Technology Assessment

Technology Assessment Program

Lifestyle Interventions for Four Conditions: Type 2 Diabetes, Metabolic Syndrome, Breast Cancer, and Prostate Cancer

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Lifestyle Interventions for Four Conditions: Type 2 Diabetes, Metabolic Syndrome, Breast Cancer, and Prostate Cancer

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Peer Reviewers

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Structured Abstract

Objectives: To synthesize evidence from randomized controlled trials (RCTs) on the effectiveness of lifestyle interventions to control progression of type 2 diabetes, progression to diabetes from metabolic syndrome, or recurrence of breast cancer and prostate cancer. Lifestyle interventions were defined as any intervention that included exercise, diet, and at least one other component (e.g., counseling, stress management, smoking cessation).

Data Sources: A systematic and comprehensive literature search was conducted to identify RCTs from 1980 to the present.

Review Methods: Study selection, quality assessment, and data extraction were completed by several investigators in duplicate and independently. Random effects models were used for meta-analyses.

Results: From 1,288 citations, we included 20 unique RCTs (plus 80 associated publications): diabetes = 10 studies, metabolic syndrome = 7, breast and prostate cancer = 3. All studies had a "high" or "unclear" risk of bias.

Type 2 diabetes: One RCT reported that, at 13 years postintervention, the lifestyle intervention group had fewer nonfatal strokes, reduced incidence of retinopathy, reduced progression of autonomic neuropathy, and reduced incidence of nephropathy. In this trial the lifestyle intervention included pharmacotherapy. A number of studies reported positive effects for lifestyle interventions on changes in body composition, metabolic variables, physical activity, and dietary intake; however, the results were not always statistically significant and were not always sustained following the end of the active intervention.

Metabolic syndrome: Four studies reported that lifestyle interventions decreased the risk of developing type 2 diabetes. Most studies also reported positive effects for changes in body composition, metabolic variables, physical activity, and dietary intake. The results were not always statistically significant and were not always sustained following the end of the active intervention.

Breast and prostate cancer: One RCT on prostate cancer reported that the lifestyle intervention decreased PSA levels. Two studies reported positive effects for changes in body composition, metabolic variables, physical activity, and dietary intake; however, the results generally were not statistically significant.

Conclusions: Comprehensive lifestyle interventions that include exercise, dietary changes, and at least one other component are effective in decreasing the incidence of type 2 diabetes mellitus in high risk patients and the benefit extends beyond the active intervention phase. In patients who have already been diagnosed with type 2 diabetes, there is some evidence to suggest long-term benefit on microvascular and macrovascular outcomes, although the evidence is from one trial of high risk diabetic patients and included pharmacotherapy. The evidence for lifestyle interventions to prevent cancer recurrence is insufficient to draw conclusions.

Comprehensive lifestyle interventions appear to have a positive impact on behavioral outcomes including exercise and dietary intake, as well as a number of metabolic variables, at least in the short-term in all populations addressed in this report.

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Introduction

Chronic diseases are the leading cause of death and disability worldwide. According to the World Health Organization, 88 percent of deaths in the United States in 2002 were attributable to chronic disease.[1] Prevention of the onset or progression of chronic disease is often promoted as the gold standard,[1] although the optimal interventions to achieve this have not been well documented. A number of lifestyle behaviors contribute to overall morbidity and mortality of chronic disease. Among these, physical activity and diet have been identified as two modifiable risk factors that may impact onset or progression of disease.

Previous research has suggested that improved diet may decrease the burden of chronic disease, particularly coronary heart disease.[2-5] However, the benefits of lifestyle modifications in preventing progression or recurrence of disease is not as well documented. In addition, it remains unclear how effective interventions are in modifying risk factors, and which chronic diseases, if any, would benefit.

The chronic diseases examined in this review are type 2 diabetes, metabolic syndrome, breast and prostate cancer. *Type 2 diabetes* is a major cause of morbidity and mortality. Diabetes was the seventh leading cause of death in the U.S. in 2006;[6] cardiovascular disease (CVD) accounted for more than 65 percent of all diabetic deaths.[7] Diabetes is also the leading cause of kidney failure, nontraumatic lower-extremity amputations, and blindness among adults in the U.S.[8]

Metabolic syndrome is defined as a constellation of interrelated metabolic risk factors that promote the development of CVD and type 2 diabetes. The most widely recognized metabolic risk factors are dyslipidemia, elevated plasma glucose, and hypertension. Its clinical utility for risk prediction is controversial. Prediabetes, which includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), has been suggested to be equally effective in identifying those at risk of developing type 2 diabetes. Our operational definition of metabolic syndrome included metabolic syndrome, insulin resistance, prediabetes, IFG, IGT, syndrome X, dysmetabolic syndrome X, and Reaven syndrome. Approximately 64 million or 25 percent of adults in the U.S. had metabolic syndrome in 2000.[9] As of 2011, the American Diabetes Association estimated that 57 million people in the U.S. had prediabetes.[10]

Many risk factors for the development of metabolic syndrome have been proposed, one of which is obesity.[11] Additional risk factors include increasing age[12,13] and physical inactivity.[14]

Breast cancer is defined as the development of malignant cells in the breast which usually originate from the ducts or lobules of the breast. The National Cancer Institute estimates that in 2010 there will be 209,060 new cases of breast cancer diagnosed, with 40,230 deaths.[15] Survival and recurrence rates depend on a number of factors including stage of the cancer at diagnosis. There is a strong correlation between obesity and increased risk of breast cancer.[16-18] Studies have suggested that increased physical activity reduces the incidence of breast cancer.[19] A recent systematic review found that physical activity could reduce the incidence of breast cancer in postmenopausal women by 20 to 80 percent.[20]

Prostate cancer. Prostate cancer is defined as a malignant growth of cells in the prostate gland. It is the second leading cause of death of males in the U.S. It is estimated that 217,730 men will be diagnosed with and 32,050 will die of prostate cancer in the U.S. in 2010.[21] The impact of lifestyle factors on the incidence or recurrence of prostate cancer is unclear. Results

from studies of the association between dietary intake and risk of prostate cancer are inconsistent.[22-24] Research has shown an association between body mass index (BMI) and incidence of prostate cancer.[25] The effect of physical activity on the incidence prostate cancer continues to be debated.[26,27]

Key Questions

The objective of this report was to synthesize the evidence from randomized controlled trials (RCTs) for the following key questions.

1. What is the evidence on the effectiveness of lifestyle interventions for breast cancer, prostate cancer, metabolic syndrome, and type 2 diabetes mellitus?
2. What is the generalizability of the evidence to the Medicare population (> 65 years)?
3. What is the evidence on whether specific components of the interventions, composition of the team, and/or patient characteristics contribute to better outcomes?

Methods

Literature Search

We systematically searched the following bibliographic databases for studies published from 1980 to March 2010: MEDLINE®, Embase, Cochrane Controlled Trials Register (CENTRAL), CINAHL®, and SCOPUS. Language restrictions were applied to restrict results to English language only. A filter for RCTs was applied to search results. Ongoing studies were identified by searching clinical trials registers; reference lists of relevant studies were searched to identify additional studies.

Study Selection

Two reviewers independently screened titles and abstracts using broad inclusion criteria. The full text of all articles identified as "include" or "unclear" were retrieved for formal review. Each article was independently assessed by two reviewers using a standardized form. Disagreements were resolved by consensus or third-party adjudication.

RCTs that included adults (≥18 years) who were survivors of breast cancer, survivors of prostate cancer, have type 2 diabetes, or metabolic syndrome were considered. The lifestyle intervention had to include an exercise component, a diet component, and at least one other component (e.g., counseling, smoking cessation, behavior modification). The comparison could be usual care, the diet and/or exercise components alone, or wait list. The duration of the intervention was at least 3 months with a minimum 6 month followup period. We made a post hoc modification to also include RCTs that had no followup if the duration of the intervention was at least 1 year. The primary outcomes were recurrence of breast or prostate cancer, progression of type 2 diabetes to additional medication or insulin or to cardiovascular problems, hypertension or neuropathies, or progression of metabolic syndrome to diabetes, heart disease, or stroke. Secondary outcomes included physical activity, dietary or nutrient intake, body composition, and metabolic variables.

Quality Assessment and Rating the Body of Evidence

Two reviewers independently assessed the methodological quality of included studies using the Cochrane Collaboration's risk of bias tool. Discrepancies were resolved through consensus or third-party adjudication.

The body of evidence was rated by one reviewer using the EPC GRADE approach. The strength of evidence was assessed for our primary outcomes and secondary outcomes related to physical activity, dietary or nutrient intake, body composition, and metabolic variables. The overall strength of evidence was graded as high, moderate, low, or insufficient.

Data Extraction

Data were extracted by one reviewer using a standardized form and verified for accuracy and completeness by a second reviewer. Reviewers resolved discrepancies by consensus or in consultation with a third party. Extracted data included study characteristics, inclusion/exclusion criteria, participant characteristics, interventions, and outcomes.

Data Analysis

Evidence tables and qualitative descriptions of results are presented. When appropriate, results were combined using random effects models. Statistical heterogeneity was quantified using the I-squared (I^2) statistic.

Results

Description of Included Studies

The search identified 1,288 studies; 20 unique RCTs (reporting data from 80 articles) were included in the review. Ten studies addressed type 2 diabetes, seven addressed metabolic syndrome, and three addressed prostate and/or breast cancer.

All studies included a diet and exercise component plus at least one additional component, including, but not limited to, individual and/or group counseling, behavior modification, a smoking cessation program, regular telephone contact, individual goal setting, stress management, medication, and regular blood glucose and blood monitoring.

The interventions were administered or delivered by a range of care providers including, but not limited to, dietitians, case managers or nurses, physicians, qualified exercise trainers, behavioral therapists, peer counselors, lay leaders, and trained support group leaders.

KQ1a. What is the evidence on the effectiveness of lifestyle interventions for type 2 diabetes mellitus?

Ten RCTs assessed the effectiveness of lifestyle interventions for type 2 diabetes. The interventions ranged from 6 to 48 months; followup periods ranged from 6 to 93 months. The number of participants ranged from 72 to 5,145 (median = 194; IQR 143, 259). Two RCTs were considered at high risk of bias; eight were unclear.

Results are presented in Table ES1 and are summarized below.

- *Primary outcomes.* One study, which included medication as part of the lifestyle intervention, found that the intervention decreased the number of nonfatal strokes, nonfatal

myocardial infarctions, amputations, and death at 13.3 year followup. There was also a difference between groups for the progression of autonomic neuropathy in favor of the lifestyle intervention, but no difference was seen in the progression of peripheral neuropathy at all followup time points.

- *Change in body composition.* Five studies reported change in weight. At the end of intervention, there was a statistically significant difference in favor of lifestyle interventions, and no difference between the groups at 6 month followup. Five studies reported change in BMI (kg/m^2). At the end of the intervention, there was a statistically significant difference in favor of the lifestyle intervention. Effect of the intervention at different postintervention timepoints was inconsistent.
- *Change in metabolic variables.* Ten studies reported on changes in metabolic variables. For lifestyle interventions that did not include medication as part of the intervention, there was no statistically significant difference between groups for any of the metabolic variables at the end of intervention. For lifestyle interventions that included medication, the results were statistically significant in favor of lifestyle for fasting plasma glucose, HDL cholesterol, and HbA1c. These differences were not always sustained during followup.
- *Systolic and diastolic blood pressure*. Eight studies reported changes in systolic and diastolic blood pressure (mmHg). For lifestyle interventions that did not include medication as a component, there was no statistically significant difference between groups for either outcome at the end of intervention. For lifestyle interventions that included medication, the results were statistically significant in favor of lifestyle for diastolic, but not systolic blood pressure. Effect of the intervention at different followup timepoints was inconsistent.
- *Change in physical activity*. Seven studies reported changes in physical activity using different outcome measures. At the end of intervention, there was a statistically significant difference in favor of the lifestyle intervention. There was a significant difference between groups at 1 and 2 years of followup.
- *Change in dietary or nutrient intake*. Four studies measured change in dietary or nutrient intake. There was a significant difference in energy intake favoring the lifestyle intervention at end of intervention. There was no difference between groups at any followup timepoint. There was no significant difference between groups in consumption of saturated fats at end of intervention; however, the lifestyle intervention was favored at all followup timepoints.

Table ES1. Summary table: type 2 diabetes

Outcome	# RCTs	Strength of evidence	Summary
Primary outcomes			
All-cause mortality (13 yr followup)	1	Low	Significant effect in favor of lifestyle intervention (RR_{meds} = 0.60; 95% CI: 0.4, 0.9)
Cumulative incidence of CVD events (13 yr followup)	1	Low	Significant effect in favor of lifestyle intervention (RR_{meds} = 0.49; 95% CI: 0.34, 0.71)
Autonomic neuropathy progression (13 yr followup)	1	Low	Significant effect in favor of lifestyle intervention (RR_{meds} = 0.75; 95% CI: 0.57, 0.99)
Development of nephropathy (13 yr followup)	1	Low	Significant effect in favor of lifestyle intervention (RR_{meds} = 0.54; 95% CI: 035, 0.85)
Development of retinopathy (13 yr followup)	1	Low	Significant effect in favor of lifestyle intervention (RR_{meds} = 0.76; 95% CI: 0.58, 0.99)
Peripheral neuropathy progression (13 yr followup)	1	Low	No significant difference between groups (RR_{meds} = 0.96; 95% CI: 0.73, 1.26)
Change in body composition			
BMI (EoI)	5	Moderate	Significant effect in favor of lifestyle intervention (MD_{all} = -0.48; 95% CI: -0.92, -0.05)
BMI (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = 1.0; 95%CI: -1.84, 3.84)
BMI (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -1.1; 95% CI: -3.14, 0.94)
Weight change (EoI)	5	Moderate	No significant difference between groups ($MD_{no\ meds}$ = -1.53; 95% CI: -2.09, -0.97; MD_{meds} = -15.4; 95% CI: -16.1, -14.5)
Weight change (6 mo postintervention)	1	Insufficient	Effect favors usual care, though not significantly (RR_{meds} = 1.14; 95% CI: -5.39, 7.67)
Weight change (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -11.62; 95% CI: -12.37, -10.87)
Metabolic variables			
Fasting plasma glucose (EoI)	4	Low	Significant effect in favor of lifestyle intervention ($MD_{no\ meds}$ = 0.33; 95% CI: -0.83, 1.49; MD_{meds} = -1.02; 95% CI: -1.85, -0.19)
Fasting plasma glucose (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -1.0; 95% CI: -2.61, 0.61)
Fasting plasma glucose (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds}= -0.16; 95% CI: -1.47, 1.15)
HbA1c (EoI)	10	Low	Significant effect in favor of lifestyle intervention ($MD_{no\ meds}$ = -0.09; 95% CI: -0.58, 0.75; MD_{meds} = 0.77; 95% CI: -1.18, -0.36)
HbA1c (6 mo postintervention)	2	Insufficient	No significant difference between groups (MD_{all} = 0.09; 95% CI: -0.58, 0.75)
HbA1c (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -0.70; 95% CI: -1.41, 0.01)

BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; EoI = end of intervention; HbA1c = glycosylated haemoglobin; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; meds = medication (as part of the lifestyle intervention); mo = month(s); RCT = randomized controlled trial; RR = risk ratio; SFA = saturated fatty acid; SMD = standardized mean difference; yr = year(s)

Table ES1. Summary table: type 2 diabetes (continued)

Outcome	# RCTs	Strength of evidence	Summary
HDL cholesterol (EoI)	6	Low	Significant effect in favor of lifestyle intervention ($MD_{no\ meds}$ = -0.01; -0.04, 0.05; MD_{meds} = 0.05; 95% CI: 0.03, 0.07)
HDL cholesterol (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion ($MD_{no\ meds}$ = -0.04; 95% CI: -0.16, 0.09)
HDL cholesterol (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = 0.08; 95% CI: -0.07, 0.22)
LDL cholesterol (EoI)	5	Low	No significant difference between groups ($MD_{no\ meds}$ = -0.09; 95% CI: -0.26, 0.08; MD_{meds} = -0.27; 95% CI: -0.92, 0.37)
LDL cholesterol (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -0.59; 95% CI: -1.07, -0.11)
LDL cholesterol (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds}= -0.05; 95% CI: -0.4, 0.3)
Total cholesterol (EoI)	5	Low	No significant difference between groups (MD_{all} = -0.13; 95% CI: -0.27, 0.01),
Total cholesterol (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion ($MD_{no\ meds}$ = 0.01; 95% CI: -0.35, 0.36)
Total cholesterol (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = 0.38; 95% CI: -0.06, 0.82)
Triglycerides (EoI)	5	Low	Significant effect in favor of lifestyle intervention (MD_{all} = -0.17; 95% CI: -0.23, -0.12)
Triglycerides (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -0.18; 95% CI: -1.47, 1.11)
Triglycerides (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -0.03; 95% CI: -0.67, 0.61)
Blood pressure			
Diastolic BP (EoI)	6	Low	No significant difference between groups ($MD_{no\ meds}$ = 0.32; 95% CI: -1.43, 20.7; MD_{meds} = -1.2; 95% CI: -1.75, 0.65)
Diastolic BP (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = 0; 95% CI: -5.07, 5.07)
Diastolic BP (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = 2.0; 95% CI: -1.90, 5.90)
Systolic BP (EoI)	6	Low	No significant difference between groups ($MD_{no\ meds}$ = -1.89; 95% CI: -0.57, 4.35; MD_{meds} -6.89; 95% CI: -14.42, 0.64)
Systolic BP (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -3.0; 95% CI: -12.4, 6.4)
Systolic BP (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -3.0; 95% CI: -9.79, 3.79)
Change in physical activity			
Exercise (EoI)	6	Low	Significant effect in favor of lifestyle intervention (SMD_{all} = 0.45; 95% CI: 0.2, 0.71)
Exercise (6 mo postintervention)	4	Low	Significant effect in favor of lifestyle intervention (SMD_{all} = 0.5; 95% CI: 0.1, 0.89)
Exercise (2 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion ($SMD_{no\ meds}$ = 0.41; 95% CI: 0.16, 0.67)
Exercise (8 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD_{meds} = 0.11; 95% CI: -0.24, 0.45)

BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; EoI = end of intervention; HbA1c = glycosylated haemoglobin; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; meds = medication (as part of the lifestyle intervention); mo = month(s); RCT = randomized controlled trial; RR = risk ratio; SFA = saturated fatty acid; SMD = standardized mean difference; yr = year(s)

Table ES1. Summary table: type 2 diabetes (continued)

Change in dietary or nutrient intake			
Energy intake (EoI)	5	Low	Significant effect in favor of lifestyle intervention (SMD_{all} = -0.17; 95% CI: -0.33, -0.01)
Energy intake (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD_{meds} = -0.12; 95% CI: -0.59, 0.36)
Energy intake (8 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD_{meds} = 0; 95% CI: -0.35, 0.34)
SFA intake (EoI)	5	Low	No significant difference between groups (SMD_{all} = -0.31; 95% CI: -0.68, 0.07)
SFA intake (6 mo postintervention	2	Insufficient	Significant effect in favor of lifestyle intervention (SMD_{all} = -0.45 95% CI: -0.79, -0.10)
SFA intake (8 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD_{meds} = -0.68; 95% CI: -1.03, -0.32)

BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; EoI = end of intervention; HbA1c = glycosylated haemoglobin; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; meds = medication (as part of the lifestyle intervention); mo = month(s); RCT = randomized controlled trial; RR = risk ratio; SFA = saturated fatty acid; SMD = standardized mean difference; yr = year(s)

KQ1b. What is the evidence on the effectiveness of lifestyle interventions for metabolic syndrome?

Seven RCTs assessed the effectiveness of lifestyle interventions for metabolic syndrome. The duration of the interventions ranged from 6 to 72 months, with followup periods ranging from 3 to 14 years. The number of participants ranged from 39 to 3,234 (median = 375; IQR = 113, 437). Three RCTs were considered to be at high risk of bias; four were unclear.

Results are presented in Table ES2 and are summarized below.

- *Primary outcomes.* Four studies assessed CVD complications, development of type 2 diabetes, and death. There were no significant differences between the groups except for the development of type 2 diabetes. Two long-term studies found that lifestyle interventions significantly decreased the risk of developing type 2 diabetes.
- *Change in body composition.* Six studies reported change in weight. At 4 years postintervention, two studies reported a statistically significant difference in favor of the lifestyle intervention. At 10 years, there was no longer a difference between groups. Four studies reported change in BMI. At both end of intervention and 4 years followup, there was a statistically significant difference favoring the lifestyle intervention. Five studies reported change in waist circumference and reported a significant difference in favor of the lifestyle group at end of intervention and 4 years followup.
- *Change in metabolic variables.* Six studies reported on changes in different metabolic variables. For fasting plasma glucose, the lifestyle group was significantly favored at end of intervention and 4 year followup. At 10 years, there was a significant difference favoring the usual care group. For HbA1C, the lifestyle group was significantly favored at both 4 and 10 year followup. For all other metabolic variables, there was no significant difference between groups at the followup timepoints.
- *Systolic and diastolic blood pressure*. Five studies reported change in systolic and diastolic blood pressure. There was a significant difference between groups for both measures at the end of intervention and at followup.
- *Change in physical activity*. Four studies reported on the change in general exercise. At end of intervention and at 4 year followup, the lifestyle group was significantly favored.

- *Change in dietary or nutrient intake*. Four studies measured change in energy intake. The lifestyle group had a significantly lower energy intake and lower consumption of saturated fat at the end of the intervention compared with usual care.

Table ES2. Summary table: metabolic syndrome

Outcome	# RCTs	Strength of evidence	Precision
Primary outcomes			
CVD events (Followup: 6-10 yr)	2	Insufficient	The evidence was too limited to draw a conclusion (RR = 1.02; 95% CI: 0.73, 1.42) (HR = 0.96; 95% CI: 0.76-1.44)
CVD events (20 yr)	1	Insufficient	No significant difference between groups (HR = 0.98; 95% CI: 0.71-1.37)
Development of type 2 diabetes (EoI: duration 1-6 yr)	3	Moderate	Significant effect in favor of lifestyle intervention (RR = 0.44; 95% CI: 0.2, 0.93)
Development of type 2 diabetes (Followup: 4-10 yr)	3	Moderate	Significant effect in favor of lifestyle intervention ($RR_{4\ yr}$ = 0.56; 95% CI: 0.48, 0.64; $RR_{6\ yr}$ = 0.44; 95% CI: 0.29, 0.68)
Death (Followup: 10-20 yr)	2	Insufficient	The evidence was too limited to draw a conclusion ($RR_{10\ yr}$ = 0.58; 95% CI: 0.21, 1.57; $HR_{20\ yr}$ = 0.83; 95% CI: 0.48, 1.40)
Body Composition			
BMI (EoI)	4	Moderate	Significant effect in favor of lifestyle intervention (MD = -0.95; 95% CI: -1.49, -0.41)
BMI (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.92; 95% CI: -1.32, -0.53)
Waist circumference (EoI)	5	Moderate	Significant effect in favor of lifestyle intervention (MD = -3.73; 95% CI: -4.87, -2.59)
Waist circumference (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD= -1.86; 95% CI: -3.49, -0.22)
Weight change (EoI)	6	Moderate	Significant effect in favor of lifestyle intervention (MD = -7.8; 95% CI: -11.92, -3.67)
Weight change (4 yr followup)	2	Low	The evidence was too limited to draw a conclusion (MD = -5.88; 95% CI: -8.05, -3.71)
Weight change (10 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.94; 95% CI: -5.07, 3.19)
Metabolic variables			
Fasting plasma glucose (EoI)	5	Moderate	Significant effect in favor of lifestyle intervention (MD = -0.29; 95% CI: -0.35, -0.23)
Fasting plasma glucose (10 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 0.10; 95% CI: 0.03, 0.18)
HbA1c (EoI)	2	Insufficient	No significant difference between groups (MD = -0.10; 95% CI: -0.28, 0.08)
HbA1c (10 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.05; 95% CI: -0.09, -0.02)
HDL cholesterol (EoI)	4	Moderate	Significant effect in favor of lifestyle intervention (MD = 0.08; 95% CI: 0.05, 0.10)

BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; EoI = end of intervention; HbA1c = glycosylated haemoglobin; HDL = high density lipoprotein; HR = hazard ratio; LDL = low density lipoprotein; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio; SFA = saturated fatty acid; SMD = standardized mean difference

Table ES2. Summary table: metabolic syndrome (continued)

Outcome	# RCTs	Strength of evidence	Precision
HDL cholesterol (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 0.05; 95% CI: 0.0, 0.10)
Impaired plasma glucose (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 0.34; 95% CI: 0.23, 0.52)
LDL cholesterol (EoI)	3	Low	No significant difference between groups (MD = 0.04; 95% CI: -0.16, 0.25)
Total cholesterol (EoI)	5	Low	No significant difference between groups (MD = 0.0; 95% CI: -0.12, 0.13)
Triglycerides (EoI)	4	Low	No significant difference between groups (MD = -0.11; 95% CI: -0.26, 0.04)
Triglycerides (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 0.09; 95% CI: -0.22, 0.05)
Blood pressure			
Diastolic BP (EoI)	5	Moderate	Significant effect in favor of lifestyle intervention (MD=-2.70; 95% CI: -3.21, -2.18)
Diastolic BP (4 yr followup)	2	Low	The evidence was too limited to draw a conclusion (MD =-1.88; 95% CI: -2.65, -1.12)
Systolic BP (EoI)	5	Moderate	Significant effect in favor of lifestyle intervention (MD =-3.17; 95% CI: -5.02, -1.33)
Systolic BP (4 yr followup)	2	Low	The evidence was too limited to draw a conclusion (MD =-4.41; 95% CI: -8.47, -0.35)
Change in physical activity			
Exercise (EoI)	4	Moderate	Significant effect in favor of lifestyle intervention (SMD = 0.40; 95% CI: 0.2, 0.59)
Exercise (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD = 0.23; 95% CI: 0.10, 0.35)
Change in dietary or nutrient intake			
Energy intake (EoI)	4	Moderate	Significant effect in favor of lifestyle intervention (SMD = -0.23; 95% CI: -0.31, -0.16)
SFA intake (EoI)	2	Low	Significant effect in favor of lifestyle intervention (SMD = -0.53; 95% CI: -0.73, -0.34)

BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; EoI = end of intervention; HbA1c = glycosylated haemoglobin; HDL = high density lipoprotein; HR = hazard ratio; LDL = low density lipoprotein; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio; SFA = saturated fatty acid; SMD = standardized mean difference

KQ1c. What is the evidence on the effectiveness of lifestyle interventions for breast and prostate cancer?

Three RCTs assessed the effectiveness of lifestyle interventions for breast and prostate cancer. One trial was assessed at high risk of bias; two were unclear. Project Leading the Way in Education Against Disease (Project LEAD) tested whether a personally tailored telephone counseling program was effective in improving diet and physical activity behavior among early stage breast and prostate cancer patients. The lifestyle intervention included a home-based diet and exercise program of telephone counseling and mailed materials. The mean age was 71.7±5.0 years. The duration of the intervention was 6 months with a 6 month followup.

Ornish et al. included men with prostate cancer who had declined conventional treatment. The lifestyle group followed a vegan diet, engaged in moderate aerobic exercise, learned stress

management techniques, and participated in a weekly support group. The mean age was 65.7±7.4 years. The duration of the intervention was 1 year with no postintervention followup.

The Reach out to ENhancE Wellness in Older Cancer Survivors (RENEW) included overweight patients with breast and prostate cancer. The lifestyle intervention was a home-based program and included personally tailored workbooks, newsletters, telephone counseling, and automated prompts. The mean age was 73.1±5.0 years. The duration of the intervention was 1 year with a planned 1 year followup.

Results are presented in Table ES3 and are summarized below.

- *Primary outcomes.* One study assessed prostate-specific antigen PSA levels and found a significant decrease in levels for lifestyle intervention participants.
- *Change in body composition.* Two studies reported change in weight (lbs) at end of intervention. There is no difference between groups for breast cancer patients but a statistically significant difference favoring the lifestyle group for prostate cancer patients. Two studies reported change in BMI (kg/m^2) and showed no statistically significant difference between groups for breast, prostate, and mixed cancer populations.
- *Change in metabolic variables.* One study reported metabolic outcomes. Statistically significant differences in favor of the lifestyle intervention were seen in all outcomes except triglycerides.
- *Change in physical activity*. Two studies looked at changes in exercise level. The difference between groups at end of intervention was statistically significant favoring the lifestyle group. One study reported a statistically significant increase in energy expenditure in favor of the lifestyle intervention at the end of intervention; this difference was no longer present at 6 months followup.
- *Change in dietary or nutrient intake*. All three studies assessed calories from fat. In two studies there was a statistically significant decrease in calories from fat in breast cancer and prostate cancer patients. One study showed no difference between groups in the mixed breast and prostate cancer populations at end of intervention and 6 months followup.

Table ES3. Summary table: breast and prostate cancer

Outcome	# RCTs	Strength of evidence	Precision
Breast cancer			
Change in body composition			
BMI (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.31; 95% CI: -1.19, 0.57)
Weight (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -3.9; 95% CI: -10.32, 2.52)
Change in physical activity			
Exercise (endurance; EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 25.6; 95% CI: 16.9, 34.8)
Change in dietary or nutrient intake			
F&V intake (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 1.08; 95% CI: 0.5, 1.66)
Fat intake (calories from fat) (EoI)	1	Insufficient	Significant effect in favor of lifestyle intervention (MD = -1.76; -2.57, -0.95)
Prostate cancer			
Primary outcome			
PSA levels (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.63; 95% CI: -1.16, -0.10)
Change in body composition			
BMI (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.61; 95% CI: -1.47, 0.25)
Weight (EoI)	2	Insufficient	Significant effect in favor of lifestyle intervention (MD = -7.55; 95% CI: -13.05, -2.05)
Change in metabolic variables			
HDL cholesterol (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -6.4; 95% CI: -9.65, -3.15)
LDL cholesterol (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -28.6; 95% CI: -40.79, -16.41)
Total cholesterol (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -34.0; 95% CI: -48.30, -19.7)
Triglycerides (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD= -9.0; 95% CI: -39.62, 21.62)
Change in physical activity			
Exercise (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD = 0.62; 95% CI: 0.20, 1.03)
Exercise (endurance; EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 16.3; 95% CI: 4.8, 28.5)
Change in dietary or nutrient intake			
Fat intake (calories from fat) (EoI)	2	Insufficient	Significant effect in favor of lifestyle intervention (MD = -16.80 [-20.29, -13.31]

BMI = body mass index; CI = confidence interval; EoI = end of intervention; F&V = fruit and vegetable; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; PSA = prostate specific antigen; RCT = randomized controlled trial; RR = risk ratio

Table ES3. Summary table: breast and prostate cancer (continued)

Outcome	# RCTs	Strength of evidence	Precision
F&V intake (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 1.4; 95% CI: 0.75, 2.05)
Mixed breast and prostate cancer			
Change in body composition			
BMI (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.10; 95% CI: 1.68, 1.48)
BMI (followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.50; 95% CI: -2.13, 1.13)
Change in physical activity			
Exercise (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD = 0.31; 95% CI: 0, 0.61)
Exercise (followup)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD = 0.13; 95% CI: -0.18, 0.44)
Change in dietary or nutrient intake			
F&V intake (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 0.4; 95% CI: -0.21, 1.01)
F&V intake (followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.10; 95% CI: -0.75, 0.55)
Fat intake (calories from fat) (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.30 [-2.41, 1.81]
Fat intake calories from fat) (followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.50 [-2.70, 1.70]

BMI = body mass index; CI = confidence interval; EoI = end of intervention; F&V = fruit and vegetable; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; PSA = prostate specific antigen; RCT = randomized controlled trial; RR = risk ratio

KQ 2. What is the generalizability of the evidence to the Medicare population (> 65 years)?

Type 2 diabetes. The trials included a wide range of patients including varying comorbidities and nationalities. The mean ages from the 10 trials ranged from 53 to 62 years and included participants up to 75 years old. The majority of these addressed our secondary outcomes, thus we believe that the results for our secondary outcomes should be generalizable to individuals aged 65 years or older.

Two trials excluded patients over the age of 65 years, including the only study that provided data for our primary outcomes. Therefore, we are uncertain whether the results for our primary outcomes (progression of diabetes, progression to micro- or macrovascular complications) are generalizable to the Medicare population.

Metabolic syndrome. The mean ages from the seven trials ranged from 44 to 58 years and included participants up to 85 years of age. Two trials excluded patients over the age of 65 years, including studies that provided data for our primary outcomes. Therefore, we are uncertain whether the results for our primary outcomes (progression to diabetes or cardiovascular events) are generalizable to the Medicare population. For our secondary outcomes, we believe that the results should be generalizable to individuals aged 65 or older.

Breast and prostate cancer. The mean age of participants in the three trials ranged from 65 to 75 years. Therefore, the results from these studies should be generalizable to the Medicare population.

KQ 3. What is the evidence on what components of the interventions, composition of the team, and/or patient characteristics contribute to better outcomes?

We were unable to address this question due to insufficient data.

Limitations of the Existing Evidence

The strength of the evidence was low or insufficient for the majority of outcomes across the various interventions and conditions. These low grades were driven by a high or unclear risk of bias within individual studies, lack of direct evidence for patient-important outcomes, and lack of consistency and precision among studies.

Although the studies providing data for this report were RCTs, all had a high or unclear risk of bias as assessed using an empirically derived tool for assessing risk of bias developed by The Cochrane Collaboration. Most of the RCTs were rated as having adequately generated the allocation sequence (70 percent); however, less than half adequately concealed allocation (40 percent). Measures to ensure that allocation occurs without foreknowledge of treatment assignments can always be undertaken by study investigators and should be routinely employed in order to avoid selection bias. Blinding of study investigators and participants was mostly unclear (65 percent). Inadequate blinding can lead to exaggerated treatment effects. Blinding of patients may not be feasible when the intervention is a "lifestyle intervention;" however, blinding of patients to the hypothesis, implementing an active intervention for the control groups, and blinding of outcome assessors may reduce the impact of nonblinding of patients, in particular for patient-reported outcomes. Incomplete outcome data was a problem in half of the trials due to loss to followup and inadequate handling of missing data in the reporting and/or analysis. This may exaggerate treatment effects.

Few trials provided data for clinically-important outcomes and we had to rely on surrogate measures to assess the impact of lifestyle interventions on our primary outcomes. Lack of consistency and precision of results across studies also contributed to the low strength of evidence rating for the majority of outcomes. Consistency was often unknown due to the few studies assessing the same outcome at the same timepoint. Precision was often poor due to the small sample sizes in many of the studies, which may have resulted in insufficient power to detect clinically-important differences. Both consistency and precision may have been affected by variations in the clinical populations assessed across the studies, such as the number, type and severity of comorbidities, and composition, intensity and duration of the lifestyle interventions.

Providing long-term data for studies comparing an active treatment with an active control may not be feasible. As such, a systematic review including observational studies might be beneficial in providing data on patients using different interventions over several years to determine the comparative benefits these interventions.

In addition to the methodological issues identified above, there are limitations that need to be discussed regarding systematic reviews. There is a possibility of publication bias in this systematic review. Since we did not include conference proceedings, unpublished literature, or non-English language publications, we may have missed some studies, and therefore may be overestimating the therapeutic benefit of the lifestyle interventions. Nonetheless, we conducted a

comprehensive and systematic search of the published literature that was supplemented by reviewing reference lists of included studies and contacting authors. Despite these efforts, we recognize that we may have missed some trials. There is also the possibility of study selection bias. However, we employed at least two independent reviewers and feel confident that the studies that were excluded from this report were done so for consistent and appropriate reasons.

Future Research

The following general recommendations for future research are based on the preceding discussion regarding the limitations of the current evidence:

- RCTs should be designed and conducted to minimize risk of bias where at all possible. Authors may find tools such as the CONSORT statement helpful in designing and reporting on RCTs.
- Future RCTs should seek to minimize risk of bias by blinding outcome assessors, implementing an active intervention for control groups, adequately concealing allocation, and handling and reporting missing data appropriately.
- Information regarding the benefit of individual components of lifestyle interventions is needed. Determination of the benefit of individual components would allow for standardization of these interventions in the literature, improve reporting, and facilitate comparisons across populations.
- Consensus on clinically- and patient-important outcomes and outcome measures is needed to ensure consistency and comparability across future studies. Moreover, consensus on minimal clinically important differences is needed to guide study design and interpretation of results.
- RCTs that are adequately powered to detect differences in cardiovascular mortality and morbidity in patients at risk for type 2 diabetes are needed.
- A systematic review of the literature, including observational studies, may provide data on the impact of different lifestyle interventions over several years in order to assess the long-term sustainability and comparative effectiveness of these interventions.
- Given that many chronic disease guidelines now recommend healthy dietary and exercise behaviors, RCTs that are designed to assess components that may improve adherence to guidelines would be beneficial.
- Specifically, research to assess which delivery settings are effective in promoting behavioral change would assist in the delivery of these interventions (i.e., primary care level vs. population-based initiatives).

Conclusions

Overall, comprehensive lifestyle interventions that include exercise, dietary changes, and at least one other component are effective in decreasing the incidence of type 2 diabetes mellitus in high risk patients and the benefit extends beyond the active intervention phase. While the interventions have a positive impact on a number of risk factors for cardiovascular disease, the impact on cardiovascular outcomes is less clear. Further trials that are adequately powered to determine cardiovascular outcomes are required.

In patients who have already been diagnosed with type 2 diabetes, evidence for benefit of comprehensive lifestyle interventions on patient-oriented outcomes is less clear. There is some evidence to suggest long-term benefit on microvascular and macrovascular outcomes, although the evidence is from one trial of high risk diabetic patients and medication was included as part of the active intervention group. One large RCT is currently ongoing in an attempt to address this issue.

The body of evidence looking at lifestyle interventions to prevent cancer recurrence is limited. We found only one RCT that attempted to address this question, however, the clinical significance of their findings is unclear.

Comprehensive lifestyle interventions appear to have a positive impact on behavioral outcomes including exercise and dietary intake, as well as a number of metabolic variables, at least in the short-term in all populations addressed in this report.

No firm conclusions can be drawn from the available evidence on which interventional strategy would be most successful in inducing and maintaining behavioral change or improving patient-oriented outcomes. In addition, it remains unclear whether comprehensive lifestyle interventions as defined by diet, exercise, and at least one other intervention are superior to diet and exercise alone.

Evidence Report

Chapter 1. Introduction

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services requested this report from The Technology Assessment Program at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the University of Alberta Evidence-based Practice Center (Contract Number: 290-2007-10021-I).

Background

Chronic diseases are the major cause of death and disability worldwide. The World Health Organization (WHO) reported that 88 percent of deaths in the United States in 2002 were attributable to chronic disease.[1] Heart disease, cancer, and stroke alone accounted for 55 percent of all deaths in the U.S. in 2005.[28]

Prevention of the onset or progression of chronic disease is often promoted as the gold standard[1] although the optimal interventions to achieve this have not been well documented in the literature. In particular, the benefit of lifestyle interventions in the prevention of chronic disease progression or recurrence has not been fully established.

A number of lifestyle behaviors have been identified as contributors to overall morbidity and mortality of chronic disease. Among these, physical activity and diet have been identified as two modifiable risk factors that may impact onset or progression of disease. The evidence for this comes largely from population based studies which report that adhering to a healthier lifestyle, including dietary and physical components, resulted in a lower risk of all-cause mortality. A 10-year cohort study reported that adhering to a Mediterranean diet and physical activity among other modifiable risk factors resulted in lower risk of all-cause mortality, including mortality from coronary heart disease (CHD), cardiovascular disease (CVD), and cancer.[29] Other longitudinal studies also report that a healthy lifestyle at older ages is related to a delay in the deterioration of health status and a reduced mortality risk.[30]

Ecological data further suggest that improved dietary intake has been beneficial in decreasing the burden of chronic disease, particularly CHD.[2-4] A recent systematic review supports this association.[5]

Despite the demonstrated benefit of improved diet and physical activity in the prevention of certain chronic diseases, the benefits of lifestyle modifications in preventing progression or recurrence of disease is not as well documented. In addition, it remains unclear if additional lifestyle interventions beyond diet and physical activity have proven benefit, how effective interventions are in modifying risk factors, and which diseases in the spectrum of chronic disease, if any, would benefit.

In theory, lifestyle interventions have significant potential for benefit, as more than one-third of all adults do not meet recommendations for aerobic physical activity based on the 2008 Physical Activity Guidelines for Americans.[31] Dietary habits are not much better. Only 24 percent of American adults reported eating five or more servings of fruits and vegetables per day[32] despite evidence from cohort studies of an inverse association between fruit and vegetable intake and risk for both CHD[33] and stroke.[34] Finally, obesity has become a major health concern. In the U.S. one in every three adults is obese.[35] Large prospective cohort studies have shown that

the risk of death from all causes, CVD, cancer, and other diseases increases throughout the range of moderate and severe overweight persons.[36,37]

Magnitude and Importance of Conditions

Type 2 Diabetes

Type 2 diabetes is defined as a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.[38] There are an estimated 23.6 million people in the U.S. with diabetes; 90 to 95 percent of these have type 2 diabetes. The total health care costs associated with diabetes in the U.S. in 2007 was estimated to be $174 billion.[6] The prevalence of self-reported diabetes increased by 49 percent over a 10-year period in the U.S., from 4.9 percent in 1990 to 7.3 percent in 2000.[39] Global estimates of diabetes prevalence suggest that without significant intervention, the burden of diabetes will continue to grow significantly in the next few decades.[40]

Type 2 diabetes is a major cause of morbidity and mortality. Diabetes was the seventh leading cause of death in the U.S. in 2006[6] and CVD accounted for more than 65 percent of all diabetic deaths.[7] Diabetes is also the leading cause of kidney failure, nontraumatic lower-extremity amputations, and blindness among adults in the U.S.[8]

With regard to improving overall morbidity and mortality, there is good evidence that improving glycemic control decreases the risk of microvascular complications[41] while the impact on macrovascular outcomes is less clear.[42-44] A recent study suggested that early intensive glycemic control may improve macrovascular outcomes over the long term.[45] Tight blood pressure control has been demonstrated to decrease the risk of microvascular and macrovascular disease in patients with type 2 diabetes.[46]

Obesity or increased body mass index (BMI) is one of the strongest predictors in the development of type 2 diabetes,[47-52] and is also an independent risk factor for CVD. Research suggests that patients with diabetes with increased weight have an increased lifetime risk of CVD.[53,54] A recent review demonstrated that weight loss in individuals with type 2 diabetes led to significant reductions in a number of CVD risk factors.[55] Furthermore, evidence from retrospective chart reviews and observational studies suggests that reductions in weight significantly decrease premature mortality in diabetic patients.[56,57]

With regard to dyslipidemia, plasma values for low-density lipoprotein (LDL) cholesterol have been reported to be a predictor of cardiovascular events in patients with diabetes. Patients with a plasma level of LDL cholesterol of approximately 3.89 mmol/L (150 mg/dL) are at a 2-fold greater risk for experiencing a cardiovascular event than the diabetic patient whose plasma value for LDL cholesterol is 1.81 mmol/L (70 mg/dL). A number of trials have demonstrated that lipid lowering therapy, regardless of baseline levels, results in decreased cardiovascular events and mortality in diabetic patients.[58,59]

Participation in regular, moderate intensity physical activity has been reported to decrease glycosylated hemoglobin (HbA1c)[60,61] and is associated with improvements in cardiovascular risk profile.[62] More importantly, low cardiorespiratory fitness and physical inactivity are independent predictors of all-cause mortality,[63] whereas increased physical activity, including

regular walking, has been associated with substantially reduced risk for cardiovascular events in individuals with type 2 diabetes.[64]

Metabolic Syndrome

The metabolic syndrome is defined as a constellation of interrelated metabolic risk factors that directly promote the development of CVD and type 2 diabetes. The most widely recognized metabolic risk factors are dyslipidemia, elevated plasma glucose, and hypertension. Significant debate exists regarding the clinical utility of metabolic syndrome to predict CVD and type 2 diabetes. Prediabetes, which includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), has been suggested to be equally effective in identifying those at risk of developing type 2 diabetes.

Diagnostic criteria for metabolic syndrome have evolved over the years. The WHO task force on diabetes first suggested insulin resistance as the dominant cause of the metabolic syndrome in 1998.[65] In 2001, alternate criteria for the diagnosis of the syndrome were introduced by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III). ATP III criteria made the presence of three of the following five factors the basis for diagnosing metabolic syndrome: abdominal obesity, elevated triglycerides, reduced HDL-C (high density lipoproteins-cholesterol), elevated blood pressure, and IFG.[66] The most current criteria for the metabolic syndrome in the U.S. comes from American Heart Association (AHA)/ National Heart, Lung, and Blood Institute (NHLBI) update of the NCEP criteria. The criteria maintain the ATP III criteria except for minor modifications in cut off values.[67]

The evolving definition of metabolic syndrome has resulted in some inconsistency in the literature. Therefore, our operational definition of metabolic syndrome included metabolic syndrome, insulin resistance, prediabetes, IFG, IGT, syndrome X, dysmetabolic syndrome X, and Reaven syndrome. Our goal was to include populations identified to be at increased risk of developing CVD and /or type 2 diabetes. One recent meta-analysis including 43 cohorts (172,573 individuals) reported that NCEP-defined metabolic syndrome conveyed a relative risk (RR) of 1.78 for CVD events and death.[13] Other data suggest that there is little or no association with metabolic syndrome and vascular risk in elderly populations .[68] In addition, the diagnosis of metabolic syndrome has been reported to increase the risk for type 2 diabetes by about 2-fold.[69] However, several studies have shown that fasting glucose concentration is as good, if not better, than metabolic syndrome in predicting onset of type 2 diabetes.[68,70,71]

IFG and IGT are frequently associated with metabolic abnormalities. One meta-analysis reported that compared with normoglycemic people, the RR for diabetes in people with IGT was 6.35 (95% CI: 4.87, 7.82), and 4.66 (95% CI: 2.47, 6.85) for IFG.[72] In addition, IFG and IGT are associated with a modest increase in the risk for CVD (RR = 1.2).[73]

Approximately 64 million or 25 percent of adults in the U.S. were estimated to have metabolic syndrome in 2000.[9] More recently, the Centers for Disease Control suggests that 34 percent of adults in the U.S. met the diagnostic criteria of metabolic syndrome between 2003-2006.[12] As of 2011, the American Diabetes Association estimated that 57 million people in the U.S. had prediabetes,[10] many of whom would overlap with metabolic syndrome.

Many risk factors for the development of metabolic syndrome or prediabetes have been proposed, one of which is obesity[11] which has increased in incidence alongside the metabolic

syndrome over the past decade.[12,74] Additional risk factors include increasing age[12,13] and physical inactivity.[14]

Since patients may be at high risk of developing diabetes for a number of reasons, proposed strategies for reducing cardiovascular risk involve the management of multiple risks. Lifestyle changes have traditionally been encouraged as first-line management,[75] particularly with regards to the modifiable underlying risk factors[76] including obesity[77,78] and physical inactivity.

Breast Cancer

Breast cancer is defined as the development of malignant cells in the breast which usually originate from the ducts or lobules of the breast. The National Cancer Institute estimates that in 2010 there will be 209,060 new cases of breast cancer diagnosed, with 40,230 deaths.[15] Based on current incidence rates, one out of eight women in the U.S. will be diagnosed with breast cancer during their lifetime. Survival and recurrence rates depend on a number of factors including stage of the cancer at diagnosis.

Estimates of 5-year cumulative incidence of recurrence of early-stage breast cancer following polychemotherapy regimens range from 25 percent (age 50) to 29 percent (age 50–69), rising to 36 to 44 percent by 10 years, Recurrence rates are lower for node-negative breast cancer.[15]

Risk factors for the recurrence of breast cancer have not been well delineated. Many epidemiological studies suggest a correlation with obesity and increased incident breast cancer risk.[16-18] The Women's Health Initiative observational study found that women weighing more than 82.2 kg had a relative risk of breast cancer of 2.85 (95% CI: 1.81, 4.49) compared with those weighing less than 58.7 kg.[79] There is also a body of epidemiological evidence suggesting that increased physical activity reduces incident breast cancer.[19] A recent systematic review found that physical activity could reduce the incidence of breast cancer in postmenopausal women by 20 to 80 percent.[20]

A number of studies have demonstrated the impact of obesity on prognosis in breast cancer.[80] A recent systematic review of 43 studies reported a pooled hazard ratio (HR) of 1.33 (95% CI: 1.21, 1.47) for breast cancer specific survival in obese versus non-obese women.[81] The benefit of weight loss on prevention of breast cancer recurrence or survival has not been demonstrated.

