetke, Stuart, & Truszczynska, 2006	9	X		
Lemon et al., 2004	10	X **		
Willaing, Ladelund, Jørgensen, Simonsen, & Nielsen, 2004	11	X **		
Wolf et al., 2004	12	X **		
Brandle et al., 2003	13		X	
Wilson, Brown, Acton, & Gilliland, 2003	14	X		
Wagner et al., 2001	15		X	
Ridgeway et al., 1999	16	X **		
Sheils, Rubin, & Stapleton, 1999	17			X
Franz, Splett et al., 1995	18			X
Franz, Monk et al., 1995	19	X		
Johnson & Valera, 1995	20	X		

* = effects are also measured, but not directly.
** = costs are also measured, but only the indirect costs.

When a study is a partial economic evaluation, the table shows if the study has focused on costs only or on effects. Only two of the 20 included articles, are complete economic evaluations, while the remaining 18 articles are all partial economic evaluations. It is very clear that more articles have focused on effects of diet advice because 15 articles did a partial economic evaluation on effects, where as only three articles focused on costs. Seven of the 15 articles with a partial economic evaluation focused on effects, also measured indirect costs. However, they are not categorized as full economic evaluations because they did not compare the costs and the consequences (effects) with each other. Table 5 shows those articles with their indirect costs.

So, more partial economic evaluations are done with a focus on effects, but not all studies measured the same effects. In table 6, all the outcome measures (also costs outcomes) are listed and noted which article used a certain outcome. The author of the article belonging by a certain number, can be found in table 5. For the rest of this thesis, the allocated number of an article will be used between brackets, when an article is referred to a certain subject. The number will be placed at the end of a sentence to clarify the particular statement.

Table 6 shows a distinction between costs and effects and specifies effects into biological and non-biological effects and distinguishes costs in direct and indirect costs. Health care utilization, medication frequency, work days lost and (risk of) disability days are categorized in the group with the indirect costs because they affects the total costs of patients with T2DM. They do not affect the costs directly, but in the long term they can influence the costs negatively or positively. Complications can also be found in the group of the indirect costs, but also in the group with the biological effects because complications can be described in terms of effects (less complications) or costs (less costs in the long term).

From all studies, 16 studies define at least one or more biological effects as outcome measures (1-5, 7, 9-12, 14-16, 18-20). Four studies define one or more non-biological effects as outcome measures (3, 10, 12, 16). Ten studies said something about costs, whether the costs where direct or indirect (1, 6, 8, 10-13, 15, 17-18). However, there are also studies who measure both biological and non-biological outcomes (3, 10, 12, 16) or measure both effects and costs (1, 10-12, 15, 18) or measure both direct and indirect costs (8, 13, 15, 17).

Table 6: measured outcomes incl. article numbers who included that outcome.			
		Outcome measures	***Number of article which included the outcome***
Effects	*Biological*	HbA_{1C}	1, 2, 3, 4, 5, 9, 10, 12, 14, 16, 18, 19
		FPG level	2, 4, 5, 7, 9, 10, 16, 18, 19, 20
		BMI	1, 2, 4, 5, 9, 10, 11, 19
		Weight	2, 3, 4, 9, 10, 11, 12, 16, 19, 20
		Waist circumference	1, 2, 4, 11, 12
		BP	1, 3, 4, 5, 10, 11
		Lipid profiles - HDL - LDL - Total cholesterol - Tryglycerides	1, 2, 4, 5, 9, 10, 11, 12, 16, 19 1, 2, 4, 5, 9, 10, 11, 12, 16, 19 1, 2, 4, 5, 9, 10, 11, 12, 16, 19 1, 2, 4, 5, 9, 10, 11, 12, 16, 19 1, 2, 4, 5, 9, 10, 11, 12, 16, 19
		Complications - Foot evaluation - Risk of CVD	1, 11, 15 1 10, 11, 15
	Non-biological	Quality of life/ health status	10, 12, 16
		Diabetes knowledge	3, 10, 16
Costs	*Direct*	Health care costs	8, 13, 15, 17, 18
	Indirect	Cost savings	8, 15, 17
		Health care utilization (e.g. primary care visits, specialty visits, hospitalization rates)	1, 8, 11, 15, 17
		Medication frequency	10, 11, 12
		Work days lost	1, 6, 10
		(risk of) Disability days	6
		Complications	8, 13, 15, 17

The costs in an economic evaluation can be categorized in four groups. A distinction can be made between direct and indirect costs. The other distinction can be made between medical and non-medical costs (Koopmanschap & Rutten, 1998; Oostenbrink, Bouwmans, Koopmanschap, & Rutten, 2004). Table 7 shows the cost categories in an economic evaluation. The cost outcome measures from table 6 are assigned to these categories.

Table 7: cost categories in economic evaluations		
	Medical costs	*Non-medical costs*
Direct costs	Health care costs (costs for diabetes care).	Patient costs (time and travelling costs).
Indirect costs	Medical costs in life-years gained (medication frequency, health care utilization, cost savings).	Production losses (work days lost, (risk of) disability days).

5.4 Risk of bias

Bias cannot always be avoided. However, when reading studies, bias can be taken into account when interpreting the results of the studies. A total of 20 articles in this thesis has been reviewed. Eleven of them are RCTs and the quality of these studies are examined by using the CONSORT Statement. Most of the studies are from good or moderate quality. Sometimes one or two points on the checklist are not checked in the study, like "outcome assessment blinding". Then it is not clear whether the study blinds the outcome assessment, but when it did not, detection bias might. Also performance bias and detection bias could have occurred, however, the ways of preventing all these types of bias are recorded in the CONSORT Statement. To know how the included studies score on all those points and to know whether there was any bias, appendix 5 will give an overview of the articles with an RCT design.

It turns out that there are two points on the checklist where articles have scored low. One point is the outcome assessment. In seven out of eleven articles it is unknown whether the outcome assessment was blinded or the answer was no. There is a chance that those articles are biased or more specifically, there could have been detection bias in these studies. However, one comment has to be made. The article of Franz, Splett, et al. (1995) is related to the article of Franz, Monk, et al. (1995) and they used both the same data. The methodology is not mentioned in the article of Franz, Splett, et al. (1995) and thus this study scores low at the quality checklist. However, the quality of the study of Franz, Monk, et al. (1995) is high with the same methodology. When this methodology was mentioned in the article of Franz, Splett, et al. (1995) the score on the quality checklist would be different.

The same happens with the articles of Wolf, et al. (2009) and Wolf, et al. (2007). These two articles are linked with the article of Wolf, et al. (2004), but the information in this study is not mentioned again in the other articles despite the fact that the quality of the first published article was high. These examples show that it is possible that the measured quality of an article is low because of unknown information. However, the overall quality of the article could have been high if the author had mentioned all the available information.

Regarding the remaining articles, in appendix 6 there are also some comments to take into account when using the results of them. Because these articles do not have an RCT as study design, these articles did not use a control group, for example, or randomization. It depends on the type of study design which methods they have used. The chance of confounding and bias is therefore higher in these articles than in the RCTs.

5.5 Results of the individual studies

Not all studies use the same outcome measures and there is not one outcome measure which is the main outcome for all studies. However, all studies use an intervention or use a descriptive way of measuring the effect of diet advice provided by a dietitian. Also the costs of diet advice is investigated by multiple studies even with direct and indirect costs.

The next chapter contains the results of the individual studies and together with the analysis of the total effectiveness and cost-effectiveness of diet advice, a coherent chapter will occur.

6. Analysis

The results found in the individual studies and this review are described in this chapter. First, the synthesis of the results of the individual studies are reported. The synthesis of the results is divided into a section with the effects and a section with the costs. Not every result has the same power due to quality of the article. In the third section some attention is paid to the power of the results. The fourth section contains the analysis of the effectiveness of diet advice. In the last part, the cost-effectiveness of diet advice is analyzed.

6.1 Synthesis of results: effects

The most common diagnostic tool for the diagnosis of diabetes is the HbA_{1C} level, which already has been explained in the background session. It turns out that this level will decrease when the patients receive diet advice or individually diet education. Every article, measuring HbA_{1C} as an outcome measure, finds a reduction of this level after diet advice, individually diet education or MNT provided by a dietitian (1-5, 9, 10, 12, 14, 16, 18, 19). However, one article did not mention a significant reduction in HbA_{1C} in the whole patient group, but only a significant reduction in the group of poorly controlled T2DM patients (5). In addition, another article did not mention whether the results were significant. The researches only state that HbA_{1C} levels had decreased (18). All the other articles find a significant reduction of the HbA_{1C} levels (1-4, 9, 10, 12, 14, 16, 19).

The other outcome measure for glucose control is the FPG level. Both the FPG level and the HbA_{1C} level are measures of glucose control. The FPG level is used for assessing day-to-day management of T2DM and HbA_{1C} provides a measure of glucose control over time (Franz, Splett et al., 1995). FPG is used in ten articles as an outcome measure and in all articles there is a reduction in the FPG level after diet advice or when diet education is provided by a dietitian (2, 4, 5, 7, 9, 10, 16, 18, 19, 20). However, not every article mentioned a significant reduction in the FPG level. Seven of ten articles mentioned a significant reduction (2, 5, 9, 10, 16, 18, 19). It is important that both the HbA_{1C} level and the FPG level improve due to diet advice because these two measures can diagnose T2DM (see table 1 in the background section).

