Abstract

Overweight and obesity are major contributors to both type 2 diabetes and cardiovascular disease (CVD). Moreover, individuals with type 2 diabetes who are overweight or obese are at particularly high risk for CVD morbidity and mortality. Although short-term weight loss has been shown to ameliorate obesity-related metabolic abnormalities and CVD risk factors, the long-term consequences of intentional weight loss in overweight or obese individuals with type 2 diabetes have not been adequately examined. The primary objective of the Look AHEAD clinical trial is to assess the long-term effects (up to 11.5 years) of an intensive weight loss program delivered over 4 years in overweight and obese individuals with type 2 diabetes. Approximately 5000 male and female participants who have type 2 diabetes, are 45–74 years of age, and have a body mass index $\geq 25$ kg/m$^2$ will be randomized to one of the two groups. The intensive lifestyle intervention is designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity. This program is compared to a control condition given diabetes support and education. The primary study outcome is time to incidence of a major CVD event. The study is designed to provide a 0.90 probability of detecting an 18% difference in major CVD event rates between the two groups. Other outcomes include components of CVD risk, cost and cost-effectiveness, diabetes control and complications, hospitalizations, intervention processes, and quality of life. © 2003 Elsevier Inc. All rights reserved.

Keywords: Type 2 diabetes mellitus; Obesity; Weight loss; Weight loss maintenance; CVD; Behavioral interventions; Lifestyle programs; Physical activity; Health promotion; Disease prevention

Introduction

The current epidemic of type 2 diabetes in the United States is largely attributable to the increased incidence of obesity [1]. Type 2 diabetes is associated with a two- to fourfold
increased risk for cardiovascular disease (CVD), and overweight or obese individuals with type 2 diabetes are at particularly high risk for CVD morbidity and mortality [2–4].

Although short-term weight loss has been demonstrated to ameliorate obesity-related metabolic abnormalities and CVD risk factors, no prospective randomized studies have examined the long-term consequences of intentional weight loss in overweight or obese populations [5]. Recently, several large randomized multicenter trials have demonstrated significant decreases in weight and increases in activity level for as long as 3 years, indicating feasibility to assess the long-term effects of interventions designed to promote and sustain weight loss [6–11]. Although previous studies have demonstrated reduction in risk of developing type 2 diabetes or hypertension with weight loss through lifestyle change, none have demonstrated that such interventions will reduce CVD morbidity or mortality [6–9]. This demonstration is an important goal, because some observational studies suggest that weight loss is associated with increased mortality [12–16].

Research goals

The primary hypothesis of Look AHEAD (Action for Health in Diabetes) is that an intensive lifestyle intervention to reduce weight and increase physical activity will reduce cardiovascular morbidity and mortality. It will compare, in overweight volunteers with type 2 diabetes, the long-term (up to 11.5 years) effects of two study conditions: an intensive lifestyle intervention designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity versus a control condition of diabetes support and education on the combined incidence of serious cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke).

Other research goals include comparisons of CVD risk factors, mortality, diabetes-related metabolic factors and complications, safety of the interventions, indices of general health, quality of life, and economic consequences.

Study design

Overview

Participants will be recruited over 2.5 years, beginning in 2001. Planned follow-up is until 2012, resulting in an average of 10.25 years of participant follow-up. The intensive intervention occurs during the first 4 years. Thereafter, participants are offered maintenance counseling and followed for study outcomes.

Eligibility criteria

Approximately 5000 volunteers with type 2 diabetes who meet inclusion and exclusion criteria summarized in Table 1 are to be recruited. Individuals ≥75 years of age are excluded due to their increased risk of competing mortality and potential safety concerns related to weight loss. Type 2 diabetes mellitus is determined by self-report with verification (medical records, current treatment, verification from personal health care provider, or fasting
Table 1. Look AHEAD inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
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<tbody>
<tr>
<td>• 45–74 years old</td>
<td>• Inadequate control of comorbid conditions (see text)</td>
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<td>• BMI ≥ 25 kg/m² (≥27 kg/m² if currently taking insulin)</td>
<td>• HbAlc &gt; 11%</td>
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<tr>
<td>• Type 2 diabetes mellitus determined by self-report with verification (see text)</td>
<td>• Blood pressure ≥ 160/100 mm Hg</td>
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</table>

