WHI CLINICAL TRIAL AND OBSERVATIONAL STUDY

The Women’s Health Initiative (WHI) Clinical Trial (CT) includes three overlapping components, each a randomized controlled comparison among women who were postmenopausal and 50 to 79 years of age at randomization. The dietary modification (DM) component randomly assigned 48,836 (target 48,000) eligible women to either a sustained low-fat eating pattern (40%) or self-selected dietary behavior (60%), with breast cancer and colorectal cancer as designated primary outcomes and coronary heart disease as a secondary outcome. The nutrition goals for women assigned to the DM intervention group have been to reduce total dietary fat to 20%, and saturated fat to less than 7% of daily calories and, secondarily, to increase daily servings of vegetables and fruits to at least five and of grain products to at least six and to maintain these changes throughout trial follow-up. The randomization of 40%, rather than 50%, of participating women to the DM intervention group was intended to reduce trial costs, while testing trial hypotheses with specified power.

The postmenopausal hormone therapy (PHT) component comprises two randomized, double-blind trials among 27,347 (target 27,500) women, with coronary heart disease (CHD) as the primary outcome, with hip and other fractures as secondary outcomes, and with breast cancer as a potential adverse outcome. Of these, 10,739 (39.3% of total) were post-hysterectomy at randomization, in which case there was a 1:1 randomized double-blind allocation between conjugated equine estrogen (E-alone) 0.625 mg/day or placebo. The remaining 16,608 (60.7%) of women, who had a uterus at baseline, were randomized 1:1 to the same preparation of estrogen plus continuous 2.5 mg/day of medroxyprogesterone (E + P) or placebo. These numbers compare with design goals of 12,375 for the unopposed estrogen comparison, and 15,125 for the E + P comparison, based on an assumption that 45% of women would be post-hysterectomy. A total of 8,050 women (29.4% of the PHT program enrollment) were randomized to both the DM and PHT components.

At their one year anniversary from DM and/or PHT trial enrollment all women were further screened for possible randomization in the calcium and vitamin D (CaD) component, a randomized double-blind trial of 1000 mg elemental calcium plus 400 international units of vitamin D3 daily, vs. placebo. Hip fracture is the designated primary outcome for the CaD component, with other fractures and colorectal cancer as secondary outcomes. A total of 36,282 (53.3% of clinical trial enrollees) were randomized to the CaD component. While the WHI design estimated that about 45,000 women would enroll in the CaD trial component, protocol planning activities also included projected sample sizes of 35,000 and 40,000 and noted that most WHI objectives could be met with these smaller sample sizes.

The total clinical trial sample size of 68,133 is only 60.7% of the sum of the individual sample sizes for the three clinical trial components, providing a cost and logistics justification for the use of a partial factorial design with overlapping components.

Age distribution goals were specified separately for the DM and PHT trials as follows: 10%, ages 50 to 54 years;
Selected Abbreviations and Acronyms

CaD = calcium and vitamin D
CC = clinical center
CCC = Clinical Coordinating Center
CHD = coronary heart disease
CT = clinical trial
DM = dietary modification
DSMB = Data and Safety Monitoring Board
ECG = electrocardiogram
E-alone = (unopposed) estrogen trial
E+P = estrogen plus progestin trial
FFQ = food frequency questionnaire
NHLBI = National Heart Lung and Blood Institute
NIH = National Institutes of Health
OBF = O'Brien-Fleming
OS = observational study
PHT = postmenopausal hormone therapy
PMC = performance monitoring committee
QA = quality assurance
WAN = wide area network
WHI = Women's Health Initiative

20%, ages 55 to 59 years; 45%, ages 60 to 69 years; and 25%, ages 70 to 79 years. While there was substantial interest in assessing the benefits and risks of each trial intervention over the entire 50- to 79-year age range, there was also interest in having a sufficient representation of younger (50 to 54 years) postmenopausal women for meaningful age group-specific intermediate outcome (biomarker) studies. Sufficient numbers of older (70 to 79 years) women allowed for studies of treatment effects on quality of life measures, including aspects of physical and cognitive function. Differing age incidence rates within the 50 to 79 years age range, and across the outcomes that were hypothesized to be affected by the interventions under study provided additional motivation for a prescribed age-at-enrollment distribution. Age distribution goals were not specified for the observational study (OS) or CaD.

The enrollment of such a large number of women, meeting designated eligibility and exclusionary criteria [see (1) and Hays' article in this issue] proved to be a challenge, particularly for the hormone component, since many women who volunteered for WHI were already taking postmenopausal hormones and did not wish to be randomized to take hormones or placebo, while other women had already made a decision against their use. Recruitment goals were increased to account for the fact that only 40 clinical centers were selected for participation, as compared with a planned 45. These issues led to some prolongation of the recruitment period and to a reduction in average follow-up in the CT to about 8.5 years, as compared with the target 9 years.

Women who were screened for the clinical trial but proved to be ineligible or unwilling to be randomized were offered the opportunity to enroll in the OS. The OS was intended to provide additional knowledge about risk factors for a range of diseases, including cancer, cardiovascular disease, and fractures. It has an emphasis on biological markers of disease risk, and on risk factor changes as modifiers of risk.

Hays' article in this issue provides further information on eligibility and exclusionary criteria for the various components of the WHI program, and provides descriptive information on the recruited cohorts.

Study Organization

In addition to the clinical centers, the study is implemented through a Clinical Coordinating Center (CCC) located in Seattle with various collaborators providing specific expertise, as described below. The National Heart, Lung, and Blood Institute (NHLBI) sponsors the program with input from the National Cancer Institute, the National Institute of Aging, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the NIH Office of Research on Women's Health, and the NIH Director's office. The directors of participating NIH institutes and offices form a consortium that advises the NHLBI Director concerning the WHI, as needed. A special working group of the National Heart, Lung, and Blood Council also advises the NHLBI Director concerning the WHI.