Other, less frequently measured, biological outcomes like BMI, weight, BP, waist circumference and lipid profiles, also have an influence on the effect of diet advice. Patients receiving diet advice have significant lower BMI values (1, 2, 4, 9, 10, 11), significant weight reductions (2, 4, 9-12, 16, 19), significant decreasing waist circumference levels (1, 2, 4, 11, 12), significant lower BP values (1, 5, 10) and significant better lipid profiles (1, 2, 9, 10, 11, 16, 19). The severity of complications is significantly reduced with diet advice, for example less foot ulcers are measured and a lower risk of CVD will take place (1, 10, 11).

Besides biological outcomes, also non-biological effects are measured. The first outcome measure is quality of life (QoL) which is significant improved when patients get diet advice (10, 12). Diabetes knowledge is another outcome measure in this category and also improved due to a treatment with diet advice (3, 10, 16).

6.2 Synthesis of results: costs

Besides the measured effects, also costs are measured. It turns out that the indirect costs will be reduced due to diet advice because of significant reductions for disability days lost (6) and work days lost (6, 10). Also a decline of health utilization took place through diet advice (1, 8, 11) and absenteeism from work is reduced, but this result is not significant (1). Furthermore, the reduction of medication frequency (10, 11, 12) is also reduced, but this is also not a significant result. Another indirect cost category is complications and it turns out that complications due to T2DM are a huge cost burden (8, 13, 15, 17). When the risk of complications can be reduced, costs regarding T2DM will reduce (13) and it turns out that diet advice provided by a dietitian will reduce the risk of complications (8, 15, 17).

As a consequence, diet advice given by a dietitian does not increase health care costs, but could even save money with risk reduction and thus fewer inpatient admissions (8). Improvements in HbA_{1C} levels can also lead to lower hospitalization rates (15, 17) and even lead to a significant reduction of primary care visits and specialty visits (15). Also a sustained reduction in HbA_{1C} level is associated with significant cost savings (15) and the savings in health care utilization will exceed the costs of providing diet advice by a dietitian (17). Only two articles measured both effects and costs and both articles conclude that diet advice provided by a dietitian is cost-effective (17, 18). Nutrition interventions can lead to improvements in metabolic control with a reasonable economic investment (18).

6.3 Power of the results

The power of a result depends on the quality of the article. The quality of every article was measured and this quality level of a specific study can be found in appendix 5 for RCT studies. Comments about the quality of non-RCT studies can be found in appendix 6. Not all results mentioned in these two sections are significant, however, more significant results are measured rather than insignificant results.

In table 8 the outcome measures are listed. The individual studies and their outcome measures are divided into significant and insignificant results. When the quality of a study was not sufficient, the relevant study is marked. It turns out that from all significant results, two studies show insufficient quality. However, from all insignificant results, four studies (inclusive the two already found within the significant results) show insufficient quality. The results of these articles should have less power and in the discussion section more attention will be paid to this subject.

Table 8: outcome measures with their significance and quality.

Outcome measures	***Number of article which included the outcome***		
	Significant	***Insignificant***	***Significance unknown***
HbA_{1C}	1-4, 9, 10, 12, 14, 16♦, 19	5, 18	
FPG level	2, 5, 9, 10, 16♦, 18, 19	4, 7♦, 20♦	
BMI	1, 2, 4, 9, 10, 11♦	5, 19	
Weight	2, 4, 9, 10-12, 16♦, 19	3, 20♦	
Waist circumference	1, 2, 4, 11♦, 12		
BP	1, 5, 10	3, 4, 11♦	
Lipid profiles	1, 2, 9, 10, 11♦, 16♦, 19	4, 5, 12	
Complications	1, 10, 11♦	15	
Quality of life/ health status	10, 12	16♦	
Diabetes knowledge	10	3, 16♦	
Health care costs	8, 15		13, 17, 18
Cost savings	8, 15, 17		
Health care utilization	1, 8, 11♦, 15, 17		
Medication frequency		10, 11♦, 12	
Work days lost	6, 10	1	
(risk of) disability days	6		
Costs of complications			8, 13, 15, 17
♦ = quality of the study is insufficient or there are some questionable issues.			

6.4 Analysis of the effectiveness of diet advice

The effects of diet advice provided by a dietitian are measured as biological and non-biological measures. However, an effectiveness or cost-effectiveness analysis uses often QoL as outcome measure. Especially, QALYs are used to refer to an individual's health state (CADTH, 2006). In this review only three articles used QoL as an outcome measure (10, 12, 16). In the article of Lemon et al. (2004), QoL was measured with a self made questionnaire. After the intervention (diet advice provided by a registered dietitian), 3% of the patients answered that their QoL was worse than before, 22% answered to have the same condition and 75% of the patients had a better till strongly improved QoL (16%). These significant results were also found in the article of Wolf et al. (2004). However, in this study the SF-36 was used as measure for HRQoL (Human Related Quality of Life). There were significant improvements in seven of nine domains. Especially the emotional role and physical role strongly improved. The last study did not show significant results, but the quality of this study of Ridgeway et al. (1999) was also poor. They also used the SF-36 as measure, but did not find a significant result. The authors claimed that this was possible because their population consisted of patients above 65 years old. It was likely that they did not have an expectation of a better health status in the near future. All these studies did not express the QoL results in QALYs and thus it is difficult to compare their qualities.

The findings in this review suggest that the biological effects will improve due to diet advice provided by a dietitian. Also the quality of life will improve, but this is based on only a few studies. It looks feasible that the quality of life will also improve when the amount of work days lost, the risk of disability days and health care utilization will drop. It turns out that those three outcome measures will significantly drop due to diet advice. However, the causality of these outcome measures with QoL is not directly investigated.

6.5 Analysis of the cost-effectiveness of diet advice

Both direct and indirect costs are measured in this review. However, due to heterogeneity across studies these costs are difficult to compare and it is also difficult to use them in a cost-effectiveness analysis. Normally, in a cost-effectiveness analysis all the costs and effects are measured and when multiple effects or costs are measured these outcomes are translated into one general outcome. However, some studies in this thesis only measure the direct costs of the intervention, while other studies also measure the indirect costs. These indirect costs are also different because different sorts of costs are measured in contrast with different research

populations, inclusion criteria and interventions. In general, all studies claim that the health care costs for diabetes care in the future will be reduced by diet advice because of the positive effects of diet advice on biological and non-biological outcomes. Improvement of these outcomes lead to less costs in the future. Costs of diabetes care in the future is mostly depended of the complications who will occur by having T2DM because complications have the greatest cost burden. The costs will reduce when the risk of complications can be reduced (10, 13). According to the results of this review, the risk of complications can be reduced by diet advice provided by a dietitian (8, 15, 17).

Two studies used in this review measured the cost-effectiveness of diet advice. Both studies measured the cost-effectiveness differently, but both concluded that diet advice provided by a dietitian is cost-effective. In the article of Sheils, Rubin and Stapleton (1999), the authors conclude that diet advice can result in a net reduction in health service utilizations and costs. The savings due to less hospital utilization and less utilization of other services will exceed the costs of providing diet advice. Therefore, diet advice is cost-effective. The other article provided a study in which FPG and HbA_{1C} levels are used as effect outcomes. This cost-effectiveness analysis of Franz, Splett et al. (1995) suggests that diet advice can lead to improvements in metabolic control and that with a relatively small monetary investment these outcomes can be achieved. Both studies conclude that diet advice is cost-effective, but both studies did not mentioned all the costs related to diabetes since only a few effect outcomes were measured.

Already mentioned in the previous section is that for a cost-effectiveness analysis QoL is the most common effect outcome. In this review there is, however, insufficient evidence to make a statement regarding this. Nevertheless, the relationship between T2DM and quality of life could be interesting for this thesis. According to Oliva, Fernandez-Bolanos, and Hidalgo (2012), a significant inverse relationship exists between T2DM and HRQoL. HRQoL drops more when diabetic patients also have risk factors for other diseases and thus it is possible to enhance the quality of life of patients by managing T2DM by controlling blood glucose levels, but also by focusing on risk factors like BP, weight and cholesterol. Also P. van Baal, an expert in this field of research, acknowledges the importance of risk factors in a cost-effectiveness analysis with several contributions to different articles. This review did not focus on this subject, but the relationship between risk factors and health effects or quality of life is important. Therefore, with help of P. van Baal, additional literature is read on this subject.

Lifestyle factors, especially a high body weight, play an important role in the development of diabetes (Hamman et al., 2006). Risk of vascular complications is high among diabetic patients and half of the patients indeed suffer from one of these complications (Redekop et al., 2002). Prevention aimed at the reduction of complications can thus reduce the burden of diabetes (Feenstra et al., 2011). Other risk factors are smoking and obesity (Van Baal, Hoogenveen, de Wit, & Boshuizen, 2006).

Risk factors of chronic diseases can be known with the help of the Chronic Diseases Model (CDM). In this model, the effects of chances in the prevalence of risk factors for chronic diseases on disease burden and mortality can be estimated (Baan, Bos, & Jacobs-van der Bruggen, 2005). When an individual has a disease the chance of dying is higher than for people without the disease. Diabetes is also included in the CDM which shows a relation between smoking, body weight (BMI) and physical activity on the one hand and diabetes on the other. The relations between diseases can also be modeled with the CDM. Individuals with diabetes have an increased risk of cardiovascular diseases. The model can be used for the calculation of the corrected quality of life for a disease. The CDM uses a disability weight to show the loss of quality of life of a disease. The disability weight of diabetes is 0.198. This means that the health of a patient with diabetes is 80,2% in comparison with optimal health (Van Baal, Engelfriet, & Hoogenveen, 2012).