Some studies have shown a reduction in overall mortality with increased physical activity after breast cancer diagnosis.[82-84] Decreased breast cancer recurrence and improved breast cancer specific survival have not been as well addressed, however, a recent systematic review of six studies reported that post-diagnosis physical activity reduced breast cancer deaths by 34 percent (HR = 0.66, 95% CI: 0.57, 0.77), all-cause mortality by 41 percent (HR = 0.59, 95% CI: 0.53, 0.65), and disease recurrence by 24 percent (HR = 0.76, 95% CI: 0.66, 0.87).[84] Exercise has also been shown to improve quality of life in breast cancer survivors.[85]

The role of nutrition in preventing recurrence of breast cancer remains unclear.[86] Two recent randomized controlled trials (RCTs) reported conflicting results in recurrence of breast cancer with a low fat diet.[87,88]

Evidence of benefit of individual lifestyle factors in preventing breast cancer recurrence is limited, and at times remains controversial.[89] Many questions remain regarding the benefit of comprehensive lifestyle interventions in modifying suspected risk factors and the consequent impact on disease recurrence.

Prostate Cancer

Prostate cancer is defined as a malignant growth of cells in the prostate gland. It is the second leading cause of death of males in the U.S. It is estimated that 217,730 men will be diagnosed with and 32,050 will die of prostate cancer in 2010 in the U.S.[21]

The impact of lifestyle factors on incidence or recurrence of prostate cancer remains an area of some controversy. While ecologic studies have demonstrated a direct relationship between a country's prostate cancer-specific mortality rate and average total calories from fat consumed by the country's population,[90,91] results from studies of the association between dietary intake of fruits and vegetables and risk of prostate cancer are not consistent.[22-24]

A weak association has been reported between BMI and incident prostate cancer,[25] and prospective cohort studies have reported a relationship between increased BMI and more advanced prostate cancer or increased prostate cancer mortality.[25,92-95] In addition, higher prostate cancer recurrence rates after radical prostatectomy or radiotherapy treatment have been reported in obese patients.[96-100] The Cancer Prevention Study suggested that men who lost weight appeared to reduce their risk of prostate cancer.[101]

Evidence regarding physical activity in the prevention of incident prostate cancer is limited. In a 1997 review of 17 studies, 9 suggested possible benefit, 5 demonstrated no effect, and 3 reported increased risk of prostate cancer with increased exercise.[26] A 2004 review suggested a probable inverse relationship between physical activity and prostate cancer incidence although the existence of conflicting evidence was noted.[27] Furthermore, two large prospective cohort studies reported conflicting results regarding the benefits of exercise in prostate cancer. One study of 293,902 men found no difference in prostate cancer risk with increased exercise,[102] while the other (n = 45,887) suggested a 20 percent reduction in prostate cancer incidence with increased physical activity.[103]

Evidence regarding effect of physical activity on recurrence or overall survivorship is lacking. One cohort study of 47,620 men suggested that among those 65 years or older vigorous physical activity was associated with decreased risk of death from cancer.[104] Studies looking at the benefit of physical activity on other outcomes, including quality of life, are more prevalent. A recent systematic review of physical activity in prostate cancer survivors reported evidence of effect of physical activity on muscular fitness, physical functioning, fatigue, and health-related quality of life although it recognized the current limitations of available evidence.[105]

Although PSA has a number of limitations, it is generally viewed as a biomarker of disease progression in patients with a history of prostate cancer in which elevated levels may indicate early recurrence of the disease.[106]

The American Cancer Society recommends that men who have been diagnosed with prostate cancer should consume diets that are rich in vegetables and fruit and low in saturated fat, and pursue a physically active lifestyle. This recommendation is likely based on the assumption that there are substantial other benefits to these recommendations, most prominently decreasing CVD risk, which is the major cause of death in prostate cancer survivors.[107]

Objective of the Report

The objective of this report was to identify and synthesize the available evidence regarding the effect of lifestyle interventions on the management of four common chronic disease conditions: type 2 diabetes, metabolic syndrome, breast cancer, and prostate cancer. For the purpose of this review, lifestyle interventions were defined as any intervention that included an exercise component, a dietary component (not necessarily weight loss), and at least one other element, including but not limited to, counseling, stress management, behavior modification, weight loss, smoking cessation or risk factor modification.

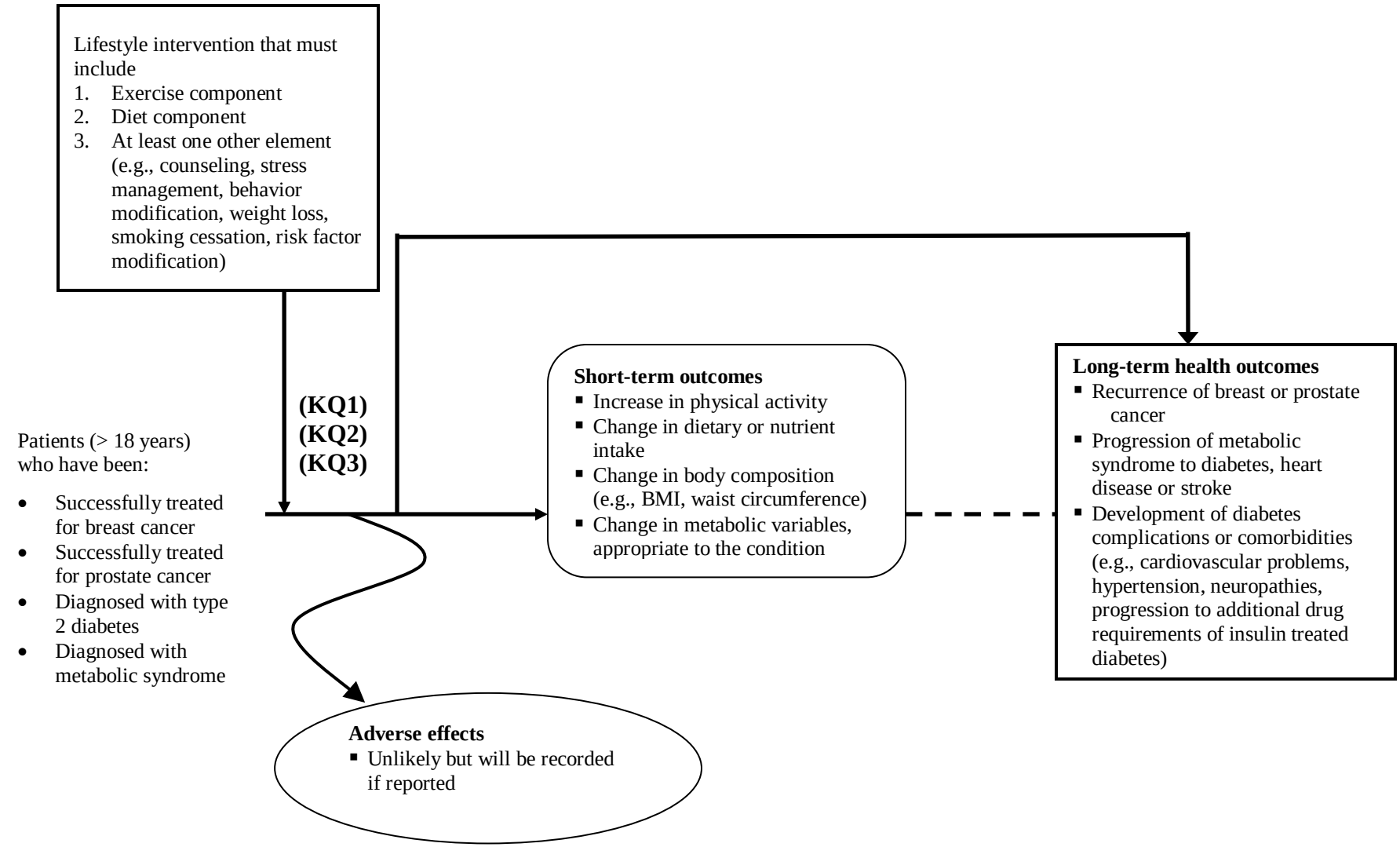
Key Questions

1. What is the evidence on the effectiveness of lifestyle interventions for type 2 diabetes mellitus, metabolic syndrome, breast cancer, and prostate cancer?
2. What is the generalizability of the evidence to the Medicare population (> 65 years)?
3. What is the evidence on whether specific components of the interventions, composition of the team, and/or patient characteristics contribute to better outcomes?

Analytic Framework

Figure 1 illustrates an analytic framework used to guide assessment of studies involving lifestyle interventions. The figure shows how lifestyle interventions will result in the prevention of progression to additional medication or insulin treated diabetes or future related morbidities in patients with type 2 diabetes, the prevention of progression to diabetes, heart disease, or stroke in those with metabolic syndrome, and the prevention of cancer recurrence in people previously treated for breast and prostate cancer. Adverse reactions that are directly related to the lifestyle intervention are unlikely, but are included in the framework.

Figure 1. Analytic framework for lifestyle interventions



Chapter 2. Methods

This chapter describes the prospectively designed protocol that the University of Alberta Evidence-based Practice Center used to synthesize the evidence on lifestyle interventions for type 2 diabetes, metabolic syndrome, breast cancer, and prostate cancer. We outline the literature search strategy, the selection process for identifying relevant articles, the process for extracting data from eligible studies, the methods for assessing the methodological quality of individual studies and for rating the overall body of evidence, and our approach to data analysis and synthesis.

Literature Search

The Research Librarians, in collaboration with the research team, developed search strategies designed to identify evidence relevant to each key question. Our search for published literature included structured searches in standard bibliographic databases. We systematically searched the following resources: MEDLINE® (1950 – 2010), Embase (1980-2010), Cochrane Controlled Trials Register (CENTRAL) (1980 – 2010), CINAHL® (1982 – 2010), and SCOPUS (1980 – 2010). The original searches were performed between March 3rd and March 23rd, 2010. Search terms were identified by reviewing search strategies of systematic reviews on similar topics and by looking at how potentially relevant studies were indexed in various databases. A combination of subject headings and text words was adapted for each electronic resource covering the four diseases/conditions and lifestyle interventions (diabet* type II or noninsulin depend$ OR MODY or NIDDM OR T2DM) OR (metabolic syndrome x or prediabet* or insulin resistance) OR (prostat* and (neoplasm* or cancer* or carcinoma or tum?or* or malignan*)) OR (breast* and (neoplasm* or cancer* or carcinoma or tum?or* or malignan*)) AND (exercise* or fitness* or exertion or activit* or endurance*) AND (lifestyle or stress or mental health or cognitive therap* or psychotherap* or health promotion or health education or behavior?r therap* or quality of life or mend-body therap* or breathing exercise* or laughter therap* or therapeutic touch* or tai chi or aromatherap* or hypnosis or meditation) AND (diet* or weight loss* or nutrition* or calori* and (intake or restriction or reduction or deficit or diet or intervention or change or program)) or fat intake or fiber intake). A RCT filter was applied to limit the searches to controlled trials. Searches were also limited to English language and a date restriction of 1980 – present was applied. See Appendix A for exact search strategies.

Study Selection

The review included RCTs published between 1980 and 2010. The population was adults (≥ 18 years) who were survivors of breast cancer (diagnosed and successfully treated), survivors of prostate cancer (diagnosed and successfully treated or diagnosed and in a watchful waiting category), with type 2 diabetes (diagnosed by a physician), or metabolic syndrome (operationally

defined as including metabolic syndrome, insulin resistance, pre-diabetes, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and Reaven syndrome) .

The lifestyle intervention had to include an exercise component, a diet component, and at least one other component (e.g., counseling, smoking cessation, stress reduction, group therapy, behavior modification). The comparison could be usual care, the diet and/or exercise components alone, or wait list. Our a priori criteria stated that the intervention must be at least 3 months with a postintervention followup period of at least 6 months. We made a post hoc modification to include RCTs in which the duration of the lifestyle intervention was at least 1 year but without a 6 month postintervention followup. We believe that such studies provide relevant information about the impact of long-term interventions.

The primary outcomes were recurrence of breast or prostate cancer, progression of type 2 diabetes to additional medication or insulin or progression to cardiovascular problems, hypertension or neuropathies, or progression of metabolic syndrome to diabetes, heart disease or stroke. The secondary outcomes were increase in physical activity, change in dietary or nutrient intake, change in body composition, change in metabolic variables, change in total number of medications taken or change in medication dose, and compliance to treatment allocation.

Article screening was conducted in two phases. In the first phase, two reviewers independently screened the titles, keywords, and abstracts (when available) to determine if an article met broad screening criteria for study design and population. Each article was rated as "include," "exclude," or "unclear". The full text of articles classified as "include" or "unclear" by at least one of the reviewers was retrieved for detailed review. Two reviewers independently assessed each study using a detailed standard inclusion/exclusion form (Appendix B). Disagreements were resolved by consensus or third-party adjudication.

Methodological Quality

The Cochrane Collaboration Risk of Bias (RoB) tool was used to assess the internal validity of the RCTs.[108] The tool examines six domains (sequence generation, concealment of allocation, blinding, incomplete outcome data, selective outcome reporting, and "other" sources of bias). Each separate domain is rated "high", "low", or "unclear". Blinding and incomplete outcome data were assessed separately for subjective outcomes (e.g., self-reported diet or exercise information) and objective clinical outcomes (e.g., weight gain, blood pressure). "Other" sources of bias included funding source, stopping early for benefit, and comparability of groups at baseline. The overall assessment was based on the responses to individual domains. If one or more individual domains were assessed as having a high risk of bias, the overall score was rated as high risk of bias. The overall risk of bias was considered low only if all components were rated as having a low risk of bias. The risk of bias for all other studies was rated as unclear.

Decision rules regarding application of the ROB tool were developed a priori and a sample of studies was used to pilot the RoB tool. Two reviewers independently assessed the methodological quality of included studies. Disagreements were resolved through consensus or third party adjudication. We contacted authors of included studies to collect missing information.

Data Extraction

Using a standardized form (Appendix B), one reviewer extracted data into an Excel® database. The data were verified for accuracy and completeness by a second reviewer. Disagreements were resolved through discussion or third party adjudication.

The following data were extracted: author identification, year of publication, source of study funding, study design characteristics and methodological quality criteria, study population (including study inclusion and exclusion criteria, duration of intervention, patient baseline characteristics (i.e., age, sex, race, weight, BMI, waist circumference, blood pressure), detailed description of the intervention and comparison, results for the outcomes of interest, and adverse events.

Data Analysis

The following assumptions were made and imputations performed to transform reported data into the form required for analysis. Graphical data were extracted using the measurement tool of Adobe Acrobat 9 Pro (Adobe Systems Inc., California, U.S.). Evidence tables and qualitative descriptions of results are presented for all included studies.

Quantitative results were meta-analyzed in Review Manager Version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark). For continuous variables where the outcome measures were on the same scale (e.g., BMI) or could be easily converted to the same scale (e.g., pounds to kilograms), the mean difference (MD) was calculated. When the same outcome was measured using different scales (e.g., physical activity), the standardized mean difference (SMD) was used. Relative risks (RR) were computed to estimate between-group differences in studies that reported dichotomous outcomes (e.g., death). If no events were reported in one treatment arm, a correction factor of 0.5 was added to each cell of the two by two table in order to obtain estimates of the risk ratio. When no events were reported in both of the treatment arms, the RR was undefined and was denoted as “not calculated (NC)” in the results tables. All results are reported with 95% CI. When data were missing, imputations had to be carried out. Missing means were approximated by medians. Missing standard deviations were computed from standard errors, confidence intervals, or p-values. If none of these were available they were estimated from ranges or inter-quartile ranges, or imputed from other similar studies with the same outcome. If a trial had three or more arms of which two or more could be classified as a “treatment”, we included the study in a meta-analysis twice, splitting the control group to prevent a unit of analysis error.

All meta-analyses used a random effects model. Statistical heterogeneity was quantified using the I-squared (I^2) statistic. When the I^2 was greater than 75 percent, we conducted sensitivity analyses to explore sources of heterogeneity including study population (age, sex, risk factors), components of the lifestyle intervention, and study quality. Potential publication bias was explored graphically through funnel plots for comparisons for which there were at least 10 studies.

Grading the Body of Evidence

We used the EPC GRADE approach[109] to assess the strength of the evidence for all our primary outcomes and the following secondary outcomes: change in body composition, metabolic variables, systolic and diastolic blood pressure, physical activity, and dietary or nutrient intake. The following four major domains were examined for each outcome: risk of bias (the degree to which outcomes have a likelihood of adequate protection against bias; rated as low, medium, or high risk of bias), consistency (the degree to which reported effect sizes appear to have the same effect direction; rated as no inconsistency, inconsistency present, unknown, or not applicable), directness (whether the evidence directly links health outcomes to interventions; rated as direct or indirect), and precision (degree of certainty related to an outcome's effect estimate; rated as precise or imprecise). Each outcome for each comparison of interest was given one of the following grades based on the ratings for the individual domains: high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research may change our confidence in the estimate of effect and may change the estimate), low (further research is likely to change the confidence in the estimate of effect and is likely to change the estimate), or insufficient (evidence either is unavailable or does not permit estimation of an effect). The body of evidence was graded by one reviewer.

Chapter 3. Results

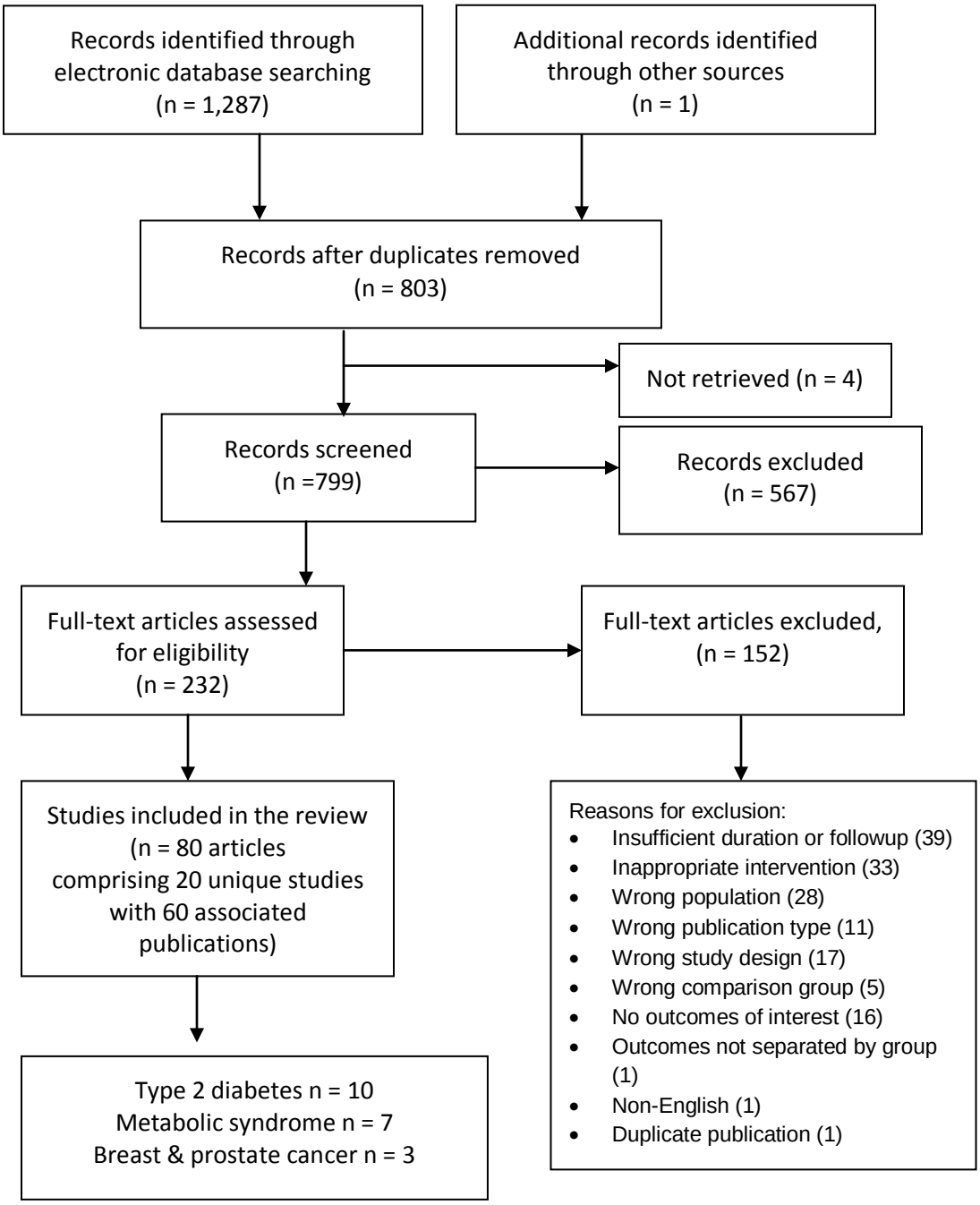
Literature Search

From our search of the electronic databases, 1,288 studies were identified (Figure 2). After duplicates were removed, 802 citations remained. We screened all the citations and identified 235 that were potentially relevant. Four studies could not be retrieved through the University of Alberta interlibrary loan system, therefore, the full text of 231 publications were reviewed for potential inclusion into this report. Of these, 20 unique RCTs (reporting data from 80 articles) were included. Ten studies[110-119] addressed type 2 diabetes, seven addressed metabolic syndrome,[120-126] and three addressed prostate and/or breast cancer.[127-129]

Many of the included trials were associated with multiple publications that either expanded on the main results, reported secondary outcomes that were not included in the primary report, or reported different followup timepoints. The publication that was the first to report outcome data was considered the primary study. See Appendix C for a list of the associated publications. Relevant baseline and outcome data were taken from the primary publication and supplemented with data from the associated publications.

The main reasons for excluding studies were: (1) insufficient length (n=39); (2) inappropriate intervention (n=33); (3) wrong population (n=28); (4) wrong publication type or study design (n=28), and other reasons (n=24). See Appendix D for a complete list of the excluded studies.

Figure 2. Flow diagram of study retrieval and selection



Key Question 1.What is the evidence on the effectiveness of lifestyle interventions for type 2 diabetes mellitus, metabolic syndrome, breast cancer, and prostate cancer?

Type 2 Diabetes

Description of Included Studies

Ten RCTs[110-119] met the inclusion criteria to address this question. There were 19 associated publications.[130-148] Five trials[111-113,115,119] had an intervention of at least 3 months and a followup period of at least 6 months postintervention. The interventions ranged from 6 to 48 months; the followup periods ranged from 6 to 93 months. The other five trials[110,114,116-118] had interventions that lasted 1 year but had no postintervention followup. One study[112] is ongoing and the investigators plan to have 10.5 to 11.5 years of followup data. For one trial, Steno-2 by Gaede et al.,[119] we present outcomes at 4 years (interim outcomes), 8 years (end of intervention), and 13 years postintervention. For the remaining trials, outcomes are reported for the end of intervention and at the longest postintervention followup timepoint.

For all 10 trials, the number of participants who were randomized ranged from 72 to 5,145 (median = 194; IQR: 143, 259). The mean ages ranged from 53.0 to 62.4 years. See Table 1 for baseline and study characteristics. From nine studies, the mean duration of diabetes ranged from newly diagnosed to 12.7±10.6 years. Duration of diabetes was not reported in one study.[110] The mean BMI ranged from 29.7±3.8 to 37.6±6.5 kg/m^2. Nine studies reported that all participants were taking oral diabetes medication, insulin, or both; one[117] did not report medication use.

While all lifestyle interventions included a diet and exercise component, they had diverse additional components (Table 2). Five studies[111,112,114,116,118] used both group and individual counseling, three incorporated only group counseling,[115,117,119] and two [110,113] had only individual counseling. Other components included a smoking cessation course,[119] regular telephone contact,[111,113] individual goal setting,[110,115,116,118] regular blood glucose and blood pressure monitoring,[118] and stress management.[115,118] In one study,[115] the participants went on a 3 day nonresidential retreat at the beginning of the intervention. In one,[117] physicians were responsible for motivating the participants. Four studies had medication use as one of the intervention components. The results of these studies are presented separately.

The interventions were administered or delivered by dietitians,[111,112,114-119] case managers or nurses,[112,116-119] physicians,[110,112,116,117,119] a qualified exercise advisor or trainer,[112,115,116] a behavioral therapist or physiologist,[112,115] a health or nonprofessional peer counselor,[111] lay leaders and trained support group leaders,[115] and a lifestyle counselor.[112] One study[113] reported that the intervention was delivered by a multidisciplinary team but did not specify the individual members.

Methodological Quality

Table 3 summarizes the methodological quality of the RCTs. Two trials[114,116] were assessed as high risk of bias; eight[110-113,115,117-119] were assessed as unclear. Most of the domains had low

risk of bias. The domain in which all studies had unclear or high risk of bias was the blinding of subjective or self-reported outcomes. Two studies stated that outcome assessors were blinded to treatment allocation.[112,119] In nine trials,[110,112-119] the baseline characteristics of the intervention and control groups were comparable. Seven studies[110,111,114,115,117-119] received funding from government, two received funding from foundations,[113,117] and two received funding from industry.[112,113] One study[116] did not report funding.

Results

Primary Outcomes. Our primary outcomes were progression of diabetes (additional medication or insulin treated diabetes) and progression to cardiovascular problems, hypertension, or neuropathies. The Steno-2 trial by Gaede et al.[119] was the only study to present data on our primary outcomes (Table 1). Data were provided at 4, 8 and 13.3 years. Medication was one of the components of the lifestyle intervention (Table 2).

Progression of diabetes, CVD complications, and death. There was a statistically significant decrease in the number of nonfatal myocardial infarctions in favor of the lifestyle group at 8 years (RR = 0.29; 95% CI: 0.11, 0.76) and 13.3 years (RR = 0.24; 95% CI: 0.12, 0.48).

At 13.3 years, 24 patients in the lifestyle group compared with 40 in the usual care group died (hazard ratio [HR] = 0.54; 95% CI: 0.32, 0.89). The lifestyle intervention was associated with a lower risk of death from cardiovascular causes (HR = 0.43; 95% CI: 0.19, 0.94) and a lower risk of cardiovascular events (HR = 0.41; 95% CI: 0.25, 0.67) including nonfatal strokes (RR = 0.17; 95% CI: 0.07, 0.42). Also, there was a statistically significant difference in the amputations (RR = 0.31; 95% CI: 0.16, 0.59) at 13 years favoring the lifestyle intervention. There was no statistically significant difference between the lifestyle and usual care groups in the number of coronary bypass grafts (RR = 0.67; 95% CI: 0.29, 1.54).

Retinopathy. At 4 years, there was no difference between groups in the development of retinopathy (RR = 0.60; 95% CI: 0.31, 1.14); at 13.3 years, the difference was statistically significant in favor of the lifestyle intervention (RR = 0.76; 95% CI: 0.58, 0.99). At 4 years and 8 years, there was a difference in progression of retinopathy in favor of the lifestyle intervention. (RR = 0.58; 95% CI: 0.36, 0.92 and RR = 0.75; 95% CI: 0.56, 0.99, respectively). At 13.3 years, progression of retinopathy occurred in 41 patients in the lifestyle intervention group compared with 54 in the control group (RR = 0.76; 95% CI: 0.58, 0.99).

Neuropathy. At both 4 and 8 years, there was a difference in favor of the lifestyle intervention for progression in autonomic neuropathy (RR = 0.36; 95% CI: 0.17, 0.77 and RR = 0.56; 95% CI: 0.38, 0.83, respectively). At 13.3 years, there was still a significant difference between the groups (RR = 0.75; 95% CI: 0.57, 0.99). In contrast, there was no difference at either 4 or 8 years for the progression of peripheral neuropathy (RR = 0.81; 95% CI: 0.50, 1.31 and RR = 0.93; 95% CI: 0.67, 1.28, respectively). Peripheral neuropathy progressed in 44 (lifestyle) and 46 (control) patients (RR = 0.96; 95% CI: 0.73, 1.26) at 13.3 years.

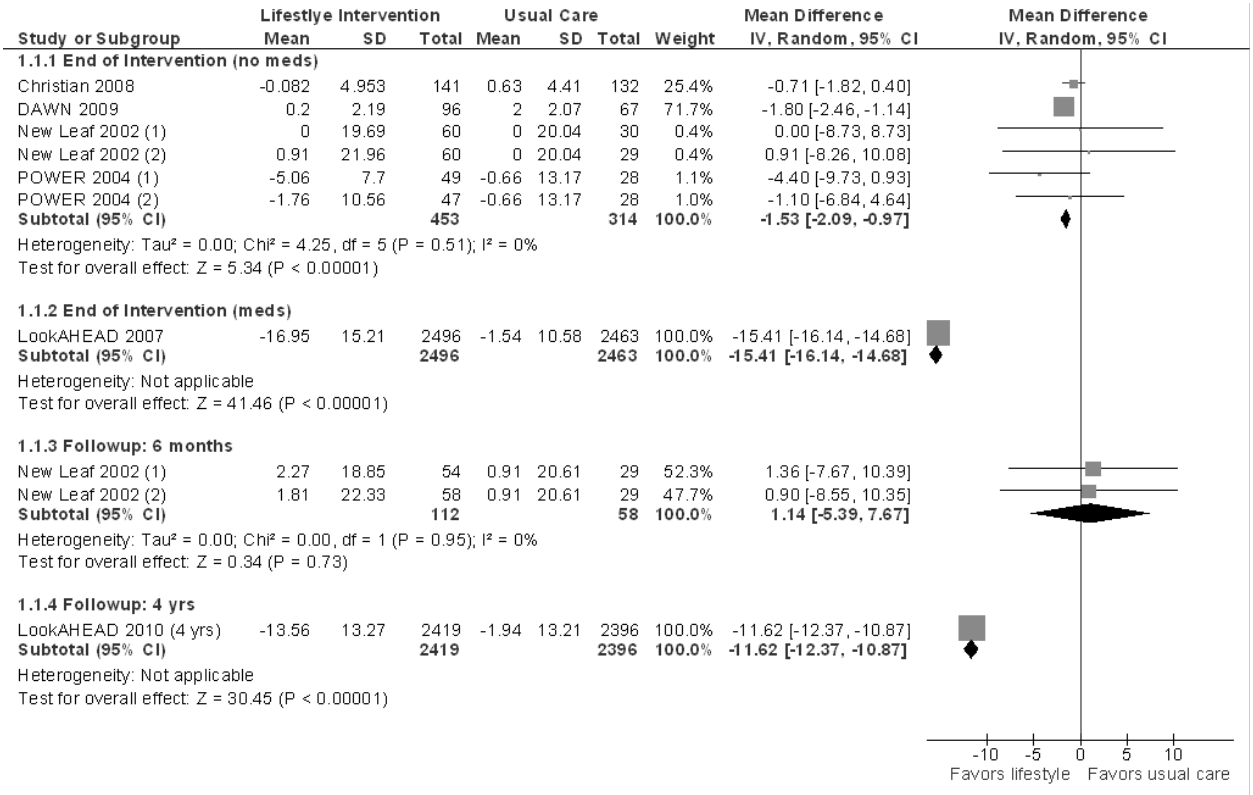
Nephropathy. There was a statistically significant difference in the development of nephropathy in favor of the lifestyle intervention at 4 years (RR = 0.42; 95% CI: 0.20, 0.91) and 8 years (RR = 0.52; 95% CI: 0.31, 0.87). At 13.3 years, 20 patients in the lifestyle group had developed nephropathy compared with 37 in the control group (RR = 0.54; 95% CI: 0.35, 0.85).

One patient in the lifestyle group had progressed to end-stage renal disease compared with four in the control group (RR = 0.45; 95% CI: 0.23, 0.86) at 13.3 years.

Secondary Outcomes. *Change in body composition*. Five studies[110-112,114,118] reported change in weight (lbs) at the end of the intervention (Figure 3). In all but one study, the lifestyle groups lost more weight than the usual care groups, although only two studies reported a statistically significant difference. The pooled mean difference (MD) was not statistically significant; however, there was substantial heterogeneity (MD = -3.50; 95% CI: -10.06, 3.06; I^2 = 99%) (data not shown). We conducted a post hoc sensitivity analysis of lifestyle interventions that included medication as part of their intervention and lifestyle interventions that did not include medications (Table 2). At the end of intervention, lifestyle groups lost more weight than the usual care groups regardless of whether medication was part of the intervention. However, the weight loss was greater in the Look Ahead trial[112] that included medication.

The New Leaf study by Keyserling et al.[111] and the Look AHEAD[112] trial reported followup data (Figure 3). There was no statistically significant difference among the groups in the New Leaf trial (MD = 1.14; 95% CI: -5.39, 7.67; I^2=0%). However, the significant weight loss in the lifestyle intervention in the Look AHEAD trial was still seen at 4 years (MD = -11.62; 95% CI: -12.37, -10.87).

Figure 3. Effect of lifestyle interventions vs. control on weight change (lbs): patients with type 2 diabetes

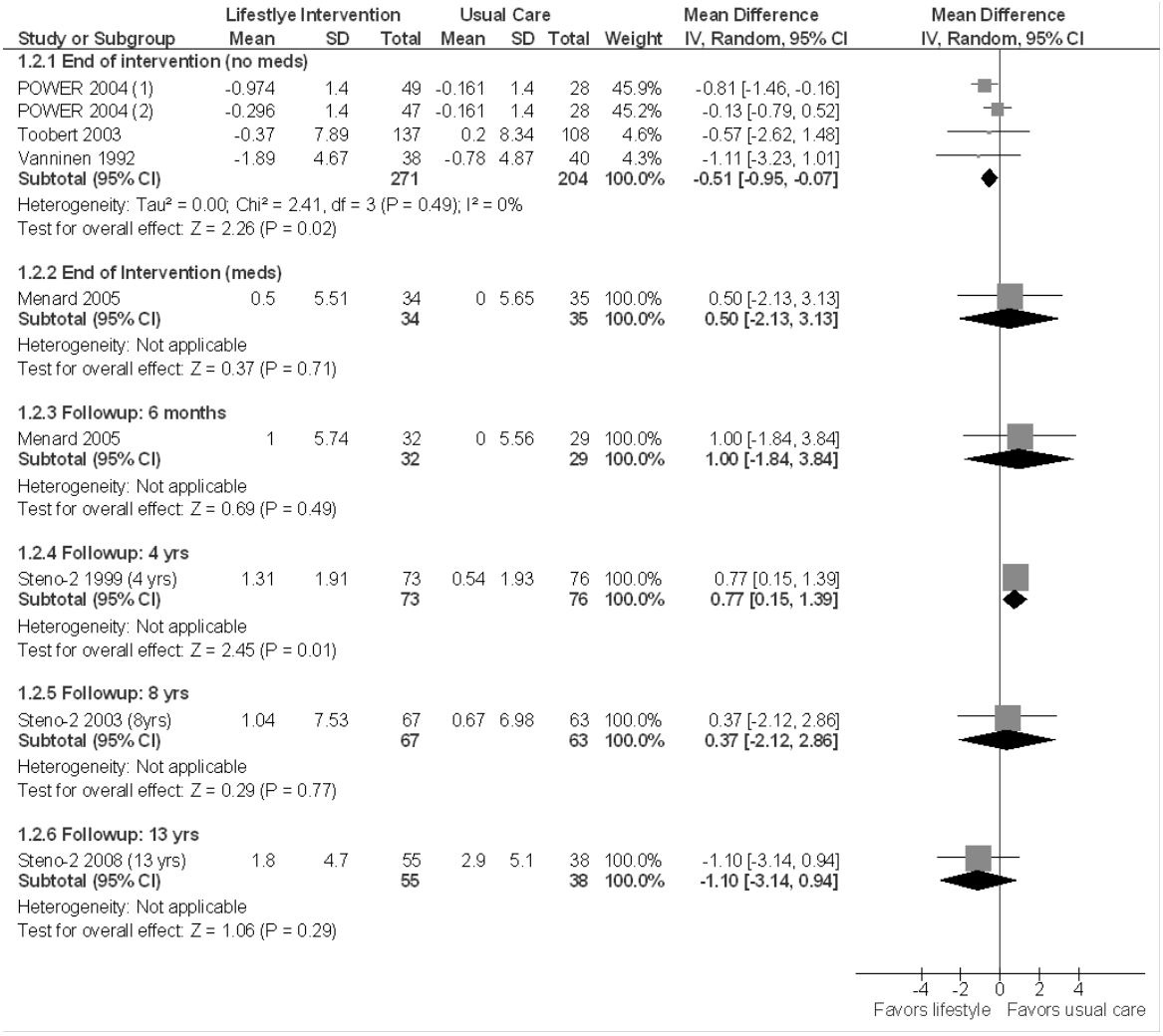


Five studies[113-115,117,119] reported change in BMI (kg/m2; Figure 4). At the end of the intervention, the pooled MD was statistically significant in favor of the lifestyle intervention (MD =

-0.48; 95% CI: -0.92, -0.05; I^2 = 0%). A post hoc sensitivity analysis of lifestyle interventions with[113] and without a medication component did not change the results substantially (data not shown).

One study[113] reported BMI at 6 months postintervention and found no difference between the groups (MD = 1.0; 95% CI: -1.84, 3.84). For the Steno-2 study by Gaede et al.[119] at 4 years, there was a statistically significant difference in favor of usual care (MD = 0.77; 95% CI: 0.15, 1.39); at 8 years, there was no difference between the groups (MD = 0.37; 95% CI: -2.12, 2.86).

Figure 4. Effect of lifestyle interventions vs. control on body mass index (kg/m2): patients with type 2 diabetes



Change in metabolic variables. Ten studies[110-119] reported on changes in different metabolic variables, including fasting plasma glucose[112,113,117,119] (Figure 5), triglycerides[110,112,113,115,117,119] (Figure 6), total cholesterol[110,111,114,115,117,119] (Figure 7), HDL and LDL cholesterol[110-115,117,119] (Figure 8, Figure 9), and HbA1c[110-119] (Figure 10). For lifestyle interventions that did not include medication as part of the intervention, there was no statistically significant difference between groups for any of the metabolic variables at the end of intervention (these were post hoc sensitivity

analyses). For lifestyle interventions that included medication, the results were statistically significant in favor of lifestyle for fasting plasma glucose, HDL cholesterol, and HbA1c; for the remaining variables, there was no statistically significant difference between groups at the end of intervention.

In the Steno-2 trial, at 4 and 8 years, changes in most metabolic variables were sustained. At 13.3 years, the differences between the lifestyle intervention and usual care were generally no longer statistically significant. The lifestyle intervention for this trial included medication as part of the intervention.

Figure 5. Effect of lifestyle interventions vs. control on fasting plasma glucose (mmol/l): patients with type 2 diabetes

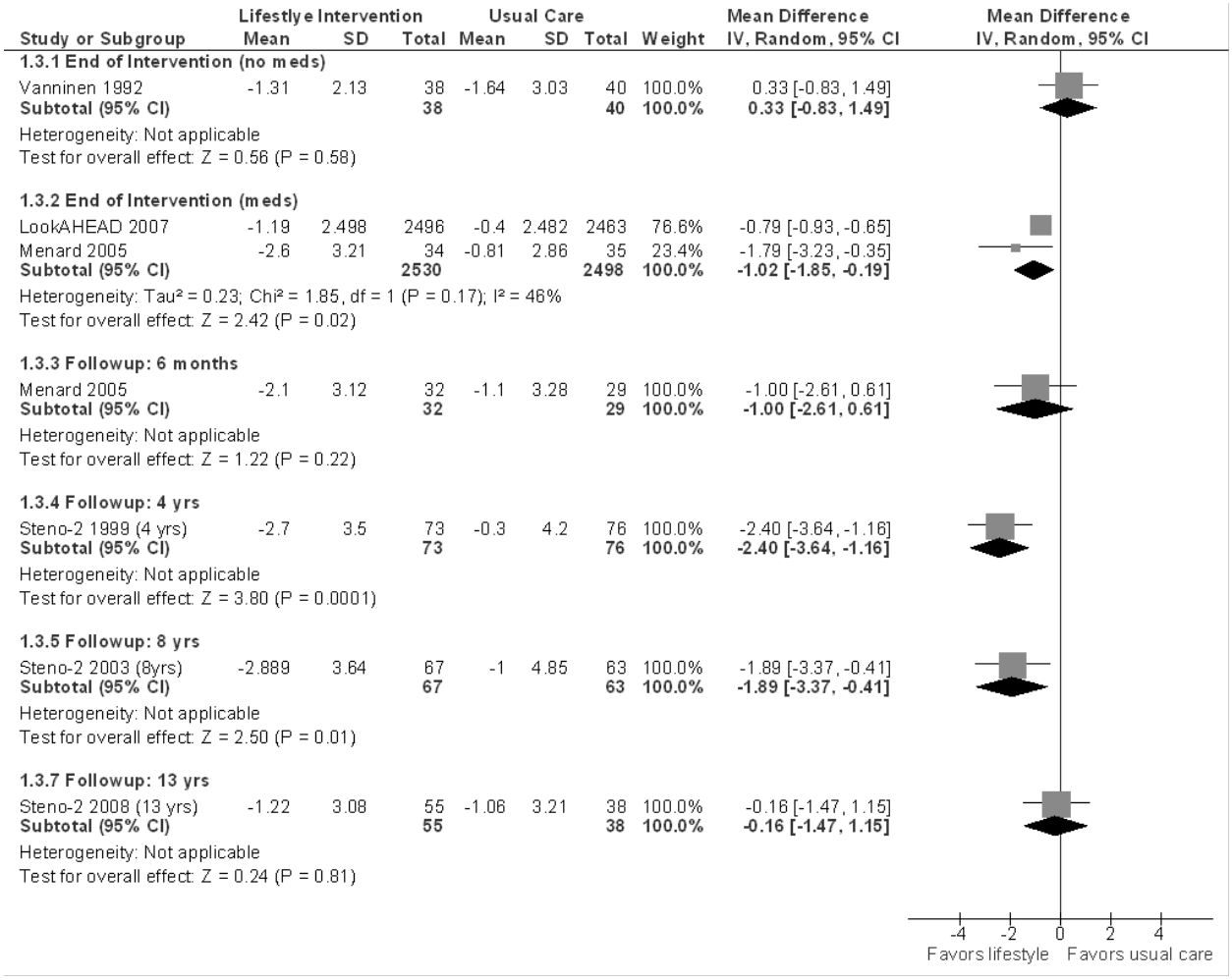


Figure 6. Effect of lifestyle interventions vs. control on triglycerides (mmol/l): patients with type 2 diabetes

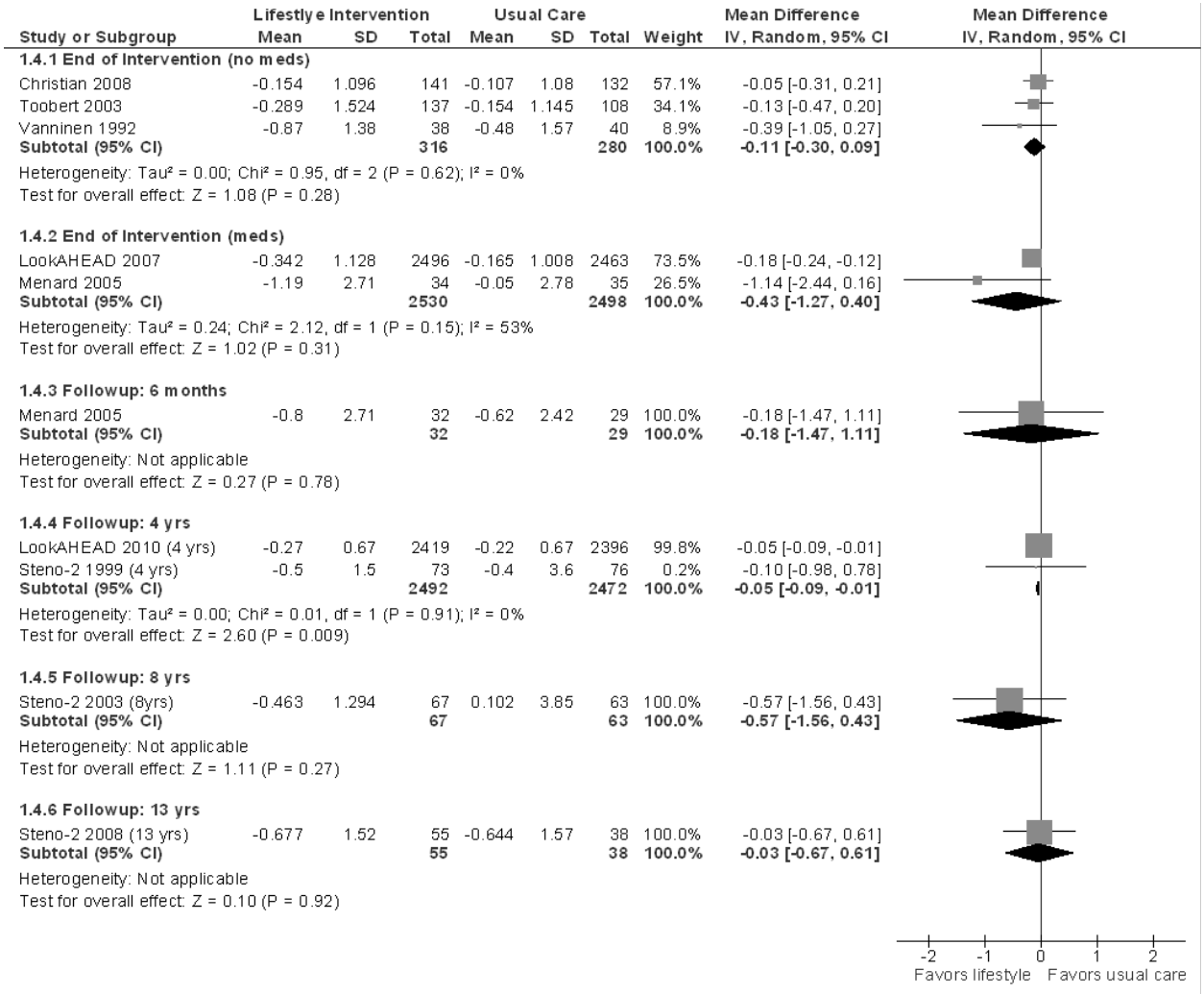


Figure 7. Effect of lifestyle interventions vs. control on total cholesterol (mmol/l): patients with type 2 diabetes

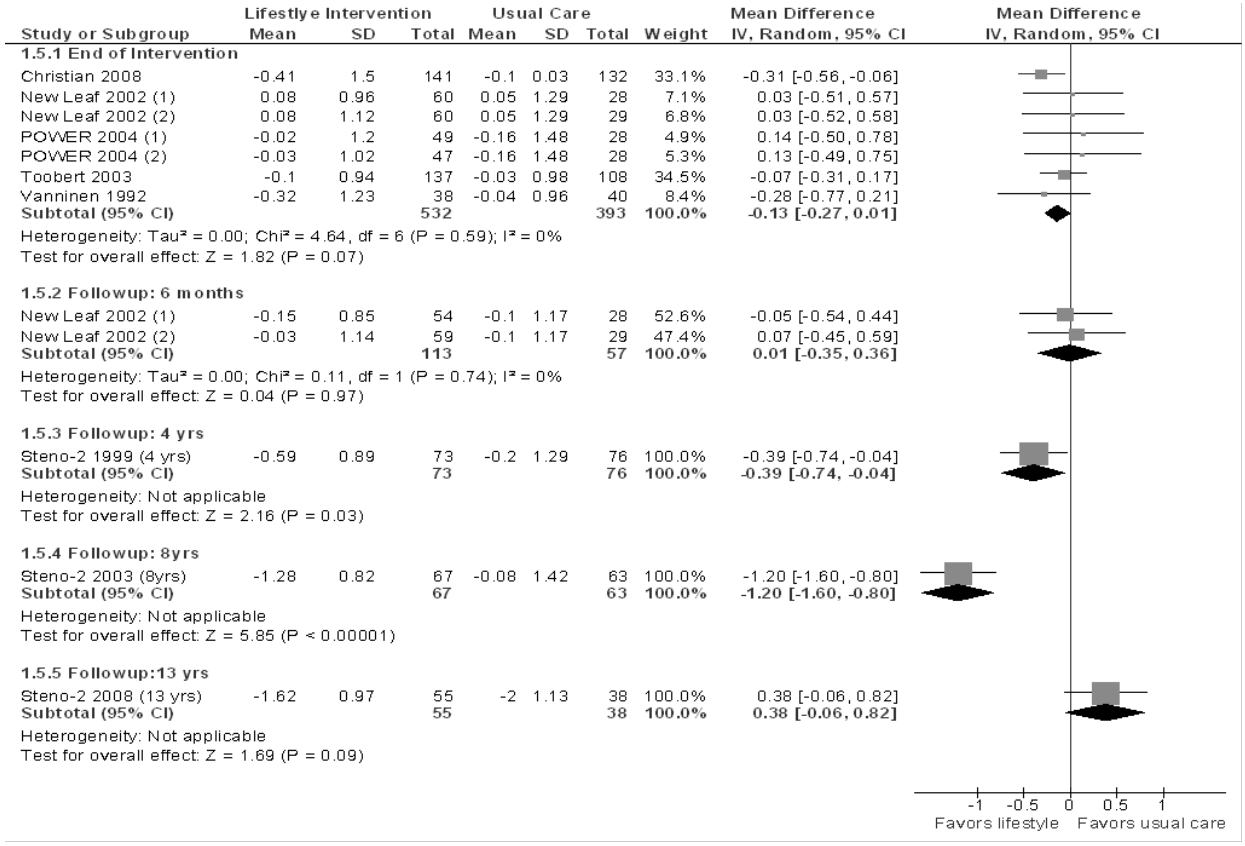


Figure 8. Effect of lifestyle interventions vs. control on HDL cholesterol (mmol/l): patients with type 2 diabetes

