Comparing hormone therapy effects in two RCTs and two large observational studies that used similar methods for comprehensive data collection and outcome assessment

Arthur Hartz,1 Tao He,2 Robert Wallace,3 John Powers4

ABSTRACT
Objectives: Prospective observational studies (OSs) that collect adequate information about confounders can validly assess treatment consequences. However, what constitutes adequate information is unknown. This study investigated whether the extensive information collected by the Women’s Health Initiative (WHI) in two OSs and two randomised controlled trials (RCTs) was adequate.

Design: Secondary analysis of WHI data. Cox regression was used to select from all baseline risk factors those that best predicted outcome. Cox regression that included these risk factors was used for two types of analyses: (1) comparing RCT and OS assessments of the effects of hormone therapy on outcome for participants with specific characteristics and (2) evaluating whether adjustment for measured confounders could eliminate outcome differences among datasets.

Setting: The WHI included more than 800 baseline risk factors and outcomes during a median follow-up of 8 years.

Participants: 151 870 postmenopausal women ages 50–79.

Primary and secondary outcome measures: Myocardial infarction and stroke.

Results: RCT and OS results differed for the association of hormone therapy with outcome after adjusting for confounding factors and stratifying on factors that were hypothesised to modulate the effects of hormone therapy (eg, age and time since menopause) or that empirically modulated the effects of hormone therapy in this dataset (eg, blood pressure, previous coronary revascularisation and private medical insurance). Some of the four WHI datasets had significantly worse outcomes than others even after adjusting for risk and stratifying by type of hormone therapy, for example, the risk-adjusted HR for myocardial infarction was 1.37 (p<0.001) in an RCT placebo group compared with an OS group not taking hormone therapy.

Conclusions: Apparently the WHI did not collect sufficient information to give reliable assessments of treatment effects. If the WHI did not collect sufficient data, it is likely that few OSs collect sufficient information.

ARTICLE SUMMARY

Article focus
- Observational studies (OSs) are frequently used to compare outcomes of patients who choose different treatments.
- Results of OSs may be invalid because of confounding due to an association between patient risk and treatment choice.
- The present study assessed whether the extensive information collected by the Women’s Health Initiative (WHI) was adequate to eliminate confounding and give valid results.

Key messages
- The effects of hormone therapy on stroke and myocardial infarction differ for OSs and randomised controlled trials even after taking advantage of extensive participant information to remove confounding and to select similar participants.
- Participants who self-selected for different studies had different outcomes that could not be explained by differences in measured risk factors.
- As comprehensive data such as collected by the WHI appear to be inadequate to ensure the validity of an observational study, it is unclear what observational study results can be accepted with confidence.

Strengths and limitations of this study
- The WHI dataset is unusually comprehensive and provided a good test of whether excellent datasets can ensure valid results for an observational study. The conditions for valid OSs were not identified.

Medical practice often depends on observational studies (OSs) that compare outcomes of similar patients treated differently. However, OS results may be erroneous because patient risk factors are confounded with treatment choice. Only if confounding
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Factors can be adequately measured, can their effects be removed with statistical methods. The success of removing confounding errors has been vigorously debated.1-3

The strongest evidence against the validity of the OSs has been discrepancies between OSs and randomised controlled trials (RCTs). In particular, RCTs from the Women’s Health Initiative (WHI) found that hormone therapy (HT) increased the risk of myocardial infarction (MI)4 or had no effect5 and increased the risk of stroke.4 5 These findings contradicted a large body of well-performed OSs suggesting that HT may reduce the risk of cardiovascular disease by 30–50%.6-8

However, RCT/OS discrepancies do not prove that the OS design is invalid. Another possibility is that the discrepancies are caused by differences in characteristics of the study population, therapy or outcome measurements (eg, duration of follow-up). For example, the women evaluated in the WHI RCT were older than those in most OSs, and there is some evidence that HT has a greater adverse effect on older women or women who began HT several years after menopause.9-12 There is also evidence that the influence of HT on MI risk is greatest soon after initiation,13 and OSs that can follow participants soon after they begin therapy may give results similar to RCTs.10 14 It may be possible that other patient characteristics (eg, obesity, smoking or health status) that differ between types of studies alter the associations between HT and outcomes.

The WHI offers an excellent opportunity to assess the value of OSs for three reasons: (1) The same type of data were collected in almost the same way for two RCTs and two OSs of HT; (2) the data collected included comprehensive information about numerous potentially relevant risk factors that are rarely available in OSs, including many often suspected to cause confounding (eg, those related to socioeconomic status, functional status, psychological status, lifestyle factors and healthcare behaviours) and (3) the sample sizes were large enough to enable subgroup comparisons.

Methods

The ability of an OS to eliminate confounding was examined by testing three hypotheses:
1. Result differences between OSs and RCTs can be eliminated by adjusting for the WHI risk factors.
2. Differences between OSs and RCTs are caused by differences in modulating factors such as the time after menopause that HT is initiated,6-12 the time OS participants are on HT prior to beginning the study,13 14 or other participant characteristics that have not been previously suggested.
3. Confounding factors associated with which specific WHI study recruited the participant can be eliminated by adjusting for the WHI risk factors.

WHI dataset

Data were obtained from the WHI, which has been described in detail.5 6 The study was approved by institutional review boards, and all participants signed informed consent forms. In brief, it was a long-term national health study that focused on strategies for preventing heart disease, breast and colorectal cancer and osteoporosis in postmenopausal women. Women aged 50–79 were enrolled from 1993 to 1998 at 40 clinical centres throughout the USA for clinical trials. Women were asked to enrol in an RCT and those who were not eligible or not interested were given the opportunity to enrol in the WHI OS.

