Hochschule für Angewandte Wissenschaften Hamburg
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Evaluation of the Effectiveness of Lifestyle Interventions in the primary prevention of diabetes mellitus type II in high-risk individuals

Master thesis

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Abstract

Background/research question: The increasing prevalence of type II diabetes mellitus (T2DM) raises the question as to whether lifestyle interventions (diet/exercise) can delay or prevent the manifestation of T2DM and reduce the risk of micro- and macrovascular complications and premature death in high-risk individuals. The primary aim of this thesis was to determine whether systematic reviews exist that are able to answer the research question and thus provide a basis for the production of evidence-based health information (EBHI). Secondly, evidence on patient relevant outcomes like cardiovascular disease and mortality on the basis of individual RCTs and epidemiological studies was to be collected.

Methods: PubMed, the Cochrane Library and DARE have systematically been searched for systematic reviews of controlled trials (CTs) in June 2013. The DIMDI, NICE and AHRQ websites were manually searched. Systematic reviews were included if they met predefined inclusion criteria and achieved an Oxman & Gyuatt Index ≥ 5. Two researchers independently screened 710 titles/abstracts and the resulting 48 full-text articles.

Results: 9 relevant systematic reviews have been identified, of which 4 had the required quality. They differed in terms of the populations, interventions and outcomes included, as well as the search date. The most appropriate review included 11 randomized CTs in a meta-analysis: The pooled hazard ratio versus controls was 0.51 (95% CI 0.43-0.62). Assuming an annual diabetes incidence of 11% as in the US Diabetes Prevention Program the calculated absolute risk of diabetes in the intervention groups would be 5.61% (95% CI 4.73- 6.82). Significant reductions in long term adverse health outcomes like CVD risk, CVD or all-cause mortality could neither be found in the 4 identified reviews nor in the individual RCTs. However, long term follow-up data of individual RCTs indicated benefits of lifestyle interventions in terms of microvascular complications like diabetic retinopathy and HRQoL.

Conclusions: Lifestyle interventions can prevent or delay the diagnosis of T2DM in high-risk individuals. The findings translate into an estimated effect of about 5 out of 100 individuals by reducing an assumed annual diabetes progression rate of 11 out of 100 to about 6 out of 100 individuals. The systematic procedure to find the best available external evidence resulted in a suitable basis for the production of EBHI on diabetes prevention in high-risk individuals. Whether the applied evaluation method is the most suitable for creating EBHI is worth consideration.

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Content

List of Abbreviations

ADA	American Diabetes Association
AHRQ	Agency for Healthcare Research and Quality
BÄK	Bundesärztekammer
BMG	Bundesministerium für Gesundheit
BMJ	Bundesministerium der Justiz
CVD	Cardiovascular Disease
CG	Control Group
DARE	Database of Abstracts of Reviews of Effects
DEGS	Studie zur Gesundheit Erwachsener in Deutschland
DPP	Diabetes Prevention Program
DPPOS	Diabetes Prevention Program Outcomes Study
DPPRG	Diabetes Prevention Program Research Group
DPS	Diabetes Prevention Study
EBM	Evidence Based Medicine
EBHI	Evidence Based Health Information
ERFC	Emerging Risk Factor Collaboration
FPG	Fasting Plasma Glucose
H(b)A1C	Glycated Hemoglobin
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IDF	International Diabetes Federation
IDPP	Indian Diabetes Prevention Program
IG	Intervention Group
IGT	Impaired Glucose Tolerance
IOM	Institute of Medicine
LI	Lifestyle Intervention
NICE	National Institute for Health and Clinical Excellence
NGT	Normal Glucose Tolerance
NNT	Number Needed to Treat
OGGT	Oral Glucose Tolerance Test
PICO	Population Intervention Control Outcome
RCT/RCTs	Randomized Controlled Trial/Randomized Controlled Trials
RKI	Robert Koch Institut
SCB	Social Code Book
SHI	Statutory Health Insurance
ST2DM	Screen detected type 2 diabetes mellitus
T2DM	Diabetes mellitus type 2
WHO	World Health Organization
YLL	Years of Life Lost

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1 Introduction

Diabetes mellitus type 2 is a disease of major public health concern in high-income countries and low- and middle-income countries alike. According to the International Diabetes Federation (IDF) the number of people with diabetes is increasing in every country (IDF, 2012). In the European region prevalence rates are rising among all ages mostly due to increases in overweight and obesity, unhealthy diet and physical inactivity (WHO EUROPE, 2013). It is estimated that about 60 million people in the European Region live with diabetes, 10.3 % of men and 9.6 % of women aged 25 and over with substantial differences between individual countries (WHO EUROPE, 2013; Thelen et al., 2013). For Germany results of the German Health Interview and Examination Survey (DEGS) indicate that at least 4.6 million Germans aged 18 to 79 years have been diagnosed with diabetes at some point in life, which would translate to a lifetime prevalence rate of 7.2% (Heidemann et al., 2013).

There are two main reasons why preventive strategies are urgently needed (Lindström et al., 2006) to limit the burden of disease resulting from T2DM and its complications for patients and health care systems: population aging and decrease of the age of onset of T2DM.

As “Age is one of the strongest risk factors for T2DM.” (Paulweber et al., 2010, p. S4) the number of individuals affected will increase in an aging society as found in Germany. In the DEGS diabetes prevalence rates ranged from under 5% among those under 50 years of age to more than 20% of those being older than 70 (Heidemann et al., 2013). Furthermore, there is evidence that the age of onset decreases in countries with increasing obesity prevalence (Paulweber et al., 2010). For Germany an increase in diabetes prevalence in the age group of 25 to 69 as well as in the adult population over the age of 18 in the last decade has been verified (Heidemann et al., 2011).

Looking from the patients` perspective, surveys have shown that an overwhelming majority is interested to learn what they themselves can do to maintain good health or reduce disease consequences. 89 % expected advice from their general practitioner on how to reduce the risk of future illness and 85% wanted to know how they could stay healthy in the future (Little et al., 2001). As time available to the individual patient is usually very limited when visiting a doctor, evidence based health information (EBHI) on the effectiveness of lifestyle changes in the prevention of T2DM could be very useful for patients, consumers and doctors alike.

2 Research Question and Objectives

As pointed out EBHI on the effectiveness of diabetes prevention could be one component of a strategy to meet the information needs of consumers and patients and at the same time promote the efforts towards preventive strategies. In Germany the Institute for Quality and Efficiency in Health Care (IQWIG) is legally obliged to provide EBHI for consumers and patients on diseases of substantial epidemiological relevance (IQWIG, 2011). As a prerequisite evidence has to be assessed according to the methods of evidence based medicine (EBM). The goal of this master thesis was therefore to evaluate the effectiveness of lifestyle interventions to prevent or delay diagnosis of T2DM in high-risk individuals applying the methods of EBM. The result of this evaluation aims to build the basis for the production of EBHI on the topic which is to be published on the IQWIG website in the near future.

Apart from evaluating the possibility of delaying or preventing T2DM, an additional objective of this thesis was to search for evidence for the benefit of LI in terms of patient relevant outcomes like CVD risk, CVD mortality, all-cause mortality, morbidity or HRQoL. Deviating from the IQWIG`s usual practice at the time of this research to use primarily systematic reviews of CT`s as a basis for EBHI, also insights that have been gained from individual RCTs or epidemiological studies will be presented in this master thesis.

Finally, using the example of prevention of T2DM, this bit of research considers the question, whether or not the search for systematic reviews of controlled trials may be an appropriate method for the assessment of evidence in primary prevention and the preparation of EBHI.

3 Theoretical Background

3.1 Diabetes mellitus type 2

3.1.1 Definition and diagnostic criteria

Diabetes mellitus type 2 (T2DM) is defined as a metabolic disorder that is primarily characterized by chronic hyperglycemia induced by disturbances in insulin secretion, insulin action or both (WHO, 1999; BÄK et al., 2013). At present there is no unique biological marker that distinguishes people with diabetes from non-diabetic but hyperglycemic individuals. Therefore plasma glucose levels remain the basis for the diagnosis of T2DM and the definition of intermediate hyperglycemia, namely Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG) (ADA, 2003; WHO, 2006). In a report of a WHO/IDF Consultation in 2006 the WHO stated: “In the absence of a more specific biological marker to define diabetes, plasma glucose estimation remains the basis of diagnostic criteria” (WHO, 2006, p.9). However, the exact cut-off points that distinguish hyperglycemia from diabetes mellitus type 2 have changed over time and still are a matter of debate (WHO, 2006).

The different, currently recommended diagnostic criteria for T2DM, IGT and IFG are summarized in table 1.

Especially the definition of IFG is contentious. The WHO pointed out, that lowering the cut-point for IFG as proposed by the ADA in 2003 would lead to a significant increase in IFG prevalence with enormous impact on individuals and health systems (WHO, 2006). Moreover, the risk of progressing to T2DM is much higher in people with FPG levels of > 6.1 mmol/l than in those with FPG levels of 5.6-6.0 mmol/l (Gillett et al., 2012). In addition the WHO stated that there is a lack of evidence of any benefit of lowering the IFG threshold with regard to progression to diabetes or adverse clinical outcomes (WHO, 2006).

Table 1: Currently recommended diagnostic criteria for diabetes mellitus type 2 (T2DM), Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG) by WHO, ADA and BÄK (WHO, 2006; ADA, 2003; ADA, 2013; BÄK et al., 2013).

Diagnostic Criteria of	**WHO, 2006 and WHO, 2011**	**ADA, 2003 and 2013**	**BÄK et al., 2013**
Diabetes			
Fasting plasma glucose	≥ 7,0 mmol/ (126 mg/dl)	≥ 7,0 mmol/ (126 mg/dl)	> 7,0 mmol/ (126 mg/dl)
	or	**or**	**and/or**
2-h plasma glucose	≥ 11,1 mmol/l (200 mg/dl)	≥ 11,1 mmol/l (200 mg/dl)	≥ 11,1 mmol/l (200 mg/dl)
	or	**or**	**and/or**
	HbA1c levels of 48 mmol/mol (6.5%)	A1C ≥ 6,5%	HbA1c ≥ 48 mmol/mol (≥ 6.5%)
IGT			
Fasting plasma glucose	< 7.0 mmol/l (126 mg/dl)	-	-
	and		
2-h plasma glucose	≥ 7.8 and < 11.1 mmol/l (140 mg/dl and 200 mg/dl)	7,8 – 11 mmol/l (140 –199 mg/dl)	≥ 7.8 and < 11.1 mmol/l (140 mg/dl and 200 mg/dl)
IFG			
Fasting plasma glucose	6.1 to 6.9 mmol/l (110 mg/dl to 125 mg/dl)	5.6–6.9 mmol/l (100–125 mg/dl)	≥ 5.6 mmol/ and < 7.0 mmol/l (≥ 100 mg/dl and < 126 mg/dl)
	and (if measured)		
2-h plasma glucose	< 7.8 mmol/l (140 mg/dl)		

3.1.2 Risk Factors

T2DM is based on a genetically determined, multi-factorial predisposition. The clinical manifestation occurs under the influence of modifiable and non-modifiable risk factors, which are summarized in table 2 (BÄK et al., 2013, WHO, 1999, Paulweber et al., 2010).

Table 2: Modifiable and non-modifiable risk factors for T2DM (Paulweber et al., 2010, p. S5)

Non-modifiable risk factors	Modifiable risk factors
▸ Age	▸ Overweight and obesity
▸ Family history/Genetic predisposition	▸ Physical inactivity
▸ Ethnicity	▸ Disturbances in intrauterine development/prematurity
▸ History of gestational diabetes (GDM)	▸ Impaired fasting glucose (IFG)/Impaired glucose tolerance (IGT)
▸ Polycystic ovary syndrome (PCOS)	▸ Metabolic syndrome (MetSy)
	▸ Dietary factors
	▸ Diabetogenic drugs
	▸ Depression
	▸ Obesigenic/diabetogenic environment
	▸ Low socio-economic status

The degree of risk for the individual of developing T2DM is principally determined by the number and severity of risk factors.

Gillett et al. emphasized the importance of overweight and obesity as a risk factor for developing T2DM (Gillett et al., 2012). Especially central adiposity – measured by waist circumference – has been shown to be a predictor of risk for developing T2DM (Diabetes Prevention Program Research Group, 2006). Moreover, central adiposity is a particular risk even in people with normal BMI (Han et al., 2006).

In a Canadian study Hart et al. investigated the relationship between BMI in middle age and risk of T2DM using data from large prospective studies. Compared with the normal weight group the odds ratios for incident diabetes in men, adjusted for age, social class, smoking and systolic blood pressure, were 2.56 (95% CI 1.91–3.42) and 6.48 (95% CI 4.65–9.03) in the overweight and the obese group, respectively. In women the numbers were 2.54 (95% CI 1.94–3.32) and 5.43 (95% CI 4.07–7.26), respectively (Hart et al., 2007).

Mozaffarian et al. investigated the impact of a combination of five lifestyle factors on the incidence of new-onset T2DM in an older general population (Mozaffarian et al., 2009). Included lifestyle factors were physical activity level, dietary score

composed of fibre intake, fat quality and mean glycemic index, smoking status, alcohol use and body weight (BMI and measures of waist circumference). They found that "..after adjustment for age, sex, race, educational level, annual income and other lifestyle factors simultaneously, each lifestyle risk factor was independently associated with incidence of diabetes, with 26%, 31%, 23%, 34%, 45%, and 46% lower risk among older adults in the low-risk groups for physical activity level, dietary habits, smoking habits, alcohol use, BMI, and waist circumference, respectively." (Mozaffarian et al., 2009, p. 801). Participants who were in the low risk group for several lifestyle factors (physical activity, dietary score, smoking and alcohol habits) reduced their risk for incident diabetes by 82% (relative risk 0,18; 95% CI 0.06- 0.56) compared to all other participants.

3.1.3 Definition of high-risk individuals

In the literature no generally acknowledged definition of individuals at high risk for developing T2DM could be found. However, people with IFG and/or IGT are usually considered to be at high risk although the progression rates from IFG and IGT to T2DM differ between studies in different populations (Gillett et al., 2012). Age, baseline levels of FPG, 2-hour glucose levels, HbA1c, grade of central adiposity and BMI have been found to be predictors of progression (Gillett et al., 2012). A report issued by the Agency for Healthcare Research and Quality (AHRQ) in 2005 found consistent evidence that IFG and IGT are both indicators for an increased risk for developing T2DM and calculated pooled relative risks. In people with IGT it was 6.02 (95% CI 4.66 to 7.38), in people with IFG it was 4.70 (95% CI 2.71 to 6.70) and in people with IFG and IGT it was 12.21 (95% CI 4.32 to 20.10) compared to the NGT groups (Santaguida et al., 2005). In addition the authors calculated estimates for the attributable risk in the exposed groups (exposure being IGT, IFG or combined IGT&IFG) over the entire study duration in more than 30 studies for the progression to T2DM. The numbers reported were AR for the IGT group: 52.8% to 97.0%, for the IFG group: 57.3% to 86.9% and for the combined IGT & IFG group: 78.6% to 93.0%. Thus the authors concluded that …"if there is a causal relationship between IFG or IGT and progression to DM, as many as 97% of cases of DM within the IGT group could be prevented by treating or eliminating dysglycemia." (Santaguida et al., 2005, p. 30).

In its position statement on the diagnosis and classification of diabetes mellitus from 2013 the ADA summarized categories of increased risk for diabetes as shown in table 3, emphasizing that the evaluation of a patient's risk should also

incorporate a global risk factor assessment for diabetes and cardiovascular disease (ADA, 2013).

Table 3: Categories for increased risk for diabetes* (ADA, 2013, p. S13)

FPG 100 mg/dl (5.6mmol/l) to 125mg/dl (6.9 mmol/l) [IFG] **or**
2-h PG in the 75-g OGTT 140 mg/dl (7.8mmol/l) to 199 mg/dl (11.0 mmol/l) [IGT] **or**
A1C 5.7–6.4%

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

Besides IGT and IFG some organizations also consider metabolic syndrome as a risk factor for the development of T2DM. In the German „Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes“ the organizations involved stated that the clinical manifestation of T2DM often occurs under the influence of risk factors which present in the form of the metabolic syndrome (BÄK et al., 2013). According to the authors the main characteristics of metabolic syndrome are: abdominal obesity (waist circumference in men > 94 cm, in women > 80 cm), insulin resistance, hyperinsulinemia, impaired glucose tolerance, dyslipidemia, albuminuria and hypertension (own translation from BÄK et al., 2013).

3.1.4 Prevalence of diabetes mellitus type 2 (T2DM)

According to the IDF the number of people with diabetes is increasing in every country. IDF estimated that in 2012 more than 371 million people suffered from diabetes worldwide (IDF, 2012). Almost 80 % of diabetes related deaths – 3.4 million annually - occur in low- and middle-income countries (WHO EUROPE, 2013). In the European Region prevalence rates are increasing among all ages mostly because of increases in overweight and obesity, unhealthy diet and physical inactivity (WHO EUROPE, 2013). It is estimated that about 60 million people in the European Region live with diabetes, 10.3 % of men and 9.6 % of women aged 25 and over with substantial differences in the individual countries (WHO EUROPE, 2013; Thelen et al., 2013).

As there is no reporting obligation or central register for T2DM in Germany prevalence estimates have mostly been based on data from regional studies, health insurance companies or general practices assessed in the past. Up to date nationwide and population based data has only recently been provided by the telephone surveys “German Health Update” (GEDA 2009 and GEDA 2010)

(Heidemann et al., 2013). Data from GEDA 2009 showed a self-reported lifetime prevalence of diabetes in a population aged 18 and older and living in private homes of 8.8% (9.3 % in women and 8.2% in men). An extrapolation of these results to the adult population in Germany would amount to 5.98 million individuals having encountered diabetes over their lifetimes.

Current prevalence data have also recently been published on the basis of the German Health Interview and Examination Survey (DEGS), which has been conducted from 2008 to 2011 by the Robert Koch Institute (RKI) in Berlin (Heidemann et al., 2013). In a representative sample of the German population aged 18 to 79 in total 591 of the 7080 participants stated that they had been diagnosed with diabetes by a doctor at some point in life. Among the 591 cases were 8 with diabetes type 1 and 42 with gestational diabetes, which means that 91.5 % of reported diabetes cases were T2DM. Lifetime prevalence for different age groups stratified for gender is shown in table 4.

Table 4: Lifetime prevalence of known diabetes – data from the DEGS (Heidemann et al., 2013)

Tab. 1 Lifetime prevalence (percent, 95% confidence interval) of known diabetes according to gender and age groups. $N_{unweighted}$=7,080

Age group in years	18–39	40–49	50–59	60–69	70–79	Overall
Gender						
Female	3.7 (2.5–5.5)	4.5 (3.0–6.8)	4.0 (2.6–6.0)	10.7 (8.2–13.8)	21.8 (17.6–26.7)	7.4 (6.5–8.5)
Male	0.9 (0.3–2.3)	2.0 (1.1–3.7)	7.3 (5.3–10.1)	17.0 (13.1–21.7)	22.0 (17.6–27.2)	7.0 (6.0–8.1)
Overall	2.3 (1.5–3.4)	3.2 (2.3–4.6)	5.7 (4.4–7.2)	13.8 (11.4–16.6)	21.9 (18.7–25.5)	7.2 (6.5–8.0)

According to the results of DEGS lifetime prevalence of known diabetes is 7.2% (7.4 % for women and 7.0% for men). The results indicate that at least 4.6 million Germans aged 18 to 79 years have been diagnosed with diabetes at some point in life. For both sexes diabetes prevalence increases with age, rising from under 5% among those under 50 years of age to more than 20% of those being older than 70 (Heidemann et al., 2013). An increase in diabetes prevalence of comparable size with age has also been found in the GEDA 2009 (Heidemann et al., 2011).

Prevalence of diabetes was also higher in those with low socioeconomic status, especially in women as table 5 shows.

Table 5: Lifetime prevalence of known diabetes according to gender and socioeconomic status– data from the DEGS (Heidemann et al., 2013)

Tab. 2 Lifetime prevalence (percent, 95% confidence interval) of known diabetes according to gender and socioeconomic status. $N_{unweighted}$=7,012

Socioeconomic status	Low	Middle	High
Gender			
Female	11.6 (8.6–15.5)	7.4 (6.3–8.7)	3.0 (2.0–4.5)
Male	10.1 (7.5–13.5)	6.1 (5.1–7.4)	6.2 (4.6–8.3)
Overall	10.9 (8.8–13.5)	6.8 (6.0–7.7)	4.8 (3.7–6.0)

Socioeconomic status: index that includes information on school and vocational education, professional position and net household income (weighted by household needs)

When compared with data from the German National Health Interview and Examination Survey (GHNIES) from 1998, the DEGS study found an absolute increase in diabetes prevalence in the last decade of 2% (lifetime prevalence of 5.2% in GNHIES 98 and 7.2% in DEGS). After taking demographic aging into account a significant increase of 1.4% remains, meaning that only 0.6 % of the increase can be attributed to population aging (Heidemann et al., 2013). An increase in diabetes prevalence in the age group of 25 to 69 as well as in the adult population over the age of 18 in the last decade has also been verified by GEDA 2009 as shown in table 6 (Heidemann et al., 2011).

Table 6: Prevalence of diagnosed diabetes in the population aged 18 years and older (Heidemann et al., 2011).

Prävalenz des diagnostizierten Diabetes der 18-jährigen und älteren Bevölkerung (Prozent, 95 %-Konfidenzintervall)
Datenbasis: GSTel03 und GEDA 2009 (RKI 2010)

Geschlecht	2003* % (95 %-KI)	2009* % (95 %-KI)
Frauen	6,8 (5,9 – 7,8)	9,3 (8,5 – 10,2)
Männer	5,4 (4,6 – 6,2)	8,2 (7,5 – 9,0)

* gewichtet nach jeweiliger Repräsentativbevölkerung

3.1.5 Health risks resulting from hyperglycemia and T2DM

Hyperglycemia or T2DM can exist in an individual over a long period of time without symptoms, nevertheless these conditions are associated with substantial health risks (RKI, 2005; WHO, 1999).

In the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab) 10428 participants were followed up for a median of 5.2 years. After adjustment for well known CVD risk factors, individuals with known diabetes at baseline had an all-cause mortality risk that was 2 times greater than those with normal glucose tolerance (Barr et al., 2007). These findings have been confirmed in 2011 by a meta-analysis of 97 prospective studies with data on 123,205 deaths among 820,900 people (Emerging Risk Factors Collaboration (ERFC), 2011). The ERFC calculated a 1.80 (95% CI 1.71 to 1.90) HR for death from any cause among persons with diabetes compared to non-diabetics and a 2.32 HR (95% CI 2.11 to 2.56) for death from vascular causes, respectively. The authors estimated that a 50-year-old person with diabetes died on average 6 years earlier than a person without diabetes. About 40% of excess deaths in diabetes patients were attributable to nonvascular deaths (ERFC, 2011). Figure 1 shows the estimated future Years of Life Lost (YLL) owing to diabetes depending on the age of onset.

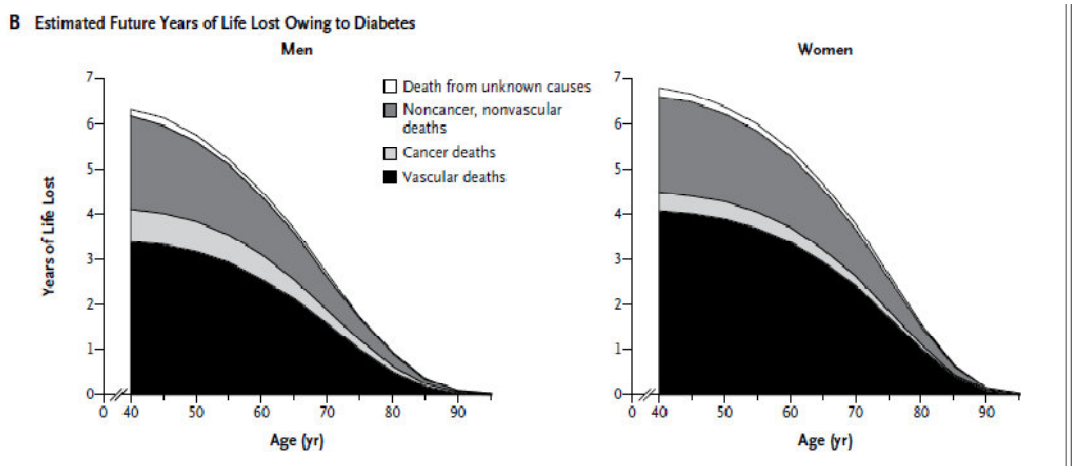

Figure 1: Estimated numbers of YLL owing to diabetes (ERFC, 2011, p. 838)

However, not only diabetes mellitus increases mortality rates but also milder forms of impaired glucose metabolism. As early as in 1999 Coutinho et al. found a progressive relationship between fasting glucose levels and cardiovascular risk for glucose levels well below the diabetes threshold in a systematic overview and meta-regression analysis of cohort studies of non-diabetic individuals (Coutinho et

al, 1999). "…compared with the reference fasting glucose of 4.2 mmol/l (75 mg/dl), a fasting glucose of 6.1 mmol/l (110 mg/dl, the threshold value for the classification of impaired fasting glucose [10]) was associated with a relative risk of cardiovascular events of 1.33 (95% CI 1.06–1.67); a 2-h glucose of 7.8 mmol/l (140 mg/dl, the threshold value for impaired glucose tolerance) was associated with a relative risk of cardiovascular events of 1.58 (95% CI 1.19–2.10)." (Coutinho et al, 1999, p. 237).