Factors that may limit adherence to interventions or affect conduct of the trial

Unable or unwilling to give informed consent or communicate with local study staff
Hospitalization for depression in past 6 months
Self-report of alcohol or substance abuse within the past 12 months
Travel plans that do not permit full participation
Lack of support from primary health care provider or family members
Failure to complete the run-in for dietary intake and exercise
In past 3 months, weight loss exceeding 10 lbs
History of bariatric surgery, small bowel resection, or extensive bowel resection
Chronic treatment with systemic corticosteroids
Another member of the household is a participant or staff member in Look AHEAD
Weight greater than 350 pounds unless exercise test equipment is available at center
Current diagnosis of schizophrenia, other psychotic disorders, or bipolar disorder
Current use of medications for weight loss
Inability to walk two blocks
Other medical, psychiatric, or behavioral limitations that in the judgment of the principal investigator may interfere with study participation or the ability to follow the intervention protocol
Amputation of lower limb for nontraumatic causes

Underlying diseases likely to limit life span and/or affect the safety of the interventions

Currently pregnant or nursing
Cancer requiring treatment in the past 5 years, unless the progress is excellent
Self-report of HIV-positive or active tuberculosis
CVD event within the past 3 months
Documented history of pulmonary embolus in past 6 months
CVD manifesting any of the following criteria: unstable angina pectoris or angina pectoris at rest; a history of cardiac arrest; complex ventricular arrhythmia at rest or with exercise; uncontrolled atrial fibrillation (heart rate of 100 beats per minute or more); New York Heart Association Class III or IV congestive heart failure; acute myocarditis, pericarditis or hypertrophic cardiomyopathy; clinically significant aortic stenosis; left bundle block or cardiac pacemaker unless approved by a cardiologist; cardiac defibrillator; history of aortic aneurysm of at least 7 cm in diameter or aortic aneurysm repair; resting heart rate <45 beats per minute or >100 beats per minute; heart transplantation
Maximum exercise stress test showing unsafe to participate in the lifestyle intervention
Renal disease: urine dipstick protein 4+, serum creatinine 1.4 mg/dL (women) or 1.5 mg/dL (men), or currently receiving dialysis
Chronic obstructive pulmonary disease that would limit ability to follow the protocol
Self-reported chronic hepatitis B or C or cirrhosis; inflammatory bowel disease requiring treatment in past year; Cushing’s syndrome; acromegaly (clinical diagnosis or self-report); any major organ transplant
Moderate to high risk for cardiac complications during exercise and/or inability to self-regulate activity, or understand the recommended activity level
glucose ≥126 mg/dL, symptoms of hyperglycemia with casual plasma glucose ≥200 mg/dL or 2-hour plasma glucose ≥200 mg/dL after a 75-g oral glucose load on at least two occasions). Individuals who have a clinical history strongly suggestive of type 1 diabetes are excluded. The number of subjects using insulin at the time of enrollment will be monitored with a goal of ≤30% of the total. There is no upper eligibility criterion for body mass index; however, exercise testing, which is required, cannot be performed at some clinics on individuals weighing more than 350 pounds due to equipment limits.

During screening, individuals who have urgent medical conditions or values of HbA1c, triglyceride, creatinine, or blood pressure that exceed eligibility limits are referred for medical care. After 3 months, those individuals who are ineligible because of HbA1c, triglyceride, or blood pressure levels may be rescreened for eligibility. It is anticipated that 10–20% of enrollees will have preexisting CVD at study entry. A history of uncomplicated myocardial infarction, coronary artery bypass surgery, percutaneous coronary angiography, atherectomy or stent placement, chronic stable angina pectoris, and stable New York Heart Association Class I or Class II congestive heart failure are permitted conditions for entry if the event or diagnosis of the condition occurred at least 3 months previously. Participants with a history of carotid or peripheral artery atherectomy, angioplasty, or vascular bypass surgery are also eligible if they meet functional criteria for inclusion. All participants undergo a supervised maximum exercise stress test using the established study protocol based on published standards [17].

