Annals of Internal Medicine | Review

Lifestyle Interventions for Patients With and at Risk for Type 2 Diabetes

A Systematic Review and Meta-analysis

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Background: The effect of multifaceted lifestyle interventions on clinically oriented outcomes across a spectrum of metabolic risk factors and abnormal glucose is unclear.

Purpose: To systematically review the effectiveness of lifestyle interventions on minimizing progression to diabetes in high-risk patients or progression to clinical outcomes (such as cardiovascular disease and death) in patients with type 2 diabetes.

Data Sources: 5 electronic databases (1980 to June 2013), reference lists, and gray literature.

Study Selection: Two reviewers independently identified randomized, controlled trials of lifestyle interventions (≥3 months' duration) that included exercise, diet, and at least 1 other component; the comparator was standard care.

Data Extraction: One reviewer extracted and a second verified data. Two reviewers independently assessed methodological quality.

Data Synthesis: Nine randomized, controlled trials with patients who were at risk for diabetes and 11 with patients who had diabetes were included. Seven studies reported that lifestyle interventions decreased the risk for diabetes from the end of intervention up to 10 years after it. In patients with diabetes, 2 randomized, controlled trials (which included pharmacotherapy) reported no improvement in all-cause mortality (risk ratio, 0.75 [95% CI, 0.53 to 1.06]). Composite outcomes for cardiovascular disease were too heterogeneous to pool. One trial reported improvement in microvascular outcomes at 13-year follow-up.

Limitation: Most trials focused on surrogate measures (such as weight change, blood pressure, and lipids) for which clinical relevance was unclear.

Conclusion: Comprehensive lifestyle interventions effectively decrease the incidence of type 2 diabetes in high-risk patients. In patients who already have type 2 diabetes, there is no evidence of reduced all-cause mortality and insufficient evidence to suggest benefit on cardiovascular and microvascular outcomes.

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Type 2 diabetes is a major cause of illness and death. Diabetes was the seventh-leading cause of death in the United States in 2007 (1), and cardiovascular disease (CVD) accounted for more than 65% of all diabetic deaths (2). Diabetes is also the leading cause of new cases of kidney failure, lower extremity amputations, and blindness not related to injury among adults (1).

Prediabetes, defined by the American Diabetes Association as impaired fasting glucose or impaired glucose tolerance, is considered a relatively high-risk state for diabetes (3). A combination of risk factors collectively known as the metabolic syndrome has also shown moderate predictive value in identifying persons at increased risk for diabetes (4, 5). Both prediabetes and the metabolic syndrome have been associated with increased risk for vascular disease (6, 7). Known modifiable risk factors for type 2 diabetes include obesity (8) and physical inactivity (9). Current guidelines recommend lifestyle changes for both prevention and management of type 2 diabetes (10).

Many systematic reviews have reported a benefit with exercise and dietary interventions in diabetes prevention (11–15). However, we are not aware of any reviews that assessed the effect of multifaceted lifestyle interventions on clinically oriented outcomes across a spectrum of metabolic risk factors and abnormal glucose.

The objective of this systematic review was to assess the effects of comprehensive lifestyle interventions in the prevention of diabetes in adults who have been identified as having increased risk for type 2 diabetes (for example, those with the metabolic syndrome or prediabetes) and the prevention of diabetic complications (such as microvascular and macrovascular outcomes) in adults diagnosed with type 2 diabetes.

Methods

We followed an a priori research protocol that met standards for conducting systematic reviews. A full technical report with detailed methods and evidence tables is available at www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id82TA.pdf.

Data Sources and Searches

A research librarian conducted searches in MEDLINE (**Appendix Table 1**, available at www.annals.org), the

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Cochrane Central Register of Controlled Trials, CINAHL, EMBASE, and SCOPUS from 1980 to March 2010. Searches were updated in MEDLINE and the Cochrane Central Register of Controlled Trials in July 2012 and June 2013. Search filters for randomized, controlled trials (RCTs) and English-language studies were applied. We also hand-searched clinical trial registries and reference lists of relevant studies and reviews.

Study Selection

Two reviewers independently screened titles and abstracts using broad inclusion criteria. The full text of potentially relevant studies was assessed independently by 2 reviewers using a standardized form. Disagreements were resolved by consensus or third-party adjudication.

Randomized, controlled trials were included if they involved adults (≥18 years) who were diagnosed with type 2 diabetes or had risk factors suggesting increased risk for it. Our operational definition for patients at risk for diabetes included the metabolic syndrome, prediabetes, insulin resistance, impaired fasting glucose, impaired glucose tolerance, syndrome X, dysmetabolic syndrome X, and the Reaven syndrome. For simplicity, we refer to these patients as "high-risk patients." The lifestyle intervention had to include an exercise component, a diet component, and at least 1 other component (such as counseling, smoking cessation, and behavior modification). The comparison could be usual care, diet or exercise components alone, or a wait list. A priori, the duration of the intervention was at least 3 months with a minimum 6-month follow-up. We made a post hoc modification also to include RCTs in which the duration of the intervention was at least 1 year even if there was no follow-up. The primary outcomes were progression to type 2 diabetes in patients at risk or development of macrovascular and microvascular complications (such as death, cardiovascular outcomes, nephropathy, retinopathy, or neuropathy) in those with type 2 diabetes. Secondary outcomes included surrogate markers for the development of vascular complications, including body composition, metabolic variables (such as fasting plasma glucose, hemoglobin A_{1c}, and lipid levels), blood pressure, physical activity, and dietary or nutrient intake.

Data Extraction and Quality Assessment

One reviewer extracted data using a standardized form, and a second reviewer verified data for accuracy and completeness. Discrepancies were resolved through consensus or in consultation with a third party. We extracted study and patient characteristics, inclusion and exclusion criteria, interventions, and outcomes.

Two reviewers independently assessed the methodological quality of studies using the Cochrane Collaboration Risk-of-Bias tool (16). Discrepancies were resolved through consensus or third-party adjudication. The source of funding was recorded for all studies (17).

One reviewer graded the strength of evidence using the Agency for Healthcare Research and Quality Evidence-based Practice Center approach (18). Four domains were examined: risk of bias, consistency, directness, and precision. We assigned an overall strength of evidence grade of high, moderate, low, or insufficient. When only 1 study was available for an outcome, we rated the strength of evidence as insufficient.

Data Synthesis and Analysis

We described the results of studies qualitatively and in evidence tables. We did meta-analyses using a DerSimonian–Laird random-effects model (19) when the populations, interventions, time points, and outcomes were sufficiently similar. Statistical heterogeneity was quantified using the I^2 statistic (20). We calculated mean differences or standardized mean differences for continuous outcomes and risk ratios (RRs) for dichotomous outcomes. If no event was reported in 1 treatment group, a correction factor of 0.5 was added to each cell of the 2×2 table to obtain estimates of the RR. We reported all results with 95% CIs and used Review Manager, version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark), to do meta-analyses.

Role of the Funding Source

The Agency for Healthcare Research and Quality suggested the initial questions and approved copyright assertion for this article but did not participate in the literature search, data analysis, or interpretation of the results.

RESULTS

The literature search identified 1289 citations. Twenty unique studies in 58 publications were included (**Figure 1**). Nine studies addressed patients at increased risk for type 2 diabetes; 11 studies addressed patients diagnosed with type 2 diabetes. A list of excluded studies and reasons for exclusion is available from the authors.

Description of Included Studies

Many included trials were associated with several publications that either expanded on the main results, reported secondary outcomes that were not included in the primary report, or reported different follow-up time points. The publication that was the first to report outcome data was considered the primary study. Relevant baseline and outcome data were taken from the primary publication and supplemented with data from the associated publications. Even if reported data were from a follow-up study, the primary article is cited. See **Table 1** of the **Supplement** (available at www.annals.org) for a list of the sentinel and associated publications.