A Steering Committee, consisting of the Principal Investigators of the 40 clinical centers, and CCC and NHLBI representatives, is responsible for major scientific and operational decisions. An Executive Committee identifies, prioritizes, and coordinates items for Steering Committee discussion. Program activities are implemented through a regional organization that categorizes clinical centers geographically (West, Midwest, Northeast, and Southeast). Principal Investigators and staff groups defined by project responsibilities (clinic manager, clinic practitioner, nutritionist, recruitment coordinator, data coordinator, outcomes coordinator) meet regularly by conference call within regions to discuss implementation plans and issues. Regional staff group representatives also confer regularly to ensure national coordination. Nine advisory committees (behavior, calcium and vitamin D, design and analysis, dietary modification, post-menopausal hormone therapy, morbidity and mortality, observational study, publications and presentations, special populations) composed of study investigators having expertise in the major substantive areas provide recommendations to the Steering Committee on relevant issues as they arise. The CCC participates and provides liaison support in these various contexts. Figure 1 shows the WHI governance, including NIH advisory committees.

Principal Clinical Trial Comparisons, Updated Power Calculations, and Safety and Data Monitoring

This section provides sample sizes by age for each clinical trial component and for the OS, and provides power calculations for key outcomes for each trial component. Relative to
the basic WHI design manuscript (1), these calculations have been updated to reflect the sample size and age distribution achieved and the projected average follow-up duration.

The target sample sizes were based on consideration of the probability of rejecting the null hypothesis of no treatment effect (i.e., power) on the designated primary outcome under a set of design specifications, including age-specific control group primary outcome incidence rates, intervention effects on incidence rates as a function of time from randomization, intervention adherence rates, and competing risk mortality rates. These assumptions have previously been listed in (1) where an extensive bibliography is cited to provide the rationale for these assumptions.

The power calculations were based on so-called weighted logrank statistics that accumulate the differences between the observed numbers of primary outcome events in the intervention group and the expected number of such events under the null hypothesis across the follow-up period. Early events, which may be less likely to be affected by intervention activities, are downweighted relative to later events. Specifically, the observed minus expected differences are weighted linearly from zero at randomization to a maximum value of one at a certain time from randomization and are constant (at one) thereafter. For cardiovascular disease and fracture incidence, this ‘certain time’ was taken to be 3 years, whereas for cancer and mortality it was taken to be 10 years. For coronary heart disease incidence, the event times are grouped into 3-year follow-up periods, to accommodate the inclusion of silent myocardial infarctions detected by routine electrocardiograms, which are to be obtained at baseline and every 3 years during follow-up for clinical trial participants. A weighted odds ratio test statistic is then used to acknowledge this grouping. Detail on related power calculations and statistical model can be found in Lakatos (2) and Self et al (3).

Table 1 shows the number of enrollees, and percentages of the total, by age category for each component of the CT and the OS.

Table 2 shows the projected power; that is, the probability of rejecting the null hypothesis, for the key outcomes for each clinical trial comparison, taking account of the age-specific sample sizes in Table 1. Projected power is given both at planned termination in mid-2005, in which case the average follow-up duration will be about 8.5 years in the DM and hormone components and about 7.5 years in the CaD component, as well as 3 years earlier in mid-2002. The intervention effects shown in Table 2 represent the projected effect size after accounting for a certain degree of non-adherence and loss to competing risks. Comparison with projected power calculations at the design stage (1)
indicates that the somewhat prolonged recruitment period and the minor departures from target in sample sizes by age category had little effect on projected study power. The CHD and hip fracture power projections for the estrogen vs. placebo comparison is somewhat reduced by a smaller than targeted sample size (10,739 vs. 12,375) in this clinical trial component.

It is also of interest to consider projected power for active hormones vs. placebo, combining the two hormone preparations. With the achieved sample sizes and projected follow-up durations the combined power at planned termination is 98% for CHD, 91% for hip fractures, greater than 99% for combined fractures, and 74% for breast cancer (98% with an additional 5 years of follow-up). Power calculations for representative comparisons in the OS have been given previously (1).

An independent Data and Safety Monitoring Board (DSMB) is charged with monitoring the clinical trial to ensure participant safety, to assess conformity to program goals, and to examine whether there is a need for early stoppage or other modification of any trial component. The DSMB is composed of senior researchers, otherwise not associated with the study, who have expertise in relevant areas of medicine, epidemiology, biostatistics, clinical trials, and ethics. The DSMB meets semi-annually to review study progress, including its status in the context of emerging external data. The board provides recommendations to the NHLBI Director (see Figure 1). The DSMB reviewed and approved the protocol and consent forms prior to study implementation and they advise NHLBI on any significant protocol changes.

Throughout the period of study conduct, the DSMB reviews data on recruitment, adherence, retention, and outcomes. The DSMB is the only group given access to treatment arm comparisons outside of the necessary CCC and NHLBI staff. As such, they determine whether the

### TABLE 1. Women’s Health Initiative sample sizes (% of Total) by age group

<table>
<thead>
<tr>
<th>Age group</th>
<th>Dietary Modification</th>
<th>Postmenopausal hormones</th>
<th>Calcium and Vitamin D</th>
<th>Observational Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E-alone</td>
<td>E + P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54</td>
<td>6961 (14)</td>
<td>1396 (13)</td>
<td>2029 (12)</td>
<td>5157 (14)</td>
</tr>
<tr>
<td>55–59</td>
<td>11,042 (23)</td>
<td>1914 (18)</td>
<td>3439 (21)</td>
<td>8265 (23)</td>
</tr>
<tr>
<td>60–69</td>
<td>22,713 (47)</td>
<td>493 (45)</td>
<td>761 (45)</td>
<td>16,502 (46)</td>
</tr>
<tr>
<td>70–79</td>
<td>8120 (17)</td>
<td>2577 (24)</td>
<td>3576 (22)</td>
<td>6340 (17)</td>
</tr>
<tr>
<td>Total</td>
<td>48,836</td>
<td>10,739</td>
<td>16,608</td>
<td>36,282</td>
</tr>
</tbody>
</table>