Recruitment

The study goal is to recruit 5000 participants over a 2.5-year period, approximately 313 in each of the 16 clinical centers. We will endeavor to recruit approximately equal numbers of men and women and to recruit a minimum of 33% from racial and ethnic minority groups including African Americans, Hispanic Americans, American Indians, and Asian Americans.

Informed consent

Approval of protocol and consent forms by the local institutional review board (IRB) was obtained at each site. Informed consent must be obtained before individuals participate in any screening procedures.

Study run-in and randomization

All potential participants are required to complete a 2-week run-in period prior to randomization. During this period they record daily information about diet and physical activity. Successful completion of self-monitoring is required for eligibility and randomization.

Eligible participants are randomly assigned to either diabetes support and education or lifestyle intervention using a web-based data management system that verifies eligibility. Randomization is stratified by clinical center and blocked with random block sizes.
Outcomes and study measures

The primary outcome of Look AHEAD is the time to incidence of the first postrandomization occurrence of any of the following events over the planned follow-up period of up to 11.5 years: (1) cardiovascular death (including fatal myocardial infarctions and stroke), (2) nonfatal myocardial infarction, or (3) nonfatal stroke.

The secondary outcome consists of the time to the first occurrence of any of the following events: (1) death (all causes), (2) coronary artery bypass grafting and/or percutaneous coronary angioplasty, (3) hospitalization for congestive heart failure, (4) carotid endarterectomy, or (5) peripheral vascular procedures such as bypass or angioplasty.

A central outcomes adjudication committee reviews the pertinent medical records and death certificates to confirm these events and procedures.

Key objectives of additional data collection are:

1. to assess the effect of lifestyle intervention on components of CVD risk including blood pressure, hypertension control, incident hypertension, lipids, incident dyslipidemia, inflammatory markers, hemostatic factors, and fitness;
2. to characterize the relative impact of lifestyle intervention on diabetes control and complications, using measures of nephropathy (including albuminuria), amputation, and glycemic control (both metabolic measures and drug use);
3. to contrast the two groups with respect to health conditions that may reflect benefit (incident obesity-related cancer, self-report of knee osteoarthritis symptoms and disability, sleep apnea, and urinary incontinence) or risk (gall bladder disease, fractures, bone mineral density) of weight loss;
4. to characterize the relative impact of lifestyle intervention on the average number of hospitalizations experienced by participants;
5. to use measures of physical activity, dietary intake, body weight, fitness, and body composition to examine delivery of the lifestyle intervention and characterize relationships between these process factors and health outcomes;
6. to examine the relative impact of the lifestyle intervention on quality of life and psychological outcomes, including physical and social functioning, pain, eating disorders and depression; and
7. to estimate cost, cost-effectiveness, health state preferences (or “utilities”), and cost-utility ratios associated with its interventions.

Tables 2 and 3 list the timing of the study measures and questionnaires and their frequency. The occurrence of cardiovascular events, surgical procedures, or hospitalization is assessed annually at the clinic visit and by phone at 6-month intervals by personnel who are blinded to treatment assignment.

Interventions

All participants continue to receive their medical care, including medical management of their diabetes (with the exception of short-term monitoring for hypoglycemia in those at high risk for this condition as described below) from their usual source of medical care, not from the Look AHEAD study staff. All participants attend a 1-hour diabetes education
Table 2. Look AHEAD measures and frequency

<table>
<thead>
<tr>
<th>Measure</th>
<th>Screening and baseline</th>
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<td>Every other year</td>
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<td>Every other year</td>
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<td>Cardiovascular fitness test</td>
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<td>Substudies</td>
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<td>Inflammation markers (collected from all</td>
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<td>assayed in n = 1700 at year 4)</td>
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* First 25% enrolled.