There were four WHI studies relevant to the present analysis: (1) an RCT of oestrogen therapy (E-alone) for women without a uterus, (2) an RCT of oestrogen plus progesterone (E+P) for women with a uterus, (3) an RCT of diet and (4) WHI OS with no interventions. The RCT of diet served as a second OS for the effects of HT because HT use was not randomised for these patients. Participants who were enrolled in the RCT for diet as well as an RCT for HT were considered to be only in the RCT for HT dataset.

For follow-up and outcome ascertainment all participants completed a self-administered, self-report. This report was completed semiannually by the RCT participants and annually by the OS participants. Adjudicated outcomes were based on medical records, autopsy reports and death certificates.

The more than 800 baseline risk factors analysed in the present study were in the following categories: demographics, general health, clinical and anthropometric, functional status, healthcare behaviours, reproductive, medical history, family history, personal habits, thoughts and feelings, therapeutic class of medication, hormones, supplements and dietary intake.

Statistical analysis

The Cox proportional hazard regression analysis was used to test the association between outcome and the primary risk factor after adjusting for covariates. The outcomes analysed in this study were MI or stroke that developed after the participants were enrolled in the study. The primary risk factors were HT (either the binary variable for any HT use or the three category variable for use of E-alone, E+P or neither) or the categorical variable for the four datasets.

The primary risk factors were represented by an indicator variable for every category except the reference category. The HR associated with an indicator variable for a category represented the risk for participants with that variable compared with the risk of participants in the reference category. The reference category for the HT variables was no HT use, and the reference category for dataset was the WHI OS.

To identify which covariates should be included in a Cox model, we first tested the statistical significance of more than 800 risk factors by including only the risk factor and age in the Cox model for a given outcome. All risk factors that were statistically significant at the p<0.01 level after adjusting for age alone were then
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Results for the covariables were imputed by the mean value for ordinal or binary variables and the mode value for variables with three or more categories. After determining which risk factors were independently associated with a given outcome at the p<0.0001 level, we created a corresponding indicator variable for each of those risk factors that indicated if the variable was missing. If the missing indicator variable was statistically significant at the p<0.05 level, participants missing the corresponding risk factor were excluded. There were 146,936 participants included in the fully adjusted Cox model for MI and 149,470 included in the fully adjusted Cox model for stroke. The ability of the Cox model to predict outcome as measured by the C statistic was not improved by excluding participants with estimated values of the covariables.

Results
Baseline participant characteristics for participants in the four datasets are compared in Table 1. For two datasets participants on HT were compared with participants without HT. That was not necessary, however, for the RCTs for E+P and for E-alone because randomisation in these studies made the treatment arm unrelated to baseline characteristics. In the OS and RCT for diet datasets the risks due to age, race, income, educational level, physical functioning and smoking were most favourable for participants on E+P and least favourable for participants not taking HT. With the exception of smoking these characteristics were also more favourable for participants in the RCT for E+P than in the RCT for E-alone. Both socioeconomic status variables (education and income levels) are lower for the two RCTs of HT datasets than for the other two datasets, p<0.0001. For this reason it was important to evaluate whether socioeconomic status influenced the association between HT and outcome.

Propensity score
The logistic regression equation to predict the probability that a participant in the OS used HT (ie, the propensity score) included 94 independent risk factors statistically significant at the p<0.0001 level and had a C statistic of 0.90, indicating that the equation was highly predictive of HT use.

Risk factors for MI and stroke
We identified 16 risk factors (in addition to dataset) that were independently associated with MI at the p≤0.0001 level. The variables and their associated $\chi^2$ value for the full dataset in parenthesis were age (594.3), taking medication for diabetes (284.3), smoking at baseline (182.4), systolic blood pressure (150.1), history of coronary artery bypass surgery (110.1), history of cardiovascular disease

Included in a backwards stepwise Cox proportional hazard regression analysis, and variables that remained statistically significant at the p<0.0001 level were retained in the model. We then used the Cox forward stepwise procedure to test whether any of the variables not already in the model could enter at the p<0.0001 level. It is unlikely that many of these variables were significant by chance alone and even less likely that adjusting for spurious variables would distort the association between HT and outcome.

To identify which risk factors modulated the association between HT and outcome we tested the interactions of HT with the risk factors that had been tested with the timing hypothesis or that had a statistically significant association with outcome at the p<0.01 level after adjusting for age and dataset.

In an analysis that only included OS participants not taking HT at baseline, follow-up began at the time the participant completed the questionnaire that first reported HT or, if they never began HT, follow-up began at the time they completed their first questionnaire after baseline. (If follow-up for these participants had begun as late as it did for the HT participants, it would have diminished the HR associated with HT.) The baseline age of participants in this analysis was computed for the time that follow-up began.

Stepwise procedures were used to find a logistic regression equation that included the risk factors independently associated at the p<0.0001 level with taking baseline HT in the WHI OS. An individual’s propensity score was the probability derived from her characteristics and the estimated parameters in this equation. We evaluated whether grouping participants with similar propensity scores decreased confounding in the OSs so that OS and RCT results became more similar.

The median follow-up time was 8 years. However, for the E+P RCT, treatment was ended after a mean follow-up of 5.2 years even though follow-up on all participants was continued. To make time on HT in the study comparable for the OS and each RCT, we ended follow-up at 5 years.

All statistical analyses were performed using SAS V.9 (SAS Institute Inc, Cary, North Carolina, USA).

Sample size
Participants available for analysis included 161,748 WHI participants: 93,651 from the observational study, 16,590 from the RCT of oestrogen plus progesterone (E+P), 10,722 from the RCT of oestrogen only (oestrogen-alone) and 40,785 additional women who were in the diet study and not in an RCT of HT. Of the 161,748 WHI participants, 9584 were excluded because they did not meet the following RCT exclusion criteria: platelets less than 100,000/mm$^3$, haematocrit less than 32%, oral daily use of a glucocorticosteroid, body mass index less than 18, systolic blood pressure greater than 200 mm Hg, diastolic blood pressure greater than 105 mm Hg, breast cancer ever, other cancers in the last 10 years, or stroke, transient ischaemic attack (TIA) or MI in the past 6 months. An additional 294 were missing information on the use of HT at baseline.