High-Risk Patients

The duration of the interventions ranged from 6 to 72 months, with follow-ups between 3 and 20 years for

5 RCTs (21–25) (**Table 2** of the **Supplement**). Four trials had long-term interventions ranging from 12 to 36 months but with no follow-up (26–29). For all studies, the number of participants ranged from 39 to 3234 (median, 210; interquartile range [IQR], 78 to 522). The mean age was between 44 and 85 years. The mean body mass index (BMI) ranged from 26.2 kg/m^2 (SD, 3.9) to 38.3 kg/m^2 (SD, 5.9).

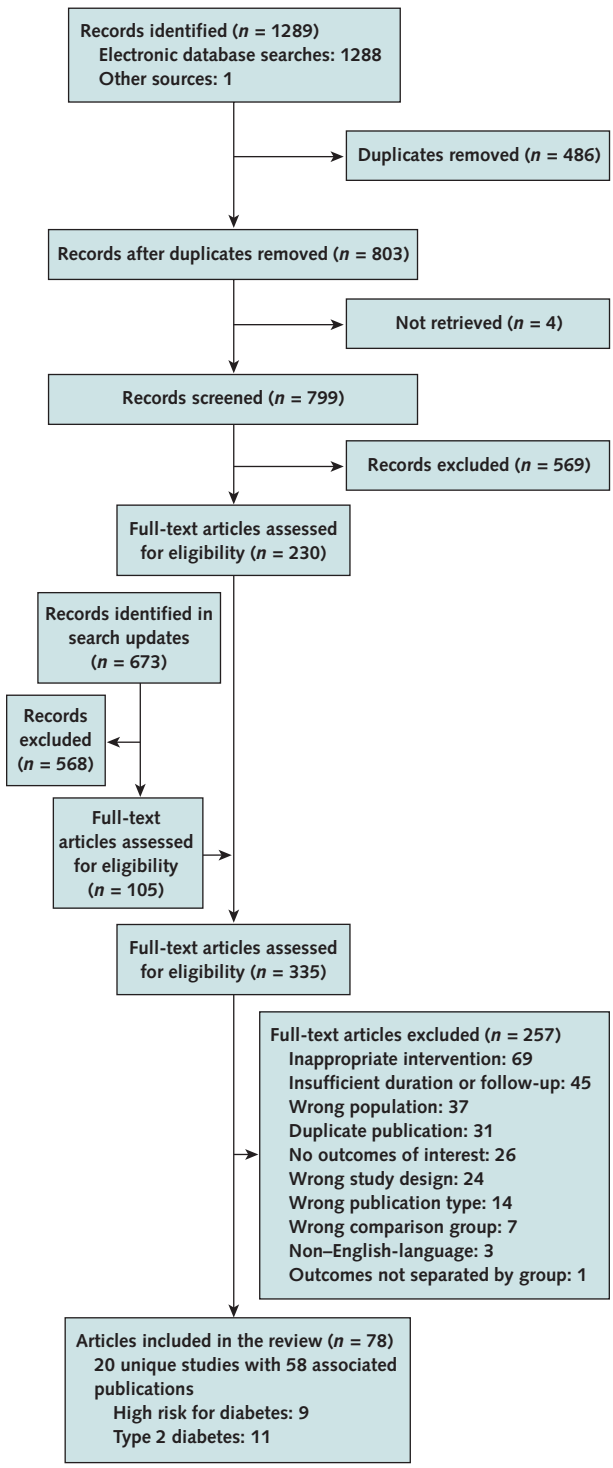
Although all lifestyle interventions included diet and exercise components, additional components were diverse (**Appendix Table 2**, available at www.annals.org). Five studies included both individual and group counseling (21–24, 26), 1 incorporated only group counseling (27), and 1 had only individual counseling (28). Other components included behavior modification (22, 28), a smoking cessation program (23, 26), regular telephone contact (22, 23), individual goal setting (21), and cooking lessons (23). One study (28) included medication (orlistat) as an intervention component.

The interventions were administered or delivered by dietitians (21–24, 26–28), exercise advisors (22, 23), physiotherapists (27), nurse managers (22, 23), nurses (21, 24), physicians (22–24), endocrinologists (21), psychologists (22), and technicians (24).

The comparison group received various interventions, including usual care by a family physician (21, 27), educational materials or advice on diet or exercise (22–26), waitlist controls (28), food diaries (23), and annual diabetes education sessions (29).

Three trials (22, 26, 28) were assessed as having high risk of bias, and 6 (21, 23–25, 27, 29) had unclear risk of bias. Most had inadequate allocation concealment. All but 1 study (24) had high or unclear risk of bias for lack of blinding for subjective or self-reported outcomes (such as hours of exercise per week). Two studies (22, 28) received funding from industry.

Figure 1. **Summary of evidence search and selection.**



Patients With Diabetes

The interventions ranged from 6 to 48 months with follow-up between 6 and 93 months for 5 trials (30–34) (**Table 3** of the **Supplement**). Six trials (35–40) had interventions that lasted 1 year but had no follow-up after intervention. For all 11 trials, the number of participants ranged from 72 to 5145 (median, 200 [IQR, 149 to 280]). The mean ages were between 53.0 and 62.4 years.

All studies included diet and exercise components plus at least 1 additional component (**Appendix Table 3**, available at www.annals.org). Five studies used both group and individual counseling (31, 32, 35, 37, 38), 3 incorporated only group counseling (30, 34, 39), and 2 had only individual counseling (33, 36). Other components included a smoking cessation course (30), regular telephone contact (32, 33), individual goal setting (34–36, 38), regular blood glucose and blood pressure monitoring (38), and stress management (34, 38). In 1 study (34), participants went on a 3-day nonresidential retreat at the beginning of the intervention. In another study (39), physicians were responsible for motivating the participants. Four studies had medication as one of the intervention components if treat-

ment targets were not met: orlistat (31) and stepwise use of medications (30, 33, 35).

The interventions were administered or delivered by dietitians (30–32, 34, 35, 37–39), case managers or nurses (30, 31, 35, 38, 39), physicians (30, 31, 35, 36, 39), qualified exercise advisors or trainers (31, 34, 35), behavioral therapists or physiologists (31, 34), health or nonprofessional peer counselors (32), lay leaders and trained support group leaders (34), and lifestyle counselors (31). One study (33) reported that a multidisplinary team delivered the intervention but did not specify the individual members.

The comparison group received standard care from their physician (30, 34, 40) or standard care plus a range of other components, including educational materials (32, 36), general health advice at regular laboratory visits (33), encouragement to take diabetes education classes (35), group support sessions (31), a nutrition training session (37), visits to a diabetes outpatient clinic (39), and encouragement to visit community health centers (39).

Two trials (35, 37) were assessed as having high risk of bias; 9 (30–34, 36, 38–40) were assessed as unclear. Most individual domains had low risk of bias; however, all studies had unclear or high risk of bias for blinding of subjective or self-reported outcomes. Two studies stated that outcome assessors were blinded to treatment allocation (30, 31). Two studies received funding from industry (31, 33).

Efficacy

High-Risk Patients

The findings are summarized in **Appendix Table 4** (available at www.annals.org). Two studies (23, 24) reported CVD events. At 10 years after the intervention, the Finnish Diabetes Prevention Study (23, 41) reported no difference between groups (RR, 1.02 [95% CI, 0.73 to 1.42]). The Da Qing Diabetes Prevention Trial reported first CVD events at 6-year (24) and 20-year (42) follow-up and found no differences between the groups at either time point (hazard ratio [HR], 0.96 [CI, 0.76 to 1.44] and 0.98 [CI, 0.71 to 1.37], respectively). The strength of evidence is insufficient for the effect of comprehensive lifestyle interventions to prevent CVD events.