LDL = low-density lipoprotein; HDL = high-density lipoprotein; ECG = electrocardiogram

class at the end of the screening process. This session provides basic education about diabetes, with particular emphasis on aspects of diabetes care related to the trial, such as management of hypoglycemia, CVD symptoms, and foot care. Participants are encouraged to use blood glucose self-monitoring equipment. Smokers are encouraged to stop smoking, but no formal smoking cessation counseling or classes are part of the study. Participants in both study arms and their physicians are given results from study examinations after each annual examination.

**Diabetes support and education**

Diabetes support and education provides three group educational/social support sessions each year for 4 years after randomization of the last volunteer. The educational sessions include one session each year on diet/nutrition and one session related to exercise. Different nutrition and exercise topics are covered each year. One social support session is offered annually throughout the trial. These provide an opportunity for participants to discuss issues related to living with diabetes. Attendance is strongly encouraged but not required. Participants will also attend regularly scheduled clinic visits for assessment of outcomes and will participate in telephone calls for data collection and safety monitoring.

**Lifestyle intervention**

The Look AHEAD lifestyle intervention is designed to induce a minimum weight loss of 7% of initial body weight during the first year. Individual participants are encouraged to
lose 10% (or more) of their initial body weight. Each clinical center is expected to achieve a mean weight loss ≥7% across all of their participants in the lifestyle intervention group. Centers that do not achieve at least a 5% mean weight loss will receive extra assistance to help them improve their weight loss outcomes.

Lifestyle intervention combines diet modification and increased physical activity with a goal of sustained weight loss. The lifestyle intervention is modeled on group behavioral programs developed for the treatment of obese patients with type 2 diabetes and includes intervention components from the Diabetes Prevention Program [18–20]. The intervention utilizes strategies that have been shown to be most effective for long-term weight loss and weight loss maintenance. These include a portion-controlled diet (which provides portions of food with a fixed calorie and macronutrient content) during the initial phase of weight loss, a multicomponent approach to intervention (including behavioral techniques, diet modification, physical activity, and social support), and ongoing regular contact throughout the follow-up period.

Table 3. Look AHEAD questionnaires and frequency

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
<th>Extended follow-up</th>
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<td>Outpatient visit questionnaire</td>
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<td>X</td>
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<td><strong>Health behaviors</strong></td>
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<td>Eating patterns</td>
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<td>Dietary assessment (n = 2500)</td>
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<td>Closeout</td>
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<td>Paffenbarger (n = 1200)(^a)</td>
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<td>Tobacco and alcohol use</td>
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<td><strong>Other medical conditions</strong></td>
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<td>Knee osteoarthritis [34]</td>
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<td>Health Utilities Index [38,39]</td>
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<td><strong>Quality of life</strong></td>
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<td>Health quality of life (SF-36)</td>
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<td>Sociodemographics</td>
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<td>Weight, personal medical, and</td>
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<td>family medical history</td>
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\(^a\) Indicates questionnaire to be conducted on a subsample.

\(^b\) Indicates administration at month 3, month 6, and month 9.
All centers utilize the same lifestyle intervention program delivered with a treatment manual containing lessons and materials for the participants and an accompanying guide for the counselors.

Participants are prescribed a diet of self-selected foods for the first 2 weeks with recommendations to consume 30% or fewer kcal from fat of which $<10\%$ kcal are from saturated fat. The calorie goal is 1200–1500 kcal/day for those who weigh $<250$ pounds, or 1500–1800 kcal/day for those whose weight exceeds 250 pounds. At session three, the participants are prescribed a more structured dietary program to help them achieve this calorie goal; the plan consists of two meal replacement products, one portion-controlled snack, and a self-selected meal each day. At week 20, participants are prescribed one meal replacement per day and two meals of self-selected foods are allowed. The maintenance dietary protocol for years 2–4 allows for continued use of one meal replacement per day.