Missing data for the covariables were imputed by the mean value for ordinal or binary variables and the mode value for variables with three or more categories. After determining which risk factors were independently associated with a given outcome at the p<0.0001 level, we created a corresponding indicator variable for each of those risk factors that indicated if the variable was missing. If the missing indicator variable was statistically significant at the p<0.05 level, participants missing the corresponding risk factor were excluded. There were 146,936 participants included in the fully adjusted Cox model for MI and 149,470 included in the fully adjusted Cox model for stroke. The ability of the Cox model to predict outcome as measured by the C statistic was not improved by excluding participants with estimated values of the covariables.
Twelve risk factors were independently associated with stroke at the $p \leq 0.0001$ level: age (667.4), systolic blood pressure (181.4), history of diabetes (110.3), medication for hypertension (85.3), current smoking (79.9), physical function (68.2), history of stroke (49.1), history of cardiovascular disease (38.8), TIAs (30.8), cardiotonic medication, especially digitalis (27.1), lower income (21.7) and lifetime HT duration (14.9). The $C$ statistics for these variables was 0.76 (95% CI 0.76 to 0.77).

### Association of HT with MI and stroke

The risk-adjusted HRs for a specific type of HT (E+P or E-alone) and for either HT are shown in table 2 for each dataset. In the WHI OS dataset E+P and E-alone had similar HRs. In the diet dataset E-alone was significantly protective for MI (HR=0.65) but E+P was not (HR=0.96, $p=0.04$ for the difference between HRs for E-alone and E+P), and there was no association of either type of HT with stroke. In the RCT datasets there was an association of E+P with an increased risk of MI (HR=1.30) as well as stroke (HR=1.54), but E-alone was not associated with MI.

To test for differences in HRs among the datasets, we combined all datasets and included main effects, interactions between HT and dataset and risk factors in the Cox model. To the contrary, the

### Influence of patient characteristics on the association between HT and outcomes

The analyses reported in tables 3 and 4 examined how OS and RCT differences might be influenced by the timing of the HT with respect to age, menopausal status and previous hormones. Also these tables show the effects of additional adjustment for confounding using propensity scores. The HRs and their CIs are presented for women on any HT. Where it might be informative, HRs without CIs are presented for women on a specific type of HT (either E+P or E-alone).

### Myocardial infarction

Table 3 presents the MI HR for HT, E+P and E-alone. The timing hypothesis suggests that HRs should be significantly lower in the 50–59 age group or in the group with menopause less than 10 years than in the other groups, but none of these differences were significantly different in the expected direction. To the contrary, the

### Table 1 Percentage of participants in a given category by dataset and type of hormone therapy

| Variables         | WHI OS | E+P | E-alone | No HT | RCT for diet | E+P | E-alone | No HT | RCTs for HT | E+P | E-alone |
|-------------------|--------|-----|---------|-------|--------------|-----|---------|-------|------------|-----|---------|
| Sample size       | 17 618 | 21 659 | 44 597 |       | 8907         | 11 880 | 19 968 | 16 581 | 10 719     |
| Age (years)       |        |      |         |       |              |      |         |       |            |     |         |
| $\leq 55$         | 25.6   | 19.0 | 13.4    |       | 27.1         | 20.6 | 14.7    | 16.6  | 14.4       |
| $>70$             | 9.3    | 16.8 | 25.0    |       | 5.6          | 11.5 | 17.8    | 17.8  | 20.1       |
| Race              |        |      |         |       |              |      |         |       |            |     |         |
| Non-white         | 11.3   | 15.5 | 19.8    |       | 10.8         | 15.5 | 22.4    | 16.0  | 24.7       |
| Family income     |        |      |         |       |              |      |         |       |            |     |         |
| $<\$35 000$      | 23.0   | 33.4 | 42.7    |       | 23.4         | 33.9 | 41.9    | 45.3  | 54.5       |
| $>\$75 000$      | 29.1   | 20.0 | 14.5    |       | 27.4         | 18.8 | 13.7    | 12.5  | 8.1        |
| Education level   |        |      |         |       |              |      |         |       |            |     |         |
| $\leq$ HS grad    | 13.2   | 20.8 | 24.8    |       | 13.7         | 21.6 | 23.5    | 26.1  | 32.4       |
| Col grad          | 54.1   | 38.4 | 38.1    |       | 50.7         | 35.3 | 37.0    | 34.6  | 23.7       |
| P Func $>75$      | 80.2   | 68.8 | 68.2    |       | 78.4         | 67.7 | 67.4    | 73.6  | 61.5       |
| Med visit         | 84.4   | 85.3 | 76.7    |       | 85.7         | 86.0 | 76.2    | 68.5  | 72.3       |
| Smoking           |        |      |         |       |              |      |         |       |            |     |         |
| Past              | 46.0   | 42.7 | 40.1    |       | 44.6         | 42.0 | 40.2    | 39.2  | 38.0       |
| Current           | 5.1    | 5.5  | 7.0     |       | 5.5          | 5.6  | 6.8     | 10.3  | 10.3       |
| Meno sympt        | 77.3   | 70.4 | 64.8    |       | 70.9         | 64.3 | 59.5    | 61.9  | 60.5       |

All characteristics differed among the four datasets and among treatment groups within the observational study and RCT for diet datasets at the $p<0.0001$ level.