A 20-year follow-up study from the Da Qing Diabetes Prevention Trial (24, 42) reported that lifestyle interventions had no benefit in severe nephropathy or neuropathy, although incidence of severe retinopathy (defined as a history of photocoagulation, blindness, or proliferative retinopathy) was 47% lower. Severe retinopathy occurred in 31 participants (9.2%) in the intervention group and 17 (16.2%) in the control group. The 20-year follow-up data had limitations, including the number of patients lost to follow-up and the fact that many patients diagnosed with severe retinopathy did not have formal retinal examinations (42). Overall, the strength of evidence for benefit of lifestyle interventions on retinopathy is insufficient.

Seven studies (21–24, 26, 27, 29) reported the development of type 2 diabetes from the end of intervention up to 10 years after it (**Figure 2**). At the end of intervention, there was an important difference in favor of the lifestyle intervention (RR, 0.35 [CI, 0.14 to 0.85]). The difference was maintained at up to 10 years of follow-up (**Figure 2**). The Da Qing Diabetes Prevention Trial (24, 42) also reported a difference in the development of type 2 diabetes in favor of lifestyle interventions at both 6 and 20 years (HR, 0.49 [CI, 0.33 to 0.73] and 0.57 [CI, 0.41 to 0.81], respectively); however, these results combine several intervention groups, including a lifestyle intervention with both diet and exercise components, a diet-only intervention, and an exercise-only intervention. The strength of evidence was moderate for development of type 2 diabetes.

Most studies reported positive effects for secondary outcomes, including changes in body composition, metabolic variables, physical activity, and dietary intake (**Appendix Table 4**). The results were not always statistically or clinically significant or sustained after the end of the active intervention.

Patients With Diabetes

The results are summarized in **Appendix Table 5** (available at www.annals.org). Two trials, Steno-2 and Look AHEAD (Action for Health in Diabetes) (30, 31, 47), reported on macrovascular outcomes, and both included pharmacotherapy as an adjunct to the lifestyle interventions. For all-cause mortality, the pooled results showed no difference between the intervention and control groups at more than 10 years of follow-up (RR, 0.75 [CI, 0.53 to 1.06]) (**Figure 3**). The strength of evidence was low for this outcome.

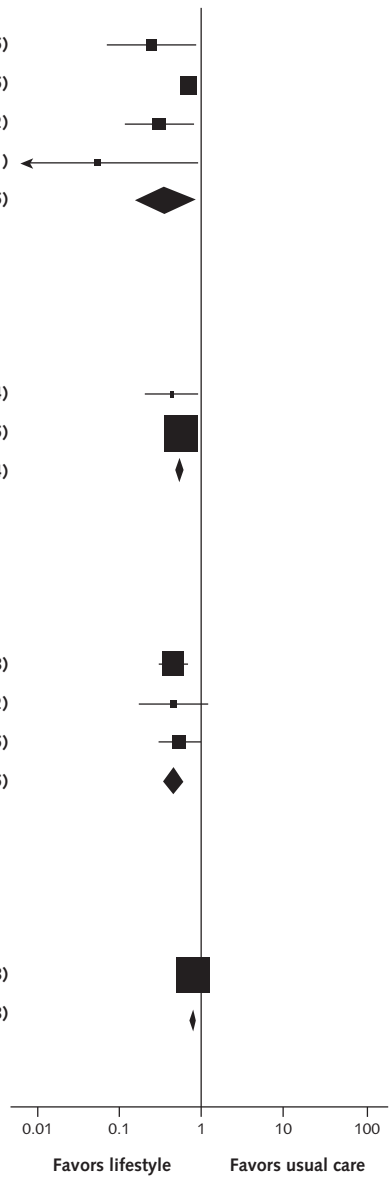
Both trials reported on a composite outcome of CVD events; however, the makeup of the outcomes was different, and we did not pool the results. The Look AHEAD trial (31, 47) found no difference between groups for their primary outcomes, which included death due to cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for angina (RR, 0.96 [CI, 0.85 to 1.09]). However, Steno-2 (30) found a difference (RR, 0.51 [CI, 0.36 to 0.74]) for their outcomes, which included death due to cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary artery bypass grafting, percutaneous coronary intervention or revascularization for peripheral atherosclerotic arterial disease, and amputation due to ischemia.

Steno-2 (30) reported a reduction in the development of nephropathy, retinopathy, and progression of autonomic neuropathy in favor of the lifestyle intervention. No difference was seen in the progression of peripheral neuropathy.

Although many studies reported positive effects for lifestyle interventions on secondary outcomes, the results were not always statistically significant, and clinical significance remains unclear. In addition, the improvements in secondary outcomes were generally not sustained beyond

Figure 2. **Effect of lifestyle interventions versus usual care on development of diabetes for high-risk patients.**

Author, Year (Reference)	Lifestyle Intervention		Usual Care		Weight, %	Risk Ratio M–H Random (95% CI)
	Events, *n*	Patients, *n*	Events, *n*	Patients, *n*		
End of intervention						
Bo et al, 2007 (21)	3	169	12	166	23.1	0.25 (0.07–0.85)
Pan et al, 1997 (24)	58	126	90	133	41.1	0.68 (0.54–0.85)
Eriksson et al, 1999 (23)	5	265	16	257	27.8	0.30 (0.11–0.82)
Lu et al, 2011 (29)	0	95	8	86	8.0	0.05 (0.00–0.91)
Total	66	655	126	642	100.0	0.35 (0.14–0.85)
Heterogeneity: tau-square = 0.49; chi-square = 9.34; I^2 = 68%						
Test for overall effect: Z = 2.31 (P = 0.02)						
4-y follow-up						
Bo et al, 2009 (43)	9	169	20	166	3.6	0.44 (0.21–0.94)
Knowler et al, 2002 (22)	210	1079	375	1082	96.4	0.56 (0.49–0.65)
Total	219	1248	395	1248	100.0	0.56 (0.48–0.64)
Heterogeneity: tau-square = 0.00; chi-square = 0.37; I^2 = 0%						
Test for overall effect: Z = 7.99 (P < 0.001)						
6-y follow-up						
Tuomilehto et al, 2001 (44)	27	265	59	257	58.2	0.44 (0.29–0.68)
Oldroyd et al, 2006 (45)	5	51	11	51	10.7	0.45 (0.17–1.22)
Mensink et al, 2003 (26)	13	63	24	62	31.1	0.53 (0.30–0.95)
Total	45	379	94	370	100.0	0.47 (0.34–0.65)
Heterogeneity: tau-square = 0.00; chi-square = 0.26; I^2 = 0%						
Test for overall effect: Z = 4.59 (P < 0.001)						
10-y follow-up						
Knowler et al, 2009 (46)	465	1079	580	1082	100.0	0.80 (0.74–0.88)
Total	465	1079	580	1082	100.0	0.80 (0.74–0.88)
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.85 (P < 0.001)						

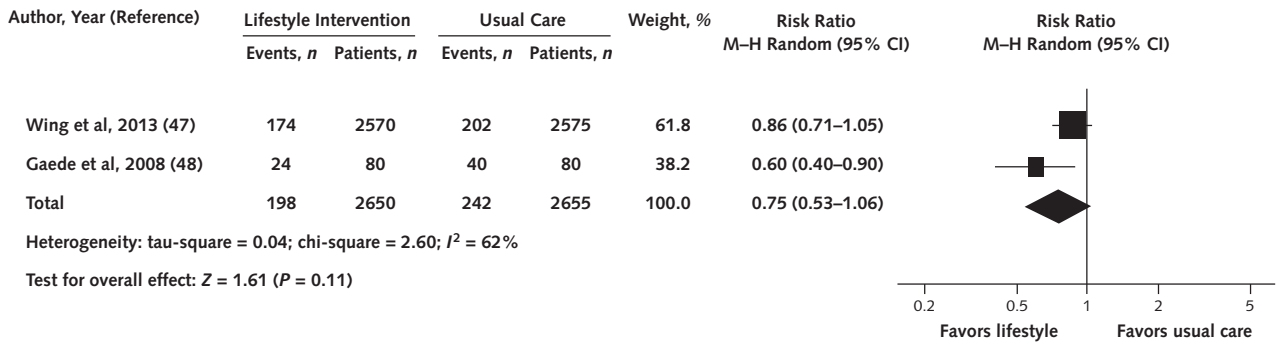


M–H = Mantel–Haenszel.

the end of the active intervention (**Appendix Table 5**). The strength of evidence was low for improvement in BMI and weight at the end of the interventions. Increased physical activity levels were sustained at all time points up to 10 years after the intervention (standardized mean difference, 0.17 [CI, 0.11 to 0.22]; I^2 = 0%) in favor of the lifestyle intervention, and the strength of evidence was low. Strength of evidence was also low for reduced energy and saturated fatty acid intake during the interventions. Energy intake was not reduced beyond the intervention period. Reduction in saturated fatty acid intake was maintained up to 7 to 8 years after the intervention in 2 trials (30, 34).

