Women’s Health Initiative

Why Now? What Is It? What’s New?

Karen A. Matthews  University of Pittsburgh
Sally A. Shumaker  Wake Forest University
Deborah J. Bowen  Fred Hutchinson Cancer Research Center
Robert D. Langer  University of California, San Diego
Julie R. Hunt  Fred Hutchinson Cancer Research Center
Robert M. Kaplan  University of California, San Diego
Robert C. Klesges  University of Memphis
Cheryl Ritenbaugh  University of Arizona

Studies collectively named the Women’s Health Initiative (WHI) are currently enrolling 164,500 postmenopausal women in several overlapping clinical trials and an observational study. The overall goals of WHI are to understand the determinants of postmenopausal women’s health and to evaluate the efficacy of practical interventions in preventing the major causes of morbidity and mortality in older women. This article reviews the research leading to the WHI studies; describes the study designs and protocols, with an emphasis on what’s new about WHI from a psychological perspective; and outlines the major psychosocial hypotheses under investigation and the major challenges WHI presents to psychological science.

Women have long been underrepresented in medical research. Historically, women’s health research focused on diseases affecting fertility and reproduction. Other disease research focused disproportionately on men because of excess premature mortality in men, concerns that women’s changing hormone levels could confound study results, and concerns about pregnancy during clinical trials. Given that older women constitute the fastest growing segment of the population in the United States and that the incidence of chronic disease increases with age, a study on the health of postmenopausal women is long overdue.

The Women’s Health Initiative (WHI) is a long-term national health study focusing on the prevention of heart disease, breast and colorectal cancer, and osteoporosis in postmenopausal women. These chronic diseases are the major causes of death, disability, and frailty in older women of all races and socioeconomic backgrounds. Behavioral and lifestyle factors strongly influence each of these diseases, and behavioral interventions may be useful for the prevention of disease. This 15-year project, sponsored by the National Institutes of Health (NIH), involves 164,500 women aged 50–79, arguably making it the largest and most ambitious study of women’s health ever conducted in the world.

There are three components of WHI: randomized, controlled clinical trials; an observational study; and a community prevention study. The clinical trials are enrolling 64,500 women in three overlapping arms to assess the efficacy of treatments in reducing the major chronic diseases of postmenopausal women. The treatments include a low-fat diet, hormone replacement therapy (HRT), and calcium–vitamin D supplementation. Primary outcomes are the incidence of breast and colorectal cancer, coronary disease, and osteoporotic fractures, with health-related quality of life and functional status among the secondary outcomes. Another 100,000 women are being enrolled in a parallel observational study of the biological and psychological determinants of chronic diseases in women. Women from diverse ethnic groups and older women are overrepresented in the sampling for both the clinical trials and the observational study. The community prevention study is a collaborative venture among the Centers for Disease Control and Prevention, the National Center for Chronic Disease Prevention and Health Promotion, and NIH. Their goal is to develop carefully evalu-
ated model programs at eight Centers for Disease Control and Prevention centers that can be implemented in a wide range of communities throughout the United States.

WHI is of major importance to psychological science. It provides opportunities to test key a priori hypotheses about the relationships between behaviors and health in women. It also presents daunting challenges to the ability of psychological techniques to change behavior in diverse groups of women, including women with differing cultural backgrounds and educational levels. It provides the forum for the longitudinal assessment of quality of life and the specific behaviors that contribute to quality of life and mortality.

This article has three objectives: (a) to describe the research leading to WHI; (b) to review the study design and protocol of the clinical trials and the observational study, with an emphasis on the behavioral and psychological aspects of WHI; and (c) to outline the major psychosocial hypotheses under investigation and the major challenges WHI presents to psychological science. Stated differently, this article addresses three questions: Why WHI now? What is WHI? What's new in WHI from the psychological perspective?

Why the Women's Health Initiative Now?

Major Causes of Morbidity and Mortality During the Postmenopausal Years

The WHI clinical trials are designed to test interventions that could prevent the leading causes of morbidity and mortality in postmenopausal women: cardiovascular disease, breast and colorectal cancer, and osteoporotic fractures. Cardiovascular disease is the major cause of death in U.S. women. Both in absolute numbers and on a percentage basis, it accounts for more deaths in women (45%) than men (39%), considering all ages (Kochanek, Maurer, & Rosenberg, 1994). Coronary heart disease alone accounts for 34% of all deaths in women. The misconception that coronary heart disease is a male disease arises principally from its earlier onset in men. At ages 45–49 years, the incidence of coronary heart disease in men is about four times the rate in women, but by ages 65–69 years this ratio declines to about two, and by 85 years it is only slightly greater than one (National Center for Health Statistics, 1990). The fact that more women than men survive to older ages accounts for the greater proportion of women dying from causes related to coronary heart disease.

Women fear breast cancer more than cardiovascular disease, despite the fact that cardiovascular disease kills 11 times as many women (Kochanek et al., 1994). This fear has been heightened by a striking 27% increase in breast cancer incidence in Caucasian women in the United States between 1975 and 1988 (National Center for Health Statistics, 1990). Colorectal cancer is the third most common cause of cancer death in women in the United States, after breast and lung cancers, and accounts for more than 30,000 deaths annually in U.S. women (American Cancer Society, 1994).

Osteoporosis, like cardiovascular disease, is increasingly prevalent with age after menopause and is strongly linked to lowered estrogen levels in women. Both men and women achieve peak bone mass by the fourth decade of life. After about age 35, both men and women begin to lose bone, and this loss accelerates in women after menopause (Marcus & Snow-Harter, 1992). On average, after menopause, women lose about 1.5% of their bone mass each year. Spinal compression fractures are common, though not necessarily symptomatic, and by 75 years of age, more than half of Caucasian women have this marker of osteoporosis. Hip fractures are not as common but are considerably more lethal—one out of six victims of hip fractures dies of complications, such as emboli, within three months after the fracture. Ten percent of Caucasian women have hip fractures by age 80 (Barrett-Connor, 1991b).