Mortality from all causes was also increased in those with IGT and IFG at baseline in the AusDiab study but to a lesser extent than those with known T2DM at baseline. Also CVD mortality was significantly higher in those with T2DM and IFG at baseline, but not in those with IGT (Barr et al., 2007). The authors concluded that there is a "…strong association between abnormal glucose metabolism and mortality, and it suggests that this condition contributes to a large number of CVD deaths in the general population." (Barr et al., 2007, p. 151). They suggest that CVD prevention strategies should address not only people with T2DM but also those with milder forms of hyperglycemia (IFG and IGT) (Barr et al., 2007).

Considering the threshold for IGT, other studies have shown that there is an increase in risk for cardiovascular disease and mortality below the IGT treshold of 7.8 mmol/l (THE DECODE STUDY GROUP, 2003; Levitan et al., 2005). Also the WHO after reviewing the literature came to the conclusion that "…the risk of future diabetes, premature mortality and cardiovascular disease begins to increase at 2–h plasma glucose levels below the IGT range." (WHO, 2006, p. 19) Therefore the WHO experts recommended to consider "…replacing this category of intermediate hyperglycaemia by an overall risk assessment for diabetes, cardiovascular disease, or both, which includes a measure of glucose as a continuous variable." (WHO, 2006, p. 19).

In summary the WHO experts concluded that…"there are an abundance of data indicating that hyperglycemia is harmful. However there are limitations in the data and the methodologies used to derive cut-points at which this level of harm is specifically increased and which clearly differentiate diabetes from non-diabetes" (WHO, 2006, p. 12). According to WHO the main problem is "…placing a specific cutpoint on a continuous variable." (WHO, 2006, p.13).

Besides increases in mortality risk long-term damage, dysfunction and functional limitations of various organs - especially the eyes, kidneys, nerves and the cardiovascular system - can be the result of chronic hyperglycemia in diabetes (BÄK et al., 2013; RKI, 2005). Diabetes mellitus type 2 "..is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease) and diminished quality of life" (WHO, 2006, p. 5).

3.1.6 Impact on Health Related Quality of Life (HRQoL)

Diabetes patients experience reduced HRQoL compared with people with no chronic disease. The presence of diabetes-related complications worsens HRQoL even more (Rubin and Peyrot, 1999). Reductions in HRQoL are associated with difficulties in performing everyday tasks like walking, climbing stairs or bending and reduced scores in "vitality" and "general heath" in the SF36 questionnaire (Tapp et al., 2006). However, HRQoL can be reduced even before the diagnosis of diabetes mellitus especially in those with IGT (Tapp et al., 2006). Tapp et al. found "…a gradual decrease in quality of life across categories of glucose tolerance status" in a cross-sectional study with 10334 participants in Australia, for whom data on the SF-36 questionnaire were available (Tapp et al., 2006, p. 158). People with IGT generally had a lower score in different dimensions of HRQoL compared to individuals with NGT. However, compared to individuals with known T2DM the mean quality of life scores for bodily pain, general health perception, physical functioning, vitality and other dimensions were higher in the IGT group (Tapp et al., 2006).

3.2 The Concept of Health Literacy and its implications for Evidence Based Health Information (EBHI)

In conjunction with the increasing importance of EBM the concept of health literacy on the patients` side has become of growing interest in the last decade. Health literacy has been defined by the Institute of Medicine (IOM) in 2004 as follows: “Health literacy is the degree to which individuals can obtain, process and understand basic health information and services they need to make appropriate health decisions.” (IOM, 2004, p. 1).

Apart from statistical literacy – that is the ability to understand the meaning of numbers, proportions and probabilities – as a basic prerequisite, other social competencies and skills are fundamental to the concept of health literacy (Miron-Shatz et al., 2011). A broader definition published by the WHO in 2010 described health literacy as “…the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways which promote and maintain good health. Health Literacy means more than being able to read pamphlets and successfully make appointments. By improving people's access to health information and their capacity to use it effectively, health literacy is critical to empowerment. Defined this way, Health Literacy goes beyond a narrow concept of health education and individual behaviour-oriented communication, and addresses the environmental, political and social factors that determine health.” (WHO, 2010)

Among the cognitive and social skills mentioned in the definition are a basic understanding of scientific concepts, the knowledge about the inherent element of uncertainty in scientific findings, the ability to judge the information source as credible or not and the understanding, that health information is interpreted differently depending on the beliefs, customs and social norms of different sub-groups of society (Miron-Shatz et al., 2011).

However, health literacy in this comprehensive sense is rather the exception than the rule among citizens or patients (see Gaissmaier & Gigerenzer, 2011 and Miron-Shatz et al., 2011). Advocates for the improvement of health literacy expect benefits in two areas: ethics and economics. The ethical aspect of the discussion about patient rights and health literacy has been reflected in the German legislation. According to German law citizens and patients have the right to comprehensive information concerning their health and disease status as well as

understandable communication of the information (BMG, 2003). In February 2013 these rights have been summarized in a dedicated patient rights law (BMJ, 2013).

Closely linked with the ethical imperative of patient information are economic considerations. Miron-Shatz et al. pointed out: “Since the Age of Enlightenment, efforts have focused on educating citizens for their personal and the greater societal good. ..., efforts to increase health literacy have been advocated as a necessary condition for a better educated population – one capable of making appropriate and informed health decisions and engaging in recommended health behaviors.” (Miron-Shatz et al., 2011, p. 209) These considerations are supported by findings that show “… that individuals with limited health literacy incur up to four times greater cost in unnecessary doctor visits and hospital care, compared to individuals with average health literacy. Increasing health literacy has been associated with a number of positive outcomes: improved decision making, better understanding of disease and treatment regimens, and adherence to prescribed treatment options. It is thus possible that increased health literacy could translate to lower costs…” (Miron-Shatz et al., 2011, pp. 209-210). Also the IOM stated in its report from 2004: “Although causal relationships between limited health literacy and health outcomes are not yet established, cumulative and consistent findings suggest such a causal connection….Studies have shown that people with low health literacy understand health information less well, get less preventive health care—such as screenings for cancer—and use expensive health services such as emergency department care more frequently.” (IOM, 2004, p. 1)

The comprehensive concept of health literacy outlined here also implies some basic requirements for EBHI, which have been summarized in the German publication “Gute Praxis Gesundheitsinformation” by Klemperer et al., 2010. The key issues are listed in table 7.

Table 7: Key requirements for evidence based health information (EBHI) according to “Gute Praxis Gesundheitsinformation” (own translation) (Klemperer et al., 2010)

- The content must be based on the best available evidence.
- EBHI rely on systematic search, selection, critical appraisal and review of the existing literature with the aim to reduce bias and to take into account the reliability of the results.
- The absence of sufficiently strong evidence should be mentioned.
- The information must be relevant for the target group and comprehensible.
- Citizens, healthcare users or appropriate organizations should be involved.
- Information on diseases should draw a realistic picture of the knowledge, the frontiers of knowledge, the causes, the diagnosis and the progression of the disease, coping strategies as well as the existing prevention, early detection and treatment options.
- Information on treatment results should focus on patient relevant outcomes (e.g. mortality, morbidity, health related quality of life).
- For the individual harm-benefit-assessment comparison of different treatment options are sensible including the no treatment option.
- Health information should be formulated in a non-directive way to allow the user to decide in accordance with his or her own values and preferences.
- The numerical representation of probabilities is useful if reliable data are available. For the representation of probabilities the absolute change in risk is of primary importance.

For the communication of risks the following recommendations are made:

- Starting point of the information should be the natural course of disease. This includes the probability that the clinical picture improves, worsens or remains constant without intervention and how often undesired outcomes occur.
- Changes in risks should be communicated as absolute risk reduction.
- The exclusive representation of relative risk reduction is unsuitable, because large effects cannot be distinguished from small effects.

- Different framing of identical numbers can lead to differences in the perception of risks and the motivation of patients.
- It might be appropriate to combine different representations of risks e.g. absolute risk, relative risk, number needed to treat, graphs or comparisons with everyday risks. (Klemperer et al., 2010, p. 67, own translation).

3.3 The Institute for Quality and Efficiency in Health Care (IQWIG)

3.3.1 Legal basis and responsibilities

The IQWIG was founded within the German Health Care Reform of 2004 as an institution which is supposed to improve quality and efficiency in health care within the German statutory health insurance. Its legal basis has been anchored in Social Code Book V, its responsibilities are described in detail in § 139a of SCB V and can be summarized as follows:

- "Search for, assessment and presentation of current scientific evidence on diagnostic and therapeutic procedures for selected diseases;
- Preparation of scientific reports, expert opinions, and comments on quality and efficiency issues of SHI services, taking age, gender, and personal circumstances into account;
- Appraisal of evidence-based clinical practice guidelines (CPGs) on the most relevant diseases from an epidemiological point of view;
- Issue of recommendations on disease management programmes (DMPs);
- Assessment of the benefit and cost of drugs;
- **Provision of easily understandable information for all patients and consumers on the quality and efficiency of health care services, as well as on the diagnosis and treatment of diseases of substantial epidemiological relevance.**"

(IQWIG, 2011 p. 1; emphasis added)

As pointed out in the Institute`s method paper, the IQWIG is legally obliged by § 139a (4) SCB V to conduct its assessments on the basis of the internationally agreed upon standards of EBM (IQWIG, 2011). The concept of EBM has been defined by Sackett et al. in 1996 as follows: "Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based

medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research." (Sackett et al., 1996). However, as the “best available evidence is often incomplete or unreliable” (IQWIG, 2011, p 4) assessments in accordance with EBM standards aim at determining uncertainty and describing it in terms of evidence levels. This is supposed to help clinicians and their patients to make informed decisions, also taking into account their own personal values (IQWIG, 2011).

According to §139b SCB V only the Federal Joint Committee (Gemeinsamer Bundesausschuss) or the Federal Ministry of Health are allowed to commission the IQWIG. In addition and in accordance with the institute`s legal remit to provide health information, the IQWIG itself can choose topics for or translate commissioned reports into health information for consumers and patients (IQWIG, 2011).

As the need for health information is potentially limitless, prioritizing is necessary. In line with the IQWIG`s responsibility to provide information about diseases with substantial epidemiological relevance, diseases with a high burden of disease are favored. These could be diseases with high mortality, incidence or prevalence, utilization of health care services or high treatment costs. Also absence from work due to illness and loss in quality of life of those affected by the disease could be relevant criteria. Furthermore, the IQWIG tries to find out and take into account what consumers and patients might be interested in by using different information sources like surveys, qualitative research and topics suggested by self help groups or users of the website. Priority is also given to questions for which evidence based answers exist (IQWIG, 2011).

Health information for patients and consumers are provided by the IQWIG Department of Health Information using a defined method of evidence retrieval and different publishing formats.

3.3.2 IQWIG Health Information

3.3.2.1 Objectives and Characteristics

The IQWIG Department of Health Information aims to improve health and patient autonomy by increasing health and scientific literacy. Published health information is therefore meant to:

- "Support active and informed decision-making about health issues;
- Promote the critical use of health care services;
- Improve understanding of physical, mental and emotional health;
- Improve understanding of medical and scientific information, including the concept of evidence-based medicine; and
- Enable support of patients by family and friends." (IQWIG, 2011, p. 69)

To reach these goals the IQWIG considers it necessary …"to to be a reliable, trusted and patient-centred information provider" (IQWIG, 2011, p. 69) which aims at integrating patient values in decision-making into EBHI. Consequently the IQWIG gives a comprehensive definition of EBHI; the characteristics are summarized in table 8.

Table 8: Characteristics of EBHI according to the IQWIG Handbook of "General Methods" version 4.0 of 23.09.2011. (IQWIG, 2011, p. 69)

- "The content is based on clear scientific evidence, particularly systematic reviews;
- The information is developed following systematic methods which aim to minimize bias and maintain neutrality;
- Evidence-based communication techniques are used to meet the goals of informing, supporting and empowering users;
- Uncertainties as well as the potential for benefit and harm are discussed;
- Language and framing are neutral and non-directive, so that people can make their decisions in accordance with their own values; and
- The information is updated so that it remains evidence-based."

As pointed out the IQWIG puts special emphasis on the requirement to only communicate findings with clear scientific evidence. Therefore the institute`s health

information products rely to a large extent on results of systematic reviews, which have to fulfill certain minimum quality requirements in order to minimize methodological flaws (details see chapter 3.3.2.4).

3.3.2.2 Patient-centered communication

A key challenge for the IQWIG Department of Health Information is to provide information, which is comprehensible for different target groups in the population while at the same time remaining scientifically accurate and objective. This challenge is increased by the fact, that (health) literacy levels show a great variation throughout the potential readers of the information (IQWIG, 2011).

However, the IQWIG "…aims at a readability below university level." (IQWIG, 2011, p. 84) and uses test readers and reader ratings as a measure to assess understandability (IQWIG, 2011).

In addition the IQWIG Department of Health Information is committed to a non-paternalistic model of patient communication. Its goal is not only to inform patients, but also strengthen them in their patients' autonomy. Key values the IQWIG tries to take into account are therefore:

- "Demonstrate sensitivity and respect for user knowledge, values and concerns, autonomy, cultural differences as well as gender, age and disability-related interests,
- Maintain a patient-centred, non-judgmental, non-directive and neutral style of language; and
- Respect readers' time." (IQWIG, 2011, p. 86)

To address the different needs of consumers the IQWIG produces health information in different formats: Fact sheets for an easy to understand, short information, feature articles providing comprehensive information and research summaries, which usually present the results of systematic reviews or larger studies. Fact sheets and research summaries focus mainly on the effects of treatments, diagnostic tests and self-management strategies, topics that are known to be of major interest to most people seeking health information. Preventive and health promotion measures like changes in diet and physical activity are included into the information product if they are regarded relevant for the individual topic (IQWIG, 2011).

In order to make the website more attractive to users, increase understanding of medical issues and support self-management strategies, supplementary items like graphics, short animated films, interactive quizzes, calculators, online polls and patient stories round off the information offered by the IQWIG Department of Health Information (IQWIG, 2011).

3.3.2.3 Patient relevant outcomes

The benefit assessment of medical interventions and treatments and the communication of the results is a predominant duty of the IQWIG. The assessment of benefit "…is based on the results of studies investigating the effects of an intervention on patient-relevant outcomes." (IQWIG, 2011, p. 28). The term "patient-relevant" relates to the patients` feelings, their functioning and their survival so usually mortality, morbidity and health-related quality of life (HRQoL) are considered as patient-relevant outcomes (IQWIG, 2011). In line with § 35b of the German Social Code Book the following outcomes, which are related to patient benefit, are especially considered by the IQWIG: Improvement of health status, reduction of disease duration, increase in life expectancy, reduction of adverse effects and improvement of quality of life (IQWIG, 2011; SCB V § 35b, 2013). For topic-related definition of patient-relevant outcomes the IQWIG involves individuals affected by the disease in question and representatives of patient organizations (IQWIG, 2011).

In contrast to patient-relevant outcomes surrogate parameters are frequently used in clinical trials, because they provide results in a shorter period of time and with less efforts and costs (IQWIG, 2011; Wieczorek et al., 2008). A surrogate marker can be defined as a substitute for a patient-relevant, clinically meaningful endpoint and is expected to predict the therapeutic effect of an intervention (Katz, 2004). Table 9 shows patient-relevant outcomes and surrogate markers often used in clinical trials with diabetic patients.

Table 9: Patient-relevant and surrogate endpoints in diabetes (Wieczorek et al., 2008, p. 131).

Patient-important (clinically important) endpoints	Surrogate endpoints
Mortality	Glycated hemoglobin level
Quality of life	Postprandial glycemia
Macrovascular complications	Fasting plasma glucose
Myocardial infarction	
Coronary heart disease	
Cerebral stroke	
Cardiovascular death	
Peripheral vascular disease (incl. amputation, claudication)	
Microvascular complications	
Blindness	
End-stage renal disease	
Foot ulceration	

Due to the fact that surrogate markers can be misleading the IQWIG only accepts surrogate endpoints of clinical trials for their health information products if they have been validated beforehand. However, there is no standard procedure or generally accepted method for surrogate endpoint validation (IQWIG, 2011).

In respect to the primary prevention of T2DM in high-risk individuals the IQWIG argues that the prevention or delay of diabetes diagnosis as such might not be a patient-relevant outcome but should be considered a surrogate marker. The main reasons for these considerations are that the diagnosis of T2DM relies on cut-points for hyperglycemia, which have been derived from data and methodologies with limitations (see chapter 3.1.5) and additionally that health risks increase below the cut-points for T2DM and even below the cut-points for IGT.

3.3.2.4 Method of information retrieval: systematic literature research, screening and quality assessment

As mentioned before the basis for health information products are usually systematic reviews which are identified by the IQWIG in a systematic literature search. Before conducting the systematic literature research, a project outline is prepared to inform the IQWIG Department of Information Management about the background and objectives of the research. It also provides information about the results of an explorative literature search which is used to identify search terms and formulate a search strategy for the bibliographic databases (IQWIG, 2011). “As a quality assurance step, it is tested whether the search strategy developed in this way identifies known relevant primary publications (test set) with sufficient certainty.” IQWIG, 2011, p. 95). Furthermore, the project outline defines the following aspects of the search:

1. The inclusion criteria with regard to
   - target population, intervention, control group and outcome
   - study design
   - formal characteristics of the publication (e.g. language, time of research, publication type, quality of review)
2. The databases included in the search.

The defined criteria are summarized in a PICO scheme (IQWIG, 2011).

The results of the systematic search usually comprise a lot of citations which are not relevant for the research question. Screening and selection of relevant publications follows a two-step approach. In the first step two independent reviewers exclude irrelevant publications by using title and abstract information. Publications which do not meet the inclusion criteria defined in the project outline are excluded. For the remaining publications full texts are obtained, which form the decision basis for inclusion or exclusion. Full texts are again assessed by two independent reviewers and disagreement is consented by discussion (IQWIG, 2011).

Identified systematic reviews will then be quality assessed with Oxman and Guyatt´s validated quality index for systematic reviews in order to minimize the risk of bias and methodological flaws. “The Institute only uses systematic reviews on the effects of an intervention for their health information if they fulfill

certain minimum requirements, which means that they are only allowed to have few methodological flaws according to the Oxman and Guyatt Index." (IQWIG, 2011, p. 81) A description of the validation procedure for the Oxman and Guyatt Index can be found in Oxman & Guyatt, 1991 and an application form of the Oxman & Guyatt index used by the IQWIG is available in appendix 1. Systematic reviews which are rated with an O&G Index ≥ 5 are considered to be of sufficient methodological quality and can form the basis for the IQWIG health information. "When more than one systematic review of adequate methodological quality addresses a particular subject or outcome, a further quality assessment is carried out." (IQWIG, 2011, p. 81) Aspects considered inter alia are the main content of the review in relation to the research question and the comprehensiveness and actuality of the search (IQWIG, 2011).

4 Methods

4.1 Literature Research

As described in chapter 3.3.2.4 the search for evidence for IQWIG health information products follows a predefined methodology. This methodology was also used for the master thesis and is described in this section in detail. In order to precisely define the research question a PICO scheme was developed. This was done in close collaboration and consultation with Dr. Martina Ehrlich and Dr. Klaus Koch from the IQWIG Department of Health Information. The PICO scheme is shown in table 10.

Table 10: PICO scheme for the literature research

Inclusion Criteria		
Population	Adults (≥ 18 years) without diagnosis of diabetes mellitus before entering study and with elevated risk of diabetes mellitus type 2 defined by study (e.g. Impaired Glucose Tolerance, elevated fasting blood glucose, obesity)	E1
Intervention	lifestyle intervention including change in diet and/or physical activity	E2
Control	General advice/usual care, pharmacological treatment, no treatment	E3
Outcome	Diagnosis of T2DM, period until diagnosis of T2DM, overall mortality, cardiovascular morbidity and mortality, microvascular diseases, quality of life or clinical parameters (reduction in blood glucose, blood pressure, BMI)	E4
Study Type	Meta-analysis or systematic review of controlled studies (CT`s), HTA	E5
Time of Research	The research was conducted in 2009 or later.	E6
Publication Language	English or German	E7
Publication	Full-text publication available/ procurable	E8
Oxman & Guyatt	Quality of Reviews according to O & G ≥ 5	E9
Scope	Topic / issue relevant	E10

Minimal inclusion criteria: E1-E8 plus E10

As pointed out no generally accepted definition of high-risk individuals for T2DM exists. Therefore the definition of the population in the PICO allowed for a broad range of groups “as defined by study”. Also the defined outcomes were

quite broad and included several outcomes of interest: For the research question of this master thesis prevention and/or delay of diabetes diagnosis was the most important outcome. The IQWIG institute was especially interested in patient relevant outcomes like overall mortality, cardiovascular morbidity and mortality, microvascular diseases and quality of life. Clinical parameters (surrogate endpoints) like reduction in blood glucose, blood pressure and BMI were included, because before the search was carried out it was unclear whether or not enough high-level evidence on the other outcomes would be retrieved.

The systematic literature research was conducted by the IQWIG Department of Information Management. To precisely inform the staff about the background and intention of the research project, a project outline was written (see appendix 2). This outline included information about the project topic, the definition of lifestyle changes in the context of this research, the PICO, the databases used for an explorative literature research and the results of this research. The explorative literature research was intended to be used as a test set for the systematic literature research. The project outline also defined the online databases that were to be used for the systematic literature review. These were Medline (Ovid), Cochrane Library, DARE and PubMed.

4.2 Screening, selection of reviews and grading with the Oxman & Guyatt Index

The literature research identified 710 data records. They were independently reviewed based on title and abstract information by Martina Ehrlich (IQWIG) and Karin Riemann-Lorenz. Disagreement was found in 42 cases and a consensus was arrived at through discussion. For 47 data records full texts were obtained and again independently reviewed. One additional systematic review and meta-analysis was identified through a manual search of the NICE website. As a first step all articles were analyzed for meeting the inclusion criteria E1-E8 and E10. Nine reviews met these criteria and were quality assessed according to the Oxman and Guyatt Index by Martina Ehrlich and a second reviewer of the IQWIG. Five of the nine systematic reviews yielded an Oxman and Guyatt Index below 5 and thus have been excluded. In the end 4 systematic reviews of controlled trials that matched all the inclusion criteria defined in the PICO scheme were identified. A flow chart of the screening process is shown in Figure 2.