### TABLE 2. Updated statistical power for each component for the Clinical Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Disease probability (%) (×100)(^1)</th>
<th>Intervention effect(^2) (%)</th>
<th>Early termination (2002)</th>
<th>Planned termination (2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Intervention</td>
<td>Avg. follow-up duration (years)</td>
<td>Power (%)</td>
</tr>
<tr>
<td>Dietary Modification component (n = 48,836)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Breast cancer</td>
<td>2.72</td>
<td>2.35</td>
<td>14</td>
<td>5.5</td>
</tr>
<tr>
<td>*Colorectal cancer</td>
<td>1.39</td>
<td>1.12</td>
<td>19</td>
<td>5.5</td>
</tr>
<tr>
<td>CHD</td>
<td>3.78</td>
<td>3.27</td>
<td>14</td>
<td>5.5</td>
</tr>
<tr>
<td>Postmenopausal hormones–E-alone (n = 10,739)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*CHD</td>
<td>4.63</td>
<td>3.67</td>
<td>21</td>
<td>5.5</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>2.86</td>
<td>2.25</td>
<td>21</td>
<td>5.5</td>
</tr>
<tr>
<td>Combined fracture(^3)</td>
<td>11.02</td>
<td>8.81</td>
<td>20</td>
<td>5.5</td>
</tr>
<tr>
<td>Breast cancer(^4)</td>
<td>4.38</td>
<td>5.36</td>
<td>(22)</td>
<td>8.5</td>
</tr>
<tr>
<td>Postmenopausal hormones–E + P (n = 16,608)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*CHD</td>
<td>4.45</td>
<td>3.52</td>
<td>21</td>
<td>5.5</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>2.74</td>
<td>2.16</td>
<td>21</td>
<td>5.5</td>
</tr>
<tr>
<td>Combined fracture(^3)</td>
<td>10.80</td>
<td>8.63</td>
<td>20</td>
<td>5.5</td>
</tr>
<tr>
<td>Breast cancer(^4)</td>
<td>4.37</td>
<td>5.34</td>
<td>(22)</td>
<td>8.5</td>
</tr>
<tr>
<td>Calcium and Vitamin D (n = 36,282)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Hip fracture</td>
<td>2.23</td>
<td>1.77</td>
<td>21</td>
<td>4.5</td>
</tr>
<tr>
<td>Combined fracture(^3)</td>
<td>8.93</td>
<td>7.23</td>
<td>19</td>
<td>4.5</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.25</td>
<td>1.02</td>
<td>18</td>
<td>4.5</td>
</tr>
</tbody>
</table>

\(^1\)Cumulative disease probability to planned termination (×100).
\(^2\)One minus ratio of control to intervention cumulative incidence rates at study termination (×100).
\(^3\)Includes proximal femur, distal forearm, proximal humerus, pelvis, and vertebra.
\(^4\)An additional five years of follow-up is planned in the hormone trials for monitoring breast cancer incidence. Intervention effects in parentheses denote a projected adverse effect.
existing data demonstrate either significant or unanticipated risk or unexpectedly strong benefits, in which case early trial termination, or modification, may be recommended. A particular complexity in this study, as often exists in prevention studies, is the need to consider effects on multiple disease processes that may differ in direction, timing, and magnitude.

In the WHI, trial monitoring for consideration of early stopping is based on the following principles and procedures:

- Each trial component (DM, PHT, and CaD) is evaluated separately, so that a stopping decision for one will not necessarily impact the continuation of the other two.
- The evaluation of each intervention includes an assessment of the overall intervention effects on health through use of a global index. This global index is defined as time to first incident event where the events included were selected based on a priori evidence for each intervention as shown in Table 3.
- Early stopping for benefit would be considered if the primary endpoint comparison crossed a 0.05 level O'Brien-Fleming (OBF) boundary and the global index provided supportive evidence defined by crossing the 0.1 level OBF boundary in favor of the intervention. For the DM, a Bonferroni correction is used to acknowledge the fact that there are two designated primary endpoints. This correction allows a stopping recommendation to be made if the boundary is crossed for either of the primary endpoints, without exceeding the designated probability (0.05) of falsely rejecting the overall null hypothesis.
- Early stopping for adverse effects uses a two-step procedure with a 0.1 level OBF boundary for primary safety endpoints, a Bonferroni-corrected 0.1 level OBF boundary for all other safety endpoints, and a lower boundary of $z = -1.0$ for the global index to signify supportive evidence for overall harm.

<table>
<thead>
<tr>
<th>Primary endpoint(s)</th>
<th>DM</th>
<th>PHT</th>
<th>CaD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer, colorectal cancer</td>
<td>CHD, death from other causes</td>
<td>Hip fractures</td>
<td></td>
</tr>
<tr>
<td>Primary safety endpoint</td>
<td>N/A</td>
<td>Breast cancer</td>
<td>N/A</td>
</tr>
<tr>
<td>Other endpoints included in global index</td>
<td>Stroke, pulmonary embolism, hip fractures, colorectal cancer, endometrial cancer (E + P trial only), death from other causes</td>
<td>Colorectal cancer, breast cancer, other fractures, death from other causes</td>
<td></td>
</tr>
</tbody>
</table>

Weighted logrank test statistics are used to test the difference between intervention and control event rates for each outcome. These weights were specified to yield efficient test statistics for the primary outcome under trial design assumptions. As such, these tests need not be sensitive to unexpected effects, whether adverse or beneficial, on any of the study outcomes. Consequently, the DSMB also informally examines unweighted logrank statistics, as well as weighted and unweighted tests for various intervals of time since randomization and for selected subgroups of participants (e.g., specific age groups), toward ensuring participant safety. Some further detail on clinical trial monitoring methods and their rationale is given in (4).

Clinical trial monitoring reports prepared on a semiannual basis throughout trial follow-up also present data on the adherence to intervention goals, the rates of participation in follow-up and other program activities, and control group incidence rates. These data are used to develop updated power calculations, along the lines of Table 2, to help assess conformity to overall design goals, and to alert the DSMB to emerging problems. Data on selected biomarkers and intermediate outcomes are also assembled, as such data can provide an objective assessment of the extent to which intervention goals are achieved, and can provide insights into processes that can explain intervention effects on disease outcomes.

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**BIOMARKERS, INTERMEDIATE OUTCOMES, AND ADDITIONAL CT/OS ANALYSES**

Beyond testing primary and secondary hypotheses, the clinical trial is designed to support specialized analyses to explain treatment effects in terms of intermediate outcomes, and both the CT and OS are designed to produce new information on risk factors for cardiovascular disease, cancers and other diseases. With appropriate informed consent, the basic WHI program stores serum and plasma from participants at baseline, and at selected follow-up times (1 year from enrollment in the CT and 3 years from enrollment in the OS). In addition, white blood cells ("buffy coats") are stored from CT and OS participants at baseline. These blood specimens are used for specialized studies related to participant safety and CT intervention adherence, and for externally funded ancillary studies. Stored blood components collected from each participant during screening include 7.2 ml serum (in 4 × 1.8 ml vials), 5.4 ml citrated plasma (in 3 × 1.8 ml vials), 5.4 ml EDTA plasma (in 3 × 1.8 ml vials), and two aliquots ofuffy coat.