Promising, but not convincing, data suggest that dietary alterations, HRT, and calcium–vitamin D supplementation may have beneficial effects on the risks of cancer, coronary heart disease, and osteoporosis. Thus, modifiable behaviors and common medical interventions may be important disease prevention strategies for postmenopausal women. The data supporting the design of the WHI clinical trials are reviewed below.

Hormone Replacement Therapy and Risk of Coronary Heart Disease, Cancer, and Osteoporosis

The results of more than 20 observational (longitudinal with no intervention) studies comparing the rates of coronary heart disease in women who have ever used HRT with those in women who have never used such therapy indicate that HRT is associated with about a 50% reduction in coronary heart disease risk in postmenopausal women (Barrett-Connor & Bush, 1989). These results
have been challenged as potentially reflecting a selection bias because women who are in better health or who have better access to health care may preferentially receive HRT (Barrett-Connor, 1991a; Matthews, Kuller, Wing, Meilahn, & Plantinga, 1996). In the only long-term randomized clinical trial of HRT on the risk of coronary heart disease (Nachtigall, Nachtigall, Nachtigall, & Beckman, 1979), 84 pairs of institutionalized women were randomly allocated to combined estrogen and progestin preparation (2.5 mg conjugated estrogen plus 10 mg medroxyprogesterone acetate for seven days of each menstrual cycle) or a placebo for 10 years. Women on active treatment had only one third the risk of coronary heart disease compared with those on placebo, but this result was not statistically significant in this small cohort. The recently completed Postmenopausal Estrogen/Progestin Interventions Trial followed 875 women for 3 years and found that HRT improved high-density lipoprotein cholesterol and fibrinogen levels (Writing Group for the PEPI Trial, 1995), thus experimentally demonstrating that HRT can reduce cardiovascular risk factors in the short run.

Nearly all of the studies that evaluated the association between HRT and cardiovascular disease collected data in an era when HRT usually meant oral estrogen alone (i.e., without progestin). Because exogenous estrogen alone is associated with an increased risk of endometrial cancer in postmenopausal women with uteri (Mack et al., 1976; Weiss, Szekely, & Austin, 1976), many women with uteri now take estrogen in combination with progestin because the combination nearly eliminates this risk. Although there is little doubt that progestins protect the endometrium, there is concern that the progestins may also attenuate the beneficial effects of estrogen on coronary disease risk factors because they possess androgen-like activity. Summarizing the results of five short-term studies on lipids, Pike, Henderson, Mack, Lobo, and Ross (1989) reported that progestins combined with estrogen replacement therapy were associated with about half the increase in high-density lipoproteins found with unopposed estrogen, suggesting that progestin may reduce the benefit of HRT on coronary risk factors. The Postmenopausal Estrogen/Progestin Interventions Trial also showed more modest benefits in coronary disease risk factors for combined hormone therapy when compared with estrogen alone (Writing Group for the PEPI Trial, 1995). Several ongoing studies (e.g., the Hormone Estrogen Replacement Study and the Estrogen Replacement and Atherosclerosis Trial) are currently testing whether hormone replacement prevents the recurrence of coronary disease in women with heart disease; they will not answer the question of whether HRT protects against the initial development of coronary heart disease.

The only studies relating HRT to breast cancer in humans are observational. Hulka (1990), in an article that reviewed more than 30 studies, concluded that there could be a 50% increase in risk for breast cancer in women who take HRT for 15 years or longer but that there was no increased risk for ever users compared with never users of HRT. Like many of the studies on coronary disease, the majority of these data was collected in the era when most HRT was unopposed estrogen. Limited evidence suggests that combined estrogen—progestin therapy could be associated with an increased risk of breast cancer (Bergkvist, Adami, Persson, Hoover, & Schairer, 1989; Colditz, 1995). In 122,000 nurses aged 30—55 years at baseline followed for 16 years in the Nurses' Health Study, current users of HRT were at increased risk for breast cancer, but past users were not (Colditz et al., 1995). The estimated risk of breast cancer associated with hormone use increased with the progestin contribution from a relative risk of 1.36 for estrogen alone, to 1.50 for combined estrogen—progestin therapy, to 2.40 for progestin alone. Investigators have speculated that estrogen may prime breast tissue so that it is more susceptible to malignant transformation through metabolic enhancement by progestin (Grady et al., 1992; Hulka, 1990).

Estrogen alone (Weiss, Ure, Ballard, Williams, & Daling, 1980) and combination HRT may conserve bone in postmenopausal women. In an elegant double-blind cross-over study that randomized 94 healthy women soon after menopause to estrogen and progestin hormones or a placebo, Christiansen, Christensen, and Transbol (1981) demonstrated that hormone replacement increased forearm bone density whereas the women on a placebo lost bone mass. The women in each group were then randomized a second time. Those who were on estrogen to begin with but who took a placebo in the second phase lost bone density in the second phase. Conversely, the women who had been on a placebo but who were randomized to HRT in the second phase had a modest improvement in bone density, although they did not achieve the levels of the women who received HRT earlier. Some evidence suggests that HRT's protective effect may be cumulative.
and that long-duration therapy could offer the best protection against fractures. Ettinger, Genant, and Cann (1985) found a highly significant reduction in fractures that was associated with greater bone mass (54% greater at the hip and 19% greater at the forearm) in 245 long-term estrogen users (mean duration of 17.6 years) compared with matched controls. These data strongly support a key role for estrogen in maintaining bone mass and suggest that early and continued treatment may minimize bone loss.

In sum, these findings suggest that HRT has the potential for preventing coronary disease and osteoporosis and might increase the risk of breast cancer after prolonged use. However, the types and the dosage of HRT have changed since these studies were completed, making it difficult to draw strong conclusions.