Col, college; E-alone, oestrogen alone; E+P, oestrogen plus progesterone; grad, graduate; HS, high school; HT, hormone therapy; Med visit, visit to a physician within the past year; Meno sympt, history of menopausal symptoms; OS, observational study; P Func, physical function score from the SF-36; RCT, randomised control trial.
E+P HR for women aged 50–59 was much higher (1.63) than it was for older women (1.01 for women age 60–69). The HR for HT during the first 3 years (1.26) is greater than the subsequent risk (1.08). For the RCT for E+P the difference is greater, 1.45 vs 1.11, and the test of the time-dependent covariables of duration of exposure was of marginal statistical significance (p<0.05). Since OS participants on HT began HT several years before enrolment, a diminished effect of HT with time could explain an OS/RCT difference. However, results of other analyses do not support this explanation: there was no evidence that previous HT exposure reduced the HR for stroke in the WHI OS dataset (ie, the HR was lower for participants with no previous exposure, 1.07, than for those with previous exposure, 1.51), and there was no indication in the WHI OS dataset of increased MI risk for participants who began HT after study baseline, the HR was lower than it was for participants who began HT at baseline. (Information on HT usage after baseline was not available for the diet RCT study.)

The last rows in table 3 are HRs stratified by propensity scores. Stratifying by propensity score in addition to adjusting for the significant covariables was expected to reduce confounding, but there was no evidence that doing this gave results similar to the RCTs.

Additional factors that significantly modulated the association between HT and MI in the OS dataset at the p<0.05 level included blood pressure, previous coronary revascularisation, hours of sleep, haematocrit, working status, thyroid disease, antineoplastics, private medical insurance, bone fracture after age 55, colon polyps, ever lived or worked on farm and hostility. Neither education nor income was a statistically significant modulating variable. No factors that significantly modulated the HT HR in the WHI OS dataset also significantly modulated this HR in the RCT datasets. The MI HRs in the RCT and OS datasets did not become similar if they were stratified by the modulating variables.

| Dataset | HT type | Myocardial infarction | Stroke |
|---------|---------|-----------------------|--------|
|         | HR      | 95% CI                | HR     | 95% CI    |
| WHI OS  | Any E   | 0.83 (0.72 to 0.95)   | 0.85 (0.70 to 1.03) |
|         | E+P     | 0.86* (0.70 to 1.05)  | 0.82* (0.65 to 1.04) |
|         | E-alone | 0.80† (0.69 to 0.94)  | 0.88‡ (0.71 to 1.11) |
| Diet RCT| Any E   | 0.75 (0.62 to 0.89)   | 1.04 (0.80 to 1.37) |
|         | E+P     | 0.96 (0.75 to 1.22)   | 1.00 (0.72 to 1.39) |
|         | E-alone | 0.65‡§ (0.53 to 0.81) | 1.07 (0.79 to 1.45) |
| HT RCT  | Any E   | 1.18 (0.99 to 1.41)   | 1.29 (1.05 to 1.58) |
|         | E+P     | 1.30 (1.02 to 1.65)   | 1.34 (1.02 to 1.77) |
|         | E-alone | 1.05 (0.81 to 1.36)   | 1.23 (0.91 to 1.67) |

*Differs from the comparable RCT HR at the p<0.01 level.
†Differs from the comparable RCT HR at the p=0.02 level.
‡Differs from the comparable RCT HR at the p=0.06 level.
§Differs from 1.00 at the p<0.0001 level.

The only variable found to significantly influence HT HR for stroke in the WHI OS dataset was endometrial aspiration; the HR was 0.85 for those who had had an endometrial aspiration and 1.16 for participants who did not (p<0.001). Stratifying on this variable did not make the OS and RCT results more similar. In addition, the lack of an obvious medical explanation, the number of factors tested and the lack of this relationship in the RCT datasets makes it more likely that this result occurred by chance.

After recalculating the HR in the WHI OS dataset for only those participants with midrange of propensity scores (those with a probability of using HT between 0.25 and 0.75), the HR for stroke was virtually unchanged. This suggests that adjusting for the propensity score did not diminish confounding.

### Adequacy of WHI information to eliminate confounding

In table 5, the MI risks are compared for participants in the four different WHI datasets who are on the same treatment at baseline (E+P, E-alone or no HT). The HR in the table represents the risk of the outcome for participants in that dataset compared with participants on the same treatment in the WHI OS dataset. If the WHI variables are adequate to eliminate confounding, the adjusted HRs should be near 1.00. Some HRs shown in the table were statistically significant at p<0.0001. For participants not taking HT the risk-adjusted HR was 1.37 for the RCT for E-alone. For

### Stroke

Although E+P and E-alone had similar associations for stroke, results in table 4 include only the HRs for HT and no HRs for E+P and E-alone. As shown in this table there was no consistent evidence that the HT HR for stroke was lower for women who were younger or had menopause recently. In contrast to the MI analyses, there was also no RCT evidence that the HT HR for stroke was stronger soon after beginning HT.
### Table 3  MI HRs for hormone therapy in subgroups defined by participant characteristics associated with hormone exposure