In light of the known benefit of pharmacologic treatment on surrogate markers, such as blood pressure, lipid levels, and hemoglobin A_{1c} levels, and glucose control, we did a sensitivity analysis of the effect of comprehensive lifestyle interventions with and without medication (**Appendix Table 5**). There was no improvement in any metabolic outcomes for interventions that did not include pharmacotherapy. Improvement was noted in high-density

Figure 3. **Effect of lifestyle interventions versus usual care on all-cause mortality for patients with type 2 diabetes.**



M–H = Mantel–Haenszel.

lipid levels (mean difference, 0.04 [CI, 0.03 to 0.05]) and hemoglobin A_{1c} levels (mean difference, −0.71 [CI, −1.31 to −0.12]) during the intervention in trials that included targeted pharmacotherapy (31, 33, 35).

Discussion

We conducted a comprehensive systematic review of clinical trials that assessed the effect of a multifaceted lifestyle intervention on patient-centered outcomes, such as progression to type 2 diabetes for high-risk patients and microvascular and macrovascular outcomes, including CVD for patients with type 2 diabetes. Four trials that included high-risk patients and 2 trials that included patients with diabetes reported on patient-important outcomes. The remaining 15 studies reported on secondary or surrogate outcomes. The risk of bias was high or unclear for this body of evidence. The strength of evidence was often insufficient for all outcomes because of the small number of studies and sample sizes.

Moderate-strength evidence showed that participation in a comprehensive lifestyle intervention reduced the risk for type 2 diabetes in persons who are at increased risk (Diabetes Prevention Program [22, 46], Finnish Diabetes Prevention Study [23], European Diabetes Prevention Study–Newcastle [27], Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht [26], Da Qing Diabetes Prevention Trial [24], and Bo and colleagues [21]). Because diabetes is associated with comorbid conditions (49, 50), it is encouraging that lifestyle interventions seem to have a positive effect on prevention. Our findings are consistent with those of other reviews that have reported substantial benefit of lifestyle interventions in the prevention of type 2 diabetes (51, 52).

Two trials reported on cardiovascular outcomes in high-risk patients, but neither found benefit with lifestyle interventions. This is consistent with the Look AHEAD trial that involved patients with type 2 diabetes, although it contrasts with the smaller Steno-2 trial.

Recent observational studies have questioned whether high-risk patients are actually at increased risk for CVD compared with the general population. The Australian Diabetes, Obesity, and Lifestyle Study reported increased risk for CVD death in those with prediabetes (53). One systematic review of observational studies found a modest increased risk for stroke (54).

The Diabetes Prevention Program Outcomes Study (46), which involves long-term follow-up of patients in the Diabetes Prevention Program, has reported plans for further follow-up in 2014. This may shed light on whether prevention or delay of diabetes is associated with a delay in development of diabetic complications.

Similar to the results for patients with type 2 diabetes, lifestyle interventions resulted in an important decrease in body weight or BMI in high-risk patients. However, in contrast to the findings in patients with type 2 diabetes, this effect persisted for up to 4 years beyond the intervention period. This must be interpreted with caution because only 1 trial reported BMI at 4 years and only 2 trials assessed weight change. Whether the weight loss is easier to maintain in persons who have not yet progressed to diabetes is unclear. Previous research has found that patients with diabetes have poor weight-loss maintenance after an intervention compared with their counterparts without diabetes (55). If this were the case, it would underscore the importance of identifying persons at risk for diabetes and intervening early.

There is low-strength evidence about the benefit of lifestyle intervention in prevention of all-cause mortality and insufficient-strength evidence about CVD and microvascular outcomes in adults with diabetes. Two studies reported on macrovascular outcomes. Look AHEAD, the largest included trial to date, with 5145 participants, was stopped early after a futility analysis (47). In contrast, Steno-2 reported long-term clinical benefit of lifestyle interventions. Both trials used pharmacotherapy as an adjunct to lifestyle interventions. Steno-2 used intensive tar-

geted pharmacologic therapy, including many medications that have been previously shown to reduce overall mortality rates (such as statins [56], angiotensin-converting enzyme inhibitors for hypertension [57], and acetylsalicylic acid for secondary prevention [58]). Look AHEAD left management of medications to the patient's physician, although they used orlistat in some patients. Long-term trials assessing the effect of orlistat on death and illness are lacking (59). Event rates between the 2 trials differed greatly. At 13-year follow-up, there was a 50% mortality rate for patients in the control group of Steno-2 compared with an 8% mortality rate for those in the control group of Look AHEAD at 10 years. The choice of pharmacotherapy in Steno-2 or inclusion of patients who were inherently more ill may have contributed to the benefit seen on clinical outcomes.

Of interest, Steno-2 found that despite evidence of long-term clinical benefit, changes in behaviors or surrogate markers for CVD were not maintained over the long term. Trials in type 1 diabetes have shown that early intensive treatment results have an extended benefit in delaying the progression of diabetic outcomes beyond the intervention (60, 61). The mechanism by which benefit occurs despite normalization of behaviors and surrogate markers is unclear.

Limitations of this review include low- or insufficient-strength evidence for most outcomes across the various interventions. These low grades were driven by high or unclear risk of bias within individual studies (largely due to inability to blind patients in the treatment group), lack of direct evidence for patient-important outcomes, and lack of consistency and precision among studies.

There was considerable heterogeneity about dietary and lifestyle interventions. In particular, the third component of the intervention was quite variable, limiting our ability to comment on which additional interventions would be beneficial. Current literature has demonstrated that pharmacotherapy, exercise, and dietary changes have a positive effect on glycemic control and other diabetic indices (62, 63). Although growing evidence shows an additive effect when several risk factors are addressed together (64), we cannot conclusively say that comprehensive lifestyle interventions are better than diet and exercise alone.

Few trials provided data for clinically important outcomes, focusing on surrogate measures for which the clinical relevance is unclear. A further possible limitation includes the group of patients that we identified as being at increased risk for diabetes. This is a controversial area, with various definitions and diagnostic cut points having been proposed over the past few years (65).

Finally, we included only RCTs in this review. A systematic review of cohort studies may provide data on the effect of different lifestyle interventions over several years to assess the long-term sustainability and comparative effectiveness of these interventions.

Comprehensive lifestyle interventions that include exercise, dietary changes, and at least 1 other component are effective in decreasing the incidence of type 2 diabetes in high-risk patients, and the benefit extends beyond the active intervention phase. In patients who have already been diagnosed with type 2 diabetes, the evidence for benefit of comprehensive lifestyle interventions on patient-oriented outcomes is less clear. There is no evidence of benefit in all-cause mortality and insufficient evidence to suggest benefit on cardiovascular and microvascular outcomes. Improvement was seen for some secondary outcomes, but it generally did not persist beyond the intervention phase, and the clinical significance is unclear.

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Appendix Table 1. Search Strategy

Lifestyle interventions review: MEDLINE
Years/issue searched: 1980–current
Search date: July 2012 and June 2013
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$).tw,kf,ot.
6. ((typ? 2 or typ? II or typ?2 or typ?II) adjdiabet$).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. (insulinadj 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.