Dietary Fat Intake and Risk for Cancer and Coronary Heart Disease

Breast cancer. The relation of breast cancer to dietary fat is controversial. A recent meta-analysis reported that in animal model studies, dietary fat has a consistent and unique role in increasing the risk of mammary tumors, apart from the risks associated with the higher energy intakes (Freedman, Clifford, & Messina, 1990). In contrast, epidemiological studies of humans have yielded equivocal results regarding the relation of diet to breast cancer (e.g., Greenwald, 1988; Hulka, 1989; Prentice et al., 1988), perhaps because of a lack of variability in diet in the study populations and problems in accurate assessment of diet. Nevertheless, a meta-analysis of raw data from 12 case-control studies showed a highly significant positive association between dietary fat and breast cancer (Howe et al., 1990). Three ongoing large-cohort studies have shown conflicting results, two with positive but nonsignificant results to date (Howe, Friedenreich, Jain, & Miller, 1991; Kushi et al., 1992) and one with null results (Willett et al., 1992). Women participating in the Women's Health Trial Feasibility Studies showed a 17% decrease in plasma estradiol when lowering the fat in their diet, providing a plausible mechanism for a protective effect of low-fat diet on breast cancer risk (Prentice et al., 1990).

Coronary heart disease. The relationship of high fat intake to the risk of coronary heart disease has been accepted for some time and has been supported by ecological data where disease rates and fat intake were correlated across populations (Keys, 1980) and by studies of migrants showing increased disease rates with Western acculturation (Robertson et al., 1977). Secondary prevention studies in people who already have coronary heart disease suggest that dietary change can reduce all-cause mortality. The effects of primary prevention with diet are less certain (Criqui, 1991). The vast majority of primary and secondary prevention studies for coronary heart disease have been conducted with men, and there is little gender-specific data for women. More important, despite public policy to encourage a low-fat diet, there are no clinical trial data documenting the benefit of a low-fat diet in the primary prevention of coronary heart disease in women.

Dietary Calcium and Vitamin D and Risk for Osteoporosis and Cancer

Osteoporosis. High dietary or supplemental intake of calcium and vitamin D is associated with reduced incidence of osteoporotic hip fractures, although this effect may not be as large as that associated with HRT (Riis, Thomsen, & Christiansen, 1987). A prospective population-based study in older adults analyzed intake of calcium by tertile and found a three times greater incidence rate of hip fractures in individuals in the lowest tertile of intake of calcium as compared with the highest. The age-adjusted hip fracture rate during the 14-year period of observation in women consuming more than 440 mg of calcium per 1,000 kcal was less than half that in women consuming less than 283 mg of calcium per 1,000 kcal (Holbrook, Barrett-Connor, & Wingard, 1988).

Cancer. Breast cancer mortality rates exhibit geographical variation and latitudinal dependence in the United States (F. C. Garland, Garland, Gorham, & Young, 1990). These mortality rates are lower in areas with more sunlight, suggesting a role for the sunlight-dependent conversion of vitamin D to its active form. Supplemental calcium and vitamin D reduced the incidence of mammary cancer in rats (Carroll, Eckel, Fraher, Frei, & Newmark, 1991), but human data are lacking.

High dietary calcium has been correlated with reduced risk of colorectal (C. F. Garland, Garland, & Gorham, 1991) and rectosigmoid (Stemmermann, Nomura, & Chyou, 1990) cancers. A large case-control study found that dietary intake of about 1,200 mg of calcium per day by women was associated with an approximately two-thirds lowering of risk for colorectal cancer (Slattery, Sorenson, & Ford, 1988). Other investi-
nations have been ambiguous, such as a case-control study in Australia that showed an inverse association between consumption of milk (the major source of dietary calcium) and colorectal cancer in women but not men (Kune, Kune, & Watson, 1987). Colorectal cancer rates also vary by latitude, suggesting a possible role for vitamin D (C. Garland & Garland, 1980).

**Rationale for the Women's Health Initiative Clinical Trials**

Coronary heart disease, breast and bowel cancer, and osteoporosis account for the majority of morbidity and mortality rates in postmenopausal women, a rapidly growing segment of the U.S. population. Evidence suggests that HRT, dietary fat, and calcium—vitamin D intake are each associated with the incidence of these diseases. Unfortunately, most of the human evidence is based on observational studies, which often provide overly optimistic estimates of benefit because of biases that cannot be adequately controlled. Moreover, in some areas, the available data are equivocal or inconsistent with the results from animal models. To further complicate matters, most of the available data were collected when patterns and types of HRT use and dietary behaviors were substantially different from those common today. Taken together, these observations suggest a compelling need for a definitive clinical trial to test practical interventions against these major chronic diseases.

**Planning the Women's Health Initiative Clinical Trials at the National Institutes of Health**

Recognizing the paucity of data on the largest segment of the population at risk for major chronic diseases, NIH examined the desirability and the feasibility of clinical trials to prevent heart disease and breast cancer in women for at least a decade (Rossouw et al., 1995). Early working groups at the National Heart, Lung, and Blood Institute and the National Cancer Institute were less than enthusiastic about implementing clinical trials on diet and hormones because of concerns about how to recruit and retain women in clinical trials and which hormone preparations should be used, doubts about whether women could maintain a low-fat diet for long periods of time, and the high costs of protocols designed to test hypotheses about a single disease. As outlined in Rossouw et al.’s article, the Postmenopausal Estrogen/Progestin Interventions Trial, the Feasibility Phase of Women's Health Trial, and the Women's Health Trial Feasibility Studies in Minority Women were designed in part to address these concerns. The data yielded from these studies provided support for the feasibility of recruitment, retention, and maintenance of behavior change. The recognition of significant cost savings from combining trials to investigate multiple diseases and simultaneous societal priorities for women's health research led to a consideration of what subsequently evolved into WHI in 1991, with recruitment beginning in 1993. The Institute of Medicine provided a detailed evaluation of the WHI design and implementation and consideration of the costs (Thaul & Hotra, 1993).

**What Is the Women's Health Initiative?**

WHI is not a single study but several different overlapping studies. As noted earlier, one component of WHI is a community prevention program, resulting from collaboration among the Centers for Disease Control and Prevention and NIH. This article concentrates on the clinical trials and the observational study, as these studies are now ongoing and completely designed.