The CDM is also used in two other surveys. One survey is conducted where the three risk factors of diabetes are used in the CDM to investigate the prevalence of diabetes with and without these risk factors. The CDM showed that the increase of patients with diabetes would be less without the three risk factors (Van Baal et al., 2006). Another survey also used the CDM to model a scenario with risk factors that have the most influence on diabetes and quality of life of a diabetes patient. This survey of Baan, Bos and Jacobs-van der Bruggen (2005), used smoking, body weight and physical activity as the most important risk factors for diabetes. Also HbA_{1C} is a risk factor for cardiovascular complications (high blood glucose level), but also a high blood pressure, cholesterol, overweight and smoking. The level of these risk factors, especially BP, cholesterol and overweight, is also higher at patients with T2DM. In this review, it is stated that all these risk factors could be significantly reduced with diet advice provided by a dietitian.

So, it looks like diet advice could be cost-effective because of positive results in outcome measures and savings in the future on diabetes care. However, due to heterogeneity this thesis could not generalize the effects and costs of all studies to do a cost-effectiveness analysis. Conclusions based on a cost-effectiveness analysis are therefore also not possible,

but it is possible to make some assumptions and give an overall, some general, conclusion. Further, the three most important risk factors for diabetes patients and their quality of life are smoking, (high) body weight and physical (in)activity. These three risk factors already show that diet advice provided by a dietitian could be helpful to reduce these risk factors and to improve the quality of life of a diabetes patient. Despite the fact that the cost-effectiveness ratio is not determined in this review, some statements can be made and these will be discussed in the discussion section. More research is necessary to investigate the actual cost-effectiveness ratio.

7. Discussion

This section contains the discussion of the results and the most important findings are presented in section one. In the second section, supporting evidence for those findings is presented and in the third section results will be commented on to nuance the findings. After this, the strengths of this thesis and the implications regarding this review will be discussed in the fourth section. In the last section some recommendations will be given.

7.1 Findings

It is shown in the results and analysis sections that there are positive effects of diet advice for patients with T2DM. Every article that is used in the search strategy noted a positive effect, which was often a decrease in the levels of HbA_{1C} and FPG. However, also positive effects in other variables, such as BMI, weight, waist circumference, BP, lipid profiles, work days lost, disability days lost, health care utilization and quality of life were noted. Every study about costs concludes that costs for diabetes care can be reduced using diet advice as the standard treatment provided by a dietitian. Especially the reduction of complications, which is the major cost burden for diabetes care, can lead to a decline in costs. However, there are even studies that show cost savings regarding diabetes care and two articles investigate the cost-effectiveness of diet advice and stated that diet advice provided by a dietitian is cost-effective.

7.2 Supporting evidence

It is not a total surprise that diet advice provided by dietitians lead to positive effects for patients with T2DM since there is substantial supporting evidence. Despite the little evidence available about this topic, two other studies have been conducted concerning this subject and they support the results found in this thesis. One review is done by Urbanski, Wolf and Herman (2008), who reviewed the literature about the cost-effectiveness of diabetes education. They include several education studies, namely self-management training, diabetes prevention and MNT. The method and inclusion criteria differ from this thesis, however, the authors support the effectiveness of MNT and also the cost-effectiveness, despite little evidence. The study did not focus specifically on the role of dietitians, however, the authors claimed that the results indirectly support the role of the dietitian providing cost-effective treatment for people with diabetes. Furthermore, the authors recommend further research

about this topic, especially about the intervention costs and economic outcomes. Then, MNT will become more widely used and reimbursed at higher rates (Urbanski, Wolf, & Herman, 2008).

Another survey was published in November 2012, in the period that this thesis was written. This cost-benefit analysis was done by order of the NVD because of a lack of evidence about the benefits of diet advice. This survey concludes that there are declines in weight, BP, cholesterol and FPG levels, a higher mental health status, a higher quality of life and productivity, and lower levels of absenteeism and savings on other health costs. The authors conclude that other health professionals like the GP do not have time and knowledge to give effective diet advice and thus diet advice provided by a dietitian is very cost-effective (Lammers & Kok, 2012).

7.3 Comments

A conclusion and answer on the research question cannot only be made on the basis of the positive findings of this thesis. There are some comments which will nuance the findings. When using the comments and the findings, but also the strengths and weaknesses of this thesis, the research question can be answered thoroughly and a sound conclusion can be drawn.

The first comment concerns the amount of articles which has been investigated. Only twenty articles are used, which are published between 1995 and 2012. The information in the articles published in the first years (1995-2000), could be dated due to increasing diabetes knowledge and technology. Applying the search strategy, there is attempted to specify the strategy and to find as much articles as possible about this subject. However, there were many reasons to exclude certain articles and thus only twenty articles were left. There is only a small amount of studies about diet advice provided by a dietitian, so it is difficult to generalize the results and conclusions of the twenty articles. Also the greater part of the used articles were partial economic evaluations and from these 18 articles, even 15 articles only measured the effects. Only two articles were complete economic evaluations. Despite the similarity in their conclusion, both studies did not mentioned all the costs related to diabetes and also only a few effect outcomes were used (health care utilization as effect outcome and FPG and HbA_{1C} levels as effect outcomes).

Another comment concerns the design of the studies. The studies referred to in this thesis did not all have the same study designs. Although most of the articles were RCTs, some

studies used other study designs. A consequence of using other study designs is that it might be difficult to compare results. Other participants and methods are used, while the results need to be compared to each other. The same problem occurred with the treatment and intervention. In general, the intervention consists of diet advice provided by a dietitian, however, sometimes a study uses MNT provided by a dietitian. Also education programs led by dietitians or individualized nutrition care provided by dietitians are examples of interventions used in the studies. So all the studies use more or less the same intervention, but they do not exactly use the same intervention. In this thesis these interventions are used together as one, exactly the same intervention, namely diet advice provided by a dietitian. So in other words the intervention is generalized. There are also differences in comparators. Some studies compare diet advice with usual care, but sometimes diet advice provided by dietitians is compared with diet advice provided by other health professionals. It is also possible that individually given diet advice is compared with group sessions. Because of different comparators, it is possible that the effect of diet advice is much higher when compared to one comparator or another comparator.

Besides the designs of the studies, the quality of the studies is also different. Some studies have a higher quality than others. The quality of articles with a study design not being an RCT, is difficult to measure because there is no standard checklist for them. On the other hand, for RCTs the quality can be measured with the CONSORT Statement. In the eleven RCTs the quality was moderate to high. When the quality of an article was not classified as high, this was mainly due to unavailable information. In general, the quality of the studies was high enough to use the results. The quality of the other non-RCT studies was difficult to measure. Nonetheless, it is important that such studies pay significant attention to randomization, bias and selection of participants. Since these subjects were not mentioned very explicitly in the articles mentioned in this thesis, the results of them should be interpreted with some caution. Nevertheless, those results are still important because another study design can be chosen because of, for example, retrospective research. The quality of each study was investigated and studies with insufficient quality are marked in a table. Also a distinction is made between significant and insignificant results. A high qualitative study with significant results has much more power than a poor qualitative study with insignificant results. For this reason, no usable results were found for medication frequency.

Bias might be present despite prevention methods like randomization and allocation concealment. In this thesis bias is taken into account while interpreting the results by looking whether bias was present in the individual studies. One type of bias is not measurable, namely

publication bias. All the studies used in this thesis showed positive outcome effects for diet advice provided by a dietitian. There was not a single study that published a negative effect and this may be the reason that negative findings were never published.

The last comment is about daily practice. Most patients, at least in the Netherlands, receive integrated care and thus other professionals are also involved in the treatment and they all work together. Also the treatment of every patient is different because every patient has individually needs. This thesis only investigated the role of the dietitian and it is unknown whether the effect of integrated care is different and at which level for patients. It is also unknown whether the effect of diabetes care could be very different for different patients.

This thesis did not provide any hard evidence for the cost-effectiveness of diet advice provided by a dietitian because of heterogeneity in study design, inclusion criteria, effect and costs outcomes and because the studies were conducted in different countries. However, this thesis shows that the effects are positive, costs are relatively small and even savings could occur. Costs of diabetes care are mostly dependent on the amount of complications that will occur in the future because complications have the greatest cost burden. The costs will reduce when the risk of complications can be reduced and according to the results, the risk of complications can be reduced by providing diet advice. Therefore, it makes sense to claim that the quality of life will improve due to diet advice because two studies in the search strategy mentioned a significant improvement of QoL and because of all positive biological outcomes measured in this thesis. Furthermore, when the amount of work days lost, the risk of disability days and the health care utilization drops, you can argue that the QoL will increase. However, the causality of these outcome measures with QoL is not directly tested in this thesis.

When focusing more on QoL, the literature shows that there is a relationship between T2DM and HRQoL. When diabetes patients also have risk factors for other diseases, their QoL will drop. An expert on this research field, P. van Baal, also investigated this important relationship. He co-operates with other specialists regarding the development of the CDM. In this model, the effects of chances in the prevalence of risk factors for chronic diseases on disease burden and mortality can be estimated. The CDM shows a relation between smoking, body weight (BMI) and physical activity on the one hand and diabetes on the other. The model also shows the loss of QoL for patients with diabetes by using a disability weight. The disability weight of diabetes is 0.198 which means that the health of a patient with diabetes is 80,2% compared with optimal health.

7.4 Strengths and implications

Despite the fact that this thesis has not found hard evidence of the cost-effectiveness of diet advice provided by a dietitian, it has found some interesting facts and relations about this subject. This thesis is the only survey available which focuses specifically on the available information about the role of dietitians for patients with T2DM and not on a multidisciplinary approach or other interventions besides individually given diet advice. When starting this research, there were no reviews available investigating the cost-effectiveness of diet advice provided by a dietitian. There are some reviews available about diabetes education, but not one review combining the information of different study designs to show the available evidence about the effectiveness and cost-effectiveness of diet advice provided by a dietitian.