Appendix Table 1—Continued

61. (breathingadj exercises).tw.
62. (laughteradj therapy).tw.
63. (relaxationadj therapy).tw.
64. (therapeuticadj touch).tw.
65. (taiadj (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. drugtherapy.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)"

Appendix Table 2. **Descriptions of Lifestyle Interventions for Patients at Risk for Diabetes**

Author, Year (Reference)	Study Duration/ Follow-up Duration	Diet	Exercise	Counseling or Other Components	Control Group
Studies with follow-up after intervention					
Bo et al, 2007 (21)	12 mo/3 y	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 sessions by trained professional on behavioral counseling and lifestyle tips	Usual/standard care provided by family physician
Knowler et al, 2002 (22)	12 mo/10 y	Followed food pyramid guidelines Goal to achieve and maintain weight loss of 7% in first 24 wk Low-fat, low-calorie diet $100/y for "tool kit" with cookbook, grocery vouchers Logbook, telephone contact, personal interview	150 min/wk moderate PA Strength training: maximum of 75 min/wk could be applied to overall goal of 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 first 24 wk and then at least once every 2 mo Group counseling: case manager; quarterly for 4- to 8-wk courses	Standard diet and exercise advice
Eriksson et al, 1999 (23)	4 y/6.6 y	Weight loss of ≥5% or goal BMI of ≤25 kg/m^2 Emphasis on decreased SFA intake, increased fiber intake to >15 g/1000 kcal If no weight loss in 6–12 mo, low-calorie diet with group meetings Detailed advice, printed material to illustrate messages and serve as reminders Logbook, telephone, progress reports, weight measured every 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 first year and then every 3 mo Group counseling: voluntary sessions with a nutritionist; included expert lectures, low-fat cooking lessons, visits to supermarkets Encouraged to quit smoking	Attention control Written/oral information on diet and exercise Food diaries before annual visits Advised to decrease energy intake to decrease BMI Advised to decrease alcohol intake and smoking Annual visits
Oh et al, 2010 (25)	6 mo/6 mo	Low-calorie and low-carbohydrate diet based on NCEP-ATP III Monitored individually to maintain <1500 kcal/d and limit carbohydrates to 55%–60% of caloric intake Encouraged to reduce high-glycemic foods	Supervised group exercise of yoga stretching, rhythmic aerobic dance (Tae Bo), and warm-up and cool-down exercises for 40 min/session Oxygen and carbon dioxide consumption measured Pedometers provided Daily exercise diary	Health information on definition of disease, exercise, diet, risk factors, related diseases, and self care Educational booklet Nurse researcher provided 20-min counseling based on food diary, exercise adherence, and health status (blood pressure, weight) at every session Discussed problems carrying out program	Received a booklet with basic education for the metabolic syndrome
Pan et al, 1997 (24)	6 y/20 y	Those with BMI ≥25 kg/m^2 to reduce calorie intake to lose weight at 0.5–1.0 kg/mo to goal BMI of 23 kg/m^2 Those with BMI <25 kg/m^2 to eat more vegetables, limit alcohol intake, reduce simple sugar intake List of commonly used foods and substitution list provided	Increased leisure PA by at least 1 unit/d or 2 units/d if aged <50 y	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 or increased leisure PA

Continued on following page

Appendix Table 2—**Continued**

Author, Year (Reference)	Study Duration/ Follow-up Duration	Diet	Exercise	Counseling or Other Components	Control Group
Studies with no follow-up after intervention					
Lu et al, 2011 (29)	2 y/0	Lecture on diet given face-to-face every 2 mo and by telephone once/mo	Lecture on exercise given face-to-face every 2 mo and by telephone once/mo	Medication: Isolated IGT: acarbose (50 mg three times/d); isolated IFG or IFG/IGT: metformin (0.25 g three times/d); hypertension: antihypertension agents; dyslipidemia: antidyslipidemia agents and aspirin (100 mg/d), except where contraindicated	Diabetic education once/y
Mensink et al, 2003 (26)	3 y/0	Followed Dutch Nutrition Council guidelines Emphasis on decreasing SFA intake Weight loss of 5%–7% Logbook, 3-d food diary every 3 mo Reduced alcohol intake	Followed ACSM recommendation: 30 min PA/d, 5 d/wk Encouraged to attend group exercise sessions Logbook, attendance, asked to participate in program with HR monitor 3 times/y, 3-d diary every 3 mo	Individual counseling: dietitian every 3 mo Group counseling: dietitian at 9, 21, and 33 mo Encouraged to quit smoking	Attention control Oral and written information on healthy diet, weight loss, and increasing PA
Oldroyd et al, 2001 (27)	2 y/0	Followed British Diabetic Association guidelines Encouraged to decrease fat and sugar and increase fruit, vegetable, and fiber intake Overweight participants were encouraged to decrease BMI to <25 kg/m^2 Educational material, personal interview	Graded PA plan designed to achieve 20–30 min aerobic activity 2–3 times/wk Information on exercise facilities provided; 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
Pinkston et al, 2006 (28)	12 mo/0	Followed a weight management program from the Dairy Council of Utah/Nevada Encouraged to decrease calories by $\geq$500 kcal/d Goal weight loss of 0.45 kg/wk Fat intake 30% of total daily calories Meal demonstrations of modified traditional foods Weekly food diary	Goal to increase PA to 5 times/wk for 30 min for total of $\geq$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 dietitian; 24 classes/wk for 1 h, then gradual tapering 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, 1 vitamin and mineral capsule daily	Wait-list control

ACSM = American College of Sports Medicine; BMI = body mass index; HR = heart rate; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NCEP-ATP III = National Cholesterol Education Program Adult Treatment Panel III; NIH = National Institutes of Health; PA = physical activity; SFA = saturated fatty acid; SLIM = Study on Lifestyle Intervention and Impaired Glucose Tolerance Maastricht.

Appendix Table 3. **Descriptions of Lifestyle Interventions for Patients With Type 2 Diabetes**

Author, Year (Reference)	Intervention Duration/ Follow-up Duration	Diet	Exercise	Counseling or Other Components	Control Group
Studies with follow-up after intervention					
Gaede et al, 1999 (30)	3 mo/13 y	Low-fat diet: fat <30% of intake, SFA <10% of intake, increased complex carbohydrate intake Dietitian every 3 mo for 1 y Educational material, examples of low-fat/ high-carbohydrate lunches and snacks served at the group meetings	Light to moderate PA ≥30 min, 3–5 times/wk Educational material, demonstrations of exercise effect on decreasing blood glucose levels	Group counseling: dietitian; groups of 20 with spouses; 2 sessions Smoking cessation course with spouses: 5 meetings in 8 wk, follow-up at 3 and 6 mo Stepwise use of pharmacologic treatment 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, vitamins C and E	Usual/standard care from primary care physician following the 1998 Danish Medical Association guidelines
Keyserling et al, 2002 (32)	6 mo/6 mo	Food for Heart Program: decreased total fat and SFA intake; improved distribution of carbohydrate intake Educational material, cookbook, logbook, workbook, monthly progress reports	Followed CDC and ACSM guidelines: >30 min/d moderate PA Caltrac accelerometer (Muscle Dynamics, Torrance, California) 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 and research assistant, 3 sessions Behavior modification principles, active discovery learning approach	Usual/standard care from primary care physician Mailed educational pamphlets
Wing et al, 2010 (31)	4 y completed; projected to end at 11.5 y	Minimum weight loss of ≥7% in first year, encouraged weight loss of ≥10% Caloric restriction, portion control, meal replacements, increased fruit and vegetable intake, lower fat intake Toolbox options for suboptimal weight loss, including written behavioral contracts, additional funds to promote adherence to behavioral goals (gym membership, cooking classes, and prepackaged 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; 1 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- to 8-wk session offered 2–3 times/y) Orlistat given to patients who did not lose >10% of initial weight	Attention control 3 group educational/social support sessions/annually Regular clinic visits and telephone calls for data collection
Ménard et al, 2005 (33)	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- to 55-min sessions 3–5 times/wk	Individual counseling: multidisciplinary team; monthly visits at the clinic Telephone contact twice between visits for information on test results, therapy adjustment and motivation Stepwise use of pharmacologic treatment if CDA goals not met, including glyburide, metformin, α-glucosidase inhibitor, intermediate-acting insulin, fosinopril, amlodipine, hydrochlorothiazide, atenolol, irbesartan, doxazosin, fibrates, and statins	Usual/standard care from primary care physician Given general health and diabetes advice at each laboratory visit (baseline and 6, 12, and 18 mo)