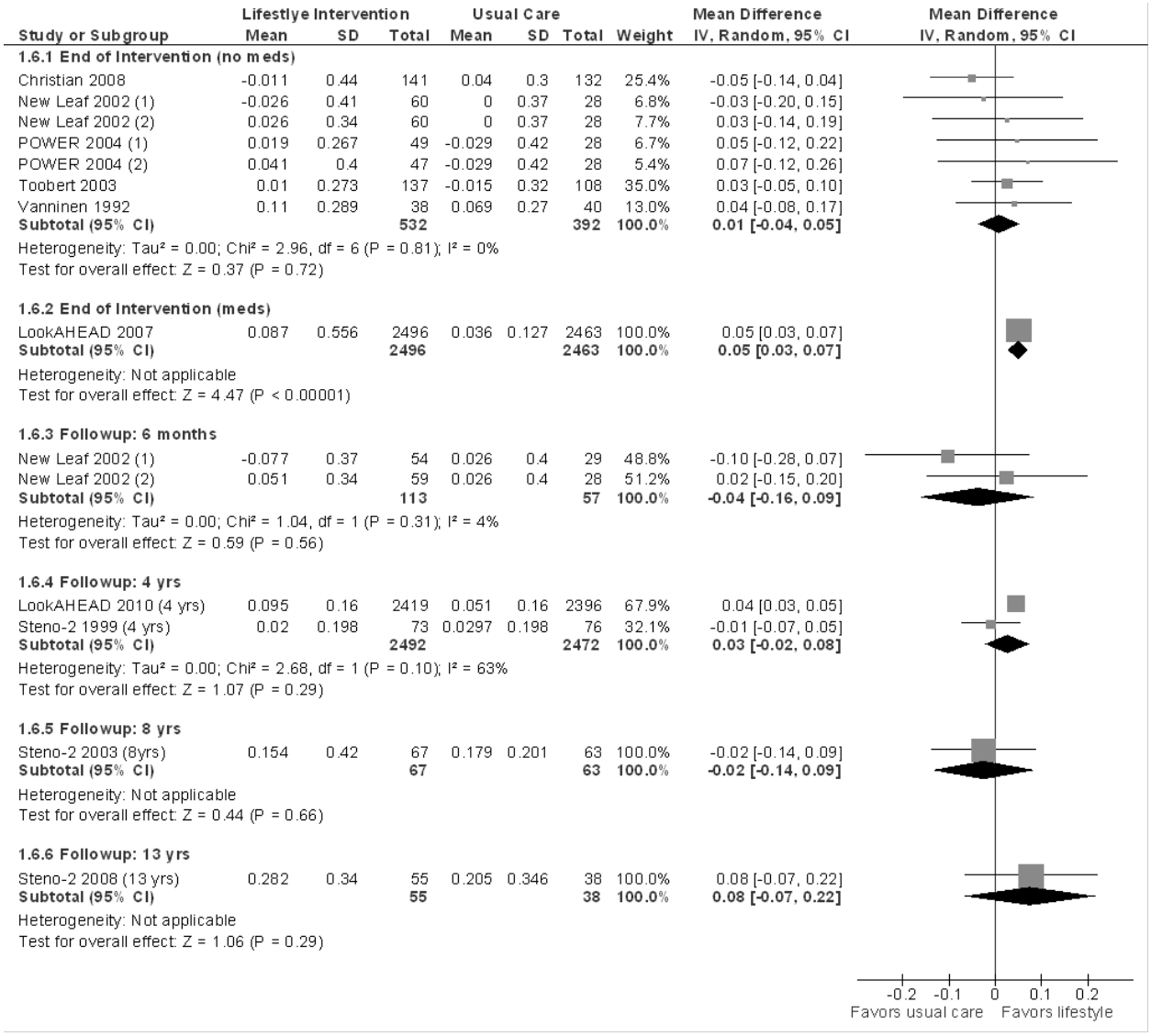


Figure 9. Effect of lifestyle interventions vs. control on LDL cholesterol (mg/dl): patients with type 2 diabetes

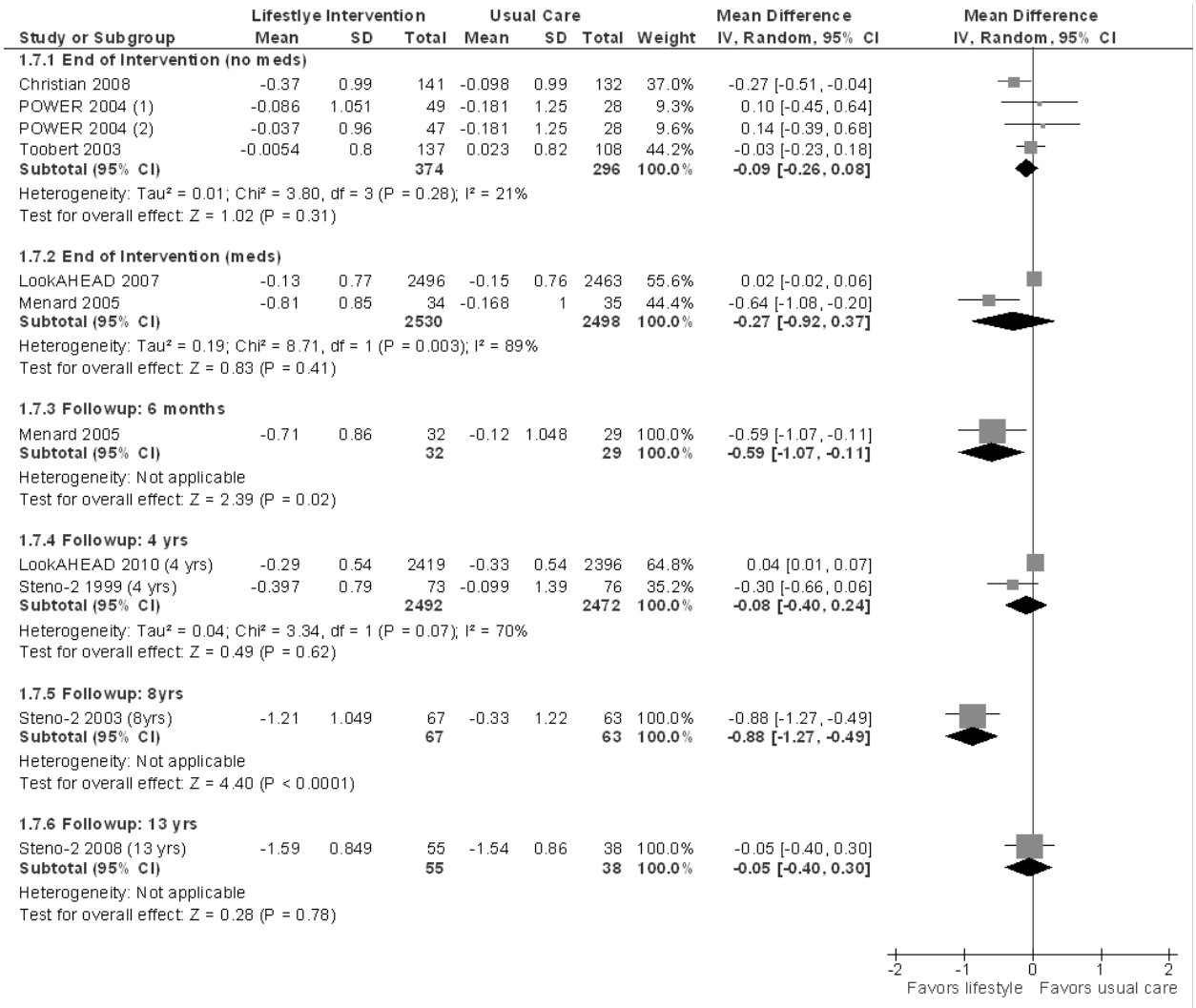
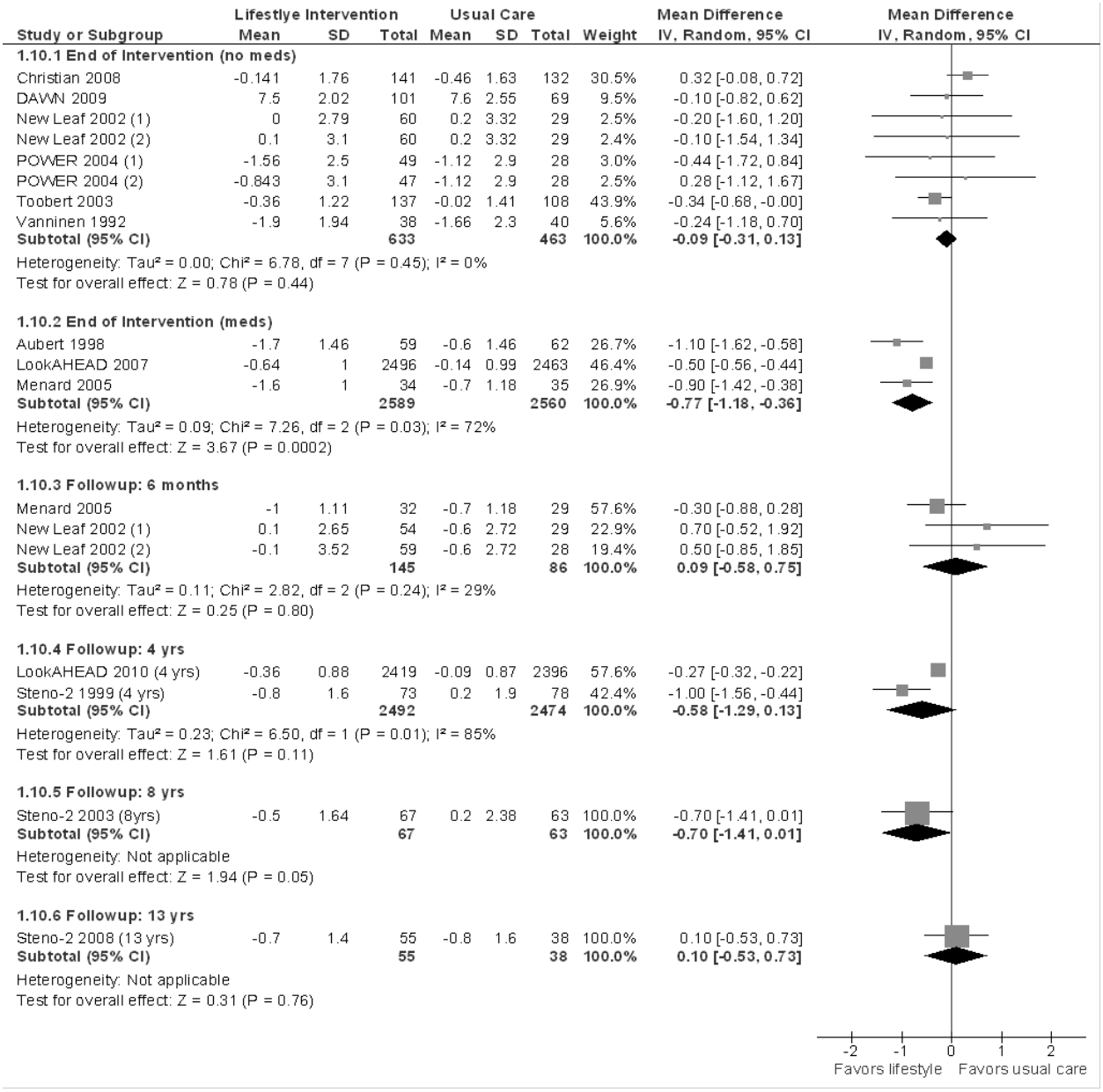


Figure 10. Effect of lifestyle interventions vs. control on HbA1c (%): patients with type 2 diabetes



Systolic and diastolic blood pressure. Changes in systolic and diastolic blood pressures (mmHg) were reported in seven studies.[110,112-115,118,119] For lifestyle interventions that did not include medication as a component, there was no statistically significant difference between groups for either outcome at the end of intervention (these were post hoc sensitivity analyses) (Figure 11, Figure 12). For lifestyle interventions that included medication, the results were statistically significant in favor of lifestyle for diastolic, but not systolic blood pressure (Figure 11, Figure 12).

For systolic blood pressure, there was a significant difference in favor of the lifestyle intervention at 4 years followup (MD = -2.38; 95% CI: -3.05, -1.72; I^2=0%) and at 8 years followup

(MD = -11.00 (95% CI: -18.07, -3.93). For diastolic blood pressure, the only significant change was seen at 4 years followup (MD = -0.46; 95% CI: -0.80, -0.12; I^2=0%)) (Figure 11, Figure 12). The lifestyle intervention for these studies included medication as part of the intervention.

Figure 11. Effect of lifestyle interventions vs. control on systolic blood pressure: patients with type 2 diabetes

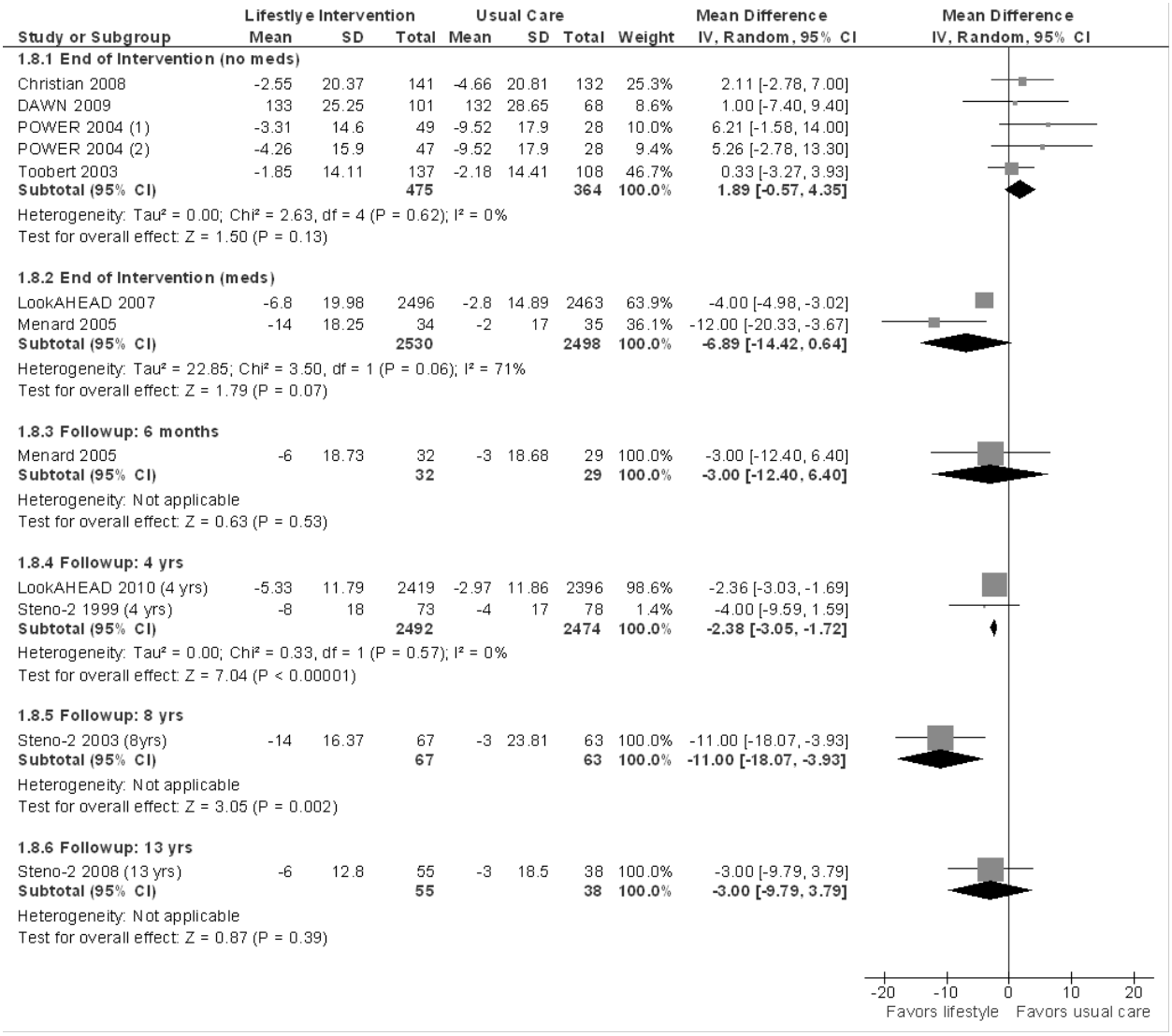
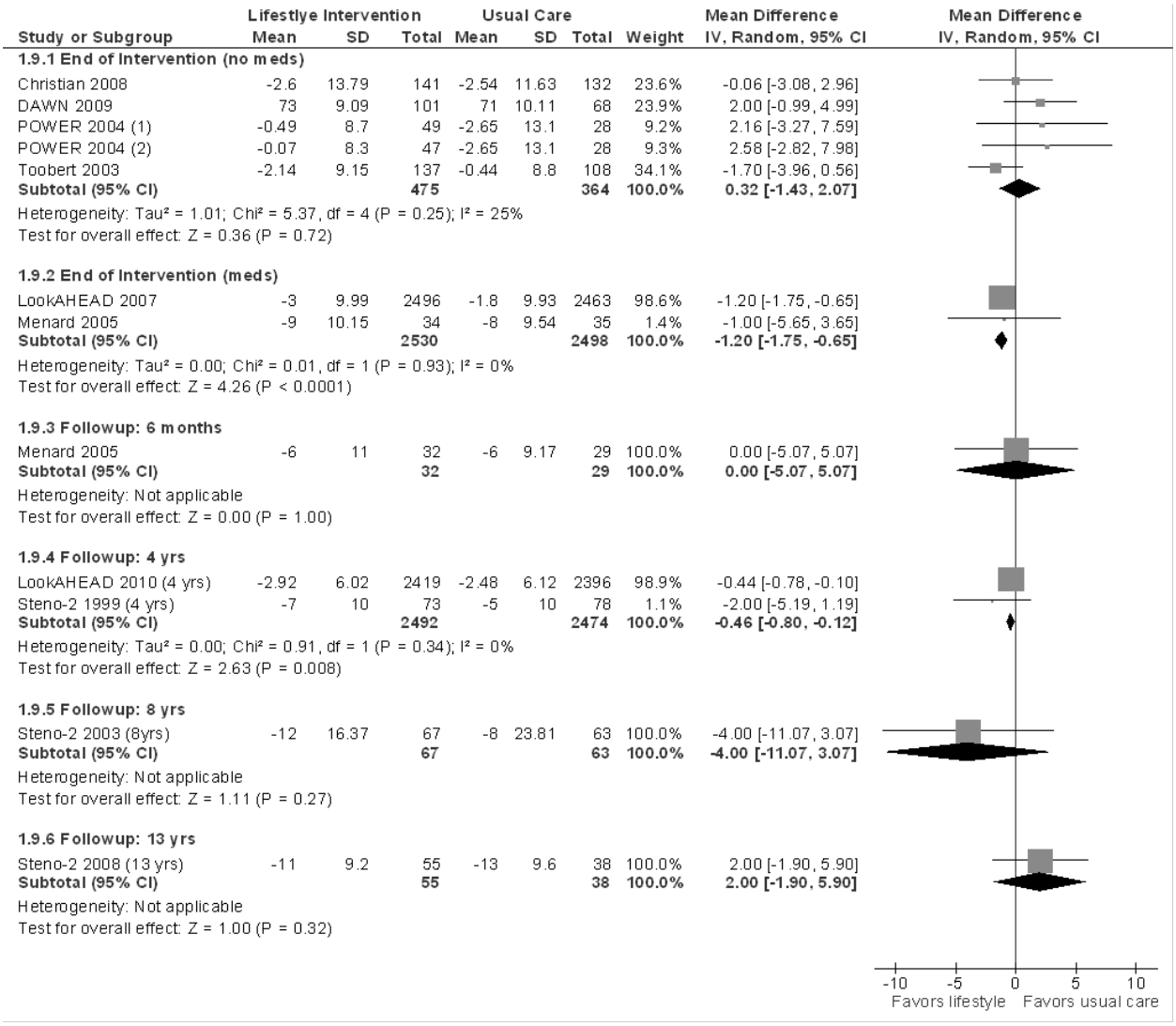


Figure 12. Effect of lifestyle interventions vs. control on diastolic blood pressure: patients with type 2 diabetes

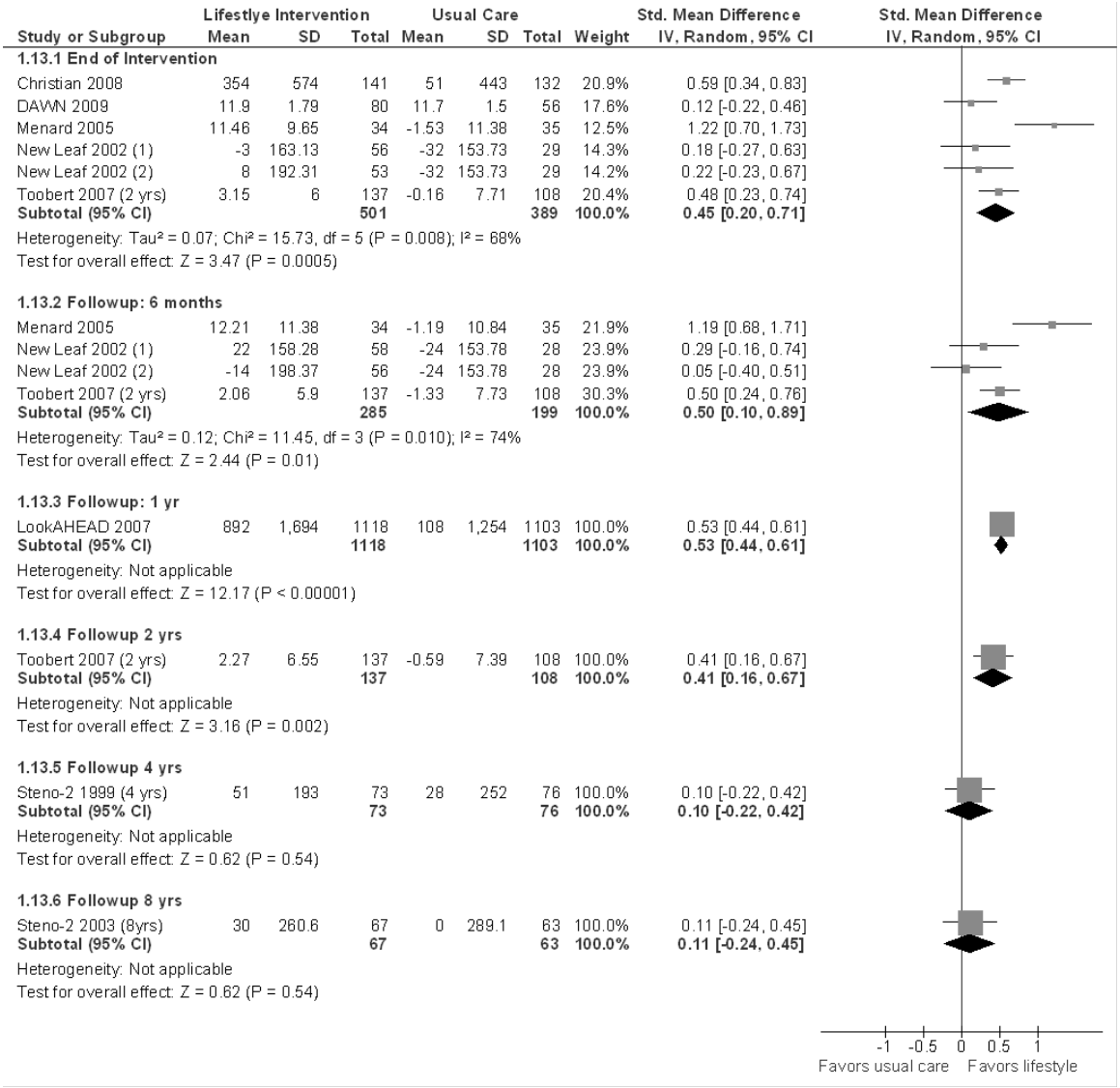


Change in physical activity. Seven studies[110-113,115,118,119] reported changes in physical activity using different outcome measures, including exercise (min/wk, kcal/kg/hr, kcal/day), exercise volume, change in leisure-time physical activity, and exercise tolerance (Figure 13). At the end of intervention, there was a statistically significant difference in favor of the lifestyle intervention (standardized MD [SMD] = 0.45; 95% CI: 0.20, 0.71, I^2 = 68%). Post hoc sensitivity analyses did not show any substantial difference between lifestyle interventions that did and did not include medication as part of the intervention (data not shown).

At 6 months postintervention, the pooled difference was still statistically significant (SMD = 0.50; 95% CI: 0.10, 0.89, I^2 = 74%). Similarly at 1 and 2 years, the difference reported in two studies[112,115] was statistically significant (SMD = 0.53; 95% CI: 0.44, 0.61; SMD = 0.41; 95% CI:

0.16, 0.67, respectively). In the Steno-2 study by Gaede et al.,[119] the difference between groups was not statistically significant at any timepoint.

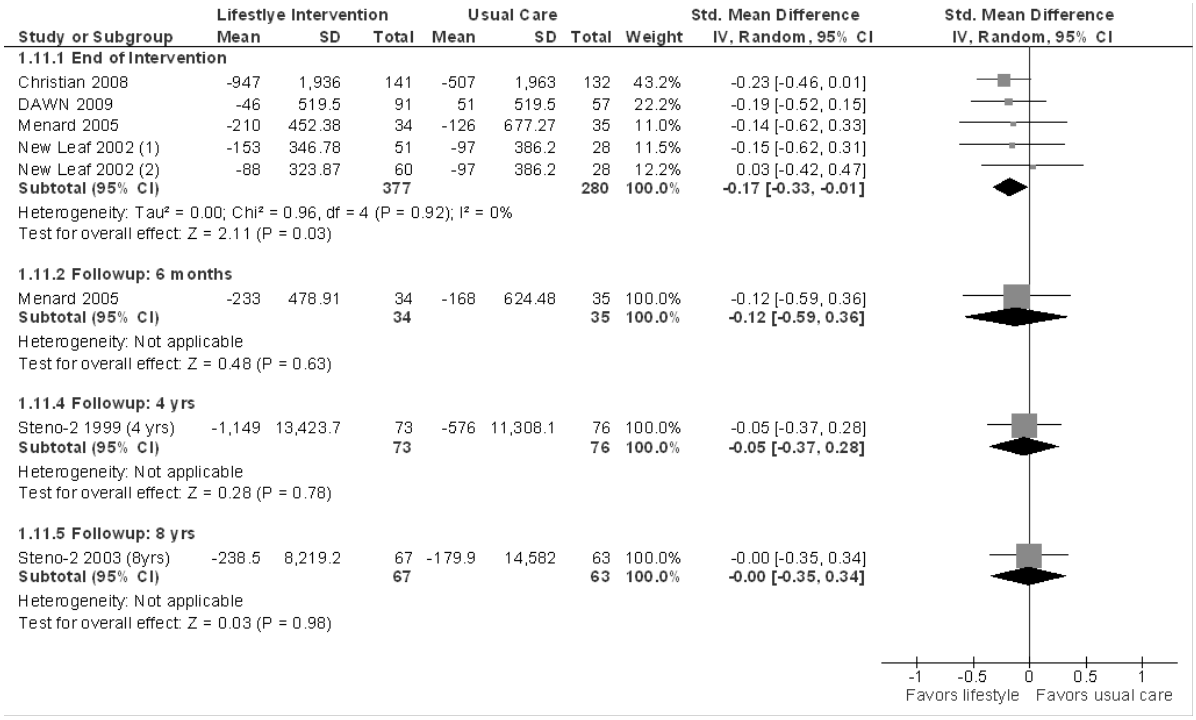
Figure 13. Effect of lifestyle interventions vs. control on physical activity outcomes: patients with type 2 diabetes



Change in dietary or nutrient intake. The change in dietary or nutrient intake was measured by energy intake and consumption of saturated fat. The pooled results of four studies[110,111,113,118] that reported energy intake at the end of the intervention showed a statistically significant difference in favor of the lifestyle intervention (SMD = -0.17, 95% CI: -0.33, -0.01; $I^2 = 0\%$; Figure 14). A post hoc sensitivity analysis did not show any substantial difference between lifestyle interventions that did and did not include medication as part of the intervention (data not shown).

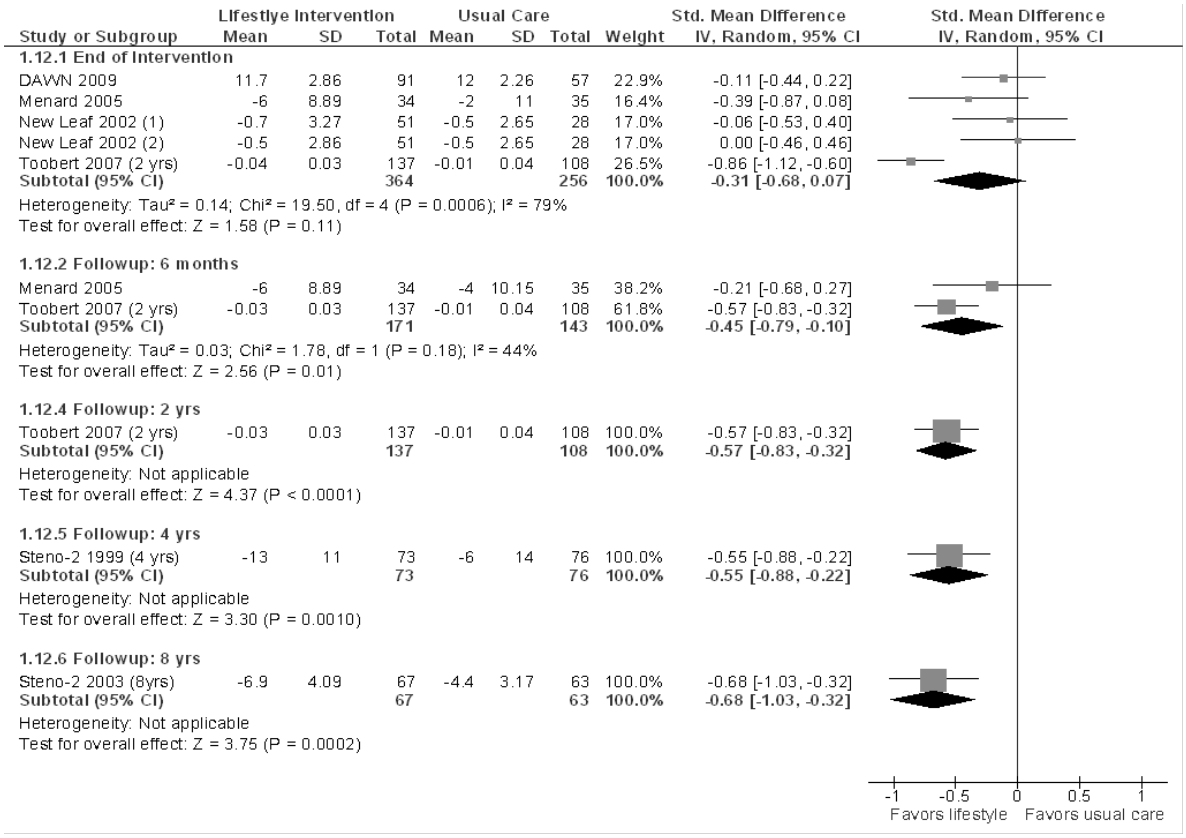
In one trial[113] with 6 month postintervention followup, the difference was no longer significant. The Steno-2 trial found no significant difference between the lifestyle and control groups at 4 and 8 years (Figure 14).

Figure 14. Effect of lifestyle interventions vs. control on energy intake: patients with type 2 diabetes



Five studies assessed change in saturated fat consumption (Figure 15).[111,113,115,118,119] Immediately postintervention, there was no significant difference between groups (SMD = -0.31; 95%CI: -0.68, 0.07, I^2 = 79%). A post hoc sensitivity analysis did not show any substantial difference between lifestyle interventions that did and did not include medication as part of the intervention (data not shown). At all followup timepoints, there was a significant difference in favor of lifestyle interventions.

Figure 15. Effect of lifestyle interventions vs. control for consumption of saturated fat: patients with type 2 diabetes



Change in medications. Two studies[113,119] reported use of medication. The different types of medication were oral hypoglycemic agents (OHA), insulin, OHA plus insulin, antihypertensive agents, and lipid-lowering agents. Both studies included medication use as part of their lifestyle interventions.

OHA. There was no significant difference between groups in the Steno-2 trial by Gaede et al.[119] at 4 years (RR = 0.79; 95% CI: 0.55, 1.14) or 8 years (RR = 1.24; 95% CI: 0.97, 1.58). At baseline, 59 percent and 60 percent of participants in the intervention and control groups, respectively, were taking OHA. At 8 years, 75 percent in the lifestyle group were taking OHA compared with 60 percent in the control group. However, at 13.3 years, there was a significant difference between groups favoring usual care (RR = 1.77; 95% CI: 1.24, 2.52). While 84 percent of participants in the intervention group were taking an OHA, only 38 percent were taking some form of OHA in the usual care group.

Menard et al.[113] presented use of OHA by the number of people taking one OHA, two OHAs, or three or more OHAs. In total, all participants in the lifestyle group and 91 percent in the control group were taking at least one OHA at baseline. There was no statistically significant change from baseline to the end of intervention or 6 months postintervention in use of OHAs for any of the groups. At the end of intervention, the RR for one OHA was 2.23 (95% CI: 0.96, 5.19); for two OHAs it was 0.77 (95% CI: 0.52, 1.14); and for three or more, the RR was 0.51

(95% CI: 0.05, 5.42). At 6 months, the RRs were 2.54 (95% CI: 1.04, 6.17), 0.69 (95% CI: 0.46, 1.04) and 0.60 (95% CI: 0.11, 3.36), respectively.

Insulin. The Steno-2 trial[119] showed a significant decrease in insulin use in the lifestyle group after 4 years. At baseline, 6 percent and 13 percent of participants in the intervention and control groups were taking insulin. At the end of 4 years, 16 percent in the intervention group compared with 37 percent in the control group were taking insulin (RR = 0.45; 95% CI: 0.25, 0.81). However, by the end of 8 years, there was no statistically significant difference (RR = 1.05; 95% CI: 0.77, 1.43). This did not change at 13.3 years (RR = 0.89; 95% CI: 0.71, 1.11).

Menard et al.[113] found no statistically significant difference between groups at the end of intervention or at the end of the 6 month followup (RR = 0.51; 95% CI: 0.10, 2.63 and RR = 0.68; 95% CI: 0.17, 2.78, respectively).

OHA plus insulin. In the Steno-2 trial,[119] a statistically significant decrease of OHA plus insulin use was found in the usual care group at the end of 4 years. At baseline, none of the participants in the intervention group and only one participant in the control group were taking both types of medication. At 4 years, 38 percent of the people in the intervention group were taking both OHA and insulin, while only 5 percent in the control group were taking both medications (RR = 7.29; 95% CI: 2.69, 19.75). By the end of 8 years, there was no longer a significant difference between groups and 33 percent of participants in the intervention group and 21 percent of participants in the control group were taking both (RR = 1.59; 95% CI: 0.88, 2.88). However, by 13.3 years, the significant difference seen at 4 years in favor of usual care reappeared (RR = 1.99; 95% CI: 1.34, 2.94).

Menard et al.[113] showed no significant differences between groups at both end of intervention and followup. At baseline, 35 percent and 23 percent of the participants in the intervention and control groups were taking both medications. At the end of intervention, the proportion of people taking both increased to 62 percent and 83 percent (RR = 2.16; 95% CI: 1.20, 3.89). By the end of the 6 month followup, 59 percent and 34 percent people were taking both OHA and insulin in the intervention and control group, respectively (RR = 1.72; 95% CI: 0.97, 3.07).

Antihypertensive agents. The Steno-2 trial[119] showed a statistically significant increase in the lifestyle group at 4 and 8 years (RR = 1.54; 95% CI: 1.29, 1.84 and RR= 1.19; 95% CI: 1.06, 1.34, respectively). At baseline, 41 percent of the patients in both the lifestyle and control groups were taking an antihypertensive agent. At 8 years, 99 percent in the lifestyle group and 83 percent in the control group were taking this medication. However, at 13.3 years, this difference was no longer seen (RR = 0.93; 95% CI: 0.86, 1.01).

Menard et al.[113] found no statistically significant difference between groups at the end of intervention or at 6 months followup (RR = 1.03; 95% CI: 0.77, 1.38 and RR = 0.91; 95% CI: 0.70, 1.18, respectively).

Lipid-lowering agents. The Steno-2 trial[119] showed a statistically significant increase in use of antihypertensive agents in use of lipid-lowering agents in the lifestyle group at both 4 years and at 8 years (RR = 6.07; 95% CI: 2.72, 13.57 and RR = 3.26; 95% CI: 2.15, 4.95, respectively). At baseline, 4 percent in the intervention group and 1 percent in the control group were taking a statin, fibrate, or both. At 4 years, 48 percent in the lifestyle group compared with 8 percent in the control group were taking a lipid-lowering agent. At 8 years, 88 percent and 27 percent of the participants in the intervention and control groups respectively were taking a lipid-lowering agent. No data were reported for the 13.3 year followup.

The study by Menard et al.[113] also reported a statistically significant increase in the use of lipid-lowering agents in the lifestyle group at both end of intervention and 6 month followup (RR = 1.99; 95% CI: 1.32, 2.99 and RR = 2.11; 95% CI: 1.34, 3.32, respectively). At baseline, 35 percent in the lifestyle group were taking a statin, fibrate, or both compared with 43 percent in the control group. At the end of intervention, 85 percent of the lifestyle group compared with 43 percent of the control group was taking a lipid-lowering agent. At the 6 month followup, 88 percent of the lifestyle group compared with 41 percent of the control group was taking a lipid-lowering medication.

Compliance with the intervention. The number of dropouts/withdrawals was used as a surrogate measure for compliance. Overall, there were more dropouts in the usual care groups compared with lifestyle interventions; however, this was not statistically significant (RR = 0.86; 95% CI: 0.61, 1.22, I^2=52%).

Adverse events. Two studies reported that participants experienced minor hypoglycemic episodes[113] and bleeding gastric ulcer;[119] however, these adverse events were not directly attributed to the exercise, diet, or other component of the lifestyle intervention.

Summary

Ten RCTs assessed the effectiveness of lifestyle interventions for type 2 diabetes. The following is a summary of results:

- *Primary outcomes.* One study, which included medication as part of the lifestyle intervention, found that the intervention decreased the number of nonfatal strokes, nonfatal myocardial infarctions, amputations, and death at 13.3 year followup. There was also a difference between groups for the progression of autonomic neuropathy in favor of the lifestyle intervention, but no difference was seen in the progression of peripheral neuropathy at all followup time points. The strength of evidence for all of these outcomes was insufficient.
- *Change in body composition.* Five studies reported change in weight. At the end of intervention, there was a statistically significant difference in favor of lifestyle interventions and no difference between the groups at 6 month followup. Five studies reported change in BMI (kg/m^2). At the end of the intervention, there was a statistically significant difference in favor of the lifestyle intervention. Effect of the intervention at different postintervention timepoints was inconsistent. The strength of evidence was moderate for BMI and weight change at end of intervention. The strength of evidence was insufficient at all followup timepoints.
- *Change in metabolic variables.* Ten studies reported on changes in metabolic variables. For lifestyle interventions that did not include medication as part of the intervention, there was no statistically significant difference between groups for any of the metabolic variables at the end of intervention. For lifestyle interventions that included medication, the results were statistically significant in favor of lifestyle for fasting plasma glucose, HDL cholesterol, and HbA1c. The strength of evidence was low for all outcomes immediately postintervention, and insufficient at all followup timepoints.

- *Systolic and diastolic blood pressure*. Eight studies reported changes in systolic and diastolic blood pressure (mmHg). For lifestyle interventions that did not include medication as a component, there was no statistically significant difference between groups for either outcome at the end of intervention. For lifestyle interventions that included medication, the results were statistically significant in favor of lifestyle for diastolic, but not systolic blood pressure. Effect of the intervention at different followup timepoints was inconsistent. The strength of evidence is low for the end of intervention timepoint; it is insufficient for all followup timepoints.
- *Change in physical activity*. Seven studies reported changes in physical activity using different outcome measures. At the end of intervention, there was a statistically significant difference in favor of the lifestyle intervention. There was a significant difference between groups at 1 and 2 years of followup. The strength of evidence was low for the end of intervention and at 6 month followup, but insufficient at other postintervention timepoints.
- *Change in dietary or nutrient intake*. Four studies measured change in dietary or nutrient intake using energy intake and consumption of saturated fat. There was a significant difference in energy intake favoring the lifestyle intervention at end of intervention. There was no difference between groups at any followup timepoint. There was no significant difference between groups in consumption of saturated fats at end of intervention. However, the lifestyle intervention is favored at all followup timepoints. The strength of evidence is low for energy intake and low for consumption of saturated fat at end of intervention. It is insufficient for all other timepoints.
- *Change in medications*. While nine studies reported medication use at baseline, only two reported followup data. At the longest followup timepoints, either the usual care group was favored or there was no significant difference between groups. The lifestyle intervention was favored in the use of insulin at end of intervention and 4 years. At 8 and 13 year followup, there was no difference between groups.
- *Compliance with intervention*. Seven studies reported withdrawals by group. There was no statistically significantly difference between groups.
- *Adverse events*. No studies reported adverse events directly attributed to the exercise, diet, or other component of the lifestyle intervention.
- Two RCTs were considered at high risk of bias; eight were unclear. The most common source of potential bias was inadequate blinding.