| Subgroup within dataset | Dataset | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 95% CI | 95% CI | 95% CI | 95% CI |
|-------------------------|---------|------------------------------------------------------------------------------------------------|--------|--------|--------|--------|
|                         | RCTs for HT |                                                                                                    |        |        |        |        |
| All participants        |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.18   | (1.30,1.05) | 0.99 to 1.41 | 0.75 (0.95,0.65) | 0.62 to 0.89 | 0.83 (0.86, 0.80) | 0.72 to 0.95 |
| Age                    |         |                                                                                                    |        |        |        |        |
| 50–59                  |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.25   | (1.63,0.69) | 0.80 to 1.96 | 0.57 (0.73,0.44) | 0.37 to 0.89 | 0.73 (0.74,0.60) | 0.54 to 0.99 |
| 60–69                  |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.01   | (1.05,0.95) | 0.78 to 1.32 | 0.73 (0.88,0.65) | 0.56 to 0.94 | 0.87 (0.97,0.81) | 0.71 to 1.07 |
| 70–79                  |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.46   | (1.46,1.20) | 0.99 to 2.15 | 0.87 (1.33,0.74) | 0.65 to 1.18 | 0.84 (0.75,0.86) | 0.68 to 1.03 |
| Years since meno       |         |                                                                                                    |        |        |        |        |
| <10                    |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.03   | (1.14,0.77) | 0.73 to 1.46 | 0.83 (1.01,0.68) | 0.60 to 1.15 | 0.85 (0.94,0.80) | 0.73 to 0.99 |
| 10–19                  |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 0.95   | (1.06,0.74) | 0.68 to 1.34 | 0.67 (0.95,0.47) | 0.48 to 0.95 | 0.77 (0.74,0.72) | 0.44 to 1.35 |
| >19                    |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.41   | (1.77,1.23) | 1.08 to 1.85 | 0.69 (0.60,0.70) | 0.50 to 0.93 | 1.35 (0.61,1.28) | 0.46 to 3.96 |
| HT after baseline      |         |                                                                                                    |        |        |        |        |
| No                     |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.07   | (0.96,1.20) | 0.86 to 1.32 | 0.86 (0.87,0.85) | 0.71 (0.76,0.72) | 0.57 to 0.88 |
| Yes                    |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.51   | (1.12,1.46) | 1.09 to 2.08 | 0.79 (0.84,0.73) | 0.64 to 0.97 |
| Follow-up for RCT      |         |                                                                                                    |        |        |        |        |
| End 3 years after enrolment |     | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.26   | (1.45,1.06) | 1.00 to 1.58 | 0.86 (0.87,0.85) | 0.71 to 1.02 |
| Begin 3 years after enrolment |    | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.08   | (1.11,1.04) | 0.82 to 1.41 | 0.79 (0.84,0.73) | 0.64 to 0.97 |
| Previous use of HT     |         |                                                                                                    |        |        |        |        |
| No                     |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.07   | (0.96,1.20) | 0.86 to 1.32 | 0.86 (0.87,0.85) | 0.71 to 1.02 |
| Yes                    |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.51   | (1.12,1.46) | 1.09 to 2.08 | 0.79 (0.84,0.73) | 0.64 to 0.97 |
| Propensity score       |         |                                                                                                    |        |        |        |        |
| <0.25                  |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.26   | (1.27,1.18) | 0.96 to 1.66 | 0.75 (0.76,0.71) | 0.48 to 1.17 | 0.98 (1.04,0.83) | 0.72 to 1.34 |
| 0.25–0.75              |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.11   | (1.32,1.02) | 0.87 to 1.42 | 0.80 (1.01,0.69) | 0.64 to 1.00 | 0.85 (0.81,0.86) | 0.72 to 1.01 |
| >0.75                  |         | MI HR for HT in the subgroup of the indicated dataset (Numbers in parentheses are HRs for E+P and E-alone) | 1.05   | (NA, 0.93) | 0.42 to 2.64 | 0.69 (1.08,0.67) | 0.34 to 1.40 | 0.76 (0.96,0.74) | 0.45 to 1.27 |

E-alone, oestrogen alone; E+P, oestrogen plus progestin; HT, hormone therapy; meno, menopause; MI, myocardial infarction; NA, not available because only one MI case in this group; OS, observational study; RCT, randomised controlled trial; WHI, Women’s Health Initiative.
participants taking E-alone the HR in the RCT was 1.44, and for participants taking E+P the HR was 1.53 for intervention participants. Risk-adjustment sometimes made HRs closer to 1.00 as expected (eg, intervention participants in the RCT for E+P), sometimes had minimal effect on HRs, and sometimes made a non-significant HR significant (eg, participants not on HT in the diet dataset).

## DISCUSSION

The WHI data analysed contained information on more than 800 possible confounders including information that made it possible to accurately predict HT use. It also contained information on factors that might have influenced response to HT. Some of these factors were related to the timing hypothesis (eg, age, time since menopause, previous HT use, beginning HT after baseline), and some were identified empirically (eg, blood pressure, previous coronary revascularisation and private medical insurance). Since OS and RCT participants differed with respect to these factors, these factors could have conceivably contributed to differences between the OSs and the RCTs. However, after taking into account all of these confounding factors and stratifying on factors that may have influenced the response to HT, OS and RCT differences remained.

The WHI data also contained information from four different studies, and the participants in these studies had different outcomes. After stratifying participants with respect to the type of HT and taking into account the information available in the WHI, we could not eliminate the outcome differences from the four studies. The above results suggest that there were important risk factors not captured by the WHI that contributed to confounding. Since the WHI dataset is unusually comprehensive, it is likely that most OSs do not capture information on these risk factors. Without including information on potentially important confounders OSs cannot give reliably valid results.

### Table 4 Stroke HRs for hormone therapy in subgroups defined by participant characteristics associated with hormone exposure