**Clinical Trials**

The clinical trials evaluate the benefits and risks of three interventions in approximately 64,500 postmenopausal women aged 50–79 recruited at 40 centers. Several sites are explicitly focusing on the enrollment of Hispanic, African American, Asian, and Native American women so that the WHI clinical trials follow a cohort that is ethnically diverse, like the U.S. population. WHI will provide a rare opportunity to explore how cultural influences interact with these major diseases and potential preventive strategies.

Major study hypotheses are that HRT will reduce the risk of coronary heart disease and osteoporosis-related fractures, with a possible attenuation of a coronary heart disease benefit by added progestin; that a low-fat eating pattern will reduce the risk of breast cancer, colorectal cancer, and coronary heart disease; and that calcium—vitamin D supplementation will reduce osteoporosis-related fractures.

Women in the clinical trials are randomized in a $2 \times 2 \times 2$ partial factorial design. They will be followed for up to 12 years. Women may elect to participate in the HRT study, the diet study, or both. Participants are encouraged to enter both components. Approximately 45% of the 27,500 women in the HRT arm are estimated to have had a hysterectomy. They are randomized in equal proportions to receive either estrogen alone (conjugated...
decide that they are unwilling to be randomized to experimental condition. All of the women in the observational study are evaluated at baseline in clinics, followed by questionnaire evaluations on an annual basis for 9–12 years. The evaluations include detailed medical histories, anthropometrics, blood pressure, blood draws, health behavior measures, and diagnosis of new morbidity and disability, with all women followed for mortality and cause of death. Like participants in trials, women in minority groups are especially targeted for inclusion in the observational study.

What's New?

WHI presents many new opportunities for and challenges to psychological science. These include unique opportunities for hypothesis testing, longitudinal assessment of health-related quality of life as key health outcomes, evaluation of psychometric properties of psychological scales for postmenopausal women of diverse ethnicity, recruitment of 64,500 women into clinical trials and 100,000 women into an observational study, dietary modification of 19,200 women, promoting the adherence of women in clinical trials to pill taking, and retention of 164,500 women during the entire length of WHI.

Unique Opportunities for Hypothesis Testing

The WHI study plan includes the opportunity to test hypotheses about the relationship between psychosocial factors and health outcomes. The WHI studies are unique to health psychology because of the size of the study populations; the focus on women, as opposed to men; the ability to assess psychosocial factors in relation to multiple health outcomes, not just to a single health outcome; the testing of the most up-to-date hypotheses and the inclusion of recent measures; and the ability to test competing hypotheses and pathways connecting psychosocial states and health outcomes.

Not all hypotheses could be tested in the WHI studies because of respondent burden, cost, and competing needs for study funds. The organizational structure of the WHI studies includes the Behavioral Committee, which was charged with the development of the behavioral and psychological measures under investigation in the observational study and the clinical trials. The Behavioral Committee's approach was to survey leading investigators across the nation about their recommendations for concepts and measures to include in WHI. On the basis of survey input from these colleagues and a thorough review of the literature, the Committee selected concepts to measure in WHI with the following criteria in mind: (a) adequate sampling of concepts in each of the major domains outlined in Figure 1 on the general relationships between psychological and behavioral states and health outcomes; (b) research findings suggesting that the concepts are important to women's health; (c) measurement by scales that have adequate reliability and validity and, when available, normative data in samples of elderly persons; and (d) brevity of measure of the concept, or the ability of the measure to
be reduced in length on the basis of analytic strategies (e.g., factor analyses). Behavioral measures have several key purposes in WHI: (a) to describe the sample; (b) to describe the life experiences of postmenopausal women; (c) to predict health outcomes; (d) to predict adherence in clinical trials; (e) to measure health-related quality of life, along with mortality, as an outcome; (f) to measure the side effects and the safety of treatment; and (g) to measure intervening variables that may explain associations between biological variables and health outcomes.

We now review the relevant literature and rationale for each of the hypotheses according to the framework in Figure 1. Table 1 shows the concepts, chosen measures, sample hypotheses, and references for each of the major psychological and behavioral constructs included in the assessment battery. Table 1 measures are administered at study entry for women in the observational study and the clinical trials; all measures except those assessing traits (which are presumed to be stable over time) are repeated at the end of the study for all women in the observational study and the clinical trials and at the first annual follow-up evaluation for women in the clinical trials and at the three-year clinic evaluation for women in the observational study. A small number of women in the clinical trials will have repeated measures during the course of the third, sixth, and ninth year of follow-up to estimate the ongoing effects of the intervention.

**Sociodemographic characteristics.** It is well-known that disadvantaged women are at higher risk for early mortality and chronic disease (Adler, Boyce, Chesney, Folkman, & Syme, 1993). The effects of severe poverty on health are mediated by poor nutrition, crowded and unsanitary conditions, and inadequate medical care. Yet, the extent of being disadvantaged above the level of poverty also relates to health risks, and in countries that have universal access to health care, the gradient between social class and health persists (Adler et al., 1993). In part, the effects of socioeconomic status may be due to its effects on exposure to adverse aspects of the social environment and on individual dispositions that are health damaging (Adler et al., 1994). It has been documented that stressful life events and subjective perceptions that demands of the environment exceed the ability to cope are associated with socioeconomic status (McLeod & Kessler, 1990). Similarly, individual differences in depressive symptoms and hostility are distributed with socioeconomic status, race, and age (Barefoot et al., 1991).

Ethnicity or race affects the types of social environments to which individuals are exposed. Those ethnic groups that suffer discrimination may in fact be exposed to a more hostile, less supportive environment, which causes individuals to become more vigilant, more likely to interpret ambiguous situations in a negative way, and perhaps less trusting of others. The observational study will permit testing of the psychological mediators between sociodemographic characteristics and the major health outcomes.