The physical activity program relies largely on unsupervised exercise, with physical activity initiated at 50 minutes per week of moderate activity. The goal is 175 minutes of moderate intensity physical activity per week at the end of the first 6 months. Exercise episodes of 10 minutes and longer are counted toward this goal. Participants are encouraged to exercise 5 days per week. In general, occupational activity is not counted toward the physical activity goal.

The lifestyle intervention involves a combination of regularly scheduled group and individual sessions delivered in the following three phases:

**Phase I (months 1–12):** During months 1–6, participants are seen weekly with three group meetings and one individual counseling session per month. Participants are scheduled for a total of 24 visits during the first 26 weeks (6 months) and missed visits may be rescheduled. During months 7–12, participants are provided one individual and two group sessions per month.

**Phase II (months 13–48):** A minimum of two contacts per month is expected during this phase. One contact is on-site and the other by phone, mail, or E-mail. More frequent contact is permissible if desired by the participant. A site, at its discretion, may offer an ongoing “open” group that is led by an individual counselor and meets regularly throughout the trial to offer group support. Refresher groups are offered three times a year. These convene once a week for up to 6 weeks and are designed to reverse weight gain or promote weight maintenance.

**Phase III (months 49+):** From month 49 on, participants have at least two on-site contacts per year. At their discretion, sites may offer additional support through newsletters, phone, or E-mail contact. Participants may also join refresher groups.

**Behavioral and medication toolbox**

Participants who fail to lose at least 1% of body weight per month during the first 6 months or who do not meet weight loss or adherence goals are given special assistance by their lifestyle counselor. After 6 months of treatment, weight loss medications will be considered as an adjunct to intensive dietary and exercise modification in participants who do not meet established weight loss goals or experience relapse, and who are medically
appropriate for use of the medication and provide informed consent. At the time of this writing, the only weight loss medication selected for use in this study is orlistat (Xenical, Roche Pharmaceuticals, Nutley, NJ). Advanced behavioral strategies also are considered for use with specific participants who meet the above criteria after 6 months of intervention. Examples include provision of exercise equipment, enrolling participants in a supervised exercise program, providing food coupons or food, or enrolling participants in a cooking class.

**Participant safety**

Participants in Look AHEAD receive their general medical care and diabetes management from a health care provider who is separate from the Look AHEAD staff. Enrollment eligibility requires having a health care provider, and if a participant loses his or her health care provider during the trial, Look AHEAD staff assist in finding an appropriate replacement.

At study entry, all participants are provided with a program of patient education on diabetes mellitus and other cardiovascular risk factors. A description of Look AHEAD, information on the therapeutic targets for diabetes (HbA1c <7%), blood pressure (<130/80 mm Hg), and lipids (low-density lipoprotein cholesterol <100 mg/dL, high-density lipoprotein cholesterol >45 mg/dL, and triglycerides <200 mg/dL) and a synopsis of current consensus recommendations for achieving these targets are sent to each participant’s health care provider.

Data related to HbA1c, blood pressure, lipid values, electrocardiogram, urine albumin, and serum creatinine values that are obtained during scheduled study visits are provided to participants and their primary care providers with normal or target ranges clearly identified.

Patients who use insulin or oral hypoglycemic medication may have increased risk of hypoglycemia, especially during the time when diet and/or physical activity interventions are implemented. Participants in the lifestyle intervention who are at risk for hypoglycemia due to medications are advised to monitor blood glucose twice daily during the period of active weight loss and the intervention staff members monitor these records. The staff members use a treatment algorithm to reduce medication doses to minimize hypoglycemia during active weight loss, which usually occurs in the first 6 months of intervention; otherwise, changes in diabetes medications are made by the patient’s own physician.

When a cardiovascular event is discovered during the trial, a study physician will decide whether it is permissible for the participant to continue interventions. If the Look AHEAD interventions are discontinued for safety reasons, they may be resumed after consultation with the participant’s primary care physician.

Safety-related events are reported in a timely fashion, as required by the data and safety monitoring board (DSMB) and the IRBs. Interventionists and other staff reporting or managing adverse events for safety purposes do not communicate information regarding these events to study assessment personnel, who are masked to group assignment. The outcome database is separate from the safety monitoring system. Staff who are masked to intervention assignment collect outcomes every 6 months at contacts that are uniform across arms and distinct from the intervention programs.