A 6% subsample of clinical trial participants, randomly selected at baseline, provides blood specimens at 3, 6, and 9 years following randomization. Several biomarkers in the
6% CT subsample will be measured to assess intervention adherence and intermediate effects of the trial interventions. These include fasting lipid subfractions (total cholesterol, LDL-C, HDL-C, HDL-2, HDL-3, triglycerides, LPa), glucose, insulin, fibrinogen, Factor VII C, Factor VII Antigen Activity, and several nutritional biomarkers (α-tocopherol, γ-tocopherol, α-carotene, β-carotene, β-cryptoxanthine, lycopene, lutein plus zeaxanthin, and retinol). A smaller fraction of women have additional biomarker measurements specific to their intervention, including hemostatic markers and more detailed hormonal and dietary analytes. To maximize data from each racial/ethnic group, as well as from each component of the trial (DM, PHT, and CaD), the sampling rates were tailored to be higher among minority women (odds for selection are at least 6-fold higher than for Caucasian women) and higher among PHT participants (8.6% sampling rate) than among DM women (4.3%). Table 4 shows the number of women in this 6% sample by study component and by racial/ethnic group. All clinical trial participants have measurement of hematocrit, white blood cell count, and platelet count at baseline.

Intermediate outcome data collected in the clinical trial include electrocardiograms (obtained as baseline, 3, 6, and 9 years among all trial participants) to ascertain "silent" myocardial infarctions and other cardiac diagnoses, and bilateral mammograms (obtained annually for PHT women and biennially for other trial participants). In the DM component, all participants complete a follow-up food frequency questionnaire at year 1, 30% at year two, and 33% at years three and beyond so that each woman is scheduled to complete a food frequency questionnaire (FFQ) every 3 years after year two. A 4.3% subcohort of DM women, randomly selected at baseline, provide 4-day food records at 1 year and 24-hour dietary recalls at 3, 6, and 9 years; an additional independent 1% sample completes 24-hour dietary recalls during each follow-up year. In the E + P trial, all participants with a uterus have a baseline pelvic exam and endometrial aspiration; follow-up pelvic exams are performed annually with a Pap smear every 3 years either through the clinical center or the participant’s personal physician. A five to six percent random sample of E + P trial participants have follow-up endometrial aspirations in years 3, 6, and 9 to ascertain endometrial hyperplasia or other pathology; a transvaginal ultrasound is performed if an endometrial aspiration cannot be obtained. In addition, all hormone component women 65 years of age and older have cognitive function assessment, and a 25% sample have functional assessment, at baseline and follow-up. A sample of women in both the CT and OS (who are enrolled at three specified clinical centers: Birmingham, Pittsburgh, and Tucson/Phoenix) have dual X-ray absorptiometry at baseline and follow-up years 1 (CT only), 3, 6, and 9 to measure change in bone mass in the hip and spine. These women also provide urine specimens, which are stored for studies of the interventions’ effects on bone metabolites.

OS participants have a baseline and 3-year clinic visit to collect exposure data, physical measurements, and blood specimens (see Langer’s article in this issue for descriptions). OS participants also have measurements of hematocrit, white blood cell count, and platelet count at baseline and year 3. Their exposure data and medical histories are updated annually through mailed questionnaires. A 1% sample of OS participants return to the clinic between 1 and 3 months after their baseline visit to participate in a measurement precision (reliability) substudy, at which time blood is redrawn and several selected exposure and physical measurements that are prone to measurement error are repeated. Several blood biomarkers (lipids, glucose, insulin, fibrinogen, nutrients, and other biomarkers described above for the clinical trial) are also measured in this substudy.

Analyses to explain trial intervention effects and CT/OS analyses to elucidate disease risk factors will generally take place in a case-control or case-cohort fashion to limit the number of specialized analyte determinations. Extensive self-report questionnaire data at baseline and selected follow-up times are also available for use in these analyses, and can be used to inform the case-control sampling procedure.

**Data Management and Computing Infrastructure**

The size and scope of the WHI creates a large and rather complex data processing load. Each clinical site has recruited at least 3000 participants, creating a local data management load as large as that for many multi-center trial coordinating centers.

The data collected for WHI fall roughly into three categories: self-report, clinical measurements, and outcomes data. Self-reported information includes demographic, medical history, diet, reproductive history, family history, and psychosocial and behavioral factors. For these areas, standardized questionnaires were developed from instruments used in other studies of similar populations. Use of medications and dietary supplements is captured directly from pill

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Table 4: Ethnicity of participants with stored blood in each component of the ‘6%’ Clinical Trial subsample

<table>
<thead>
<tr>
<th>Component</th>
<th>DM</th>
<th>PHT</th>
<th>CaD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>American Indian/Alaska</td>
<td>76</td>
<td>2.7</td>
<td>64</td>
</tr>
<tr>
<td>Native</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>197</td>
<td>7.0</td>
<td>176</td>
</tr>
<tr>
<td>Black/African American</td>
<td>807</td>
<td>28.6</td>
<td>696</td>
</tr>
<tr>
<td>Hispanic</td>
<td>317</td>
<td>11.2</td>
<td>411</td>
</tr>
<tr>
<td>White</td>
<td>1,375</td>
<td>48.7</td>
<td>1,296</td>
</tr>
<tr>
<td>Unknown</td>
<td>52</td>
<td>1.8</td>
<td>57</td>
</tr>
<tr>
<td>Total</td>
<td>2,824</td>
<td>100</td>
<td>2,700</td>
</tr>
</tbody>
</table>
bottles that participants bring to the clinic. To capture details of hormone use prior to WHI enrollment, an in-person interview was conducted with each woman to determine her entire history of postmenopausal hormone use. For additional diet information, four-day food records and 24-hour recall of diet were obtained from a subsample of women as described above. Dietary records were completed by the participant, reviewed and documented by certified clinic staff; a subsample was sent to the CCC for nutrient coding and analysis. The 24-hour recalls of diet were obtained by telephone contact from the coordinating center and these data were coded using the same methods as for the dietary records.