**Social environment.** Stressful life events are linked to a modest increase in risk of a variety of chronic diseases as well as an increase in recurrent health problems in those already suffering from disease and can alter the effectiveness of treatment (e.g., Cohen & Lichtenstein, 1990; Harris, 1991). Stressful life events are common among elderly adults because of high rates of mortality of spouses and friends, retirement from work, and changes in household location and composition. In fact, Rodin (1986) suggested that part of the effects of aging on health are actually due to the losses of control associated with aging, rather than an innate biological process. Life events that are recognized as particularly disturbing are assessed in WHI to evaluate hypotheses linking sociodemographic characteristics, environment, and health; to describe the prevalence of key life events.
<table>
<thead>
<tr>
<th>Concept</th>
<th>Description</th>
<th>Sample hypothesis</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Social environment</td>
<td></td>
<td>High social support predicts survival</td>
<td>Sherbourne &amp; Stewart (1991)</td>
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<tr>
<td>Social support</td>
<td>9 items selected from a 15-item scale from the Medical Outcomes Study</td>
<td>High involvement in networks predicts survival</td>
<td>Antonucci &amp; Akikango (1987); Berkman &amp; Syme (1979); Ellison (1991)</td>
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<td>Social integration</td>
<td>12 items from measures used in the Alameda County Study and the EPSE (e.g., involvement in clubs, religiosity, pet ownership, living arrangements)</td>
<td>Strain from being a caregiver predicts new morbidity, independent of social support</td>
<td>Brown, Potter, &amp; Foster (1990)</td>
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<td>Caregiver burden</td>
<td>2 items from the Cardiovascular Health Study</td>
<td>High social strain offsets benefits of social support</td>
<td>Rook (1986)</td>
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<tr>
<td>Social strain</td>
<td>4 items from surveys on social resources</td>
<td>High number of events and being upset by them interfere with participation in clinical trial activities</td>
<td>Barkman &amp; Syme (1979); Ruberman, Weinblatt, Goldberg, &amp; Chaudhary (1984)</td>
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<tr>
<td>Life events</td>
<td>List of 11 common events, with ratings of extent of being upset by event, used in the Alameda County Study and the BHAT Study</td>
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<td>Individual differences</td>
<td></td>
<td>High depressive symptoms predict morbidity and mortality</td>
<td>Burnam, Wells, Leake, &amp; Landsverk (1988); Weissman, Sholomskas, Pottenger, Purslow, &amp; Locke (1977)</td>
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<tr>
<td>Depression</td>
<td>CES-D (short version)</td>
<td>Optimism protects against new morbidity from cardiovascular disease and cancer</td>
<td>Scheier, Carver, &amp; Bridges (1994)</td>
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<td>Optimism</td>
<td>Life Orientation Test–Revised</td>
<td>Cynical attitudes predict new cardiovascular disease morbidity</td>
<td>Barefoot, Dodge, Peterson, Dahlstrom, &amp; Williams (1989); Cook &amp; Medley (1954)</td>
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<td>Hostile attitudes</td>
<td>Cynicism subscale of Cook–Medley questionnaire</td>
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<td>Lack of expression of</td>
<td>7 items from Emotional Expressiveness Questionnaire</td>
<td>Lack of expression of negative emotion predicts onset of cancer</td>
<td>King &amp; Emmons (1990)</td>
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<td>negative emotions</td>
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<td>Health-related quality of life</td>
<td></td>
<td>Quality of life increases for women in active treatment arms of clinical trial</td>
<td>Ware &amp; Sherbourne (1992)</td>
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<td>behaviors affected by</td>
<td></td>
<td>High levels of symptoms predict mortality</td>
<td>Matthews, Wing, Kaller, Meilahn, &amp; Plantinga (1994); Writing Group for the PEPI Trial (1995)</td>
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<td>disease–intervention</td>
<td></td>
<td>Sleep quality improves on active hormone replacement therapy and low-fat diet</td>
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<tr>
<td>Quality of life</td>
<td>Rand 36-item Health Survey measuring pain and social, emotional, cognitive, and physical functioning</td>
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<tr>
<td>Symptoms</td>
<td>34 items measuring occurrence and severity of symptoms used by PEPI, Healthy Women Study, and others</td>
<td>Urinary incontinence improves on active hormone replacement therapy</td>
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<tr>
<td>Sleep disturbance</td>
<td>10 items designed by research consultants</td>
<td>Sexuality functioning improves on active hormone replacement therapy</td>
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<tr>
<td>Urinary incontinence</td>
<td>7 items from Hormone Estrogen Replacement Study</td>
<td>Age-related declines in memory prevented among women on active hormone replacement therapy</td>
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<tr>
<td>Sexual function</td>
<td>5 items measuring sexual activity and satisfaction from miscellaneous sources</td>
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<td>Cognitive function</td>
<td>Short Mini-Mental Survey Evaluation</td>
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Note. EPSE = Established Populations for Epidemiologic Studies of the Elderly; BHAT = Beta-Blocker Heart Attack Trial; CES-D = Community Epidemiologic Studies of Depression; PEPI = Postmenopausal Estrogen/Progester Interventions Trial.
instruments selected to assess women's social support, gender differences in social networks and perceptions of social support, and the exclusion of social environment variables that may be more relevant to women than men (e.g., network strain, caregiver strain). (See Shumaker & Hill, 1991, for a review.)

The reasons why social support or social integration might be protective against a variety of chronic diseases (e.g., heart disease, cancer) are unclear, although a number of hypotheses have been put forward, including: Social support may indirectly affect disease by buffering the effects of stress on the body; social networks may positively influence health behaviors associated with diseases (e.g., diet, activity); the onset of disease may reduce social networks and perceived support; social support may be a "proxy" for social class, poverty, or mood states like depression; and social support may directly affect underlying mechanisms associated with disease onset and progression. (See Cohen, Kaplan, & Manuck, 1994, for a discussion of these issues.) Most likely, social support and social integration influence health outcomes through a variety of pathways, but we were not able to disentangle competing hypotheses within the context of a single study because studies to date have not been designed to assess alternative explanations.