| Subgroup within dataset | Dataset | RCTs for HT | RCT for diet | WHI OS |
|-------------------------|---------|-------------|--------------|--------|
|                         |         | Stroke HR for HT in the subgroup of the indicated dataset | 95% CI | 95% CI | 95% CI |
| All patients, full follow-up | | 1.29 | (1.05, 1.58) | 1.04 | (0.80, 1.37) | 0.85 | (0.70, 1.03) |
| Age 50–59 | | 1.03 | 0.59 to 1.82 | 0.48 | (0.24, 0.98) | 1.04 | 0.61 to 1.78 |
| Age 60–69 | | 1.65 | 1.20 to 2.27 | 1.33 | 0.90, 1.96 | 0.96 | 0.71 to 1.29 |
| Age 70–79 | | 1.11 | 0.81 to 1.51 | 1.14 | 0.74, 1.77 | 0.75 | 0.55 to 1.01 |
| Years since menopause <10 | | 1.33 | 0.87 to 2.05 | 0.85 | 0.52, 1.40 | 0.79 | 0.62 to 1.00 |
| Years since menopause 10–19 | | 1.4 | 0.96 to 2.06 | 1.05 | 0.61, 1.82 | 0.67 | 0.39 to 1.17 |
| Years since menopause ≥20 | | 1.22 | 0.91 to 1.63 | 1.21 | 0.81, 1.80 | 0.93 | 0.38 to 2.27 |
| Follow-up for RCT End 3 years after enrolment | | 1.33 | 1.02 to 1.73 | 0.75 | 0.58 to 0.98 |
| Follow-up for RCT Begin 3 years after enrolment | | 1.26 | 0.92 to 1.74 | 0.96 | 0.72 to 1.27 |
| Previous use of HT | | | | | | |
| No | | 1.33 | 1.03 to 1.72 | |
| Yes | | 1.21 | 0.86 to 1.71 | |
| Propensity scores <0.25 | | 1.18 | 0.86 to 1.63 | 0.80 | 0.41 to 1.55 | 0.91 | 0.59 to 1.42 |
| Propensity scores 0.25–0.75 | | 1.34 | 1.02 to 1.76 | 1.30 | 0.95 to 1.79 | 0.88 | 0.70 to 1.12 |
| Propensity scores >0.75 | | 2.57 | 0.78 to 8.43 | 0.50 | 0.19 to 1.32 | 0.79 | 0.41 to 1.51 |

HT, hormonal therapy; OS, observational study; RCT, randomised controlled trial; WHI, Women’s Health Initiative.

### Table 5 MI HRs comparing participants in each of the three RCT datasets to WHI OS participants

| Outcome | Dataset | Unadjusted | Adjusted† | Unadjusted | Adjusted† |
|---------|---------|------------|-----------|------------|-----------|
|         |         | HR | χ² | HR | χ² |
| Patients not on HT (N=78 069) | RCT E+P | 0.97 | 0.15 | 1.20 | 6.14 |
|Patients not on HT (N=78 069) | RCT E alone | 1.43*** | 24.98 | 1.37*** | 18.69 |
|Patients not on HT (N=78 069) | RCT diet | 1.01 | 0.07 | 1.14** | 7.08 |
|Patients on E+P (N=35 021) | RCT E+P | 2.43*** | 97.23 | 1.53*** | 19.08 |
|Patients on E+P (N=35 021) | RCT diet | 1.29* | 5.97 | 1.37** | 8.86 |
|Patients on E-only (N=38 672) | RCT E only | 1.89*** | 58.17 | 1.44*** | 17.23 |
|Patients on E-only (N=38 672) | RCT diet | 0.99 | 0.00 | 1.04 | 0.22 |

*p<0.05. *p<0.01. ***p<0.001.
†Covariables used for the adjustment are described in the text.

E+P, oestrogen plus progestin; HT, hormone therapy; MI, myocardial infarction; OS, observational study; RCT, randomised controlled trial; WHI, Women’s Health Initiative.

Hartz A, He T, Wallace R, et al. BMJ Open 2013;3:e002556. doi:10.1136/bmjopen-2013-002556
Comparison to previous studies

OSs prior to WHI suggested a 30–50% reduction in coronary heart disease incidence among women using HT.6–8 There was a smaller benefit shown in the analyses of the observational data in the present study: a 17% reduction in the OS and a 25% reduction in the RCT for diet.

After the WHI results were published, six studies of the association between HT and stroke or MI compared RCT results from the WHI with observational study results: three of these studies used observational data from the WHI13,15,16 and three used observational data from the Nurses’ Health Study.9,10,14 Two of the WHI studies found, after controlling for time on HT and covariables, E+P HRs for MI did not significantly differ for the two study designs but HRs for stroke were higher in the RCT.

The goals and analytic methods of the present study differ substantially from previous studies using WHI data. The lead author believed that the extensive WHI data would be sufficient to give reliably valid results and extraordinary efforts were made to confirm this hypothesis. These efforts included an assessment of more than 800 risk factors as potential confounders and evaluating all marginally significant or previously suggested factors as potential effect modifiers. Even when the OS and RCT results were not the same, it was possible that the OS results were still valid. As a more definitive test of the adequacy of the WHI data we tried to eliminate differences in risk-adjusted outcomes from different datasets, which few if any other studies have attempted.

The present study differed from previous WHI studies in the following ways: (1) it included participants with and without a uterus, which made it possible to assess the effect of HT preparation. (2) It included participants in the diet RCT, which made it possible to compare risk-adjusted outcomes for two RCT and two OS datasets. (3) It evaluated more than 800 possible risk factors including those often suspected to cause confounding such as socioeconomic status, health behaviours, life style, stress and psychological characteristics. (4) It screened numerous participant characteristics for possible modulating effects on the association between HT and outcomes. (5) It analysed the risk for OS participants who began taking HT after enrolment. (6) It compared participants on the same treatment in different datasets and demonstrated that adjusting for WHI variables does not necessarily eliminate risk differences between datasets.

One of the WHI studies previously evaluated the timing hypothesis and did not find effects of prior HT use or menopause within 5 years.16 Another analysis of WHI data has been often cited as supporting the timing hypothesis.17 Although we tried to define coronary heart disease and years since menopause to get the same results, we could not. This suggests that the trends in the previous analysis were not robust to changing definitions.

A WHI study also found, as we did in the present study that the MI HR for E+P was greatest in the early years of treatment. This could explain OS and RCT differences because most OS participants taking HT at baseline began HT several years prior to baseline. However, some analyses in the present study did not support this explanation: (1) the RCT did not find that the effect of E-alone on MI changed over time; (2) none of the datasets found that the effect of any HT on stroke changed over time; (3) WHI OS participants who began HT after baseline had low MI risk and (4) prior HT exposure did not reduce the association between HT and cardiovascular disease.