Table 1. Description of studies and baseline characteristics of participants: type 2 diabetes

Studies with postintervention followup

Author, Year	Randomized (N); Withdrawals (N)	Age (mean ± SD) Males: N (%); Ethnicity	Socioeconomic status (%≤$20,000/yr income); Education (%≤ high school); Smokers: (%)	Weight (kg); BMI (km/m^2); Waist circumference (cm)	HbA1c (%); Plasma Fasting Glucose (mmol/L); Insulin Resistance (HOMA: IR); Blood pressure (mmHg)	Duration of Diabetes (yrs); Type of medication: (%)
Gaede, 1999, Steno-2[119]	I: 80; 13 C: 80; 17	I: 54.9±7.2; 63.0(79.0); NR C: 55.2±7.2; 56.0(70.0); NR;	I: NR; NR; 40.0 C: NR; NR; 33.8	I: 91.4±13.6; 29.7±3.8; NR C: 89.9±17.3; 29.9±4.9; NR	I: 8.4±1.6; 10.1±3.1; NR; 146±20/85±10 C: 8.8±1.7; 10.5±3.0; NR; 149±19/86±11	I: 5.5 (2.0-8.8); OHA: 59; insulin: 63; both: 0; lipid lowering: 38 C: 6.0 (4.0-10.0); OHA: 60; insulin: 13; both: 1; lipid lowering: 1
Keyserling, 2002, New Leaf Program[111]	I: 67; 13 C: 67; 9 Grp3: 66; 7	I: 58.5; 0; 100 Black C: 59.2; 0; 100 Black Grp3: 58.8; 0; 100 Black	I: 34.3 (<$10,000/yr); NR; 14.9 C: 22.4 (<$10,000/yr); NR; 16.4 Grp3: 30.3 (<$10,000/yr); NR; 19.7	I: 95.0; 36.2; NR C: 95.7; 36.2; NR Grp3: 91.9; 34.6; NR	I: 10.7±0.3; NR; NR; NR C: 11.3±0.3; NR; NR; NR Grp3: 11.1±0.4; NR; NR; NR	I: 10.8; OHA: 57; insulin: 43; both: 12 C: 9.9; OHA: 58; insulin: 42; both: 9 Grp3: 10.7; OHA: 57; insulin 41; both: 8
Look Ahead Research Group, 2009, Look AHEAD[112]	I: 2570; 74 C:2575; 112	I: 58.6±6.8; 1046.0 (40.7); 63.1 White, 15.5 Black, 21.3 Other C: 58.9±6.9; 1040.0 (40.4); 63.3 White, 15.7 Black, 20.9 Other	I: NR; NR; NR C: NR; NR; NR	I: 100.54±19.65; 35.89±6.01; 113.8±14.35 C: 100.86±18.83 36.0±5.76; 114.06±13.55	I: 7.25±0.02; 151.9±0.9(mg/dl); NR; 128.2±0.4/ 69.9±0.2 C: 7.29±0.02; 153.6±0.9 (mg/dl); NR; 129.4±0.3/ 70.4±0.2	Both groups: 6.7±4.5 yr; I: diabetes medication: 87; insulin: 15; antihypertensives: 75; lipid lowering: 49 C: diabetes medication: 87; insulin: 16; antihypertensives: 74; lipid lowering: 48
Menard, 2005[113]	I: 36; 4 C: 36; 7	I: 53.7±7.5; 27 (75); NR C:55.9±8.6; 22 (61); NR	I: NR; NR; 13.9 C: NR; NR; 16.7	I: 93.5±20.1; 32.8±5.5; NR C: 88.5±18.5; 32.7±5.7; NR	I: 9.1±1.0; 10.8±3.5; NR; 144±21/85±11 C: 9.3±1.0; 10.7±3.0; NR;143 ±17/86± 10	I: 10.6±6.7; OHA ≥1: 38; insulin: 3; both: 35 C: 10.0±7.7; OHA ≥1: 17; insulin: 11; both: 23

AHEAD = Action for Health in Diabetes; BP = blood pressure; DAWN = Diabetes Awareness and Wellness Network; NR = not reported; OHA = oral hypoglycemic agent; POWER = Pounds Off With Empowerment; T1D = Type 1 diabetes; T2D = Type 2 diabetes

Table 1. Description of studies and baseline characteristics of participants: type 2 diabetes (continued)

Author, Year	Randomized (N); Withdrawals (N)	Age (mean ± SD) Males: N (%); Ethnicity	Socioeconomic status (%≤$20,000/yr income); Education (%≤ high school); Smokers: (%)	Weight (kg); BMI (km/m^2); Waist circumference (cm)	HbA1c (%); Plasma Fasting Glucose (mmol/L); Insulin Resistance (HOMA: IR); Blood pressure (mmHg)	Duration of Diabetes (yrs); Type of medication: (%)
Toobert, 2003; Mediterranean Lifestyle Program[115]	I: 163; 26 C: 116; 8	I: 61.1±8.0; 0; 92 White C:60.7±7.8; 0; 94.8 White	I: 30.3, 33.7, 8.7 C: 36.8, 36.2, 10.3	I: 92.3±21.2; 35.34±7.93; NR C: 93.9±23.8; 34.87±8.2; NR	I: 7.43±1.3; NR; NR; 136.06±13.91/ 79.29±9.49 C: 7.4±1.48; NR; NR; 134.01 ±14.17/ 77.38± 9.2	I: 8.2±7.3; OHA: 55, insulin: 7, both: 13, lipid lowering: 39, BP lowering: 46 C: 8.5±8.3; OHA: 61, insulin: 12; both: 10; lipid lowering: 41, BP lowering: 47
Studies with no postintervention followup						
Aubert, 1998[116] (T1D & T2D-14% had T1D)	I: 71 C: 67 Total 38	I: 53 (median); 26 (37); 83 White C: 54 (median); 29 (43); 70 White	I: NR; NR;17 C: NR; NR;11	I: NR; 32 (median); NR C: NR; 34 (median); NR	I: 8.8 (median); NR; NR; NR C: 8.4 (median); NR; NR; NR	I: 6 (median); insulin: 44 C: 6 (median); insulin: 33
Christian, 2008[110]	I: 155; 14 C: 155; 23	I: 53±11.25; 55(35); 100 Hispanic/Latino C:53.4±10.7; 50(32); 100 Hispanic/Latino	I: NR; NR; NR C: NR; NR; NR	I: 207±47.3 lbs; 35.4±6.62; 118.1±14.95 C: 200.2±44.7 lbs; 34.8±7.11; 116.6±15.23	I: 8.08±2.02; NR; NR; 131.8±17.02/76.56 ±10.53 C: 8.29±1.93; NR; NR; 132.26 ±17.43/77.83± 9.58	I: NR; diabetic drugs taken by 98% of participants C: NR; diabetic drugs taken by 95% of participants

AHEAD = Action for Health in Diabetes; BP = blood pressure; DAWN = Diabetes Awareness and Wellness Network; NR = not reported; OHA = oral hypoglycemic agent; POWER = Pounds Off With Empowerment; T1D = Type 1 diabetes; T2D = Type 2 diabetes

Table 1. Description of studies and baseline characteristics of participants: type 2 diabetes (continued)

Author, Year	Randomized (N); Withdrawals (N)	Age (mean ± SD) Males: N (%); Ethnicity	Socioeconomic status (%≤$20,000/yr income); Education (%≤ high school); Smokers: (%)	Weight (kg); BMI (km/m^2); Waist circumference (cm)	HbA1c (%); Plasma Fasting Glucose (mmol/L); Insulin Resistance (HOMA: IR); Blood pressure (mmHg)	Duration of Diabetes (yrs); Type of medication: (%)
Mayer-Davis, 2004, POWER[1][14]	Total: 189; 37	I: 59.7±8.6; 11 (22); 14.3 White, 83.7 Black, 2 Other C: 62.4±9.5; 12 (21); 26.8 White, 73.2 Black Grp 3: 58.9±7.8; 7 (15); 10.6 White, 89.4 Black	I: NR; 38.8 (<High School); NR C: NR; 60 (<High School); NR Grp 3: NR; 44.7 (<High School); NR	I: 99.5±17.1; 37.6±6.5; NR C: 93±20.3; 35.2±7.5; NR Grp 3: 100±19.8; 37.5±6.7; NR	I: 10.2±2.5; NR; NR; NR C: 9.6±2.9; NR; NR; NR Grp 3: 9.7±3.1; NR; NR; NR	I: 8.4±6.5; OHA: 47; insulin: 27, both: 24 C: 12.7±10.6; OHA: 57; insulin: 32; both: 9 Grp 3: 11.6±10; OHA: 53; insulin: 26, both: 17
Samuel-Hodge, 2009, DAWN[118]	I: 117;16 C: 84; 15	I: 57±0.9; 42(35.9); 100 Black C: 61.3±1.3; 31(36.9); 100 Black	I: 43 (<$30,000 household income); NR;10 C:46 (<$30,000 household income); NR; 7	I: 96.8±2; 34.6±0.7; NR C: 98.2±2.6; 35.1±0.8; NR	I: 7.7±0.2; NR; NR; 139±1.7/75±0.6 C: 7.9±0.3; NR; NR; 140±2.2/76±1.2	I: 8.8±0.8; OHA: 71; insulin: 32; both: 19; insulin ≥ 1/day: 76 C: 9.2±0.9; OHA: 79; insulin: 25; both: 13; insulin ≥ 1/day: 59
Vanninen, 1992[117]	Total: 90 total; 12 total	Total: 53.7±7 for males (n=45); 54±6 for females (n=33) I: 21(55.3) C: 17(44.7) NR	Total: NR; NR; 18	I: NR; 32.13±5.3; NR C: NR; 31.74±4.96; NR	I: 7.1±1.48; NR; NR; NR C: 7.62±2.02; NR; NR; NR	I: newly diagnosed; NR; NR C: newly diagnosed; NR; NR

AHEAD = Action for Health in Diabetes; BP = blood pressure; DAWN = Diabetes Awareness and Wellness Network; NR = not reported; OHA = oral hypoglycemic agent; POWER = Pounds Off With Empowerment; T1D = Type 1 diabetes; T2D = Type 2 diabetes

Table 2. Description of lifestyle interventions: type 2 diabetes

Studies with postintervention followup

Author, Year, Study name	Duration of intervention; followup	Diet	Exercise	Counseling or other component(s)	Control group
Gaede, 1999, Steno-2[119]	3 mo; 13 yr	• Low fat diet: fat < 30% of intake, SFA < 10% of intake, increased complex CHO • Dietician; every 3 mo for 1 yr • Educational material, examples of low fat/high CHO lunches and snacks served at the group meetings	• Light to moderate PA ≥ 30 min, 3-5 x/wk • Educational material, demonstrations of exercise effect on decreasing blood glucose	• Group counseling: dietician; groups of 20 with spouses; 2 sessions • Smoking cessation course with spouses: 5 meetings in 8 wk, followup at 3 & 6 mo • Stepwise use of pharmacologic tx if glycemic goals not met including metformin, gliclazide, NPH insulin, thiazides, calcium-channel blockers, β-blockers • Statins and fibrates were used for dyslipidemia and hypertriglyceridemia • All received ACE inhibitor, vitamin C & E	• Usual/standard care from primary care physician following the 1998 guidelines of the Danish Medical Association
Keyserling, 2002, New Leaf Program[111]	6 mo; 6 mo	• Food for Heart Program: decreased total fat and SFA; improved distribution of CHO intake • Educational material, cookbook, logbook, workbook, monthly progress reports	• Followed CDC & ACSM guidelines: >30 min/day moderate PA • Caltrac accelerometer worn for 1 wk • Educational materials, logbook, workbook	• Individual counseling: health counselor, 4 sessions; peer counselor, monthly telephone contact; community diabetes advisor, 1 session/mo • Group counseling: health counselor & research assistant, 3 sessions • Behavior modification principles, active discovery learning approach	• Usual/standard care from primary care physician • Mailed educational pamphlets

ACE = angiotensin-converting enzyme, ACSM = American College of Sports Medicine; AHEAD = Action for Health in Diabetes; ALA = α-linolenic acid; BP = blood pressure; CDC = Centers for Disease Control; CHO =carbohydrate; d = day(s); DAWN = Diabetes Awareness and Wellness Network; DPP = Diabetes Prevention Program; HR=heart rate; info = information; min = minutes; mo = month(s); MUFA = monounsaturated fatty acids; PA = physical activity; pg = page; POWER = Pounds Off With Empowerment; SFA = saturated fatty acids; tx = treatment; wk = week(s); x = times; yr = year

Table 2. Description of lifestyle interventions: type 2 diabetes (continued)

Author, Year, Study name	Duration of intervention; followup	Diet	Exercise	Counseling or other component(s)	Control group
Look AHEAD Research Group, 2009, Look AHEAD[112]	4 yr completed; projected to end at 11.5 yr	• Minimum wt loss of ≥7% in 1st yr, encouraged wt loss of ≥ 10% • Caloric restriction, portion control, meal replacements, increased F&V intake, lower fat • Toolbox options for sub-optimal weight loss, including: written behavioral contracts, additional funds to promote adherence to behavioral goals (gym membership, cooking classes, pre-packaged meals)	• Mainly unsupervised exercise at home • Started with 50 min/wk moderate PA; increased to >175 min/wk by 6 mo; 5 d/wk • Strength training encouraged up to 25% of weekly goal • Educational material, logbook, progress reports, pedometers • Centers offered supervised activity • Regularly weighed and tracked min of PA/wk, attendance taken	• Group and individual behavioral program (with curriculum similar to DPP) delivered by lifestyle counselor • Individual counseling: lifestyle counselor; one visit/mo provided throughout the study • Group counseling: done in 3 phases; 3 visits/mo for first 1-6 mo; 2 visits/mo for mo 7-12; intermittent group sessions thereafter (typically 6-8 wk session offered 2-3 times/yr) • Orlistat given to pts who did not lose >10% of initial wt	• Attention control • 3 group educational/social support sessions per yr for 4 yr • Regular clinic visits and telephone calls for data collection

ACE = angiotensin-converting enzyme, ACSM = American College of Sports Medicine; AHEAD = Action for Health in Diabetes; ALA = α-linolenic acid; BP = blood pressure; CDC = Centers for Disease Control; CHO =carbohydrate; d = day(s); DAWN = Diabetes Awareness and Wellness Network; DPP = Diabetes Prevention Program; HR=heart rate; info = information; min = minutes; mo = month(s); MUFA = monounsaturated fatty acids; PA = physical activity; pg = page; POWER = Pounds Off With Empowerment; SFA = saturated fatty acids; tx = treatment; wk = week(s); x = times; yr = year

Table 2. Description of lifestyle interventions: type 2 diabetes (continued)

Author, Year, Study name	Duration of intervention; followup	Diet	Exercise	Counseling or other component(s)	Control group
Menard, 2005[113]	12 mo; 6 mo	• Followed Canadian Nutrition Recommendations	• Home-based program on exercise bike; use of elastic exercise bands • Used HR monitor • 4 phases: warm-up, cardiovascular, resistance, cool-down stretching • Aimed for 45-55 min sessions 3-5 x/wk	• Individual counseling: multidisciplinary team; monthly visits at the clinic • Telephone contact 2 times between visits for information on test results, therapy adjustment and motivation • Stepwise use of pharmacologic tx if CDA goals not met including glyburide, metformin, α-glucosidase inhibitor, intermediate-acting insulin, fosinopril, amlodipine, hydrocholorothiazide, atenolol, irbesartan, doxazosin, fibrates, statins	• Usual/standard care from primary care physician • Given general health and diabetes advice at each laboratory visit (baseline, 6, 12, 18 mo)

ACE = angiotensin-converting enzyme, ACSM = American College of Sports Medicine; AHEAD = Action for Health in Diabetes; ALA = α-linolenic acid; BP = blood pressure; CDC = Centers for Disease Control; CHO =carbohydrate; d = day(s); DAWN = Diabetes Awareness and Wellness Network; DPP = Diabetes Prevention Program; HR=heart rate; info = information; min = minutes; mo = month(s); MUFA = monounsaturated fatty acids; PA = physical activity; pg = page; POWER = Pounds Off With Empowerment; SFA = saturated fatty acids; tx = treatment; wk = week(s); x = times; yr = year

Table 2. Description of lifestyle interventions: type 2 diabetes (continued)

Toobert, 2003, Mediterranean Lifestyle Program[115]	6 mo; 18 mo	• Followed CDC & ACSM guidelines • Mediterranean ALA-rich diet: low in SFA, moderately high in MUFA • Meal planning, recipes, logbook, progress reports, attendance taken, monetary rewards, contests	• 10 strength-training exercises 2d/wk, building to 3 sets of 12 repetitions • Increase PA by 5 min/session, increase number of d/wk; goal= 1 hr session >3x per wk	• 3 d non-residential retreat at start of intervention • Initial consultation: exercise physiologist; goal setting • Group counseling: weekly 4 h meetings involving social support, PA, relaxation, meditation, potluck dinner • Stress management: 1 hr/d with an audiocassette, included 20 min of yoga, 15 min of progressive deep relaxation techniques, 15 min of meditation and 5 min of directed or receptive imagery	• Usual/standard care from primary care physicians
Studies with no postintervention followup					
Aubert, 1998[116]	12 mo; 0	• General healthy eating including meal planning • Telephone calls, blood glucose log	• General, self-directed increase in PA with reinforcement via telephone calls	• Individual and group counseling: registered dietician, exercise therapist; 5-wk education program; 12 hr • Included goal setting • Stepwise use of pharmacologic tx if glycemic or wt loss goals not met after 1-3 mo including sulfonylurea, metformin, precise, regular and NPH insulin	• Attention control • Given blood glucose meters and strips • Encouraged to discuss enrollment in diabetes education class with physicians • Continued to received diabetes care and followup from primary care physician

ACE = angiotensin-converting enzyme, ACSM = American College of Sports Medicine; AHEAD = Action for Health in Diabetes; ALA = α-linolenic acid; BP = blood pressure; CDC = Centers for Disease Control; CHO =carbohydrate; d = day(s); DAWN = Diabetes Awareness and Wellness Network; DPP = Diabetes Prevention Program; HR=heart rate; info = information; min = minutes; mo = month(s); MUFA = monounsaturated fatty acids; PA = physical activity; pg = page; POWER = Pounds Off With Empowerment; SFA = saturated fatty acids; tx = treatment; wk = week(s); x = times; yr = year

Table 2. Description of lifestyle interventions: type 2 diabetes (continued)

Author, Year, Study name	Duration of intervention; followup	Diet	Exercise	Counseling or other component(s)	Control group
Christian, 2008[110]	12 mo; 0	• Decreased caloric intake • Computer generated 4-5 pg individualized, tailored report providing feedback on participant-identified barriers to improve PA and diet • 30 pg planning guide with supplemental info on diabetes and healthy lifestyle	• Feedback to enhance participants' motivation to increase PA	• Individual counseling: physician; regularly scheduled study-related visits; included self-management goal setting of 2-3 dietary and/or PA goals • All subjects received 3 mo of diabetes education prior to randomization	• Usual/standard care from primary care physician • Health education materials provided at baseline visit addressing diabetes, diet, and exercise
Mayer-Davis, 2004, POWER[114]	12 mo; 0	• Followed the Intensive Lifestyle Intervention modeled after the DPP study with modifications • Goal was to achieve and maintain wt loss of 10% over 12 mo • Aimed for 25% of calories from dietary fat • Education materials, monetary incentives provided for completing 3, 6 and 12 mo	• Goal of ≥150 min/wk of low to moderate PA • Suggestions for PA were provided (e.g.: safe places to walk, chair exercises for people with lower-extremity pain) • Written materials, monetary incentives provided for completing 3, 6 and 12 mo	• Individual counseling: nutritionist; gradually decreased frequency over 12 mo; 1 hr sessions; included behavioral strategies to achieve wt loss • Group counseling: nutritionist; gradually decreased frequency over 12 mo; 1 hr sessions • 1 individual session for every 3 group sessions	• Attention control • 1 individual session by nutritionist at the beginning of study • Information about diet and PA provided from the ADA

ACE = angiotensin-converting enzyme, ACSM = American College of Sports Medicine; AHEAD = Action for Health in Diabetes; ALA = α-linolenic acid; BP = blood pressure; CDC = Centers for Disease Control; CHO =carbohydrate; d = day(s); DAWN = Diabetes Awareness and Wellness Network; DPP = Diabetes Prevention Program; HR=heart rate; info = information; min = minutes; mo = month(s); MUFA = monounsaturated fatty acids; PA = physical activity; pg = page; POWER = Pounds Off With Empowerment; SFA = saturated fatty acids; tx = treatment; wk = week(s); x = times; yr = year

Table 2. Description of lifestyle interventions: type 2 diabetes (continued)

Author, Year, Study name	Duration of intervention; followup	Diet	Exercise	Counseling or other component(s)	Control group
Samuel-Hodge, 2009, DAWN[118]	8 mo; 4 mo	• General healthy eating • Each group session had taste testings of 1-2 recipes • Telephone calls, postcard messages of encouragement	• General increase in PA • Every group session had 15 min of chair exercises • Actigraph monitor worn for 1 wk • Telephone contact, postcard messages of encouragement	• Individual counseling: registered dietician for 1 session, 1 hr; stress management and goals • Group counseling: registered dietician for first 7 sessions, health professional from local community for 4 sessions, 1 group potluck for total of 12 sessions (biweekly); 90-120 min • Prior to each group session, all participants checked their blood glucose and BP, and received feedback	• Attention control • Received 2 pamphlets in the mail published by the ADA and 3 bimonthly newsletters providing general health information and study updates
Vanninen, 1992[117]	12 mo; 0	• Reduction in total energy, total fat and dietary cholesterol, with emphasis on reduction of SFA • Moderate increment of MUFA, PUFA, and complex CHO with focus on soluble fiber • Target food habits were regular eating patterns and to moderate amount of food consumed	• Goal was to increase PA to 3-4 x/wk for 30-60 min • Recommended mean heart rate was 110-140 beats/min • Types of exercise were suggested (e.g.: walking, jogging, cycling, swimming)	• Group counseling: physician, dietician, nurse specialized in diabetes; 6 meetings at 2 mo intervals • Physician was responsible for motivation	• Usual/standard care by primary care physician • Advised to visit the local community health centers regularly at 2-3 mo intervals • Visited the outpatient clinic at 6 and 12 mo

ACE = angiotensin-converting enzyme, ACSM = American College of Sports Medicine; AHEAD = Action for Health in Diabetes; ALA = α-linolenic acid; BP = blood pressure; CDC = Centers for Disease Control; CHO =carbohydrate; d = day(s); DAWN = Diabetes Awareness and Wellness Network; DPP = Diabetes Prevention Program; HR=heart rate; info = information; min = minutes; mo = month(s); MUFA = monounsaturated fatty acids; PA = physical activity; pg = page; POWER = Pounds Off With Empowerment; SFA = saturated fatty acids; tx = treatment; wk = week(s); x = times; yr = year

Table 3. Risk of bias assessment for studies of type 2 diabetes

Author Year	Sequence generation	Allocation concealment	Blinding: Objective outcomes	Blinding: Self-reported outcomes	Incomplete outcome data	Selective outcome reporting	Other sources: Baseline imbalance	Other sources: Funding	Overall risk of bias
Aubert 1998[116]	Unclear	Unclear	Low	High	Unclear	Low	Low	Unclear	High
Christian 2008[110]	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Unclear
Gaede 1999[119]	Low	Low	Low	Unclear	Low	Low	Low	Low	Unclear
Keyserling, 2002[111]	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Unclear
Look AHEAD Research Group 2009[112]	Low	Low	Low	Unclear	Low	Low	Low	Low	Unclear
Mayer-Davis 2004[114]	Unclear	Low	Low	High	Unclear	Low	Low	Low	High
Menard 2005[113]	Low	Low	Low	Unclear	Unclear	Low	Low	Unclear	Unclear
Samuel-Hodge 2009[118]	Low	Low	Low	Unclear	Low	Low	Low	Low	Unclear
Toobert 2003[115]	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Unclear
Vanninen 1992[117]	Unclear	Unclear	Low	Unclear	Unclear	Low	Low	Low	Unclear

High = high risk of bias; Low = low risk of bias; Unclear = unclear risk of bias

Metabolic Syndrome

Description of Included Studies

Four RCTs[122,123,125,126] met our a priori inclusion criteria. The duration of the interventions ranged from 6 to 72 months, with followup periods ranging from 3 to 20 years. We also included three studies that had long-term interventions of at least 12 months but with no postintervention followup period.[120,121,124] There were 34 associated publications.[149-181] The duration of these interventions ranged from 12 to 36 months. For all seven studies, the number of participants randomized ranged from 39 to 3,234 (median = 375; IQR: 113, 437). The mean age ranged from 44 to 85 years. BMI ranged from 26.2±3.9 to 38.3±5.9.

All studies included a diet and exercise component plus at least one additional component (Table 5). These included both individual and group counseling,[121-123,125,126] individual counseling,[124] group counseling,[120] behavior modification,[120,122] a smoking cessation program,[121,123] regular telephone contact,[122,123] individual goal setting,[125]and cooking lessons.[123] The interventions were delivered by dieticians,[120-125] exercise advisors,[122,123] physiotherapists,[124] nurse managers,[122,123] nurses,[125,126] physicians,[122,123,126] endocrinologists,[125] psychologists,[122] and technicians.[126] One study had medication use as an intervention component.

Methodological Quality

The methodological quality of the RCTs is summarized in Table 6. Three studies[120-122] were assessed as having a high risk of bias and four[123-126] an unclear risk of bias. All seven studies were RCTs, and only two[120,126] did not describe the method by which participants were randomized to groups. Allocation was concealed in only two studies.[123,125] All but one study[126] were at high or unclear risk of bias for lack of blinding for subjective or self-reported outcomes (e.g., number of hours of exercise per week). One study[122] stated that the allocation to metformin or placebo was double blinded; however, we did not extrapolate this double blinding to the diet and exercise components of the intervention. Three studies[121-123] were at unclear risk of bias for incomplete outcome data; the remaining studies[120,124-126] had low risk of bias for this domain. There was no evidence of selective outcome reporting. Two studies[120,122]received funding from industry. Three studies received funding from foundations,[121-123] one from the World Bank,[126] and three from government.[120,122,123] Two studies[124,125] did not report funding.

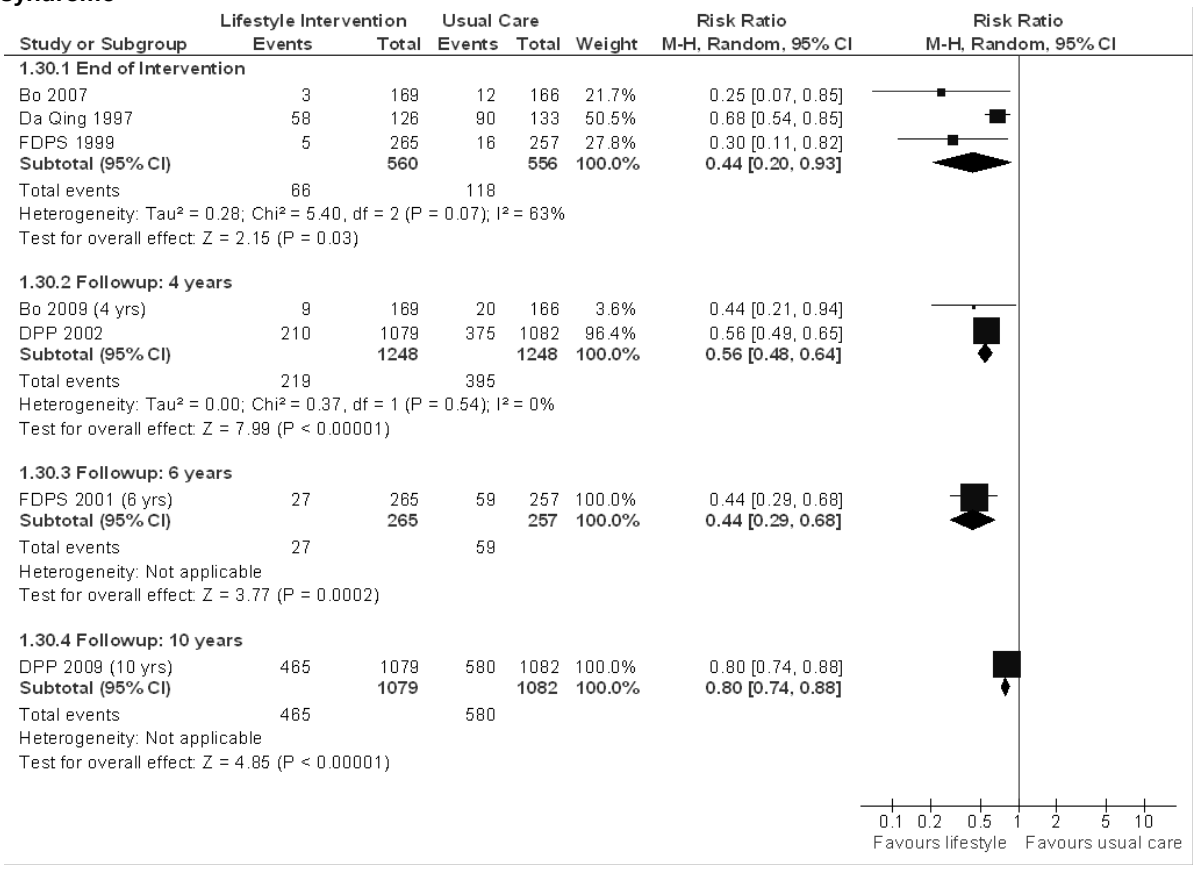
Results

Primary Outcomes. Our primary outcomes were CVD complications, and development of type 2 diabetes. Four studies[122,123,125,126] reported data for at least one of these outcomes. No studies reported nonfatal myocardial infarction or nonfatal stroke.

Cardiovascular disease complications. Two studies[123,126] reported CVD events. The Finnish Diabetes Prevention Study (FDPS)[123] by Eriksson et al. reported that at 10 years postintervention there was no statistically significant difference between the lifestyle and usual care groups (RR = 1.02; 95% CI: 0.73, 1.42). There were 57/257 (22 percent) CVD events in the intervention group compared with 54/248 (22 percent) in the control group. The Da Qing Diabetes Prevention Trial[126] reported any first CVD event at 6 and 20 years of followup. There were no statistically significant differences between the groups at either timepoint (HR = 0.96; 95% CI: 0.76-1.44 and HR = 0.98; 95% CI: 0.71-1.37, respectively).

Development of type 2 diabetes. Four studies[122,123,125,126] reported the development of type 2 diabetes. Bo et al.[125] found a significant difference in favor of the lifestyle intervention at both end of intervention (RR = 0.25; 95% CI: 0.07, 0.85) and at the 4 year followup (RR = 0.44; 95% CI: 0.21, 0.94). There were 3/169 (2 percent) individuals who developed type 2 diabetes in the intervention group compared with 12/166 (7 percent) in the usual care group at the end of intervention; while at 4 years, 9/169 (5.4 percent) individuals in the intervention group and 20/166 (10.2 percent) in the control group developed diabetes. The Da Qing study[126] also reported a significant difference in favor of the lifestyle intervention at both 6 and 20 years (HR = 0.49; 95% CI: 0.33, 0.73 and HR = 0.57; 95% CI: 0.41, 0.81, respectively). The hazard ratios combined several intervention groups, therefore the results for our primary outcomes included a lifestyle intervention with both diet and exercise components, a diet only intervention, and an exercise only intervention. The FDPS by Eriksson et al.[123] showed a significant difference in favor of lifestyle intervention at both end of intervention and 6 years (10 year data were not reported). There were 5/265 (2 percent) in the intervention group that developed type 2 diabetes compared with 16/257 (6 percent) in the usual care group. At 6 years, this rose to 27/265 (10 percent) and 59/257 (23 percent), respectively. The Diabetes Prevention Program (DPP) by Knowler et al.[122] also found a significant difference between the intervention and usual care groups at both 4 years (210/1,079, 19 percent and 375/1,082, 35 percent, respectively) and 10 years (465/1,079, 43 percent and 580/1,082, 54 percent).

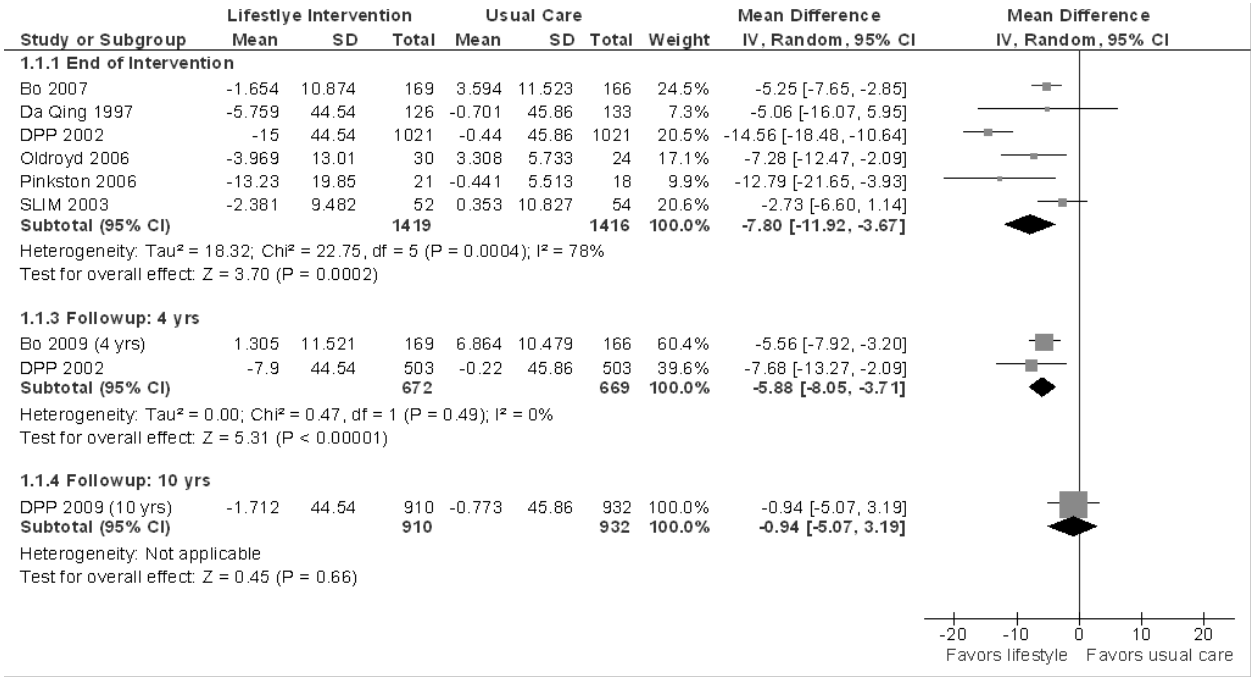
Figure 16. Effect of lifestyle interventions vs. control on development of diabetes: patients with metabolic syndrome



Death. Two studies[123,126] reported the number of deaths. The FDPS[123] reported no difference between the groups at 10 years (RR = 0.58; 95% CI: 0.21, 1.57). There were 6/257 deaths in the lifestyle group and 10/248 in the usual care group. The Da Qing study[126] found no difference between groups for CVD mortality at 20 years (HR = 0.83; 95% CI: 0.48, 1.40). There were no deaths in either group at 6 years. There were no differences for all-cause mortality at either timepoint (HR = 1.33; 95% CI: 0.45, 3.92 and HR = 0.96; 95% CI: 0.65, 1.41, respectively).

Secondary Outcomes. *Change in body composition.* There were 6 studies[120-122,124-126] that reported weight (lbs) at the end of intervention (Figure 17). The pooled MD was -7.80 (95% CI: -11.92, -3.67, I^2=78%). At 4 years postintervention, Bo et al.[125] reported a statistically significant difference between groups in favor of the lifestyle intervention (MD = -5.56; 95% CI: -7.92, -3.20). At 4 years postintervention the DPP Study by Knowler et al.[122] also reported a statistically significant difference between groups in favor of the lifestyle intervention (MD = -7.68, 95% CI: -13.27, -2.09). At 10 years, the difference between groups had disappeared. We conducted a post hoc sensitivity analysis to assess the impact of medication use on changes in body composition in the study by Pinkston et al.[120] and found no statistically significant differences.

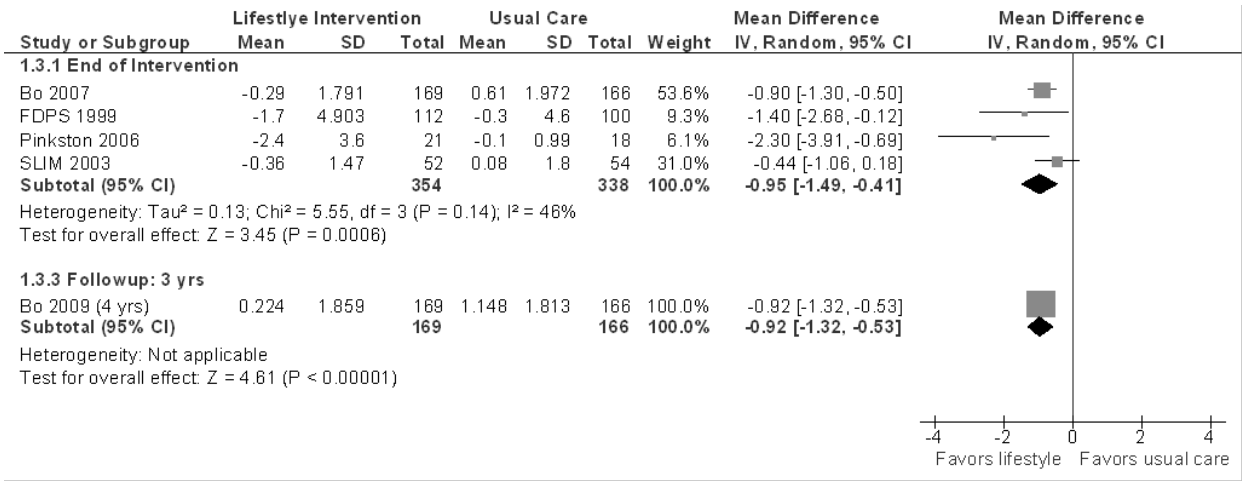
Figure 17. Effect of lifestyle interventions vs. control on weight change (lbs): patients with metabolic syndrome



The FDPS by Eriksson et al.[123] reported whether participants achieved the goal of losing five percent or more of their body weight. The difference between the lifestyle and control groups was statistically significant in favor of the lifestyle intervention (MD = 3.35; 95% CI: 2.37, 4.74).

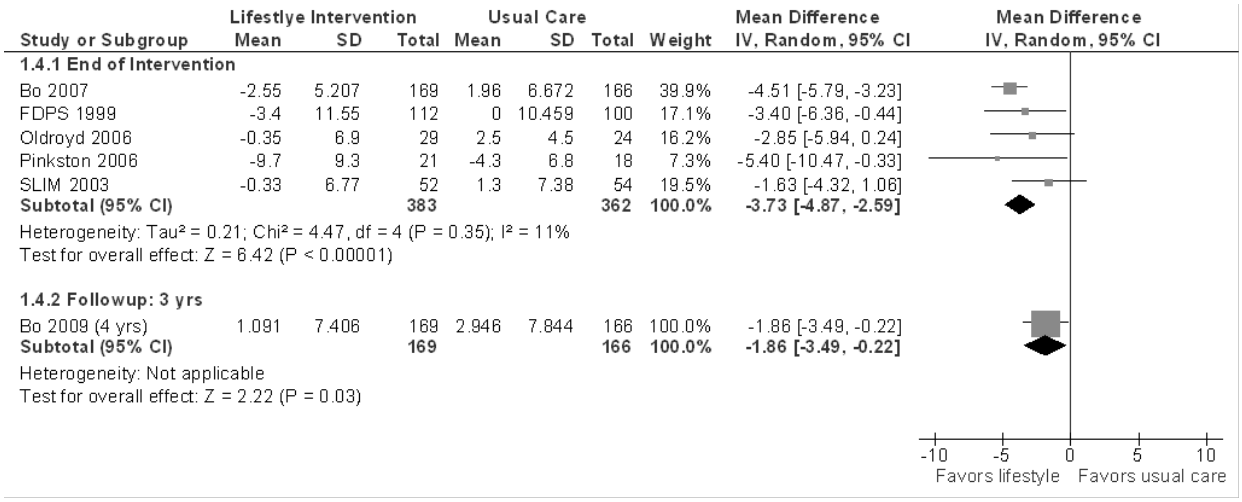
BMI (kg/m^2) was reported in four studies[120,121,123,125] (Figure 18). At the end of the intervention, the pooled MD was statistically significant in favor of the lifestyle group (MD = -0.95; 95% CI: -1.49, -0.41; I^2 = 46%). At 4 years, Bo et al.[125] reported a statistically significant difference that favored the lifestyle intervention (MD = -0.92; 95% CI: -1.32, -0.53).

Figure 18. Effect of lifestyle interventions vs. control on BMI (kg/m^2): patients with metabolic syndrome



Waist circumference was another outcome that measured change in body composition and was reported in five studies[120,121,123-125] (Figure 19). The pooled MD -3.73 (95% CI: -4.87, -2.59, I^2 = 11%). At 4 years, the difference had decreased, however, it was still statistically significant in favor of the lifestyle intervention (MD = -1.86, 95% CI: -3.49, -0.22).

Figure 19. Effect of lifestyle interventions vs. control on change in waist circumference (cm): patients with metabolic syndrome



Change in metabolic variables. Seven studies reported on changes in different metabolic variables, including fasting plasma glucose[121-125] (Figure 20), triglycerides[120,121,123,125] (Figure 21), total cholesterol[120,121,123-125] (Figure 22), HDL[120,121,123,125] and LDL cholesterol[120,121,124] (Figure 23, Figure 24), and HbA1c[110-119] (Figure 25). In general, lifestyle interventions appear to improve metabolic variables more than usual care, although the differences were not always statistically significant. The changes in metabolic variables were sustained at 4 years of followup. However, at 10 years of followup, the DPP study reported that usual care was more effective in lowering fasting plasma glucose compared with the lifestyle intervention (RR = 0.10; 95% CI: 0.03, 0.18). At 10 years, the lifestyle intervention was more effective than usual care in controlling HbA1c (RR = -0.05; 95% CI: -0.09, -0.02).

Figure 20. Effect of lifestyle interventions vs. control on fasting plasma glucose (mmol/l): patients with metabolic syndrome

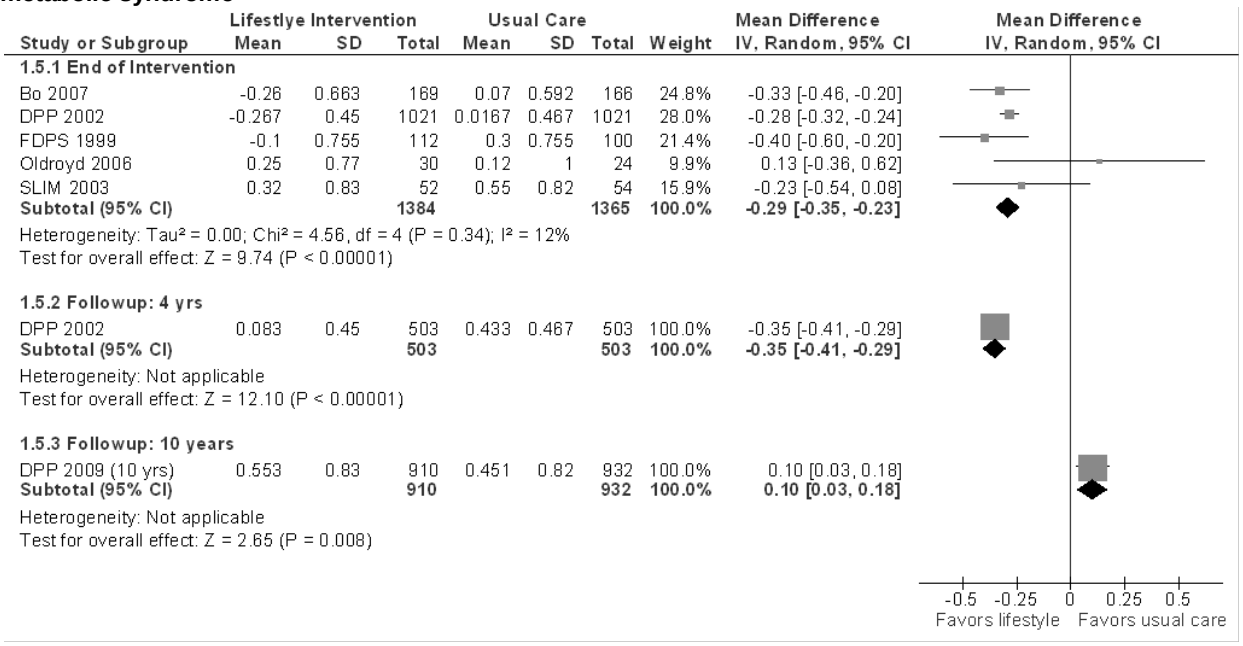


Figure 21. Effect of lifestyle interventions vs. control on triglycerides (mmol/l): patients with metabolic syndrome

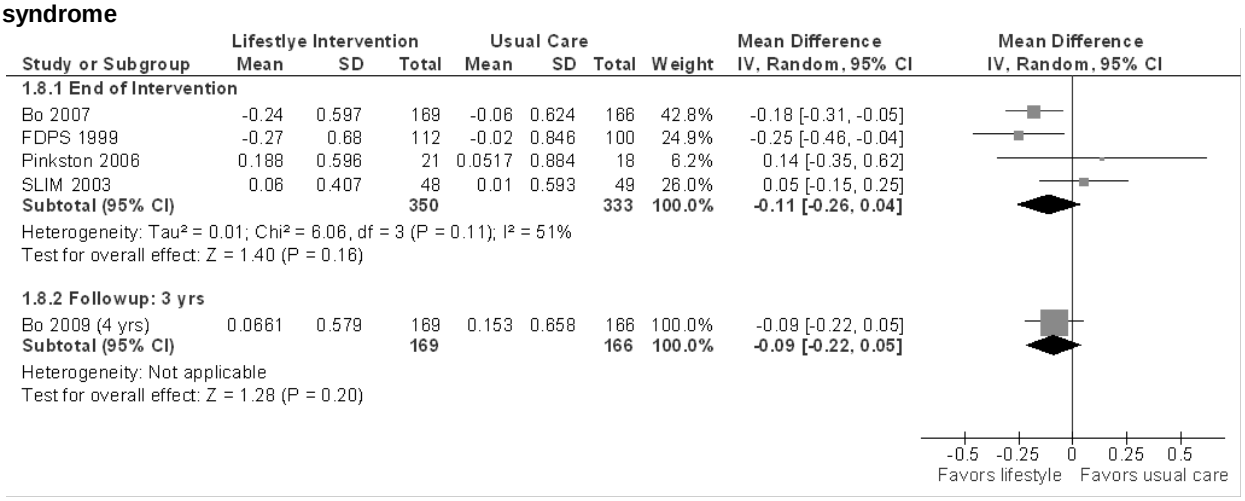


Figure 22. Effect of lifestyle interventions vs. control on total cholesterol (mmol/l): patients with metabolic syndrome

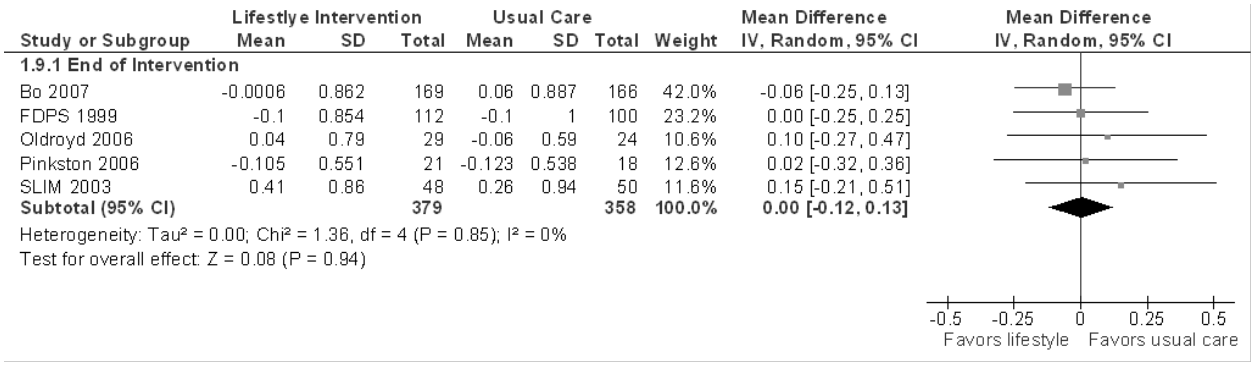


Figure 23. Effect of lifestyle interventions vs. control on HDL cholesterol (mmol/l): patients with metabolic syndrome

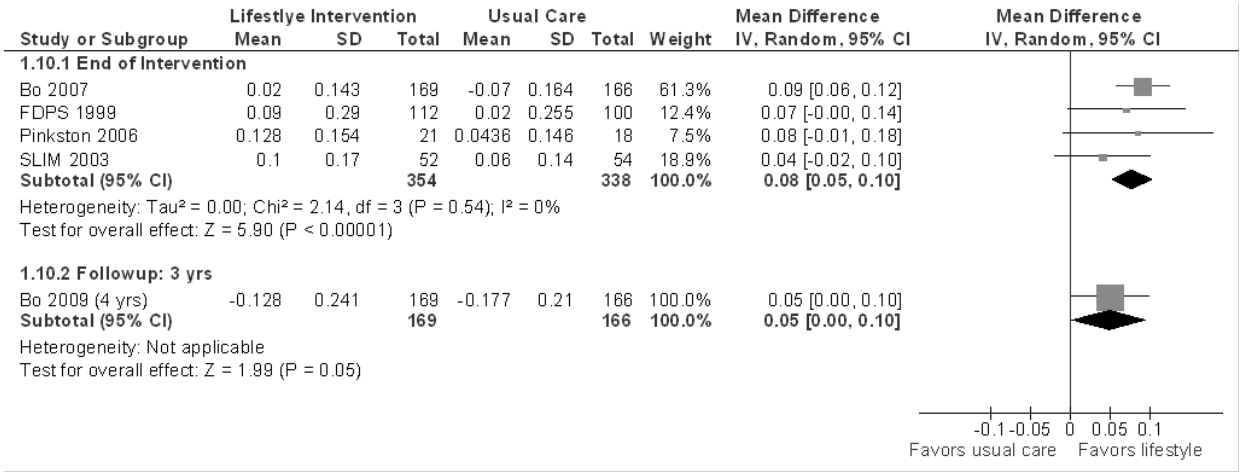


Figure 24. Effect of lifestyle interventions vs. control on LDL cholesterol (mg/dl): patients with metabolic syndrome

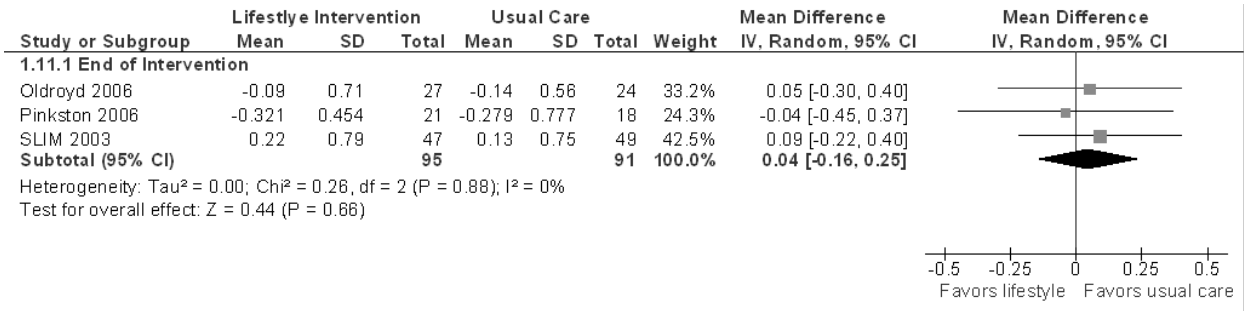
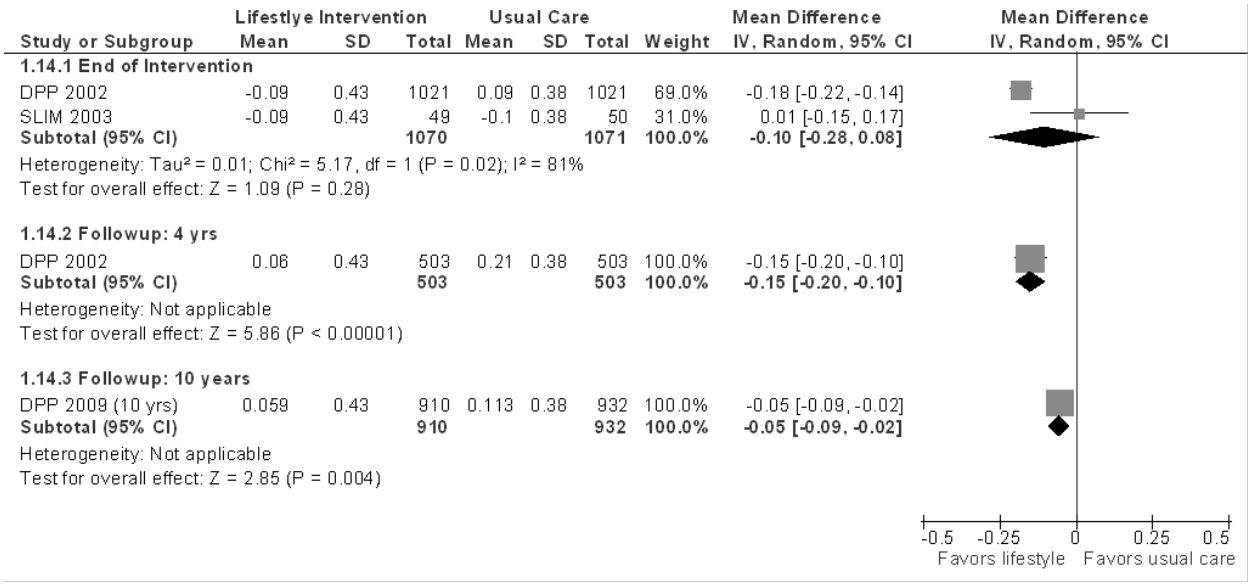


Figure 25. Effect of lifestyle interventions vs. control on HbA1c (%): patients with metabolic syndrome



Systolic and diastolic blood pressure. Changes in systolic and diastolic blood pressure (mmHg) were reported in five studies.[120-123,125] There was a statistically significant difference between groups for both systolic blood pressure (MD = -3.17; 95% CI: -5.02, -1.33; I^2 = 27%) and diastolic blood pressure (MD = -2.70; 95% CI: -3.21, -2.18; I^2 = 0%) at the end of intervention (Figure 26 and Figure 27). At the followup timepoint, there was still a statistically significant difference seen for both systolic (MD = -4.41; 95% CI: -8.47, -0.35) and diastolic (MD = -1.88; 95% CI: -2.65, -1.12) blood pressure.