Clinical measures such as anthropometrics, blood pressure, functional status, and results from gynecologic exams are obtained by certified WHI clinic staff using standardized procedures and data collection forms and key-entered into the local study database. Limited blood specimen analyses were conducted locally and recorded. The remaining blood specimens were sent to a central blood repository where they are housed until the appropriate subsamples are identified and sent to the central laboratory for the selected analyses. Electrocardiogram and bone densitometry data are submitted electronically to respective central reading and coordination facilities. The Foreword provides the Principal Investigator name and location for these various CCC subcontractors. Additional details on data collection and analysis are provided in the appendix to this article.

Information on significant health outcomes is initially obtained by self-report. If the type of event is of interest for WHI research, additional documentation is obtained from local health care providers and a clinic physician uses this information to classify and code the event. Further details of this process may be found in Curb's article in this issue.

Data quality assurance mechanisms are incorporated at several levels, in addition to the overall quality assurance program described below. Data entry screens incorporate range and validity checks, and scanning software rejects forms containing critical errors. Routine audits of randomly selected charts document errors and provide feedback to clinical center and CCC staff. Additional data quality checks are used in creating analytic data sets. Multiple versions of most forms have been used so some data items require mapping across versions.

To support the large requirement of local operations as well as central analyses and reporting, the CCC developed and implemented a standardized computing and database management system that serves each clinical center site and the coordinating center. This computing system can be logically divided into three major areas: computing at the clinical centers; computing at the CCC; and a private wide area network (WAN). The study-wide database uses this infrastructure to provide the appropriate data management tools to all sites.

Each clinical center is equipped with its own local area network consisting of a file server, ethernet switch, 10 to 20 workstations, two or more printers, a mark sense form reader, bar code readers and a router. The router provides connectivity back to the CCC over the WAN. In some cases, the router also provides connectivity to the parent institution. The file server is configured with Windows NT Advance Server and runs its own instance of the study’s Oracle database. The server also provides standardized office applications (Microsoft Office) and e-mail (Microsoft Exchange Web client). The workstations are Windows 98 clients.

The CCC maintains a cadre of application servers dedicated to the development, testing, and warehousing of the consolidated database, currently requiring 100 gigabytes. The CCC also maintains several other servers dedicated to statistical analysis, administrative support for CCC staff, website and e-mail services for study-wide communication, and centralized automated back-up for all study servers. The website and e-mail system dedicated to WHI staff and investigators is critical to study communications. With nearly 1,500 WHI staff members and investigators spread across the country including five time-zones, study-wide communication is an ongoing challenge. The website provides a kind of electronic glue for bringing together disparate groups. Investigators and staff access their e-mail through the website either over the WAN or through the Internet.

The WHI WAN is a private network, which connects clinical centers to the CCC using a combination of 56k and T1 frame-relay circuits. The WAN enables the CCC to conduct nightly back-ups of clinical center file servers. It also facilitates remote management and troubleshooting of clinical center equipment. In addition, it provides clinical centers direct access to the WHI e-mail system and website.

The WHI database management system is a distributed replicated database, implemented in Oracle 8.0 for Windows NT. Database design and table structure are identical across clinical centers but are populated only with data specific to that site. The average clinical center database currently requires approximately 15 gigabytes of space. Data acquisition relies heavily on mark sense scanning, supplemented with traditional key entry and barcode reading. The database supports and enforces the study protocol through its participant eligibility confirmation, randomization, drug dispensing and collection, visit and task planning, and outcomes processing functions. Security is provided both by password protection and by limiting access to specific data based on the identified role of the user. Local access to clinical site-specific data is supported through centrally defined reports and a flexible data extract system.
The CCC database provides the superstructure into which the clinical center data are consolidated routinely. Additional data are obtained from the central laboratories and specimen repository and are merged with, and checked against, the corresponding participant data. The central database serves as the source of all data reports and analyses.

**Quality Assurance Program Overview**

The WHI program involves a complex protocol, with an extensive set of required procedures. A quality assurance (QA) program was designed to allow the identification and correction of emerging problems. Quality assurance was considered an integral part of the study protocol, procedures, and database; hence, it covers all aspects of WHI. To balance the need to assure scientific quality of the study with available resources, priorities were established to guide clinical center and CCC quality assurance activities.

A task force comprised of WHI investigators and staff developed QA priorities under the premise that aspects critical to the main components of WHI would be of highest priority. As the centerpiece of WHI, the fundamental elements of the CT are considered the highest priority. The next highest priority is given to key elements of the OS and elements of the trial that are important for interpretive analyses. The remaining elements are given a lower priority. Table 5 provides the priorities of both clinical center and CCC quality assurance activities for both the CT and OS. The implementation of these priorities is manifested in the CCC quality assurance activities for both the CT and OS. The implementation of these priorities is manifested in the frequency and level of detailed quality assurance methods as follows: priority 1 items receive rigorous routine review and monitoring, both centrally and locally; priority 2 items receive review at a reduced level, often with only local monitoring or central review limited to data monitoring; and, priority 3 items are addressed on a time available basis. Since training and QA for some priority 3 items are identical to those of higher priority, there may be adequate carry-over effects to assure adequate performance. Continued monitoring of these priority 3 areas is done to allow the detection of severe problems.

Quality assurance activities are performed at the clinical centers as well as by the CCC. The program includes extensive documentation of procedures; training and certification of staff; routine quality assurance visits conducted by the CCC (all clinical centers received an initial and 1-year visit while subsequent visits are done approximately every other year, or more frequently as needed); and, database reports for pertinent committees and each clinical center describing the completeness, timeliness, and reliability of tasks at the clinical centers. For example, monthly intervention adherence rates, and major task completeness rates for each clinical center are used as up-to-date indicators of performance.

WHI established performance goals for various important tasks that are centrally monitored. These goals were determined on the basis of design assumptions and, where available, on previously published standards of quality and safety.

The performance of each clinical center is also reviewed on a regular basis under a comprehensive performance monitoring plan. This plan is used to identify clinic-specific performance issues in a timely fashion, to reinforce good performance, and to provide assistance or to institute corrective action if performance is inadequate. Much of this work is conducted under the auspices of a Performance Monitoring Committee (PMC), comprised of representatives of the CCC, clinical centers, and Project Office. The PMC follows up on persistent issues with specific clinical centers, and conducts site visits to facilitate the resolution of specific areas of concern.