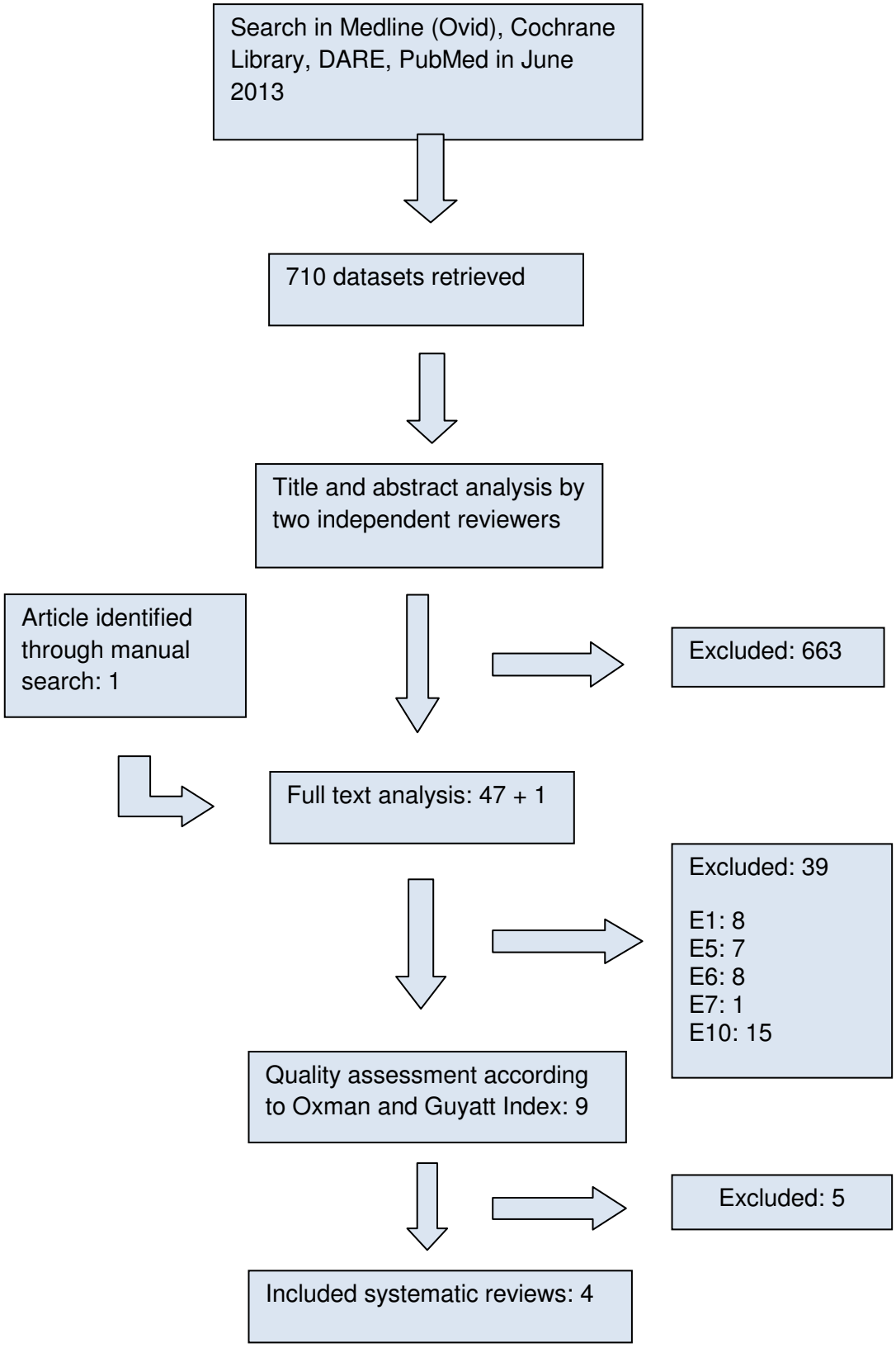

Figure 2: Flow chart of screening process

A list of the 44 full text articles, which were excluded in the second step of the screening process, as well as the reasons for exclusion can be found in appendix 3.

5 Results

5.1 Identified Systematic Reviews

The systematic literature research, screening process and quality assessment identified the following 4 systematic reviews:

- Dunkley A.J., Charles, K., Gray, L.J., Camosso-Stefinovic, J., Davies, M.J., Khunti, K. (2012) Effectiveness of interventions for reducing diabetes and cardiovascular disease risk in people with metabolic syndrome: systematic review and mixed treatment comparison meta-analysis. Diabetes, Obesity and Metabolism, 14(7), 616-625.
- Jones, R., Freeman, C., Johnson, M., Stevens, J., Buckley Woods, H., Guillaume, L., Gillies, C., Goyder, E., Chilcott, J., Payne, N. (2011) Preventing the progression of pre-diabetes to type 2 diabetes in adults. Systematic review and meta-analysis of lifestyle, pharmacological and surgical interventions, ScHARR Public Health Collaborating Centre, retrieved from http://www.nice.org.uk/guidance/index.jsp?action=download&o=57043 on 20th of September 2013
- LeBlanc, E.S., O'Connor, E., Whitlock, E.P., Patnode, C.D., Kapka, T. (2011). Screening for and Management of Obesity and Overweight in Adults. Evidence Report No. 89. AHRQ Publication No. 11-05159-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; October 2011
- Sumamo, E., Ha, C., Korownyk, C., Vandermeer, B., Dryden, D.M.(2011). Lifestyle interventions for four conditions: type 2 diabetes, metabolic syndrome, breast cancer, and prostate cancer. Rockville, MD, USA: Agency for Healthcare Research and Quality. AHRQ Technology Assessment Program. 2011.

The main characteristics and results of the systematic reviews are shown in table 11.

Table 11: Main characteristics and results of the systematic reviews included

Review	Time of Search	Specific Research Question (PICO)	Included Studies with Lifestyle Intervention on primary prevention of T2DM	O&G Score	Results /Conclusions of the authors	Ability to answer the research question/ Limitations
Dunkley et al., 2012	01/2010	**Effectiveness of interventions for reducing diabetes and cardiovascular disease risk in people with metabolic syndrome.** **P:** individuals with metabolic syndrome **I:** Lifestyle (Diet and Exercise), pharmacological therapy or surgery **C:** placebo, usual care or active control **O:** Incidence of T2DM, Cardiovascular Disease, reversal of metabolic syndrome Minimum follow up of 24 weeks	Meta-analysis performed for 13 studies (lifestyle and pharmacological) on reversal of metabolic syndrome. Only two studies included, which reported on T2DM incidence: • Bo et al., 2007 • Ramachandran et al., 2007 (IDPP)	6	LI and pharmacological interventions can reverse metabolic syndrome, but it remains unclear, if these benefits are sustained and translate into longer term prevention of T2DM and/or CVD. LI appear to be the most clinically effective. Evidence for reduction of T2DM incidence was found in two LI trials. .	Score: - **Limitations:** • Population restricted to individuals with metabolic syndrome. • Primary outcome "prevention of T2DM" only in 2 of 16 studies. • 3 studies with outcome "CVD event or mortality" but limited to pharmacological interventions

Abbreviations: LI = Lifestyle interventions, DPP=Diabetes Prevention Program, DPPRG = Diabetes Prevention Program Research Group, DPS=Diabetes Prevention Study, IDPP= Indian Diabetes Prevention Program

Table 11: Main characteristics and results of the systematic reviews included (con`t)

Review	Time of Search	Specific Research Question (PICO)	Included Studies with Lifestyle Intervention on primary prevention of T2DM	O&G Score	Results /Conclusions of the authors	Ability to answer the research question/ Limitations
LeBlanc et al., 2011 AHRQ	09/2010	**Effectiveness and harms of primary care-relevant weight-loss interventions for overweight and obese adults.** **P**: overweight or obese adults **I:** Behavioral or pharmacological interventions for weight loss **C**: usual care - no personalized intervention that would overlap with low-intensity intervention groups **O**: Weight loss and maintenance, improved health outcomes (morbidity from several diseases, emotional and physical functioning and mortality)	2 RCTs: Knowler et al., 2002 (DPP) Tuomilehto et al., 2001 (DPS)	6	Behaviorally based LI are safe and effective for weight loss and maintenance. Behaviorally based interventions which led to weight loss (4 to 7 kg) reduced diabetes incidence by about 30 to 50%. Data on effects of weight-loss on long-term health outcomes like CVD or death are insufficient.	Score: - **Limitations:** • Population of overweight and obese adults is a broader target group than high-risk individuals for T2DM. Not all of them must be considered as high-risk individuals. • Primary aim of inter-ventions was “weight loss” and not prevention of T2DM – so only 2 of 21 included behavioral interventions reported on T2DM incidence.

Abbreviations: LI = Lifestyle interventions, DPP=Diabetes Prevention Program, DPPRG = Diabetes Prevention Program Research Group, DPS=Diabetes Prevention Study, IDPP= Indian Diabetes Prevention Program

Table 11: Main characteristics and results of the systematic reviews included (con`t)

Review	Time of Search	Specific Research Question (PICO)	Included Studies with Lifestyle Intervention on primary prevention of T2DM	O&G Score	Results /Conclusions of the authors	Ability to answer the research question/ Limitations
ScHARR Review; Jones et al., 2011 , ScHARR Public Health Collaborating Centre	2011	**Effectiveness of lifestyle, pharmacological and surgical interventions for preventing the progression of pre-diabetes to type 2 diabetes in adults.** **P:** Individuals with IGT or IGF **I:** Lifestyle intervention, drugs or surgical interventions **C:** Standard advice, placebo **O:** Progression to T2DM	13 relevant RCTs: Jarrett et al., 1979 Pan et al., 1997 (Da Qing) Wein et al., 1999 Knowler et al., 2002 (DPP) DPPRG, 2009 Liao, 2002 Lindström et al., 2003+2006 (DPS) Kosaka et al., 2005 Ramachandran et al., 2006 (IDDP) Roumen et al., 2008 (SLIM) Penn et al, 2009 Li et al., 2008 Lindahl et al., 2009	6	Each type of lifestyle inter-vention can reduce the progress to diabetes in people with pre-diabetes. In a meta-analysis of 13 studies the pooled HR for lifestyle interventions was 0,51, 95% CI 0.43-0.62. A combination of diet and exercise appears to have more effect than diet or exercise alone.	Score: + Limitations: None

Abbreviations: LI = Lifestyle interventions, DPP=Diabetes Prevention Program, DPPRG = Diabetes Prevention Program Research Group, DPS=Diabetes Prevention Study, IDPP= Indian Diabetes Prevention Program

Table 11: Main characteristics and results of the systematic reviews included (con`t)

Review	Time of Search	Specific Research Question (PICO)	Included Studies with Lifestyle Intervention on primary prevention of T2DM	O&G Score	Results /Conclusions of the authors	Ability to answer the research question/ Limitations
Sumamo et al., 2011 (AHRQ)	03/2010	**Effectiveness of lifestyle interventions to control progression of T2DM, progression to DMT2 from metabolic syndrome or recurrence of breast and prostate cancer.** **P:** Individuals with MS, T2DM, breast and prostate cancer patients **I:** Exercise and Diet and one additional component (e.g. counseling, stress management). **C:** Usual care, diet or exercise alone or wait list. **O:** Progression of existing DMT2 (more medication, CVD etc.) progression of metabolic syndrome to DMT2, heart disease or stroke, recurrence of breast or prostate cancer.	4 relevant RCTs that reported on T2DM incidence, two of which also reported on CVD events: - Bo et al., 2007 - Knowler et al., 2002 (DPP) - Eriksson et al., 1999 (DPS) - Pan et al., 1997, (Da Qing) Meta-analyses were performed for surrogate parameters like blood pressure, change in diet and physical activity, weight loss etc.	7	Development of T2DM was significantly de-creased in the LI groups in 4 RCTs. In two studies this was also shown in long-term (10 and 20 years). No significant differences could be found for CVD-events and mortality in 2 studies (DPS und Da Qing) For different surrogate markers advantages could be shown for the LI groups (details see review p. 53-54)	Score: - **Limitations:** • Population restricted to individuals with metabolic syndrome. • Considerable hetero-geneity of LI, because additional component besides diet and exercise differed between interventions.

Abbreviations: LI = Lifestyle interventions, DPP=Diabetes Prevention Program, DPPRG = Diabetes Prevention Program Research Group, DPS=Diabetes Prevention Study, IDPP= Indian Diabetes Prevention Program

5.1.1 Overall results of identified systematic reviews

In general all systematic reviews came to the conclusion that lifestyle interventions can reduce diabetes incidence in high-risk individuals. LeBlanc et al. stated that behaviorally based interventions, which led to weight loss of 4 to 7 kg, reduced diabetes incidence by about 30 to 50% (LeBlanc et al., 2011). Sumamo et al. reported that development of T2DM was significantly decreased in the LI groups in 4 RCTs. In two studies this held true in long-term follow-up (10 and 20 years) (Sumamo et al., 2011). The systematic review of Dunkley et al. concluded that LI and pharmacological interventions can reverse metabolic syndrome, but that it remained unclear if these benefits are sustained and translate into longer term prevention of T2DM and/or CVD. LI appeared to be the most clinically effective. Evidence for reduction of T2DM incidence was found in two LI trials (Dunkley et al., 2012). The results of the ScHARR review will be described in detail in chapter 5.1.2.

However, the overview table also reveals that the systematic reviews showed considerable differences, most of which can be attributed to the broad definitions of population and outcomes in the PICO used for the systematic literature research. Two of the systematic reviews (Dunkley et al., 2012 and Sumamo et al., 2011) used the metabolic syndrome as the qualifying condition to identify individuals at high risk of developing T2DM. The systematic review of LeBlanc et al. included RCTs that considered overweight and obese individuals as having a high risk for diabetes whereas the ScHARR review included all RCTs that defined high-risk individuals by IGT (LeBlanc et al., 2011, Jones et al., 2011). Furthermore, it becomes obvious that in addition the range of included outcomes differs among the reviews. Besides incidence of T2DM the systematic reviews of Dunkley et al., 2012, LeBlanc et al., 2011 and Sumamo et al., 2011 also listed surrogate parameters like weight loss and physical functioning, reversal of metabolic syndrome and endpoints like mortality, CVD mortality and CVD morbidity as outcomes of interest in their PICO schemes. Three systematic reviews (Dunkley et al., 2012; the ScHARR Review 2011 and LeBlanc et al., 2011) assessed not only the effectiveness of LI but also the effectiveness of pharmacological interventions for different outcomes. As the authors provided information on LI separately from information about drug interventions, it was nevertheless possible to include the reviews.

Consequently the systematic reviews also differ in the RCTs included in their investigations. Dunkley et al. included only two studies, which reported on T2DM incidence (Bo et al., 2007 and Ramachandran et al., 2007 (IDPP)). Sumamo et al. (AHRQ) found 4 relevant RCTs that reported on T2DM incidence (Bo et al., 2007; Knowler et al., 2002 (DPP); Eriksson et al., 1999 (DPS); Pan et al., 1997, (Da Qing)), two of which also reported on CVD events. LeBlanc et al. included 2 RCTs (Knowler et al., 2002 (DPP) and Tuomilehto et al., 2001 (DPS)). In contrast the ScHARR review by Jones et al. discovered 13 RCTs that matched their inclusion criteria (details see table 11).

In summary one can say that due to the broad definitions of population and outcomes used in the PICO for the systematic literature research of this master thesis, the retrieved systematic reviews differ in the specific research question they try to answer and in scope.

In order to identify the systematic review which has the best ability to answer the research question of this thesis, scoring has been necessary. Systematic reviews, which fell within the PICO but had limitations in answering the research question, were scored: - . Limitations could inter alia be

- a narrow definition of the study population, which resulted in evaluating the effectiveness of LI on the prevention of T2DM in only a certain subgroup of high-risk individuals or a very broad definition which led to the inclusion of subjects other than high-risk individuals in the RCTs

and/or

- prevention of T2DM being not the only and not the most important primary outcome of the systematic review.

Systematic reviews that had no such limitations were scored: + and considered the most suitable for answering the research question of this master thesis. The result of this assessment is provided in table 11, last column. The assessment shows that the ScHARR review performed by Jones et al. in 2011 is considered to be the most suitable to answer the primary research question of this master thesis. Hereafter only the results of this systematic review will be provided in detail.

5.1.2 The ScHARR Review

The ScHARR Review by Jones et al. comprises several aspects, which are not within the scope of this master thesis. Among them are a meta-analysis of the effectiveness of pharmacological interventions, an assessment of the effectiveness of interventions especially for South Asian populations and an estimation of a treatment ranking, which might be interesting for the evidence based patient information by the IQWIG. However, these aspects will not be discussed in this master thesis.

5.1.2.1 Methods

Jones et al. performed a systematic literature research in several databases (Medline In Process and Other Non Indexed Citations and Medline 1950-Current via OVID SP, Embase via OVID SP, Cochrane Library (DARE, CENTRAL, HTA) via Wiley, CINAHL via EBSCO, BNI via OVID, Science and Social Science Citation Indices via Web of Knowledge, PsycINFO via OVID SP and EPPI Centre) and additionally searched for grey literature and on websites of relevant organizations (e.g. National Library for Public Health, Diabetes and Obesity Research Network (DORN)) (Jones et al., 2011). To be considered in the review studies needed to include subjects with pre-diabetes, lifestyle, drug or surgical interventions and development of T2DM as a required outcome measure. Search was limited to RCTs. Screening was done by two independent reviewers. In the end 26 articles were included in the review. All articles were quality assessed with the Jadad score and additionally with the NICE quality assessment criteria checklist. On the whole the authors judged the quality of papers as very good, with 21 papers being rated as very good (++), three as good (+) and two as poor (-). Thirteen studies or study subgroups from 11 RCTs, which provided enough data, were included in a meta-analysis.

5.1.2.2 Included RCTs

Basic characteristics and results of the RCTs included in the meta-analysis can be found in table 12. It becomes obvious that there is considerable clinical heterogeneity between the different RCTs in terms of study population, intervention characteristics, follow-up period and quality of the studies, which will be briefly summarized in the following section.

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002

Study (RCT)	Study/Author: Da Qing Study/ Pan et al., 1997 Country: China Quality: NICE ++
Population Characteristics	No of participants: 577 Definition of high risk: IGT Ethnicity: Chinese Mean age: 45 +/- 9.1 Mean BMI (kg/m^2): 25.8 +/- 3.8 % BMI ≥ 30: NR
Intervention	**Intervention groups**: diet only, exercise only, diet & exercise **Lifestyle change**: Diet: Low fat, high carbohydrate diet – weight loss recommended for people with BMI > 25 at a rate of 0.5-1.0 kg per month until they achieved a BMI of 23; participants were encouraged to consume more vegetables, control their intake of alcohol, and reduce their intake of simple sugars. Exercise: participants were encouraged to increase the amount of leisure physical exercise by at least one unit per day (such as slow walking for 30 minutes, fast walking for 20 minutes etc) and by two units per day if possible for those <50 years of age with no evidence of cardiovascular disease or arthritis. **Administration of advice**: individual and small group counseling; sessions were conducted weekly for one month, monthly for three months, and then once every three months for the remainder for 6 years **Behavioral change strategies**: NR
Control	General information about lifestyle and diabetes risk. No individual or group counseling.
Randomization	by clinical centre; cluster-randomization
Follow- up	6 years
Study attrition	8.1%

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: Da Qing Study/ Pan et al., 1997 con`t Country: China Quality: NICE ++
Primary Outcomes	**Incidence of T2DM:** Diet: 10.0 (95% CI, 7.5-12.5) per 100 person years Exercise: 8.3 (6.4-10.3) per 100 person years Diet & Exercise: 9.6 (7.2-12.0) per 100 person-years Control: 15.7 (95% CI 12.7-18.7) per 100 person-years **Relative Risk Reduction compared to Control after 6 years:** Diet: – 33% Exercise: – 47% Diet & Exercise: - 38% **Cumulative incidence of T2DM after 6 years** Exercise: 41% Diet 44% Diet & Exercise: 46% Control: 68%
Secondary Outcomes	**Weight loss:** Only the diet & exercise group had a mean weight loss of 1.77 kg , the other groups gained weight
Authors Conclusions	• Diet and/or exercise interventions led to a significant decrease in the incidence of diabetes over a six year period among those with IGT. • No benefit in terms of CVD or all-cause mortality maybe do to a lack of power

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: DPP/ Knowler et al., 2002 Country: US Quality: NICE ++
Population Characteristics	No of participants: 3234 Definition of high risk: IGT Ethnicity: 54,7% white, 19.9 % African, 15.7 % Hispanic, 5.3 % Am. Indian, 4.4% Asian Mean age: 50.6 +/- 10.7 y Mean BMI (kg/m^2): 34 kg/m^2 % BMI ≥ 30: 67,7%
Intervention	**Intervention groups:** diet & exercise AND standard advice + metformin **Lifestyle change:** Low fat, low calorie diet and moderate PA (≥ 150 min./week) and 7% weight loss **Administration of advice:** 16 individual sessions in 24 weeks, during maintenance phase offer of group sessions **Behavioral change strategies:** Yes. Goal-setting, self-monitoring, stimulus control, problem-solving and relapse prevention.
Control	Standard advice + placebo
Randomization	by clinical centre; cluster-randomization
Average follow- up	2.8 years
Study attrition	8%
Primary Outcomes	**Incidence of T2DM:** Diet & Exercise: 4.8 per 100 person years Metformin: 7.8 per 100 person years Control: 11 per 100 person years **Relative Risk Reduction compared to Control:** Diet & Exercise: - 58% (95% CI 48%-66%) Metformin: -31% (95% CI 17%-43%) **Cumulative incidence of T2DM after 3 years:** Diet & Exercise: 14.4% Metformin: 21.7% Placebo: 28.9% **NNT after 3 years:** Diet & Exercise: 6.9 (95% CI 5.4-9.5); Metformin: 13.9 (95% CI 8.7-33.9)

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: DPP/ Knowler et al., 2002 con`t Country: US Quality: NICE ++
Secondary Outcomes	• The advantage of LI over Metformin was greater in older persons and those with a lower BMI than in younger persons and those with a higher BMI. • 50% of the participants in the LI group achieved the goal of a 7% or more weight loss by the end of 24 weeks. • Participants in the lifestyle intervention group had a greater weight loss and a greater increase in leisure activity than the participants in the metformin and placebo groups. • The average weight loss was 0.12 kg in the placebo group, 2.1 kg in the metformin group and 5.6 kg in the lifestyle intervention group
Authors Conclusions	Lifestyle changes and treatment with Metformin both reduced the incidence of diabetes in persons at high risk. The lifestyle intervention was more effective than Metformin.

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: Diabetes Prevention Program Outcomes Study (DPPOS)/ Diabetes Prevention Program Research Group, 2009 Country: US Quality: NICE ++
Population Characteristics	No of participants: 2766 Definition of high risk: follow up of eligible participants from DPP with IGT Ethnicity: - Mean age: 55.2 +/- 10.3 y Mean BMI (kg/m^2): male: 31.1 + 5.9; female: 34.2 + 7.2 % BMI ≥ 30: -
Intervention	**Intervention groups:** diet & exercise AND standard advice + Metformin **Lifestyle change:** Low fat, low calorie diet and moderate PA (≥ 150 min./week)and 7% weight loss **Administration of advice:** 16 individual sessions in 24 weeks, during maintenance phase offer of group sessions **Behavioral change strategies:** Yes. Goal-setting, self-monitoring, stimulus control, problem-solving and relapse prevention.
Control	Standard advice + placebo
Randomization	by clinical centre; cluster-randomization
Average follow- up	10 years after DPP randomization
Study attrition	-
Primary Outcomes	**Relative Risk Reduction compared to Placebo:** Diet & Exercise: - 34% (95% CI 24%-42%); Metformin: -18% (95% CI 7%-28%) The lifestyle effect was greatest in participants aged 60–85 years at randomization (49% risk reduction), in whom metformin had no significant effect. The median delay to onset of diabetes was approximately 4 years by lifestyle and 2 years by metformin, compared with placebo.
Secondary Outcomes	At the most recent yearly examination, 23% in the lifestyle, 19% in the metformin, and 19% of participants in the placebo groups had become normoglycaemic by criteria defined and reported previously (fasting glucose <6.1 mmol/L, 2-h glucose <7.8 mmol/L, and no previous diagnosis of diabetes.
Authors Conclusions	During follow-up after DPP, incidences in the former placebo and metformin groups fell to equal those in the former lifestyle group, but the cumulative incidence of diabetes remained lowest in the lifestyle group. Prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years.