**Feasibility evaluation**

The feasibility of the trial will be formally assessed by the DSMB to ensure that the trial interventions are being successfully delivered. Data from the first 25% of participants recruited
will be examined when these participants have all reached year 1 and again when they have reached year 2. Three criteria will be used to judge the success of the intervention:

1. The difference in the average percentage change in weight from baseline to year 1 between participants assigned to the lifestyle intervention versus those assigned to diabetes support and education must equal or exceed 5%.
2. The average absolute percent weight loss from baseline to year 1 among the first 25% of lifestyle intervention participants not using insulin at baseline must be at least 5%. (Among participants using insulin at baseline, Look AHEAD will also track weight loss, which is anticipated to average at least 3% at year 1, but there will be too few of these individuals to define a separate stopping rule.)
3. For the first 25% of participants there must be at least a 5% difference in the average percent change in weight or submaximal graded exercise test results from baseline to year 2 between participants assigned to the lifestyle intervention compared to those assigned to diabetes support and education.

The DSMB will consider these feasibility criteria in the context of early trends in glucose control, atherogenic risk factors, and, as the study proceeds, cardiovascular event rates and safety.

**Interim analysis**

Incidence rates of the primary and secondary composite outcomes will be monitored throughout the trial and used for interim analyses of efficacy and futility. Group sequential methods for events rates will be used to control the type I error to be 0.05 across these repeated analyses [21–23]. Critical values for interim testing will be defined based on an O’Brien-Fleming bound and will use a spending function to allow flexibility in the number and timing of interim analyses [24,25]. With this approach, interim tests early in the trial are conservative and the reduction in the overall power of the trial caused by interim testing is small. Conditional power calculations will be used to assess the futility of continuation in the presence of a negative treatment effect [26].

At each meeting, the DSMB will review data on adverse events and other safety issues to make an overall recommendation to the National Institutes of Health (NIH) concerning the safety of continuing the study.

**Biostatistical considerations**

**Sample size**

Look AHEAD will recruit 5000 participants who will be followed for a planned maximum follow-up of 11.5 years. This is expected to provide approximately 92% power at the (two-sided) 0.05 significance level to detect an 18% relative decrease in the rate of primary outcomes among participants assigned to lifestyle intervention under the following assumptions:

- Primary outcomes among participants assigned to diabetes support and education occur at a rate of 3.125% per year.
Recruitment is uniform over 2.5 years.
Two percent of the participants are lost annually with respect to endpoint ascertainment in each arm.

The projected event rate for the diabetes support and education arm was based on data available at the design of the trial. The projected risk of the enrolled cohort is monitored during recruitment. Table 4 describes the power calculations for testing the primary study hypothesis across a range of event rates and lengths of follow-up, based on standard formulae [27]. These calculations indicate that adequate (>80%) power is anticipated across a range of event rates, even if the planned length of follow-up is not fully achieved.

**Primary and secondary hypotheses: analysis plan**

The primary study hypothesis will be tested based on a two-tailed significance level of 0.05. The “intention-to-treat” approach will be used, meaning that participants are grouped according to randomization assignment regardless of compliance. Secondary analyses will be performed that account for actual changes in weight and fitness regardless of treatment assignment.

The main comparisons of intervention groups with respect to the distribution of time until the first postrandomization occurrence of a primary outcome will be based on survival analyses [28–31]. To compare intervention arms, we will use a Mantel-Haenszel test with unit weighting, which is stratified by clinical center. This test is equivalent to a log-rank test and, if the proportional hazards assumption is warranted, to a Cox proportional hazards model [32]. Since the primary outcome measure is the first occurrence of fatal or nonfatal myocardial infarction or stroke or other fatal cardiovascular event, all other causes of death will be treated as competing risks. This means that Kaplan-Meier estimates of “disease-specific survival” may not have a straightforward interpretation [33]. Estimates for the proper cumulative incidence function and the associated confidence intervals will be constructed for each study arm [32]. To compare intervention arms in secondary analyses involving additional covariates, we will use the Cox proportional hazards model [30], after testing underlying assumptions. Clinical center- and baseline-prevalent CVD will be used as covariates. Log–log plots of survival will be used to examine the assumption of proportional hazards.