The quality of the used articles are, sometimes partially, measured and much attention was paid to the risk of bias. These two issues make this review reliable and are a major strength of this thesis. Also the search strategy is a strength regarding this thesis. The strategy is very extensive and complete, but also specific for this subject. All the synonyms are found by searching and reading, so an accurate strategy was followed. Using this method, the chance of missing some important related articles concerning this subject is rather small.

The results of this thesis can be very important for policymaking because there is not much information available about the role of the dietitian and the effect of diet advice on patients with T2DM. In the introduction section, the discussion about the reimbursement of diet advice shows that this topic is very actual in the political debate and that also people in the community think that it is a relevant debate, especially due to spending cuts. Because of the little evidence of the cost-effectiveness, the results in this thesis could contribute to decision making. However, meanwhile, the Minister already decided that three hours of diet advice will be reimbursed from the first of January 2013. Given the results presented in this thesis, this was a wise decision of the Minister.

7.5 Recommendations

Despite the comments, the effects of diet advice provided by a dietitian are found to be very positive. The costs for this intervention are not very high and are also compensated by the effects. Thus, the claim that diet advice provided by a dietitian is cost-effective is sound. However, more research is necessary to investigate the actual cost-effectiveness of diet advice provided by a dietitian. This thesis shows the positive effects of diet advice and this result strengthens the already taken decision from the Minister to reimburse the costs for diet advice

for patients with T2DM. However, this thesis did not investigate whether the three hours reimbursement is enough. In 2010, almost 35% of the patients treated by a dietitian, needed more than three hours that year. The average time a patient needed was 4,5 hours (Tol, Swinkels, de Bakker, & Veenhof, 2011). However, this research regarding the needed time also included patients with another disease or multiple co morbidities. So, it is difficult to say whether the three hours is enough. From the articles used in this thesis it is known that, in general, long lasting dietary treatment will lead to better outcomes than diet advice given for only three months. The exact differences are not known and it might be a good opportunity to investigate this.

The costs savings for diet advice are investigated by Lammers and Kok (2012), and they conclude that every euro invested in a treatment provided by a dietitian will save four Euros to other health costs within five years. So, when diet advice is not reimbursed, the number of patients going to a dietitian will reduce, which leads to more costs for the society in the future. However, this conclusion is based on every treatment a dietitian performs. It is not known what the exact costs (or savings) are when diet advice is provided as a treatment to patients with T2DM. Further research could determine the influence on diabetes care.

Another recommendation for further research concerns the CDM. A scenario where diet advice provided by a dietitian for patients with T2DM is not modeled before with the CDM. It might be a good opportunity to model this scenario and to investigate the cost-effectiveness. Only lifestyle interventions for patients with T2DM are already modeled with CDM. The conclusion was that those interventions are cost-effective (Hamberg-van Reenen, 2011). Also an integrated analysis of cost-effectiveness will be a good possibility to investigate the relation between a chronic disease like T2DM and care chains (Feenstra, van Baal, de Wit, Polder, & de Hollander, 2006).

8. Conclusion

A systematic review was performed to analyze the available information about the effectiveness and cost-effectiveness of diet advice provided by dietitians for people with T2DM and to answer the research question. The research question was: *To what extent is diet advice for diabetic patients cost-effective and under which conditions?*

This review showed that diet advice provided by dietitians is effective because of all positive effects in biological and non-biological outcomes. The studies showed positive effects regarding HbA_{1C} level, FPG level, BMI, weight, waist circumference, BP, lipid profiles, work days lost, disability days lost, health care utilization, complications and quality of life. Despite only a few studies mentioned something about the costs of diet advice, these studies conclude that the costs for diabetes care can be reduced when using diet advice provided by dietitians as the standard treatment, especially when complications will be reduced. There could be even cost savings. However, because of a lack of information and heterogeneity it is not possible to quantify diet advice provided by a dietitian as cost-effective for patients with T2DM. Nevertheless, results show positive effects in outcomes and there is also a relationship between T2DM and QoL. Especially smoking, body weight (BMI) and physical activity are the main risk factors that can contribute to the level of QoL of a patient. Diet advice provided by a dietitian could help to reduce these risk factors.

In general, it is concluded that diet advice is effective and maybe even cost-effective, when taking the conditions of this thesis into account. These conditions set diet advice as the only available treatment and, in addition, these conditions require that diet advice is not a part of multidisciplinary care of a care chain. Further, only dietitians are involved in the treatment and patients do not have huge other diseases or complications besides T2DM. Last, a decrease of complications and health care utilization in other health sectors can occur because of the treatment of T2DM through diet advice. This decrease can lead to cost savings and these cost savings are part of diabetes care (and thus involved in the cost-effectiveness of diet advice for diabetes care).

Further research should be conducted to investigate if dietitians really deliver a contribution to the health status of patients with T2DM and if this contribution is cost-effective. Also the optimal amount of hours could be investigated and, in addition, one might want to evaluate the relation between T2DM and care chains and their cost-effectiveness.

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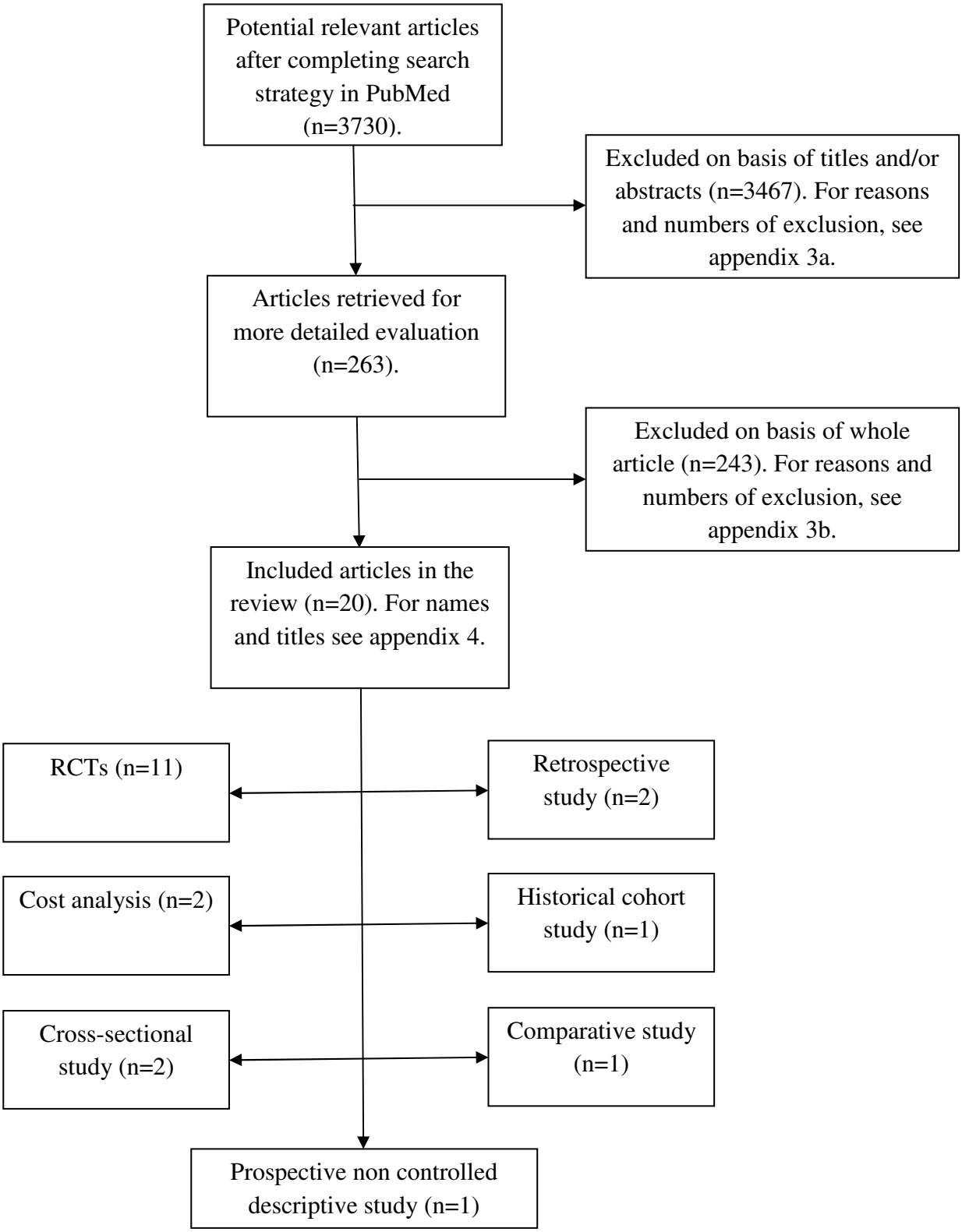
Appendix 1: Search strategy