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Appendix Table 3—**Continued**

Author, Year (Reference)	Intervention Duration/ Follow-up Duration	Diet	Exercise	Counseling or Other Components	Control Group
Toobert et al, 2003 (34)	24 mo/10 y	Followed CDC and 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 2 d/wk, building to 3 sets of 12 repetitions Increase PA by 5 min/session, increase number of d/wk; goal of 1-hr session >3 times/wk	3-d nonresidential 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 h/d with an audio cassette, 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 physician
Toobert et al, 2011 (40)	6 mo/12 mo	Mediterranean diet adapted for Latin American subcultures	30 min/d physical exercise	2.5-d retreat followed by weekly meetings Encouraged to stop smoking Problem solving–based support groups Stress management techniques daily	Usual care
Studies with no follow-up after intervention					
Aubert et al, 1998 (35)	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 dietitian, exercise therapist; 5-wk, 12-h education program Included goal setting Stepwise use of pharmacologic treatment if glycemic or weight-loss goals not met after 1–3 mo, including sulfonylurea, metformin, precise, and regular and NPH insulin	Attention control Usual/standard care from primary care physician Given blood glucose meters and strips Encouraged to discuss enrollment in diabetes education class with physicians
Christian et al, 2008 (36)	12 mo/0	Decreased caloric intake Computer generated 4- to 5-page individualized, tailored report providing feedback on participant-identified barriers to improve PA and diet 30-page 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 or PA goals All participants received 3 mo of diabetes education before randomization	Usual/standard care from primary care physician Health education materials provided at baseline visit on diabetes, diet, and exercise
Mayer-Davis et al, 2004 (37)	12 mo/0	Followed the Intensive Lifestyle Intervention modeled after the DPP study with modifications Goal was to achieve and maintain weight 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 persons 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-h sessions; included behavioral strategies to achieve weight loss Group counseling: nutritionist; gradually decreased frequency over 12 mo; 1-h 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 from the ADA

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Appendix Table 3—**Continued**

Author, Year (Reference)	Intervention Duration/ Follow-up Duration	Diet	Exercise	Counseling or Other Components	Control Group
Samuel-Hodge et al, 2009 (38)	8 mo/4 mo	General healthy eating Each group session had taste testings of 1 or 2 recipes Telephone calls, postcard messages of encouragement	General increase in PA Every group session had 15 min of chair exercises ActiGraph monitor (ActiGraph, Shalimar, Florida) worn for 1 wk Telephone contact, postcard messages of encouragement	Individual counseling: registered dietitian for one 1-h session; stress management and goals Group counseling: registered dietitian for first 7 sessions, health professional from local community for 4 sessions, 1 group potluck for total of 12 sessions (biweekly); 90–120 min Before each group session, all participants checked their blood glucose levels 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 et al, 1992 (39)	12 mo/0	Reduction in total energy, total fat, and dietary cholesterol, with emphasis on reduction of SFA intake Moderate increment of unsaturated fatty acids and complex carbohydrate with focus on soluble fiber Target food habits were regular eating patterns and moderate amount of food consumed	Goal was to increase PA to 3–4 times/wk for 30–60 min Recommended mean HR was 110–140 beats/min Types of exercise were suggested (e.g., walking, jogging, cycling, and swimming)	Group counseling: physician, dietitian, 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- to 3-mo intervals Visited the outpatient clinic at 6 and 12 mo

ACE = angiotensin-converting enzyme, ACSM = American College of Sports Medicine; ADA = American Diabetes Association; ALA = α-linolenic acid; BP = blood pressure; CDA = Canadian Diabetes Association; CDC = Centers for Disease Control and Prevention; DPP = Diabetes Prevention Program; HR = heart rate; MUFA = monounsaturated fatty acid; NPH = neutral protamine Hagedorn; PA = physical activity; SFA = saturated fatty acid.

Appendix Table 4. Summary of Results for Patients at Risk for Diabetes

Outcome	RCTs, *n* (Reference)	Strength of Evidence	Precision
Primary outcome			
CVD events (6- to 10-y follow-up)	2 (24, 41)	Insufficient	Evidence too limited to draw conclusion: RR, 1.02 (95% CI, 0.73 to 1.42); HR, 0.96 (CI, 0.76 to 1.44)
CVD events (20-y follow-up)	1 (42)	Insufficient	Evidence too limited to draw conclusion: HR, 0.98 (95% CI, 0.71 to 1.37)
Severe retinopathy (cumulative incidence) (20-y follow-up)	1 (42)	Insufficient	Evidence too limited to draw conclusion: HR, 0.53 (95% CI, 0.29 to 0.99)
Severe nephropathy (cumulative incidence) (20-y follow-up)	1 (42)	Insufficient	Evidence too limited to draw conclusion: HR, 1.05 (95% CI, 0.16 to 7.05)
Neuropathy (abnormal touch sensation with ≥1 insensate sites) (20-y follow-up)	1 (42)	Insufficient	Evidence too limited to draw conclusion: RR, 0.97 (95% CI, 0.43 to 2.19)
Development of type 2 diabetes			
EoI: duration, 1–6 y	4 (21, 23, 24, 29)	Moderate	In favor of lifestyle intervention: RR, 0.35 (95% CI, 0.14 to 0.85)
Follow-up: 4–10 y	5 (22, 26, 43–46)	Moderate	In favor of lifestyle intervention: $RR_{4\text{-}y}$, 0.56 (95% CI, 0.48 to 0.64); $RR_{6\text{-}y}$, 0.47 (CI, 0.34 to 0.65); $RR_{10\text{-}y}$, 0.80 (CI, 0.74 to 0.88)
Death (10- to 20-y follow-up)	2 (24, 41)	Insufficient	Evidence too limited to draw conclusion: $RR_{10\text{-}y}$, 0.58 (95% CI, 0.21 to 1.57); $HR_{20\text{-}y}$, 0.83 (CI, 0.48 to 1.40)
Body composition			
BMI			
EoI: duration, 6 mo–4 y	6 (21, 23, 25, 26, 28, 29)	Low	In favor of lifestyle intervention: MD, −1.02 (95% CI, −1.43 to −0.61)
6-mo follow-up	1 (25)	Insufficient	Evidence too limited to draw conclusion: MD, −1.30 (95% CI, −1.92 to −0.68)
4-y follow-up	1 (21)	Insufficient	Evidence too limited to draw conclusion: MD, −0.92 (95% CI, −1.32 to −0.53)
20-y follow-up	1 (42)	Insufficient	Evidence too limited to draw conclusion: MD, 0.70 (95% CI, −0.14 to 1.54)
Waist circumference			
EoI: duration, 6 mo–4 y	7 (21, 23, 25–29)	Low	In favor of lifestyle intervention: MD, −4.08 (95% CI, −5.60 to −2.57)
6-mo follow-up	1 (25)	Insufficient	Evidence too limited to draw conclusion: MD, −8.80 (95% CI, −11.87 to −5.73)
4-y follow-up	1 (21)	Insufficient	Evidence too limited to draw conclusion: MD, −1.86 (95% CI, −3.49 to −0.22)
Weight change			
EoI: duration, 6 mo–6 y	8 (21, 22, 24–29)	Low	In favor of lifestyle intervention: MD, −7.00 (95% CI, −9.97 to −4.03)
6-mo follow-up	1 (25)	Insufficient	Evidence too limited to draw conclusion: MD, −7.48 (95% CI, −12.64 to −2.32)
4-y follow-up	2 (21, 22)	Insufficient	Evidence too limited to draw conclusion: MD, −5.88 (95% CI, −8.05 to −3.71)
10-y follow-up	1 (22)	Insufficient	Evidence too limited to draw conclusion: MD, −0.94 (95% CI, −5.07 to 3.19)
Metabolic variables			
Fasting plasma glucose			
EoI: duration, 6 mo–4 y	7 (21–23, 25–27, 29)	Low	In favor of lifestyle intervention: MD, −0.28 (95% CI, −0.33 to −0.23)
6-mo follow-up	1 (25)	Insufficient	Evidence too limited to draw conclusion: MD, −0.93 (95% CI, −1.37 to −0.49)
10-y follow-up	1 (22)	Insufficient	Evidence too limited to draw conclusion: MD, 0.10 (95% CI, 0.03 to 0.18)
20-y follow-up	1 (42)	Insufficient	Evidence too limited to draw conclusion: MD, −0.90 (95% CI, −1.55 to −0.25)
2-h plasma glucose			
EOI: duration, 1–4 y	5 (23, 26–29)	Low	In favor of lifestyle intervention: MD, −0.54 (95% CI, −1.06 to −0.02)
20-y follow-up	1 (42)	Insufficient	Evidence too limited to draw conclusion: MD, −2.30 (95% CI, −3.53 to −1.07)
Hemoglobin A_{1c}			
EoI: duration, 1–3 y	3 (22, 26, 29)	Low	No statistically significant difference: MD, −0.10 (95% CI, −0.22 to 0.01)
4-y follow-up	1 (22)	Insufficient	Evidence too limited to draw conclusion: MD, −0.15 (95% CI, −0.20 to −0.10)
10-y follow-up	1 (22)	Insufficient	Evidence too limited to draw conclusion: MD, −0.05 (95% CI, −0.09 to −0.02)
HDL cholesterol			
EoI: duration, 6 mo–4 y	6 (21, 23, 25, 26, 28, 29)	Low	In favor of lifestyle intervention: MD, 0.08 (95% CI, 0.05 to 0.10)
6-mo follow-up	1 (25)	Insufficient	Evidence too limited to draw conclusion: MD, 0.11 (95% CI, −0.12 to 0.34)
4-y follow-up	1 (21)	Insufficient	Evidence too limited to draw conclusion: MD, 0.05 (95% CI, 0.00 to 0.10)
LDL cholesterol (EoI: duration, 1–3 y)	4 (26–29)	Low	No statistically significant difference: MD, 0.01 (95% CI, −0.13 to 0.15)
Total cholesterol (EoI: duration, 1–4 y)	5 (21, 23, 26–28)	Low	No statistically significant difference: MD, 0.00 (95% CI, −0.12 to 0.13)
Triglycerides			
EoI: duration, 6 mo–4 y	6 (21, 23, 26–29)	Low	In favor of lifestyle intervention: MD, −0.13 (95% CI, −0.25 to −0.01)
6-mo follow-up	1 (25)	Insufficient	Evidence too limited to draw conclusion: MD, 0.03 (95% CI, −0.45 to 0.51)
4-y follow-up	1 (21)	Insufficient	Evidence too limited to draw conclusion: MD, −0.09 (95% CI, −0.22 to 0.05)