Time to event is measured from the time of randomization. Some minor biases may occur due to this choice, for example, if there is a differential dropout rate between randomization and the start of interventions. To reduce bias, the period of time between randomization and the first intervention session is kept as short as possible by not performing the randomization

<table>
<thead>
<tr>
<th>Annual event rate for diabetes support and education (%)</th>
<th>Maximum length of follow-up (years)</th>
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<td>9.5</td>
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<tr>
<td>2.750</td>
<td>0.83</td>
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<td>3.000</td>
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<td><strong>3.125</strong></td>
<td><strong>0.87</strong></td>
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<td>3.250</td>
<td>0.88</td>
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<td>3.500</td>
<td>0.90</td>
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until groups of potential eligible participants accrue. Prespecified subgroup analyses, including formal tests for interactions with intervention effects, will be conducted; these will include subgroups defined according to history of CVD, gender, ethnicity, and other factors.

The composite outcome defining the secondary hypothesis will also be assessed at significance level 0.05 using similar approaches.

**Management**

**Clinical centers**

Each of the 16 clinical centers participates fully in trial activities, enrolling and following participants, conducting interventions, and assessing results. Staff includes a principal investigator, a program coordinator, recruitment coordinators, dietitians, behaviorists, exercise physiologists, physicians, nurses, and data collectors.

**Coordinating center**

The coordinating center has primary responsibility for randomization, analyzing data generated by the clinical centers, developing the experimental statistical design of the trial, organizing training sessions, coordinating central resources, providing detailed reports to the DSMB, and collaborating for manuscript preparation describing trial results.

**Central resources centers**

The trial includes four resource centers: a central laboratory, an electrocardiogram reading center, a dual energy X-ray absorptiometry reading center, and a diet assessment center.

**Federal sponsors**

Look AHEAD is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the NIH. The NIDDK Project Office is responsible for the administration and monitoring of the study. Other federal sponsors of Look AHEAD include the National Heart, Lung, and Blood Institute; the National Institute of Nursing Research; and the Centers for Disease Control and Prevention. Members of these agencies actively participate as scientists on subcommittees and in steering committee deliberations. In addition, the National Center on Minority Health and Health Disparities and the Office of Research on Women’s Health have provided funding to advance research on health disparities and women’s health, and the Indian Health Service contributes professional personnel.

**Steering committee**

The steering committee is the governing body that provides the leadership for the study and establishes scientific and administrative policy for the study. The steering committee is comprised of the principal investigators of each clinical center, the principal investigator of the coordinating center, and the NIDDK project coordinator. An executive committee comprised of the study chair and co-chair, the principal investigator of the coordinating center, and the NIDDK project coordinator is convened to effect management decisions required between steering committee meetings, as needed, for efficient progress of the trial. Committees appointed by the executive committee, comprised of investigators and staff from the clinical
centers and coordinating center, and other consultants are involved in design of the protocol and manual of operations and in ongoing functions of the trial (e.g., review of ancillary studies and preparation of publications). The following committees collaborated to design the trial: core measurement, economic, eligibility, lifestyle intervention, medical care, pharmacology, policy and protocol, recruitment, and substudies and ancillary studies.

Data and safety monitoring board

An independent DSMB was appointed by the NIDDK director to review periodically the progress of the Look AHEAD trial. This board oversees participant safety, evaluates performance, monitors data quality, and provides operational and policy advice to the steering committee and to the NIDDK regarding the status and continuation of the overall study, study components, and study sites.