Search	Query	Items found
#1	Search “diabetes mellitus type 2”	73556
#2	Search “diabetes mellitus, type 2/diet therapy”	1834
#3	Search “diabetes mellitus, type 2/economics”	966
#4	Search “diabetes mellitus/diet therapy”	1662
#5	Search “diabetes mellitus/education”	2
#6	Search “diabetes mellitus/nutrition and diet”	26
#7	Search “diabetes mellitus diet”	14
#8	Search ((((((#1) OR #2) OR #3) OR #4) OR #5) OR #6) OR #7	75081
#9	Search “dietitian”	1718
#10	Search “dietitian/certified”	1
#11	Search “dietitian/educator”	1
#12	Search “dietitian/nutritionist”	10
#13	Search “dietitian/registered”	1
#14	Search “dietitian advice”	3
#15	Search “dietitian consultations”	3
#16	Search “dietitian counseling”	5
#17	Search “dietitian reviewed”	3
#18	Search “dietitians role”	2
#19	Search “dietitian’s role”	43
#20	Search “dietitian intervention”	6
#21	Search “diet advice”	46
#22	Search “diet advisor”	1
#23	Search “dietitian consults”	2
#24	Search “dietitian education”	4
#25	Search “diet control”	1091
#26	Search “diet/education”	13
#27	Search “diabetes education”	1300
#28	Search “diabetes diets”	5
#29	Search “patient education”	73608
#30	Search “medical nutrition therapy”	329
#31	Search “diabetic diet”	4501
#32	Search “nutrition education”	2654
#33	Search “clinical nutrition”	4292
#34	Search “clinical nutrition and diabetes”	1
#35	Search “clinical nutrition and diet therapy”	1
#36	Search “glycemic”	17064
#37	Search “glycemic control”	11449
#38	Search “glycemic control management”	3
#39	Search “dietary weight loss”	92
#40	Search “dietary weight management”	4
#41	Search “improve glycemic control”	565
#42	Search “hba1c”	11622
#43	Search “hba1c diabetes”	1

#44	Search “glycated hemoglobin”	2337
#45	Search “nutrition intervention”	744
#46	Search “lifestyle intervention”	1413
#47	Search “dietician”	539
#48	Search “dietician/nutritionist”	1
#49	Search “dietician care”	5
#50	Search “dietician counseling”	4
#51	Search “dietician led”	3
#52	Search “dietician’s advice”	3
#53	Search “dieticians/education”	27
#54	Search “dieticians/nutritionists”	2
#55	Search “dieticians education”	27
#56	Search ((#9) OR #10) OR #11) OR #12) OR #13) OR #14) OR #15) OR #16) OR #17) OR #18) OR #19) OR #20) OR #21) OR #22) OR #23) OR #24) OR #25) OR #26) OR #27) OR #28) OR #29) OR #30) OR #31) OR #32) OR #33) OR #34) OR #35) OR #36) OR #37) OR #38) OR #39) OR #40) OR #41) OR #42) OR #43) OR #44) OR #45) OR #46) OR #47) OR #48) OR #49) OR #50) OR #51) OR #52) OR #53) OR #54) OR #55	115420
#57	Search “cost effectiveness”	30851
#58	Search “cost effectiveness/cost benefit”	3
#59	Search “cost effectiveness/cost benefit analysis”	2
#60	Search “cost effectiveness/cost utility”	12
#61	Search “cost effectiveness analyses”	1268
#62	Search “cost effectiveness analysis”	4826
#63	Search “cost effectiveness calculation”	5
#64	Search “cost effectiveness relationship”	19
#65	Search “cost effectiveness outcomes”	36
#66	Search “cost effect”	154
#67	Search “cost effect analysis”	20
#68	Search “cost effect relationship”	3
#69	Search “cost effective”	45021
#70	Search “cost effective approach”	1028
#71	Search “cost effective diet”	4
#72	Search “cost effective education”	9
#73	Search “cost effective intervention”	399
#74	Search “cost/benefit effectiveness”	1
#75	Search “cost/benefit analysis”	156
#76	Search “cost/effectiveness”	162
#77	Search “cost effectiveness utility”	13
#78	Search “cost/effectiveness evaluation”	2
#79	Search “cost/effectiveness relationship”	1
#80	Search “costs and benefits”	3166
#81	Search “costs”	163852
#82	Search “effects analyses”	151
#83	Search “effects analysis”	682
#84	Search “effects”	4656196
#85	Search “effectiveness”	243307

#86	Search “health care costs”	28968
#87	Search “cost/utility”	36
#88	Search “cost outcomes”	272
#89	Search “cost outcomes analysis”	21
#90	Search “economic evaluation”	4502
#91	Search “economic analyses”	1008
#92	Search “economic analysis”	2725
#93	Search ((((((((((((((((((((((((((((((((((((#57) OR #58) OR #59) OR #60) OR #61) OR #62) OR #63) OR #64) OR #65) OR #66) OR #67) OR #68) OR #69) OR #70) OR #71) OR #72) OR #73) OR #74) OR #75) OR #76) OR #77) OR #78) OR #79) OR #80) OR #81) OR #82) OR #83) OR #84) OR #85) OR #86) OR #87) OR #88) OR #89) OR #90) OR #91) OR #92	4969131
#94	Search ((#8) AND #56) AND #93	5335
#95	Search (#94) AND “english”[Filter]	4947
#96	Search (#95) NOT “review”[Filter]	3898
#97	Search (#96) AND “humans”[Filter]	3730

Appendix 2: Trial flow



Appendix 3a: Exclusion reasons in the first exclusion round.

Exclusion reason	Numbers of articles
Intervention contains drug treatment (e.g. metformin, leptin, sitagliptin, peptidase, rosiglitazone, etc.).	1164
Intervention contains insulin therapy.	825
Intervention contains a specific diet (e.g. Mediterranean diet, carbohydrates, olives, cinnamon, vitamin D, low caloric diet).	605
Intervention is specific related to complications e.g. CVD, kidney failure, depression, foot ulcers, etc.).	221
Intervention contains self-management or self-monitoring.	76
Intervention is focused on relation with body specific elements, like mitochondrial complex, leukocytes, lipid profiles, pancreas, colon, etc.).	72
Intervention contains exercise only.	60
Article is about prevention (or screening) instead of treatment.	49
Intervention contains surgery (e.g. gastric sleeve, stem cell transplantation, liposuction).	47
Diet advice is not given by a dietitian (but by nurse or GP).	39
Education is given in a community setting (it is cultured tailored and specific related to a cultural community and its habits).	36
Intervention contains a motivational intervention.	28
Intervention contains education given with printed material, via websites or ICT-technology or telemedicine.	28
Intervention contains a multidisciplinary approach.	27
Intervention contains weight loss only.	27
Intervention focused on the relation with genetic elements.	22
Intervention contains group education.	21
Article is a review or meta-analysis.	15
Intervention is specific related to alcohol and/or smoking consumption.	14
Intervention contains family involvement.	13
Intervention contains medical records or computer technology.	12
Intervention contains physiological and/or cognitive elements.	12
Intervention contains cost issues not related to diet advice.	9
Intervention focuses on adherence.	8
Intervention is specific related to children and/or youth.	7
Intervention is specific related to pregnant women.	7
Article describes guidelines.	6
Article focuses on different health insurance systems.	6
Intervention is specific related to health literacy and the effects.	4
Intervention is specific related to Ramadan and its consequences.	3
Intervention is specific related to uncertainty and confidence of patients with this intervention.	2
Article is a comment or editorial.	2

Appendix 3b: Exclusion reasons in the second exclusion round.

Exclusion reasons	Numbers of articles
Intervention is not led by a dietitian (but by another professional).	40
Intervention contains a multidisciplinary approach.	32
Intervention contains a specific diet (e.g. Mediterranean diet, carbohydrates, olives, cinnamon, vitamin D, low caloric diet).	25
Intervention is specific related to complications e.g. CVD, kidney failure, depression, foot ulcers, etc.).	20
Intervention contains group sessions.	17
Intervention is related to high risk patients and is focused on prevention and/or screening.	15
Intervention contains insulin therapy.	14
Intervention gives general information about T2DM.	12
Article describes guidelines.	7
Intervention is only related to weight loss.	6
Intervention is specific related to a community (culturally depended intervention).	5
Intervention involved the dietitian, but not for diet advice.	5
Article is about testing and/or measuring T2DM.	4
Article is an editorial.	4
Intervention contains self-management or self-monitoring.	4
Intervention is based on health promotion in general.	3
Article describes health insurance in combination with diets.	2
Article describes reasons of poor control of glucose level and not the interventions to treat.	2
Intervention contains surgery (e.g. gastric sleeve, stem cell transplantation, liposuction).	2
Intervention contains physical activity alone.	2

Appendix 4: Included articles from the search strategy

Search strategy result	Title article	Author(s)	Source
1.	Patients' education, and its impact on care outcomes, resource consumption and working conditions: data from the International Diabetes Management Practices Study (IDMPS).	Gagliardino JJ, Aschner P, Baik SH, Chan J, Chantelot JM, Ilkova H, Ramachandran A; IDMPS investigators.	Diabetes & Metabolism (2012), 38(2):128-134.
2.	Effectiveness of medical nutrition treatment delivered by dietitians on glycaemic outcomes and lipid profiles of Arab, Omani patients with Type 2 diabetes.	Al-Shookri A, Khor GL, Chan YM, Loke SC, Al-Maskari M.	Diabetic Medicine (2012), 29(2):236-244.
3.	Comparative effectiveness of patient education methods for type 2 diabetes: a randomized controlled trial.	Sperl-Hillen J, Beaton S, Fernandes O, Von Worley A, Vazquez-Benitez G, Parker E, Hanson A, Lavin-Tompkins J, Glasrud P, Davis H, Adams K, Parsons W, Spain CV.	Archives of Internal Medicine (2011), 171(22):2001-2010.
4.	Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimized drug treatment – lifestyle over and above drugs in diabetes (LOADD) study: randomized controlled trial.	Coppell K, Kataoka M, Williams S, Chisholm A, Vorgers S, Mann J.	BMJ (2010), 341: 3337-3343.
5.	Prospective randomized controlled trial to evaluate effectiveness of registered dietitian-led diabetes management on glycemic and diet control in a primary care setting in Taiwan.	Huang M, Hsu C, Wang H, Shin S.	Diabetes Care (2010), 33(2): 233-239.
6.	Impact of lifestyle intervention on lost productivity and disability: improving control with activity and nutrition (ICAN).	Wolf A, Siadaty M, Crowther J, Nadler J, Wagner D, Cavalieri S, Elward K, Bovbjerg V.	Journal of Occupational and Environmental Medicine (2009), 51(2): 139-145.