Figure 26. Effect of lifestyle interventions vs. control on systolic blood pressure: patients with metabolic syndrome

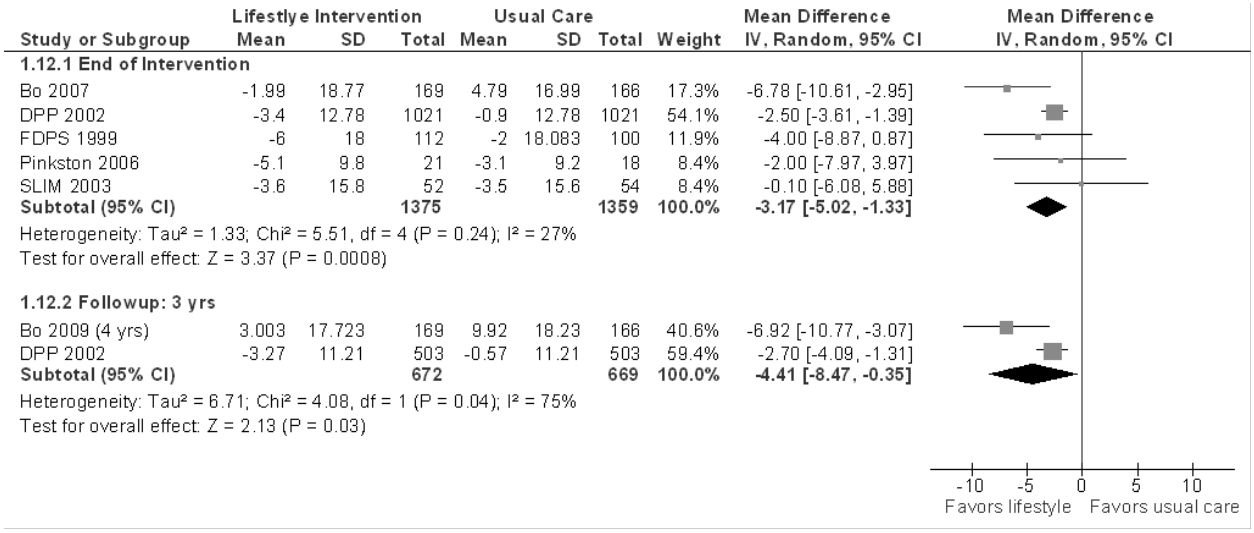
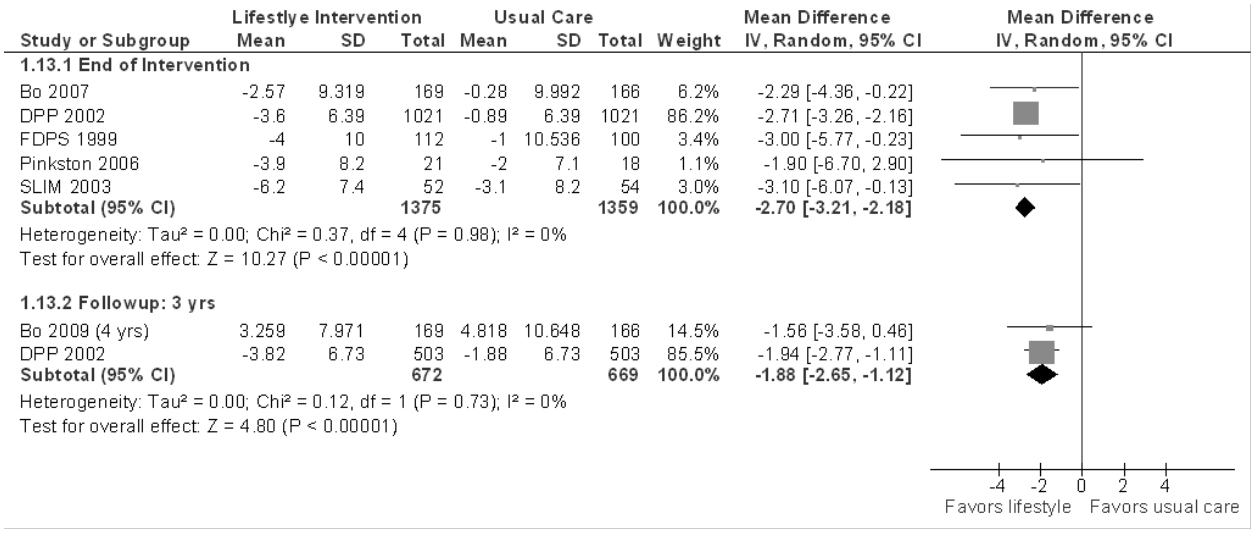
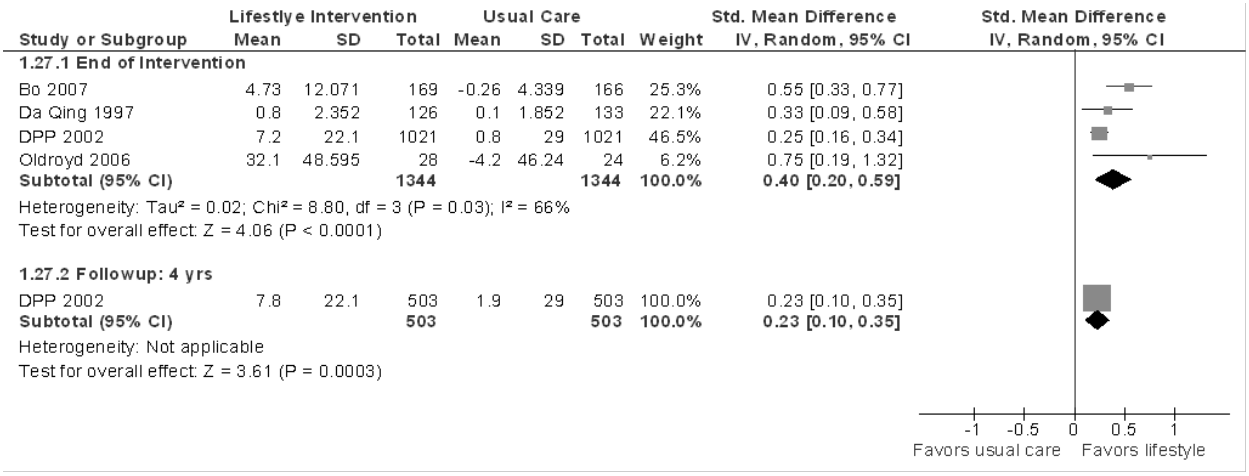


Figure 27. Effect of lifestyle interventions vs. control on diastolic blood pressure: patients with metabolic syndrome



Change in physical activity. Four studies[122,124-126] reported on the change in general exercise (Figure 28). At the end of the intervention, all showed a statistically significant increase in exercise that favored the lifestyle intervention (SMD = 0.40; 95% CI: 0.20, 0.59, I^2 = 66%). At 4 years postintervention, the DPP Research Group[122] reported a statistically significant difference between the groups in favor of the lifestyle group (SMD = 0.23; 95% CI: 0.10, 0.35).

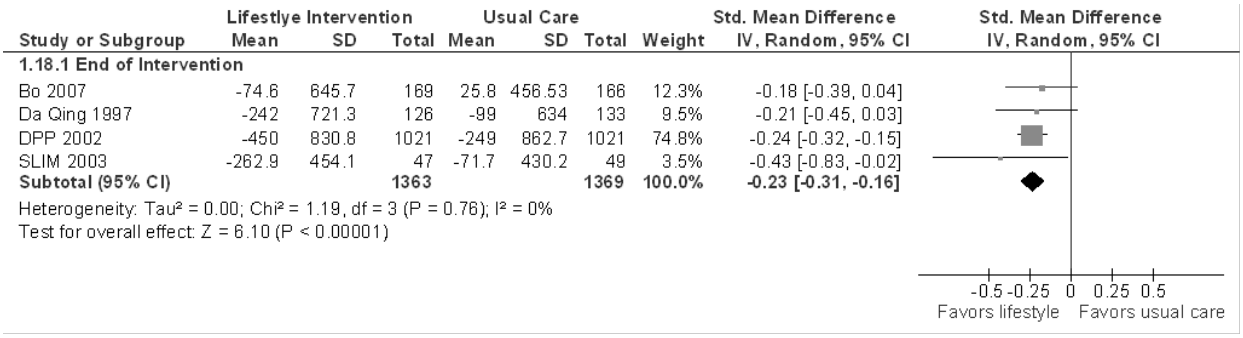
Figure 28. Effect of lifestyle interventions vs. control on change in physical activity: patients with metabolic syndrome



Change in dietary intake. Four studies[121,122,125,126] measured change in energy intake (Figure 29) and reported that participants in the lifestyle groups had a significantly lower energy intake at the end of the intervention compared with the usual care group (SMD = -0.23; 95% CI: -0.31, -0.16, I^2 = 0%). All three studies that measured fiber intake reported that the lifestyle group had a higher fiber intake than the usual care group (SMD = 0.39; 95% CI: 0.21, 0.57, I^2 = 0%) (data not shown). The FDPS[123] by Eriksson et al. reported whether participants reached their goal of consuming at

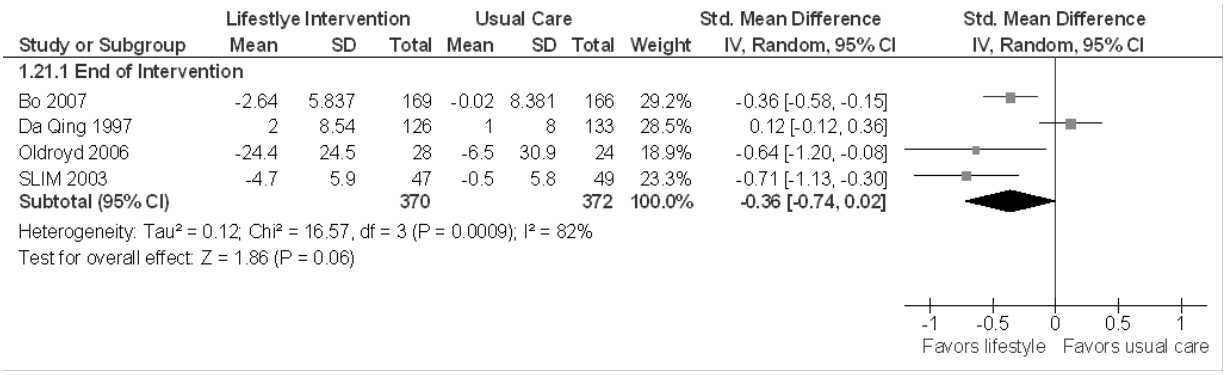
least 15 grams of fiber per 1000 kcal and found that significantly more participants in the lifestyle group achieved this goal compared with the usual care group (RR = 2.06; 95% CI: 1.40, 3.05).

Figure 29. Effect of lifestyle interventions vs. control on change in energy intake: patients with metabolic syndrome



Four studies[121,124-126] assessed fat intake (Figure 30). The pooled difference was not statistically significant (SMD = -0.36; 95% CI: -0.74, 0.02, $I^2 = 82\%$). However, two studies[121,125] reported saturated fat intake and found a statistically significant difference between the lifestyle and usual care group (SMD=-0.53; 95% CI: -0.73, -0.34, $I^2 = 0\%$).

Figure 30. Effect of lifestyle interventions vs. control on change in fat intake: patients with metabolic syndrome



In the FDPS,[123] the increase in vegetable consumption was significantly greater in the lifestyle intervention group at the end of intervention (RR = 1.16; 95% CI: 1.03, 1.32).

Change in medications. One study[122] reported medication use. All groups increased their use of antidiabetic medication over 10 years but the lifestyle intervention group had a smaller increase in use compared with usual care. The lifestyle group also used fewer antihypertensive drugs compared with usual care, though this was not statistically significant. The lifestyle intervention group used significantly fewer lipid-lowering drugs than the usual care group, with a mean of 18.4 percent versus 22.7 percent, respectively (p = 0.02).

Compliance with the intervention. Compliance was measured by the number of dropouts/withdrawals. The FDPS[123] was the only study that showed a statistically significant

difference in favor of the lifestyle group (RR = 0.61; 95% CI: 0.41, 0.90). Five studies[121,122,124-126] found no difference between groups. One study[120] did not report withdrawal data. Overall, there was no statistically significant difference in dropout rates (RR = 0.92; 95% CI: 0.76, 1.11).

Adverse events. Two studies reported the following adverse events: fatty stool and related complications[120] and gastrointestinal symptoms.[122] The adverse events were not directly attributed to the exercise, diet, or other component of the lifestyle intervention.

Summary

Seven RCTs assessed the effectiveness of lifestyle interventions for metabolic syndrome. The following is a summary of results:

- *Primary outcomes.* Four studies assessed the primary outcomes of CVD complications, development of type 2 diabetes, and death. There were no significant differences between the groups except for the development of type 2 diabetes. Two long-term studies found that lifestyle interventions significantly decreased the risk of developing type 2 diabetes. The strength of evidence is moderate for development of type 2 diabetes at end of intervention and for followup timepoints. The strength of evidence is insufficient for CVD events and death.
- *Change in body composition.* Six studies reported weight (lbs) at the end of intervention. At 4 years postintervention, two studies reported a statistically significant difference between groups in favor of the lifestyle intervention. At 10 years, there was no longer a difference between groups. Four studies reported change in BMI (kg/m^2). At both end of intervention and 4 years followup, there was a statistically significant difference between groups favoring the lifestyle intervention. Waist circumference was measured in five studies. The lifestyle group was favored at end of intervention and the 4 year followup. The strength of evidence is moderate for BMI, moderate for weight change, and moderate for waist circumference at end of intervention. The strength of evidence is low in weight change at 4 year followup. It is insufficient for BMI and waist circumference at followup.
- *Change in metabolic variables.* Six studies reported on changes in different metabolic variables. For fasting plasma glucose, the lifestyle group was significantly favored at end of intervention and at 4 year followup. At 10 years, there was a significant difference between groups favoring the usual care group. For HbA1C, the lifestyle group was significantly favored at both 4 and 10 year followup. For all other metabolic variables, there was no significant difference between groups at the followup timepoints. The strength of evidence is moderate for fasting plasma glucose and HDL cholesterol at end of intervention. It is low for LDL cholesterol, total cholesterol and triglycerides at end of intervention and is insufficient for HbA1c and impaired glucose at end of intervention. The strength of evidence is insufficient for all outcomes at all followup timepoints.
- *Systolic and diastolic blood pressure*. Five studies reported change in systolic and diastolic blood pressure (mmHg). There was a significant difference between groups for both systolic and diastolic blood pressure at the end of intervention. At the followup timepoint, there was still a difference seen for both systolic and diastolic blood pressure. The strength of evidence is moderate for end of intervention for both outcomes and low for 4 year followup.

- *Change in physical activity*. Four studies reported on the change in general exercise. At end of intervention and at 4 year followup, the lifestyle group was significantly favored. The strength of evidence is moderate at end of intervention and insufficient at 4 year followup.
- *Change in dietary or nutrient intake*. Four studies measured change in energy intake. The lifestyle group had a significantly lower energy intake at the end of the intervention compared with the usual care group. The lifestyle group also had significantly lower consumption of saturated fat compared with the usual care group. The strength of evidence is moderate for energy intake and low for saturated fat intake at end of intervention. There were no followup data for either of these outcomes.
- *Change in medications*. None of the studies reported use of diabetic medication.
- *Compliance with intervention*. Compliance was measured by the number of dropouts/withdrawals. One study that showed a statistically significant difference in favor of the lifestyle group while five studies found no difference between groups.
- *Adverse events*. No studies reported adverse events directly attributed to the exercise, diet, or other component of the lifestyle intervention.
- Three RCTs were considered to be at high risk of bias; four were unclear. The most common sources of potential bias were unclear concealment of allocation, inadequate blinding, and incomplete outcome data. Two studies received funding from industry.

Table 4. Description of studies and baseline characteristics of participants: metabolic syndrome

Studies with postintervention followup

Author, Year, Study name	Randomized (N); Withdrawals (N)	Age (mean ± SD); Males: N (%); Ethnicity	Socioeconomic status (%≤$20,000/yr income); Education (%≤ high school); Smokers (%)	Weight (kg); BMI (km/m^2); Waist circumference (cm)	HbA1c (%); Plasma Fasting Glucose (mmol/l); Insulin resistance (HOMA-IR); Blood pressure (mmHg)	Number of medications; Type
Bo, 2007[125]	I: 187;18 C: 188;22	I: 55.7±5.7; 77 (41.4); 100 White C: 55.7±5.6; 79 (42.2); 100 White	I: NR; 92.9; 21.9 C: NR; 97.0; 21.7	I: 81.7±14.9; 29.7±4.1; 99.6±11.6 C: 81.3±13.5; 29.8±4.6; 99.8±10.6	I: NR; 5.8±0.8; 0.81±1.11; 142.6±14.1/88.2± 9.8 C: NR; 5.8±0.7; 0.84±1.33; 141.5±15.2/ 87.8± 9.5	I: NR C: NR
DPP Research Group, 2002, DPP[122]	I:1079;20 C:1082;16 Grp3: 1073; 16	I: 50.6+11.3; 345 (32.0); 53.8 White, 18.8 Black, 27.4 Other C: 50.3+10.4; 335.0(31.0); 54.2 White, 20.3 Black, 25.5 Other Grp3: 50.9+10.3; 363 (33.8); 56.1 White, 20.6 Black, 23.3 Other	I: NR; NR; NR C: NR; NR; NR Grp3: NR; NR; NR Total ≤high school= 25.8	I: 94.1±20.8; 33.9±6.8; 105.1±14.8 C: 94.3±20.2; 34.2±6.7; 105.2±14.3 Grp3: 94.3±19.9; 33.9±6.6; 104.9±14.4	I: 5.9±0.5;106.3±8.1 (mg/dl); 7±4.3; 123.7+14.8/78.6+9.2 C: 5.91±0.5; 106.7±8.4 (mg/dl); 7.1±4.2; 123.5+14.4/78.0+9.2 Grp3: 5.9±0.5; 106.5±8.5 (mg/dl); 7.2±4.1; 124.0+14.9/78.2+9.5	I: Antidiabetic drugs: 0 C: Antidiabetic drugs: 0 Grp3: Antidiabetic drugs: 0
Eriksson, 1999, FDPS[123]	I: 265; 34 C: 257; 54	I: 55.0±7.0; 91.0 (34.4);100 White C: 55.0±7.0; 81.0 (31.5);100 White	I: NR; 67.0; 7.0 C: NR; 67.0; 7.3	I: 86.7±14.0; 31.4±4.5; 102.0±11.0 C: 85.5±14.4; 31.1±4.5; 100.5±10.9	I: 5.7±0.6; 6.1±0.08; NR; 140.0±18/86±9 C: 5.6±0.6; 6.2±0.7; NR; 136±17/86±10	I: NR C: NR

DPP = Diabetes Prevention Program; FDPS = Finnish Diabetes Prevention Study; NR = not reported; SLIM = Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht

Table 4. Description of studies and baseline characteristics of participants: metabolic syndrome (continued)

Author, Year, Study name	Randomized (N); Withdrawals (N)	Age (mean ± SD); Males: N (%); Ethnicity	Socioeconomic status (%≤$20,000/yr income); Education (%≤ high school); Smokers (%)	Weight (kg); BMI (km/m^2); Waist circumference (cm)	HbA1c (%); Plasma Fasting Glucose (mmol/l); Insulin resistance (HOMA-IR); Blood pressure (mmHg)	Number of medications; Type
Pan, 1997, Da Qing Study[126]	I: 438; 133 C: 138; 43	I: 44.4±9.2; 70.0 (55.6); 100 Chinese C: 46.5±9.3; 73 (54.9); 100 Chinese	I: NR; NR; NR C: NR; NR; NR	I: NR; 26.3±3.9; NR C: NR; 26.2±3.9; NR	I: NR; 5.67±0.8; 1.71±0.08; all 3 interventions combined mean(SE): 132.2±1.1/87.2±0.7 C: NR; 5.52±0.82; 1.72±0.07; 134.3±2/88.5±1.5	I: NR C: NR
Studies with no postintervention followup						
Mensink, 2003, SLIM Trial[121]	I: 74; 22 C: 73; 19	I: 54.2±5; 8; 28 (53.8); 100 White C:58.4±6.8; 30 (55.6); 100 White	I: NR; NR; NR C: NR; NR; NR	I: 87.5±13.7; 29.6±3.8; 103.2±10.6 C: 83.0±11.7; 29.2±3.3; 102.4±9.2	I: 5.6±0.5; 6.0±0.87; 4.82±2.04(HOMA); 142±16/90±9 C: 5.8±0.5; 5.9±0.7; 4.55±2.05(HOMA); 145±14/88±7	I: NR C: NR
Oldroyd, 2001[124]	I: 39; 4 C: 39; 7	I: 58.2 (range 41-75); 17.0 (46.0);100 White C: 57.5 (range 41-73); 22.0 (69.0); 100 White	I: NR; NR; NR C: NR; NR; NR	I: 83.3±16.1; 30.4±5.6; 97.9±11.1 C: 85.5±14.2; 29.9±4.9; 99.6±11.3	I: 5.8±0.7; 6.0±0.9; 3.6±1.9; 137.2±19.9/ 77±12.6 C: 5.9±0.5; 6.2±0.9; 3.8±2.3(HOMA); 132.8±16.4/ 75.5±9.8	I: NR C: NR
Pinkston, 2006[120]	I: 21; NR C: 18; NR	I: 44.9±9.2; 0 (0); 100 Hispanic C:45.8±8.2;0 (0); 100 Hispanic	I: NR; 19 (<high school); NR C: NR; 11.1 (<high school); NR	I: 95.9±8.3; 37.9±5.1; 113.3±13.8 C: 97.6±21.2; 38.3±5.9; 111.8±10.3	I: NR; NR; NR; 126.4±17.7/80.3±11 C: NR; NR; NR; 124.3±14.1/ 80.1±10.4	I: NR C: NR

DPP = Diabetes Prevention Program; FDPS = Finnish Diabetes Prevention Study; NR = not reported; SLIM = Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht

Table 5. Descriptions of lifestyle interventions: metabolic syndrome

Studies with postintervention followup

Author, Year	Duration of study; Duration of followup	Diet	Exercise	Counseling or other component(s)	Control group
Bo, 2007[125]	12 mo, 3 yr	• Followed NIH Guidelines • Recommended daily caloric distribution • Individualized, written recommendations from trained professionals; food pyramid; individual goals	• 150 min/wk moderate PA • Individualized, written recommendations; individual goals	• Individual counseling: 1 session by trained professional • Group counseling: 4 group sessions by trained professional on behavioral counseling & lifestyle tips	• Usual/standard care provided by family physician
Diabetes Prevention Program Research Group, 2002, DPP[122]	12 mo; 10 yr	• Followed Food Pyramid Guidelines • Goal to achieve & maintain wt loss of 7% in first 24 wk • Low fat, low calorie diet • $100/yr for "tool kit" with cookbook, grocery vouchers • Logbook, telephone contact, personal interview	• 150 min/wk moderate PA • Strength training: max 75 min/wk could apply to 150 min/wk • Clinic supervised sessions twice/wk; activity varied • Logbook, personal interview, weighed at every session	• Individual counseling: case manager trained in nutrition, exercise or behavior modification; 16 sessions using curriculum for 1st 24 wk then at least once every 2 mo • Group counseling: case manager; quarterly for 4-8 wk courses.	• Standard diet and exercise advice

BMI = body mass index; CHO =carbohydrate; d = day(s); DPP = Diabetes Prevention Program; F&V = fruits and vegetables; FDPS = Finnish Diabetes Prevention Study; hr = hour(s); kcal = kilocalories; lb = pound(s); max = maximum; meds = medications; min = minute(s); mo = month(s); NIH = National Institutes of Health; PA = physical activity; SLIM = Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht; SFA = saturated fatty acids; wk = week(s); wt = weight; x = times

Table 5. Description of lifestyle interventions: metabolic syndrome (continued)

Author, Year	Duration of study; Duration of followup	Diet	Exercise	Counseling or other component(s)	Control group
Eriksson, 1999, FDPS[123]	4 yr; 6.6 yr	• Wt loss of ≥ 5% or goal BMI of ≤ 25 kg/m² • Emphasis on decreased SFA, increased fiber to >15g/1000 kcal • If no wt loss in 6-12 mo, low calorie diet with group meetings was considered • Detailed advice, printed material to illustrate messages and serve as reminders • Logbook, telephone, progress reports, wt measured/ 3 mo	• >30 min/d moderate PA • Nutritionist counseled on PA at visits, reinforced by physician annually; offered supervised progressive resistance training twice/wk • Voluntary group walking and hiking • Telephone contact, progress reports	• Individual counseling: nutritionist; 7 sessions for 1st yr then every 3 mo • Group counseling: voluntary group sessions with a nutritionist; included expert lectures, low fat cooking lessons, visits to supermarkets • Encouraged to quit smoking	• Attention control • Written and oral information on diet and exercise • Completed food diaries prior to annual visits • Advised to decrease energy intake to decrease BMI below 25 kg/m2 with <30% daily energy from fat • Advised to decrease alcohol and smoking as appropriate • General information on benefits of recreational exercise • Annual visits

BMI = body mass index; CHO =carbohydrate; d = day(s); DPP = Diabetes Prevention Program; F&V = fruits and vegetables; FDPS = Finnish Diabetes Prevention Study; hr = hour(s); kcal = kilocalories; lb = pound(s); max = maximum; meds = medications; min = minute(s); mo = month(s); NIH = National Institutes of Health; PA = physical activity; SLIM = Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht; SFA = saturated fatty acids; wk = week(s); wt = weight; x = times

Table 5. Description of lifestyle interventions: metabolic syndrome (continued)

Author, Year	Duration of study; Duration of followup	Diet	Exercise	Counseling or other component(s)	Control group
Pan, 1997, Da Qing[126]	6 yr; 14 yr	• Those with BMI ≥ 25 kg/m² to reduce caloric intake to lose wt at rate of 0.5-1.0 kg/mo to goal BMI of 23 kg/m² • Those with BMI < 25 kg/m² to eat more vegetables, limit alcohol, reduce simple sugars • List of commonly used foods and substitution list provided	• Increased leisure PA by at least 1 unit/d or 2 units/d if < 50 yr	• Individual counseling by physician; individual counseling on daily food intake • Individual goal setting for diet and exercise • Group counseling: all met in small groups (decreasing frequency over time)	• Attention control • Information about diabetes and IGT provided • Given information brochures with general instructions for diet and/or increased leisure PA
Studies with no postintervention followup					
Mensink, 2003, SLIM Trial[121]	3 yr; 0	• Followed Dutch Nutrition Council guidelines • Emphasis on decreasing SFA intake • Wt loss of 5-7% • Log book, 3 d food diary/3 mo • Reduced alcohol intake	• Followed ACSM recommendation: 30 min moderate PA/d, 5 d/wk • Encouraged to attend group exercise sessions • Log book, attendance, asked to participate in program with HR monitor 3 x/yr, 3 d diary/3 mo	• Individual counseling: dietician every 3 mo • Group counseling: dietician at 9, 21, 33 mo • Encouraged to quit smoking	• Attention control • Oral and written information on healthy diet, wt loss, and increasing PA
Oldroyd, 2001[124]	2 yr; 0	• Followed British Diabetic Association guidelines • Encouraged to decrease fat and sugar and increase F&V and fiber intake • Overweight subjects were encouraged to decrease BMI to < 25 kg/m² • Educational material, personal interview	• Graded PA plan designed to achieve 20-30 min aerobic activity 2-3 x/wk • Information on exercise facilities provided; City Card offered (up to 80% discount on use of public leisure facilities)	• Individual counseling: dietitian and physiotherapist; 12 review appointments over 24 mo (gradually decreased frequency of appointments over time)	• Usual/standard care by primary care physician • Asked to live normal day-to-day life during the study

BMI = body mass index; CHO =carbohydrate; d = day(s); DPP = Diabetes Prevention Program; F&V = fruits and vegetables; FDPS = Finnish Diabetes Prevention Study; hr = hour(s); kcal = kilocalories; lb = pound(s); max = maximum; meds = medications; min = minute(s); mo = month(s); NIH = National Institutes of Health; PA = physical activity; SLIM = Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht; SFA = saturated fatty acids; wk = week(s); wt = weight; x = times

Table 5. Description of lifestyle interventions: metabolic syndrome (continued)

Pinkston, 2006[120]	12 mo; 0	• Followed LIFESTEPSr: your personal plan for weight management, 3rd edition, 1998, Dairy Council of Utah, Nevada • Encouraged to decrease calories by at least 500 kcal/d • Goal wt loss 1 lb/wk • Fat intake was 30% of total daily calories • Meal demonstrations of modified traditional foods • Weekly food diary	• Goal to increase PA to 5 x/wk for 30 min for total of ≥150 min/wk • Encouraged to use walking as primary form of PA • Suggestions provided (e.g.: using stairs, taking short walks) • Exercise contracts used to promote PA • Incentives provided for motivation	• Group counseling: bilingual dietician; 24 weekly classes for 1 hr, then gradual tapering of classes • Included problem-solving and role-playing of behavioral change skills (e.g.: identifying difficult eating situations, setting exercise objectives) • Instructed to take 120 mg of orlistat 3 times/d with meals, 1 vitamin/mineral capsule daily	• Wait-list control

BMI = body mass index; CHO =carbohydrate; d = day(s); DPP = Diabetes Prevention Program; F&V = fruits and vegetables; FDPS = Finnish Diabetes Prevention Study; hr = hour(s); kcal = kilocalories; lb = pound(s); max = maximum; meds = medications; min = minute(s); mo = month(s); NIH = National Institutes of Health; PA = physical activity; SLIM = Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht; SFA = saturated fatty acids; wk = week(s); wt = weight; x = times

Table 6. Risk of bias assessment for studies of metabolic syndrome

Author Year	Sequence generation	Allocation concealment	Blinding: Objective outcomes	Blinding: Self-reported outcomes	Incomplete outcome data	Selective outcome reporting	Other sources: Baseline imbalance	Other sources: Funding	Overall risk of bias
Bo 2007[125]	Low	Low	Low	Unclear	Low	Low	Low	Low	Unclear
DPP Research Group 2002[122]	Low	Unclear	Low	Unclear	Unclear	Low	Low	High	High
Eriksson 1999[123]	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Unclear
Mensink 2003[121]	Low	Unclear	Low	High	Unclear	Low	Low	Low	High
Oldroyd 2001[124]	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Unclear
Pan 1997[126]	Unclear	Unclear	Low	Low	Low	Low	Low	Low	Unclear
Pinkston 2006[120]	Unclear	Unclear	Low	High	Low	Low	Unclear	High	High

High = high risk of bias; Low = low risk of bias; Unclear = unclear risk of bias

Breast and Prostate Cancer

Description of Included Studies

Three RCTs[127-129] met our inclusion criteria. There were 6 associated publications.[182-187] One trial[129] included patients with breast and prostate cancer but did not separate the data by type of cancer; therefore, this section presents the results for both types of cancer. We describe the three studies separately (Tables 7 and 8).

Project Leading the Way in Education Against Disease (Project LEAD)[129] by Demark-Wahnefried et al. tested whether a personally tailored telephone counseling program is effective in improving diet and physical activity behavior among early stage breast and prostate cancer patients. There were 104 breast and 78 prostate cancer survivors randomized to either a lifestyle intervention that included a home-based diet and exercise program of telephone counseling and mailed materials or to an active control group that received a mailed workbook and telephone counseling on other health-related areas. The mean age was 71.7±5.0 years. The duration of the intervention was 6 months with a 6 month postintervention followup. The intervention was delivered by a dietician and exercise physiologist.

In the trial by Ornish et al.,[128] 93 men diagnosed with prostate cancer and who had chosen not to undergo any conventional treatment were randomized to either a comprehensive lifestyle change intervention or usual care. Participants in the lifestyle group followed a vegan diet, were asked to do moderate aerobic exercise, learned stress management techniques, and participated in a 1 hour per week support group. Their nutrition education and counseling was provided by a registered dietitian; participants were contacted by phone by a nurse case manager. The control group followed their physicians' advice regarding lifestyle changes. The mean age was 65.7±7.4 years. The duration of the intervention was 1 year with no postintervention followup.

The Reach out to ENhancE Wellness in Older Cancer Survivors (RENEW) study by Morey et al.[127] included overweight participants who were long-term survivors (≥5 years) of breast, prostate, and colorectal cancer. For the purposes of this review, we report only the data for breast and prostate cancer patients (data provided by the authors of the study). There were 250 breast cancer and 225 prostate cancer patients. For 12 months, the intervention group participated in a home-based program based on social cognitive theory and transtheoretical models. They received personally tailored workbooks, quarterly newsletters, telephone counseling, and automated prompts. The intervention was delivered by health counselors. No details were provided on the type of training these individuals had. The control group comprised patients on a wait list; they received the same lifestyle intervention at the end of the study. The mean age was 73.1±5.0 years. The duration of the intervention was 1 year with a planned 1 year followup; however, only immediate postintervention followup data have been reported.

Methodological Quality

The methodological quality of the three RCTs is summarized in Table 9. One trial[128] was assessed at high risk of bias; for two, the risk of bias was unclear.[127,129] All three stated that they were RCTs; one[128] did not describe the sequence generation. One stated that there was concealment of allocation.[127] For the blinding domain, one study[128] was assessed as having a high risk of bias associated with self-reported outcomes such as changes in diet and physical activity; two studies were rated as unclear.[127,129] The studies were at low risk of bias for the remaining components (selective outcome reporting, baseline imbalances or the funding source). Funding was provided by government and foundations.

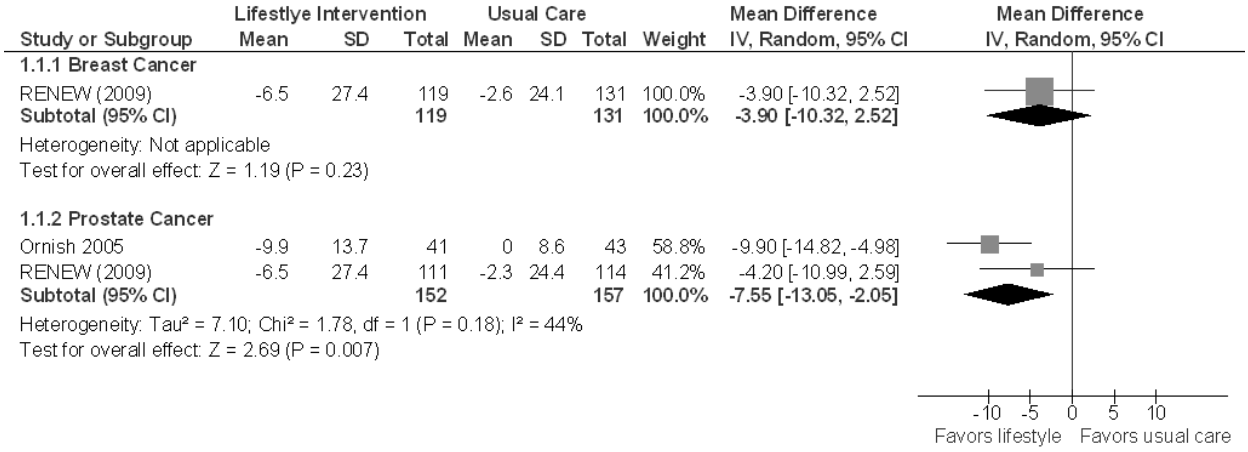
Results

Primary outcome. Our primary outcome was the recurrence of cancer, or for patients with prostate cancer undergoing watchful waiting, a change in PSA levels that required active treatment.

Recurrence of cancer. Ornish et al.[128] reported that at the end of the 12 month intervention serum PSA levels had decreased in the lifestyle intervention group (6.23±1.7 to 5.98±1.7) and had increased in the control group (6.36±1.7 to 6.74±2.1). The difference between the groups was statistically significant in favor of the lifestyle intervention group (MD = -0.63; 95% CI: -1.41, -0.12). Among the control group, six participants underwent conventional therapy, four due to an increase in PSA and two due to progression of prostate cancer. None of the lifestyle group underwent conventional therapy during the study. Demark-Wahnefried et al.[129] and Morey et al.[127] did not report data for this outcome.

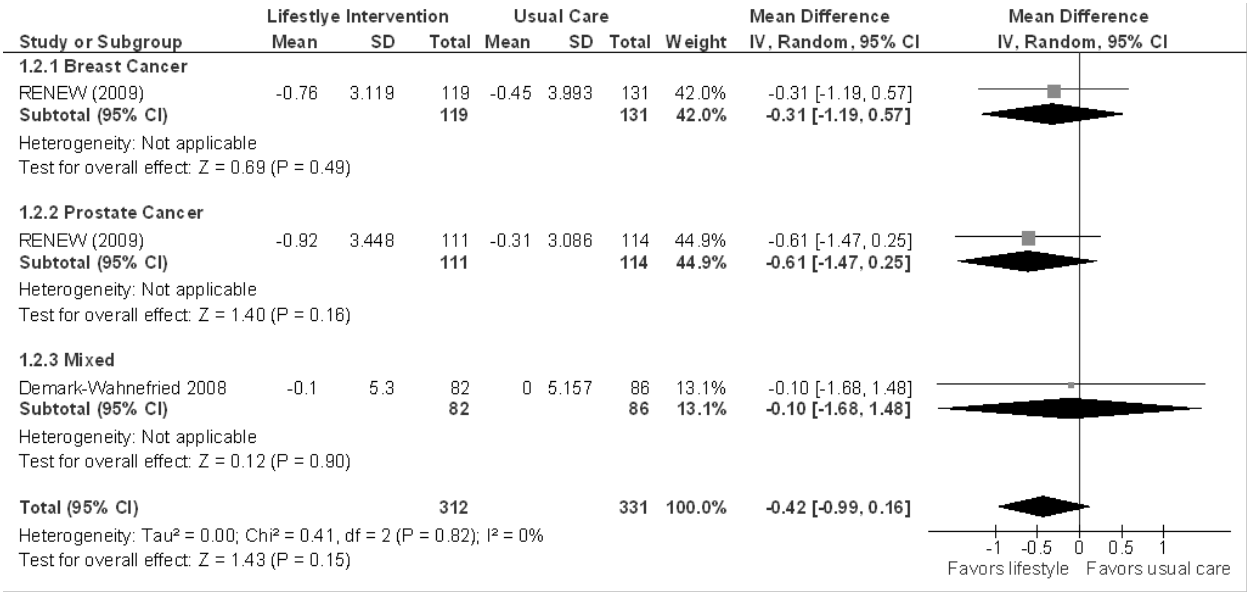
Secondary outcomes. *Change in body composition*. Two studies[127,128] reported weight change (lbs) at end of intervention (Figure 31). For prostate cancer, the pooled estimate reported a statistically significant difference in favor of the lifestyle intervention (MD = -7.55; 95% CI: -13.05, -2.05, I^2=44%). For breast cancer, there was no difference between groups (MD= -3.90; 95% CI: -10.32, 2.52)

Figure 31. Effect of lifestyle interventions vs. control on weight change (lbs): breast or prostate cancer



Two studies reported BMI[127,129] at end of intervention and found no statistically significant difference between groups (Figure 32). One study by Demark-Wahnefried[129] showed no significant difference between groups at 6 month followup (data not presented).

Figure 32. Effect of lifestyle interventions vs. control on change in BMI: breast or prostate cancer



Change in metabolic variables. Ornish et al.[128] was the only study that reported metabolic outcomes. They reported total cholesterol (MD = -34.00; 95% CI: -47.69, -20.31), LDL cholesterol (MD = -28.60; 95% CI: -40.23, -16.97), HDL cholesterol (MD = -6.40; 95% CI: -9.50, -3.30), and triglycerides (MD = -9.00; 95% CI: -38.06, 20.06). A statistically significant difference in favor of the lifestyle intervention was seen in all except triglycerides.

Change in physical activity. Two studies looked at changes in exercise level.[128,129] The difference between groups in changes from baseline to the end of the intervention was statistically significant favoring the lifestyle group (SMD = 0.43; 95% CI: 0.13, 0.72, I^2 = 28%).

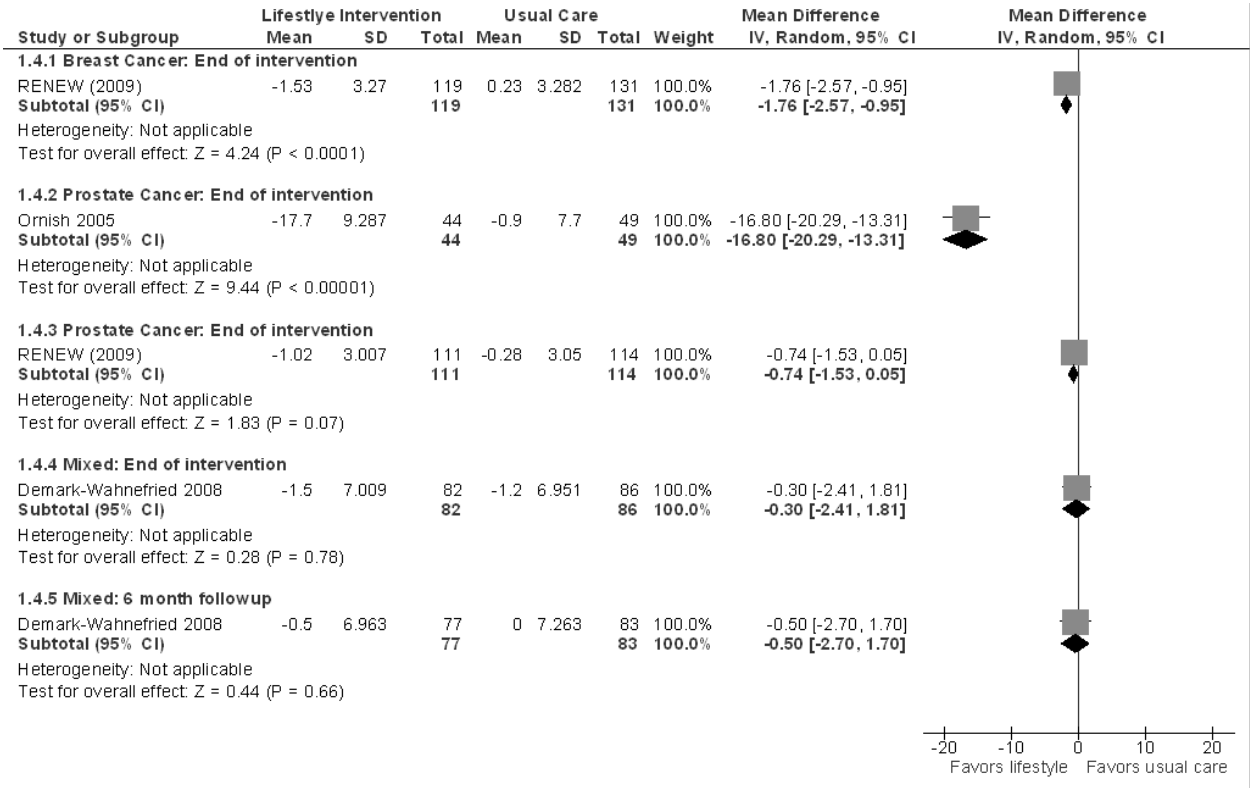
Demark-Wahnefried et al. assessed energy expenditure. There was a statistically significant increase in energy expenditure in favor of the lifestyle intervention at the end of intervention (SMD = 511.11; 95% CI: 20.56, 1001.44). This difference disappeared at the 6 month followup (SMD = -245.0; 95% CI: -813.14, 323.14).

The RENEW study[127] looked at moderate minutes of endurance and strength exercise. The pooled results for both breast and prostate cancer patients for moderate minutes of endurance was statistically significant in favor of the lifestyle intervention (MD = 15.04; 95% CI: 0.09, 29.99; I^2 = 0%). The pooled results for both breast and prostate cancer patients for moderate minutes of strength exercise was also statistically significant in favor of the lifestyle intervention (MD = 21.91; 95% CI: 13.30, 30.51, I^2 = 26%).

The RENEW study[127] also looked at sessions per week of both endurance and strength exercises and reported a significant difference in the breast cancer participants only for both endurance and strength exercises in favor of the lifestyle intervention (MD = 1.17; 95% CI: 0.38, 1.96 for endurance and MD = 1.67; 95% CI: 1.18, 2.16 for strength). There was no significant difference seen in the prostate cancer participants for either types of exercise. The pooled mean difference for sessions per week of endurance exercises for both breast and prostate cancer patients was statistically significant (MD = 0.98; 95% CI: 0.38, 1.59, I^2 = 0%). For sessions per week of strength exercises, the pooled results favored the lifestyle intervention. However, the results were not statistically significant (MD = 1.06; 95% CI: -0.17, 2.29, I^2 = 89%).

Change in dietary or nutrient intake. All three studies[127-129] assessed calories from fat (Figure 33). For breast cancer patients in the RENEW study,[127] there was a statistically significant decrease in calories from fat (MD = -1.76; 95% CI: -2.57, -0.95). In prostate cancer patients, there was a statistically significant decrease in calories from fat only in the study by Ornish et al.[128] (MD = -16.80; 95% CI: -20.29, -13.31). This was not seen in the prostate cancer participants in the RENEW study (MD = -0.74; 95% CI: -1.53, 0.05). There was no significant difference seen in the study by Demark-Wahnefried et al.[129] at the end of intervention or at the 6 month followup.

Figure 33. Effect of lifestyle interventions vs. control on fat consumption (calories): patients with breast or prostate cancer



Two studies[127,129] reported intake of fruits and vegetables. Both breast and prostate cancer participants in the RENEW study, the lifestyle group significantly increased their intake of fruits and vegetables. The MD was 1.08 (95% CI: 0.50, 1.66) for the breast cancer participants and 1.40 (95% CI: 0.75, 2.05) for the prostate cancer participants. There was no statistical difference seen in the study by Demark-Wahnefried et al.[129] at the end of intervention or at the 6 month followup. The overall pooled MD of 0.95 (95% CI: 0.39, 1.52; $I^2 = 61\%$) shows a statistically significant increase of fruits and vegetables favoring the lifestyle intervention.

Demark-Wahnefried et al.[129] also reported a Diet Quality Index. There was a statistically significant difference in favor of the lifestyle intervention at the end of intervention. The MD was 5.10 (95% CI: 1.04, 9.16). This difference was not seen at the 6 month followup (MD = 0.80; 95% CI: -3.20, 4.80).

Compliance with the intervention. Compliance was measured by withdrawals/dropouts from the studies. There was no statistical difference seen in the studies by Ornish et al.[128] and Demark-Wahnefried et al.[129] The pooled MD was 1.01 (95% CI: 0.53, 1.94; $I^2 = 0\%$). The RENEW study did not report withdrawals separated by group.