Discussion

Since Look AHEAD is an efficacy study designed to evaluate the health impact of interventions designed to produce and maintain weight loss, a decision was made to compare a control condition of diabetes support and education with a maximal weight loss program (rather than comparing several different approaches to weight loss). Prior research suggests that there is a dose-response relationship between the magnitude of weight loss and the observed change in cardiovascular risk factors, including lipids, blood pressure, and glycemic control. It is also clear that long-term maintenance of weight loss increases the chance of producing long-term changes in these risk factors. Therefore, the Look AHEAD lifestyle intervention incorporates strategies expected to maximize long-term weight loss success, including the combination of diet, exercise, and behavior modification, ongoing contact through a combination of group and individual sessions, and use of weight loss medications as appropriate.

To maximize the potential health benefits of the lifestyle intervention, a low-calorie, moderate-fat diet (<30% of kcal from fat with <10% saturated fat) and increased physical activity are key components of the intervention. Exercise is essential to the lifestyle intervention, not only to maximize the long-term maintenance of weight loss but also because physical activity and fitness, independent of body weight, are strongly associated with CVD risk in both diabetic and nondiabetic persons [33].

Budget considerations limit the contact time that is provided over the 11.5 years. The lifestyle intervention is structured to have the most frequent visits during the active weight loss phase and then twice monthly through 4 years. After the first 4 years, participants in the lifestyle intervention enter an observational period, with required visits only twice yearly; however, participants are allowed to have additional contacts in refresher groups during the observation period. These measures are intended to maximize the chance of successful long-term weight maintenance within budget constraints of the trial.

As of April 1, 2003, 67% of the planned 5000 participants have been enrolled in the trial. Recruitment is projected to be completed in January 2004. Study goals for minority and gender representation are being met. Studywide retention appears to be excellent.
Conclusions

Look AHEAD addresses a major public health problem in the United States, cardiovascular morbidity and mortality in persons with type 2 diabetes. It is well known that obesity predisposes to diabetes and promotes CVD both in persons with and those without diabetes. This randomized clinical trial will determine whether an intensive weight loss intervention program, superimposed on standard medical management of diabetes and treatment of CVD risk factors, will reduce the incidence of CVD in type 2 diabetes. A positive effect of the intensive lifestyle intervention on cardiovascular events would provide a simple, powerful public health message. On the other hand, a finding that this intervention had no effect or was detrimental would be equally important and would indicate that efforts to improve diabetes care should be directed elsewhere.

Acknowledgments

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Appendix: Look AHEAD research investigators during the planning phase

Clinical sites


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George L. Blackburn, Ph.D.; Linda Delahanty, M.S., R.D.; Barbara Steiner, Ed.M.; Enrico Cagliero, M.D.; Christos Mantzoros, M.D., D.S.C.

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Brown University: Rena Wing, Ph.D.; Renee Bright, M.S.; Vincent Pera, Jr., M.D.; John Jakicic, Ph.D.; Amy Gorin, Ph.D.

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Vitolins, Dr.P.H.; Gary Miller, Ph.D.; Wei Lang, Ph.D.; G. John Chen, M.D., Ph.D.; Jeffery Smith, Ph.D.; Kathy Dotson, B.A.; Patricia Hogan, M.S.; Carol Wasilauskas, M.S., R.N.; Kathy Lane, B.S.; Christian Speas, B.S.; Steven N. Blair, P.E.D.; William Herman, M.D., M.P.H.

Central resources centers

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**Central Laboratory, Northwest Lipid Research Laboratories:** Santica M. Marcovina, Ph.D., Sc.D.

**ECG Reading Center, EPICARE, Wake Forest University School of Medicine:** Ronald J. Prineas, M.D., Ph.D.

**Diet Assessment Center, University of South Carolina:** Elizabeth J. Mayer-Davis, Ph.D., R.D.

Federal sponsors

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**National Heart, Lung, and Blood Institute:** Denise Simons-Morton, M.D., Ph.D.; Eva Obarza-nek, Ph.D., M.P.H., R.D.

**National Institute of Nursing Research:** Nell Armstrong, Ph.D., R.N.

**Centers for Disease Control and Prevention:** Edward Gregg, Ph.D.; David F. Williamson, Ph.D.

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**References**