7.	Effects of dietary pattern and education on glycemic control in patients with type 2 diabetes mellitus at Dr. Sardjito Central General Hospital, Yogyakarta.	Sinorita H, Saádah, Jazakillah S.	Acta Medica Indonesia (2008), 40(2):55-58.
8.	Effects of lifestyle intervention on health care costs: improving control with activity and nutrition (ICAN).	Wolf A, Siadaty M, Yaeger B, Conaway M, Crowther J, Nadler J, Bovbjerg V.	Journal of the American Dietetic Association (2007), 107(8): 1365-1373.
9.	A single nutrition counseling session with a registered dietitian improves short-term clinical outcomes for rural Kentucky patients with chronic diseases.	Gaetke LM, Stuart MA, Truszczynska H.	Journal of the American Dietetic Association (2006), 106(1):109-112.
10.	Outcomes monitoring of health, behavior, and quality of life after nutrition intervention in adults with type 2 Diabetes.	Lemon C, Lacey K, Lohse B, Hubacher D, Klawitter B, Palta M.	Journal of the American Dietetic Association (2004), 104(12): 1805-1815.
11.	Nutritional counseling in primary health care: a randomized comparison of an intervention by general practitioner or dietician.	Willaing I, Ladelund S, Jørgensen T, Simonsen T, Nielsen L.	European Journal of Cardiovascular prevention & rehabilitation (2004), 11(6): 513-520.
12.	Translating lifestyle intervention to practice in obese patients with type 2 diabetes.	Wolf A, Conaway M, Crowther J, Hazen K, Nadler J, Oneida B, Bovbjerg V.	Diabetes Care (2004), 27(7): 1570-1576.
13.	The direct medical cost of type 2 diabetes.	Brandle M, Zhou H, Smith B, Marriott D, Burke R, Tabaei B, Brown M, Herman W.	Diabetes Care (2003), 26(8): 2300-2304.
14.	Effects of clinical nutrition education and educator discipline on glycemic control outcomes in the Indian health service.	Wilson C, Brown T, Acton K, Gilliland S.	Diabetes Care (2003), 26(9): 2500-2504.
15.	Effect of improved glycemic control on health care costs and utilization.	Wagner E, Sandhu N, Newton K, McCulloch D, Ramsey S, Grothaus L.	Journal of the American Dietetic Association (2001), 285(2): 182-189.
16.	Improved control of type 2 Diabetes Mellitus: a practical education/behavior modification program in a primary care clinic.	Ridgeway N, Harvill D, Harvill L, Falin T, Forester G, Gose O.	Southern Medical Journal (1999), 92(7): 667-672.
17.	The estimated costs and savings of medical nutrition therapy: the medicare population	Sheils J, Rubin R, Stapleton D.	Journal of the American Dietetic Association (1999), 99(4): 428-435.

18.	Cost-effectiveness of medical nutrition therapy provided by dietitians for persons with non-insulin-dependent diabetes mellitus.	Franz M, Splett P, Monk A, Barry B, McClain K, Weaver T, Upham P, Bergenstal R, Mazze R.	Journal of the American Dietetic Association (1995), 95(9): 1018-1024.
19.	Effectiveness of medical nutrition therapy provided by dietitians in the management of non-insulin-dependent diabetes mellitus: a randomized, controlled clinical trial.	Franz M, Monk A, Barry B, McClain K, Weaver T, Cooper N, Upham P, Bergenstal R, Mazze R.	Journal of the American Dietetic Association (1995), 95(9): 1009-1017.
20.	Medical nutrition therapy in non-insulin-dependent diabetes mellitus improves clinical outcome.	Johnson E, Valera S.	Journal of the American Dietetic Association (1995), 95(6): 700-701.

Appendix 5: Characteristics and quality of RCTs

RCT	Participants	Intervention	Quality
Al-Shookri et al. (2012) *Search strategy result: 2.* *Objective:* To evaluate the effectiveness of MNT delivered by a dietitian in Oman. *Timeline:* 6 months *Method:* Recruitment at the outpatient diabetes clinic. Two groups were assigned randomly and by random selection one group was assigned to receive practice guidelines nutritional care and the other group usual care.	*Number:* 170 (85 participants in each group). *Inclusion criteria:* T2DM, no complications, age between 30-70. *Age (mean):* 50.7 *Treatment:* One group: practice guidelines nutritional care, consists of three appointments with a dietitian with specific intervention measures. An educational intervention and a nutrition prescription are planned and implemented. Other group: usual care, consists of one appointment with dietitian to develop a nutrition care plan.	Patients were randomly assigned to a group receiving usual nutritional care, and a group who receive practice guidelines nutritional care. Patients were given 1-3 appointments over 6 months. *Measured:* Anthropometric variables: weight, height, BMI, waist circumference. Biochemical variables: HbA_{1C}, FPG, lipid profiles. *Conclusion:* Significant improvements in anthropometric and biochemical outcomes by MNT provided by dietitians. Better results in the practice guidelines nutritional care group.	*Trial design and participants described:* yes *Randomization described:* yes *Allocation concealment:* yes. *Outcome assessment blinded:* yes. *Adequate power:* probably. *Follow-up reported:* yes. *ITT analysis performed:* yes. *Statistical analysis appropriate:* yes. *Baseline characteristics appropriate:* yes *Funding of study reported:* no funding. **Overall quality:** High, almost the whole process was explained.

Sperl-Hillen et al. (2011) *Search strategy result: 3.* *Objective:* To determine if group education improves glucose control compared with usual care and individual care. *Timeline:* 24.8 months.	*Number:* 623 *Inclusion criteria:* adult, T2DM *Age (mean):* 61.8 years. *Treatment:* One group was assigned to individual education with a dietitian for 3 times 1-hour sessions. The other group consisted of 4 times 2-hour sessions. The third group did not get any intervention or treatment. Participants in the individual education group were scheduled for 3 times 1-hour sessions with nurses and dietitians within 1-month intervals. Participants in the group education were scheduled for 4 times 2-hour sessions with groups at 1-week intervals. The group with usual care did not receive any intervention.	The education methods used, were consistent with the ADA recognized education programs. Content areas were monitoring, problem solving, healthy eating, taking medications, healthy coping, being active and risk reduction. *Measured:* HbA_{1C}, BMI, waist circumference, BP, diabetes knowledge *Conclusion:* Individual education resulted in better glucose control outcomes than did group education. Also better psychosocial and behavioral outcomes.	*Trial design and participants described:* yes. *Randomization described:* yes. *Allocation concealment:* yes *Outcome assessment blinded:* unknown. *Adequate power:* yes. *Follow-up reported:* yes. *ITT analysis performed:* yes. *Statistical analysis appropriate:* yes. *Baseline characteristics appropriate:* yes. *Funding of study reported:* yes, funded by Merck and Co Inc. **Overall quality:** High, because the methodology is well described.
Coppell et al. (2010) *Search strategy result: 4.* *Objective:* To determine the extent to which intensive dietary intervention can influence	*Number:* 93 (45 intervention group ; 48 control group). *Inclusion criteria:* under 70 years old, resident of the city Dunedin, T2DM, HbA_{1C} level of more than 7%. *Age (mean):* 56.6 (intervention	Both groups received general information about physical activity (30 min a day). The intervention group received intensive dietary intervention by a dietitian. They get specific diet advice for them	*Trial design and participants described:* yes. *Randomization described:* yes. *Allocation concealment:* yes. *Outcome assessment blinded:* probably. *Adequate power:* yes. *Follow-up reported:* yes. *ITT analysis performed:* yes.

glycaemic control. *Timeline:* 6 months.	group) ; 58.4 (control group) *Treatment:* Intensive dietary intervention.	in individual sessions. *Measured:* HbA_{1C}, weight, BMI, waist circumference, BP, FPG, lipid profiles. *Conclusion:* Intensive dietary advice improves glycaemic control and anthropometric measures.	*Statistical analysis appropriate:* yes. *Baseline characteristics appropriate:* yes. *Funding of study reported:* yes, but funders had no impact in the study. **Overall quality:** High, because the methodology was well described.
Huang et al. (2010) *Search strategy result: 5.* *Objective:* To evaluate the effect of registered dietitian-led management of diabetes on glycemic control. *Timeline:* 12 months.	*Number:* 154 (75 intervention group ; 79 control group). *Inclusion criteria:* T2DM, aged between 30-70 years (excluded: pregnant women, people with severe complications) *Age (mean):* 56.6 (intervention group) ; 56.9 (control group) *HbA_{1C}:* 8.0 (intervention group) ; 8.4 (control group). *Treatment:* Usual care in the control group. Intervention group receive added treatment by a dietitian (diet advice).	Patients in the intervention group receive usual care and receive education about self-monitoring of glucose, exercise and complications and they got individualized nutrition counseling and dietary plans by a registered dietitian. *Measured:* HbA_{1C}, FPG, BP, BMI, lipid profiles. *Conclusion:* Dietitian-led management of diabetes can improve glycemic control in patients with T2DM.	*Trial design and participants described:* yes. *Randomization described:* yes. *Allocation concealment:* yes. *Outcome assessment blinded:* unknown. *Adequate power:* probably. *Follow-up reported:* yes. *ITT analysis performed:* no. *Statistical analysis appropriate:* yes. *Baseline characteristics appropriate:* yes. *Funding of study reported:* yes, but no conflicting interests. **Overall quality:** Moderate, because information about the methods is not complete. For example it is not known if the outcome assessment was blinded and there was no ITT analysis performed.