Adverse events. The RENEW study reported five adverse events.[127] One participant had increased blood pressure with exercise and four experienced hip pain during exercise, a pulled hamstring, a fall during hiking, or calf pain and stiffness using the exercise bands. The study

stated that there was no difference between the intervention and control groups regarding the number of adverse events.

Summary

Three RCTs[127-129] assessed the effectiveness of lifestyle interventions for breast and prostate cancer. The following is a summary of results:

- *Primary outcomes.* One study assessed our primary outcome of PSA levels in prostate cancer participants. There was a significant decrease in levels for lifestyle intervention participants. The strength of evidence for this outcome is insufficient.
- *Change in body composition.* Two studies reported change in weight (lbs) at end of intervention. There was no difference between groups for breast cancer patients but a statistically significant difference favoring the lifestyle group for prostate cancer patients. Two studies reported change in BMI (kg/m^2) and showed no statistically significant difference between groups for breast, prostate, and mixed cancer populations. The strength of evidence for change in BMI or weight is insufficient.
- *Change in metabolic variables.* One study reported metabolic outcomes. A statistically significant difference in favor of the lifestyle intervention was seen for total cholesterol, and HDL and LDL cholesterol. The strength of evidence is insufficient.
- *Change in physical activity.* Two studies looked at changes in exercise level. The difference between groups at end of intervention was statistically significant favoring the lifestyle group. One study reported a statistically significant increase in energy expenditure in favor of the lifestyle intervention at the end of intervention; this difference was no longer present at 6 month followup. One study looked at moderate minutes of endurance and found no statistically significant difference between the groups for both breast and prostate cancer patients. The strength of evidence is insufficient for all outcomes.
- *Change in dietary or nutrient intake.* All three studies[127-129153,154,525153,154,525153,154,526127-12948,140,152127-129] assessed calories from fat. In two studies there was a statistically significant decrease in calories from fat in breast cancer and prostate cancer patients. One study showed no difference between groups in the mixed breast and prostate cancer populations at end of intervention and 6 month followup.
- *Compliance with intervention.* Two studies showed no statistically significant difference between groups. One study did not report withdrawals separated by group.
- *Adverse events.* One study stated that there was no difference between the intervention and control groups regarding the number of adverse events.
- One trial was assessed as high risk of bias; two were unclear. The most common sources of potential bias were inadequate allocation concealment and inadequate blinding.

Table 7. Description of studies and baseline characteristics of participants: breast and prostate cancer

Author, Year, Study name	Randomized (N); Withdrawals (N)	Age (mean ± SD); Ethnicity	Socioeconomic status; Education (%≤ high school); Smokers: (%)	Weight (kg); BMI (km/m^2); Waist circumference (cm)	Type of prostate cancer; Time since diagnosis (yrs); Time since treatment (yrs); Mean Gleason score (sum); PSA levels (ng/ml)	Type of breast cancer; Time since diagnosis (yrs); Time since treatment (yrs)
Demark-Wahnefried, 2006, Project LEAD[129]	I: 89; 12 C: 93; 10	I: 71.5±4.4; 82.0 White,14.6 Black, 3.4 Other C: 71.9±5.6; 82.8 White, 15.0 Black, 2.2 Other	I: 10.1 earn <$12,000 per year; 29.2; 13.5 C: 8.6 earn <$12,000 per year; 36.6; 5.4	I: NR; 27.7±5.3; NR C:NR; 28.3±5.3; NR Total: 71% had BMI≥25.0	I: Locoregional; ≤ 1.5 yrs; NR; NR C: Locoregional; ≤ 1.5 yrs; NR; NR; NR	I: Locoregional; ≤ 1.5 yrs; NR C: Locoregional; ≤ 1.5 yrs; NR
Ornish, 2005, PCL Trial[128]	I: 44; 4 C: 49; 7	I: 64.8±7.1; 84.1 White, 6.8 Black, 9.1 Other C:66.5±7.6; 96 White, 2 Black, 2 Other	I: NR; 6; NR C: NR; 4; NR	I: 80.0±13.6 26.0±4.2 NR C: 80.0±11.3 25.9±4.2 NR	I: Biopsy with Gleason score < 7, serum PSA 4-10ng/ml and stages T1 and T2 disease; NR; have refused conventional tx; 5.7±0.5; 6.32±1.72 C: Biopsy with Gleason score < 7, serum PSA 4-10 ng/ml and stages T1 and T2 disease; NR; have refused conventional tx; 5.7±0.7; 6.28±1.66	NA
Morey, 2009, RENEW (Breast)[127]	I: 119 C: 131 Total withdrawals: 83	I: 71.84±5.00; 89.0; White, 10.92 Other C: 72.20±4.77; 86.26 White, 13.74 Other	I: NR; 55.46 any college education; 3.36 C: NR; 54.96 any college education; 5.34	I: 78.28±9.16; 28.97±2.97; NR C: 78.88±10.57; 29.40±3.90; NR	NA	I: *In situ*, localized, regional; ≥5 years; NR C: *In situ*, localized, regional; ≥5 years; NR
Morey, 2009, RENEW (Prostate)[127]	I: 111 C: 114 Total withdrawals: 83	I: 73.98±1.72; 90.99 White, 9.01 Other C: 73.68±4.96; 91.23 White, 8.77 Other	I: NR; 73.87 any college education; 5.51 C: NR; 72.81 any college education; 8.77	I: 94.33±12.74; 29.20±3.53; NR C: 90.51±10.86; 28.39±3.04; NR	I: *In situ*, localized, regional; ≥5 years; NR; NR; NR C: *In situ*, localized, regional; ≥5 years; NR; NR; NR	NA

BMI = body mass index; Br = breast cancer; mo = month(s); LEAD = Leading the Way in Exercise and Diet; NR = not reported; PCL = Prostate Cancer Lifestyle; RENEW = Reach Out to Enhance Wellness; tx = treatment

Table 8. Description of lifestyle intervention for breast and prostate cancer studies

Author, Year, Study name	Duration of intervention; followup	Diet	Exercise	Counseling or other component(s)	Control group
Demark-Wahnefried, 2006, Project LEAD[129]	6 mo; 6 mo	• Followed US National Guidelines • Home-based diet program: increased diet diversity, F&Vs, whole grains; decreased total fat, SFA, cholesterol; adequate iron and calcium • Workbook, telephone contact, tailored mailed materials	• Home-based exercise program: specific exercises tailored to functional limitations • Recommendation of ≥30 min of moderate PA on 5 or more days • Pedometer, logbook, workbook, telephone contact, tailored mailed materials	• Individual counseling: 12 telephone calls for 6 mo; dietician first 3 mo, exercise physiologist for next 3 mo to improve PA • Counselors helped to achieve behavioral goals	• Attention control • Health promotion materials (not tailored and unrelated to diet and exercise) • Bi-monthly telephone counseling for 6 mo on general health topics
Ornish, 2005, PCL Trial[128]	12 mo; 12 mo	• Followed vegan diet; predominately F&V, whole grains, legumes and soy products, low in simple CHO with approx 10% of calories from fat; supplemented with fish oil, vitamin E, selenium and vitamin C • Met with dietitian and chef to learn food preparation techniques • Telephone contact, mailings	• Moderate aerobic PA; walking 30 min 6 d/wk • Telephone contact, mailings	• Individual counseling: RD for nutrition education; nurse case manager for telephone contact weekly for first 3 mo, 1/ mo after • Group-based counseling: 1-hr weekly support group • Stress management: yoga based stretching, breathing, meditation, imagery and progressive relaxation; 60 min daily	• Usual/standard care by primary care physician
Morey, 2009, RENEW[127]	12 mo; 0	• Followed U.S. National Guidelines • Home-based diet program: increased F&Vs, <10% of calories from SFA • Personalized record logs, automated telephone prompts, quarterly progress reports	• Home-based exercise program: aerobic goal of 30 min/d, 15 min strength exercises every other d • Pedometer, Therabands, exercise poster, personalized record logs, telephone prompts, progress reports 4/yr	• Individual counseling: counselor, 15 sessions via telephone for 15-30 min including behavioral modification and goal setting	• Wait-list control

approx = approximately; CHO =carbohydrate; d = day(s); F&V = fruits and vegetables; LEAD = Leading the Way in Exercise and Diet; min = minute(s); mo = month(s); PA = physical activity; PCL = Prostate Cancer Lifestyle; RD = registered dietitian; RENEW = Reach Out to Enhance Wellness; SFA = saturated fatty acids; wk = week(s)

Table 9. Risk of bias assessment for studies of breast or prostate cancer

Author Year	Sequence generation	Allocation concealment	Blinding: Objective outcomes	Blinding: Self-reported outcomes	Incomplete outcome data	Selective outcome reporting	Other sources: Baseline imbalance	Other sources: Funding	Overall risk of bias
Demark-Wahnefried 2006[129]	Low	Unclear	Low	Unclear	Low	Low	Low	Low	Unclear
Morey 2009[127]	Low	Low	Low	Unclear	Low	Low	Low	Low	Unclear
Ornish 2005[128]	Unclear	Unclear	Low	High	Unclear	Low	Low	Low	High

High = high risk of bias; Low = low risk of bias; Unclear = unclear risk of bias

Key Question 2. What is the generalizability of the evidence to the Medicare population (> 65 years)?

Type 2 diabetes. The trials included a wide range of patients including varying comorbidities and nationalities. The mean ages from the 10 trials ranged from 53 to 62 years and included participants up to 75 years old. The majority of these addressed our secondary outcomes, thus we believe that the results for our secondary outcomes should be generalizable to individuals aged 65 years or older. Two trials excluded patients over the age of 65 years,[117,119] including the only study[119] that provided data for our primary outcomes. Therefore, we are uncertain whether the results for our primary outcomes (progression of diabetes, progression to micro- or macrovascular complications) are generalizable to the Medicare population.

Metabolic syndrome. The mean ages from the seven trials ranged from 44 to 58 years and included participants up to 85 years of age. Two trials excluded patients over the age of 65 years,[123,125] including studies that provided data for our primary outcomes. Therefore, we are uncertain whether the results for our primary outcomes (progression to diabetes or cardiovascular events) are generalizable to the Medicare population. For our secondary outcomes, we believe that the results should be generalizable to individuals aged 65 years or older.

Breast and prostate cancer. The mean age of participants in the three trials ranged from 65 to 75 years. Therefore, the results from these studies should be generalizable to the Medicare population.

Key Question 3. What is the evidence on whether specific components of the interventions, composition of the team, and/or patient characteristics contribute to better outcomes?

We were unable to address this question due to insufficient data.

Chapter 4. Discussion

Type 2 Diabetes Mellitus

Ten RCTs met our inclusion criteria for assessing the effectiveness of lifestyle interventions in patients with type 2 diabetes. Two of the trials reported results for one of our primary outcomes of progression to microvascular or macrovascular complications. See Table 10 for a summary of the findings and Appendix E for GRADE assessments.

The Steno-2 trial,[119] which looked at multifactorial, intensive treatment of diabetic patients with microalbuminuria was designed with a primary outcome of nephropathy and secondary endpoints of retinopathy and neuropathy. At 4 years, significant improvement in microvascular outcomes including nephropathy, retinopathy, and autonomic neuropathy was observed. These findings were maintained over 13 years. Eight years following initiation of the intervention, the authors reported a statistically significant reduction in cardiovascular events, primarily from a reduction in non-fatal MIs, in the treatment group. The reported number needed to treat (NNT) was five. The strength of evidence is low.

Despite intensive lifestyle interventions and improvement in cardiovascular outcomes, the trial did not maintain significant changes in most lifestyle behaviors at 8 or 13 years. In addition, while benefit was initially seen for a number of cardiovascular risk factors, this was not maintained. The majority of patients also did not achieve target levels. Nonetheless, at 13 years, statistically significant decreases in total mortality, cardiovascular mortality, and composite cardiovascular endpoints were reported in the intensive treatment group (38 percent, 54 percent, and 60 percent, respectively).[188] These are arguably the most patient-important outcomes. The strength of evidence is low.

The mechanism by which benefit occurs despite normalization of cardiac risk factors and limited behavioral change is not entirely clear. Trials in type 1 diabetes have demonstrated that early intensive treatment results in an extended benefit in delaying the progression of diabetic outcomes beyond the intervention.[189,190] It is important to note however that this trial included medication use as part of its intensive treatment arm which may have overestimated the benefits of lifestyle intervention.

The Look AHEAD trial[112] also addressed our primary outcome and was designed to assess cardiovascular morbidity and mortality in type 2 diabetes. At 4 years, significant improvements were reported in a number of cardiovascular risk factors with intensive lifestyle intervention and these results are similar to those in the majority of trials included in this review.

Across the trials, methods of reporting of changes in weight were not consistent. While some reported weight change, others reported change in BMI. The Look AHEAD trial reported weight change as a percentage of initial weight. Despite these differences, results were consistent. The pooled mean difference (MD) of each measurement (weight change and BMI) was statistically significant in favor of lifestyle intervention. Similarly, the Look AHEAD trial found a statistically significant change in weight in the intervention group after 1 year and after 4 years of intervention.[191] However, the Look AHEAD trial also employed medication directly targeted for weight loss in those who failed to lose 10 percent of their initial weight. Given that many patients with diabetes require insulin therapy, which is usually associated with weight increases,[192] maintenance of stable weight is a positive outcome. It is notable that those

interventions that included pharmacotherapy not specifically targeted to weight loss as part of the lifestyle intervention[113,119] were unable to demonstrate significant weight loss. However, as exercise was a component of all interventions, it is also possible that change in body composition may have affected the amount of weight lost. It is noteworthy that none of the trials found that the change in weight persisted following the end of the intervention. This is consistent with previous research suggesting that diabetic patients demonstrate poor weight loss maintenance following an intervention compared with their non-diabetic counterparts.[193]

All studies reported a number of metabolic variables. Sensitivity analyses demonstrated improvement in some metabolic outcomes including HDL and glycemic control in those interventions that included targeted pharmacotherapy; however, no statistical improvement in any metabolic variable was noted for those interventions that did not include pharmacotherapy. . In trials that did not include medication as part of the intervention, the impact of diet and lifestyle alone is difficult to tease out as the control groups in many trials received at minimum the "standard of care," which includes pharmacotherapy.

Lifestyle interventions appear to be beneficial in increasing physical activity levels in the short term, and in a number of trials this benefit persisted beyond the initial intervention. The Steno-2 trial was the only trial reporting no change in activity at followup even though it reported improvements in cardiovascular outcomes. The interventions and methods of reporting physical activity levels were heterogeneous across studies and many were subject to possible reporting bias. The Look AHEAD trial reported change in fitness as opposed to physical activity levels as an outcome and found that it was significantly improved in the intervention group after 1 year. Other trials such as the one by Vanninen et al.[117] reported both changes in physical activity and aerobic capacity. While not analyzed in this review, reporting of fitness levels may help offset the potential bias of personal reporting of physical activity levels.

The impact of lifestyle interventions on dietary intake is not as clear, and also may be subject to reporting bias. Energy intake seems to decrease in the short term, although this improvement does not appear to be sustained beyond the intervention.

Changes in medication potentially reflect overall diabetic control, with increases in the numbers of oral hypoglycemic agents (OHAs) or progression to insulin representing worsening control. However, it is also possible that increased medications may simply reflect an intensive intervention that aims for stricter control of certain diabetic indices. Only two trials[113,119] reported medication use, and at the end of both interventions, no significant difference was noted in OHAs or insulin.

A number of trials have demonstrated benefit with single risk factor interventions, such as those to improve blood pressure, lipids, or glycemic control, or to reduce both macrovascular and microvascular complications in type 2 diabetes.[41,46,194-196] Pharmacotherapy, exercise, and dietary changes have all been shown to have a positive impact on glycemic control and other diabetic indices,[197,198] and there is growing evidence for an additive effect when multiple risk factors are addressed together.[199] Few studies have evaluated the impact of diet and exercise plus at least one other intervention.

The Steno-2 trial is the only completed trial to report on the progression to type 2 diabetic outcomes. Unfortunately the sample size was small, and the trial was assessed as having an unclear risk of bias. It does, however, underscore the probability of additional, long-term benefits of a multifactorial intervention in improving patient oriented outcomes in high risk diabetic patients. These results have not been replicated, thus the results of the Look AHEAD trial will be

important in validating these findings. It is important to note, however, that targeted pharmacotherapy is part of the lifestyle intervention for both trials.

There remain a number of questions regarding which lifestyle interventions are most effective. None of the trials included in this review were designed to assess this. Improvement in secondary outcomes was seen in trials that utilized more intensive interventions,[113,114] and those that employed brief interventions.[110] In addition, while statistical improvement was seen for some secondary outcomes, the clinical significance of this is unclear. There was considerable variability among the studies with regard to the dietary and lifestyle interventions. There is currently no consensus on optimal behavioral regimens. In addition, it remains unclear which interventions are sustainable over the long term. There was limited success in the achievement of permanent lifestyle changes. Long-term change is dependent on a number of factors including patient motivation and compliance. In our review we measured compliance by the number of withdrawals. Overall, there were more withdrawals in the lifestyle group, although this was not statistically significant. A true measure of compliance with lifestyle intervention is complex, particularly when a number of trials rely on self-reported data. One of the central objectives of therapeutic lifestyle interventions is to modify and shape healthy lifestyle behaviors over the long term. Improved measurement and reporting of this outcome would be beneficial for the development of future interventions.

Table 10. Summary table: type 2 diabetes

Outcome	# RCTs	Strength of evidence	Summary
Primary outcomes			
All-cause mortality (13 yr followup)	1	Low	Significant effect in favor of lifestyle intervention (RR_{meds} = 0.60; 95% CI: 0.4, 0.9)
Cumulative incidence of CVD events (13 yr followup)	1	Low	Significant effect in favor of lifestyle intervention (RR_{meds} = 0.49; 95% CI: 0.34, 0.71)
Autonomic neuropathy progression (13 yr followup)	1	Low	Significant effect in favor of lifestyle intervention (RR_{meds} = 0.75; 95% CI: 0.57, 0.99)
Development of nephropathy (13 yr followup)	1	Low	Significant effect in favor of lifestyle intervention (RR_{meds} = 0.54; 95% CI: 035, 0.85)
Development of retinopathy (13 yr followup)	1	Low	Significant effect in favor of lifestyle intervention (RR_{meds} = 0.76; 95% CI: 0.58, 0.99)
Peripheral neuropathy progression (13 yr followup)	1	Low	No significant difference between groups (RR_{meds} = 0.96; 95% CI: 0.73, 1.26)
Change in body composition			
BMI (EoI)	5	Moderate	Significant effect in favor of lifestyle intervention (MD_{all} = -0.48; 95% CI: -0.92, -0.05)
BMI (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = 1.0; 95%CI: -1.84, 3.84)
BMI (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -1.1; 95% CI: -3.14, 0.94)
Weight change (EoI)	5	Moderate	No significant difference between groups ($MD_{no\ meds}$ = -1.53; 95% CI: -2.09, -0.97; MD_{meds} = -15.4; 95% CI: -16.1, -14.5)
Weight change (6 mo postintervention)	1	Insufficient	Effect favors usual care, though not significantly (RR_{meds} = 1.14; 95% CI: -5.39, 7.67)
Weight change (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -11.62; 95% CI: -12.37, -10.87)
Metabolic variables			
Fasting plasma glucose (EoI)	4	Low	Significant effect in favor of lifestyle intervention ($MD_{no\ meds}$ = -0.33; 95% CI: -0.83, 1.49; MD_{meds} = -1.02; 95% CI: -1.85, -0.19)
Fasting plasma glucose (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -1.0; 95% CI: -2.61, 0.61)
Fasting plasma glucose (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds}= -0.16; 95% CI: -1.47, 1.15)
HbA1c (EoI)	10	Low	Significant effect in favor of lifestyle intervention ($MD_{no\ meds}$ = -0.09; 95% CI: -0.58, 0.75; MD_{meds} = 0.77; 95% CI: -1.18, -0.36)
HbA1c (6 mo postintervention)	2	Insufficient	No significant difference between groups (MD_{all} = 0.09; 95% CI: -0.58, 0.75)
HbA1c (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -0.70; 95% CI: -1.41, 0.01)

BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; EoI = end of intervention; HbA1c = glycosylated haemoglobin; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; mo = month(s); RCT = randomized controlled trial; RR = risk ratio; SFA = saturated fatty acid; SMD = standardized mean difference; yr = year(s)

Table 10. Summary table: type 2 diabetes (continued)

Outcome	# RCTs	Strength of evidence	Summary
HDL cholesterol (EoI)	6	Low	Significant effect in favor of lifestyle intervention ($MD_{no\ meds}$ = -0.01; 95% CI: -0.04, 0.05; MD_{meds} = 0.05; 95% CI: 0.03, 0.07)
HDL cholesterol (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion ($MD_{no\ meds}$ = -0.04; 95% CI: -0.16, 0.09)
HDL cholesterol (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = 0.08; 95% CI: -0.07, 0.22)
LDL cholesterol (EoI)	5	Low	No significant difference between groups ($MD_{no\ meds}$ = -0.09; 95% CI: -0.26, 0.08; MD_{meds} = -0.27; 95% CI: -0.92, 0.37)
LDL cholesterol (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -0.59; 95% CI: -1.07, -0.11)
LDL cholesterol (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds}= -0.05; 95% CI: -0.4, 0.3)
Total cholesterol (EoI)	5	Low	No significant difference between groups (MD_{all} = -0.13; 95% CI: -0.27, 0.01),
Total cholesterol (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion ($MD_{no\ meds}$ = 0.01; 95% CI: -0.35, 0.36)
Total cholesterol (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = 0.38; 95% CI: -0.06, 0.82)
Triglycerides (EoI)	5	Low	Significant effect in favor of lifestyle intervention (MD_{all} = -0.17; 95% CI: -0.23, -0.12)
Triglycerides (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -0.18; 95% CI: -1.47, 1.11)
Triglycerides (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -0.03; 95% CI: -0.67, 0.61)
Blood pressure			
Diastolic BP (EoI)	6	Low	No significant difference between groups ($MD_{no\ meds}$ = 0.32; 95% CI: -1.43, 20.7; MD_{meds} = -1.2; 95% CI: -1.75, 0.65)
Diastolic BP (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = 0; 95% CI: -5.07, 5.07)
Diastolic BP (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = 2.0; 95% CI: -1.90, 5.90)
Systolic BP (EoI)	6	Low	No significant difference between groups ($MD_{no\ meds}$ = -1.89; 95% CI: -0.57, 4.35; MD_{meds} -6.89; 95% CI: -14.42, 0.64)
Systolic BP (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -3.0; 95% CI: -12.4, 6.4)
Systolic BP (13 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD_{meds} = -3.0; 95% CI: -9.79, 3.79)
Change in physical activity			
Exercise (EoI)	6	Low	Significant effect in favor of lifestyle intervention (SMD_{all} = 0.45; 95% CI: 0.2, 0.71)
Exercise (6 mo postintervention)	4	Low	Significant effect in favor of lifestyle intervention (SMD_{all} = 0.5; 95% CI: 0.1, 0.89)
Exercise (2 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion ($SMD_{no\ meds}$ = 0.41; 95% CI: 0.16, 0.67)

BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; EoI = end of intervention; HbA1c = glycosylated haemoglobin; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; mo = month(s); RCT = randomized controlled trial; RR = risk ratio; SFA = saturated fatty acid; SMD = standardized mean difference; yr = year(s)

Table 10. Summary table: type 2 diabetes (continued)

Exercise (8 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD_{meds} = 0.11; 95% CI: -0.24, 0.45)
Change in dietary or nutrient intake			
Energy intake (EoI)	5	Low	Significant effect in favor of lifestyle intervention (SMD_{all} = -0.17; 95% CI: -0.33, -0.01)
Energy intake (6 mo postintervention)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD_{meds} = -0.12; 95% CI: -0.59, 0.36)
Energy intake (8 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD_{meds} = 0; 95% CI: -0.35, 0.34)
SFA intake (EoI)	5	Low	No significant difference between groups (SMD_{all} = -0.31; 95% CI: -0.68, 0.07)
SFA intake (6 mo postintervention	2	Insufficient	Significant effect in favor of lifestyle intervention (SMD_{all} = -0.45 95% CI: -0.79, -0.10)
SFA intake (8 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD_{meds} = -0.68; 95% CI: -1.03, -0.32)

BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; EoI = end of intervention; HbA1c = glycosylated haemoglobin; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; mo = month(s); RCT = randomized controlled trial; RR = risk ratio; SFA = saturated fatty acid; SMD = standardized mean difference; yr = year(s)

Metabolic Syndrome

Seven studies met our inclusion criteria for our operational definition of metabolic syndrome. See Table 11 for a summary of the findings and Appendix E for GRADE assessments.

Four trials looked at progression to type 2 diabetes (DPP,[122,166] FDPS,[123] Da Qing,[126] Bo et al.[125]), and all reported a significant reduction in the development of type 2 diabetes with comprehensive lifestyle intervention at timepoints ranging from 1 year to 10 years following the initiation of the intervention. Bo et al. reported a NNT of 19 to prevent one patient progressing to diabetes; the DPP reported a NNT of 7 over 3 years; and the FDPS reported a NNT of five over 4 years. The strength of evidence is moderate. Interestingly, the DPP found that lifestyle interventions were more effective than metformin in preventing the onset of type 2 diabetes during the active intervention phase. Since a diagnosis of diabetes is associated with a significant increase in cardiovascular risk, this is an important outcome. These findings are consistent with those of other reviews that have reported significant benefit of lifestyle intervention in the prevention of type 2 diabetes.[200,201]

There were some differences in the baseline characteristics of the different study populations. Some trials included patients with impaired glucose tolerance (DPP) while others assessed patients with a predefined “dysmetabolic syndrome” (Bo et al.), although all are at increased risk of developing diabetes.

Two trials reported on cardiovascular outcomes and overall mortality and neither found a statistically significant difference between lifestyle interventions and usual care following the initial intervention period nor at followup over 10 (DPS) to 20 years (Da Qing). The result contrasts with the Steno-2 trial which demonstrated long-term benefit on clinical outcomes with lifestyle intervention; however, the Steno 2 trial assessed high risk diabetic patients (with microalbuminuria), whereas the DPS and Da Qing trials included those who had not yet been diagnosed with diabetes and were at lower risk for macrovascular complications. As a result, the statistical power may not have been sufficient to detect a difference. In addition, the Steno 2

utilized intensive pharmacotherapy in the intervention group. The strength of evidence for the impact of lifestyle interventions on cardiovascular disease and mortality is insufficient.

The Diabetes Prevention Program Outcomes Study,[166] which involves long-term followup of patients in the Diabetes Prevention Program, has reported plans for further followup in 2014. Perhaps this will shed further light on whether prevention or delay of diabetes is associated with a delay in development of diabetic complications. In view of the strong relationship between hyperglycemia and long-term diabetes complications, the hypothesis that preventing or delaying the onset of diabetes would also prevent or delay macrovascular and microvascular complications seems reasonable.

Similar to the results for type 2 diabetic patients, lifestyle interventions in patients with metabolic syndrome and/or prediabetes resulted in a significant decrease in body weight, BMI, or percentage of body weight. In contrast to the findings in patients with type 2 diabetes, this effect persisted for up to 4 years beyond the intervention period. It is unclear if the weight loss is easier to maintain in those who have not yet progressed to diabetes. If this were the case, it would underscore the importance of identifying those at risk of developing diabetes and intervening early.

Lifestyle interventions also improve cardiovascular risk factors more than usual care, although the differences were not always statistically significant. Changes in physical activity and diet were also found to be improved with comprehensive lifestyle interventions.

While lifestyle interventions have demonstrated benefit in patients at risk for developing diabetes, the implementation of lifestyle interventions faces a number of barriers. The DPP, for example, was very time and resource intensive and could be difficult to implement on a large population basis.[202] The intervention by Bo et al. was intentionally less intensive, and yet maintained a significant reduction in the progression to diabetes in the intervention group.

Patient adherence is another barrier to successful implementation of lifestyle changes. Overall, there was no statistically significant difference in dropout rates between the groups in this review. Because much of the measurement in lifestyle interventions relies on self-reported data, true measures of compliance are difficult to obtain. Bo et al. reported a weak positive correlation between the number of metabolic syndrome components at baseline and patient compliance: the average number of sessions attended increased from 4.1 for those with two components to 4.5 for those with four or more components (p for trend test = 0.28).

There was also significant variability associated with program composition and administration. In particular, the third component of the intervention was variable, limiting our ability to comment on which additional interventions would be beneficial. It is difficult to determine if diet, exercise, and at least one other component had a benefit over diet and exercise alone. Systematic reviews that have assessed diet and exercise included a number of trials that overlap with our review.[201] We considered interventions such as smoking cessation, stress reduction, group therapy, and behavior modification as separate components, whereas other reviews may have viewed them as part of the diet and exercise intervention.

Table 11. Summary table: metabolic syndrome

Outcome	# RCTs	Strength of evidence	Precision
Primary outcomes			
CVD events (Followup: 6-10 yr)	2	Insufficient	The evidence was too limited to draw a conclusion (RR = 1.02; 95% CI: 0.73, 1.42) (HR = 0.96; 95% CI: 0.76-1.44)
CVD events (20 yr)	1	Insufficient	No significant difference between groups (HR = 0.98; 95% CI: 0.71-1.37)
Development of type 2 diabetes (EoI: duration 1-6 yr)	3	Moderate	Significant effect in favor of lifestyle intervention (RR = 0.44; 95% CI: 0.2, 0.93)
Development of type 2 diabetes (Followup: 4-10 yr)	3	Moderate	Significant effect in favor of lifestyle intervention ($RR_{4\ yr}$ = 0.56; 95% CI: 0.48, 0.64; $RR_{6\ yr}$ = 0.44; 95% CI: 0.29, 0.68)
Death (Followup: 10-20 yr)	2	Insufficient	The evidence was too limited to draw a conclusion ($RR_{10\ yr}$ = 0.58; 95% CI: 0.21, 1.57; $HR_{20\ yr}$ = 0.83; 95% CI: 0.48, 1.40)
Body Composition			
BMI (EoI)	4	Moderate	Significant effect in favor of lifestyle intervention (MD = -0.95; 95% CI: -1.49, -0.41)
BMI (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.92; 95% CI: -1.32, -0.53)
Waist circumference (EoI)	5	Moderate	Significant effect in favor of lifestyle intervention (MD = -3.73; 95% CI: -4.87, -2.59)
Waist circumference (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD= -1.86; 95% CI: -3.49, -0.22)
Weight change (EoI)	6	Moderate	Significant effect in favor of lifestyle intervention (MD = -7.8; 95% CI: -11.92, -3.67)
Weight change (4 yr followup)	2	Low	The evidence was too limited to draw a conclusion (MD = -5.88; 95% CI: -8.05, -3.71)
Weight change (10 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.94; 95% CI: -5.07, 3.19)
Metabolic variables			
Fasting plasma glucose (EoI)	5	Moderate	Significant effect in favor of lifestyle intervention (MD = -0.29; 95% CI: -0.35, -0.23)
Fasting plasma glucose (10 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 0.10; 95% CI: 0.03, 0.18)
HbA1c (EoI)	2	Insufficient	No significant difference between groups (MD = -0.10; 95% CI: -0.28, 0.08)
HbA1c (10 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.05; 95% CI: -0.09, -0.02)
HDL cholesterol (EoI)	4	Moderate	Significant effect in favor of lifestyle intervention (MD = 0.08; 95% CI: 0.05, 0.10)
HDL cholesterol (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 0.05; 95% CI: 0.0, 0.10)

BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; EoI = end of intervention; HbA1c = glycosylated haemoglobin; HDL = high density lipoprotein; HR = hazard ratio; LDL = low density lipoprotein; MD = mean difference; mo = month(s); RCT = randomized controlled trial; RR = risk ratio; SFA = saturated fatty acid; SMD = standardized mean difference; yr = year(s)

Table 11. Summary table: metabolic syndrome (continued)

Outcome	# RCTs	Strength of evidence	Precision
Impaired plasma glucose (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 0.34; 95% CI: 0.23, 0.52)
LDL cholesterol (EoI)	3	Low	No significant difference between groups (MD = 0.04; 95% CI: -0.16, 0.25)
Total cholesterol (EoI)	5	Low	No significant difference between groups (MD = 0.0; 95% CI: -0.12, 0.13)
Triglycerides (EoI)	4	Low	No significant difference between groups (MD = -0.11; 95% CI: -0.26, 0.04)
Triglycerides (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 0.09; 95% CI: -0.22, 0.05)
Blood pressure			
Diastolic BP (EoI)	5	Moderate	Significant effect in favor of lifestyle intervention (MD=-2.70; 95% CI: -3.21, -2.18)
Diastolic BP (4 yr followup)	2	Low	The evidence was too limited to draw a conclusion (MD =-1.88; 95% CI: -2.65, -1.12)
Systolic BP (EoI)	5	Moderate	Significant effect in favor of lifestyle intervention (MD =-3.17; 95% CI: -5.02, -1.33)
Systolic BP (4 yr followup)	2	Low	The evidence was too limited to draw a conclusion (MD =-4.41; 95% CI: -8.47, -0.35)
Change in physical activity			
Exercise (EoI)	4	Moderate	Significant effect in favor of lifestyle intervention (SMD = 0.40; 95% CI: 0.2, 0.59)
Exercise (4 yr followup)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD = 0.23; 95% CI: 0.10, 0.35)
Change in dietary or nutrient intake			
Energy intake (EoI)	4	Moderate	Significant effect in favor of lifestyle intervention (SMD = -0.23; 95% CI: -0.31, -0.16)
SFA intake (EoI)	2	Low	Significant effect in favor of lifestyle intervention (SMD = -0.53; 95% CI: -0.73, -0.34)

BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; EoI = end of intervention; HbA1c = glycosylated haemoglobin; HDL = high density lipoprotein; HR = hazard ratio; LDL = low density lipoprotein; MD = mean difference; mo = month(s); RCT = randomized controlled trial; RR = risk ratio; SFA = saturated fatty acid; SMD = standardized mean difference; yr = year(s)

Prostate and Breast Cancer

Three RCTs examined the impact of comprehensive lifestyle interventions on prostate and breast cancer recurrence. Two assessed both breast and prostate cancer and one assessed prostate cancer alone. See Table 12 for a summary of the findings and Appendix E for GRADE assessments.

The trial by Ornish et al. was the only study that addressed our primary outcome—recurrence or progression of cancer. The trial reports a modest statistically significant decrease in PSA in the lifestyle intervention group; however, this result should be interpreted with caution as there were methodological limitations and the trial was assessed at high risk of bias. Furthermore, the clinical significance of this outcome is unclear. The natural variability of PSA assays has been previously recognized, with a coefficient of variation (CV) between 10 and 15 percent as reported in prospective studies.[203,204] A recent systematic review of 12 studies reported a mean CV of 20 percent.[205] There is evidence that PSA increases at a faster rate in men with prostate cancer and that PSA kinetics may enable better selection of men for further investigation.[206] In addition, PSA is currently used to measure treatment effect for most cancer treatments. However, there is currently no evidence that directly correlates increased PSA with progression of, or survival following prostate cancer. Indeed PSA can actually decrease and normalize in men with clinically significant prostate cancer.[207,208] Ultimately, progression of cancer and survival are the patient-oriented outcomes that we are seeking to improve. The strength of evidence is insufficient.

Similarly for breast cancer, there is insufficient evidence to draw conclusions regarding the impact of comprehensive lifestyle interventions in preventing recurrence.

Practically, recurrence of cancer is a difficult question to address, given the potentially long followup that would be required to obtain sufficient numbers for recurrence. Reported 5-year cure rates for localized breast and prostate cancer are 98 and nearly 100 percent, respectively.[209] Direct benefit of any intervention on long-term survivorship will be difficult to demonstrate. There is some evidence, albeit weak, that body composition, physical activity, and dietary intake may affect cancer recurrence.[80-88]

There is a large body of evidence regarding lifestyle factors on prevention of incident cancers, with most focusing on the impact of obesity and physical activity on the development of cancer.[16-20,79] While it may not be appropriate to extrapolate evidence regarding incident cancers to recurrence, it seems plausible that factors that contributed to the incident cancer would also contribute to its recurrence.

Overall, the included trials demonstrated that comprehensive lifestyle interventions were successful in modifying behaviors in cancer survivors. Changes in physical activity, fruit and vegetable intake, and decreased fat intake[127,128] were observed in both breast and prostate cancer groups.

The assessment of the impact of lifestyle intervention on behavior is complex. Lifestyle interventions require active participation by participants. Often adherence to the interventions is based on self-report, which has inherent bias. In addition, those who agree to participate in lifestyle interventions trials are generally more motivated for change, as noted in the study by Demark-Wahnefried et al.[129] in which 54 percent of those interested in participating reported exercising regularly, contrasting with research that found that only 25 percent of elderly cancer survivors are physically active.[210]

As in other chronic diseases, optimal interventions to effect behavioral change in cancer survivors remain an area of controversy. Research on interventions to improve physical activity and diet has been conducted in a number of populations with conflicting results.[211-213] A recent systematic review suggested there is insufficient evidence for interventions targeting only single risk factors (i.e., physical activity).[214] Other research suggests that interventions targeting multiple risk factors may be beneficial in effecting change.[215]

Two of the included studies reported weight change. While only one demonstrated a statistically significant decrease in body weight,[128] the pooled MD was statistically significant with minimal heterogeneity. No difference was seen in BMI. This discrepancy reflects the variability in current evidence and the need for further research in this area. Studies in other populations have shown that exercise, particularly in combination with dietary change, can result in statistically significant weight loss.[216]

One trial reported on metabolic variable change following lifestyle intervention and found a significant improvement in all lipids except for triglycerides. The importance of metabolic variables in cancer recurrence is largely unknown. Recent trials looking at statin use for prostate cancer prevention suggest that statin use resulted in decreased PSA recurrence and improved relapse-free survival; however, whether the benefit was from the statin or decreased lipids is unknown.[217] Outcomes such as comorbidity, functional decline, and quality of life were not included in this review. While prevention of cancer recurrence would be a laudable goal, research assessing the impact of lifestyle changes on these outcomes may be equally as valuable.

Overall, the strength of body of evidence looking at lifestyle interventions to prevent cancer recurrence is insufficient. Considering the magnitude of these conditions, including both the personal and global impact, it is disappointing that more research has not been completed. Given the potentially long latency period before cancer recurrence, observational studies may be better suited to further delineate the benefits of lifestyle interventions in this population. Research looking at a reduction in the incidence of cancer has been top priority for years. As more people are surviving the incident diagnosis of breast and prostate cancer, investigation of potential interventions to decrease cancer recurrence is becoming of key importance.

Table 12. Summary table: breast and prostate cancer

Outcome	# RCTs	Strength of evidence	Precision
Breast cancer			
Change in body composition			
BMI (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.31; 95% CI: -1.19, 0.57)
Weight (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -3.9; 95% CI: -10.32, 2.52)
Change in physical activity			
Exercise (endurance; EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 25.6; 95% CI: 16.9, 34.8)
Change in dietary or nutrient intake			
F&V intake (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 1.08; 95% CI: 0.5, 1.66)
Fat intake (calories from fat) (EoI)	1	Insufficient	Significant effect in favor of lifestyle intervention (MD = -1.76; -2.57, -0.95)
Prostate cancer			
Primary outcome			
PSA levels (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.63; 95% CI: -1.16, -0.10)
Change in body composition			
BMI (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.61; 95% CI: -1.47, 0.25)
Weight (EoI)	2	Insufficient	Significant effect in favor of lifestyle intervention (MD = -7.55; 95% CI: -13.05, -2.05)
Change in metabolic variables			
HDL cholesterol (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -6.4; 95% CI: -9.65, -3.15)
LDL cholesterol (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -28.6; 95% CI: -40.79, -16.41)
Total cholesterol (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -34.0; 95% CI: -48.30, -19.7)
Triglycerides (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD= -9.0; 95% CI: -39.62, 21.62)
Change in physical activity			
Exercise (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD = 0.62; 95% CI: 0.20, 1.03)
Exercise (endurance; EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 16.3; 95% CI: 4.8, 28.5)
Change in dietary or nutrient intake			
Fat intake (calories from fat) (EoI)	2	Insufficient	Significant effect in favor of lifestyle intervention (MD = -16.80 [-20.29, -13.31]

BMI = body mass index; CI = confidence interval; EoI = end of intervention; F&V = fruit and vegetable; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; PSA = prostate specific antigen; RCT = randomized controlled trial; RR = risk ratio

Table 12. Summary table: breast and prostate cancer (continued)

Outcome	# RCTs	Strength of evidence	Precision
F&V intake (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 1.4; 95% CI: 0.75, 2.05)
Mixed breast and prostate cancer			
Change in body composition			
BMI (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.10; 95% CI: 1.68, 1.48)
BMI (followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.50; 95% CI: -2.13, 1.13)
Change in physical activity			
Exercise (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD = 0.31; 95% CI: 0, 0.61)
Exercise (followup)	1	Insufficient	The evidence was too limited to draw a conclusion (SMD = 0.13; 95% CI: -0.18, 0.44)
Change in dietary or nutrient intake			
F&V intake (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = 0.4; 95% CI: -0.21, 1.01)
F&V intake (followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.10; 95% CI: -0.75, 0.55)
Fat intake (calories from fat) (EoI)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.30; 95% CI: -2.41, 1.81)
Fat intake calories from fat) (followup)	1	Insufficient	The evidence was too limited to draw a conclusion (MD = -0.50; 95% CI: -2.70, 1.70)

BMI = body mass index; CI = confidence interval; EoI = end of intervention; F&V = fruit and vegetable; HDL = high density lipoprotein; LDL = low density lipoprotein; MD = mean difference; PSA = prostate specific antigen; RCT = randomized controlled trial; RR = risk ratio

Limitations of the Existing Evidence

The strength of the evidence was low or insufficient for the majority of outcomes across the various interventions and conditions (Appendix E). These low grades were driven by a high or unclear risk of bias within individual studies, lack of direct evidence for patient-important outcomes, and lack of consistency and precision among studies.

Although the studies providing data for this report were RCTs, all had a high or unclear risk of bias as assessed using an empirically derived tool for assessing risk of bias developed by The Cochrane Collaboration. Most of the RCTs were rated as having adequately generated the allocation sequence (70 percent); however, less than half adequately concealed allocation (40 percent). Measures to ensure that allocation occurs without foreknowledge of treatment assignments can always be undertaken by study investigators and should be routinely employed in order to avoid selection bias. Blinding of study investigators and participants was mostly unclear (65 percent). Inadequate blinding can lead to exaggerated treatment effects. Blinding of patients may not be feasible when the intervention is a "lifestyle intervention;" however, blinding of patients to the hypothesis, implementing an active intervention for the control groups, and blinding of outcome assessors may reduce the impact of nonblinding of patients, in particular for patient-reported outcomes. Incomplete outcome data was a problem in half of the trials due to loss to followup and inadequate handling of missing data in the reporting and/or analysis. This may exaggerate treatment effects.

Few trials provided data for clinically-important outcomes, and we had to rely on surrogate measures to assess the impact of lifestyle interventions on our primary outcomes. Lack of consistency and precision of results across studies also contributed to the low strength of evidence rating for the majority of outcomes. Consistency was often unknown due to the few studies assessing the same outcome at the same timepoint. Precision was often poor due to the small sample sizes in many of the studies, which may have resulted in insufficient power to detect clinically-important differences. Both consistency and precision may have been affected by variations in the clinical populations assessed across the studies, such as the number, type and severity of comorbidities, and composition, intensity and duration of the lifestyle interventions.

This review included only RCTs because they are considered the highest level of evidence to evaluate the effectiveness of an intervention. However, providing long-term data for studies comparing an active treatment with an active control may not be feasible. While we identified some trials that had very long periods of followup, we acknowledge that observational studies may also provide long-term data to address the questions included in this review. As such, a systematic review including observational studies might be beneficial in providing data on patients using different interventions over several years to determine the comparative benefits these interventions.

In addition to the methodological issues identified above, there are limitations that need to be discussed regarding systematic reviews. There is a possibility of publication bias in this systematic review. Since we did not include conference proceedings, unpublished literature, or non-English language publications, we may have missed some studies, and therefore may be overestimating the therapeutic benefit of the lifestyle interventions. Nonetheless, we conducted a comprehensive and systematic search of the published literature that was supplemented by reviewing reference lists of included studies and contacting authors. Despite these efforts, we recognize that we may have missed some trials. There is also the possibility of study selection

bias; however, we employed at least two independent reviewers and feel confident that the studies that were excluded from this report were done so for consistent and appropriate reasons.

Future Research

The following general recommendations for future research are based on the preceding discussion regarding the limitations of the current evidence:

- RCTs should be designed and conducted to minimize risk of bias where at all possible. Authors may find tools such as the CONSORT[218] statement helpful in designing and reporting on RCTs.
- Future research should seek to minimize risk of bias by blinding outcome assessors, including an active intervention for control groups, adequately concealing allocation, and handling and reporting missing data appropriately.
- Information regarding the benefit of individual components of lifestyle interventions is needed. Determination of the benefit of individual components would allow for standardization of these interventions in the literature, improve reporting, and facilitate comparisons across populations.
- Consensus on clinically- and patient-important outcomes and outcome measures is needed to ensure consistency and comparability across future studies. Moreover, consensus on minimal clinically important differences is needed to guide study design and interpretation of results.
- RCTs that are adequately powered to detect differences in cardiovascular mortality and morbidity in patients at risk for type 2 diabetes are needed.
- A systematic review of the literature, including observational studies, may provide data on the impact of different lifestyle interventions over several years in order to assess the long-term sustainability and comparative effectiveness of these interventions.
- Given that many chronic disease guidelines now recommend healthy dietary and exercise behaviors, RCTs that are designed to assess components that may improve adherence to guidelines would be beneficial.
- Specifically, research to assess which delivery settings are effective in promoting behavioral change would assist in the delivery of these interventions (i.e., primary care level vs. population-based initiatives).

Conclusions

Overall, comprehensive lifestyle interventions that include exercise, dietary changes, and at least one other component are effective in decreasing the incidence of type 2 diabetes mellitus in high risk patients, and the benefit extends beyond the active intervention phase. While the interventions have a positive impact on a number of risk factors for cardiovascular disease, the impact on cardiovascular outcomes is less clear. Further trials that are adequately powered to determine cardiovascular outcomes are required.

In patients who have already been diagnosed with type 2 diabetes, evidence for benefit of comprehensive lifestyle interventions on patient-oriented outcomes is less clear. There is some evidence to suggest long-term benefit on microvascular and macrovascular outcomes, although the evidence is from one trial of high risk diabetic patients and medication was included as part of the active intervention group. One large RCT is currently ongoing in an attempt to address this issue.

The body of evidence looking at lifestyle interventions to prevent cancer recurrence is limited. We found only one RCT that attempted to address this question; however, the clinical significance of their findings is unclear.

Comprehensive lifestyle interventions appear to have a positive impact on behavioral outcomes including exercise and dietary intake, as well as a number of metabolic variables, at least in the short-term in all populations addressed in this report.

No firm conclusions can be drawn from the available evidence on which interventional strategy would be most successful in inducing and maintaining behavioral change or improving patient-oriented outcomes. In addition, it remains unclear whether comprehensive lifestyle interventions as defined by diet, exercise, and at least one other intervention are superior to diet and exercise alone.