One of the major problems with the published studies is that epidemiological investigations tend to use simple measures of network size or group associations as proxies for social support. In contrast, contemporary psychologists use much more sophisticated measures of social support. However, most of their research has been in smaller groups with mental as opposed to physical health outcomes. Modern measures of social support now include subscales for different types of social support (e.g., tangible, emotional). In addition to these more sophisticated measures of social support, social scientists make clear distinctions among social support, network size and structure, social integration, and network strain and reciprocity, as opposed to treating these as interchangeable variables. These distinctions are supported by data that suggest that when both social strain and social support are measured in the same study, social strain may actually be more predictive of declines in mental health in women than is poor social support (Rook, 1984). This point, coupled with the conflicting evidence on women and social support, underscores the need for a broader assessment of the social environment as well as the use of well-designed instruments to more fully understand the influence of social systems on the health of women. WHI affords such an opportunity.

Individual dispositions. Key dispositions in the context of risk for chronic disease and early mortality are optimism, hostility, and emotional expressiveness. Optimism or the expectancies for positive outcomes have been linked to speedy recovery from illness, good adaptation to breast cancer surgery (Carver et al., 1994), low levels of depressive symptoms (Bromberger & Matthews, 1996), and alterations in immune function (Scheler & Carver, 1992). Hostility or a cynical attitude toward oth-
ers has predicted all-cause mortality rates and coronary heart disease incidence rates in men, although there have been failures to replicate these effects (Smith, 1992). High levels of negative affectivity, which includes feelings of anger, anxiety, and depressive symptoms, are thought to be a vulnerability factor for poor mental health outcomes. Some data, almost all in men, also suggest that high levels of negative affect predict new cases of coronary heart disease, hypertension, and recurrent cases of nonfatal myocardial infarction. However, some theorists argue that negative affectivity is related to behaviors of seeking treatment and complaining of symptoms, rather than to biological processes linked to disease (Costa & McCrae, 1987).

Styles of expressing emotion have long been suspected of playing a role in the development of cardiovascular diseases as well as cancers. Potential for outwardly expressing anger predicted coronary heart disease incidence rates in the Multiple Risk Factor Intervention Trial (Dembroski, MacDougal, Costa, & Grandits, 1989) and the Western Collaborative Group Study of men (Matthews, Glass, Rosenman, & Bortner, 1977), whereas suppression of feelings has been suspected of leading to the development of hypertension (Cottington, Matthews, Talbott, & Kuller, 1986). Recent research has identified several potential coping styles that may be related to the progression of cancer, for example, fighting spirit (Levy, 1986), denial (Temoshek, 1987), and minimalistic bias (Taylor & Brown, 1988), but none have been tested in large-scale prospective studies of initial incidence of cancer. WHI provides a unique opportunity to test relationships among individual dispositions, coping styles, and health outcomes in diverse groups of women.

Health behaviors and intermediate biological outcomes. The model in Figure 1 suggests that the effects of the social environment and individual dispositions influence health outcomes through health behaviors and intermediate biological outcomes. The structure of WHI includes an oversight committee for the observational study, which was charged with developing these measures. The measures include standard biological markers (e.g., blood pressure), standard health behaviors (e.g., smoking history, alcohol consumption, dietary intake of fat, physical activity), and more exploratory measures (e.g., weight cycling, stored serum for later assays of new markers of disease). In summary, the observational study and the clinical trials permit evaluation of the relationships among sociodemographic characteristics, social environment, individual differences, and health outcomes in a large sample of postmenopausal women of diverse ethnicity, with the unique opportunity to test the framework outlined in Figure 1.

Extensive Longitudinal Assessment of Health-Related Quality of Life as a Key Health Outcome

The purpose of health care is to extend life expectancy and maintain quality of life. Historically, major clinical trials and observational studies have used mortality or severe morbidity as primary end points. In addition to mortality, diseases such as cancer, heart disease, and osteoporosis cause differential reductions in quality of life and activities of daily living. Furthermore, standard medical treatment for the diseases and the clinical trial treatments may have not only positive effects but also adverse consequences. For example, HRT may result in the reduction of a variety of symptoms without necessarily changing the probability of death. Conversely, HRT may cause other symptoms or health problems. A low-fat diet not only may result in health benefits but also may cause fatigue or depression. Although these outcomes are important to patients, they are not often measured in clinical trials.

To comprehensively evaluate health outcomes, WHI includes measures of health-related quality of life that were selected or developed by the Behavioral Committee (see Table 1). Health-related quality of life is viewed by most researchers as a multidimensional construct. Although the terminology used to define each of the key dimensions varies somewhat across investigators, there is general agreement that the following represent fundamental components that are critical in characterizing a population’s health-related quality of life: physical functioning, psychological or emotional status, social functioning and role activities, perceived health, and general life satisfaction (Berzon, Hays, & Shumaker, 1993). A generic and widely used measure of quality of life was selected for WHI, allowing for comparisons with other study populations and across different populations and conditions within WHI.

This generic measure was then augmented with dimension-specific instruments that tap into specific treatment or aging effects that are either not included at all or not included in sufficient detail within the generic instrument. These dimension-specific measures include...
measures of pain, sleep disturbance, intimacy and sexual functioning, and symptoms of aging.

In addition, a key specific dimension, cognitive function, is being measured in older women enrolled in the HRT arm of the clinical trials. Declines in memory have been reported during menopause (cf. Kopera, 1972; Malleson, 1953). Furthermore, women using estrogen replacement therapy have been reported to be less likely to suffer from Alzheimer-related dementias than are women not using estrogen replacement therapy (V. W. Henderson, Paganini-Hill, Emanuel, Dunn, & Buckwalter, 1994; Paganini-Hill & Henderson, 1994). Women with Alzheimer-related dementias assigned randomly to use HRT had slower progression of the disease in several small clinical trials (Fillit et al., 1986; Honjo et al., 1995; Ohkura et al., 1994). In contrast, no relationship between the use of HRT and cognitive function was obtained in the Rancho Bernardo Study (Barrett-Connor & Kritz-Silverstein, 1993). WHI tests the hypothesis that HRT will attenuate the age-related decline in cognitive function in women over 65 years of age at study entry.