Results from the OS performed by the Nurses’ Health Study differed from our analysis of the WHI OS in important respects. One was that there was no protective association of HT and CHD for women over the age of 60.9 (Other studies have also suggested that HT is less protective for older women.11,12) A second was that there was increased risk for new initiators of HT during the first 2 years after initiation and the risk increased 10 years after menopause.14 Based on these findings the researchers in the Nurses’ Health Study hypothesised that the OS results might be influenced by timing of HT initiation in relation to menopause onset or age and by length of follow-up. A third result that differed from ours was that HT significantly increased the risk of stroke.10 Since this later result was similar to the WHI RCTs and the previous results might have explained differences between OSs and RCTs, the Nurses’ Health Study suggested that OSs of HT could get the same results as RCTs.

The disagreements between our results and the results of the Nurses’ Study do not show that the analyses or interpretation in either study are necessarily incorrect. The disagreements do demonstrate, however, the difficulty of getting valid results from OSs.

In addition to OSs of the Nurses’ Health Study that give results similar to RCTs there is also an RCT that found oestradiol had an extraordinary protective effect on cardiovascular disease, which is consistent with the weaker protective effect of a different oestrogen preparation in the WHI OS.12

A previously published analysis of the WHI data shows that WHI risk factors cannot eliminate the association of adherence to placebo with MI, stroke or breast cancer.18 Since the effect of adherence to placebo is probably a marker of unmeasured confounders, that study supports the implication of the present study that WHI risk factors are inadequate to eliminate unmeasured confounders.

Limitations

This study provided strong evidence that the WHI did not collect information on important risk factors related to MI or stroke. Although the WHI is unusually comprehensive, other datasets may provide information about these risk factors or about the risk factors that could
cause confounding for the outcomes they assessed. It is also possible that the WHI did collect the necessary information on the confounding factors, but the analytic methods used here were inadequate to take advantage of this information. However, the concerns raised by this study are still valid because both the dataset and the analytic methods used were much more comprehensive than is practical for almost all OSs.

Conclusion and future directions
We did not find that the comprehensive data provided by the WHI were adequate to overcome problems often attributed to OSs. The findings do not imply that most OSs are invalid. They do suggest, however, that given the current methodologic, even very good OS datasets may not be adequate to give reliably valid results.

Owing to the key role that OSs are likely to play in studies of comparative effectiveness, it is critical to find ways to make OSs more valid. Although there has been some research on OS methodology, more is required. There should be investigations to learn why some OSs agree with RCTs and others do not. More specific research goals include the following: (1) identify criteria for treatments unlikely to have confounding problems (eg, when there is little patient input to treatment, and one treatment is not preferred for higher risk patients), (2) find new risk factors that better adjust for patient behaviours that affect outcomes (eg, factors related to choosing or adhering to treatment) and (3) develop methods for assessment of confounding after data collection (eg, finding good markers for important unmeasured confounding factors). Without better OS methodology there will be underuse or misuse of OSs for comparative effectiveness research.

Author affiliations
1Huntsman Cancer Institute at the University of Utah, St Louis, Missouri, USA
2Health Services Research, University of Utah College of Medicine, Salt Lake City, Utah, USA
3Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, Iowa, USA
4Department of Medicine, George Washington University School of Medicine, District of Columbia, DC, USA

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Total 869 variables

Form 2 Eligibility Screening (45)