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: DPS/ Lindström et al., 2003 and update 2006 Country: Finland Quality: NICE ++
Population Characteristics	No of participants: 522 Definition of high risk: IGT Ethnicity: - Mean age: 55 +/- 7 years Mean BMI (kg/m^2): 31 % BMI ≥ 30: 96. 5% ♂; 66.3% ♀
Intervention	**Intervention groups**: Diet & Exercise **Lifestyle change**: Low-fat, high fibre diet, increase of PA and ≥ 5% weight loss **Administration of advice:** 15 individual sessions over 3 years with nutritionist. Group activities like cooking and supermarket visits encouraged. Printed material was used to illustrate the messages and to serve as a reminder at home. Individualized and supervised exercise sessions. Endurance exercise and moderate intensity resistance training sessions were also offered free of charge. **Behavioral change strategies:** Yes. Problem-solving
Control	General information about lifestyle and diabetes risk, but not individualized.
Randomization	Individual randomization at the first study visit after the screening phase
Average follow- up	3.2 years (active phase and post-intervention follow-up: 7 years)
Study attrition	8%
Primary Outcomes	**Incidence of T2DM after mean follow up of 7 years:** Diet & Exercise: 4.3 per 100 person years Control: 7.4 per 100 person years **Relative Risk Reduction after mean post follow up of 7 years:** Diet & Exercise: - 42% **Cumulative incidence of T2DM after 6 years:** Diet & Exercise: 23% Control: 38% **Absolute risk reduction of 15% (CI 7.2–23.2)** **NNT:** 22 for 1 year

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: DPS/ Lindström et al., 2003 and update 2006 con`t Country: Finland Quality: NICE ++
Secondary Outcomes	• weight loss was greater in the IG than in the CG after 3 years: IG: -3.5 kg ; CG: .- 0.9 kg • 10 % in the intervention group and 27% in the control group did not achieve any of the predefined goals by the 3-year examination • 14% in the intervention and 6% in the control group achieved four or five goals. • There was a strong inverse correlation between the success score and the incidence of diabetes during the total follow-up.
Authors Conclusions	Lifestyle intervention in people at high risk for type 2 diabetes resulted in sustained lifestyle changes and a reduction in diabetes incidence, which remained after the individual lifestyle counseling was stopped. No benefit in terms of CVD or all-cause mortality maybe do to a lack of power

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: IDDP/ Ramachandran et al., 2006 Country: India Quality: NICE ++
Population Characteristics	No of participants: 531 Definition of high risk: IGT Ethnicity: Asian Indians, middle class Age range: 35-55 years Mean BMI (kg/m^2): 25.6 – 26.3 +/- 3.7 % BMI ≥ 30: -
Intervention	**Intervention groups**: LI; LI + Metformin; Metformin only **Lifestyle change:** Reduction of total calorie, refined CH and fats + increase of fibre. Individual advice on PA. Aim: ≥ 30 min. of brisk walking per day **Administration of advice:** Monthly telephone calls and individual sessions every 6 months for lifestyle advice **Behavioral change strategies**: NR
Control	Standard advice
Randomization	-
Average Follow- up	3 years
Study attrition	5%
Primary Outcomes	**Relative Risk Reduction after 3 years:** Diet & Exercise: - 28.5% Diet & Exercise + Metformin: -26.4 % Metformin only:- 28.2 % **Cumulative incidence of T2DM after 3 years** Diet & Exercise: 39.3%; Diet & Exercise + Metformin: 39.5 % Metformin only: 40.5%; Control: 55 % **NNT after 3 years:** Diet & Exercise: 6.4 ; Diet & Exercise + Metformin: 6.9; Metformin only: 6.5
Secondary Outcomes	No significant weight loss in the IG`s – reduction of risk occurred without weight loss
Authors Conclusions	LI showed significant reduction of diabetes incidence after 3 years from 55% to 40 %.

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: Jarrett Study/ Jarrett et al. 1979 Country: UK Quality: NICE +
Population Characteristics	No of participants: 204 (all male) Definition of high risk: Survey blood sugar elevated and IGT (for details see Jarrett et al., 1979) Ethnicity:- Mean age: - Mean BMI (kg/m^2): - % BMI ≥ 30: -
Intervention	Intervention groups: 1) low CH diet (120g CH/d) + placebo; 2) "limit sucrose intake" + placebo 3) low CH diet (120g CH/d) + 50 mg phenformin S.A. /d 4) "limit sucrose intake" + 50 mg phenformin S.A. /d Lifestyle change: The LI groups + placebo served as control groups Administration of advice: The diet was taught with a specially developed booklet. Intensity is NR. Behavioral change strategies: NR
Control	1) low CH diet (120g CH/d) + placebo AND 2) "limit sucrose intake" + placebo
Randomization	Individually at first visit to clinic
Average follow- up	5 years
Study attrition	-
Primary Outcomes	"Worsening to diabetes" which was arbitrarily defined by the study authors (for details see Jarrett et al., 1979): 1) low CH diet (120g CH/d) + placebo : 18.2% (8/44) 2) "limit sucrose intake" + placebo: 13.3% (6/45) 3) low CH diet (120g CH/d) + 50 mg phenformin S.A. /d: 9.3% (4/43) 4) "limit sucrose intake" + 50 mg phenformin S.A. /d: 18.4% (9/49)
Secondary Outcomes	-
Authors Conclusions	The outcome „worsened to diabetes" was not significantly different in any of the treatment groups. Treatment was not predictive for the outcome.

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: Kosaka Study/ Kosaka et al., 2005 Country: Japan Quality: NICE ++
Population Characteristics	No of participants: 485 (all male, 356 control, 102 intervention) Definition of high risk: IFG + IGT (1980 WHO criteria for prediabetes) Ethnicity: Japanese Mean age: NR, age range: 87% between 40 and 60 y Mean BMI (kg/m^2): 24 kg/m^2 % BMI ≥ 30:-
Intervention	**Intervention groups:** diet & exercise **Lifestyle change:** Individually tailored dietary advice (fat, alcohol, calorie intake, vegetables) and recommendation of moderate intensity leisure time PA. Weight reduction was recommended to a BMI of 22 **Administration of advice**: individual advice every 2-3 months **Behavioral change strategies**: NR
Control	Standard advice on lifestyle change every 6 months
Randomization	Individuals randomly assigned to IG or CG
Follow- up	4 years
Study attrition	4.7 – 5.5 %
Primary Outcomes	**Cumulative incidence of T2DM after 4 years** Diet & Exercise: 3% (3/102) Control: 9.3% (33/356) **Regression to NGT:** IG: 53 %; CG: 33.9%
Secondary Outcomes	**Weight loss:** Diet & Exercise: - 2.18 kg Control: -0.39 kg
Authors Conclusions	A lifestyle intervention designed to achieve and maintain ideal body weight (BMI <22 kg/m^2) is an effective means of reducing incidence of type 2 diabetes in Japanese males with IGT. Reduction in the incidence by lifestyle intervention was successfully carried out in a clinical outpatient setting for diabetic patients.

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: The China Da Qing Diabetes Prevention Study/ Li et al., 2008 (follow-up from Da Qing Study) Country: China Quality: NICE -
Population Characteristics	No of participants: 577 Definition of high risk: IGT Ethnicity: Chinese Mean age: 45 +/- 9.1 Mean BMI (kg/m^2): 25.8 +/- 3.8; % BMI ≥ 30: NR
Intervention	**Intervention groups**: diet only, exercise only, diet + exercise **Lifestyle change**: Diet: Low fat, high carbohydrate diet – weight loss recommended for people with BMI > 25 at a rate of 0.5-1.0 kg per month until they achieved a BMI of 23; participants were encouraged to consume more vegetables, control their intake of alcohol, and reduce their intake of simple sugars. Exercise: participants were encouraged to increase the amount of leisure physical exercise by at least one unit per day (such as slow walking for 30 minutes, fast walking for 20 minutes etc) and by two units per day if possible for those <50 years of age with no evidence of cardiovascular disease or arthritis. **Administration of advice**: individual and small group counseling; sessions were conducted weekly for one month, monthly for three months, and then once every three months for the remainder for 6 years **Behavioral change strategies**: NR
Control	General information about lifestyle and diabetes risk. No individual or group counseling.
Randomization	By clinical centre /cluster-randomization
Follow- up	20 years
Study attrition	-
Primary Outcomes	**Cumulative incidence of T2DM after 20 years:** IG: 80%; CG: 93% **NNT: 6**
Secondary Outcomes	Participants in the intervention group had an average of 3.6 fewer years with diabetes
Authors Conclusions	Group-based lifestyle interventions over 6 years can prevent or delay diabetes for up to 14 years after the active intervention. However, whether lifestyle intervention also leads to reduced CVD and mortality remains unclear.

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: Liao Study/ Liao et al., 2002 Country: US Quality: NICE +
Population Characteristics	No of participants: 64 Definition of high risk: IGT Ethnicity: Japanese Mean age: IG: 55.8 years ± 1.8; CG: 52.2 years ± 1.8 Mean BMI (kg/m^2): IG: 25.6 ± 0.8; CG: 26.6 ± 0.8 % BMI ≥ 30: -
Intervention	**Intervention group**: diet & exercise **Lifestyle change**: Endurance exercise training and a low fat, high CH diet (<30% of total calories as fat (<7% as saturated fat), 55% as carbohydrate, the balance as protein, and <200 mg cholesterol daily.) **Administration of advice:** exercise training was directed by an exercise physiologist for the first 6 months. **Behavioral change strategies**: NR
Control	Supervised stretching exercise training and a "healthy diet" (30% of total calories as fat (10% as saturated fat), 50% as carbohydrate, 20% as protein, and <300 mg cholesterol daily.)
Randomization	Adaptive randomization
Average follow- up	24 months
Study attrition	
Primary Outcomes	Study was not designed to demonstrate prevention of diabetes **Cumulative incidence of T2DM after 6 months:** one person in each group had developed diabetes. **Cumulative incidence T2DM after 12 months:** one person from the intervention group had diabetes (1/32, 3.1%), and two from the control group had diabetes (2/32, 6.3%)
Secondary Outcomes	Weight loss: At 6 and 12 months the IG showed greater weight loss than the CG.
Authors Conclusions	Diet and endurance exercise improved BMI, body composition, and body fat distribution and, thus, may delay or prevent type 2 diabetes in Japanese Americans with IGT.

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: Lindahl Study/ Lindahl et al., 2009 Country: Sweden Quality: NICE ++
Population Characteristics	No of participants: 301 Definition of high risk: IGT and BMI > 27 kg/ m^2 Ethnicity: - Mean age: IG: 52.2 +9.0 y, CG: 53.5 + 8.4 y Mean BMI (kg/m^2): IG: 31.2 + 3.1, CG: 30.2 +3.4 % BMI ≥ 30: -
Intervention	**Intervention groups:** diet & exercise **Lifestyle change:** 1 month residential intensive program with ~ 140 h of scheduled activities. Moderate intensity PA training 2.5 h/d and low-fat and high fibre diet. No alcohol allowed and smoking cessation program offered. Additional learning sessions were repeated during a 4-day follow-up 12 months later. **Administration of advice**:- **Behavioral change strategies**: Yes, goalsetting, self-monitoring, problem-solving, stress management and relapse prevention
Control	A health survey was performed, including a physical examination, a 2-h OGTT and blood sampling. The survey was followed by a 30–60-min counseling session, where the participants were given both oral and written advice. The same examination protocol was repeated after 1, 3 and 5 years.
Randomization	Individual randomization to IG or CG
Follow- up	1, 3 and 5 years
Study attrition	

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: Lindahl Study/ Lindahl et al., 2009 con`t Country: Sweden Quality: NICE ++
Primary Outcomes	**Incidence of T2DM at 1 year:** LI: 7%; CG: 25%; RRR: 70% **Incidence of T2DM at 3 years:** LI: 17%; CG: 25%; RRR: 40% **Incidence of T2DM at 5 years:** LI: 24%; CG: 29%; RRR: 25% The risk reductions at 3 and 5 years were not significant.
Secondary Outcomes	
Authors Conclusions	The intervention affected several important cardio-metabolic risk variables beneficially and reduced the risk for type 2 diabetes, but the effects persisted only as long as the new lifestyle was maintained. Increased physical activity seemed to be the behaviour that was most easy to preserve.

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: Penn Study/ Penn et al., 2009 Country: UK Quality: NICE ++
Population Characteristics	No of participants: 102 Definition of high risk: IGT Ethnicity: Mean age: IG: 56.8 y, CG: 57.4 y Mean BMI (kg/m^2): IG: 34.1, CG: 33.5 % BMI ≥ 30: -
Intervention	**Intervention group**: diet & exercise **Lifestyle change:** high CH and fibre, low fat diet to achieve weight loss to a BMI < 25 kg/m2. Moderate PA of 30 minutes/d was encouraged. **Administration of advice:** individual advice and motivational interviewing **Behavioral change strategies**: NR
Control	Minimal intervention control group
Randomization	Individual randomization stratified by sex and by 2 hour plasma glucose value
Mean follow-up	3.11 years
Study attrition	
Primary Outcomes	**Incidence of T2DM:** IG: 32.7 (95% CI 10.7 to 74.6) per 1000 person years of follow-up CG: 67.1 (95% CI 34.2 to 117.5) per 1000 person years of follow-up **RR:** 0.45 (95% CI 0.2 to 1.2)
Secondary Outcomes	Weight loss:at year 1 follow-up IG had a significantly higher mean weight change: -2.3 kg than CG: -0.01 kg. Only three participants achieved BMI < 25 kg/m^2.
Authors Conclusions	The results are consistent with other diabetes prevention trials. This study was designed as part of a larger study and although the sample size limits statistical significance, the results contribute to the evidence that T2DM can be prevented by lifestyle changes in adults with IGT. In explanatory analysis small sustained beneficial changes in weight, physical activity or dietary factors were associated with reduction in T2DM incidence.

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: SLIM Study/ Roumen et al., 2008 Country: The Netherlands Quality: NICE ++
Population Characteristics	No of participants: 147 Definition of high risk: IGT Ethnicity:- Mean age: IG: 54.2 + 5.8 y; CG: 58.4 + 6.8 y Mean BMI (kg/m^2): IG: 29.6 + 3.8, CG: 29.2 + 3.3 % BMI ≥ 30:-
Intervention	**Intervention group**: diet & exercise **Lifestyle change**: Dietary recommendations based on the Dutch guidelines for a healthy diet and increase level of PA to at least 30 min. a day for at least 5 days a week. Weight loss of 5–7% was another objective. **Administration of advice:** Individual advice on how to reach dietary and PA goals. Participation in a combined aerobic and resistance exercise program was encouraged. **Behavioral change strategies**: self-monitoring , goal-setting
Control	Standard advice on the benefits of lifestyle change, but no individual counseling.
Randomization	Individual randomization with stratification for sex and mean 2-h plasma glucose concentration.
Follow- up	Data analyses of the 3-year results include those subjects still participating in the study (completers, n= 106: 52 IG subjects and 54 CG subjects).
Study attrition	28% (41 dropouts of 147 subjects origionally included)
Primary Outcomes	**Cumulative incidence of T2DM after 3 years (completers):** IG: 18% (8/44); CG: 38% (18/47) The P-value of the log-rank test was 0.025, and the relative risk was 0.42 [95% confidence interval (CI) 0.18–0.96] **Cumulative incidence in the intention to treat analysis:** IG: 18% (11/61); CG: 32% (19/60) The P-value from the log-rank test was 0.07 and the relative risk 0.52 (95% CI 0.25–1.10).

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: SLIM Study/ Roumen et al., 2008 (con`t) Country: The Netherlands Quality: NICE ++
Secondary Outcomes	Decrease in body weight correlated with a decrease in 2 h glucose levels.
Authors Conclusions	The lifestyle intervention showed a sustained beneficial effect on 2-h glucose concentrations, insulin resistance and 2-h FFA, even after 3 years. The lifestyle intervention is effective, but for implementation more information is needed about factors influencing adherence.
Comments	The authors noted that incidence of diabetes was not the primary outcome of the study and although it was examined, the results have to be interpreted with caution because the study was underpowered for those analyses.

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Table 12: Basic characteristics of included RCTs – information compiled from Gillett et al. 2012, and Jones et al., 2011; Jarrett et al., 1979, Knowler et al., 2002 (con`t)

Study (RCT)	Study/Author: Wein Study/ Wein et al., 1999 Country: Australia Quality: NICE -
Population Characteristics	No of participants: 200 (all female) Definition of high risk: IGT Ethnicity: Mean age: IG: 39.5 years (95% CI 38.2 to 40.8) ; CG: 37.8 years (95% CI 36.5 to 39.0) Mean BMI (kg/m^2): IG: 25.2 (95% CI 24.1 to 26.4); CG: 25.6 (95% CI 24.5 to 26.8) % BMI ≥ 30:-
Intervention	**Intervention group**: diet **Lifestyle change**: group received dietary questionnaires and standard diet advice sheet. Telephone contact with the dietician was arranged three-monthly. The importance of regular exercise (e.g. brisk walking for 30 minutes three times per week) was stated. **Administration of advice:-** **Behavioral change strategies**: -
Control	Like intervention group but without telephone calls.
Randomization	NR
Mean follow- up	51 months, IG: 58.6 months, CG: 47.9 months
Study attrition	-
Primary Outcomes	**Cumulative Incidence of T2DM:** IG: 26.8% CG: 28.1 % No significant difference
Secondary Outcomes	-
Authors Conclusions	In women with impaired glucose tolerance, this randomized controlled study showed no significant benefit in women given dietary guidelines reinforced with continued, regular contact with a dietician, compared with those given dietary guidelines alone. However, compared with the Da Qing study, the results in the control group were encouraging, and combined with the results of other trials, suggest that dietary intervention is warranted in individuals with impaired glucose tolerance.

PA= Physical Activity; NR = Not reported; CH= carbohydrate

Legend:

Study quality (using NICE methodology) (Jones et al., 2011, p. 32)

Grade	Criteria
++	All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions are thought very unlikely to alter.
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or adequately described are thought unlikely to alter the conclusions.
–	Few or no criteria have been fulfilled. The conclusions of the study are thought likely or very likely to alter.

Study populations: Studies have been carried out in several different countries and included populations with varying ethnicity. 5 RCTs included individuals of Asian ethnicity only and two US studies included populations of mixed ethnicity (Whites, African, Hispanic, Asian). For the five European studies implemented in the Netherlands, Finland, Sweden and UK and the only Australian study, details about ethnicity of populations has not always been reported. The number of participants in the different RCTs ranged from 64 in a small US study with individuals of Japanese ancestry only to 3234 participants in the US DPP. Mean BMI at baseline differed substantially between the different study populations (range: 24 kg/m^2 in the Japanese Kosaka study to 34 kg/m^2 in the US DPP). Generally mean BMI was lower in the study populations with Asian ethnicity than in the American and European study groups.

Intervention characteristics: Three of the studies reported on a diet only intervention, one study on an exercise only intervention and nine on a combined diet and exercise intervention. Change in diet usually comprised a low fat, high carbohydrate diet with restricted calorie intake in order to achieve weight loss. However, other diet components like alcohol or sugar restrictions as well as the targets set for weight loss differed substantially. The same was true for the exercise component which ranged from merely encouraging participants to have more leisure time activity to instructed physical activity training of 2.5 h/d in a 1 month residential intensive program.

Also the administration of dietary and physical activity advice differed widely in terms of duration and intensity between the interventions. In one study (Wein et al., 1999) the intervention goals were reinforced by three-monthly telephone calls with a dietician only whereas other participants received individual and small-group counseling for up to 6 years (Da Qing Study, Pan et al., 1997). The use of behavioral change strategies like goal-setting, self-monitoring, problem solving and relapse prevention was reported by 5 studies.

Follow-up-period: Mean follow up of study participants was lowest in the study of Liao et al. with 2 years (Liao et al., 2002). Three studies included in the meta-analysis provided long-term follow up data of participants. These were Lindström et al. with a 7 year follow-up of the Finnish DPS (Lindström et al. 2006), the Diabetes Prevention Program Outcomes Study (DPPOS) with a 10 year follow-up

of the US DPP (DPPRG, 2009) and Li et al. with a 20 year follow-up of the Da Qing study (Li et al., 2008).

Quality of RCTs: As mentioned in the methods part quality assessment was done with the NICE instrument. Jones et al. classified the included RCTs as follows: 2 studies with NICE: - (poor quality), 2 studies with NICE: + (good quality) and 9 studies with NICE: ++ (very good quality) (Jones et al., 2011). “Study quality did not determine inclusion into or exclusion from the review.” (Jones et al., 2011, p. 30). The results of the quality assessment for the individual RCTs can be seen in table 12.

5.1.2.3 Meta-analysis on prevention of T2DM

Jones et al. found that in all studies the LI groups had lower progression rates to T2DM than the control groups (Jones et al., 2011). The results of the meta-analysis can be seen in Figure 3:

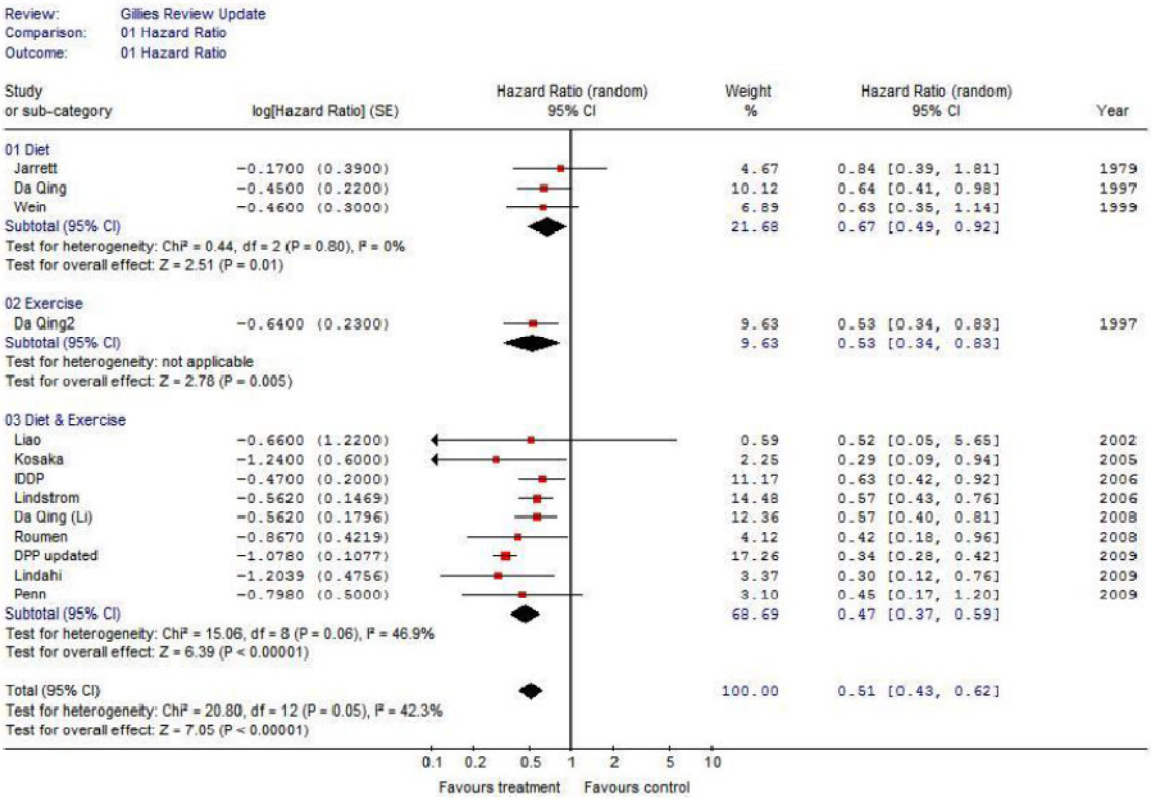

Figure 3: Meta-analysis of lifestyle interventions (Jones et al., 2011, p. 51)

As an outcome effect measure Jones et al. calculated HRs with 95% CI; the meta-analysis was performed using a random-effects model. When comparing 13 studies or study arms in a meta-analysis a pooled HR of 0.51 (95% CI 0.43 – 0.62) was obtained (p-value of 0.00001, using standard meta-analysis with Z-scores). Figure 3 shows that the HRs of all included studies or study subgroups are left to the line of no effect which indicates that all studies favor treatment. Confidence intervals overlap the line of no effect in 4 studies (Jarrett et al., 1979, Wein et al., 1999, Liao et al., 2002, Penn et al., 2009) which means that in these studies the effects were not statistically significant. The test for statistical heterogeneity resulted in an I^2 of 42.3 % which indicates moderate heterogeneity among studies and is in conformity with the differences in basic study characteristics described in chapter 5.1.2.2.

Figure 3 shows the HR for the different types of interventions (diet only, exercise only, diet and exercise). Based on three studies (Jarrett et al., 1979, Da Qing Study (Pan et al., 1997) and Wein et al., 1999) for diet only interventions the HR was 0.67 (95% CI 0.49-0.92). Only one study arm of the Da Qing Study reported on an exercise only intervention with a HR of 0.53 (95% CI 0.34 -0.83). Nine studies provided data for combined diet and exercise interventions with a pooled HR of 0.47 (95% CI 0.37 – 0.59). The pooled HR of all LI was 0.51 (95% CI 0.43 – 0.62) and statistically significant (Jones et al., 2011).