**TABLE 5. WHI Quality Assurance Priorities**

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<thead>
<tr>
<th>Priority 1</th>
<th>CT informed consent</th>
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<td>Priority 2</td>
<td>CT randomization</td>
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<td>CT interventions, adherence and retention</td>
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<td>CT/OS ancillary study interference</td>
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**SUMMARY AND DISCUSSION**

The WHI CT and OS were implemented in close correspondence to design specifications (1). Departures from design assumptions concerning sample size, age distribution and projected average trial follow-up have limited effect on the adequacy of study power for the primary outcome for each of the clinical trial components, with the possible exception of the estrogen alone vs. placebo comparison where some power reduction for coronary heart disease arises from a smaller than targeted sample size. A substantial infrastructure for specimen storage, routine analyte determination, data management and computing, and for data and protocol quality control was implemented in close correspondence to design specifications.

Ongoing challenges in the CT and OS include retaining the active participation of study subjects over a lengthy follow-up period, ensuring the unbiased and timely ascertainment of outcome events in each trial component and
in the OS and, perhaps the most challenging, ensuring an adequate adherence to intervention goals for each clinical trial intervention. These areas are actively monitored as a part of WHI quality assurance efforts, and initiatives are undertaken as needed to ensure that the WHI provides reliable and informative answers to clinical trial hypotheses, and contributes additional valuable scientific knowledge concerning the major causes of morbidity and mortality among postmenopausal women in our society.

APPENDIX: DATA PROCESSING AND STATISTICAL METHODS, WHI CLINICAL COORDINATING CENTER STATISTICAL UNIT

DATA COLLECTION METHODS

All data collected for the WHI were obtained using standardized instruments. Initially, self-administered forms were formatted as traditional key entry forms and required duplicate data entry. With experience, all of these forms were reformatted to optical mark recognition (bubble) forms. Consequently, most of these variables were assessed with categorical responses. Data collection instruments used by clinic staff were typically formatted as key entry forms. The WHI data entry software incorporated standard, within form, quality assurance checks (range, valid response, and so forth). Problems at this step generated warnings or errors requiring action on the part of the clinical center staff. Additional quality assurance, including cross-form checks, were applied to the central database, and problems arising at this point resulted in either resolution based on Clinical Coordinating Center (CCC) assessment of the reliability of the individual data items and/or unresolvable data being eliminated. Because most forms underwent some revision, each item was mapped to the version on the most recent (and most prevalent) questionnaire, after review for the appropriateness of the possible mapping by CCC statisticians and epidemiologists.

DATA DEFINITIONS

Demographic and General Health Characteristics

Demographic factors were based on self-report of birth date, ethnicity, education, income, marital status and living situation. Categories for age at screening were created for these displays using 10-year strata based on birth date (50–59, 60–69, and 70–79 years old at initial contact). Consistent with the 1990 U.S. Census, women were asked to select one race/ethnicity from the following categories: Black/African-American (not of Hispanic origin); Hispanic/Latino; White (not of Hispanic origin); American Indian/Alaskan Native; Asian/Pacific Islander; and Other. A woman was considered to be living alone if she did not report living with her husband, children, siblings, other relatives, or friends. Birthplace (state and country) and years lived in the current state were collected only from Observational Study (OS) participants. Region of current residence was classified by state: Northeast (MA, NJ, NY, PA, RI), Southeast (AL, DC, FL, GA, NC, TN, TX), Midwest (IA, IL, MI, MN, OH, WI), and West (AZ, CA, HI, NV, OR, WA).

Occupation was based on a woman’s current job, or if not currently employed, the job held the longest. The managerial/professional category listed as examples jobs that generally require a college degree or higher, including teacher, guidance counselor, registered nurse, doctor, lawyer, accountant, architect, computer analyst, personnel manager, and sales manager. Examples of technical/sales/administrative positions provided were office work and sales work. The category of service/laborer included employment such as food service, factory work, and protective service (police, fire).

Smoking status and alcohol intake were based on self-report questions about personal habits. Never smokers were women who smoked fewer than 100 cigarettes in their entire life. Past smokers were those who had ever smoked at least 100 cigarettes but did not currently smoke. Current smokers were those who had ever smoked at least 100 cigarettes and were currently smoking. Exposure to passive smoking was collected in the OS. OS participants were asked if they had ever lived with someone who smoked cigarettes inside their homes, both when they were less than 18 years old and when they were 18 years or older. If so, the number of years lived with a smoker was assessed. Alcohol intake was similarly defined. Nondrinkers were those who had less than 12 drinks of any kind of alcoholic beverage in their entire life. Past drinkers were those who had ever had at least 12 alcoholic beverages in their life but did not currently drink. Current drinkers were further classified by current alcohol intake, based on the sum of beer, wine, and liquor intake, adjusted for portion size, from the food frequency questionnaire.

Recreational physical activity was assessed by questions on the frequencies and duration of four speeds of walking, and three other types of recreational activity classified by intensity (strenuous, moderate, or light). These data were summarized into episodes per week of moderate or strenuous activity of 20 minutes or more duration, and expenditure of energy from recreational physical activity estimated by total METs per week. Episodes per week of moderate and strenuous activity included those with MET scores of at least 4.0 as classified by Ainsworth (5), including walking...
“fairly fast (3.5 mph)” or “very fast (4.5 mph)”, or participating in moderate or strenuous activities, such as jogging, aerobics, tennis, swimming, biking, use of an exercise machine, calisthenics, or popular or folk dancing. Those who reported no recreational physical activity were classified as no activity; those who reported some activity but none that met the criteria based on duration of at least 20 minutes, intensity at least moderate (MET score 4.0), and frequency at least twice per week, were placed in the category “limited activity”; and others were classified as participating in moderate or strenuous activity from 2 to <4 times per week, or 4+ times per week. Total energy expenditure (in METs per week) from recreational physical activity, including walking, mild, moderate and strenuous physical activity, was assessed and categorized into four groups based approximately on quartiles of the distribution of the overall Clinical Trial (CT) and OS participants. In addition to physical activity, participants were asked to report hours per day of sedentary activity including sitting, sleeping and lying down.