In summary, the WHI studies describe changes over time in key aspects of women’s lives as well as permit evaluation of the effects of three treatments, alone and in combination, on overall quality of life and specific components of women’s daily lives. These efforts, in combination with tracking more traditional mortality and morbidity indicators, will provide an overall picture of the determinants of women’s health in the postmenopausal years. In addition, quality-of-life indicators will be used to predict adherence and other psychosocial outcomes.

Testing the Adequacy of the Psychometric Properties of Scales for Postmenopausal Women of Diverse Ethnicity

A key challenge that faces the WHI clinical trials and observational study is how to measure psychological concepts in ethnically diverse groups of women aged 50–79 at study entry. Although many of the scales selected (see Table 1) have been used in non-Hispanic Caucasian samples of middle-aged and younger individuals, experience with the scales is quite limited in samples of older women and minorities such as American Indians, Hispanics and Asians of many origins, and African Americans. Furthermore, because of time limitations, subsets of items from established scales were included, usually based on factor analyses and item–total correlations. Nonetheless, how these subsets of items function in a large-scale population study is for the most part unknown. The Behavioral Committee developed an analysis plan to evaluate the standard psychometric properties of the scales, including scale structure, response biases, missing data, and interrelationships with total scale scores. The psychometric evaluation will be completed within and across ethnic groups to allow for comparisons. From these early analyses, we will learn how well the psychosocial scales are performing in WHI and make alterations in measures accordingly.

Recruitment of 64,500 Women Into the Clinical Trials and 100,000 Women Into the Observational Study

The magnitude of the task of recruitment for WHI is quite daunting, given the large sample size goals. Nonetheless, the WHI investigators benefited from the long history of successfully using recruitment strategies in other large-scale studies (e.g., Multiple Risk Factor Intervention Trial, Pawtucket Heart Study, Oregon Family Heart Study, Women’s Health Trial Feasibility Studies in Minority Populations). These studies guided the development of the overall recruitment plan, while theories, such as communications theory and social learning theory, were used in the development of the recruitment materials. Specific strategies include identification of suitable reinforcers and incentives, social support from staff, and encouragement of personal identification with WHI’s mission for women’s health. In the minority centers, more intense community-based approaches have been used to supplement the trialwide plan.

Recruitment efforts in WHI occur on both local and national levels. Each clinic has at least one staff member devoted to recruitment. The Coordinating Center provides recruitment materials that can be customized by the local centers. All participant materials are written at a sixth-grade reading level and have been translated into broadcast Spanish for use where needed. A national media campaign has been designed to bolster the local efforts.

Recruitment strategies vary among clinical centers, depending on the local environment and target population characteristics. A primary approach for many nonminority centers has been mass mailings, with address lists obtained from a variety of sources including lists of women eligible for Medicare, drivers’ licenses, voter registration, and so forth. Media efforts have been helpful and occur at the local and national levels. These include use of newspapers, radio, television, press releases, and public service announcements. Clinical centers present materials at health fairs, meetings, churches, work sites, and other relevant sites to increase awareness of and interest in the study. Messages are provided by local leaders and other credible sources in the relevant languages and are of two types: direct appeals and testimonials. Both types of messages are designed to garner family support for trial participation and generate interest and personal identification by potential participants.

Minority centers have developed a second, more focused form of recruiting that acknowledges the special needs of women from cultures where clinical trials like WHI are unfamiliar. These approaches involve close personal contact with participants, recruitment from within established community institutions like churches and community health centers, recognition of the unique social networks within minority communities, and invitations through family and friends who are already participating in the study. Once contact is made, the study has evolved procedures that recognize the cultural and educational backgrounds of minority women with verbal and
written materials designed by bicultural staff that address cultural and regional concerns.

**Dietary Modification of 19,200 Women**

The challenge of designing an adequate intervention protocol to help women lower their fat intake to 20% for nine years is substantial. Behavioral scientists have years of experience trying to bring about permanent behavior change and are well aware of how difficult it is to maintain dietary changes. WHI relies on previously tested diet interventions developed through decades of research by behavioral scientists, including psychologists and nutritionists, and used in the Feasibility Phase of the Women’s Health Trial (M. M. Henderson et al., 1990; White et al., 1992). Starting in 1984, these studies randomized more than 2,000 postmenopausal women to intervention or comparison dietary conditions and resulted in the development of an intervention package that successfully maintained the reductions of dietary fat for up to four years. Subsequently, in 1991, the National Cancer Institute launched a study to test the feasibility of the dietary intervention in minority women (Rossouw et al., 1995).

The conceptual bases of the dietary intervention design are available elsewhere (Bowen et al., 1995). Briefly here, the nutritional and behavioral intervention package consists of 18 group sessions in the first year and regular contact in the maintenance years, written materials for both the participants and the nutritionists who deliver the intervention, extensive training for the nutritionists in behavioral concepts and delivery of the intervention, and regular and close monitoring of dietary variables, with mechanisms for feedback to clinical center staff and participants.

Reinforcements and motivators are addressed in the first few sessions to help each participant strengthen her own resolve to change her diet. Different motivators are emphasized later in the behavior change process, including improved self-confidence and self-efficacy, a sense of empowerment and self-control, greater or improved social support, and healthier living (Bandura, 1977, 1982, 1986; Peterson & Stunkard, 1988; Rodin, 1986; Rotter, 1966). Perceived barriers to change (Eraker, Becker, Strecher, & Kirsch, 1985) are identified and addressed early in the trial, including time and financial costs, increased awkwardness in social and eating situations, guilt from nonadherence, and decreased enjoyment of eating preferred foods.