The authors concluded that "**...**lifestyle interventions have an effect in delaying or preventing progress to diabetes in people with IGT." and "…the combination of diet and exercise appears to have more effect in the delaying or preventing the progression from IGT to a diagnosis of diabetes." (Jones et al., 2011, p. 52) In comparison with pharmacological interventions the authors stated that "…lifestyle interventions seem to be at least as effective as pharmacological interventions." and "…incur fewer and less serious side effects than drug treatment." (Jones et al., 2011, p. 14). When considering the sustainability of effects Jones et al. noted that short-term interventions showed greater effects than medium-term interventions. According to the authors possible explanations could be a reduction in compliance in the intervention group with time and, in addition, individuals in placebo groups might take up alternative strategies for dealing with their risk and might not stick to their original lifestyle habits (Jones et al., 2011). They concluded that "…advice on diet and exercise needs to be regularly reinforced in order to maintain behavioural changes." (Jones et al., 2011, p. 14).

5.1.2.4 Secondary Outcomes

Secondary outcomes of interest examined by Jones et al. were BMI change, weight change, change in blood pressure, blood glucose, waist circumference and cholesterol. The authors investigated the possibility of performing a meta-regression or a network meta-analysis but stated that too few studies reported on the outcomes of interest to do so (Jones et al., 2011). Hence, only a description of findings in the individual RCTs is provided in the ScHAAR Review and summarized to evidence statements. In essence the authors concluded that in the short-term (two to five/six years), both lifestyle interventions and pharmacological interventions showed a greater reduction in BMI**,** a greater weight change, a slightly greater reduction in systolic blood pressure, diastolic blood pressure, fasting blood glucose, two hour glucose and waist circumference in the intervention group than in control groups. For change in cholesterol there was mixed evidence in the intervention groups and the control groups, respectively (Jones et al., 2011).

5.2 Patient-relevant outcomes

The evaluation of the effect of LI on patient relevant outcomes has not been within the scope of the ScHARR Review. However, some of the other reviews identified by our systematic literature research and some of the RCTs included in the reviews reported on patient relevant outcomes. The basic results will be summarized here.

5.2.1 CVD events, CVD mortality and all-cause mortality

In their review on the effectiveness of LI in patients with metabolic syndrome Dunkley et al. stated that LI and pharmacological interventions can reverse metabolic syndrome, but that it remained unclear whether or not these benefits could be sustained and would translate into longer term prevention of CVD (Dunkley et al., 2012). Sumamo et al. found no significant differences for CVD events and mortality in 2 studies included in their review (DPS und Da Qing) (Sumamo et. al, 2011). In addition LeBlanc et al. stated, that behaviorally based LI are safe and effective for weight loss and maintenance and can reduce diabetes incidence. However, data on long-term health outcomes of weight loss interventions on CVD or death were classified insufficient by the review authors (LeBlanc et al., 2011).

As mentioned by Sumamo et al. two RCTs reported on long-term outcomes on CVD risk and mortality. Data on cardiovascular morbidity and mortality has been presented in a secondary analysis of the Finnish DPS. After a median follow-up time of 10.2 years, CVD morbidity (incidence rates of 22.9 and 22.0 per 1000 person-years (HR=1.04, 95% CI: 0.72-1.51 IG compared to CG)) and total mortality rates did not differ between intervention and control group (Uusitupa et al., 2009). The study authors considered different explanations for their findings. First they pointed out that the DPS initially had not been designed to investigate endpoints and therefore might lack statistical power to detect small differences between intervention and control group. Secondly they considered that lifestyle changes in the IG might have been extensive enough to prevent T2DM but not extensive enough to lower CVD risk or total mortality. Thirdly they explained that the DPS cohort had a more favorable risk profile compared to a population cohort (FINRISK) and thus represented "…the healthier proportion of people with IGT" (Uusitupa et al., 2009, p. 7), which could explain why no differences in CVD morbidity or total mortality could be observed (Uusitupa et al., 2009).

In line with the DPS findings, the long term follow-up of the Da Qing study also did not find significant differences between LI groups and control groups concerning CVD morbidity, CVD mortality or all-cause mortality. The authors noted: "The incidence of first CVD events and all cause mortality did not differ significantly between the combined intervention group and the control group. The overall adjusted HRR of death from CVD, however, was 17% lower in the intervention group, but 95% CIs were wide and the difference was not significant. The observation that each of the outcomes (all-cause mortality, CVD mortality, CVD incidence) seem to have a reduced incidence for people who had received the intervention is encouraging. Nevertheless, our findings leave the relation between lifestyle-based diabetes prevention and effect on CVD and mortality unresolved." (Li et al., 2008, p. 1787).

Moreover, in a 3-year follow-up of the DPP no differences in all-cause mortality between the three treatment groups have been observed (Knowler et al., 2002). Although the lifestyle intervention group showed improvements in CVD risk factor status compared with placebo and metformin therapy, no differences in CVD event rates could be observed after 3 years (Ratner et al., 2005).

5.2.2 Microvascular complications

Impact of LI on microvascular complications or HRQoL have not been reported in either the systematic reviews or in the original papers of the included RCTs. However, secondary analyses of long term outcome data of DPS, DPP and Da Qing study participants report on retinopathy and HRQoL.

In a 20 year follow-up of the original Da Qing study Gong et al. reported that "…the cumulative incidence of severe retinopathy was 9.2% in the combined intervention group and 16.2% in the control group (p=0.03, logrank test). After adjusting for clinic and age, the incidence of severe retinopathy was 47% lower in the intervention group than the control group (hazard rate ratio 0.53, 95% CI 0.29–0.99, p=0.048)." (Gong et al., 2011, p. 300). Interestingly enough all the individuals, who had been diagnosed with severe retinopathy, had also developed diabetes. The authors concluded that the main reason for the lower incidence of retinopathy in the intervention groups was the lower incidence of T2DM and the associated delay of manifestation of T2DM in the IG. For nephropathy and neuropathy no significant differences in the incidence between IG and CG could be found (Gong et al., 2011).

In a subgroup of the DPP study population Nathan et al. compared the prevalence of diabetic retinopathy in persons with recently diagnosed T2DM (mean duration of T2DM 3.1 years) to the prevalence of diabetic retinopathy in persons without T2DM but with elevated FPG and IGT. They found that retinopathy is also present in persons with elevated FPG and IGT, but prevalence is substantially higher in those individuals who had developed T2DM during the course of the DPP (Nathan et al., 2007). "Retinopathy consistent with diabetic retinopathy was detected in 12.6 and 7.9% of the diabetic and non-diabetic participants, respectively (P=0.03, comparing prevalence in the two groups)." (Nathan et al., 2007, p. 137)

5.2.3 Health Related Quality of Life (HRQoL)

Health related quality of life has been assessed in a sample of 3210 study participants in the DPP. It was measured with the short-form health-related quality of life (SF-36) survey at enrollment and annually thereafter (Marrero et al., 2013). The results showed that those who remained diabetes-free had a higher score in HRQoL no matter to which treatment arm they belonged. Diagnosis of T2DM led to

a marked decrease in HRQoL in all groups and did not return to baseline scores thereafter.

In addition Florez et al. tested the hypothesis that LI in the DPP would lead to a better HRQoL compared to the placebo intervention or pharmacotherapy with metformin. They found that "…during the first year of intervention, physical function, general health and vitality scores improved significantly in ILS participants, reaching MID when compared to those treated with PLB or MET." (Florez et al., 2012, p. 1596) (ILS = intensive Lifestyle intervention, MID =minimal important difference; PLB = Placebo; MET= metformin treatment) Furthermore, HRQoL worsened in all three study groups during DPP follow-up, but the decline was slower in the LI group. The authors concluded that lifestyle interventions in the DPP that resulted in weight loss and increased physical activity lead to a modest improvement of most physical HRQoL and vitality scores in overweight or obese individuals at high risk of developing T2DM (Florez et al., 2012).

Decline of HRQoL in all DPP groups during follow-up was also reported by Marrero et al. As one possible explanation the authors pointed out, that HRQoL declined with age anyway (Marrero et al., 2013).

5.3 Results of interest for EBHI

In this chapter selected results from RCTs on diabetes prevention or additional systematic reviews, which might be of special interest to patients and citizens and thus should possibly be included in an EBHI, will be presented.

5.3.1 Adherence to lifestyle change and dose-response relationship

The results presented so far compared the change in diabetes incidence between intervention and control groups and not between individuals in the different groups. Consequently the effects observed did not measure the effect of implemented lifestyle change, but to a certain degree measured how successful intervention programs were in helping participants to change their habits. Although it is important to know that changing lifestyle and maintaining changes is usually not achieved by the majority of participants, from the perspective of an individual affected it might also be interesting what the effects of implemented lifestyle change are.

Data from the Finnish DPS have shown that about one third of the participants in the lifestyle intervention group reached none or only one of the predefined targets of lifestyle change at the year one examination. On the other hand a certain number of participants in the control group also changed their lifestyle without having intensive advice (Lindström et al., 2006). Therefore Lindström et al. calculated success scores depending on the number of predefined targets reached (0 to 5) and compared incidence rates between the different groups. They found a strong inverse relationship between success score and diabetes incidence during total follow-up of the DPS. “Incidence rate per 100 person-years ranged from 8.4 (95% CI 6.2–11.3) in the participants who did not achieve any of the goals at the 3-year visit, to 2.0 (1·0–4·3) in those who achieved four or five of the goals. The hazard ratios were 1·00, 0·85 (0·57–1·28), 0.66 (0·40–1·09), 0·69 (0·38–1·26), and 0·23 (0·10–0·52) for success score from 0, 1, 2, 3, to 4–5, respectively (test for trend p=0·0004).” (Lindström et al., 2006, p. 1676). In addition Lindström et al. found that most people who had maintained their lifestyle change at the 3-year-visit remained diabetes-free during the follow-up period of 7 years (Lindström et al., 2006).

The authors concluded that “…the true effect of healthy lifestyle results in a dramatically better outcome than that seen by the intention-to-treat analysis of the treatment effect.” (Lindström et al., 2006, p. 1677).

However, changing lifestyle habits is a problem for a substantial number of individuals with pre-diabetes and a challenge for diabetes prevention programs relying on lifestyle change (Gillett et al., 2012 and Lindström et al., 2006). Gillett et al. concluded that “…even among the volunteers in the trials, many did not succeed and others succeeded in the short term (such as the first 6 months) but not in the longer term. The key to success is sustained lifestyle change, especially weight loss. In conclusion, lifestyle measures can be highly effective in reducing progression to diabetes but adherence to lifestyle change is the most important factor.” (Gillett et al., 2012, p. 69).

5.3.2 Quality criteria of effective interventions

The question of implementation of and adherence to lifestyle change is closely linked to the question what characterizes interventions which enable participants to change dietary intake and physical activity habits.

For individuals affected it would be helpful if an EBHI on prevention of T2DM through LI would also provide information about how different intervention components are linked to success in changing behavior of participants. With this information at hand patients could ask for intervention programs in their health care system which would help them to achieve their goals.

Two systematic reviews of reviews tried to identify intervention components causing or being associated with increased effectiveness of lifestyle changes in individuals with increased risk for T2DM. Greaves et al. reviewed the literature for the IMAGE study group and Johnson et al. for the NICE (Greaves et al., 2011; Johnson et al., 2011).

Both reviews identified the following intervention components to be *causally linked* to intervention effectiveness:

- Using well-defined/established behavior change techniques,
- organizing or encouraging social support and
- aiming at changes in both diet and physical activity. (Greaves et al., 2011; Johnson et al., 2011).

In addition increased effectiveness "…was also *associated with* increased contact frequency and using a specific cluster of "self-regulatory" behavior change techniques (e.g. goal-setting, self-monitoring)." (Greaves et al., 2011, p. 119). For other intervention components like setting, delivery mode or provider and study population no clear relationships could be detected. Greaves et al. also stressed the importance of implementing behavior maintenance strategies into the programs in order to be successful in the long run (Greaves et al., 2011).

In summary both reviews concluded that intervention components, which increase effectiveness, should be used when designing and implementing LI programs (Greaves et al., 2011; Johnson et al., 2011).

5.3.3 Absolute Risk Reduction and long term progression rates to T2DM

As pointed out in chapter 3.2 it is strongly recommended that changes in risk should be communicated as absolute risk reduction, because the exclusive representation of relative risk reduction does not allow for the distinction of large effects from small effects. In order to do so base rates must be available. The progression rates from IGT to overt T2DM differ substantially between the different population groups in the RCTs included in the ScHARR review. Table 13 shows progression rates from the larger trials calculated by Gillett et al., 2012.

Table 13: Progression to diabetes and regression to NGT in larger trials (Gillett et al., 2012, p. 68)

	Progression to diabetes, % (95% CI)		Regression to NGT, %	
Study (no. of recruits)	Intervention group	Control group	Intervention group	Control group
DPP (3234) 10-year annual incidence	4.8 (4.1 to 5.7)	11 (9.3 to 13.3)	54	44
Kosaka (500+)	3 (1.2 to 4.8)[a]	9.3 (3.6 to 15)	54	34
Da Qing (577) incidence per 100 patient-years	7.9 (6.8 to 9.1)	11.3 (9.3 to 13.3)	–	–
Ramachandran (531) 3-year prevalence	39 (30.4 to 48.5)	55 (46 to 63.5)	–	–
DPS (523) annual incidence	4.3 (3.4 to 5.4)	7.4 (6.1 to 8.9)	–	–

a CIs not given in paper – our calculations.

Data for the German population could not be found in the literature therefore the calculation of absolute risk will be based on the base rate of the largest trial – the US DPP with a 10-year annual incidence of 11 (9.3 – 13.3). Assuming a HR of 0.51 (95% CI 0.43 - 0.62) as calculated in the meta-analysis of the ScHARR review, the calculated absolute risk in the intervention group would be 5.61 (95% CI 4.73 - 6.82). In plain words this would mean that without lifestyle intervention 11 of 100 persons would have a diabetes diagnosis each year, with lifestyle intervention the number would be reduced to about 5 to 6 of 100 persons per year.

One can assume that patients might also be interested in longer term outcomes and not just annual progression rates. The DPPOS provided data on cumulative incidence of T2DM in the different treatment groups which are shown in figure 4.

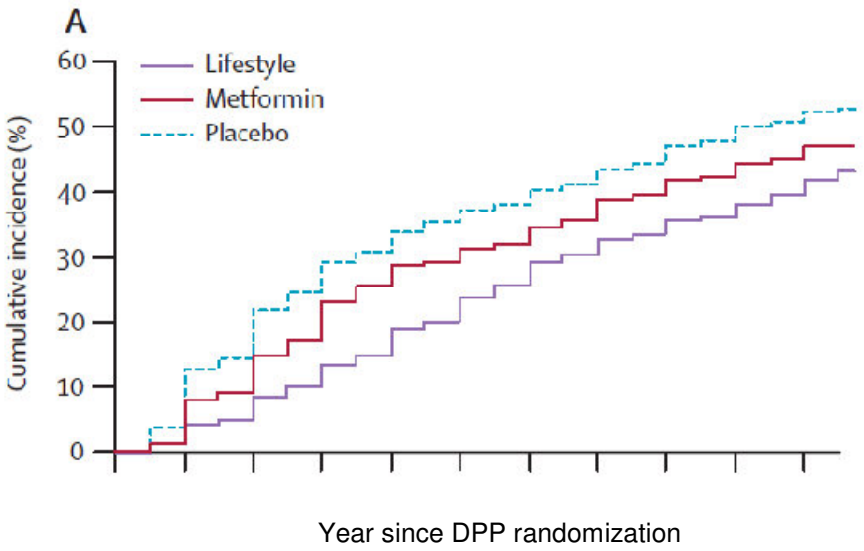

Figure 4: Cumulative incidence of diabetes in the DPP from randomization to year 10 all participants (Diabetes Prevention Program Research Group, 2009, p. 1682)

Figure 4 shows that the cumulative incidence in the placebo group exceeds 50% after 10 years, is about 47% in the metformin group and lower (about 40%) in the original lifestyle intervention group. It should be noted that due to the benefits seen in the DPP for the LI group, for ethical reasons participants of all intervention groups were offered group-implemented lifestyle intervention after unmasking the original assignment and starting the DPPOS. Nevertheless diabetes incidence "…was reduced by 34% (24–42) in the lifestyle group and 18% (7–28) in the metformin group compared with placebo" (DPPOS, 2009, p. 1677) 10 years after DPP randomization. In line with the numbers presented in the DPPOS data from the Finnish DPS showed that "…around 50% of people with impaired glucose tolerance will develop diabetes during 10 years when no active intervention is applied." (Lindström et al., 2006, p. 1678). In addition the DPPOS showed that "…onset of diabetes was delayed about 4 years by lifestyle intervention and 2 years by metformin compared with placebo" (DPPOS, 2009, p. 1683).

6 Discussion

The main objective of this master thesis has been the evaluation of the effectiveness of LI in the prevention of T2DM in high-risk individuals with the methods of EBM in order to inform EBHI which is supposed to be written by the IQWIG Department of Health Information in the near future. Three systematic reviews and one meta-analysis have been identified, which consistently show that the progression to T2DM in high-risk individuals can be delayed or prevented with LI. In addition and in contrast with the IQWIG method I have also looked for evidence from study types other than systematic reviews of controlled trials concerning reduction of CVD risk, mortality, microvascular complications, HRQoL and other aspects that might be of interest to individuals reading EBHI on diabetes prevention.

In this chapter the results which have been presented in chapter 5 will be compared with previous reviews and with guidelines for prevention of T2DM from relevant organizations. Moreover, methodological considerations concerning the information basis for EBHI will be made. Finally the relative importance of EBHI on diabetes prevention at the population level will be discussed from a public health perspective.

6.1 Comparison of results with previous reviews

According to our search strategy only systematic reviews, in which the literature search had been performed 2009 or later, have been included. However, previous systematic reviews and meta-analyses came to similar conclusions as the reviews identified by our search. The AHRQ published a systematic review in 2005 on the diagnosis, prognosis and treatment of IGT and IFG and included 4 trials of combined diet and exercise interventions into a meta-analysis. A relative risk of 0.54 (95% CI 0.42-0.70) was calculated comparing the intervention to the control group (Santaguida et al., 2005), which is in good agreement with the results of the ScHARR review by Jones et al. from 2011. Another meta-analysis was carried out by Gillies et al. in 2007 and found a HR of 0.49 (95% CI 0.40 -0.59) for combined diet and exercise interventions and a HR of 0.51 (95% CI 0.44 -0.60) when studies on all intervention types (diet-only, exercise-only, diet & exercise) were pooled (Gillies et al., 2007). Other systematic reviews also came to the conclusion, that progression from IGT to T2DM can be

delayed or prevented by LI and that combined diet and exercise interventions are more effective than diet-only or exercise-only interventions (Diabetes Australia, 2008 and Orozco et al., 2008).

6.2 Comparison with guidelines of relevant organizations

Evidence based guidelines for the treatment and prevention of T2DM are provided by different organizations. The basic recommendations concerning T2DM prevention through LI published by the American Diabetes Association and a European study group – the IMAGE Study Group – will be summarized and compared to the results of the ScHARR review by Jones et al. from 2011. In addition interesting aspects of a public health guidance prepared by the NICE on the basis of the ScHARR Review by Jones et al. and other sources of information will be discussed.

Table 14 provides information about the guideline recommendations, the methodology of evidence search and - where applicable - the evidence levels of the given recommendations.

In line with the evidence provided by the ScHARR Review by Jones et al. that LI can delay or prevent the progression to T2DM in high-risk individuals, all organizations recommend that those affected should be offered lifestyle change programs, which will help them to increase physical activity, change dietary habits and lose weight. A sustained weight loss of (5 to) 7% is considered desirable and sufficient to substantially lower the risk of T2DM by the ADA and the IMAGE study group (both evidence level A).

Both organizations also provide recommendations concerning the amount of physical activity and the adequate dietary change. ADA recommends at least 150 min/week of moderate activity such as walking, which corresponds with the targets set in the DPP. The recommendation of the IMAGE study group of 30 minutes per day of moderate exercise is in a similar range.

The IMAGE study group recommends a high-fibre, moderate fat diet with a reduced amount of saturated and trans-fat and ADA adds the recommendation to reduce calorie intake and to limit intake of sugar-sweetened beverages. The recommendations of the NICE public health guidance are similar.

Table 14: Overview of recommendations from ADA, IMAGE Study Group and NICE

Organization/ Guideline	**American Diabetes Association (ADA) 2013 Standards of Medical Care in Diabetes - 2013**	
Source: American Diabetes Association (ADA) (2013). Standards of Medical Care in Diabetes - 2013, Diabetes Care, Volume 36, Supplement 1, S11-66, January 2013		**Evidence level**
Recommendations	• Patients with IGT, IFG, or an A1C of 5.7–6.4% should be referred to an effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 min/week of moderate activity such as walking. • Among individuals at high risk for developing type 2 diabetes, structured programs that emphasize lifestyle changes that include moderate weight loss (7% body weight) and regular physical activity (150 min/week), with dietary strategies including reduced calories and reduced intake of dietary fat, can reduce the risk for developing diabetes and are therefore recommended.	(IGT) A IFG(E) A1C of 5.7–6.4% (E) A
	• Individuals at risk for type 2 diabetes should be encouraged to achieve the U.S. Department of Agriculture (USDA) recommendation for dietary fiber (14 g fiber/1,000 kcal) and foods containing whole grains (one-half of grain intake). • Individuals at risk for type 2 diabetes should be encouraged to limit their intake of sugar-sweetened beverages(SSBs).	B
	• Follow-up counseling appears to be important for success.	B
	• Metformin therapy for prevention of type 2 diabetes may be considered in those with IGT, IFG, or an A1C of 5.7–6.4% (E), especially for those with BMI >.35 kg/m2, aged < 60 years, and women with prior GDM.	IGT (A) IFG(E) A1C of 5.7–6.4% (E) BMI >.35 kg/m2 + aged < 60 years, and women with prior GDM. (A)
	• Screening for and treatment of modifiable risk factors for CVD is suggested.	B
Evidence search and included studies /RCTs on lifestyle intervention	ADA Professional Practice Committee members systematically searched Medline for human studies published since 1 January 2011. Recommendations were revised based on new evidence or, in some cases, to clarify the prior recommendation or match the strength of the wording to the strength of the evidence. A table linking the changes in recommendations to new evidence can be reviewed at http://professional.diabetes.org/CPR. Included studies: DPP, DPS, Da Qing, IDPP	
Grading system	ADA evidence grading system for clinical practice recommendations (details see appendix 4)	

Table 14: Overview of recommendations from ADA, IMAGE Study Group and NICE (con`t)

Organization/ Guideline	**IMAGE Study Group, Paulweber et al., 2010 A European Evidence-Based Guideline for the Prevention of Type 2 Diabetes**	
Source: Paulweber, B. et al., (2010). A European Evidence-Based Guideline for the Prevention of Type 2 Diabetes. Hormone and Metabolic Research, Volume 42, page S1–S64, April 2010		**Evidence level**
Recommendations (A+B level Evidence)	• Intensive lifestyle interventions that encourage people to change their diet and to increase their level of physical activity should be used to prevent or delay the onset of T2DM in adults with IGT. The NNT for prevention of one case of T2DM of 6.4 [95% CI 5.0, 8.4] at mean follow up ranging from 1.83 to 4.62 years.	A
	• Weight reduction is an essential element of T2DM prevention. Sustained weight reduction by 5–7% is sufficient to substantially lower the risk of T2DM.	A
	• An increase in physical activity even at a level of 30 minutes per day of moderate exercise reduces the risk of T2DM and is therefore recommended.	B
	• A diet with high fibre (≥ 15 g per 1000 kcal), moderate fat (≤ 35% of total energy) reduced saturated and trans fat (< 10% of total energy) can lower body weight and reduce the risk of T2DM and is therefore recommended.	B

	• Interventions should
	  • aim to promote changes in both diet and physical activity
	  • use established, well defined behavior change techniques (e. g., specific goal-setting, relapse prevention, self-monitoring, motivational interviewing).
	  • encourage participants to engage social support for the planned behaviour change
	  • include a strong focus on maintenance.
	  • maximize the frequency of number of contacts within the resources available.
		