Wolf et al. (2009) *Search strategy result: 6.* *Objective:* To evaluate the effectiveness of a dietitian-led lifestyle intervention in reducing work loss and disability days. *Timeline:* 1 year.	*Number:* 147 (73 control group ; 74 intervention group). *Inclusion criteria:* T2DM, BMI > 27 kg/m2, age > 20 years (exclusion: pregnancy, other complications). *HbA_{1C}:* 7,7 % *Treatment:* Dietitian gives individually tailored diet advice.	Lifestyle intervention group receive individually tailored diet medical nutrition therapy. The control group receive usual care, which include written education material. *Measured:* Days absent from work and days with disability. *Conclusion:* A registered dietitian-led lifestyle intervention reduce work loss and disability days associated with diabetes and obesity. It also improves glycemic control, HRQoL and health care utilization.	*Trial design and participants described:* yes. *Randomization described:* yes. *Allocation concealment:* unknown. *Outcome assessment blinded:* unknown. *Adequate power:* unknown. *Follow-up reported:* yes. *ITT analysis performed:* no. *Statistical analysis appropriate:* yes. *Baseline characteristics appropriate:* yes. *Funding of study reported:* yes. **Overall quality:** Poor, because there is too much information unknown or not reported. However, this article is a continuation of the article of Wolf et al. (2007) and Wolf et al. (2004) and when using these articles for information about the methodology, the overall quality is very high.
Wolf et al. (2007) *Search strategy result: 8.* *Objective:* To evaluate program and health care costs of a lifestyle intervention. *Timeline:* 12 months.	*Number:* 147 (74 control group ; 73 intervention group). *Inclusion criteria:* T2DM, BMI <27 kg/m2, age < 20 years. (ICAN project) *Age (mean):* 53.4 (control group) ; 53.3 (intervention group). *Treatment:* Individually tailored diet advice by a dietitian.	Lifestyle intervention group receive individually tailored diet medical nutrition therapy. The control group receive usual care, which include written education material. *Measured:* Direct cost of the inter-vention, inpatient admissions	*Trial design and participants described:* yes. *Randomization described:* yes. *Allocation concealment:* yes. *Outcome assessment blinded:* yes. *Adequate power:* unknown. *Follow-up reported:* yes. *ITT analysis performed:* no. *Statistical analysis appropriate:* yes. *Baseline characteristics appropriate:* yes. *Funding of study reported:* yes.

		(health care utilization) and costs, total health care costs. *Conclusion:* A registered dietitian-led lifestyle management intervention did not increase health care costs and suggested cost savings.	**Overall quality:** Moderate – high quality. There are some factors unknown. However, when using the article of Wolf et al. (2004) for additional information about the methodology, all factors can be answered with a yes and the study is of high quality then.
Willaing et al. (2004) *Search strategy result: 11.* *Objective:* To compare health effects of nutritional counseling by a GP or dietitian. *Timeline:* 12 months.	*Number:* 503 (191 control group ; 312 intervention group). *Inclusion criteria:* BMI > 39 kg/m2, T2DM, large waist circumference, high lipid levels, age > 18 years. *Age (mean):* 50 (dietitian group) ; 54 (GP group). *Treatment:* Individual counseling session by a dietitian.	Intervention by GPs consisted of usual treatment with general advice and delivery of written information on healthy diet. Intervention by the dietitian consisted of individual counseling, focused on principles of good nutrition, diet advice, cooking methods, and exercise. *Measured:* Weight, waist circumference, BP, BMI, lipid profiles, risk of CVD, consumption of medicine, use of health care. *Conclusion:* It is more effective to refer to a long-term nutritional counseling by a dietitian instead of a program led by a GP.	*Trial design and participants described:* yes. *Randomization described:* yes. *Allocation concealment:* no. *Outcome assessment blinded:* no. *Adequate power:* unknown. *Follow-up reported:* yes. *ITT analysis performed:* yes. *Statistical analysis appropriate:* yes. *Baseline characteristics appropriate:* yes. *Funding of study reported:* there was no funding for this study. **Overall quality:** Moderate – poor, because allocation concealment and outcome assessment blinded was answered with a no. Also it is unknown if this study has adequate power.

Wolf et al. (2004) *Search strategy result: 12.* *Objective:* To assess the efficacy of a lifestyle intervention program for obese patients with T2DM. *Timeline:* 12 months.	*Number:* 144 (71 control group ; 73 intervention group). *Inclusion criteria:* T2DM, BMI > 27 kg/m2, age > 20 years (exclusion: pregnancy, other severe complications). *Age (mean):* 53.4 (control group); 53.3 (intervention group). *Treatment:* Individual tailored dietary counseling by a dietitian.	Participants met a registered dietician individually (and sometimes in groups or by phone). Tailored dietary goals were set and physical activity recommended. In the other group of participants, they received usual care, which includes educational material (written) *Measured:* Weight, waist circumference, HbA_{1C}, lipid levels, use of medications, HrQoL. *Conclusion:* A dietitian-led lifestyle case management may improve multiple health indicators among patients with T2DM.	*Trial design and participants described:* yes. *Randomization described:* yes. *Allocation concealment:* yes. *Outcome assessment blinded:* yes. *Adequate power:* yes. *Follow-up reported:* yes. *ITT analysis performed:* yes. *Statistical analysis appropriate:* yes. *Baseline characteristics appropriate:* yes. *Funding of study reported:* yes by the ADA. **Overall quality:** High.
Ridgeway et al. (1999) *Search strategy result: 16.* *Objective:* To determine the efficacy of education for improving control of T2DM. *Timeline:* 12 months.	*Number:* 56 (28 control group ; 28 intervention group). *Inclusion criteria:* T2DM, at least 20% over ideal weight. *Age (mean):* 65 (control group) ; 62 (intervention group). *Treatment:* Individual diet and exercise prescriptions by a dietitian and nurse, but also a few group	The intervention group received diet and exercise education in individual setting and group sessions, but led by a dietitian (with help of a nurse). The control group receive usual care from GPs. *Measured:* Weight, FPG, HbA_{1C}, lipid	*Trial design and participants described:* yes. *Randomization described:* yes. *Allocation concealment:* unknown. *Outcome assessment blinded:* no. *Adequate power:* probably. *Follow-up reported:* yes. *ITT analysis performed:* unknown. *Statistical analysis appropriate:* yes. *Baseline characteristics appropriate:* yes. *Funding of study reported:* no funding reported.

	sessions.	levels, diabetes knowledge, HRQOL. *Conclusion:* A education program led by a dietitian is clinically worthwhile, because of significant reductions in FPG, $HbA_{1C,}$ lipid profiles and weight. Also it is easy to administer.	**Overall quality:** Poor, because there is some information unknown or not described. It is possible that the study included these points, but did not described it. However, there is too much uncertainty.
Franz, Splett et al. (1995) *Search strategy result: 18.* *Objective:* To determine the cost-effectiveness of nutrition care provided by dietitians. *Timeline:* 6 months.	*Number:* 179 (n=85 control group; n=94 intervention group). *Inclusion criteria:* T2DM, adults, free of complications. *Treatment:* Medical Nutrition Therapy.	The intervention group received, individualized nutrition care by a dietitian, the control group only basic nutrition care (also by a dietitian, but only once). *Measured:* HbA_{1C}, FPG, costs. *Conclusion:* Individualized nutrition interventions delivered by dietitians with a reasonable investment of resources can be effective. When dietitians are engaged in active decision making cost-effectiveness could also be enhanced.	*Trial design and participants described:* yes. *Randomization described:* yes. *Allocation concealment:* unknown. *Outcome assessment blinded:* unknown. *Adequate power:* unknown. *Follow-up reported:* yes. *ITT analysis performed:* unknown. *Statistical analysis appropriate:* yes. *Baseline characteristics appropriate:* yes. *Funding of study reported:* Yes, by the ADA. **Overall quality:** Poor, because there is too much uncertainty or factors who are not described. However, this study is a part of the study of Franz, Monk, et al (1995), where the methodology is well described. When using that information, this study is of high quality.

Franz, Monk et al. (1995) *Search strategy result: 19.* *Objective:* To assess the effect of MNT provided by dietitians on medical outcomes for adults with NIDDM. *Follow-up:* 6 months.	*Number:* 179 (n=85 control group; n=94 intervention group). *Inclusion criteria:* NIDDM, adults, free of diabetes complications. *Age (mean):* 55.9 (control group) ; 56.9 (intervention group). *Treatment:* MNT provided by a dietitian.	One group had one visit with a dietitian to improve glycemic control in general. The other group receive MNT from the dietitian. *Measured:* FPG, HbA_{1C}, lipid levels, weight, BMI. *Conclusion:* MNT provided by dietitians resulted in significant improvements in clinical outcomes. Because of the upward trend in glucose levels after 3 months, ongoing MNT by dietitians is important for long-term metabolic control.	*Trial design and participants described:* yes. *Randomization described:* yes. *Allocation concealment:* yes. *Outcome assessment blinded:* probably. *Adequate power:* yes. *Follow-up reported:* yes. *ITT analysis performed:* yes. *Statistical analysis appropriate:* yes. *Baseline characteristics appropriate:* yes. *Funding of study reported:* yes, by the ADA. **Overall quality:** High quality.