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Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ACSM	American College of Sports Medicine
AHA	American Heart Association
AHEAD	Action for Health in Diabetes
ALA	α-linolenic acid
ATP III	Adult Treatment Panel III
approx	approximately
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control
CHD	coronary heart disease
CHO	carbohydrate
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CV	coefficient of variation
CVD	cardiovascular disease
d	day(s)
DAWN	Diabetes Awareness and Wellness Network
DPP	Diabetes Prevention Program
EoI	end of intervention
EPC	Evidence-based practice center
F&V	fruits and vegetables
FDPS	Finnish Diabetes Prevention Study
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
KQ	key question
HbA1c	glycosylated haemoglobin
HDL	high density lipoprotein
HR	heart rate
hr	hour(s)
lb	pound(s)
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
LDL	low density lipoprotein
LEAD	Leading the Way in Exercise and Diet
max	maximum
MD	mean difference
meds	medications
min	minute(s)
mo	month(s)
MUFA	monounsaturated fatty acids
NC	not calculated
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health

NNT	number needed to treat
NR	not reported
OHA	oral hypoglycaemic agent
PA	physical activity
PCL	Prostate Cancer Lifestyle
pg	page
POWER	Pounds Off With Empowerment
PUFA	polyunsaturated fatty acids
PSA	prostate-specific antigen
RCT	randomized controlled trial
RENEW	Reach Out to Enhance Wellness
RoB	Risk of Bias
RR	risk ratio
SFA	saturated fatty acids
SLIM	Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht
SMD	standardized mean difference
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
tx	treatment
US	United States of America
WHO	World Health Organization
wk	week(s)
wt	weight
x	times
yr	year

Appendices

Appendix A. Search Strategies

Table A1. Lifestyle interventions review – MEDLINE

Years/issue searched: 1980-current **Search date**: June 8, 2010 **Number of Results**: 354
1. exp Diabetes Mellitus, Type 2/ 2. exp Diabetes Complications/ 3. (obes$ adj6 diabet$).tw,kf,ot. 4. (MODY or NIDDM or T2DM).tw,kf,ot. 5. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or non insulin?depend$).tw,kf,ot. 6. ((typ? 2 or typ? II or typ?2 or typ?II) adj diabet$).tw,kf,ot. 7. (diabet$ adj (typ? 2 or typ? II or typ?2 or typ?II)).tw,kf,ot. 8. ((adult$ or matur$ or late or slow or stabl$) adj6 diabet$).tw,kf,ot. 9. or/1-8 10. exp Diabetes Insipidus/ 11. diabet$ insipidus.tw,kf,ot. 12. 10 or 11 13. 9 not 12 14. Metabolic Syndrome X/ 15. (metabolic adj syndrome*).tw. 16. Prediabetic State/ 17. (prediabetes or pre-diabetes).tw. 18. Insulin Resistance/ 19. (insulin adj resistance).tw. 20. or/14-19 21. Prostatic Neoplasms/ 22. (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or adeno$)).ti,ab. 23. or/21-22 24. exp Breast Neoplasms/ 25. (breast$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or adeno$)).ti,ab. 26. or/24-25 27. exp Exercise/ 28. Physical Exertion/ 29. exp exercise movement techniques/ 30. exp exercise therapy/ 31. exp sports/ 32. Physical Fitness/ 33. "Physical Education and Training"/ 34. $exercise*.tw. 35. (aerobic adj2 exercise*).tw. 36. (Physical adj2 (fitness or training or exertion or activit*)).tw. 37. ((Endurance adj2 (exercise* or training)) or endurance).tw. 38. (Exercise adj2 (movement* or therap* or training or counsel*)).tw. 39. $fitness*.tw. 40. or/27-39 41. exp Life Style/ 42. exp Stress, Psychological/pc [Prevention & Control] 43. Mental Health/ 44. Cognitive Therapy/ 45. exp Relaxation Therapy/ 46. exp Psychotherapy/mt, tu, ut [Methods, Therapeutic Use, Utilization] 47. exp Behavior Therapy/mt [Methods] 48. social support/ 49. exp Self Concept/

50. health education/
51. exp health promotion/
52. exp Health Behavior/
53. Patient Education as Topic/mt, ut [Methods, Utilization]
54. Health Knowledge, Attitudes, Practice/
55. "Quality of Life"/px [Psychology]
56. Counseling/mt, ut [Methods, Utilization]
57. exp "Tobacco Use Cessation"/
58. Smoking/pc [Prevention & Control]
59. exp Mind-Body Therapies/
60. (aromatherap* or biofeedback or hypnosis or imagery or meditation or psychodrama or psychophysiology or yoga).tw.
61. (breathing adj exercises).tw.
62. (laughter adj therapy).tw.
63. (relaxation adj therapy).tw.
64. (therapeutic adj touch).tw.
65. (tai adj (ji or chi)).tw.
66. or/41-65
67. exp Diet/
68. nutrition therapy/ or exp diet therapy/
69. exp Feeding Behavior/
70. Weight Loss/
71. $diet*.tw.
72. (weight adj2 (loss or reduction or change or program*)).tw.
73. ((Weight or diet* or nutrition*) adj2 counsel*).tw.
74. (counsel* adj3 (weight or diet* or nutrition)).tw.
75. (Caloric adj2 (intake or restriction or reduction or deficit)).tw.
76. (calorie* adj2 (intake or restriction or reduction or deficit)).tw.
77. (Diet* adj2 (intervention or change or restriction or program*)).tw.
78. (healthy adj2 eating).tw.
79. ((fat or fiber or fibre) adj2 intake).tw.
80. or/67-79
81. randomized controlled trial.pt.
82. controlled clinical trial.pt.
83. randomi?ed.ab.
84. placebo.ab.
85. drug therapy.fs.
86. randomly.ab.
87. trial.ab.
88. groups.ab.
89. or/81-88
90. humans/ not (animals and humans).hw,sh.
91. 89 and 90
92. and/13,40,66,80,91
93. and/20,40,66,80,91
94. and/23,40,66,80,91
95. and/26,40,66,80,91
96. or/92-95
97. limit 96 to (english language and humans and yr="1980 -Current")
98. limit 97 to "all adult (19 plus years)"

Table A2. Lifestyle interventions review - CENTRAL

Years/issue searched: 1980-current
Search date: March 23, 2010
Number of Results: 186

1. exp Diabetes Mellitus, Type 2/
2. exp Diabetes Complications/
3. (obes$ adj6 diabet$).tw,ot.
4. (MODY or NIDDM or T2DM).tw,ot.
5. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or non insulin?depend$).tw,ot.
6. ((typ? 2 or typ? II or typ?2 or typ?II) adj diabet$).tw,ot.
7. (diabet$ adj (typ? 2 or typ? II or typ?2 or typ?II)).tw,ot.
8. ((adult$ or matur$ or late or slow or stabl$) adj6 diabet$).tw,ot.
9. or/1-8
10. exp Diabetes Insipidus/
11. diabet$ insipidus.tw,ot.
12. 10 or 11
13. 9 not 12
14. Metabolic Syndrome X/
15. Insulin Resistance/
16. (metabolic adj syndrome*).tw.
17. (insulin adj resistance).tw.
18. or/14-17
19. Prostatic Neoplasms/
20. (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or adeno$)).ti,ab.
21. or/19-20
22. exp Breast Neoplasms/
23. (breast$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or adeno$)).ti,ab.
24. or/22-23
25. exp Exercise/
26. Physical Exertion/
27. exp exercise movement techniques/
28. exp exercise therapy/
29. exp sports/
30. Physical Fitness/
31. "Physical Education and Training"/
32. $exercise*.tw.
33. (aerobic adj2 exercise*).tw.
34. (Physical adj2 (fitness or training or exertion or activit*)).tw.
35. ((Endurance adj2 (exercise* or training)) or endurance).tw.
36. (Exercise adj2 (movement* or therap* or training or counsel*)).tw.
37. $fitness*.tw.
38. or/25-37
39. exp Life Style/
40. exp Stress, Psychological/pc [Prevention & Control]
41. Mental Health/
42. Cognitive Therapy/
43. exp Relaxation Therapy/
44. exp Psychotherapy/mt, tu, ut [Methods, Therapeutic Use, Utilization]
45. exp Behavior Therapy/mt [Methods]
46. social support/
47. exp Self Concept/
48. health education/
49. exp health promotion/
50. exp Health Behavior/
51. Patient Education as Topic/mt, ut [Methods, Utilization]
52. Health Knowledge, Attitudes, Practice/
53. "Quality of Life"/px [Psychology]
54. Counseling/mt, ut [Methods, Utilization]
55. exp "Tobacco Use Cessation"/

56. Smoking/pc [Prevention & Control]
57. exp Mind-Body Therapies/
58. (aromatherap* or biofeedback or hypnosis or imagery or meditation or psychodrama or psychophysiology or yoga).tw.
59. (breathing adj exercises).tw.
60. (laughter adj therapy).tw.
61. (relaxation adj therapy).tw.
62. (therapeutic adj touch).tw.
63. (tai adj (ji or chi)).tw.
64. or/39-63
65. exp Diet/
66. nutrition therapy/ or exp diet therapy/
67. exp Feeding Behavior/
68. Weight Loss/
69. $diet*.tw.
70. (weight adj2 (loss or reduction or change or program*)).tw.
71. ((Weight or diet* or nutrition*) adj2 counsel*).tw.
72. (counsel* adj3 (weight or diet* or nutrition)).tw.
73. (Caloric adj2 (intake or restriction or reduction or deficit)).tw.
74. (calorie* adj2 (intake or restriction or reduction or deficit)).tw.
75. (Diet* adj2 (intervention or change or restriction or program*)).tw.
76. (healthy adj2 eating).tw.
77. or/65-76
78. and/13,38,64,77
79. and/18,38,64,77
80. and/21,38,64,77
81. and/24,38,64,77
82. or/78-81
83. limit 82 to yr="1980 -Current"

Table A3. Lifestyle interventions review - CINAHL

Years/issue searched: 1980-current; English only; publication type: clinical trials
Search date: March 23, 2010
Number of Results: 160

#	Query
S78	S74 or S75 or S76 or S77
S77	S19 AND S31 AND S60 AND S73
S76	S16 AND S31 AND S60 AND S73
S75	S13 AND S31 AND S60 AND S73
S74	S8 AND S31 AND S60 AND S73
S73	S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72
S72	TX healthy eating
S71	TX calorie intake or TX calorie restriction or TX calorie reduction or TX calorie deficit
S70	TX caloric intake or TX caloric restriction or TX caloric reduction or TX caloric deficit
S69	TX diet counseling or TX diet counselling
S68	TX Weight loss or TX weight reduction or TX weight change or TX weight loss program or TX (weight counselling or weight counseling)
S67	TX diet* or TX diet intervention or TX diet change or TX diet restriction or TX diet program*
S66	(MH "Nutritional Counseling")
S65	(MH "Weight Reduction Programs")
S64	(MH "Weight Loss")
S63	(MH "Eating Behavior+")
S62	(MH "Diet Therapy+")
S61	(MH "Diet+")
S60	S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59
S59	TX qi gong
S58	TX tai chi OR tai ji
S57	TX therapeutic touch
S56	TX relaxation therap*
S55	TX laughter therap*
S54	TX breathing exercise*
S53	TX aromatherap* OR biofeedback OR hypnosis OR imagery OR meditation OR psychodrama OR psychophysiology OR yoga
S52	(MH "Mind Body Techniques+")
S51	(MH "Smoking Cessation Programs") or (MH "Smoking Cessation")
S50	(MH "Counseling+")
S49	(MH "Counseling")
S48	(MH "Quality of Life+")
S47	(MH "Health Knowledge")

S46	(MH "Patient Education+")
S45	(MH "Health Behavior+")
S44	(MH "Health Promotion+")
S43	(MH "Health Education+")
S42	(MH "Self Concept+")
S41	(MH "Support, Psychosocial+")
S40	(MH "Behavior Therapy+")
S39	(MH "Psychotherapy+")
S38	(MH "Alternative Therapies+")
S37	(MH "Cognitive Therapy")
S36	(MH "Community Mental Health Services")
S35	(MH "Stress Management")
S34	(MH "Stress, Psychological/PC")
S33	(MH "Health Behavior+") or (MH "Health Behavior Component (Saba CCC)+") or (MH "Health Seeking Behavior Alteration (Saba CCC)") or (MH "Domain IV: Health-Related Behaviors Domain (Omaha)+") or (MH "Health Seeking Behaviors (NANDA)+") or (MH "Health Behavior (Iowa NOC) (Non-Cinahl)+") or (MH "Health Knowledge and Behavior (Iowa NOC) (Non-Cinahl)+") or (MH "Health Promoting Behavior (Iowa NOC)")
S32	(MH "Life Style+") or (MH "Life Style Changes")
S31	S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
S30	TX fitness OR physical fitness
S29	TX endurance exercise* OR endurance training OR endurance
S28	TX physical fitness OR physical training OR physical exertion OR physical activit*
S27	(MH "Aerobic Exercises") or TX aerobic exercise*
S26	(MH "Physical Activity")
S25	(MH "Physical Education and Training+")
S24	(MH "Physical Fitness+")
S23	(MH "Sports+")
S22	(MH "Therapeutic Exercise+")
S21	(MH "Exertion")
S20	(MH "Exercise+")
S19	S17 or S18
S18	TX Breast cancer or TX breast neoplasm* or TX (breast tumor* OR breast tumour*)
S17	(MH "Breast Neoplasms+")
S16	S14 or S15
S15	TX prostat* cancer or TX prostat* neoplasm* or TX (prostat* tumor* OR prostat* tumour*)
S14	(MH "Prostatic Neoplasms")
S13	S9 or S10 or S11 or S12
S12	TX insulin resistance
S11	TX metabolic syndrome or TX metabolic syndrome x
S10	(MH "Insulin Resistance+")

S9	(MH "Metabolic Syndrome X+")
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7
S7	TX diabetes insipidus
S6	TX MODY OR NIDDM OR T2DM
S5	TX non-insulin dependent diabetes
S4	TX diabetes insipidus
S3	TX diabetes type 2
S2	(MH "Diabetes Insipidus")
S1	(MH "Diabetes Mellitus, Non-Insulin-Dependent")

Table A4. Lifestyle interventions review - SCOPUS

Years/issue searched: 1980-current; English
Search date: March 23, 2010
Number of Results: 320

1(((TITLE-ABS-KEY((breast PRE/0 cancer) OR (breast PRE/0 carcinoma) OR (breast W/2 tumour*) OR (breast W/2 tumor*) OR (breast W/2 neoplasm*))) AND ((TITLE-ABS-KEY((exercise) OR (exercise W/2 movement) OR (exercise W/2 therap*) OR (exercise W/2 training) OR (exercise W/2 counsel*) OR (aerobic W/2 exercise))) OR (TITLE-ABS-KEY((physical W/2 fitness) OR (physical W/2 training) OR (physical W/2 exertion) OR (physical W/2 activit*) OR (physical W/2 exercise*))) OR (TITLE-ABS-KEY((endurance W/2 exercise*) OR (endurance W/2 training) OR (endurance))) OR (TITLE-ABS-KEY((sport*) OR (fitness)))) AND ((TITLE-ABS-KEY(("lifestyle") OR ("cognitive therapy") OR ("stress management") OR (relaxation PRE/0 therapy) OR (psychotherap*) OR (behavior PRE/0 therap*) OR (social PRE/0 support) OR (health PRE/0 education) OR (health PRE/0 promotion) OR (health PRE/0 behavior) OR (patient PRE/0 education) OR ("quality of life") OR (counsel*) OR (tobacco PRE/0 cessation))) OR (TITLE-ABS-KEY(("mind-body therap*") OR aromatherap* OR biofeedback OR (hypnosis) OR mediation OR psychodrama OR psychophysiology OR yoga OR qi-gong OR (tai chi) OR (tai ji))) OR (TITLE-ABS-KEY((breathing PRE/0 exercises) OR (laughter PRE/0 therap*) OR (relaxation PRE/0 therap*) OR (therapeutic PRE/0 touch)))) AND ((TITLE-ABS-KEY((diet) OR (diet PRE/0 therapy) OR (nutrition PRE/0 therapy))) OR (TITLE-ABS-KEY((weight W/2 counsel*) OR (weight W/2 loss) OR (weight W/2 reduction) OR (weight W/2 change) OR (weight W/2 program*))) OR (TITLE-ABS-KEY((diet W/2 counsel*) OR (nutrition W/2 counsel*))) OR (TITLE-ABS-KEY((caloric W/2 intake) OR (caloric W/2 restriction) OR (caloric W/2 reduction) OR (caloric W/2 deficit))) OR (TITLE-ABS-KEY((calorie W/2 intake) OR (calorie W/2 restriction) OR (calorie W/2 reduction) OR (calorie W/2 deficit))) OR (TITLE-ABS-KEY((diet W/2 intervention) OR (diet W/2 change) OR (diet W/2 restriction) OR (diet W/2 program*))) OR (TITLE-ABS-KEY((healthy PRE/0 eating))))) OR ((TITLE-ABS-KEY((prostat* PRE/0 cancer) OR (prostat* PRE/0 carcinoma) OR (prostat* W/2 tumour*) OR (prostat* W/2 tumor*) OR (prostat* W/2 neoplasm*))) AND ((TITLE-ABS-KEY((exercise) OR (exercise W/2 movement) OR (exercise W/2 therap*) OR (exercise W/2 training) OR (exercise W/2 counsel*) OR (aerobic W/2 exercise))) OR (TITLE-ABS-KEY((physical W/2 fitness) OR (physical W/2 training) OR (physical W/2 exertion) OR (physical W/2 activit*) OR (physical W/2 exercise*))) OR (TITLE-ABS-KEY((endurance W/2 exercise*) OR (endurance W/2 training) OR (endurance))) OR (TITLE-ABS-KEY((sport*) OR (fitness)))) AND ((TITLE-ABS-KEY(("lifestyle") OR ("cognitive therapy") OR ("stress management") OR (relaxation PRE/0 therapy) OR (psychotherap*) OR (behavior PRE/0 therap*) OR (social PRE/0 support) OR (health PRE/0 education) OR (health PRE/0 promotion) OR (health PRE/0 behavior) OR (patient PRE/0 education) OR ("quality of life") OR (counsel*) OR (tobacco PRE/0 cessation))) OR (TITLE-ABS-KEY(("mind-body therap*") OR aromatherap* OR biofeedback OR (hypnosis) OR mediation OR psychodrama OR psychophysiology OR yoga OR qi-gong OR (tai chi) OR (tai ji))) OR (TITLE-ABS-KEY((breathing PRE/0 exercises) OR (laughter PRE/0 therap*) OR (relaxation PRE/0 therap*) OR (therapeutic PRE/0 touch)))) AND ((TITLE-ABS-KEY((diet) OR (diet PRE/0 therapy) OR (nutrition PRE/0 therapy))) OR (TITLE-ABS-KEY((weight W/2 counsel*) OR (weight W/2 loss) OR (weight W/2 reduction) OR (weight W/2 change) OR (weight W/2 program*))) OR (TITLE-ABS-KEY((diet W/2 counsel*) OR (nutrition W/2 counsel*))) OR (TITLE-ABS-KEY((caloric W/2 intake) OR (caloric W/2 restriction) OR (caloric W/2 reduction) OR (caloric W/2 deficit))) OR (TITLE-ABS-KEY((calorie W/2 intake) OR (calorie W/2 restriction) OR (calorie W/2 reduction) OR (calorie W/2 deficit))) OR (TITLE-ABS-KEY((diet W/2 intervention) OR (diet W/2 change) OR (diet W/2 restriction) OR (diet W/2 program*))) OR (TITLE-ABS-KEY((healthy PRE/0 eating))))) OR (((TITLE-ABS-KEY(("metabolic syndrome x") OR (metabolic PRE/0 syndrome))) OR (TITLE-ABS-KEY(("insulin resistance") OR (insulin PRE/0 resistance))) OR (TITLE-ABS-KEY("pre-diabetes"))) AND ((TITLE-ABS-KEY((exercise) OR (exercise W/2 movement) OR (exercise W/2 therap*) OR (exercise W/2 training) OR (exercise W/2 counsel*) OR (aerobic W/2 exercise))) OR (TITLE-ABS-KEY((physical W/2 fitness) OR (physical W/2 training) OR (physical W/2 exertion) OR (physical W/2 activit*) OR (physical W/2 exercise*))) OR (TITLE-ABS-KEY((endurance W/2 exercise*) OR (endurance W/2 training) OR (endurance))) OR (TITLE-ABS-KEY((sport*) OR (fitness)))) AND ((TITLE-ABS-KEY(("lifestyle") OR ("cognitive therapy") OR ("stress management") OR (relaxation PRE/0 therapy) OR (psychotherap*) OR (behavior PRE/0 therap*) OR (social PRE/0 support) OR (health PRE/0 education) OR (health PRE/0 promotion) OR (health PRE/0 behavior) OR (patient PRE/0 education) OR ("quality of life") OR (counsel*) OR (tobacco PRE/0 cessation))) OR (TITLE-ABS-KEY(("mind-body therap*") OR aromatherap* OR biofeedback OR (hypnosis) OR mediation OR psychodrama OR psychophysiology OR yoga OR qi-gong OR (tai chi) OR (tai ji))) OR (TITLE-ABS-KEY((breathing PRE/0 exercises) OR (laughter PRE/0 therap*) OR (relaxation PRE/0 therap*) OR (therapeutic PRE/0 touch)))) AND ((TITLE-ABS-KEY((diet) OR (diet PRE/0 therapy)

OR (nutrition PRE/0 therapy))) OR (TITLE-ABS-KEY((weight W/2 counsel*) OR (weight W/2 loss) OR (weight W/2 reduction) OR (weight W/2 change) OR (weight W/2 program*))) OR (TITLE-ABS-KEY((diet W/2 counsel*) OR (nutrition W/2 counsel*))) OR (TITLE-ABS-KEY((caloric W/2 intake) OR (caloric W/2 restriction) OR (caloric W/2 reduction) OR (caloric W/2 deficit))) OR (TITLE-ABS-KEY((calorie W/2 intake) OR (calorie W/2 restriction) OR (calorie W/2 reduction) OR (calorie W/2 deficit))) OR (TITLE-ABS-KEY((diet W/2 intervention) OR (diet W/2 change) OR (diet W/2 restriction) OR (diet W/2 program*))) OR (TITLE-ABS-KEY((healthy PRE/0 eating))))) OR (((TITLE-ABS-KEY("diabetes type 2" OR "diabetes type II")) OR (TITLE-ABS-KEY(mody OR niddm OR t2dm)) OR (TITLE-ABS-KEY(non-insulin PRE/2 diabetes))) AND ((TITLE-ABS-KEY((exercise) OR (exercise W/2 movement) OR (exercise W/2 therap*) OR (exercise W/2 training) OR (exercise W/2 counsel*) OR (aerobic W/2 exercise))) OR (TITLE-ABS-KEY((physical W/2 fitness) OR (physical W/2 training) OR (physical W/2 exertion) OR (physical W/2 activit*) OR (physical W/2 exercise*))) OR (TITLE-ABS-KEY((endurance W/2 exercise*) OR (endurance W/2 training) OR (endurance))) OR (TITLE-ABS-KEY((sport*) OR (fitness)))) AND ((TITLE-ABS-KEY(("lifestyle") OR ("cognitive therapy") OR ("stress management") OR (relaxation PRE/0 therapy) OR (psychotherap*) OR (behavior PRE/0 therap*) OR (social PRE/0 support) OR (health PRE/0 education) OR (health PRE/0 promotion) OR (health PRE/0 behavior) OR (patient PRE/0 education) OR ("quality of life") OR (counsel*) OR (tobacco PRE/0 cessation))) OR (TITLE-ABS-KEY(("mind-body therap*") OR aromatherap* OR biofeedback OR (hypnosis) OR mediation OR psychodrama OR psychophysiology OR yoga OR qi-gong OR (tai chi) OR (tai ji))) OR (TITLE-ABS-KEY((breathing PRE/0 exercises) OR (laughter PRE/0 therap*) OR (relaxation PRE/0 therap*) OR (therapeutic PRE/0 touch)))) AND ((TITLE-ABS-KEY((diet) OR (diet PRE/0 therapy) OR (nutrition PRE/0 therapy))) OR (TITLE-ABS-KEY((weight W/2 counsel*) OR (weight W/2 loss) OR (weight W/2 reduction) OR (weight W/2 change) OR (weight W/2 program*))) OR (TITLE-ABS-KEY((diet W/2 counsel*) OR (nutrition W/2 counsel*))) OR (TITLE-ABS-KEY((caloric W/2 intake) OR (caloric W/2 restriction) OR (caloric W/2 reduction) OR (caloric W/2 deficit))) OR (TITLE-ABS-KEY((calorie W/2 intake) OR (calorie W/2 restriction) OR (calorie W/2 reduction) OR (calorie W/2 deficit))) OR (TITLE-ABS-KEY((diet W/2 intervention) OR (diet W/2 change) OR (diet W/2 restriction) OR (diet W/2 program*))) OR (TITLE-ABS-KEY((healthy PRE/0 eating)))))) AND (INDEXTERMS((randomized controlled trial) OR (controlled clinical trial))) AND (DOCTYPE(ar)) AND (((PUBYEAR IS 1980 OR PUBYEAR AFT 1980) AND (LANGUAGE(english))))

Table A5. Lifestyle interventions review - PsycINFO

Years/issue searched: 1980-current; English
Search date: March 23, 2010
Number of Results: 14

1. exp diabetes mellitus/
2. (diabetes adj type adj "2").mp. [mp=title, abstract, heading word, table of contents, key concepts]
3. (MODY or NIDDM or T2DM).tw.
4. (non-insulin adj depend*).tw.
5. or/1-4
6. exp Metabolic Syndrome/
7. (metabolic adj syndrome adj x).tw.
8. (metabolic adj syndrome).tw.
9. (insulin adj resistance).tw.
10. (impaired adj glucose adj tolerance).tw.
11. or/6-10
12. (prostate adj3 (cancer or carcinoma or neoplasm* or tumo?r)).tw.
13. exp breast neoplasms/
14. (breast$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or adeno$)).ti,ab.
15. or/13-14
16. exp Exercise/
17. exp Physical Activity/
18. exp aerobic exercise/
19. exp Sports/
20. exp Physical Fitness/
21. exp Physical Endurance/ or exp Endurance/
22. (Physical adj2 (fitness or training or exertion or activit*)).tw.
23. ((Endurance adj2 (exercise* or training)) or endurance).tw.
24. (Exercise adj2 (movement* or therap* or training or counsel*)).tw.
25. or/16-24
26. exp Lifestyle Changes/ or exp Lifestyle/
27. exp Psychological Stress/
28. exp Stress Management/
29. exp Cognitive Therapy/
30. exp Relaxation Therapy/
31. exp Psychotherapy/
32. exp Behavior Therapy/
33. exp Social Support/
34. exp Self Concept/
35. exp Health Education/
36. exp Client Education/
37. exp Health Promotion/
38. exp "Quality of Life"/
39. exp Counseling/
40. exp Smoking Cessation/
41. exp Relaxation Therapy/
42. exp Aromatherapy/
43. exp Biofeedback/
44. exp Hypnosis/
45. exp Meditation/
46. exp Yoga/
47. exp Relaxation/
48. exp Tactual Stimulation/
49. (tai chi or tai ji).tw.
50. or/26-49
51. exp Diets/
52. exp Nutrition/
53. exp Eating Behavior/
54. exp Weight Loss/
55. (weight adj2 (loss or reduction or change or program*)).tw.

56. ((Weight or diet* or nutrition*) adj2 counsel*).tw.
57. (counsel* adj3 (weight or diet* or nutrition)).tw.
58. (Caloric adj2 (intake or restriction or reduction or deficit)).tw.
59. (calorie* adj2 (intake or restriction or reduction or deficit)).tw.
60. (Diet* adj2 (intervention or change or restriction or program*)).tw.
61. (healthy adj2 eating).tw.
62. or/51-61
63. 4 and 25 and 50 and 62
64. 11 and 25 and 50 and 62
65. 12 and 25 and 50 and 62
66. 15 and 25 and 50 and 62
67. or/63-66
68. (randomi?ed or random*).tw.
69. 67 and 68
70. limit 69 to (human and english language and yr="1980 -Current")

Table A6. Lifestyle interventions review - EMBASE

Years/issue searched: 1980-current; English; RCTs
Search date: March 23, 2010
Number of Results: 453

1. exp Diabetes Mellitus, Type 2/
2. exp Diabetes Complications/
3. (obes$ adj6 diabet$).tw,kf,ot.
4. (MODY or NIDDM or T2DM).tw,kf,ot.
5. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or non insulin?depend$).tw,kf,ot.
6. ((typ? 2 or typ? II or typ?2 or typ?II) adj diabet$).tw,kf,ot.
7. (diabet$ adj (typ? 2 or typ? II or typ?2 or typ?II)).tw,kf,ot.
8. ((adult$ or matur$ or late or slow or stabl$) adj6 diabet$).tw,kf,ot.
9. or/1-8
10. exp Diabetes Insipidus/
11. diabet$ insipidus.tw,kf,ot.
12. 10 or 11
13. 9 not 12
14. Metabolic Syndrome X/
15. (metabolic adj syndrome*).tw.
16. impaired glucose tolerance/
17. (prediabetes or pre-diabetes).tw.
18. Insulin Resistance/
19. (insulin adj resistance).tw.
20. or/14-19
21. Prostatic Neoplasms/
22. (prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or adeno$)).ti,ab.
23. or/21-22
24. exp Breast Neoplasms/
25. (breast$ adj3 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or adeno$)).ti,ab.
26. or/24-25
27. exp Exercise/
28. Physical Exertion/
29. exp exercise movement techniques/
30. exp exercise therapy/
31. exp sports/
32. Physical Fitness/
33. "Physical Education and Training"/
34. $exercise*.tw.
35. (aerobic adj2 exercise*).tw.
36. (Physical adj2 (fitness or training or exertion or activit*)).tw.
37. ((Endurance adj2 (exercise* or training)) or endurance).tw.
38. (Exercise adj2 (movement* or therap* or training or counsel*)).tw.
39. $fitness*.tw.
40. or/27-39
41. exp Life Style/
42. Stress Management/
43. Cognitive Therapy/
44. exp Relaxation Therapy/
45. Psychotherapy/
46. Behavior Therapy/
47. social support/
48. exp Self Concept/
49. health education/
50. exp health promotion/
51. exp Health Behavior/
52. Patient Education/
53. Health Knowledge, Attitudes, Practice/
54. "Quality of Life"/
55. Counseling/

56. exp "Tobacco Use Cessation"/
57. exp Mind-Body Therapies/
58. (aromatherap* or biofeedback or hypnosis or imagery or meditation or psychodrama or psychophysiology or yoga).tw.
59. (breathing adj exercises).tw.
60. (laughter adj therapy).tw.
61. (relaxation adj therapy).tw.
62. (therapeutic adj touch).tw.
63. (tai adj (ji or chi)).tw.
64. or/41-63
65. exp Diet/
66. $diet*.tw.
67. nutrition therapy/ or exp diet therapy/
68. Weight Loss/
69. (weight adj2 (loss or reduction or change or program*)).tw.
70. ((Weight or diet* or nutrition*) adj2 counsel*).tw.
71. (counsel* adj3 (weight or diet* or nutrition)).tw.
72. (Caloric adj2 (intake or restriction or reduction or deficit)).tw.
73. (calorie* adj2 (intake or restriction or reduction or deficit)).tw.
74. (Diet* adj2 (intervention or change or restriction or program*)).tw.
75. (healthy adj2 eating).tw.
76. or/65-75
77. randomi?ed.ti,ab.
78. random*.ti,ab.
79. trial*.ti,ab.
80. or/77-79
81. humans/ not (animals and humans).hw,sh.
82. 80 and 81
83. and/13,40,64,76,82
84. and/20,40,64,76,82
85. and/23,40,64,76,82
86. and/26,40,64,76,82
87. or/83-86
88. limit 87 to (english language and humans and yr="1980 -Current")
89. limit 88 to adult <18 to 64 years>

Table A7. Results summary

Database	Dates Searched	Date search ran	Number of results
MEDLINE (OVID)	1980 - current	22Mar10	354
CENTRAL (OVID)	1980 - current	23Mar10	186
CINAHL (EBSCO)	1980 - current	23Mar10	160
SCOPUS (Elsevier)	1980 - current	23Mar10	320
PsycINFO (OVID)	1980 - current	23Mar10	14
EMBASE (OVID)	1980 - current	23Mar10	253
Total results (with duplicates)			1287
Total results (duplicates removed)			802

Appendix B. Sample Forms

B.1. Inclusion Criteria Worksheet: Lifestyle interventions review

Reviewer ID: **Date:** / /2010 **Record ID:**

Criteria	Yes	No	Unclear
1. ENGLISH LANGUAGE	☐	☐	
2. PUBLICATION TYPE must be published ≥ 1980			
a. Report of primary research	☐	☐	☐
b. Sub-study of a referenced original study (we will have to screen the ref first)	☐	☐	☐
3. STUDY DESIGN			
a. Randomized controlled trial (cluster or individually randomized)	☐	☐	☐
4. POPULATION			
a. Adults ≥ 18 yrs with one of the following conditions EXCLUDE if participants are healthy but overweight and sedentary only	☐	☐	☐
b. Breast cancer survivors (diagnosed and successfully treated)	☐	☐	☐
c. Prostate cancer survivors (diagnosed and successfully treated or dx but in a watchful waiting category pre-treatment)	☐	☐	☐
d. Diabetes type 2 (diagnosed by physician)	☐	☐	☐
e. Metabolic syndrome (MetS) (diagnosed by physician; defined below) Also called insulin resistance, pre-diabetes, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and Reaven syndrome)	☐	☐	☐
American Heart Assoc definition: When 3 of 5 of the following are present: 1. Abdominal obesity, given as waist circumference: Men ≥102 cm (≥40 in); Women ≥88 cm (≥35 in) 2. Triglycerides≥150 mg/dL (1.7 mmol/L) 3. HDL cholesterol: Men <40 mg/dL (1.03 mmol/L); Women < 50 mg/dL(1.29 mmol/L) 4. Blood pressure≥130/≥85 mm Hg. 5. Fasting glucose≥110 mg/dL			
5. INTERVENTION (Lifestyle intervention with a minimum of 3 components)			
a. MUST BE **Exercise** plus **diet** plus at least one other component (e.g., smoking cessation, stress reduction, group therapy, behavior modification, education re risk factor modification, counseling or a drug, etc. BUT NOT a diet supplement, diabetic education or intensive management only)	☐	☐	☐
b. Duration of intervention must be ≥ 3 months	☐	☐	☐
c. Followup must be ≥ 6 months	☐	☐	☐
6. COMPARATOR GROUP			
Usual care (may involve passive education methods etc.), wait list control, diet alone, exercise alone, But NOT a less intensive lifestyle intervention (i.e sort of a dose response comparison)	☐	☐	☐
7. OUTCOME			
a. Reports delay of disease progression or recurrence of disease (this is our primary outcome)	☐	☐	☐
b. Report surrogate measures of disease progression or improvement or risk reduction (may be the primary outcome in the trial but will be 2ndary outcomes for this review)	☐	☐	☐

Comments:

REVIEWER'S DECISION : **Include** ☐ **Exclude** ☐ **Unsure** ☐

FINAL DECISION: Include ☐ **Exclude** ☐ **Unsure** ☐

B.2. Data Extraction Form: Lifestyle interventions: T2D & Metabolic Syndrome

This study is related to another study yes ☐ ID(s)_____ NO ☐

1. General information and study characteristics

Study author:			Source of funding: industry ☐ government ☐ NR ☐ Association/Foundation ☐ other ☐		
Country(ies):	Year of publication:		Recruitment period _____		
Publication type Abstract ☐ Journal article ☐ Thesis/Dissert. ☐			Source of population Community (volunteers) ☐ Clinic(s) ☐ Inpatients ☐ Registry ☐ Other (describe) ☐		
Trial characteristics			Number of Centers		
RCT ☐	Individual randomization ☐	Cluster randomization ☐	Single centre ☐	Multicentre ☐	

2. Population

Inclusion Criteria	
Age	Disease(s) stage or description
Other	
Exclusion criteria Not described ☐	

3. Study objective(s) circle main objective(s)

a. ↓ risk factors for recurrence or progression of cancer: yes
b. ↓ risk factors for coronary heart/vascular disease: yes
c. Improve measures of metabolic variables: yes
d. Prevent adverse clinical events due to MetS or T2DM: yes
e. Weight loss: yes
f. Improve psychological wellbeing: yes
g. Improve self-sufficiency: yes
h. Increase physical activity and intensity: yes
i. Improve dietary behaviors: yes
j. Other

_____

4. Characteristics of lifestyle intervention Circle or check all that apply and fill in blanks where indicated

Length of intervention in months: _____
Total Duration of followup in months: _____

A. General program description

a. Participant specific –individually tailored and regularly monitored: yes
b. Self-directed – participant given a program to follow at home, occasional fu: yes
c. Group focused: yes
d. Other components: _____

B. Based on a framework: yes NR
a. Transtheoretical model (stages of readiness): yes
b. Social cognitive theory: yes
c. Cognitive behavioral theory: yes
d. Self determination theory; yes
e. Other _____

C. Diet component (intervention 1)
a. Weight loss: yes no
b. Follow established guidelines: yes name _____
c. Specific diet: circle. vegan, lo fat, hi F&V, hi fish, lo glycemic, hi protein, other: name or general description _____
d. General healthy eating no specific program: yes
e. Other: _____

Delivery mode (intervention 1)
a. Individual counseling/education: yes
Who/Frequency/duration _____
b. Group counseling/education: yes
Who/Frequency/duration _____
c. Self directed change in eating habits only: yes
d. Materials/food provided: yes _____
e. Follow-up/reinforcement: circle: educational material, log book, workbook, telephone contact, survey completion, newsletter, personal interview, progress reports, other _____

D. Exercise component (intervention 1)
a. Aerobic/endurance activities: yes
b. Strength/resistance exercises: yes
c. Stretching: yes
d. General increase in physical activity only: yes

Delivery mode (intervention 1)
a. Individual counseling/supervision sessions: yes
Who/frequency/duration _____
b. Group counseling/supervision sessions: yes
Who/frequency/duration _____
c. Self directed exercise only: yes
d. Materials/equipment provided: yes _____
e. Follow-up/reinforcement: circle: educational material, log book, workbook, telephone contact, survey, newsletter, personal interview, progress reports, other _____

E. Component(s) in addition to exercise and diet (intervention 1)
a. Stress management: yes method _____
b. Behavioral change/modification/motivational guidance: yes
c. Goal setting and monitoring: Yes
d. Smoking cessation: yes method _____

e. Group discussions/support groups/education beyond diet and exercise: yes
f. Scheduled telephone contact/counseling beyond diet and exercise: yes
g. Drug therapy name: _____
h. Other _____

F. Intervention 2 : NA
Diet and exercise same as Intervention 1: yes (if not document under "other information")

Delivery mode intervention 2:
a. Individual counseling/supervision sessions: yes
Who/frequency/duration _____
b. Group counseling/supervision sessions: yes
Who/frequency/duration _____
c. Self directed exercise only: yes
d. Materials/equipment provided: yes _____
e. Follow-up/reinforcement: circle: educational material, log book, workbook, telephone contact, survey, newsletter, personal interview, progress reports, other _____

Other information re Intervention 2

G. Personnel involved in the study: NR
a. Qualified dietitian: yes
b. Qualified exercise advisor/consultant/instructor/trainer: yes
c. Case/nurse manager/counselor: yes
d. Physician: yes
e. Behavior therapist/psychologist: yes
f. Other _____

5. Characteristics of Control group intervention
a. Usual/standard care: yes
b. Attention control (i.e. attention/education/materials in addition to usual care): yes
Describe _____
c. Wait list: yes
d. Diet only e. Exercise only
e.
f. Drug treatment only
g. Other _____

6. Demographic characteristics of included population

Variable	Group 1 Intervention 1	Group 2 (Control grp)	Group 3 Intervention 2	Total
Number of participants randomized				
Number of participants analyzed				
Number of dropouts/withdrawals				
Reasons for dropouts/withdrawal				

Variable	Group 1 Intervention 1	Group 2 (Control grp)	Group 3 Intervention 2	Total
Age (*mean-SD or SE; median-IQR)*				
Gender M/F n (%)				
Ethnic distribution (%) or NR				
1. White				
2. African American				
3. Native American				
4. Hispanic				
5. Other				
SES or NR				
1. Education ≤/> hi school (%)				
2. Income ≤/> $20,000 US (%)				
Duration of T2 DM yrs				

Were there more than 2 groups NO ☐ YES ☐ If yes print extra page to extract data

7a. Baseline measures with Outcome measures reported: INTERVENTION GROUP Please enter/circle units reported

Document all times when outcomes are reported but only extract end of trial and last FU for now

Outcome	INTERVENTION GROUP			
	Baseline (mean SD) or n(%)	End trial Time: N=	Mid points data are reported	Last FU Time: N=
Primary outcome				
Secondary outcomes				
A. Weight related				
Weight (kg; lbs)				
BMI (kg/m^2)				
Waist (cm; in)				
Waist/Hip Ratio				
% body fat (how measured)				
B. Diet related				
Energy intake (kcal/day				
Author's statement on success/maintenance/failure of diet uptake				
C. Exercise related (add additional measures if appropriate)				
Min/day				

Outcome	INTERVENTION GROUP			
	Baseline (mean SD) or n(%)	End trial Time: N=	Mid points data are reported	Last FU Time: N=
Times/week				
D. Component 3 related (add additional measures if appropriate)				
Current smokers				
QoL				
E. T2DM or MetS related				
Progress to T2DM				
Progress to MetS				
HbA1c %				
Fasting glucose				
Insulin resistance				
Blood Pressure: S/D				
Triglycerides				
Total cholesterol				
HDL				
LDL				
F. Adverse clinical events				
G. Diabetic Drug use				

7b. Baseline measures with Outcome measures reported: CONTROL GROUP

Please enter units reported

Document all times when outcomes are reported but only extract end of trial and last FU for now

Outcome	CONTROL GROUP			
	Baseline (mean SD) or n(%)	End trial Time: N=	Other time points reported	Last FU Time: N=
Primary outcome				
Secondary outcomes				
A. Weight related				
Weight (kg; lbs)				
BMI (kg/m^2)				
Waist (cm; in)				
Waist/Hip Ratio				
% body fat (how measured)				
B. Diet related				
Energy intake (kcal/day)				
Author's statement on success/maintenance/failure of diet uptake				
C. Exercise related (add additional measures if appropriate)				
Min/day				
Times/week				
D. Component 3 related (add additional measures if appropriate)				
Current smokers				
QoL				
E. T2DM or MetS related				
Progress to T2DM				
Progress to MetS				
HbA1c				
Fasting glucose				
Insulin resistance				
Blood Pressure: s/d				
Triglycerides				
Total cholesterol				
HDL				

Outcome	CONTROL GROUP			
	Baseline (mean SD) or n(%)	End trial Time: N=	Other time points reported	Last FU Time: N=
LDL				
F. Adverse clinical events				
G. Diabetic Drug use				

8. Adverse events

Note: try to report event/person (e.g if a person gets 3 rashes it is only 1 rash/1 person) (not 3 rashes in the group)

Event	Intervention grp: n/N (%)	Control grp: n/N (%)	Total events

9. Study conclusion

10. Additional comments / additional information

B. 3. Data Extraction Form: Lifestyle interventions review- Breast and Prostate Cancer

This study is related to another study yes ☐ ID(s)_____ NO ☐

1. General information and study characteristics

Study author:			Source of funding: industry ☐ government ☐ foundation ☐ other ☐		
Country(ies):	Year of publication:		Recruitment period _____ Source of population Community (volunteers) ☐ Clinic pts ☐ Outpatient ☐ Inpatient ☐ Registry pts ☐ Other (describe) ☐		
Publication type Abstract ☐ Journal article ☐ Thesis/Dissert. ☐					
Trial characteristics			Number of Centers		
RCT ☐	Individual randomization ☐	Cluster randomization ☐	Single centre ☐	Multicentre ☐ # of centres _____	

2. Population – general characteristics/inclusion exclusion

Inclusion Criteria	
Age	Disease(s) stage or description
Other	
Exclusion criteria Not described ☐	

3. Study objective(s) circle main objective(s)

k. ↓ risk factors for recurrence or progression of cancer: yes
l. ↓ risk factors for coronary heart/vascular disease: yes
m. Improve measures of metabolic variables (e.g. Pr specific antigen, LNCaP cell growth; ↓ C reactive protein, etc): yes
n. Weight loss: yes
o. Prevent functional decline: yes
p. Improve psychological wellbeing: yes
q. Improve self-sufficiency: yes
r. Increase physical activity and intensity: yes
s. Improve dietary behaviors: yes
t. Other _____

4. Characteristics of lifestyle intervention Circle or check all that apply and fill in blanks where indicated

Length of intervention in months: _____
Total Duration of followup in months: _____

H. General program description
   e. Participant specific –individually tailored and regularly monitored: yes

f. Self-directed – participants given program to follow at home, have occasional/regular fu: yes
g. Group focused: most of the program delivered to participants in grp format: yes
h. Other: _____

I. Based on a framework: yes NR
f. Transtheoretical model (stages of readiness): yes
g. Social cognitive theory: yes
h. Cognitive behavioral theory: yes
i. Self determination theory; yes
j. Other _____

J. Diet component
f. Weight loss: yes no
g. Follow established guidelines: name _____
h. Specific diet: circle: vegan, lo fat, hi F&V, hi fish, lo glycemic, hi protein, other: name or general description _____
i. General healthy eating no specific program: yes
j. Other: _____

Delivery mode
f. Individual counseling/education: yes
Who/Frequency/duration
_____
g. Group counseling/education: yes
Who/Frequency/duration
_____
h. Self directed change in eating habits only: yes
i. Materials/food provided: yes _____
j. Follow-up/reinforcement: circle: educational material, log book, workbook, telephone contact, survey completion, newsletter, personal interview, progress reports, other _____

K. Exercise component
e. Aerobic/endurance activities: yes
f. Strength/resistance exercises: yes
g. Stretching: yes
h. General increase in physical activity: yes

Delivery mode
f. Individual counseling/supervision sessions: yes
Who/frequency/duration
_____
g. Group counseling/supervision sessions: yes
Who/ frequency/duration
_____
h. Self directed exercise only: yes
i. Materials/equipment provided: yes _____
j. Follow-up/reinforcement: circle: educational material, log book, workbook, telephone contact, survey, newsletter, personal interview, progress reports, other _____

L. Component(s) in addition to exercise and diet
   i. Stress management: method _____
   j. Behavioral change/modification/motivational guidance: yes
   k. Goal setting and monitoring: Yes
   l. Group discussions/support/education beyond diet and exercise: yes
   m. Scheduled telephone contact/counseling beyond diet and exercise: yes
   n. Other _____

M. Personnel involved: NR
   g. Qualified dietitian: yes
   h. Qualified exercise advisor/consultant/instructor/trainer: yes
   i. Case/nurse manager/counselor: yes
   j. Physician: yes
   k. Behavior therapist: yes
   l. Other _____

5. Characteristics of Control group intervention
   h. Usual/standard care: yes
   i. Attention control (i.e. attention/education/materials in addition to usual care): yes
      Describe _____
   j. Wait list: yes
   k. Diet only
   l. Exercise only
   m. Other _____

Were there more than 2 groups NO ☐ YES ☐ If yes print an outcomes page to extract data

6. Demographic characteristics

Variable	Group 1 Intervention 1	Group 2 (Control grp)	Group 3 Intervention 2	Total
Number of participants randomized				
Number of participants analyzed				
Number of dropouts/withdrawals				
Reasons for dropouts/withdrawal				
Age (*mean-SD or SE; median-IQR)*				
Gender M/F n (%)				
Ethnic distribution (%) or NR				
6. White				
7. African American				

Variable	Group 1 Intervention 1	Group 2 (Control grp)	Group 3 Intervention 2	Total
8. Native American				
9. Hispanic				
10. Other				
SES				
3. Education ≤/> hi school (%)				
4. Income ≤/> $20,000 US (%)				
Time since Dx /completed Tx with Ca				

7a. Baseline measures with Outcome measures reported: INTERVENTION GROUP

Please enter or circle units reported

Document all times when outcomes are reported but only extract end of trial and last FU for now

Outcome	INTERVENTION GROUP			
	Baseline N=	End trial Time: N=	Other time points reported	Last FU Time: N=
Primary outcome: mean; median; SD; SE; IQR; range; n(%); other				
Secondary outcomes				
H. Weight related				
Weight (kg; lbs)				
BMI (kg/m^2)				
Waist (cm; in)				
Waist/Hip Ratio				
% body fat (how measured)				
I. Diet related				
Energy intake				
Author's statement on success/maintenance/failure of diet uptake				
J. Exercise related (add additional measures if appropriate)				
Min/day				

Outcome	INTERVENTION GROUP			
	Baseline N=	End trial Time: N=	Other time points reported	Last FU Time: N=
Times/week				
K. Component 3 related (add additional measures if appropriate)				
Current smokers				
QoL				
L. Breast or prostate cancer related				
Recurrence of Ca				
Additional tx for original or metastatic Ca				
New primary Ca				
Pr specific antigen				
LNcaP cell growth				

b. Baseline measures with Outcome measures reported: CONTROL GROUP

Please enter units reported

Document all times when outcomes are reported but only extract end of trial and last FU for now

Outcome	CONTROL GROUP			
	Baseline (mean SD) or n(%)	End trial Time: N=	Other time points reported	Last FU Time: N=
Primary outcome				
Secondary outcomes				
A. Weight related				
Weight (kg;				

Outcome	CONTROL GROUP			
	Baseline (mean SD) or n(%)	End trial Time: N=	Other time points reported	Last FU Time: N=
lbs)				
BMI (kg/m^2)				
Waist (cm; in)				
Waist/Hip Ratio				
% body fat (how measured)				
B. Diet related				
Energy intake				
Author's statement on success/maintenance/failure of diet uptake				
C. Exercise related (add additional measures if appropriate)				
Min/day				
Times/week				
D. Component 3 related (add additional measures if appropriate)				
Current smokers				
QoL				
E. Breast or prostate cancer related				
Recurrence of Ca				
Additional tx for original or metastatic Ca				
New primary Ca				
Pr specific antigen				
LNcaP cell growth				

8. Adverse events

Note: try to report event/person (e.g if a person gets 3 rashes it is only 1 rash/1 person) (not 3 rashes in the group)

Event	Intervention grp: n/N (%)	Control grp: n/N (%)	Total events

9. Study conclusion

10. Additional comments / additional information

B.3. Risk of Bias: Lifestyle interventions review

Cochrane Collaboration's tool for assessing risk of bias: Lifestyle Interventions

Reviewer's initials: _____ Study ID: _____ Date (dd/mm/yy): _____

Domain	Description	Review authors' judgment	Consensus (circle)
Sequence generation		Was the allocation sequence adequately generated? YES / NO / UNCLEAR	YES NO UNCLEAR
Allocation concealment		Was allocation adequately concealed? YES / NO / UNCLEAR	YES NO UNCLEAR
Blinding of participants, personnel and outcome assessors,	Objective outcomes: Self-reported outcomes:	Was knowledge of the allocated intervention adequately prevented during the study? Objective: YES / NO / UNCLEAR Self-reported: YES / NO / UNCLEAR	Objective: YES NO UNCLEAR Self-reported: YES NO UNCLEAR
Incomplete outcome data, *Outcome:*	Objective outcomes: Self-reported outcomes:	Were incomplete outcome data adequately addressed? Objective: YES / NO / UNCLEAR Self-reported: YES / NO / UNCLEAR	Objective: YES NO UNCLEAR Self-reported: YES NO UNCLEAR
Selective outcome reporting		Are reports of the study free of suggestion of selective outcome reporting? YES / NO / UNCLEAR	YES NO UNCLEAR
Other sources of bias	Baseline imbalance: Funding:	Was the study apparently free of other problems that could put it at a high risk of bias? Baseline: YES / NO / UNCLEAR Funding: YES / NO / UNCLEAR	Baseline: YES NO UNCLEAR Funding: YES NO UNCLEAR
Overall risk of bias	Objective outcomes	HIGH / LOW / UNCLEAR	HIGH/ LOW/ UNCLEAR
	Self-reported outcomes	HIGH / LOW / UNCLEAR	HIGH/ LOW/ UNCLEAR

Guidelines and Decision Rules for Risk of Bias Assessments: Lifestyle Interventions

Sequence generation:
If computer-generated, random number list, flipping coins, randomly picking envelopes, etc. is specified → YES
If the description only includes 'random', 'randomly generated', 'randomized', etc, do not assume additional details → UNCLEAR
If the description is quasi-randomized (e.g. alternate randomization, day of the year, day of the month, birth date, birth month, beginning letter of last name, availability of investigator or specialist, etc) → NO
Allocation concealment:
If the assignment is conducted by central telephone, pharmacy, etc → YES
If dark (or opaque), sealed, sequentially-numbered envelopes are used → YES
If the envelopes are not stated to dark and sealed, or sequentially-numbered → UNCLEAR
Note: sequential numbering of the envelopes is only required for adequate allocation concealment if the method of randomization was anything other than randomly picking envelopes (i.e. the envelopes were only used for allocation concealment and not as part of the randomization process).