		A
		A
		A
		A
		A
		B

Evidence search and included studies /RCTs on lifestyle intervention	• systematic search for primary studies, systematic reviews and meta-analyses of research on preventing the onset of T2DM. • initial search was undertaken using MEDLINE with follow-up of cited references. • final selection limited to randomized controlled trials (RCTs) published in English between1979 and 2008, which featured development of T2DM as a study endpoint and used standard criteria for the diagnosis of diabetes mellitus. Included studies: DPP, DPS, Da Qing, IDPP, Japanese trial in IGT males (Kosaka et al., 2005)	
Grading system	SIGN (details see appendix 4)	

Table 14: Overview of recommendations from ADA, IMAGE Study Group and NICE (con`t)

Organization/ Guideline	**National Institute for Health and Care Excellence (NICE) (2012). Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. (NICE public health guidance 38)**	
Source: National Institute for Health and Care Excellence (NICE) (2012). Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. NICE public health guidance 38, retrieved from http://www.nice.org.uk/nicemedia/live/13791/59951/59951.pdf on 18th of November 2013		**Evidence level**
Recommendations	• For people confirmed as being at high risk a referral to a local, evidence-based, quality-assured intensive lifestyle change program should be offered.	

	• Intensive lifestyle-change programs should offer ongoing tailored advice, support and encouragement to help people:
	  • undertake a minimum of 150 minutes of 'moderate-intensity' physical activity per week
	  • gradually lose weight to reach and maintain a BMI within the healthy range
	  • increase their consumption of whole grains, vegetables and other foods that are high in dietary fibre
	  • reduce the total amount of fat in their diet
	  • eat less saturated fat.	

	• Established behaviour-change techniques should be used, inter alia information provision, exploration and reinforcement of participants' reasons for wanting to change, goal setting, action planning, coping plans and relapse prevention	
	• Participants should be encouraged to involve a family member, friend or carer who can offer emotional, information, planning or other practical support to help them make the necessary changes.	
	• Participants should be encouraged to use self-regulation techniques.	
Evidence search and included studies /RCTs on lifestyle intervention	• Evidence relies on the ScHAAR review and meta-analysis by Jones et al., 2011, which has been described in detail in chapter 5.1.2 and on additional systematic reviews and expert papers which can be found on http://publications.nice.org.uk/preventing-type-2-diabetes-risk-identification-and-interventions-for-individuals-at-high-risk-ph38/appendix-e-supporting-documents	
Grading system	-	

Interestingly enough none of the organizations raises the question, whether prevention of T2DM should be considered a surrogate parameter only or if T2DM is a valid surrogate for CVD or mortality. Furthermore, the organizations do not discuss if hard endpoints like CVD risk or mortality reduction should be proven in order to recommend lifestyle interventions to patients and health care providers. One reason could be that the evidence base of the reviews, on which the recommendations are based, is broader and also included study types other than RCTs.

As pointed out in chapter 5.2 significant reductions in long term adverse health outcomes like CVD risk, CVD or all-cause mortality could neither be found in the 4 identified reviews nor in the individual RCTs that have been included in the ScHARR review by Jones et al. However, risk calculations from a population-based reference study cohort (FINRISK) of the Finnish DPS show that all-cause mortality in people with IGT is higher than in those with NGT, but lower than all-cause mortality rates of people with known T2DM. The mortality rates were 6.6, 16.4, 21.0, and 28.8 per 1000 person-years in the NGT, IGT, ST2DM and known T2DM groups, respectively. The adjusted HRs for all-cause mortality were 0.52 (0.36–0.74) and 1.96 (1.15–3.34) for NGT and known T2DM compared to IGT, respectively (Uusitupa et al., 2009). Furthermore, there was also a statistically significant - albeit marginal - difference in CVD event rates between individuals with IGT compared to those with known T2DM (adjusted HR for known T2DM compared to IGT: 1.64 (1.02–2.15) (Uusitupa et al., 2009).

In addition Kowall et al. investigated all-cause and cause-specific mortality in an older German population, a total of 1466 subjects aged 55-74 years from the KORA population based survey (Kowall et al., 2011). They found that the age and sex adjusted mortality rate for 1000 person years was substantially higher in individuals with undiagnosed or known T2DM compared to individuals with IGT (IGT: 10.52 (7.67–14.42), undiagnosed T2DM: 33.05 (21.88–49.91), known T2DM: 28.78 (20.62–40.16)). Kowall et al. concluded that "… all-cause mortality in persons with undiagnosed or known diabetes is strongly increased compared with persons with prediabetes and NGT." (Kowall et al., 2011, p. 643)

In conclusion there is evidence from population-based observational studies but not from RCTs in high-risk individuals that mortality rates are lower in people with IGT compared to individuals with T2DM. In addition the likelihood of remaining

diabetes free or returning to NGT is greater for individuals in the IGs than those in the CGs in all included reviews or large RCTs, respectively (see figure 4) (Gillett et al., 2012).

There are several possible explanations why no significant risk reductions for CVD or mortality could be observed in the lifestyle groups compared to the control groups. As Uusitupa et al. pointed out the Finnish DPS - and most of the other trials - had initially not been designed to investigate endpoints and therefore might lack statistical power to detect small differences (Uusitupa et al., 2009). Furthermore, it is well known that volunteers in randomized controlled trials usually are not representative for the whole population, because they tend to be more health-conscious, motivated and educated than the general population. This also applies for the control group and has been shown for the Finnish DPS (Uusitupa et al., 2009). In addition data from the Finnish DPS has revealed that a certain number of participants in the control group also changed lifestyle habits over the years. At first post-intervention follow-up visit 40% of the control group participants had achieved one of the lifestyle goals and 7% had achieved at least four out of five predefined targets (Lindström et al., 2006). This kind of “contamination” in the control group could be one additional reason for the lack of significant differences in CVD risk and mortality between control and intervention group in the trials.

Besides those methodological considerations it cannot be ruled out that lifestyle interventions in high-risk individuals simply are not able to reduce CVD risk and mortality. Reasons could be that the implemented lifestyle changes might be sufficient to reduce T2DM incidence but not intensive enough to reduce CVD event rates and mortality. Another reason could be that lifestyle change came too late to reverse the deleterious effects of overweight, lack of physical activity and unhealthy diet which presumably have acted upon the organism of most high-risk participants for years. As pointed out in the Joint ESC Guidelines from 2012 evidence has increased over the last decades that cardiovascular disease risk starts to develop at a young age and thus a healthy lifestyle in the young is crucial to prevent CVD events (European Society of Cardiology, 2012). In addition Lindström et al. concluded that “The high diabetes incidence even in the intervention group of our study suggests that preventive actions should probably be targeted to all high-risk individuals, even before impaired glucose tolerance is present.” (Lindström et al., 2006, p. 1678)

Last but not least cardiovascular disease has a multi-factorial genesis (European Society of Cardiology, 2012) and it can be assumed that many of the trial participants had multiple risk factors in addition to IGT since many of them had been diagnosed with metabolic syndrome, at least in the IDPP, the DDP, the DPS and the Da Qing trial. Therefore other risk factors like elevated blood pressure, blood cholesterol levels and abdominal obesity might be responsible for the fact that improved glycemic control or prevention of T2DM did not translate into reduced CVD event rates or reduced mortality.

6.3 Methodological considerations

This chapter deals with methodological considerations. First of all it will be discussed if systematic reviews and meta-analyses are the appropriate method for the evaluation of complex interventions. Secondly the question will be raised whether relying solely on reviews of controlled studies as information source for EBHI is appropriate with respect to the patients' or citizens' information needs.

From a methodological point of view lifestyle intervention programs should be considered as complex interventions. Complex interventions are defined by Mühlhauser et al. as follows: "They comprise interdependent components differently interacting within various complex settings." (Mühlhauser et al., 2011, p. 752).

Applying this definition to lifestyle interventions for the prevention of T2DM, interdependent intervention components would be, for example, a change in dietary fat intake, calorie intake and weight loss. Furthermore, the intervention components used to deliver the program can also be regarded as complex: the use or selection of behavior change strategies, skills of program delivery personnel or the delivery mode are examples of program characteristics which are likely to interact and distinguish different programs from each other. In addition the interventions would typically address different target groups in different settings (e.g. people of Asian ethnicity in an Indian, Chinese, Japanese or US cultural setting compared to Finnish participants in a European cultural setting). Furthermore, the trial participants are part of social systems in their families or at their workplace which influence success in lifestyle change and it can be assumed that the influences differ substantially between the different settings.

Although there is "…no sharp boundary between simple and complex interventions" (Craig et al., 2008) it is obvious that the success of changing eating behavior or physical activity patterns depends on more influencing factors than for example drug treatment and thus can be regarded as complex. This might have consequences concerning the appropriate method of evaluation.

Mühlhauser et al. pointed out that "….Appraising the efficacy, benefit and harm of complex interventions is far more difficult than appraising single interventions like specific drug treatments." (Mühlhauser et al., 2011, p. 752). In addition Lenz et al. argued that meta-analysis might not be the appropriate method to appraise complex interventions and that "…pooling of outcome measures across different programmes is usually inappropriate" (Lenz et al., 2007, p. 1375). After reviewing the literature and methodological guidance of international organizations on the appraisal and synthesis of complex interventions they concluded: "Complex interventions require multistage development, use of different methods, reporting on all developing phases and new approaches for synthesis. Presentation of the complete evidence on a specific complex intervention might be more useful than synthesis of a variety of different complex interventions by customarily applied methods of (metaanalytical) systematic review." (Mühlhauser et al., 2011, p. 752)

Applying this line of reasoning to the topic of this master thesis it is worth discussing if systematic reviews or meta-analyses are the (only) appropriate method of evaluating effectiveness of lifestyle interventions or gaining information for EBHI.

First of all it should be considered that the included RCTs in the ScHARR review showed substantial differences concerning intervention type, intensity and duration, follow-up time, recruits in terms of ethnicity, age, BMI and other characteristics as well as study quality. Nevertheless all RCTs were included in the meta-analysis. In contrast Gillett et al. pointed out that in their review from 2012 meta-analysis was not performed because of these differences (Gillett et al., 2012).

Secondly, one could argue that valuable information provided by single RCTs is lost, when only evidence from systematic reviews is considered appropriate. As illustrated in chapter 5.2 there is evidence on the basis of RCTs that lifestyle interventions provide benefits in terms of development of retinopathy and HRQoL

in high-risk individuals. In addition results of population based observational studies indicate that mortality rates are lower in people with IGT compared to individuals with T2DM. Accordingly as pointed out in chapter 6.2 all organizations, which prepared evidence based guidelines on diabetes prevention, did not question the view that delay or prevention of T2DM is a benefit to patients.

In addition a wider use of all evidence and not just evidence from systematic reviews of controlled trials may be justified by the information needs of consumers and patients. In a paper of the European Medicines Agency, which deals with the expectations of patients, consumers and healthcare professionals, the authors pointed out that "…a great deal of information on the benefits and risks of medicines is expected; qualitative and quantitative descriptions of the benefits and risks, data in specific sub-populations, comparative data with alternative treatments, success factors and risk factors." (EMEA, 2009) Relating this general description of information needs to the topic of this master thesis it became obvious that in depth information on adherence, quality of interventions, dose-effect-relationships and long term outcomes has not been available on the level of systematic reviews but in contrast is available from individual RCTs (see chapter 5.3).

The main argument for relying mainly on systematic reviews of RCTs from the IQWIG point of view is the higher certainty of findings and statements. On the other hand the concept of health literacy comprises also the consumers` knowledge about the inherent element of uncertainty in scientific findings. Therefore EBHI could also aim to raise awareness of uncertainty in medical knowledge by presenting knowledge on different evidence levels rather than only giving information which has been proven on the level of systematic reviews.

It should therefore be considered whether a system, which is similar to the levels of evidence in evidence based guidelines, could be developed, which would inform patients and consumers in an easily understandable way about the certainty of the communicated information. This would make it more likely that statements could be made in EBHI about issues, which are relevant to patients and consumers. However, it is well known that the knowledge about different study types and their ability to provide evidence is very limited in the general population (Klemperer and Dierks, 2012). Therefore close collaboration with users and evaluation of understanding of such an information system would be desirable.

With respect to evidence levels and study types it should be considered that the Oxford Centre of Evidence Based Medicine in its publication on “Levels on Evidence” from March 2009 also regards individual RCTs with narrow confidence intervals as level 1b evidence which could translate into a grade A recommendation (see appendix 5) (Oxford Centre for Evidence Based Medicine, 2009). In addition organizations that are primarily concerned with issues of prevention like WHO or the World Cancer Research Fund have developed systems of evidence synthesis that take into account evidence from study types other than RCTs (WHO, 2003; WCRF, 2007). Summing up, the following questions should be answered before preparing EBHI on the prevention of T2DM:

1. Should T2DM be considered a surrogate endpoint and if yes, is it a valid surrogate marker for patient-relevant outcomes?
2. Should the term “sufficiently strong evidence” (see table 7) be translated into evidence on the basis of systematic reviews only or should evidence from other types of studies also be included in order to meet the information needs of consumers and patients.
3. What are the questions of high-risk and also lower risk individuals (i.e. consumers in general) that should be answered by EBHI?
4. What do experts in the field think about the issues discussed here?

6.4 The relative importance of EBHI on diabetes prevention from a public health perspective.

As this master thesis has been written in order to attain the degree of a Master of Public Health brief consideration will be given to the relative importance of EBHI from a public health perspective.

EBHI on the effectiveness of lifestyle changes on diabetes risk may be a necessary but not sufficient condition for behavior change for the individual. It is well known that reading and understanding information is not the same as acting according to that information. As Marstedt and Rosenbrock put it: “Between the knowledge and the understanding of a health message and its transposition into one`s own way of life, a number of hurdles (Rosenbrock and Michel 2006) appear, which make the great majority even of those, who would like to follow the message, fail.” (Marstedt and Rosenbrook, 2010, own translation). As experts in the field are well aware of this problem, simply providing information on a healthy lifestyle has been the control intervention in most of the trials. In other words, EBHI

on the effectiveness of lifestyle changes may generate the desire for behavioral change in high risk individuals, but other factors may determine whether such intentions result in an actual change of lifestyle and risk.

On the other hand it is conceivable that an evidence based statement of the IQWIG about the effectiveness of LI on the prevention of T2DM could also reach policy makers, change their knowledge, alter attitudes to the topic and eventually lead to implementation of lifestyle intervention programs for high-risk individuals in Germany.

From a broader public health perspective strategies to reduce diabetes incidence, which focus solely on programs that aim at behavior change of the individual affected, do not seem to be very promising. As Dahlgren and Whitehead pointed out in 1991 already, health is determined by a variety of influences which can be grouped into different categories as shown in figure 5. General socio-economic, cultural and environmental living conditions as well as the material and social conditions people live in are of major influence on health. Furthermore, the social networks – that is support of family, friends and communities – greatly influence health but also lifestyle habits of the individual (Dahlgren and Whitehead, 1991).

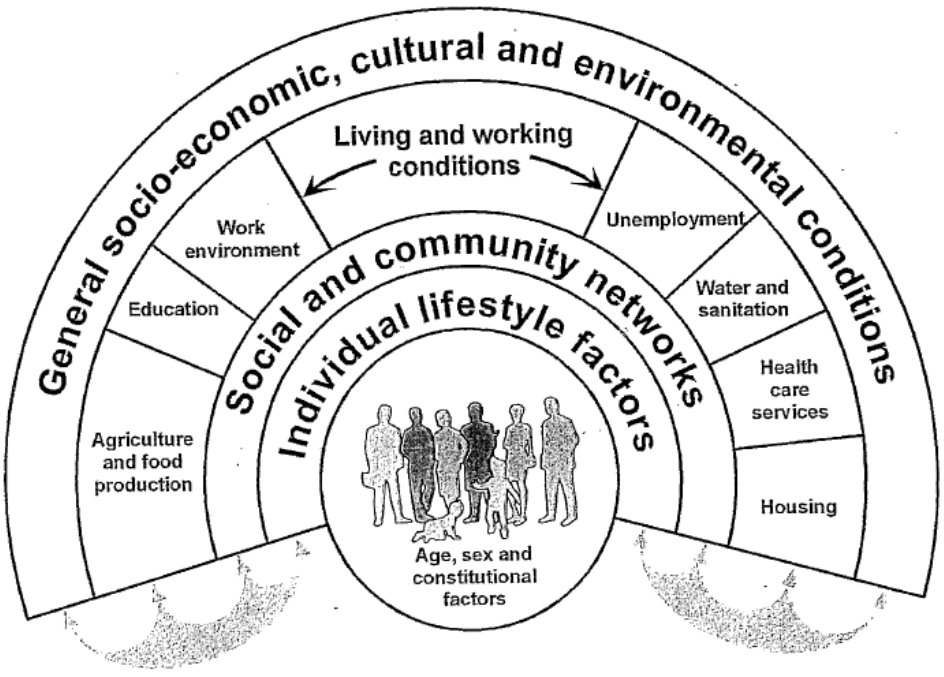

Figure 5: The main determinants of health (Dahlgren and Whitehead, 1991, p.11)

This might partially explain why so many participants in the LI programs had difficulty making or maintaining lifestyle changes. Dahlgren and Whitehead pointed out: “All too often, strategies are only considered at one policy level, yet concerted effort at several levels would in many cases be far more effective. The reinforcing – synergetic – effects of this type of vertical health policy is in fact the very key for improving the impact of health policies in general and strategies to reduce social inequities in particular.” (Dahlgren and Whitehead, 1991, p. 11)

Translated to the topic of this master thesis it can be concluded that a public health approach on diabetes prevention should tackle different layers of influence on health simultaneously, identify and possibly change the behavioral incentives in the living environments (Marstedt and Rosenbrock, 2010), so that a healthy lifestyle can be implemented more easily.

Elements included in a public health diabetes prevention strategy could for example encompass legislative changes (policies to reduce specific nutrients in foods e.g. trans fats, and to improve labeling and advertising regulations), sustained media and educational campaigns, multi-component school and workplace interventions, economic incentives (e.g. strategies to lower prices of healthier foods and beverages) and community support to produce favorable environments for physical activity (e.g. access to sport facilities and urban design) (Paulweber et al., 2010; Mozaffarian et al., 2012). Also the WHO stated: “The public and private sectors also have an important role to play in developing and implementing policies and programmes that increase knowledge about diabetes, its prevalence and consequences, encourage and provide greater opportunities for greater physical activity, and improve the availability and accessibility of healthy foods.” (WHO Europe, 2013)

Summing up it seems most likely that the implementation of lifestyle intervention programs for high-risk individuals combined with comprehensive public health policies will be the most promising strategy to reduce diabetes incidence at the population level. This view is supported by scientific papers by NICE and the IMAGE study group alike (NICE, 2011; Paulweber et al., 2010)

7 Conclusions and Outlook

The systematic search for evidence has shown that lifestyle interventions can delay or prevent the progression to T2DM in high-risk individuals. The pooled HR of the intervention groups versus controls was 0.51 (95% CI 0.43-0.62) in a meta-analysis of 11 randomized controlled trials. Assuming an annual diabetes incidence of 11% as in the DPP study, the calculated absolute risk of diabetes would be 5.61% (95% CI 4.73- 6.82) in the intervention groups. Thus it can be concluded that the systematic search for the best available external evidence resulted in a suitable basis for the production of EBHI on diabetes prevention. These results are, however, restricted to a very specific population, namely high-risk individuals. However, results from epidemiological studies in the general population also show that individuals adhering to a healthy lifestyle combining several factors like physical activity, diet, smoking and alcohol habits can substantially lower their risk for T2DM (Mozaffarian et al., 2009).

Evidence for the benefit of LI in terms of patient relevant outcomes like CVD risk, CVD mortality, all-cause mortality, morbidity or HRQoL in high-risk individuals is less clear. As pointed out in chapter 5.2 significant reductions in long term adverse health outcomes could neither be found in the 4 identified reviews nor in the individual RCTs that have been included in the ScHARR review. However, long term follow-up data of individual RCTs indicated benefits of LI in terms of microvascular complications like diabetic retinopathy and HRQoL. Open questions, which should be addressed by future research, therefore relate to the optimal time of intervention, the required intensity of lifestyle change and above all, how adherence to and maintenance of lifestyle change can be supported. Moreover, it will be a task for the future to translate the success from randomized controlled trials to everyday patient care in health care systems.

Methodological considerations lead to the question, whether or not EBHI on preventive issues should solely rely on the results of systematic reviews of controlled trials. Although this systematic literature research retrieved enough high-level, external evidence on the preventive effects of LI in high-risk individuals, it can be doubted that a similar search for evidence focusing on the general population would yield enough evidence on the basis of reviews of CTs or even individual RCTs, simply because such studies are unlikely to be feasible in practice nor fundable. Therefore EBHI on preventive issues relying solely on high-level

evidence is in danger of being flawed by inherent methodological problems of studies in primary prevention and issues of research agenda bias. Consequently, it should be considered to develop a communication tool similar to the evidence levels used in guidelines that would help consumers and patients understand the different levels of certainty/evidence in scientific knowledge. This would probably allow for communicating also findings from well-designed cohort studies, describing detailed information from individual RCTs, disseminating EBHI on a broader range of topics and thus meet the information needs of the general population concerning questions in primary prevention. In addition, once understood patients and consumers themselves could decide which level of evidence they consider sufficient or necessary for their decisions, which would strengthen patient and consumer autonomy.

For the future it will be very interesting in which way the IQWIG Department of Health Information will develop their methods for the preparation of EBHI on issues of primary prevention.

References:

American Diabetes Association (ADA) (2003). Follow-up Report on the Diagnosis of Diabetes Mellitus. Diabetes Care, 26 (11), 3160-3167

American Diabetes Association (ADA) (2013). Standards of Medical Care in Diabetes – 2013. Diabetes Care, 36, Supplement 1, S11-66

Barr, E.L.M., Zimmet, P.Z., Welborn,T.A., Jolley, D., Magliano, D.J., Dunstan, D.W., Cameron, A.J., Dwyer, T., Taylor, H.R., Tonkin, A.M., Wong, T.Y., McNeil, J., Shaw, J.E. (2007). Risk of Cardiovascular and All-Cause Mortality in Individuals With Diabetes Mellitus, Impaired Fasting Glucose and Impaired Glucose Tolerance: The Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Circulation, 116, 151-157

Bo, S., Ciccone, G., Baldi, C., Dusio, F., Forastiere, G., Lucia, C., Nuti, C.,, Durazzo, M., Cassader, M., Gentile, L., Pagano, G. (2007). Effectiveness of a lifestyle intervention on metabolic syndrome. A randomized controlled trial. Journal of General Internal Medicine, 22(12), 1695-1703

Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) (2013). Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes – Kurzfassung. Version 1.0. 2013. Retrieved from http://www.versorgungsleitlinien.de/themen/diabetes2/dm2_Therapie on 30th of October 2013

Bundesministerium für Gesundheit, Bundesministerium für Justiz. (2003). Patientenrechte in Deutschland. Leitfaden für Patienten und Ärzte. Retrieved from http://www.uke.de/studierende/downloads/zg-studierende/Patientencharta.pdf on 30th of October 2013

Bundesministerium für Justiz.. Patientenrechte im Klartext. Retrieved from http://www.bmj.de/DE/Buerger/gesellschaft/Patientenrechte/_node.html on 30th of October 2013

Coutinho, M., Gerstein, H.C., Wang, Y., Yusuf, S. (1999). The Relationship Between Glucose and Incident Cardiovascular Events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care, 22, 233–240

Craig, P. Dieppe, P. Macintyre, S., Mithcie, S. Nazareth, I. Petticrew, M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. British Medical Journal, 25 October 2008, 337, 979-983

Dahlgren, G., Whitehead, M. (1991). Policies and strategies to promote social equity in health. Background document to WHO-Strategy paper in Europe. Institute for Future Studies. Retrieved from http://www.framtidsstudier.se/wp-content/uploads/2011/01/20080109110739filmZ8UVQv2wQFShMRF6cuT.pdf on 15th of November 2013

Diabetes Australia (2008). Evidence based guideline for the primary prevention of type 2 diabetes. Retrieved from www.diabetesaustralia.com.au/PageFiles/763/Primarypreventionguideline.pdf on 30th of October 2013

Diabetes Prevention Program Research Group (2006). Relationship of body size and shape to the development of diabetes in the diabetes prevention program. Obesity, 14, 2107-17

Diabetes Prevention Program Research Group (2009). 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. The Lancet, 374, 1677-1686.