Supplement use was ascertained by a computer-driven inventory of all vitamin and mineral supplements taken by the woman. The data entry screens included definitions and common examples of the multiple-vitamin classes, prompts to enter information on all types of supplements, flexibility to enter any unit of measure on the label, and quality assurance range checks. During the interview, the interviewer examined the participants’ supplement bottles and recorded information on the use of: three classes of multiple vitamins (one-a-day without minerals, one-a-day with minerals, and stress supplements); all single supplements (pills containing a single vitamin or mineral); and all other mixtures. Exact doses were required for all single supplements and other mixtures. For multivitamins, exact doses were required only for the subset of nutrients of special interest: vitamin C, beta-carotene, calcium, and selenium. For other vitamins and minerals in multiple-vitamin preparations, default doses were assumed based on leading brands and characteristics of supplements products in the U.S. Additional details of this assessment procedure and its validity have been published (6).

A computer-driven medication inventory system was developed to capture use of all other usual medications. This was conducted as an in-person interview at the first screening visit. Participants were asked to bring all prescription and over-the-counter preparations used regularly (at least twice a week) for the previous 2 weeks. The product or generic name was used to match the pharmacy database (Master Drug Data Base [MDDB]: Medi-Span, Indianapolis, IN) incorporated into the study data management system. Once the appropriate medication (and, wherever possible, strength of the formulation) was selected, duration of use was recorded. When appropriate, information from supplements and medication use was combined (e.g., use of antacids as a medication is included in total supplemental calcium intake).

Height, weight, hip, and waist circumference, and blood pressure were measured at the first clinic visit by certified clinic staff. Participants were asked to remove their shoes for anthropomorphic measures. Height (cm) was measured using a wall-mounted stadiometer. Weight (kg) was measured using a balance beam scale, after participants were asked to empty their pockets and remove any heavy clothing. Body mass index was calculated as weight (kg) / height (m). Waist and hip circumferences (in cm) were obtained using a standardized measuring tape. Participants were asked to remove all except for nonbinding undergarments and stand on both feet. After following the protocol for identifying the level of the natural waist and hips, and assuring that the tape was level, clinic staff recorded hip circumference. Waist circumference was similarly measured at the end of a participant’s normal expiration. Blood pressures were measured twice after a 5-minute rest period using a conventional mercury sphygmomanometer and appropriately sized cuffs. Systolic blood pressure was defined as the pressure level at which the first of two or more regular Korotkoff sounds were heard. Diastolic blood pressure was defined as pressure level of the last of these rhythmic sounds.

Reproductive, Medical, and Family History

Self-reported reproductive history data included menstruation, pregnancy, lactation, and benign breast disease. Menstrual history information included ages at first and last menses, first birth, hysterectomy, oophorectomy, and tubal ligation, where applicable. Age at first birth was the woman’s age at the end of her first pregnancy lasting at least 6 months. Abortion history was estimated by subtracting the number of live births, stillbirths, miscarriages and ectopic pregnancies from total pregnancies. History of benign breast disease was concluded if participants with no history of breast cancer reported a previous breast biopsy. If participants were still having menstrual bleeding or periods at time of screening (due to hormone use), participants were asked to enter their current age, in lieu of age at last menstrual bleeding.

Self-reported medical history included information on the participant’s current health care provider, use of screening procedures (e.g., mammogram, Pap smear), hormone use and duration (e.g., estrogen only, estrogen + progesterone), health events, physician diagnoses of major diseases, and use of specified medications. For these presentations, hormone history reflected use of pills and patches only (creams and shots excluded); current or past use of less than three months or use of other preparations is not presented. History
of hypertension was defined by a physician’s diagnosis regardless of treatment by oral medication. History of diabetes and history of high cholesterol were defined as a physician’s diagnosis that required oral medication or insulin (diabetes only).

Depression was assessed using a self-administered, eight-item questionnaire. Participants were asked to rate the frequency of specific depressive symptoms over the previous week and to indicate the occurrence of diagnostically relevant periods of depression in the past. The weighting of the items and the cutoff for classification as depressed were based on Burnam (7).

Participants reported on specific health conditions and events associated with cardiovascular disease, circulatory problems, cancer, bone fractures, and other health outcomes associated with aging. For each, the report was based on a physician diagnosis. For cardiovascular disease, the conditions included history of myocardial infarction, coronary bypass surgery (CABG), angioplasty (PTCA), stroke, congestive heart failure, angina, carotid endarterectomy/angioplasty, deep vein thrombosis, pulmonary embolism, and peripheral arterial disease. Women who reported a history of cancer were asked to indicate what kind(s) from a list of 17 most common sites (e.g., breast, lung, colorectal, endometrial, melanoma, cervical) or other. History of colon polyp removal was collected. The risk factors ascertained for their association with bone fractures were osteoporosis, number of falls in the past 12 months, loss of consciousness, and personal history of fractures. Participants at three designated osteoporosis clinical centers (Tucson/Phoenix, AZ; Birmingham, AL; and Pittsburgh, PA) were given baseline dual x-ray absorptiometry to estimate bone density of the hip, spine, and total body, as well as to obtain lean and fat body mass. Women were classified as normal, osteopenic, or osteoporotic based on total hip bone density measures using World Health Organization criteria (8).

Family history of a limited number of conditions was obtained from the participant—without verification—for full-blooded, first-degree relatives. The conditions included heart attacks, stroke, diabetes, and cancer of the breast, colon, rectum, ovary, and prostate. Family members’ histories for breast cancer included the aforementioned female relatives and both grandmothers. Only parental history was collected for fractures.

**Dietary intake**

Food and nutrient intake were assessed by a semiquantitative food frequency questionnaire (FFQ), based on instruments previously used in the Women's Health Trial Vanguard (9) and Full Scale Studies (10) and the Women's Health Trial Feasibility Study in Minority Populations (11). The FFQ is divided into three sections: adjustment questions, food line items, and summary questions. The 19 adjustment questions allow more refined analysis of fat intake (e.g., by asking about types of added fats) and fiber intake (e.g., by asking about usual types of breakfast cereals). The main section—food line items—consists of questions on the frequency and portion size of 122 foods consumed over the last 3 months. Food items were added to incorporate regional and ethnic foods in the United States. The four summary questions ask about the usual intake of fruits, vegetables, and fats added to foods or in cooking. These questions reduce the bias toward overreporting of total food consumption when there are long lists within food groups (e.g., 25 vegetables) (Nutrition Coordinating Center, Minneapolis, MN) (12, 13). Nutrient intake excludes nutrients from supplements.