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Appendix Table 4—**Continued**

Outcome	RCTs, *n* (Reference)	Strength of Evidence	Precision
Blood pressure			
Diastolic			
EoI: duration, 6 mo–4 y	7 (21–23, 25, 26, 28, 29)	Low	In favor of lifestyle intervention: MD, −2.84 (95% CI, −3.94 to −1.74)
6-mo follow-up	1 (25)	Insufficient	Evidence too limited to draw conclusion: MD, 1.90 (95% CI, −2.44 to 6.24)
4-y follow-up	2 (21, 22)	Low	In favor of lifestyle intervention: MD, −1.88 (95% CI, −2.65 to −1.12)
20-y follow-up	1 (42)	Insufficient	Evidence too limited to draw conclusion: MD, 0.90 (95% CI, −2.52 to 4.32)
Systolic			
EoI: duration, 6 mo–4 y	7 (21–23, 25, 26, 28, 29)	Low	In favor of lifestyle intervention: MD, −5.28 (95% CI, −8.83 to −1.72)
6-mo follow-up	1 (25)	Insufficient	Evidence too limited to draw conclusion: MD, −2.70 (95% CI, −10.12 to 4.72)
4-y follow-up	2 (21, 22)	Low	In favor of lifestyle intervention: MD, −4.41 (95% CI, −8.47 to −0.35)
20-y follow-up	1 (42)	Insufficient	Evidence too limited to draw conclusion: MD, 1.70 (95% CI, −3.40 to 6.80)
Change in physical activity			
Exercise			
EoI: duration, 1–6 y	4 (21, 22, 24, 27)	Low	In favor of lifestyle intervention: SMD, 0.40 (95% CI, 0.20 to 0.59)
4-y follow-up	1 (22)	Insufficient	Evidence too limited to draw conclusion: SMD, 0.23 (95% CI, 0.10 to 0.35)
Change in dietary or nutrient intake			
Energy intake (EoI: duration, 12 mo–6 y)	4 (21, 22, 24, 26)	Low	In favor of lifestyle intervention: SMD, −0.23 (95% CI, −0.31 to −0.16)
SFA intake (EoI: duration, 12 mo–3 y)	2 (21, 26)	Low	In favor of lifestyle intervention: SMD, −0.53 (95% CI, −0.73 to −0.34)

BMI = body mass index; CVD = cardiovascular disease; EoI = end of intervention; 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.

Appendix Table 5. Summary of Results for Patients With Type 2 Diabetes

Outcome	RCTs, *n* (Reference)	Strength of Evidence	Summary
Primary outcome			
All-cause mortality (≥10-y follow-up)	2 (47, 48)	Low	No statistically significant difference: RR_{meds}, 0.75 (95% CI, 0.53 to 1.06)
Composite of CVD events (death due to CV causes, nonfatal MI, nonfatal stroke, CABG, percutaneous coronary intervention, revascularization for peripheral atherosclerotic arterial disease, and amputation due to ischemia) (13-y follow-up)	1 (48)	Insufficient	Evidence too limited to draw conclusion: RR_{meds}, 0.49 (95% CI, 0.34 to 0.71)
Composite of CVD events (death due to CV causes, nonfatal MI, nonfatal stroke, and hospitalization for angina) (10-y follow-up)	1 (47)	Insufficient	Evidence too limited to draw conclusion: RR_{meds}, 0.96 (95% CI, 0.85 to 1.09)
Development of nephropathy (≥10-y follow-up)	1 (48)	Insufficient	Evidence too limited to draw conclusion: RR_{meds}, 0.54 (95% CI, 0.35 to 0.85)
Development of retinopathy (≥10-y follow-up)	1 (48)	Insufficient	Evidence too limited to draw conclusion: RR_{meds}, 0.76 (95% CI, 0.58 to 0.99)
Autonomic neuropathy progression (≥10-y follow-up)	1 (48)	Insufficient	Evidence too limited to draw conclusion: RR_{meds}, 0.75 (95% CI, 0.57 to 0.99)
Peripheral neuropathy progression (≥10-y follow-up)	1 (48)	Insufficient	Evidence too limited to draw conclusion: RR_{meds}, 0.96 (95% CI, 0.73 to 1.26)
Change in body composition			
BMI			
EoI: duration, 1–2 y	5 (33, 34, 37, 39, 40)	Low	No statistically significant difference: MD_{all}, −0.10 (95% CI, −0.91 to 0.72)
6 mo after intervention	1 (33)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, 1.00 (95% CI, −1.84 to 3.84)
2 y after intervention	1 (66)	Insufficient	Evidence too limited to draw conclusion: $MD_{no\ meds}$, 0.10 (95% CI, −1.57 to 1.77)
≥10-y follow-up	1 (48)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, −1.10 (95% CI, −3.14 to 0.94)
Weight change			
EoI: duration, 6 mo–4 y	5 (31, 32, 36–38)	Low Insufficient	In favor of lifestyle intervention: $MD_{no\ meds}$, −1.53 (95% CI, −2.09 to −0.97); MD_{meds}, −11.62 (CI, −12.37 to −10.87)
6 mo after intervention	1 (32)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, 1.14 (95% CI, −5.39 to 7.67)
≥10-y follow-up	1 (47)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, −3.54 (95% CI, −5.78 to −1.30)
Metabolic variables			
Fasting plasma glucose			
EoI: duration, 1 y	2 (33, 39)	Insufficient Insufficient	Evidence too limited to draw conclusion: $MD_{no\ meds}$, 0.33 (95% CI, −0.83 to 1.49) In favor of lifestyle intervention: MD_{meds}, −1.79 (95% CI, −3.23 to −0.35)
6 mo after intervention	1 (33)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, 1.00 (95% CI, −2.61 to 0.61)
≥10-y follow-up	1 (48)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, 0.16 (95% CI, −1.47 to 1.15)
Hemoglobin A_{1c}			
EoI: duration, 3 mo–4 y	10 (31–40)	Low Low	No statistically significant difference: $MD_{no\ meds}$, −0.19 (95% CI, −0.46 to 0.08) In favor of lifestyle intervention: MD_{meds}, −0.71 (CI, −1.31 to −0.12)
6 mo after intervention	3 (32, 33, 40)	Low	No statistically significant difference: MD_{all}, 0.14 (95% CI, −0.43 to 0.14)
2 y after intervention	1 (66)	Insufficient	Evidence too limited to draw conclusion: $MD_{no\ meds}$, 0.60 (95% CI, 0.52 to 0.68)
≥10-y follow-up	2 (47, 48)	Low	No statistically significant difference: MD_{meds}, −0.10 (95% CI, −0.19 to 0.00)