The standard steps of self-management (Marlatt & Parks, 1982; Meichenbaum, 1991) used here include self-monitoring of target behaviors, defining specific behaviors to be changed, setting quantifiable intervention goals, breaking down behaviors into smaller steps, specifying an action plan, evaluating and obtaining feedback, and reinforcing progress. Skills training relates to modifying fat in the diet and includes problem solving, assertiveness, stress management, and cognitive-restructuring skills. These skills are linked to appropriate nutritional topics and are taught and reinforced throughout the first year (Cameron & Meichenbaum, 1982; Kendall & Hol- lon, 1979).

Social support can be important in the maintenance of behavior change (Institute of Medicine, 1982; Sarason & Sarason, 1985). The dietary intervention promotes social support in three ways: The group facilitator is a main source of support and encouragement, the group serves as a supportive environment, and the intervention allows women to involve their significant others in the change process because changing a woman’s eating habits may affect family’s and friends’ eating habits as well.

Because of the high relapse rates of appetitive and addictive behaviors, relapse prevention techniques are included in the later sessions (Marlatt & Gordon, 1985). High-risk situations, such as holidays, parties, and restaurants, are identified, and participants learn to label high-fat dietary behavior as a momentary lapse. Substitution of low-fat dietary behavior is used to prevent relapse back to original high-fat consumption. Slow, unconscious slipping into old dietary patterns is also addressed as a form of relapse. These two types of relapse prevention strategies are a major focus after the first year of the study and beyond.

**Pill Taking by Women in the Clinical Trials**

To test hypotheses regarding the effects of HRT and calcium–vitamin D supplementation, participants who are recruited and enrolled must continue to follow pill regimens. Taking a pill on a daily basis might appear easier to accomplish than altering diet. Nonetheless, the literature on adherence to pill taking suggests that keeping women adherent to the treatment protocols in the clinical trials is a daunting task. Classic reviews estimate that people adhere to clinical pill regimens between 35% and 90% of the time (Gritz, DiMatteo, & Hays, 1989; Haynes, Sackett, Taylor, Roberts, & Johnson, 1977), and current clinical information indicates similar rates of adherence.

Retention and treatment adherence require significantly different strategies for the HRT and calcium–vitamin D arms. In the calcium–vitamin D clinical trial arm, women may experience few side effects of the preparation. In contrast, those women in the HRT clinical trial arm may experience significant side effects, including fluid retention, breast tenderness, nausea, and vaginal bleeding. Women who are former users of HRT who are randomly assigned to a placebo may experience a return of vasomotor symptoms, which can be uncomfortable and inconvenient. It is worthwhile noting that one purpose of the Postmenopausal Estrogen/Progestin Interventions Trial (Writing Group for the PEPI Trial, 1995) was to evaluate if most women in the trial would be compliant with pill taking for up to three years. From this standpoint, the study was successful.

Because of the importance of good adherence to the basic design of WHI, the WHI investigators, with the Behavioral Committee’s input, focused attention on designing an effective adherence promotion protocol. The adherence programs for the HRT and the calcium–vitamin D trials contain similar components, although the
content of each is very different. The basic components of the adherence intervention are written materials for participants describing all aspects of the intervention, manual chapters for clinical center staff to guide their interactions with participants, training for clinical center staff in all aspects of adherence and adherence promotion, and careful symptom and adherence monitoring throughout the trial follow-up period. Monitoring includes pill weighing, attendance recording, and repeated monitoring of food intake on a subsample of women.

Retaining 164,500 Women in the Women's Health Initiative

To test hypotheses with minimal bias and sufficient sample size, participants who are recruited and enrolled must continue to provide clinical and self-reported information at the key assessment points. Therefore, the largest behavioral task of WHI is collecting full data from the 164,500 participants, including women in the observational study and the clinical trials. This task is particularly important among women in the observational study and in the control group of the dietary modification arm because they are not involved in the intervention and may lose interest. The overall WHI retention plan consists of both studywide and local activities, each with the goal of increasing retention. Studywide activities include protocols for continued regular contact, annual incentive items, a studywide newsletter, and studywide health information materials. Local retention activities include training of interviewers in interpersonal skills, coordination of prompt visits and contacts, local incentives and context, and other activities designed to enhance the participants' identification with WHI.

Local retention strategies are considered key because the barriers to participation (such as transportation or parking) vary greatly among sites. Although such issues may sound trivial, it has been our experience that participants drop out of clinical trials as a result of minor irritants, including failing to find a parking spot, judging a staff member as rude, or being required to walk or travel to another building for a needed medical test.

All of the elements promoting adherence and retention were designed on the basis of empirical support. Where possible, and when such empirical information was not available, principles and clinical judgment guided the choice of strategy. The results of contemporaneous trials, such as the Postmenopausal Estrogen/Progestin Interventions Trial (Writing Group for the PEPI Trial, 1995), the Hormone Estrogen Replacement Study, and other ongoing research funded by NIH, continue to guide the choice of strategies used to promote adherence and retention in WHI.

Concluding Comment: Looking Ahead

The WHI observational study and clinical trial studies have been developed with extensive input from behavioral scientists on key hypotheses to test, how to design the interventions, how to recruit and retain women in the study, and how to enhance adherence. The Coordinating Center, in collaboration with the NIH WHI Project Office and an outside Data Safety and Monitoring Board, monitors the success of the protocols and may advise alterations to the protocols, including their behavioral aspects, to ensure that WHI achieves its goals. Already, the WHI design changed in response to findings from the Postmenopausal Estrogen/Progestin Interventions Trial showing the unacceptable of estrogen replacement therapy without progestin to a substantial minority of women with uteri (Finnegan, Rossouw, & Harlan, 1995). In addition, ancillary studies testing novel hypotheses that are not part of the WHI mission can be carried out in the WHI populations, provided they do not harm the success of WHI. We anticipate learning a great deal about how psychosocial factors affect postmenopausal women's health, how common interventions affect women's behavior and their quality of life, and the utility of behavioral principles in contributing to the success of the studies. Psychological science will undoubtedly be challenged by the enormity of the size, scope, and length of the WHI studies and the uniqueness of the diverse study population. The challenge, if adequately met, will benefit millions of postmenopausal women in the years to come.

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