Dunkley A.J., Charles, K., Gray, L.J., Camosso-Stefinovic, J., Davies, M.J., Khunti, K. (2012) Effectiveness of interventions for reducing diabetes and cardiovascular disease risk in people with metabolic syndrome: systematic review and mixed treatment comparison meta-analysis. Diabetes, Obesity and Metabolism, 14(7), 616-625.

Emerging Risk Factor Collaboration (The) (ERFC) (2011). Diabetes mellitus, Fasting Glucose and Risk of Cause-Specific Death. New England Journal of Medicine, 364, 829-41

Eriksson, J., Lindström, J., Valle, T., Aunola, S., Hämäläinen, H., Ilanne-Parikka, P., Keinänen-Kiukaanniemi, S., Laakso, M., Lauhkonen, M., Lehto, P. Louheranta, A., Mannelin, M., Martikkala, V. Rastas, M., Sundvall, J., Turpeinen, A., Viljanen, T., Uusitupa, M., Tuomilehto, J. (1999). Prevention of Type II diabetes in subjects with impaired glucose tolerance: the Diabetes Prevention Study. Study Design and one year interim report on the feasibility of the lifestyle intervention programme. Diabetologica, 42 (7), 793-801

European Medicines Agency (2009). Information on benefit-risk of medicines: patients', consumers' and healthcare professionals' expectations. Report by the Patients' and Consumers' Working Party (PCWP) and the Healthcare Professionals' Working Group (HCP WG). Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500018433.pdf on 14th of November 2013

European Society of Cardiology (2012). European Guidelines on cardiovascular disease prevention in clinical practice (Version 2012). European Heart Journal, 33, 1635-1701

Florez, H., Pan, Q., Ackermann, R.T., Marrero, D.G., Barrett-Connor, E., Delahanty, L., Kriska, A., Saudek, C.D., Goldberg, R.B., Rubin, R.R. for the Diabetes Prevention Program Research Group (2012). Impact of Lifestyle Intervention and Metformin on Health-Related Quality of Life: the Diabetes Prevention Program Randomized Trial. Journal of General and Internal Medicine, 27(12), 1594-1601

Gaissmaier, W., Gigerenzer, G. (2011). When Misinformed Patients Try to Make Informed Health Decisions. In: G. Gigerenzer and J.A. Muir Gray (Hrsg.), Better Doctors, Better Patients, Better Decisions – Envisioning Health Care 2020 (pp 29-43). Cambridge, Massachusetts, London, England: The MIT Press

Gillies, C.L., Abrams, K.R., Lambert, P.C., Cooper, N.J., Sutton, A.J., Hsu, R.T., Khunti, K. (2007). Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. British Medical Journal, 334, 299-302

Gillett, M., Royle, P., Snaith, A., Scotland, G., Poobalan, A., Imamura, M., Black, C., Boroujerdi, M., Jick, S., Wyness, L., McNamee, P., Brennan, A., Waugh, N. (2012). Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: a systematic review and economic evaluation. Health Technology Assessment 2012, 16(33)

Gong, Q., Gregg, W., Wang, J. An, Y., Zhang, P., Yang, W. Li, H., Jiang, Y., Shuai, Y., Zhang, B., Zhang, J., Gerzoff, R.B., Roglic, G., Hu, Y., Li, G., Bennett, P.H. (2011). Long-term effects of a randomised trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study. Diabetologia, 54, 300–307

Greaves, C.J., Sheppard, K.E., Abraham, C., Hardeman, W., Roden, M., Evans, P.H., Schwarz, P., The IMAGE Study Group (2011). Systematic review of reviews of intervention components associated with increased effectiveness in dietary and physical activity interventions. BioMed Central Public Health 2011, 11:119

Han, T.S., Sattar, N., Lean, M. (2006). ABC of obesity. Assessment of obesity and its clinical implications. British Medical Journal, 333, 695-698

Hart, C.L., Hole, D.J., Lawlor, D.A., Davey, S.G. (2007). How many cases of type 2 diabetes mellitus are due to being overweight in middle age? Evidence from the Midspan prospective cohort studies using mention of diabetes mellitus on hospital discharge or death records. Diabetic Medicine, 24, 73-80

Heidemann C., Du Y., Scheidt-Nave, C. (2011). Diabetes mellitus in Deutschland. in: Robert Koch-Institut Berlin (Hrsg.), GBE kompakt 2(3) www.rki.de/gbe-kompakt (Stand: 06.05.2011), Retrieved from http://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsK/2011_3_diabetes.html?nn=2531734 on 16th of August 2013

Heidemann, C., Du, Y., Schubert, I., Rathmann, W., Scheidt-Nave, C. (2013). Prevalence and temporal trend of known diabetes mellitus. Bundesgesundheitsblatt, 56, 668-677

Institute of Medicine (IOM) (2004) Health Literacy: A prescription to end the confusion. Report Brief, Retrieved from http://www.iom.edu/~/media/Files/Report%20Files/2004/Health-Literacy-A-Prescription-to-End-Confusion/healthliteracyfinal.pdf on 16th of August 2013

International Diabetes Federation (IDF) (2012). IDF Diabetes Atlas Update 2012, Retrieved from http://www.idf.org/diabetesatlas/5e/Update2012 on 15th of August 2013

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) (2011). General Methods Version 4.0 of 23.09.2011, Retrieved from https://www.iqwig.de/download/IQWiG_Methoden_Version_4_0.pdf on 16th of August 2013

Jarrett, R. J., Keen, H., Fuller, J. H., McCartney, M. (1979) Worsening to Diabetes in Men with Impaired Glucose Tolerance ("Borderline Diabetes"). Diabetologia, 16(1), 25-30.

Jones, R., Freeman, C., Johnson, M., Stevens, J., Buckley Woods, H., Guillaume, L., Gillies, C., Goyder, E., Chilcott, J., Payne, N., ScHARR Public Health Collaboration Centre (2011). Preventing the progression of pre-diabetes to type 2 diabetes in adults. Systematic review and meta-analysis of lifestyle, pharmacological and surgical interventions. Retrieved from http://guidance.nice.org.uk/PH38/SupportingEvidence on 18th of September 2013

Johnson, M., Jones, R., Freeman, C., Buckley Woods, H., Gillett, M., Ram, V., Sidwell, A., Goyder, E., Chilcott, J., Payne, N. ScHARR Public Health Collaboration Centre (2011). Prevention of type 2 diabetes: Reviewing mechanisms of successful interventions and translation of major trial evidence to practice. Retrieved from http://guidance.nice.org.uk/PH38/SupportingEvidence on 18th of September 2013

Katz, R. (2004). Biomarkers and Surrogate Markers: An FDA Perspective. NeuroRx_: The Journal of the American Society for Experimental NeuroTherapeutics, 1, 189–195

Klemperer, D., Lang, B., Koch, K., Hilda, B., Brunsmann, F., Burckhardt, M., Dierks, M-L., Ehrmann, U., Günther, J., Härter, M., Mühlhauser, I., Sänger, S., Simon, D., Steckelberg, A. (2010). Die „Gute Praxis Gesundheitsinformation“ Zeitschrift für Evidenz, Fortbildung und Qualität im Gesundheitswesen (ZEFQ), 104, 66-68

Klemperer, D., Dierks, M-L. (2012). Evidenzbasierte Medizin und Qualitätssicherung medizinischer Leistungen: Erfahrungen und Einschätzungen der Bürger. in: Jan Böcken, Bernard Braun, Uwe Repschläger (Hrsg.). Gesundheitsmonitor 2011 (pp. 32-55). Gütersloh, Verlag Bertelsmann Stiftung

Knowler, W.C., Barrett-Connor, E., Fowler, S.E., Hamman, R.F., Lachin, J.M., Walker, E.A., Nathan, D.M.(2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New England Journal of Medicine, 346(6), 393-403

Kosaka, K., Noda, M., Kuzuya, T. (2005) Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Research & Clinical Practice, 67(2), 152-162.

Kowall, B. Rathmann, W., Heier, M., Giani, G., Peters, A., Thorand, B., Huth, C., Icks, A., Meisinger, C. (2011). Categories of glucose tolerance and continuous glycemic measures and mortality. European Journal of Epidemiology, 26, 637–645

LeBlanc, E.S., O'Connor, E., Whitlock, E.P., Patnode, C.D., Kapka, T. (2011). Screening for and Management of Obesity and Overweight in Adults. Evidence Report No. 89. AHRQ Publication No. 11-05159-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; October 2011

Levitan, E.B., Song, Y., Ford, E.S., Liu, S. (2005). Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Journal of the American Medical Association, 293, 194-202 cited in WHO ((2006). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. Geneva 2006 Retrieved from http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf on 12th of August 2013

Li, G., Zhang, P., Wang, J., Gregg, E.W., Yang, W., Gong, Q., Li, H. Li, H. Jiang, Y., An, Y. Shuai, Y., Zhang, B. Zhang, J. Thompson, T.J., Gerzoff, R.B., Roglic, G. Hu, Y. Bennett, P.H. (2008). The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. The Lancet, 371, 1783–89

Liao, D., Asberry, P. J., Shofer, J. B., Callahan, H., Matthys, C., Boyko, E. J., Leonetti, D., Kahn, S. E., Austin, M., Newell, L., Schwartz, R. S., Fujimoto, W. Y. (2002). Improvement of BMI, body composition and body fat distribution with lifestyle modification in Japanese Americans with impaired glucose tolerance. Diabetes Care, 25, 1504-1510.

Lindahl, B., Nilsson, T.K., Borch-Johnsen, K., Röder, M.E., Soderberg, S., Widman, L., Johnson, O., Hallmanns, G., Jansson, J.H. (2009). A randomized lifestyle intervention with 5-year follow-up in subjects with impaired glucose tolerance: Pronounced short-term impact but long-term adherence problems. Scandinavian Journal of Public Health, 37(4), 434-442.

Lindström, J., Eriksson, J.G.,. Valle, T.T., Aunola, S., Cepaitis, Z., Hakumaki, M., Hämäläinen, H., Ilanne-Parikka, P., Keinänen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Mannelin, M., Martikkala, V., Moltchanov, V., Rastas, M., Salminen, V., Sundvall, J., Uusitupa, M., Tuomilehto, J. (2003). Prevention of Diabetes Mellitus in Subjects with Impaired Glucose Tolerance in the Finnish Diabetes Prevention Study: Results from a Randomized Clinical Trial. Journal of the American Society of Nephrology; 14, S108-S113.

Lindström J., Ilanne-Parikka, P., Peltonen, M., Aunola, S., Eriksson, J.G., Hemiö, K., Hämäläinen, H., , Härkönen, P., Keinänen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Mannelin, M., Paturi, M., Sundvall, J., Valle T.T., Uusitupa, M., Tuomilehto, J. (2006). Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. The Lancet, 368(11), 1673-1679.

Little, P. Everitt, H., Williamson, I., Warner, G., Moore, M., Gould, C., Ferrier, K., Payne, S. (2001). Preferences of patients for patient centred approach to consultation in primary care: observational study. British Medical Journal, 322, 1–7

Marrero, D., Pan, Q., Barrett-Connor, E., de Groot, m., Zhang, P. Percy, C., Florez, H., Ackermann, R., Montez, M., Rubin, R.R. (DPPOS Research Group) (2013). Impact of diagnosis of diabetes on health-related quality of life among high risk individuals: the Diabetes Prevention Program outcomes study. Quality of Life Research. Retrieved from http://download.springer.com/static/pdf/200/art%253A10.1007%252Fs11136-013-0436-3.pdf?auth66=1383566131_86cf77d12a0fd8fc179617aeccf4c5d4&ext=.pdf on 2th of November 2013

Marstedt, G., Rosenbrock, R. (2010). Verhaltensprävention: Guter Wille allein reicht nicht. in: Jan Böcken, Bernard Braun, Juliane Landmann (Hrsg.): Gesundheitsmonitor 2009 (pp. 12-37). Gütersloh, Verlag Bertelsmann Stiftung

Miron-Shatz, T., Mühlhauser, I., Bower, B., Diefenbach, M., Goldacre, B., Smith, R.S.W., Spiegelhalter, D., Wegwarth, O. (2011). Barriers to Health Information and Building Solutions. In: G. Gigerenzer and J.A. Muir Gray (Hrsg.), Better Doctors, Better Patients, Better Decisions – Envisioning Health Care 2020 (pp 191-212). Cambridge, Massachusetts, London, England: The MIT Press

Mozaffarian, D., Kamineni, A. Carnethon, M., Djoussé, L., Mukamal, K.-J., Siscovick, D. (2009). Lifestyle Risk Factors and New-Onset Diabetes Mellitus in Older Adults: The Cardiovascular Health Study, Archives of Internal Medicine, 169(8), 798-807

Mozaffarian, D., Afshin, A., Benowitz, N.L., Bittner, V., Daniels, S.R., Franch, H.A., Jacobs, D.R. Jr., Kraus, W.E., Kris-Etherton, P.M., Krummel, D.A., Popkin, B.M., Whitsel, L.P., Zakai, N.A. on behalf of the American Heart Association Council on Epidemiology and Prevention, Council on Nutrition, Physical Activity and Metabolism, Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on the Kidney in Cardiovascular Disease, Council on Peripheral Vascular Disease, and the Advocacy Coordinating Committee. (2012). Population approaches to improve diet, physical activity, and smoking habits: a scientific statement from the American Heart Association. Circulation, 126, 1514 –1563.

National Institute for Health and Clinical Excellence (2011). Preventing type 2 diabetes: population and community level interventions. NICE public health guidance 35. Retrieved from http://www.nice.org.uk/nicemedia/live/13472/54345/54345.pdf on 15th of November 2013

National Institute for Health and Care Excellence (NICE) (2012). Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. NICE public health guidance 38.
Retrieved from http://www.nice.org.uk/nicemedia/live/13791/59951/59951.pdf on 18th of November 2013

Nathan, D.M., Chew, E., Christophi, C.A., Davis, M.D., Fowler, S. Goldstein, B.J., Hamman, R.F., Hubbard, L.D. Knowler, W.C., Molitch, M.E. (Diabetes Prevention Program Research Group) (2007). The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. Diabetic Medicine, 24, 137–144

Orozco L.J., Buchleitner, A.M., Gimenez-Perez, G., Roque, I.F., Richter, B., Mauricio, D. (2008). Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database of Systematic Reviews, cited in Gillett et al., 2012

Oxford Centre for Evidence Based Medicine (2009). Levels of Evidence (March 2009). Retrieved from http://www.cebm.net/index.aspx?o=4590 on 14th of November 2013

Oxman, A.D., Guyatt, G.H. (1991). Validation of an index of the quality of review articles. Journal of Clinical Epidemiology, 44(11), 1271-1278.

Pan, X.R., Li, G.W., Hu, Y.H., Wang, J.X., Yang, W.Y., An, Z.X., Hu, Z.X., Lin, J., Xiao, J.Z., Cao, H.B., Liu, P.A., Jiang, X.G., Jiang, Y.Y., Wang, J.P., Zheng, H., Zhang, H., Bennett, P.H., Howard, B.V. (1997). Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: The Da Qing IGT and diabetes study. Diabetes Care, 20(4), 537-44

Paulweber, B., Valensi, P., Lindström,J., Lalic, N.M., Greaves, J.J., McKee, M., Kissimova-Skarbek, K., Liatis, S., Cosson, E., Szendroedi, J., Sheppard, K.E., Charlesworth, K., Felton, A.-M., Hall, M., Rissannen, A., Tuomilehto, J., Schwarz, P. E., Roden, M. for the Writing Group,on behalf of the IMAGE Study Group (2010). A European Evidence-Based Guideline for the Prevention of Type 2 Diabetes. Hormone and Metabolic Research, 42, S1–S64

Penn, L.W., White, M., Oldroyd, J., Walker, M., Alberti, K.G.M.M., Mathers, J.C. (2009). Prevention of type 2 diabetes in adults with impaired glucose tolerance: The European Diabetes Prevention RCT in Newcastle upon Tyne, UK. BioMed Central Public Health 2009; 9, 342

Ramachandran, A., Snehalatha, C., Mary, S., Mukesh, B., Bhaskar, A. D., Vijay, V. (2006) The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia, 49(2), 289-297.

Ramachandran, A., Snehalatha, C., Satyavani, K., Sivasankari, S. Vijay, V. (2007). Metabolic syndrome does not increase the risk of conversion of impaired glucose tolerance to diabetes in Asian Indians: result of Indian diabetes prevention programme. Diabetes Research and Clinical Practice, 76, 215-218

Ratner, R., Goldberg, R., Haffner, S., Marcovina, S., Orchard, T., Fowler.,S., Temprosa, M. (2005). Impact of Intensive Lifestyle and Metformin Therapy on Cardiovascular Disease Risk Factors in the Diabetes Prevention Program. Diabetes Care, 28(4), 888–894

Robert Koch Institut (RKI) (2005). Gesundheitsberichterstattung des Bundes. Heft 24. Diabetes mellitus, Berlin, 14. März 2005 Retrieved from http://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsT/diabetes_mellitus.pdf?__blob=publicationFile on 6th of December 2013

Roumen, C., Corpeleijn, E., Feskens, E.J., Mensink, M., Saris, W.H., Blaak, E.E. (2008). Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabetic Medicine; 25(5), 597-605.

Rubin, R.R., Peyrot, M. (1999). Quality of Life and Diabetes. Diabetes/Metabolism Research and Reviews; 15, 205-218.

Sackett, D.L., Rosenberg, W.M,. Gray, J.A., Haynes, R.B., Richardson, W.S. (1996). Evidence based medicine: what it is and what it isn't". British Medical Journal, 312, 71-72

Santaguida, P.L., Balion, C., Hunt, D., Morrison, K., Gerstein, H., Raina, P., Booker, L., Yazdi, H. (2005). Diagnosis, Prognosis, and Treatment of Impaired Glucose Tolerance and Impaired Fasting Glucose. Summary, Evidence Report/Technology Assessment No. 128. AHRQ Pub. No 05-E026-1. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved from http://archive.ahrq.gov/downloads/pub/evidence/pdf/impglucose/impglucose.pdf on 14th of August 2013

Scottish Intercollegiate Guidelines Network (2011). SIGN 50 - A guideline developer's handbook, First published 2008, Revised November 2011. Retrieved from www.sign.ac.uk on 30th of October 2013

Social Code Book V, Gesetzliche Krankenversicherung, §35 b, Stand: Zuletzt geändert durch Art. 3 G v. 7.8.2013. Retrieved from http://www.sozialgesetzbuch-sgb.de/sgbv/35b.html on 30th of October 2013

Sumamo, E., Ha, C., Korownyk, C., Vandermeer, B., Dryden, D.M. (2011). Lifestyle interventions for four conditions: type 2 diabetes, metabolic syndrome, breast cancer, and prostate cancer. Rockville, MD, USA: Agency for Healthcare Research and Quality. AHRQ Technology Assessment Program. 2011. Retrieved from http://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id82TA.pdf on 18th of September 2013

Tapp, R.J., Dunstan, D.W., Phillips, P. Tonkin, A., Zimmet, P.Z., Shaw, J.E. (2006). Association between impaired glucose metabolism and quality of life: Results from the Australian diabetes obesity and lifestyle study. Diabetes Research and Clinical Practice, 74, 154–161

Thelen, J., Kirsch, N., Hoebel, J. (2012). Gesundheit in Europa - Daten des Gesundheits-monitorings der EU. in: Robert Koch-Institut Berlin (Hrsg.). GBE kompakt 3(6) www.rki.de/gbe-kompakt (Stand: 17.01.2013). Retrieved from http://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsK/2012_6_EU-Gesundheitsmonitoring.pdf;jsessionid=4BE0D8ECE925EBA15BEAD57D8D6D7645.2_cid290?__blob=publicationFile on 15th of August 2013

Tuomilehto, J., Lindstrom, J., Eriksson, J.G., Valle, T., Aunola, S., Hämäläinen, H., Ilanne-Parikka, P., Keinänen-Kiukaanniemi, S., Laakso, M., Louheranta, A., Rastas, M., Salminen, V., Uusitupa, M. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New England Journal of Medicine; 344, 1343-50.

Uusitupa, M., Peltonen, M., Lindström, J., Aunola, S., Ilanne-Parikka, P., Keinänen-Kiukaanniemi, S., Valle, T.T., Eriksson, J.G:, Tuomilehto, J. for the Finnish Diabetes Prevention Study Group (2009). Ten-Year Mortality and Cardiovascular Morbidity in the Finnish Diabetes Prevention Study—Secondary Analysis of the Randomized Trial. PLoS ONE 4(5): e5656. doi:10.1371/journal.pone.0005656

Vadstrup, E.S., Frølich, A., Perrild, H., Borg, E., Røder, M. (2011). Health-related quality of life and self-related health in patients with type 2 diabetes: Effects of group-based rehabilitation versus individual counseling. Health and Quality of Life Outcomes, 9, 110. Retrieved from http://www.hqlo.com/content/9/1/110 on 16th of August 2013

Wein, P., Beischer, N., Harris, C., Permezel, M. (1999). A trial of simple versus intensified dietary modification for prevention of progression to diabetes mellitus in women with impaired glucose tolerance. Australian & New Zealand Journal of Obstetrics & Gynaecology, 39(2), 162-166.

Wieczorek, A., Rys, P., Skrzekowska-Baran, I., Malecki, M. (2008). The Role of Surrogate Endpoints in the Evaluation of Efficacy and Safety of Therapeutic Interventions in Diabetes Mellitus. The Review of Diabetic Studies, 5(3), 128-135

World Cancer Research Fund/ American Institute for Cancer Research (2007). Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007 Retrieved from http://www.dietandcancerreport.org/cancer_resource_center/downloads/Second_Expert_Report_full.pdf on 18th of December 2013

WHO (1999). Definition, diagnosis and classification of diabetes mellitus and its complications, WHO Consultation, Retrieved from http://www.staff.ncl.ac.uk/philip.home/who_dmg.pdf on 16th of August 2013

WHO (2003). Diet, Nutrition and the Prevention of chronic diseases. Report of a joint WHO/FAO expert consultation, Geneva, 28 January -- 1 February 2002., Retrieved from http://whqlibdoc.who.int/trs/who_trs_916.pdf on 18th of December 2013

WHO (2006). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. Geneva 2006. Retrieved from http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf on 16th of August 2013

WHO (2010). 7th Global Conference on Health Promotion Track 2: Health literacy and health behavior. Retrieved from http://www.who.int/healthpromotion/conferences/7gchp/track2/en/index.html on 30th of October 2013

WHO (2011). Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Abbreviated Report of a WHO Consultation. Retrieved from http://www.who.int/diabetes/publications/report-hba1c_2011.pdf, on 26th of September 2013

WHO Europe (2013). Diabetes. Facts and Figures. Retrieved from http://www.euro.who.int/en/what-we-do/health-topics/noncommunicable-diseases/diabetes/facts-and-figures on 15th of August 2013

Statutory Declaration

I hereby declare that I wrote this thesis without any assistance and used only the aids listed. Any material taken from other works, either as a quote or idea have been indicated under “References”.

The conclusions of this thesis were reached by the author and do not necessarily represent the views of IQWIG or its employees.

Appendix

Appendix 1: Application form of the O&G Index used by the IQWIG

OXMAN & GUYATT INDEX (METHODOLOGICAL QUALITY)

1. Were the search methods used to find evidence (original research) on the primary question(s) stated?

❑ Yes ❑ Partially ❑ No

2. Was the search for evidence reasonably comprehensive?

❑ Yes ❑ Can't tell ❑ No

3. Were the criteria used for deciding which studies to include in the overview reported?

❑ Yes ❑ Partially ❑ No

4. Was bias in the selection of studies avoided?

❑ Yes ❑ Can't tell ❑ No

5. Were the criteria used for assessing the validity of the included studies reported?

❑ Yes ❑ Partially ❑ No

6. Was the validity of all studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analysing the studies that are cited)?

❑ Yes ❑ Can't tell ❑ No

7. Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?

❑ Yes ❑ Partially ❑ No

8. Were the findings of the relevant studies combined appropriately relative to the primary question the overview addresses?

❑ Yes ❑ Can't tell ❑ No

9. Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?