Blinding: Objective outcomes
No blinding, but outcome measures are not likely to be influenced by lack of blinding → YES
Blinding: Self-reported outcomes
If the study was stated to be blinded (masked) and the blinding is considered to be possible (i.e., participants and key personnel blinded to study hypothesis), and not likely to be broken → YES
If the study is only stated to be blinded, double-blinded, etc. without any further details → UNCLEAR
If the study states the use of a placebo (dummy) but with no further details → UNCLEAR
If no mention of blinding → NO

Incomplete outcome data (all outcomes):
Look for intention-to-treat analysis (all randomized pts. are analyzed) → YES
If all participants were accounted for (i.e. no drop-outs or censored analysis conducted) → YES
If the numbers and reasons for withdrawal/drop-outs were described and comparable across groups (and ≤ approximately 10%) → YES
If there is between 10% - 30% drop-out and no ITT analysis → UNCLEAR
If there is greater 30% drop-out and no ITT analysis → NO

Selective outcome reporting:
If the study protocol is available (referenced in the manuscript), compare the outcomes reported in the publication to those specified in the protocol. If they match → YES
If the study protocol is available (referenced in the manuscript), compare the outcomes reported in the publication to those specified in the protocol. If they do not match, but there is reference to another publication with this information presented → YES
If the study protocol is not available, compare the outcomes reported in the Methods and Results sections. If they match → YES

Other sources of bias:
Assess for baseline imbalances that could have biased the results (or were not accounted for).
Assess for inappropriate influence of funders that could have biased the results:
If industry sponsor is acknowledged and there is a clear statement regarding no involvement of sponsor in trial conduct or data management/analysis, or co-authorship → YES
If industry sponsor is acknowledged with no further information provided or (co)author works for industry → NO
If there is no mention of funding source → UNCLEAR

Overall assessment of ROB:
Low risk of bias → if reviewer said YES for all domains
Unclear risk of bias → if reviewer said UNCLEAR for one or more key domain
High risk of bias → if reviewer said NO for one or more key domain

Table 8.5.c: Criteria for judging risk of bias in the 'Risk of bias' assessment tool

SEQUENCE GENERATION Was the allocation sequence adequately generated? [Short form: Adequate sequence generation?]	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	The investigators describe a random component in the sequence generation process such as: Referring to a random number table; Using a computer random number generator; Coin tossing; Shuffling cards or envelopes; Throwing dice; Drawing of lots; Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgment of 'NO' (i.e. high risk of bias).	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: Sequence generated by odd or even date of birth; Sequence generated by some rule based on date (or day) of admission; Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgment or some method of non-random categorization of participants, for example: Allocation by judgment of the clinician; Allocation by preference of the participant; Allocation based on the results of a laboratory test or a series of tests; Allocation by availability of the intervention.
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgment of 'Yes' or 'No'.
ALLOCATION CONCEALMENT Was allocation adequately concealed? [Short form: Allocation concealment?]	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: Central allocation (including telephone, web-based, and pharmacy-controlled, randomization); Sequentially numbered drug containers of identical appearance; Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgment of 'NO' (i.e. high risk of bias).	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: Using an open random allocation schedule (e.g. a list of random numbers); Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); Alternation or rotation; Date of birth; Case record number; Any other explicitly unconcealed procedure.
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgment of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS Was knowledge of the allocated interventions adequately prevented during the study? [Short form: Blinding?]	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	Any one of the following: No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; Either participants or some key study personnel were not blinded, but outcome

	assessment was blinded and the non-blinding of others unlikely to introduce bias.
Criteria for the judgment of 'NO' (i.e. high risk of bias).	Any one of the following: No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: Insufficient information to permit judgment of 'Yes' or 'No'; The study did not address this outcome.
INCOMPLETE OUTCOME DATA Were incomplete outcome data adequately addressed? [Short form: Incomplete outcome data addressed?]	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	Any one of the following: No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods.
Criteria for the judgment of 'NO' (i.e. high risk of bias).	Any one of the following: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; Potentially inappropriate application of simple imputation.
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: Insufficient reporting of attrition/exclusions to permit judgment of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided); The study did not address this outcome.
SELECTIVE OUTCOME REPORTING Are reports of the study free of suggestion of selective outcome reporting? [Short form: Free of selective reporting?]	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	Any of the following: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgment of 'NO' (i.e. high risk of bias).	Any one of the following: Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that

	they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgment of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.
OTHER POTENTIAL THREATS TO VALIDITY Was the study apparently free of other problems that could put it at a risk of bias? [Short form: Free of other bias?]	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	The study appears to be free of other sources of bias.
Criteria for the judgment of 'NO' (i.e. high risk of bias).	There is at least one important risk of bias. For example, the study: Had a potential source of bias related to the specific study design used; or Stopped early due to some data-dependent process (including a formal-stopping rule); or Had extreme baseline imbalance; or Has been claimed to have been fraudulent; or Had some other problem.
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	There may be a risk of bias, but there is either: Insufficient information to assess whether an important risk of bias exists; or Insufficient rationale or evidence that an identified problem will introduce bias.

Appendix C. List of Companion Publications

Type 2 Diabetes

Main publication	Companion studies
Gaede P, Vedel P, Parving HH, et al. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: The Steno type 2 randomized study. Lancet 1999;353(9153):617-22.	Gaede P, Beck M, Vedel P, et al. Limited impact of lifestyle education in patients with Type 2 diabetes mellitus and microalbuminuria: results from a randomized intervention study. Diabet Med 2001;18(2):104-8.
	Gaede P, Lund-Andersen H, Parving HH, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358(6):580-91.
	Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348(5):383-93.
Keyserling TC, Samuel-Hodge CD, Ammerman AS, et al. A randomized trial of an intervention to improve self-care behaviors of African-American women with type 2 diabetes: impact on physical activity. Diabetes Care 2002;25(9):1576-83.	Keyserling TC, Ammerman AS, Samuel-Hodge CD, et al. A diabetes management program for African American women with type 2 diabetes. Diabetes Educ 2000;26(5):797-805.
Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care 2007;30(6):1374-83.	Bray GA. Baseline characteristics of the randomized cohort from the Look AHEAD (Action for Health in Diabetes) study. Diab Vasc Dis Res 2006;3(3):202-15.
	Espeland M. Look AHEAD (Action for Health in Diabetes): Design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Control Clin Trials 2003;24(5):610-28.
	Gorin AA, Niemeier HM, Hogan P, et al. Binge eating and weight loss outcomes in overweight and obese individuals with type 2 diabetes: results from the Look AHEAD trial. Arch Gen Psychiatry 2008;65(12):1447-55.
	Jakicic JM, Jaramillo SA, Balasubramanyam A, et al. Effect of a lifestyle intervention on change in cardiorespiratory fitness in adults with type 2 diabetes: results from the Look AHEAD Study. Int J Obes 2009;33(3):305-16.
	Wadden TA. The look AHEAD study: A description of the lifestyle intervention and the evidence supporting it. Obesity 2006;14(5):737-52.
	Wadden TA, West DS, Neiberg RH, et al. One-year weight losses in the Look AHEAD study: factors associated with success. Obesity 2009;17(4):713-22.
	Williamson DA, Rejeski J, Lang W, et al. Impact of a weight management program on health-related quality of life in overweight adults with type 2 diabetes. Arch Intern Med 2009;169(2):163-71.
Mayer-Davis EJ, D'Antonio AM, Smith SM, et al. Pounds off with empowerment (POWER): A clinical trial of weight	Culturally appropriate lifestyle interventions promote weight loss in rural dwelling people with type 2 diabetes. Evidence-

management strategies for black and white adults with diabetes who live in medically underserved rural communities. Am J Public Health 2004;94(10):1736-42.	Based Healthcare and Public Health 2005;9(3):231-2.
	Mayer-Davis EJ, D'antonio A, Martin M, et al. Pilot study of strategies for effective weight management in type 2 diabetes: Pounds off with empowerment (POWER). Fam Commun Health 2001;24(2):27-35.
	Parra-Medina D, D'antonio A, Smith SM, et al. Successful recruitment and retention strategies for a randomized weight management trial for people with diabetes living in rural, medically underserved counties of South Carolina: the POWER study. J Am Diet Assoc 2004;104(1):70-5.
Menard J, Payette H, Baillargeon J-P, et al. Efficacy of intensive multitherapy for patients with type 2 diabetes mellitus: A randomized controlled trial. Can Med Assoc J 2005;173(12):1457-63.	Menard J, Payette H, Dubuc N, et al. Quality of life in type 2 diabetes patients under intensive multi-therapy. Diabetes Metab 2007;33(1):54-60.
Toobert DJ, Glasgow RE, Strycker LA, et al. Biologic and quality-of-life outcomes from the Mediterranean Lifestyle Program: A randomized clinical trial. Diabetes Care 2003;26(8):2288-93.	Barrera M, Jr., Toobert DJ, Angell KL, et al. Social support and social-ecological resources as mediators of lifestyle intervention effects for type 2 diabetes. J Health Psychol 2006;11(3):483-95.
	Toobert DJ, Glasgow RE, Strycker LA, et al. Long-term effects of the Mediterranean lifestyle program: A randomized clinical trial for postmenopausal women with type 2 diabetes. International Journal of Behavioral Nutrition and Physical Activity 4, 2007 Article Number: 1 Date of Publication: 2007 2007.
	Toobert DJ, Strycker LA, Glasgow RE, et al. Effects of the Mediterranean lifestyle program on multiple risk behaviors and psychosocial outcomes among women at risk for heart disease. Ann Behav Med 2005;29(2):128-37.
	Toobert DJ, Strycker LA, Glasgow RE, et al. Enhancing support for health behavior change among women at risk for heart disease: the Mediterranean Lifestyle Trial. Health Educ Res 2002;17(5):574-85.

Metabolic Syndrome

Main publication	Companion studies
Bo S, Ciccone G, Baldi C, et al. Effectiveness of a lifestyle intervention on metabolic syndrome. A randomized controlled trial. J Gen Intern Med 2007;22(12):1695-703.	Bo S, Ciccone G, Baldi I, et al. Plasma visfatin concentrations after a lifestyle intervention were directly associated with inflammatory markers. Nutr Metab Cardiovasc Dis 2009;19(6):423-30.
	Bo S, Ciccone G, Guidi S, et al. Diet or exercise: What is more effective in preventing or reducing metabolic alterations? Eur J Endocrinol 2008;159(6):685-91.
	Bo S, Gambino R, Ciccone G, et al. Effects of TCF7L2 polymorphisms on glucose values after a lifestyle intervention. Am J Clin Nutr 2009;90(6):1502-8.
Eriksson J, Lindstrom J, Valle T, et al. Prevention of Type II diabetes in subjects with impaired glucose tolerance: The Diabetes Prevention Study (DPS) in Finland. Study design and 1-year interim report on the feasibility of the lifestyle intervention programme. Diabetologia 1999;42(7):793-801.	Evans MF. Can we prevent high-risk patients from getting type 2 diabetes? Can Fam Phys 2002;48(FEB.):279-81.
	Hamalainen H, Ronnemaa T, Virtanen A, et al. Improved fibrinolysis by an intensive lifestyle intervention in subjects with impaired glucose tolerance. The Finnish Diabetes Prevention Study. Diabetologia 2005;48(11):2248-53.
	Herder C, Peltonen M, Koenig W, et al. Anti-inflammatory effect of lifestyle changes in the Finnish Diabetes Prevention Study. Diabetologia 2009;52(3):433-42.
	Kilpelainen TO, Lakka TA, Laaksonen DE, et al. Physical activity modifies the effect of SNPs in the SLC2A2 (GLUT2) and ABCC8 (SUR1) genes on the risk of developing type 2 diabetes. Physiological Genomics 2007;31(2):264-72.
	Kubaszek A, Pihlajamaki J, Komarovski V, et al. Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: The Finnish Diabetes Prevention study. Diabetes 2003;52(7):1872-6
	Laaksonen DE, Lindstrom J, Lakka TA, et al. Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study. Diabetes 2005;54(1):158-65.
	Laukkanen O. Common polymorphisms in the genes regulating the early insulin signalling pathway: effects on weight change and the conversion from impaired glucose tolerance to Type 2 diabetes. The Finnish Diabetes Prevention Study. Diabetologia 2004;(5):871-7.
	Lindstrom J. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006;(9548):1673-9.
	Lindstrom J, Eriksson JG, Valle TT, et al. Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. J Am Soc Nephrol 2003;14(7:Suppl 2):Suppl-13.
	Lindstrom J, Louheranta A, Mannelin M, et al. The Finnish

	Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 2003;26(12):3230-6.
	Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New Engl J Med 2001;344(18):1343-50.
	Tuomilehto H, Peltonen M, Partinen M, et al. Sleep duration, lifestyle intervention, and incidence of type 2 diabetes in impaired glucose tolerance: The Finnish Diabetes Prevention Study. Diabetes Care 2009;32(11):1965-71.
	Uusitupa M, Peltonen M, Lindstrom J, et al. Ten-year mortality and cardiovascular morbidity in the Finnish Diabetes Prevention Study - Secondary analysis of the randomized trial. PLoS ONE 2009;4(5).
	Wikstrom K, Peltonen M, Eriksson JG, et al. Educational attainment and effectiveness of lifestyle intervention in the Finnish Diabetes Prevention Study. Diabetes Res Clin Pract 2009;86(1).
Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346(6):393-403.	Diabetes Prevention Program Research Group, Crandall J, Schade D, et al. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 2006;61(10):1075-81.
	Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374(9702):1677-86.
	Fujimoto WY, Jablonski KA, Bray GA, et al. Body size and shape changes and the risk of diabetes in the diabetes prevention program. Diabetes 2007;56(6):1680-5.
	Goldberg RB, Temprosa M, Haffner S, et al. Effect of progression from impaired glucose tolerance to diabetes on cardiovascular risk factors and its amelioration by lifestyle and metformin intervention: the Diabetes Prevention Program randomized trial by the Diabetes Prevention Program Research Group. Diabetes Care 2009;32(4):726-32.
	Haffner S, Temprosa M, Crandall J, et al. Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. Diabetes 2005;54(5):1566-72.
	Orchard TJ, Temprosa M, Goldberg R, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med 2005;142(8):611-9.
	Perreault L, Ma Y, gogo-Jack S, et al. Sex differences in diabetes risk and the effect of intensive lifestyle modification in the Diabetes Prevention Program. Diabetes Care

	2008;31(7):1416-21.
	Ratner R, Goldberg R, Haffner S, et al. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. Diabetes Care 2005;28(4):888-94.
	The Diabetes Prevention Program (DPP): Description of lifestyle intervention. Diabetes Care 2002;25(12):2165-71.
Mensink M, Feskens EJ, Saris WH, et al. Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht (SLIM): preliminary results after one year. Int J Obes Relat Metab Disord 2003;27(3):377-84.	Corpeleijn E, Feskens EJ, Jansen EH, et al. Improvements in glucose tolerance and insulin sensitivity after lifestyle intervention are related to changes in serum fatty acid profile and desaturase activities: the SLIM study. Diabetologia 2006;49(10):2392-401.
	Corpeleijn E FEJEM. Lifestyle intervention and adipokine levels in subjects at high risk for type 2 diabetes: the Study on Lifestyle intervention and Impaired glucose tolerance Maastricht (SLIM). Diabetes Care 2007;(12):3125-7.
	Mensink M, Blaak EE, Corpeleijn E, et al. Lifestyle intervention according to general recommendations improves glucose tolerance. Obes Res 2003;11(12):1588-96.
	Mensink M, Blaak EE, Wagenmakers AJ, et al. Lifestyle intervention and fatty acid metabolism in glucose-intolerant subjects. Obes Res 2005;13(8):1354-62.
	Mensink M, Corpeleijn E, Feskens EJ, et al. Study on lifestyle-intervention and impaired glucose tolerance Maastricht (SLIM): design and screening results. Diabetes Res Clin Pract 2003;61(1):49-58
	Roumen C, Corpeleijn E, Feskens EJ, et al. Impact of 3-year lifestyle intervention on postprandial glucose metabolism: the SLIM study. Diabet Med 2008;25(5):597-605.
Oldroyd JC, Unwin NC, White M, et al. Randomised controlled trial evaluating the effectiveness of behavioural interventions to modify cardiovascular risk factors in men and women with impaired glucose tolerance: Outcomes at 6 months. Diabetes Res Clin Pract 2001;52(1):29-43.	Oldroyd JC, Unwin NC, White M, et al. Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance. Diabetes Res Clin Pract 2006;72(2):117-27.
Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: The Da Qing IGT and diabetes study. Diabetes Care 1997;20(4):537-44.	Li G, Hu Y, Yang W, et al. Effects of insulin resistance and insulin secretion on the efficacy of interventions to retard development of type 2 diabetes mellitus: the DA Qing IGT and Diabetes Study. Diabetes Res Clin Pract 2002;58(3):193-200.
	Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet 2008;371(9626):1783-9.

Breast and Prostate Cancer

Main publication	Companion studies
Demark-Wahnefried W, Clipp EC, Morey MC, et al. Lifestyle intervention development study to improve physical function in older adults with cancer: Outcomes from project LEAD. J Clin Oncol 2006;24(21):3465-73.	DeMark-Wahnefried W, Morey MC, Clipp EC, et al. Leading the way in exercise and diet (Project LEAD): Intervening to improve function among older breast and prostate cancer survivors. Control Clin Trials 2003;24(2):206-23.
Morey MC, Snyder DC, Sloane R, et al. Effects of home-based diet and exercise on functional outcomes among older, overweight long-term cancer survivors: RENEW: a randomized controlled trial. Journal of the American Medical Association 2009;301(18):1883-91.	Mosher CE, Sloane R, Morey MC, et al. Associations between lifestyle factors and quality of life among older long-term breast, prostate, and colorectal cancer survivors. Cancer 2009;115(17):4001-9.
	Snyder DC, Morey MC, Sloane R, et al. Reach out to ENhancE Wellness in Older Cancer Survivors (RENEW): design, methods and recruitment challenges of a home-based exercise and diet intervention to improve physical function among long-term survivors of breast, prostate, and colorectal cancer. PSYCHO ONCOL 2009;18(4):429-39.
Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. J Urol 1069;174(3):1065-9.	Daubenmier JJ, Weidner G, Marlin R, et al. Lifestyle and health-related quality of life of men with prostate cancer managed with active surveillance. Urology 2006;67(1):125-30.
	Frattaroli J, Weidner G, Dnistrian AM, et al. Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. Urology 2008;72(6):1319-23.
	Ornish DM LKFWPECP. Dietary trial in prostate cancer: Early experience and implications for clinical trial design. Urology 2001;4(Suppl 1):200-1.

Appendix D. Excluded Studies

156 studies were excluded from the review. Reasons for exclusion include: publication type (n=11), study design (n=17), population (n=28), intervention (n=33), length of intervention or postintervention followup (n=39), comparator (n=5), outcomes (n=16), outcomes not separated by group (n=1), language (n=1), and duplicate (n=1). In addition, we were unable to obtain copies of 4 studies.

Publication type (n = 11)

1. Culturally appropriate lifestyle interventions promote weight loss in rural dwelling people with type 2 diabetes. Evidence-Based Healthcare and Public Health 2005;9(3):231-2.
2. Lifestyle therapy for prostate cancer: does it work? Harv Mens Health Watch 2007;11(12):1-3.
3. Preventing type 2 diabetes: lifestyle changes work better than drugs. Health News 2002;8(4):6.
4. Avenell A, Brown TJ, McGee MA, et al. What interventions should we add to weight reducing diets in adults with obesity? A systematic review of randomized controlled trials of adding drug therapy, exercise, behaviour therapy or combinations of these interventions. Journal of Human Nutrition and Dietetics 2004;17(4):293-316.
5. Blumenthal JA, Sherwood A, Gullette ECD, et al. Biobehavioral approaches to the treatment of essential hypertension. J Consult Clin Psychol 2002;70(3):569-89.
6. Davies M. The reality of glycaemic control in insulin treated diabetes: Defining the clinical challenges. Int J Obes 2004;28(SUPPL. 2):S14-S22.
7. Khare MM, Huber R, Carpenter RA, et al. A lifestyle approach for reducing cardiovascular risk factors in underserved women: Design and methods of the Illinois WISEWOMAN program. J Women's Health 2009;18(3):409-19.
8. Rollins G. Modest lifestyle changes significantly reduce the risk of diabetes, study finds. Report on Medical Guidelines & Outcomes Research 2005;12(18):1-2.
9. Wylie-Rosett J, Herman WH, Goldberg RB. Lifestyle intervention to prevent diabetes: intensive and cost effective. Curr Opin Lipidol 2006;17(1):37-44.
10. Yamaoka K, Tango T. Efficacy of lifestyle education to prevent type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetes Care 2005;28(11):2780-6.
11. Young D, Furler J, Vale M, et al. Patient Engagement and Coaching for Health: The PEACH study - A cluster randomised controlled trial using the telephone to coach people with type 2 diabetes to engage with their GPs to improve diabetes care: A study protocol. BMC Fam Pract 2007;8.

Study design (n = 17)

1. Brunzell JD. Hypertriglyceridemia. New Engl J Med 2007;357(10):1009-17.
2. Doggrell SA. Metformin & lifestyle intervention prevent type 2 diabetes: Lifestyle intervention has the greater effect. Expert Opinion on Pharmacotherapy 2002;3(7):1011-3.
3. Domenech MI, Assad D, Mazzei ME, et al. Evaluation of the effectiveness of an ambulatory teaching/treatment programme for non-insulin dependent (type 2) diabetic patients. Acta Diabetol 1995;32(3):143-7.
4. Fredrikson GN, Hedblad B, Nilsson JA, et al. Association between diet, lifestyle, metabolic cardiovascular risk factors, and plasma C-reactive protein levels. Metab Clin Exp 2004;53(11):1436-42.
5. Harwell TS, Moore K, McDowall JM, et al. Cardiovascular risk factors in Montana American Indians with and without diabetes. Am J Prev Med 2003;24(3):265-9.
6. Hernandez-Ronquillo L, Tellez-Zenteno JF, Garduno-Espinosa J, et al. Factors associated with therapy noncompliance in type-2 diabetes patients. Salud Publica Mex 2003;45(3):191-7.
7. Kaati G, Bygren L-O, Vester M, et al. Outcomes of comprehensive lifestyle modification in inpatient setting. Patient Educ Couns 2006;62(1):95-103.
8. Kosmala W, O'Moore-Sullivan T, Plaksej R, et al. Improvement of left ventricular function by lifestyle intervention in obesity: Contributions of weight loss and reduced insulin resistance. Diabetologia 2009;52(11):2306-16.
9. Krook A, Holm I, Pettersson S, et al. Reduction of risk factors following lifestyle modification programme in subjects with type 2 (non-insulin

dependent) diabetes mellitus. Clin Physiol Funct Imaging 2003;23(1):21-30.
10. Linday LA. Trivalent chromium and the diabetes prevention program. Med Hypotheses 1997;49(1):47-9.
11. Lowe J, Linjawi S, Mensch M, et al. Flexible eating and flexible insulin dosing in patients with diabetes: Results of an intensive self-management course. Diabetes Res Clin Pract 2008;80(3):439-43.
12. McBride PE, Einerson JA, Grant H, et al. Putting the Diabetes Prevention Program into practice: a program for weight loss and cardiovascular risk reduction for patients with metabolic syndrome or type 2 diabetes mellitus. Journal of Nutrition, Health & Aging 2008;12(10):745S-9S.
13. Ornish D, Lin J, Daubenmier J, et al. Increased telomerase activity and comprehensive lifestyle changes: a pilot study. Lancet Oncology 2008;9(11):1048-57.
14. Oza N, Eguchi Y, Mizuta T, et al. A pilot trial of body weight reduction for nonalcoholic fatty liver disease with a home-based lifestyle modification intervention delivered in collaboration with interdisciplinary medical staff. J Gastroenterol 2009;44(12):1203-8.
15. Prueksaritanond S, Tubtimtes S, Asavanich K, et al. Type 2 diabetic patient-centered care. J Med Assoc Thailand 2004;87(4):345-52.
16. Satoh N, Shimatsu A, Kato Y, et al. Evaluation of the cardio-ankle vascular index, a new indicator of arterial stiffness independent of blood pressure, in obesity and metabolic syndrome. Hypertens Res 2008;31(10):1921-30.
17. Schafer S, Kantartzis K, Machann J, et al. Lifestyle intervention in individuals with normal versus impaired glucose tolerance. Eur J Clin Invest 2007;37(7):535-43.

Population (n = 28)

1. Ades PA, Savage PD, Toth MJ, et al. High-calorie-expenditure exercise: A new approach to cardiac rehabilitation for overweight coronary patients. Circulation 2009;119(20):2671-8.
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Length of intervention or postintervention followup (n=39)

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Comparator (n=5)

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Outcomes (n=16)

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Outcomes not separated by group (n=1)

1. Djuric Z, DiLaura NM, Jenkins I, et al. Combining weight-loss counseling with the Weight Watchers plan for obese breast cancer survivors. Obes Res 2002;10(7):657-65.

Language (n=1)

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Unable to retrieve (n=4)

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Duplicate (n=1)

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Appendix E. GRADE Tables

Grading the body of evidence: type 2 diabetes

Outcome	# RCTs; # subjects	Risk of bias	Consistency	Directness	Precision	Strength of evidence
Primary outcomes						
All-cause mortality (13 yr followup)	1; 93	Unclear	Unknown (single study)	Direct	Precise (RR_{meds} = 0.60; 95% CI: 0.4, 0.9)	Low
Cumulative incidence of CVD events (13 yr followup)	1; 93	Unclear	Unknown (single study)	Direct	Precise (RR_{meds} = 0.49; 95% CI: 0.34, 0.71)	Low
Autonomic neuropathy progression (13 yr followup)	1; 93	Unclear	Unknown (single study)	Direct	Precise (RR_{meds} = 0.75; 95% CI: 0.57, 0.99)	Low
Development of nephropathy (13 yr followup)	1; 93	Unclear	Unknown (single study)	Direct	Precise (RR_{meds} = 0.54; 95% CI: 035, 0.85)	Low
Development of retinopathy (13 yr followup)	1; 93	Unclear	Unknown (single study)	Direct	Precise (RR_{meds} = 0.76; 95% CI: 0.58, 0.99)	Low
Peripheral neuropathy progression (13 yr followup)	1; 93	Unclear	Unknown (single study)	Direct	Imprecise (RR_{meds} = 0.96; 95% CI: 0.73, 1.26)	Low
Change in body composition						
BMI (EoI)	4; 544	Unclear	Consistent	Indirect	Precise (MD_{all} = -0.48; 95% CI: -0.92, -0.05)	Moderate
BMI (6 mo postintervention)	1; 61	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = 1.0; 95%CI: -1.84, 3.84)	Insufficient
BMI (13 yr followup)	1; 93	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = -1.1; 95% CI: -3.14, 0.94)	Insufficient
Weight change (EoI)	5; 5,726	Unclear	Consistent	Indirect	Precise ($MD_{no\ meds}$ = -1.53; 95% CI: -2.09, -0.97; MD_{meds} = -15.4; 95% CI: -16.1, -14.5)	Moderate
Weight change (6 mo postintervention)	1; 171	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = 1.14; 95% CI: -5.39, 7.67)	Insufficient
Weight change (4 yr followup)	1; 4,815	Unclear	Unknown (single study)	Indirect	Precise (MD_{meds} = -11.62; 95% CI: -12.37, -10.87)	Insufficient

Metabolic variables						
Fasting plasma glucose (EoI)	3; 5,106	Unclear	Inconsistent	Indirect	Imprecise ($MD_{no\ meds}$ = -0.33; 95% CI: -0.83, 1.49; MD_{meds} = -1.02; 95% CI: -1.85, -0.19)	Low
Fasting plasma glucose (6 mo postintervention)	1; 61	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = -1.0; 95% CI: -2.61, 0.61)	Insufficient
Fasting plasma glucose (13 yr followup)	1; 93	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = -0.16; 95% CI: -1.47, 1.15)	Insufficient
HbA1c (EoI)	10; 6,411	Unclear	Inconsistent	Indirect	Imprecise ($MD_{no\ meds}$ = -0.09; 95% CI: -0.58, 0.75; MD_{meds} = 0.77; 95% CI: -1.18, -0.36)	Low
HbA1c (6 mo postintervention)	2; 232	Unclear	Inconsistent	Indirect	Imprecise (MD_{all} = 0.09; 95% CI: -0.58, 0.75)	Insufficient
HbA1c (13 yr followup)	1; 130	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = -0.70; 95% CI: -1.41, 0.01)	Insufficient
HDL cholesterol (EoI)	6; 5,923	Unclear	Inconsistent	Indirect	Imprecise ($MD_{no\ meds}$ = -0.01; -0.04, 0.05; MD_{meds} = 0.05; 95% CI: 0.03, 0.07)	Low
HDL cholesterol (6 mo postintervention)	1; 171	Unclear	Unknown (single study)	Indirect	Imprecise ($MD_{no\ meds}$ = -0.04; 95% CI: -0.16, 0.09)	Insufficient
HDL cholesterol (13 yr followup)	1; 93	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = 0.08; 95% CI: -0.07, 0.22)	Insufficient
LDL cholesterol (EoI)	5; 5,735	Unclear	Inconsistent	Indirect	Imprecise ($MD_{no\ meds}$ = -0.09; 95% CI: -0.26, 0.08; MD_{meds} = -0.27; 95% CI: -0.92, 0.37)	Low
LDL cholesterol (6 mo postintervention)	1; 61	Unclear	Unknown (single study)	Indirect	Precise (MD_{meds} = -0.59; 95% CI: -1.07, -0.11)	Insufficient
LDL cholesterol (13 yr followup)	1; 93	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = -0.05; 95% CI: -0.4, 0.3)	Insufficient
Total cholesterol (EoI)	5; 964	Unclear	Inconsistent	Indirect	Imprecise (MD_{all} -0.13; 95% CI: -0.27, 0.01),	Low
Total cholesterol (6 mo postintervention)	1; 170	Unclear	Unknown (single study)	Indirect	Imprecise ($MD_{no\ meds}$ = 0.01; 95% CI: -0.35, 0.36)	Insufficient
Total cholesterol (13 yr followup)	1; 93	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = 0.38; 95% CI: -0.06, 0.82)	Insufficient

Triglycerides (EoI)	5; 5,583	Unclear	Consistent	Indirect	Imprecise (MD_{all} = -0.17; 95% CI: -0.23, -0.12)	Low
Triglycerides (6 mo postintervention)	1; 61	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = -0.18; 95% CI: -1.47, 1.11)	Insufficient
Triglycerides (13 yr followup)	1; 93	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = -0.03; 95% CI: -0.67, 0.61)	Insufficient
Blood pressure						
Diastolic BP (EoI)	6; 5,905	Unclear	Inconsistent	Indirect	Imprecise ($MD_{no\ meds}$ = 0.32; 95% CI: -1.43, 20.7; MD_{meds} = -1.2; 95% CI: -1.75, 0.65)	Low
Diastolic BP (6 mo postintervention)	1; 61	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = 0; 95% CI: -5.07, 5.07)	Insufficient
Diastolic BP (13 yr followup)	1; 93	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds} = 2.0; 95% CI: -1.90, 5.90)	Insufficient
Systolic BP (EoI)	6; 5,905	Unclear	Inconsistent	Indirect	Imprecise ($MD_{no\ meds}$ = -1.89; 95% CI: -0.57, 4.35; MD_{meds} -6.89; 95% CI: -14.42, 0.64)	Low
Systolic BP (6 mo postintervention)	1; 61	Unclear	Unknown (single study)	Indirect	Imprecise (MD_{meds}= -3.0; 95% CI: -12.4, 6.4)	Insufficient
Systolic BP (13 yr followup)	1; 93	Unclear	Unknown (single study)		Imprecise (MD_{meds} = -3.0; 95% CI: -9.79, 3.79)	Insufficient
Change in physical activity						
Exercise (EoI)	5; 973	Unclear	Consistent	Indirect	Precise (SMD_{all} = 0.45; 95% CI: 0.2, 0.71)	Low
Exercise (6 mo postintervention)	3; 469	Unclear	Consistent	Indirect	Precise (SMD_{all} = 0.5; 95% CI: 0.1, 0.89)	Low
Exercise (1 yr followup)	1; 2556	Unclear	Unknown (single study)	Indirect	Precise (SMD_{meds} = 0.53; 95% CI: 0.44, 0.61)	Insufficient
Exercise (2 yr followup) postintervention)	1; 245	Unclear	Unknown (single study)	Indirect	Precise ($SMD_{no\ meds}$ = 0.41; 95% CI: 0.16, 0.67)	Insufficient
Exercise (8 yr followup)	1; 130	Unclear	Unknown (single study)	Indirect	Imprecise (SMD_{meds} = 0.11; 95% CI: -0.24, 0.45)	Insufficient
Change in dietary or nutrient intake						
Energy intake (EoI)	4; 728	Unclear	Inconsistent	Indirect	Imprecise (SMD_{all} = -0.17; 95% CI: -0.33, -0.01)	Low
Energy intake (6 mo postintervention)	1; 61	Unclear	Unknown (single study)	Indirect	Imprecise (SMD_{meds} = -0.12; 95% CI: -0.59, 0.36)	Insufficient
Energy intake (8 yr followup)	1; 130	Unclear	Unknown (single study)	Indirect	Imprecise (SMD_{meds} = 0;	Insufficient

					95% CI: -0.35, 0.34)	
SFA intake (EoI)	4; 663	Unclear	Consistent	Indirect	Imprecise (SMD_{all} = -0.31; 95% CI: -0.68, 0.07)	Low
SFA intake (6 mo postintervention	2; 298	Unclear	Consistent	Indirect	Imprecise (SMD_{all} = -0.45 95% CI: -0.79, -0.10)	Insufficient
SFA intake (8 yr followup)	1; 130	Unclear	Unknown (single study)	Indirect	Precise (SMD_{meds} = -0.68; 95% CI: -1.03, -0.32)	Insufficient

Grading the body of evidence: metabolic syndrome

Outcome	# RCTs; # subjects	Risk of bias	Consistency	Directness	Precision	Strength of evidence
Primary outcomes						
CVD events (Followup: 6-10 yr)	2; 1,035	Unclear	Consistent	Direct	Imprecise (RR = 1.02; 95% CI: 0.73, 1.42) Imprecise (HR = 0.96; 95% CI: 0.76-1.44)	Insufficient
CVD events (Followup: 20 yr)	1; 400	Unclear	Unknown (single study)	Direct	Imprecise (HR = 0.98; 95% CI: 0.71-1.37)	Insufficient
Development of type 2 diabetes (EoI: duration 1 -6 yr)	3; 1,371	Unclear	Consistent	Direct	Precise (RR = 0.44; 95% CI: 0.2, 0.93)	Moderate
Development of type 2 diabetes (Followup: 4-10 yr)	3; 2,611	Unclear	Consistent	Direct	Precise ($RR_{4\ yr}$ = 0.56; 95% CI: 0.48, 0.64; $RR_{6\ yr}$ = 0.44; 95% CI: 0.29, 0.68)	Moderate
Death (Followup: 10-20 yr)	2; 905	Unclear	Consistent	Direct	Imprecise ($RR_{10\ yr}$ = 0.58; 95% CI: 0.21, 1.57; $HR_{20\ yr}$ = 0.83; 95% CI: 0.48, 1.40)	Insufficient
Change in body composition						
BMI (EoI)	4; 914	Unclear	Consistent	Indirect	Precise (MD = -0.95; 95% CI: -1.49, -0.41)	Moderate
BMI (4 yr followup)	1; 335	Unclear	Unknown (single study)	Indirect	Precise (MD = -0.92; 95% CI: -1.32, -0.53)	Insufficient
Waist circumference (EoI)	5; 968	Unclear	Consistent	Indirect	Precise (MD = -3.73; 95% CI: -4.87, -2.59)	Moderate
Waist circumference (4 yr followup)	1; 335	Unclear	Unknown (single study)	Indirect	Precise (MD = -1.86; 95% CI: -3.49, -0.22)	Insufficient
Weight change (EoI)	6; 3,106	Unclear	Consistent	Indirect	Precise (MD = -7.8; 95% CI: -11.92, -3.67)	Moderate
Weight change (4 yr followup)	2: 1,341	Unclear	Consistent	Indirect	Precise (MD= -5.88; 95% CI: -8.05, -3.71)	Low
Weight change (10 yr followup)	1; 1,842	Unclear	Unknown (single study)	Indirect	Imprecise (MD = -0.94; 95% CI: -5.07, 3.19)	Insufficient
Change in metabolic variables						
Fasting plasma glucose (EoI)	5; 2,971	Unclear	Inconsistent	Indirect	Precise (MD = -0.29; 95% CI: -0.35, -0.23)	Moderate
Fasting plasma glucose (10 yr followup)	1; 1,842	High	Unknown (single study)	Indirect	Precise (MD = 0.10; 95% CI: 0.03, 0.18)	Insufficient

HbA1c (EoI)	2; 2,148	High	Inconsistent	Indirect	Imprecise (MD = -0.10; 95% CI: -0.28, 0.08)	Insufficient
HbA1c (10 yr followup)	1; 1,842	High	Unknown (single study)	Indirect	Precise (MD = -0.05; 95% CI: -0.09, -0.02)	Insufficient
HDL cholesterol (EoI)	4; 914	Unclear (50% high, 50% unclear)	Consistent	Indirect	Precise (MD= 0.08; 95% CI: 0.05, 0.10)	Moderate
HDL cholesterol (4 yr followup)	1; 335	Unclear	Unknown (single study)	Indirect	Imprecise (MD = 0.05; 95% CI: 0.0, 0.10)	Insufficient
LDL cholesterol (EoI)	3; 199	High	Inconsistent	Indirect	Imprecise (MD = 0.04; 95% CI: -0.16, 0.25)	Low
Total cholesterol (EoI)	5; 968	Unclear	Inconsistent	Indirect	Imprecise (MD = 0.0; 95% CI: -0.12, 0.13)	Low
Impaired plasma glucose (EoI)	1; 335	Unclear	Unknown (single study)	Indirect	Precise (MD = 0.34; 95% CI: 0.23, 0.52)	Insufficient
Triglycerides (EoI)	4; 914	Unclear (50% high, 50% unclear)	Inconsistent	Indirect	Imprecise (MD = -0.11; 95% CI: -0.26, 0.04)	Low
Triglycerides (4 yr followup)	1; 335	Unclear	Unknown (single study)	Indirect	Imprecise (MD = 0.09; 95% CI: -0.22, 0.05)	Insufficient
Blood pressure						
Diastolic BP (EoI)	5; 2,734	Unclear	Consistent	Indirect	Precise (MD =-2.70; 95% CI: -3.21, -2.18)	Moderate
Diastolic BP (4 yr followup)	2; 1,341	Unclear	Consistent	Indirect	Precise (MD = -1.88; 95% CI: -2.65, -1.12)	Low
Systolic BP (EoI)	5; 2,734	Unclear	Consistent	Indirect	Precise (MD = -3.17; 95% CI: -5.02, -1.33)	Moderate
Systolic BP (4 yr followup)	2;1,341	Unclear	Consistent	Indirect	Precise (MD = -4.41; 95% CI: -8.47, -0.35)	Low
Change in physical activity						
Exercise (EoI)	4; 2,688	Unclear	Consistent	Indirect	Precise (SMD = 0.40; 95% CI: 0.2, 0.59)	Moderate
Exercise (4 yr followup)	1; 1,006	High	Unknown (single study)	Indirect	Precise (SMD = 0.23; 95% CI: 0.10, 0.35)	Insufficient
Change in dietary or nutrient intake						
Energy intake (EoI)	4; 2,732	Unclear	Consistent	Indirect	Precise (SMD = -0.23; 95% CI: -0.31, -0.16)	Moderate
SFA intake (EoI)	2; 441	Unclear	Consistent	Indirect	Precise (SMD = -0.53; 95% CI: -0.73, -0.34)	Low

Grading the body of evidence: breast or prostate cancer

Outcome	# RCTs; # subjects	Risk of bias	Consistency	Directness	Precision	Strength of evidence
Breast cancer						
Change in body composition						
BMI (EoI)	1; 250	Unclear	Unknown (single study)	Indirect	Imprecise (MD = -0.31; 95% CI: -1.19, 0.57)	Insufficient
Weight (EoI)	1; 250	Unclear	Unknown (single study)	Indirect	Imprecise (MD = -3.9; 95% CI: -10.32, 2.52)	Insufficient
Change in physical activity						
Exercise (endurance; EoI)	1; 250	Unclear	Unknown (single study)	Indirect	Precise (MD = 25.6; 95% CI: 16.9, 34.8)	Insufficient
Change in dietary or nutrient intake						
F&V intake (EoI)	1; 250	Unclear	Unknown (single study)	Indirect	Precise (MD = 1.08; 95% CI: 0.5, 1.66)	Insufficient
Fat intake (calories from fat) (EoI)	1; 250	Unclear	Unknown (single study)	Indirect	Imprecise (MD = -1.76; -2.57, -0.95)	Insufficient
Prostate cancer						
Primary outcome						
PSA levels (EoI)	1; 84	High	Unknown (single study)	Direct	Precise (MD = -0.63; 95% CI: -1.16, -0.10)	Insufficient
Change in body composition						
BMI (EoI)	1; 225	High	Unknown (single study)	Indirect	Imprecise (MD = -0.61; 95% CI: -1.47, 0.25)	Insufficient
Weight (EoI)	2; 309	High	Consistent	Indirect	Imprecise (MD = -7.55; 95% CI: -13.05, -2.05)	Insufficient
Change in metabolic variables						
HDL cholesterol (EoI)	1; 84	High	Unknown (single study)	Indirect	Precise (MD = -6.4; 95% CI: -9.65, -3.15)	Insufficient
LDL cholesterol (EoI)	1; 84	High	Unknown (single study)	Indirect	Precise (MD = -28.6; 95% CI: -40.79, -16.41)	Insufficient
Total cholesterol (EoI)	1; 84	High	Unknown (single study)	Indirect	Precise (MD = -34.0; 95% CI: -48.30, -19.7)	Insufficient

Triglycerides (EoI)	1; 84	High	Unknown (single study)	Indirect	Imprecise (MD= -9.0; 95% CI: -39.62, 21.62)	Insufficient
Change in physical activity						
Exercise (EoI)	1; 84	High	Unknown (single study)	Indirect	Precise (SMD = 0.62; 95% CI: 0.20, 1.03)	Insufficient
Exercise (endurance; EoI)	1; 225	High	Unknown (single study)	Indirect	Precise (MD = 16.3; 95% CI: 4.8, 28.5)	Insufficient
Change in dietary or nutrient intake						
Fat intake (calories from fat) (EoI)	2; 307	High	Consistent	Indirect	Precise (MD = -16.8; 95% CI: -20.3, -13.3)	Insufficient
F&V intake (EoI)	1; 225	High	Unknown (single study)	Indirect	Precise (MD = 1.4; 95% CI: 0.75, 2.05)	Insufficient
Mixed breast and prostate cancer						
Change in body composition						
BMI (EoI)	1; 168	Unclear	Unknown (single study)	Indirect	Imprecise (MD = -0.10; 95% CI: 1.68, 1.48)	Insufficient
BMI (followup)	1; 160	Unclear	Unknown (single study)	Indirect	Imprecise (MD = -0.50; 95% CI: -2.13, 1.13)	Insufficient
Change in physical activity						
Exercise (EoI)	1; 168	Unclear	Unknown (single study)	Indirect	Imprecise (SMD = 0.31; 95% CI: 0, 0.61)	Insufficient
Exercise (followup)	1; 160	Unclear	Unknown (single study)	Indirect	Imprecise (SMD = 0.13; 95% CI: -0.18, 0.44)	Insufficient
Change in dietary or nutrient intake						
F&V intake (EoI)	1; 168	Unclear	Unknown (single study)	Indirect	Imprecise (MD = 0.4; 95% CI: -0.21, 1.01)	Insufficient
F&V intake (followup)	1; 160	Unclear	Unknown (single study)	Indirect	Imprecise (MD = -0.10; 95% CI: -0.75, 0.55)	Insufficient
Fat intake (calories from fat) (EoI)	1; 168	Unclear	Unknown (single study)	Indirect	Imprecise (MD = -0.30 [-2.41, 1.81]	Insufficient
Fat intake calories from fat) (followup)	1; 160	Unclear	Unknown (single study)	Indirect	Imprecise (MD = -0.50 [-2.70, 1.70]	Insufficient