Appendix 6: Characteristics of observational and non-randomized studies

Study	Participants	Interventions
Gagliardino et al. (2012) *Search strategy result: 1.* *Design:* cross-sectional (observational) *Timeline:* 5 years *Objective:* To evaluate the impact of diabetes education on quality of care, conditions of employment and resource consumption. *Funding:* yes, funded by Sanofi-Aventis.	*Total number:* 11384 (5692 in each group). *Age (mean):* 57.7 years. *Inclusion criteria:* adults, T2DM, diabetes for more than 5 years. *Treatment:* diabetes education. *Conclusion:* Diabetes education significant improved the blood control levels of patients with T2DM. Diabetes education is an efficient toll to improve health care without a major impact on the costs.	*Comparison:* educated vs. non educated participants. *Intervention:* two groups were available: participants who received diabetes education from the nurse, dietitian or educator, or participants were referred to ad-hoc group-education programmes. They include healthy lifestyle changes, active participation in disease control and self-care. The other group did not get any education. *Outcomes:* clinical data (body weight, waist circumference, BP, foot evaluation), metabolic control measures (HbA_{1C}, lipid profiles), and working days lost and resource consumption. *Comment about quality:* A lot of information about participants and method are given, but it is not a randomized study, and there are different education strategies available. So selection bias will occur. However, the sample size is large and because of the pared comparison performed, those limitations are less important.

Sinorita et al. (2008) *Search strategy result: 7.* *Design:* cross-sectional. *Timeline:* 1 month. *Objective:* To recognize the effect of education and diet on glycemic control. *Funding:* not reported.	*Total number:* 88 (41 poor ; 47 well). *Age (mean):* 59.63 years. *Inclusion criteria:* T2DM patients who had routine visit in 3 months. *Treatment:* diabetes education. *Conclusion:* Education and diet advice provided by a dietitian lead to a significant correlation between regulation of dietary pattern and glycemic control.	*Comparison:* effect of dietary pattern compared to the effect of education on glycemic control. *Intervention:* both dietary pattern and education are determine in two groups: a group with well glycemic control group (FPG < 126 mg/dl) and a poor glycemic control group (FPG > 126 mg/dl). *Outcomes:* FPG. *Comment about quality:* Only one outcome is measured and there is less information about the participants. Further, it is unknown if dietitian really gives the information. The information about the methodology is poor, but the data analyses are well done.
Gaetke et al. (2006) *Search strategy result: 9.* *Design:* retrospective *Timeline:* 12 months. *Objective:* To evaluate the effectiveness of a single nutrition counseling provided by a registered dietitian in improving outcome measures for patients with T2DM. *Funding:* yes, supported by the University of Kentucky.	*Total number:* 175 (81 diabetes ; 81 CVD ; 13 both). *Age (mean):* 60. *Inclusion criteria:* adults with T2DM or CVD, free of major complications, same registered dietitian. *Treatment:* medical nutrition therapy (individualized dietary instruction by the registered dietitian). *Conclusion:* An individual nutrition counseling session with a dietitian is an effective approach to treat T2DM.	*Comparison:* educated vs. non-educated patients. *Intervention:* within the two groups of diabetes and CVD, half of the patients within such group receive MNT and the other half not. MNT includes one nutrition counseling session with the dietitian. *Outcomes:* HbA_{1C}, FPG, lipid levels, weight, BMI. *Comment about quality:* Clear overview of the method section, but data collection could be more precise (also author's conclusion). Confounding is playing a role and also bias, but this is mentioned in the article.

Lemon et al. (2004) *Search strategy result: 10.* *Design:* prospective non controlled descriptive study. *Timeline:* 6 months intervention, 4 months following to complete the data section. *Objective:* To examine changes in health in persons with T2DM receiving nutrition counseling from a registered dietitian. *Funding:* yes, by the Wisconsin Dietetic Association.	*Total number:* 244 *Inclusion criteria:* T2DM, age > 20 years, no severe diseases. *Treatment:* diabetes nutrition education/counseling by a registered dietitian (face-to-face). *Conclusion:* Nutrition intervention provided by dietitian lead to positive outcomes in weight, glycemic control, cholesterol levels and missed workdays.	*Comparison:* baseline characteristics of patients with T2DM and patient characteristics after 6 months of MNT. *Intervention:* dietitians had a one-on-one session (at least one) with patients about relationship of food, medications, exercise and blood glucose, weight control, diets and individualized meal plans were made (MNT). *Outcomes:* HbA_{1C}, FPG, weight, BMI, BP, lipid profiles, missed workdays, health status (QoL), medication frequency. *Comment about quality:* Very clear performed study. There is no control group, but there is tried to avoid selection bias by randomization. Data collection is well described, however the sample size was small.
Brandle et al. (2003) *Search strategy result: 13.* *Design:* cost-analysis. *Timeline:* 1 year. *Objective:* To describe the direct medical costs associated with T2DM. *Funding:* yes, by the Centers for Disease Control and Prevention.	*Total number:* 1364. *Age (mean)*: 66. *Inclusion criteria:* T2DM, age > 18 years, nonpregnant, community-dwelling, and enrolled in the health plan for at least 18 months. *Conclusion:* Diabetes complications have a huge impact on the direct medical costs of T2DM.	*Comparison:* costs for different treatments, characteristics and complications). *Intervention:* direct medical costs were examined and different costs for different treatments compared. *Outcomes:* direct medical costs (by demographic characteristics, treatments, and complications). *Comment about quality:* In this study, only the costs are determined and not the effects of diet advice at the same time. It is an economic model, so it is difficult to say something

		about randomization, blinding and bias. However, the costs are measured for the US, so the comparability with the Netherlands could be questioned.
Wilson et al. (2003) *Search strategy result: 14.* *Design:* comparative. *Follow-up:* 1 year. *Objective:* To compare the effectiveness of clinical nutrition education when it was delivered by a registered dietitian compared with another educator. *Funding:* not reported.	*Total number:* 7490. *Age (mean):* 55.2 years. *Inclusion criteria:* adults with T2DM. *Treatment:* clinical nutrition education. *Conclusion:* Clinical nutrition education provided by dietitians is associated with positive outcomes in glycemic control.	*Comparison:* education delivered by a dietitian or another professional/educator. *Intervention:* Clinical data was examined and two recent HbA_{1C} levels were used and compared. One group received diet education from a registered dietician, the other group by a non-RD. *Outcomes:* HbA_{1C}. *Comment about quality:* Only one outcome is measured and compared, namely HbA_{1C}. The data was already available from medical records, so this was not an intervention. Because of the observational character of the study, the causality to the associations cannot be identified and patient characteristics could have been influenced the process and outcomes.
Wagner et al. (2003) *Search strategy result: 15.* *Design:* Historical cohort study. *Follow-up:* 1 year *Objective:* To determine if improvements in HbA_{1C} levels results in reductions in health care utilization and costs.	*Total number:* 4744. *Age (mean)*: 60.2 (improved group) ; 60.7 (not improved group). *Inclusion criteria:* age > 18 years, T2DM, recorded HbA_{1C} measurement in laboratory data. *Treatment:* No treatment, just analyzing available data.	*Comparison:* costs between cohort with improved glucose control and cohort with unimproved glucose control. *Intervention:* no intervention, but just analyze the available data in two groups and the associated costs. *Outcomes:* health care utilization (hospital admissions, specialty care visits, primary care visits), total health care costs, complications (e.g. CVD).

Funding: yes, but unrestricted.	*Conclusion:* A reduction in HbA_{1C} level is associated with significant cost savings.	*Comment about quality:* Only available data is used. The study did not investigated a treatment or intervention. However, the methods are very clear described, even as the data collection. The study population was a stable population with regularly visits to the physician, bias could have been occurred. Also confounding can play a role, because the participants could have been used drugs (or changed their drugs behavior) which can influence the outcome.
Sheils et al. (2003) *Search strategy result: 17.* *Design:* cost-analysis. *Follow-up:* unknown. *Objective:* To measure the potential savings of MNT. *Funding:* yes, by the ADA.	*Total number:* 26.531 (n = 12.308 diabetes ; n = 10.895 CVD ; n = 3.328 renal disease). *Age (mean)*: 71 (diabetes) ; 72 (CVD) ; 75 (renal disease). *Inclusion criteria:* DM or CVD or renal disease, age > 55 years. *Treatment:* Use of MNT. *Conclusion:* MNT can result in net reduction in health services utilization and costs . The savings in utilization of hospital and other services will exceed the cost of providing the MNT benefit. MNT is provided by dietitians.	*Comparison:* there is no actual comparison, but only measurement of the intervention (no control group). *Intervention:* Use of MNT was measured for patients with diabetes, CVD, or renal disease. *Outcomes:* hospital admissions, physician visits, hospital outpatient visits, cost of MNT benefits, savings, net cost. *Comment about quality:* It is a cost analysis, but effects and savings are also measured (but not with an RCT design). The methods and data collection was very clear described and the statistical analysis too. However, the group of participants was very specific, so the applicability to other settings could be low.

Johnson & Valera (1995) *Search strategy result: 20.* *Design:* retrospective study. *Follow-up:* 6.4 months. *Objective:* To measure the effect of MNT provided by a dietitian. *Funding:* not registered.	*Total number:* 21 *Age (mean)*: unknown. *Inclusion criteria:* NIDDM, adults, receiving MNT. *Treatment:* MNT provided by a dietitian. *Conclusion:* MNT programs provided by registered dietitians lead to decreasing levels of blood glucose and weight reduction.	*Comparison:* Only the effects of providing MNT by dietitians to patients is measured. *Intervention:* Use of MNT. *Outcomes:* FPG, weight. *Comment about quality:* There is little information available about methods and data collection. The article recommends additional research to investigate the causality between MNT and improved health and cost savings.