The time reference for all questions was “in the last 3 months”. Instructions on completing the FFQ were limited to directions and examples printed on the questionnaire itself and an additional page with portion size pictures on one side and instructions on the other side. For quality control purposes, all adjustment questions, all summary questions, 90 percent of the foods, and at least one half of every food group section (e.g., fruits, vegetables, breakfast foods) had to be completed.

The number of servings of fruits and vegetables per day was the sum of servings of fruits, fruit juices, potatoes, salads, and other vegetables, based on the summary questions and individual food items. The number of servings of grains per day was the sum of servings of rice, grains, plain noodles, beans (e.g., refried, baked), potato or pasta salads, bean soups (pea, lentil, black bean, chili with beans—with and without meat), pizza, pasta dishes (e.g., spaghetti, lasagna), many Mexican dishes (e.g., quesadillas, tacos, enchiladas), a wide range of breads (e.g., bagels, muffins, pitas, tortillas, white and dark breads), snacks (e.g., chips, popcorn), and cold or hot cereals.

Details of the measurement characteristics of the WHI FFQ have been published (14).

**BLOOD SPECIMEN ANALYSES**

Blood analytes were obtained from stored sera in the WHI repository at McKesson Bioservices (Rockville, MD). A fasting blood sample was obtained from each woman attending the initial screening visit. To improve the consistency of results, participants were asked to fast (nothing by mouth except water) for 12 hours before all blood collection; take all regular medications except for insulin or oral medication used to control diabetes; take no aspirin or nonsteroidal anti-inflammatory drugs for 48 hours before the visit, except those taken regularly; refrain from smoking for at least 1 hour before the blood draw; and perform no vigorous physical activity (such as jogging or bicycling) for at least 12
hours before the blood draw. Blood was drawn in a sitting position, and all samples were processed locally using a standardized protocol and with specific time limits. The resultant specimens—serum, plasma, buffy coat, and RBC—were labeled and stored at −70°C until shipment on dry ice to the central repository for long-term storage. A small fraction of clinical trial (CT) participants was selected at enrollment (8.6% cohort of postmenopausal hormone therapy (PHT) participants, 4.3% cohort of dietary modification (DM) participants, with oversampling of minorities) for prospective assessment of core analytes. A sample of 1% of observational study (OS) participants was randomly selected with stratification by race/ethnicity at baseline to be in the OS Measurement Precision Study (OS-MPS). These women had a second blood collection at 3 months and core analytes were measured in their baseline and 3 month blood.

Blood specimens from women in the 6% CT blood sample and the OS-MPS were analyzed prospectively for lipids, lipoproteins, micronutrients, clotting factors, insulin and glucose levels. Participant serum and plasma samples were pulled from the repository based on length of storage and sent on dry ice to Medical Research Laboratories (Highland Heights, Kentucky) where these tests were conducted. Assay methods are described briefly below. Specimens were labeled with only vial identification numbers. Blind duplicates and quality control pooled samples were included in each batch. Results were provided to the CCC by vial number where the data were reviewed for internal quality control and merged to participant level information.

LABORATORY METHODS

Lipids, Lipoproteins and Apolipoproteins

All lipid, lipoprotein, and apolipoprotein fractions were analyzed using ethylene diamine tetra-acetic acid (EDTA)-treated plasma. Total cholesterol and triglycerides were analyzed by enzymatic methods on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) as previously described (15). High-density lipoprotein cholesterol (HDL-C) was isolated using heparin manganese chloride (16). HDL3 was separated directly from whole plasma by precipitation of VLDL, LDL, and HDL2 with dextran sulfate (MW 50,000) and MgCl2 (17). The supernate was measured enzymatically on the Hitachi 747. The HDL2 was calculated as the difference in cholesterol between the previously isolated HDL fraction and this HDL3 fraction. Lipoprotein (a) (Lp(a)) was quantitated using an isomorph independent bi-site ELISA assay procedure based on the linkage of apo(a) to apoB (18). Standardization and ongoing quality control was established and maintained with Northwest Lipid Research Clinic. Throughout the study, the laboratory participated in and remained certified by the National Heart, Lung, and Blood Institute, Centers for Disease Control Part III program (19).

Micronutrients

Vitamin A, vitamin E, and the carotenoids were measured by high-performance liquid chromatography (20,21). After the addition of an internal standard, serum was extracted into hexane and injected onto a C18 reverse phase column. The analytes were measured at wavelengths of 292 nm and 452 nm.

Clotting Factors

All clotting factors were measured in citrated plasma. Factor VII activity was measured on a MLA ELECTRA 1400C (Medical Laboratory Instrumentation Inc., Mt. Vernon, NY) using a turbidometric detection system and using Factor VII–deficient plasma (George King Bio-Medical, Overland Park, KS) in preparation of the standard curve (22). Factor VII antigen was measured using a sandwich ELISA assay (Asserchrom VIIag, Diagnostica Stago, France) in which specific rabbit antihuman Factor VII antibodies were used (23). Fibrinogen is measured on a MLA ELECTRA 1400C (Medical Laboratory Automation Inc., Mt. Vernon, NY) using a clot-based turbidometric detection system (24).

Glucose was measured in serum using the hexokinase method on the Hitachi 747 (25, 26). Serum insulin was measured in a step-wise sandwich ELISA procedure on an ES 300 (Boehringer Mannheim Diagnostics, Indianapolis, IN). In the assay a monoclonal insulin antibody bound to the tube in turn binds insulin in proportion to its concentration in the sample. The bound insulin is then quantitated using a second monoclonal antibody labeled with peroxidase (POD) which then reacts with a chromogenic substrate to generate a photometrically monitored chromogen (27). An ongoing monthly quality assurance program was maintained with the Diabetes Diagnostic Laboratory at the University of Missouri.

STATISTICAL METHODS

As the intent of this publication is to describe the WHI participants, unadjusted descriptive statistics are presented throughout with the exception of summary blood results, where weighting by race/ethnicity of the corresponding cohort was used. Missing values occurred in most variables, either because of participant nonresponse or the data did not meet the defined quality assurance checks. Participants with missing data were included in all analyses except those involving variables for which data were not available or were considered unreliable.
This work was supported by NIH contracts for the WHI and by NCI grant CA 53996.

REFERENCES