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Appendix Table 5—**Continued**

Outcome	RCTs, *n* (Reference)	Strength of Evidence	Summary
HDL cholesterol			
EoI: duration, 6 mo–4 y	6 (31, 32, 34, 36, 37, 39)	Low Low	No statistically significant difference: $MD_{no\ meds}$, 0.01 (95% CI, −0.04 to 0.05) In favor of lifestyle intervention: MD_{meds}, 0.04 (CI, 0.03 to 0.05)
6 mo after intervention	1 (32)	Insufficient	Evidence too limited to draw conclusion: $MD_{no\ meds}$, −0.04 (95% CI, −0.16 to 0.09)
≥10-y follow-up	2 (47, 48)	Low	In favor of lifestyle intervention: MD_{meds}, 0.05 (95% CI, 0.01 to 0.10)
LDL cholesterol			
EoI: duration, 1–4 y	5 (31, 33, 34, 36, 37)	Low	No statistically significant difference: $MD_{no\ meds}$, −0.09 (95% CI, −0.26 to 0.08); MD_{meds}, −0.26 (CI, −0.93 to 0.40)
6 mo after intervention	1 (33)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, −0.59 (95% CI, −1.07 to −0.11)
≥10-y follow-up	2 (47, 48)	Low	No statistically significant difference: MD_{meds}, −0.01 (95% CI, −0.12 to 0.11)
Total cholesterol			
EoI: duration, 6 mo–2 y	5 (32, 34, 36, 37, 39)	Low	No statistically significant difference: $MD_{no\ meds}$, −0.13 (95% CI, −0.27 to 0.01)
6 mo after intervention	1 (32)	Insufficient	Evidence too limited to draw conclusion: $MD_{no\ meds}$, 0.01 (95% CI, −0.35 to 0.36)
≥10-y follow-up	1 (48)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, 0.38 (95% CI, −0.06 to 0.82)
Triglycerides			
EoI: duration, 1–4 y	5 (31, 33, 34, 36, 39)	Low	No statistically significant difference: $MD_{no\ meds}$, −0.11 (95% CI, −0.30 to 0.09); MD_{meds}, −0.39 (CI, −1.39 to 0.60)
6 mo after intervention	1 (33)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, −0.18 (95% CI, −1.47 to 1.11)
≥10-y follow-up	2 (47, 48)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, −0.05 (95% CI, −0.26 to 0.17)
Blood pressure			
Diastolic			
EoI: duration, 8 mo–4 y	6 (31, 33, 34, 36–38)	Low Low	No statistically significant difference: $MD_{no\ meds}$, 0.32 (95% CI, −1.43 to 2.07) In favor of lifestyle intervention: MD_{meds}, −0.44 (CI, −0.79 to −0.10)
6 mo after intervention	1 (33)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, 0.00 (95% CI, −5.07 to 5.07)
≥10-y follow-up	2 (47, 48)	Low	In favor of usual care: MD_{meds}, 0.83 (95% CI, 0.23 to 1.43)
Systolic			
EoI: duration, 8 mo–4 y	6 (31, 33, 34, 36–38)	Low	No statistically significant difference: $MD_{no\ meds}$, 1.89 (95% CI, −0.57 to 4.35); MD_{meds}, −6.25 (CI, −15.52 to 3.02)
6 mo after intervention	1 (33)	Insufficient	Evidence too limited to draw conclusion: MD_{meds}, −3.0 (95% CI, −12.4 to 6.4)
≥10-y follow-up	2 (47, 48)	Low	No statistically significant difference: MD_{meds}, −0.06 (95% CI, −1.06 to 0.93)
Change in physical activity			
Exercise			
EoI: duration, 6 mo–2 y	6 (32–34, 36, 38, 40)	Low	In favor of lifestyle intervention: SMD_{all}, 0.41 (95% CI, 0.20 to 0.63)
6 mo after intervention	4 (32–34, 40)	Low	In favor of lifestyle intervention: SMD_{all}, 0.40 (95% CI, 0.07 to 0.73)
5- to 10-y follow-up	3 (47, 48, 67)	Low	In favor of lifestyle intervention: SMD_{all}, 0.17 (95% CI, 0.11 to 0.22)

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Appendix Table 5—**Continued**

Outcome	RCTs, *n* (Reference)	Strength of Evidence	Summary
Change in dietary or nutrient intake			
Energy intake			
EoI: duration, 6 mo–1 y	4 (32, 33, 36, 38)	Low	In favor of lifestyle intervention: SMD_{all}, −0.17 (95% CI, −0.33 to −0.01)
6 mo after intervention	1 (33)	Insufficient	Evidence too limited to draw conclusion: SMD_{meds}, −0.12 (95% CI, −0.59 to 0.36)
8-y follow-up	1 (48)	Insufficient	Evidence too limited to draw conclusion: SMD_{meds}, 0 (95% CI, −0.35 to 0.34)
SFA intake			
EoI: duration, 6 mo–1 y	5 (32–34, 38, 40)	Low	In favor of lifestyle intervention: SMD_{all}, −0.38 (95% CI, −0.68 to −0.08)
6 mo after intervention	3 (33, 34, 40)	Low	In favor of lifestyle intervention: SMD_{all}, −0.41 (95% CI, −0.61 to −0.21)
2 y after intervention	1 (34)	Insufficient	Evidence too limited to draw conclusion: SMD_{all}, −0.57 (95% CI, −0.83 to −0.32)
4 y after intervention	2 (34, 48)	Low	In favor of lifestyle intervention: SMD_{all}, −0.39 (95% CI, −0.66 to −0.13)
7- to 8-y follow-up	2 (34, 48)	Low	In favor of lifestyle intervention: SMD_{all}, −0.46 (95% CI, −0.84 to −0.07)

BMI = body mass index; CABG = coronary artery bypass grafting; CV = cardiovascular; CVD = cardiovascular disease; EoI = end of intervention; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MD = mean difference; meds = medication; MI = myocardial infarction; RCT = randomized, controlled trial; RR = risk ratio; SFA = saturated fatty acid; SMD = standardized mean difference.