❑ Yes ❑ Partially ❑ No

10. How would you rate the scientific quality of the overview?

Extensive Flaws		Major flaws		Minor flaws		Minimal flaws
❑	❑	❑	❑	❑	❑	❑
1	2	3	4	5	6	7

Projektskizze für Recherche

Projekt: Primärprävention des Diabetes mellitus Typ 2 durch Lebensstil-Veränderungen

Projektcode: Z99-96-X-E0

Stand: **08. Mai 2013**

Bearbeiterin: Martina Ehrlich und Karin Riemann-Lorenz

Hintergrund

Im Rahmen des Generalauftrags des Ressorts Gesundheitsinformation soll ein Informationsprodukt zum Thema „Primärprävention des Diabetes mellitus Typ 2 durch Lebensstil-Veränderungen“ erstellt werden. Außerdem soll auf Grundlage der Recherche eine Masterarbeit (Master of Public Health) an der Fakultät Life Sciences der HAW Hamburg, Department Gesundheitswissenschaften durch Frau Karin Riemann-Lorenz erstellt werden.

Ziel des Projekts „Primärprävention des Diabetes mellitus Typ 2 durch Lebensstil-Veränderungen“ ist es, die Wirksamkeit von Lebensstilveränderungen (Änderung des Ess- und Bewegungsverhaltens) auf die Primärprävention von Diabetes mellitus Typ 2 bei Individuen mit erhöhtem Diabetes-Risiko nach Evidenz basierten Kriterien zu überprüfen und darzustellen.

Die Lebensstilveränderung im Bereich Ernährung kann die Verzehrshäufigkeit bestimmter Lebensmittelgruppen (zum Beispiel Obst- und Gemüsekonsum, Fleischkonsum, alkoholische Getränke) betreffen, eine Änderung der Lebensmittelauswahl hinsichtlich der Lebensmittelqualität (z.B. fettreduzierte Milchprodukte, Vollkornprodukte) umfassen und die Nährstoffzufuhr beeinflussen (zum Beispiel Reduktion der Fettaufnahme bzw. der Aufnahme gesättigter Fettsäuren, Erhöhung der Ballaststoffaufnahme, Reduzierung der Energieaufnahme, Alkoholrestriktion). Supplemente und Nahrungsergänzungsmittel sowie die Einnahme von Medikamenten zur Gewichtsreduktion sind mit Lebensstilveränderung im Bereich Ernährung nicht gemeint. Die Lebensstilveränderung im Bereich Bewegung bezieht sich auf eine Steigerung der körperlichen Aktivität hinsichtlich der Häufigkeit, Dauer und/oder der Intensität. Dabei ist sowohl die Bewegung im Alltag als auch die sportliche Betätigung gemeint.

explorative Recherche

- **Sichtung von Uptodate, Clinical Evidence**
- **PubMed** (02.05.2013; limits: review; letzte 5 Jahre; Erwachsene ≥18 Jahre; deutsch + englisch)
- **BioMed Central** (http://www.biomedcentral.com) – Jan. bis März 2013

- **Cochrane summaries** (http://summaries.cochrane.org) - Jan. bis März 2013
- **Wiley online library** (http://onlinelibrary.wiley.com/) - Jan. bis März 2013
- **Springer Link** (http://link.springer.com/) - Jan. bis März 2013

Testset

a. Angermayr L. Melchart D, Linde K: Multifactorial lifestyle interventions in the primary and secondary prevention of cardiovascular disease and type 2 diabetes mellitus--a systematic review of randomized controlled trials. Ann Behav Med. 2010 Aug;40(1):49-64. doi: 10.1007/s12160-010-9206-4

b. Michael K. Baker a, Kylie Simpson, Bradley Lloyd, Adrian E. Bauman, Maria A. Fiatarone Singh Behavioral strategies in diabetes prevention programs: A systematic review of randomized controlled trials. Diabetes Research and Clinical Practice, 91(2011), S.1–12.

c. Davis N, Forges B, Wylie-Rosett J Role of obesity and lifestyle interventions in the prevention and management of type 2 diabetes. Minerva Med. 2009 Jun;100(3):221-8

d. Dunkley AJ, Charles K, Gray LJ, Camosso-Stefinovic J, Davies MJ, Khunti K. Effectiveness of interventions for reducing diabetes and cardiovascular disease risk in people with metabolic syndrome: systematic review and mixed treatment comparison meta-analysis. Diabetes Obes Metab. 2012 Jul;14(7):616-25. doi: 10.1111/j.1463-1326.2012.01571.x. Epub 2012 Feb 21

e. Gillett M, Royle P, Snaith A, Scotland G, Poobalan A, Imamura M, Black C, Boroujerdi M, Jick S, Wyness L, McNamee P, Brennan A, Waugh N. Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: a systematic review and economic evaluation. Health Technol Assess. 2012 Aug;16(33):1-236, iii-iv. doi: 10.3310/hta16330

f. Horton ES Effects of lifestyle changes to reduce risks of diabetes and associated cardiovascular risks: results from large scale efficacy trials. Obesity (Silver Spring). 2009 Dec;17 Suppl 3:S43-8. doi: 10.1038/oby.2009.388

g. Roumen C, Blaak EE, Corpeleijn E. Lifestyle intervention for prevention of diabetes: determinants of success for future implementation. Nutr Rev. 2009 Mar;67(3):132-46. doi: 10.1111/j.1753-4887.2009.00181.x

h. C. Sanz, J.-F.Gautier, H. Hanaire Physical exercise for the prevention and treatment of type 2 diabetes Doi : 10.1016/j.diabet.2010.06.001

i. Thomas GN, Jiang CQ, Taheri S, Xiao ZH, Tomlinson B, Cheung BM, Lam TH, Barnett AH, Cheng KK A systematic review of lifestyle modification and glucose intolerance in the prevention of type 2 diabetes. Curr Diabetes Rev. 2010 Nov;6(6):378-87.

j. Tuomilehto, Jaakko Nonpharmacologic Therapy and Exercise in the Prevention of Type 2 Diabetes Care 32 (Suppl. 2):S189–S193, 2009

k. Yamaoka, Kazue and Toshiro Tango 2012. Effects of lifestyle modification on metabolic syndrome: a systematic review and meta-analysis. BMC Medicine 2012, 10:138 http://www.biomedcentral.com/1741-7015/10/138.

l. Yoon, Uzung, Kwok, Lai Lai. and Magkidis, Athanasios. Efficacy of lifestyle interventions in reducing diabetes incidence in patients with impaired glucose tolerance: A systematic review of randomized controlled trials. Metabolism - Clinical and Experimental Volume 62, Issue 2 , Pages 303-314, February 2013

m. Yuen, Agnes, Sugeng, Yulia, Weiland, Tracey J. and George A. Jelinek, Lifestyle and medication interventions for the prevention or delay of type 2 diabetes mellitus in prediabetes: a systematic review of randomised controlled trials. Australian and New Zealand Journal of Public Health, 34(2), pages.172–178, April 2010 DOI: 10.1111/j.1753-6405.2010.00503.x

PICO

Einschlusskriterien		
Population	Adults (≥ 18 years) without diagnosis of diabetes mellitus before entering study and with elevated risk of diabetes mellitus type 2 defined by study (e.g. Impaired Glucose Tolerance, elevated fasting blood glucose, obesity)	E1
Intervention	lifestyle intervention including change in diet and/or physical activity	E2
Control	General advice/usual care, pharmacological treatment, no treatment	E3
Outcome	Diagnosis of DM 2, period until diagnosis of DM 2,overall mortality, cardiovascular morbidity and mortality, microvascular diseases, quality of life or clinical parameters (reduction in blood glucose, blood pressure, BMI)	E4
Studientyp	Meta-analysis or systematic review of controlled studies (CT`s), HTA	E5
Recherche	Die der Arbeit zugrunde liegende Recherche erfolgte 2009 oder später.	E6
Publikationssprache	Englisch oder Deutsch	E7
Veröffentlichung	Volltext-Publikation beschaffbar/vorhanden	E8
Oxman & Guyatt	Qualität des Reviews nach O & G ≥ 5	E9
Scope	Thema/Fragestellung relevant	E10

Informationsbeschaffung

gesuchte Studientypen

- Systematische Reviews aus kontrollierten Studien
- HTAs

Bibliografische Literaturrecherche

Die systematische Literaturrecherche nach relevanten systematischen Übersichten soll in folgenden Quellen durchgeführt werden:

- Medline (Ovid)
- PubMed
- Cochrane Database of Systematic Reviews (Cochrane Reviews)
- Database of Abstracts of Reviews of Effects
- Health Technology Assessment Database (Technology Assessments)

Autorenanfragen sind nicht vorgesehen.

Appendix 3: Exclusion criteria for studies in the full text screening process – results of consenting process

Study	Reason for exclusion
Allende-Vigo, M. Z. Diabetes Mellitus Prevention. Am J Ther 2011	E5
Angermayr, Lucia; Melchart, Dieter; Linde, Klaus Multifactorial lifestyle interventions in the primary and secondary prevention of cardiovascular disease and type 2 diabetes mellitus—a systematic review of randomized controlled trials. Annals of Behavioral Medicine 2010; 40(1):49- 64	E1
Baker, Michael K.; Simpson, Kylie; Lloyd, Bradley; Bauman, Adrian E.; Singh, Maria A. Fiatarone Behavioral strategies in diabetes prevention programs: a systematic review of randomized controlled trials. Diabetes Research & Clinical Practice 2011; 91(1):1-12	E9
Bonfioli, E.; Berti, L.; Goss, C.; Muraro, F.; Burti, L. Health promotion lifestyle interventions for weight management in psychosis: a systematic review and meta-analysis of randomized controlled trials. BMC Psychiatry 2012; 12():78	E1
Brown, T.; Avenell, A.; Edmunds, L. D.; Moore, H.; Whittaker, V.; Avery, L.; Summerbell, C. Systematic review of long-term lifestyle interventions to prevent weight gain and morbidity in adults. Obesity Reviews 2009; 10(6):627-38	E6
Cardona-Morrell, Magnolia; Rychetnik, Lucie; Morrell, Stephen L.; Espinel, Paola T.; Bauman, Adrian Reduction of diabetes risk in routine clinical practice: are physical activity and nutrition interventions feasible and are the outcomes from reference trials replicable? A systematic review and meta-analysis. BMC Public Health 2010; 10():653	E10
Conn, V. S.; Hafdahl, A. R.; Brown, L. M. Meta-analysis of quality-of-life outcomes from physical activity interventions (Structured abstract). Nursing Research 2009; 58(3):175-183	E1
Dombrowski, S. U.; Avenell, A.; Sniehott, F. F. Behavioural interventions for obese adults with additional risk factors for morbidity: aystematic review of effects on behaviour, weight and disease risk factors (Structured abstract). Obesity Facts 2010; 3(6):377-396	E6
Dyson, P. A. The therapeutics of lifestyle management on obesity. Diabetes, Obesity & Metabolism 2010; 12(11):941-6	E10
Esposito, Katherine; Maiorino, Maria Ida; Ceriello, Antonio; Giugliano, Dario Prevention and control of type 2 diabetes by Mediterranean diet: a systematic review. Diabetes Research & Clinical Practice 2010; 89(2):97-102	E1
Esposito, K.; Kastorini, C. M.; Panagiotakos, D. B.; Giugliano, D. Mediterranean diet and weight loss: meta-analysis of randomized controlled trials (Structured abstract). Metabolic Syndrome and Related Disorders 2011; 9(1):1-12	E10
Gillett M, Royle P, Snaith A, Scotland G, Poobalan A, Imamura M, Black C, et al. Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: a systematic review and economic evaluation. Health Technol Assess 2012; 16(33): 1-236.	E9
Hopper, Ingrid; Billah, Baki; Skiba, Marina; Krum, Henry Prevention of diabetes and reduction in major cardiovascular events in studies of subjects with prediabetes: meta-analysis of randomised controlled clinical trials. European Journal of Cardiovascular Prevention & Rehabilitation 2011; 18(6):813-23	E9
Hu, Tian; Mills, Katherine T; .; Yao, Lu; Demanelis, Kathryn; Eloustaz, Mohamed; Yancy, William S., Jr.; Kelly, Tanika N.; He, Jiang; Bazzano, Lydia A. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. American Journal of Epidemiology 2012; 176 Suppl 7():S44-54	E10
Jackson, Lindsey Translating the Diabetes Prevention Program into practice: a review of community interventions. Diabetes Educator 2009; 35(2):309-20	E5

Johnson, M.; Jones, R.; Freeman, C.; Woods, H. B.; Gillett, M.; Goyder, E.; Payne, N. Can diabetes prevention programmes be translated effectively into real-world settings and still deliver improved outcomes? A synthesis of evidence. Diabetic Medicine 2013; 30(1):3-15	E5
Kastorini, Christina-Maria; Milionis, Haralampos J.; Esposito, Katherine; Giugliano, Dario; Goudevenos, John A.; Panagiotakos, Demosthenes B. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. Journal of the American College of Cardiology 2011; 57(11):1299-313	E10
Katzmarzyk, P. T.; Lear, S. A. Physical activity for obese individuals: a systematic review of effects on chronic disease risk factors (Structured abstract). Obesity Reviews 2012; 13(2):95-105	E10
Koivula, R. W.; Tornberg, A. B.; Franks, P. W. Exercise and diabetes-related cardiovascular disease: systematic review of published evidence from observational studies and clinical trials. Current Diabetes Reports 2013; 13(3):372-80	E1
Leao, Leila Sicupi; ra Carneiro de Souza; de Moraes, Milena Miranda; de Carvalho, Giulia Xavier; Koifman, Rosalina Jorge Nutritional interventions in metabolic syndrome: a systematic review. Arquivos Brasileiros de Cardiologia 2011; 97(3):260-5	E10
Leblanc, Erin S.; O; '; Connor, Elizabeth; Whitlock, Evelyn P.; Patnode, Carrie D.; Kapka, Tanya Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. Annals of Internal Medicine 2011; 155(7):434-47	E10
Liu, Zhao-Min; Chen, Yu-Ming; Ho, Suzanne C. Effects of soy intake on glycemic control: a meta-analysis of randomized controlled trials. American Journal of Clinical Nutrition 2011; 93(5):1092-101	E10
Lukacova-Zib, Ivana; Gopalakrishnan, Geetha Therapeutic options for the prevention of type 2 diabetes mellitus in the metabolic syndrome. Mount Sinai Journal of Medicine 2010; 77(5):524-32	E5
Osei-Assibey, G and and C Boachie Dietary interventions for weight loss and cardiovascular risk reduction in people of African ancestry (blacks): a systematic review Public Health Nutrition: 15(1), 110–115	E1
Pattyn, N.; Cornelissen, V. A.; Eshghi, S. R.; Vanhees, L. The effect of exercise on the cardiovascular risk factors constituting the metabolic syndrome: a meta-analysis of controlled trials. Sports Medicine 2013; 43(2):121-33	E10
Rawal, Lal B.; Tapp, Robyn J.; Williams, Emily D.; Chan, Carina; Yasin, Shajahan; Oldenburg, Brian Prevention of type 2 diabetes and its complications in developing countries: a review. International Journal of Behavioral Medicine 2012; 19(2):121-33	E10
Schwingshackl, L.; Strasser, B.; Hoffmann, G. Effects of monounsaturated fatty acids on glycaemic control in patients with abnormal glucose metabolism: a systematic review and metaanalysis. Annals of Nutrition & Metabolism 2011; 58(4):290-6	E10
Shirani, F.; Salehi-Abargouei, A.; Azadbakht, L. Effects of Dietary Approaches to Stop Hypertension (DASH) diet on some risk for developing type 2 diabetes: A systematic review and meta-analysis on controlled clinical trials. Nutrition 2013;	E1
Shrestha, Prabha; Ghimire, Laxmi A review about the effect of life style modification on diabetes and quality of life. Global Journal of Health Science 2012; 4(6):185-90	E5
Sievenpiper, J. L.; Kendall, C. W.; Esfahani, A.; Wong, J. M.; Carleton, A. J.; Jiang, H. Y.; Bazinet, R. P.; Vidgen, E.; Jenkins, D. J. Effect of non-oil-seed pulses on glycaemic control: a systematic review and meta-analysis of randomised controlled experimental trials in people with and without diabetes (Structured abstract). Diabetologia 2009; 52(8):1479-1495	E6
Steyn, Nelia P.; Lambert, Estelle V.; Tabana, Hanani Conference on "Multidisciplinary approaches to nutritional problems". Symposium on "Diabetes and health". Nutrition interventions for the prevention of type 2	E6

diabetes. Proceedings of the Nutrition Society 2009; 68(1):55-70	
Strasser, B.; Siebert, U.; Schobersberger, W. Resistance training in the treatment of the metabolic syndrome: a systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism (Provisional abstract). Sports Medicine 2010; 40(5):397-415	E6
Thomas, G. Neil; Jiang, Chao Q.; Taheri, Shahrad; Xiao, Zheng H.; Tomlinson, Brian; Cheung, Bernard M. Y.; Lam, Tai H.; Barnett, Anthony H.; Cheng, Kar K. A systematic review of lifestyle modification and glucose intolerance in the prevention of type 2 diabetes. Current Diabetes Reviews 2010; 6(6):378-87	E9
Thompson, Elizabeth; Berry, Diane; Nasir, Laura Weight management in African-Americans using church-based community interventions to prevent type 2 diabetes and cardiovascular disease. Journal of National Black Nurses Association 2009; 20(1):59-65	E6
Tourlouki, Eleni; Matalas, Antonia-Leda; Panagiotakos, Demosthenes B. Dietary habits and cardiovascular disease risk in middle-aged and elderly populations: a review of evidence. Clinical Interventions In Aging 2009; 4():319-30	E5
Tschentscher, M.; Niederseer, D.; Niebauer, J. Health benefits of nordic walking: a systematic review. American Journal of Preventive Medicine 2013; 44(1):76-84	E10
Whittemore, R. A systematic review of the translational research on the Diabetes Prevention Program (Provisional abstract). Translational Behavioral Medicine 2011; 1(3):480-491	E5
Wolfram, Taylor; Ismail-Beigi, Faramarz Efficacy of high-fiber diets in the management of type 2 diabetes mellitus. Endocrine Practice 2011; 17(1):132-42	E1
Wycherley, T. P.; Moran, L. J.; Clifton, P. M.; Noakes, M.; Brinkworth, G. D. Effects of energyrestricted high-protein, low-fat compared with standard-protein, low-fat diets: a meta-analysis of randomized controlled trials (Provisional abstract). Database of Abstracts of Reviews of Effects 2012; (2):1281-1298	E10
Yamaoka, K.; Tango, T. Efficacy of lifestyle education in preventing type 2 diabetes: an updated version (Provisional abstract). Salud (i) Ciencia 2009; 17(1):29-33	E7
Yamaoka, Kazue; Tango, Toshiro Effects of lifestyle modification on metabolic syndrome: a systematic review and meta-analysis. BMC Medicine 2012; 10():138	E10
Yeh, G. Y.; Wang, C.; Wayne, P. M.; Phillips, R. Tai chi exercise for patients with cardiovascular conditions and risk factors: a systematic review (Structured abstract). Journal of Cardiopulmonary Rehabilitation and Prevention 2009; 29(3):152-160	E6
Yoon, Uzung, Lai Lai Kwok, Athanasios Magkidis Efficacy of lifestyle interventions in reducing diabetes incidence in patients with impaired glucose tolerance: A systematic review of randomized controlled trials, Metabolism Clinical and Experimental 62 (2013) 303-314	E9
Yuen, A.; Sugeng, Y.; Weiland, T. J.; Jelinek, G. A. Lifestyle and medication interventions for the prevention or delay of type 2 diabetes mellitus in prediabetes: a systematic review of randomised controlled trials. Aust N Z J Public Health 2010; 34(2):172-8	E6

Appendix 4: Evidence grading systems (ADA and SIGN)

Sign Criteria

LEVELS OF EVIDENCE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation	
A	• At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or • A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	• A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or • Extrapolated evidence from studies rated as 1++ or 1+
C	• A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or • Extrapolated evidence from studies rated as 2++
D	• Evidence level 3 or 4; or • Extrapolated evidence from studies rated as 2+

Source: Scottish Intercollegiate Guidelines Network (2011). SIGN 50 - A guideline developer's handbook, First published 2008, Revised November 2011, download from www.sign.ac.uk

ADA evidence grading system for clinical practice recommendations

A	Clear evidence from well-conducted, generalizable RCTs that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling non-experimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford Supportive evidence from well-conducted RCTs that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
D	Expert consensus or clinical experience

Source: ADA (2013). Standards of Medical Care in Diabetes- 2013. Position Statement. Diabetes Care, Volume 36, Supplement 1, January 2013 S.11-S.66

Appendix 5: Oxford Centre for Evidence Based Medicine: Levels of Evidence (March 2009) download from http://www.cebm.net/index.aspx?o=4590

Levels of Evidence (March 2009) www.cebm.net

Level 1A	Therapy/Prevention, Aetiology/Harm	1a SR (with homogeneity*)of RCTs
	Prognosis	SR (withhomogeneity*) of inception cohort studies; CDR† validated in different populations
	Diagnosis	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres
	Differential diag/symptom prevalence	SR (with homogeneity*) of prospective cohort studies
	Economic and decision analyses	SR (with homogeneity*) of Level 1 economic studies
Level 1b	Therapy/Prevention, Aetiology/Harm	Individual RCT (with narrow Confidence Interval‡)
	Prognosis	Individual inception cohort study with > 80% follow-up; CDR† validated in asingle population
	Diagnosis	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre
	Differential diag/symptom prevalence	Prospective cohort study with good follow-up****
	Economic and decision analyses	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
Level 1c	Therapy/Prevention, Aetiology/Harm	All or none§
	Prognosis	All or none case series
	Diagnosis	Absolute SpPins and SnNouts††
	Differential diag/symptom prevalence	All or none case-series
	Economic and decision analyses	Absolute better-value or worse-value analyses ††††
Level 2a	Therapy/Prevention, Aetiology/Harm	SR (with homogeneity*) of cohort studies
	Prognosis	SR (withhomogeneity*) of either retrospective cohort studies or untreated control groups in RCTs
	Diagnosis	SR (with homogeneity*) of Level >2 diagnostic studies
	Differential diag/symptom prevalence	SR (with homogeneity*) of 2b and better studies
	Economic and decision analyses	SR (withhomogeneity*) of Level >2 economic studies
Level 2b	Therapy/Prevention, Aetiology/Harm	Individual cohort study (including low quality RCT; e.g., <80% followup)
	Prognosis	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split sample §§§ only
	Diagnosis	Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases
	Differential diag/symptom prevalence	Retrospective cohort study, or poor follow-up
	Economic and decision analyses	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
Level 2c	Therapy/Prevention, Aetiology/Harm	"Outcomes" Research; Ecological studies
	Prognosis	"Outcomes" Research
	Diagnosis	
	Differential diag/symptom prevalence	Ecological studies
	Economic and decision analyses	Audit or outcomes research
Level 3a	Therapy/Prevention, Aetiology/Harm	SR (with homogeneity*) of case-control studies
	Prognosis	
	Diagnosis	SR (with homogeneity*) of 3b and better studies
	Differential diag/symptom prevalence	SR (with homogeneity*) of 3b and better studies
	Economic and decision analyses	SR (with homogeneity*) of 3b And better studies
Level 3b	Therapy/Prevention, Aetiology/Harm	Individual Case-Control Study
	Prognosis	
	Diagnosis	Non-consecutive study; or without consistently applied reference standards
	Differential diag/symptom prevalence	Non-consecutive cohort study, or very limited population
	Economic and decision analyses	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses IIncorporatingclinically sensible variations.
Level 4	Therapy/Prevention, Aetiology/Harm	Case-series (and poor quality cohort and casecontrol studies§§)
	Prognosis	Case-series (and poor quality prognostic cohort studies***)
	Diagnosis	Case-control study, poor or nonindependent reference standard
	Differential diag/symptom prevalence	Case-series or superseded reference standards
	Economic and decision analyses	Analysis with no sensitivity analysis
Level 5	Therapy/Prevention, Aetiology/Harm	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
	Prognosis	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
	Diagnosis	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
	Differential diag/symptom prevalence	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
	Economic and decision analyses	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)
(for definitions of terms used see glossary at http://www.cebm.net/?o=1116)

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NOTES

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because:

EITHER a single result with a wide Confidence Interval

OR a Systematic Review with troublesome heterogeneity.

Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
‡	See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and nonexposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 - 5 years chronic)

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation.

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009)
(for definitions of terms used see glossary at http://www.cebm.net/?o=1116)

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