| Variable    | Label                                                                 |
|-------------|----------------------------------------------------------------------|
| AGEHYST     | Hysterectomy age group                                               |
| AVAILDM     | Available for regular dietary meetings                                |
| AVAILHRT    | Consider taking only HRT from CC                                      |
| BLDPROB     | Bleeding problem ever                                                |
| CHF_F2      | Heart failure ever                                                   |
| COMECC      | Able to come to clinic                                                |
| DDBDIETF2   | Special diet for diabetes                                             |
| DIAB        | Diabetes ever                                                         |
| DIABAGE     | Age first told had diabetes                                           |
| DIABCOMA    | Hospitalized for a diabetic coma                                      |
| DIABNW      | Diabetes now                                                          |
| DIABPILL    | Pills for diabetes ever                                               |
| DIABTRT     | Diabetes treated (pills or shots)                                     |
| DIALYSIS    | Kidney dialysis for kidney failure                                    |
| DVT_F2      | DVT ever                                                              |
| HARDSTDY    | Problems make it hard to participate                                  |
| HELPCC      | Kind of help needed to come to clinic                                 |
| HELPFILL    | Need someone to help fill out forms                                   |
| HORM        | Female hormones ever                                                  |
| HORM3M      | Female hormones last 3 months                                         |
| HORMBK      | Hormones to treat osteoporosis fracture                               |
| HORMSTAT    | HRT use ever                                                          |
| HRTINFDR    | Send HRT info to Doctor                                               |
| HYST_F2     | Hysterectomy ever                                                     |
| HYST3M      | Hysterectomy last 3 months                                            |
| HYSTAGE     | Age at hysterectomy                                                   |
| INSULIN     | Insulin shots ever                                                    |
| INSULINW    | Insulin shots now                                                     |
| INTDM       | Interested in DM part of study                                        |
| INTHRT_F2   | Interested in HRT part of study                                       |
| L15LBS6M    | Lost 15 lbs in the last 6 mo w/o trying                               |
| LF DIETF2   | Special low-fiber diet                                                |
| LIVERDIS    | Liver disease ever                                                    |
| MALDIET     | Special malabsorption diet                                            |
| MEALOUT     | 10 or more meals prepared away from home                              |
| MENSELST    | Last time had any menstrual bleeding                                  |
| MI_F2       | MI ever                                                               |
| MIAGE       | Age first had MI                                                      |
| OSTEOBK     | Osteoporosis-related fracture ever                                    |
| OTHCHRON    | Other long-term illness                                               |
| PE_F2       | Pulmonary embolism ever                                               |
| Variable   | Label                                                |
|------------|------------------------------------------------------|
| ABNPAP3Y   | Abnormal Pap smear last 3 years                      |
| ANYINS     | Any Insurance                                       |
| CAREPROV   | Current Health Care Provider                         |
| CERVDYS    | Cervical dysplasia ever                              |
| DISABLED   | Currently disabled                                   |
| EMPLOYED   | Currently employed (full- or part-time)              |
| ENDOASP    | Endometrial aspiration ever                          |
| HMOINS     | Pre-paid private insurance                           |
| HOMEMKR    | Currently homemaker                                  |
| INCOME     | Family Income                                        |
| JOBHMMKR   | Job as homemaker                                     |
| JOBLABOR   | Job as operator, fabricator, laborer                 |
| JOBMANGR   | Job as managerial, professional                       |
| JOBOTH     | Job as other than listed                              |
| JOBSERV    | Job as service                                       |
| JOBTECH    | Job as technical, sales, admin support               |
| LSTASPDY   | Days from rand to last aspiration                    |
| LSTMAMDY   | Days from rand to last mammogram                     |
| LSTPAPDY   | Days from rand to last pap smear                     |
| LSTVISDY   | Days from rand to last visit                         |
| MAINJOB    | Occupation                                           |
| MAMMO      | Mammogram ever                                      |
| MARITAL    | Marital status                                       |
| MEDICAID   | Medicaid                                             |
| MEDICARE   | Medicare                                             |
| MLTRYINS   | Military or VA insurance                             |
| NOINS      | No insurance                                         |
| NOMAM2YR   | No mammogram in last 2 years                         |
| NOPAP3YR   | No pap smear in last 3 years                         |
| NOTWRK     | Currently not working                                |
| OTHPRVIN   | Private insurance (other than pre-paid)              |
| OTHWRK     | Other current job status                             |
| PAPSMEAR   | Pap smear ever                                       |
| PAYOTH     | Other insurance than listed                          |
| PDISABLE   | Partner currently disabled                           |
| PEDUC      | Partner highest level of education                   |
| PEMPLY     | Partner currently employed                           |
| Variable       | Label                                      |
|---------------|--------------------------------------------|
| PHOMEMKR      | Partner currently homemaker                |
| PMAINJOB      | Partner's main job                         |
| PNOTWRK       | Partner currently not working               |
| POTHWRK       | Partner currently other job                 |
| PRETIRED      | Partner currently retired                   |
| RETIRED       | Currently retired                           |
| TIMELAST      | Time Since Last Medical Visit (months)      |
| TIMELSTS      | Last Medical Visit within 1 Year            |
| USSERVE       | Served in US armed forces                   |
| VAMEDCTR      | Used a VA medical center ever               |

Form 30 Medical History  (95)

| Variable       | Label                                      |
|---------------|--------------------------------------------|
| ALS           | ALS ever                                   |
| ALZHEIM       | Alzheimer's disease ever                   |
| ANGINA        | Angina ever                                |
| ANGNPILN      | Pills for angina now                       |
| AORTICAN      | Aortic aneurysm ever                       |
| ARTHRIT       | Arthritis ever                             |
| ASTHMA        | Asthma ever                                |
| ATRIALFB      | Atrial fibrillation ever                   |
| BKBACK        | Broke spine ever                           |
| BKBACK55      | Broke spine first time 55 or older         |
| BKBONE        | Broke bone ever                            |
| BKFOOT        | Broke foot ever                            |
| BKFOOT55      | Broke foot first time 55 or older          |
| BKHAND        | Broke hand ever                            |
| BKHAND55      | Broke hand first time 55 or older          |
| BKHIP         | Broke hip ever                             |
| BKHIP55       | Broke hip first time 55 or older           |
| BKLARM        | Broke lower arm ever                       |
| BKLARM55      | Broke lower arm first time 55 or older     |
| BKLLEG        | Broke lower leg ever                       |
| BKLLEG55      | Broke lower leg first time 55 or older     |
| BKOTHB        | Broke other bone ever                      |
| BKOTHB55      | Broke other bone first time 55 or older    |
| BKUARM        | Broke upper arm ever                       |
| BKUARM55      | Broke upper arm first time 55 or older     |
| BLADCA        | Bladder cancer ever                        |
| BRCA_F30      | Breast cancer ever                         |
| BRCA55        | Breast cancer 55 or older                  |
| CABG          | Coronary bypass surgery ever               |
| CANC_F30      | Cancer ever                                |
| CARDCATH      | Cardiac catheterization ever               |
| Condition          | Description                                      |
|-------------------|--------------------------------------------------|
| CARDREST          | Cardiac arrest ever                              |
| CAROTID           | Carotid endarterectomy/angioplasty ever          |
| CATARACT          | Cataract ever                                    |
| CERVCA            | Cervix cancer ever                               |
| CHF_F30           | Congestive heart failure ever                    |
| COLITIS           | Ulcerative colitis ever                          |
| COLN_F30          | Colorectal cancer ever                           |
| COLNCDT           | Date of last colonoscopy                         |
| COLNSCPY          | Colonoscopy ever                                 |
| COLOCA55          | Colorectal cancer 55 or older                    |
| CVD               | Cardiovascular disease ever                      |
| DIVERTIC          | Diverticulitis ever                              |
| EMPHYSEM          | Emphysema ever                                   |
| FAINTED           | Fainted last 12 months                           |
| FRACT55           | Fracture at Age 55+                              |
| GALLBLRM          | Gallbladder removed                              |
| GALLBS            | Gallbladder disease or gallstones ever           |
| GALLBSNW          | Gallbladder disease or gallstones now            |
| GALLSTRM          | Gallstones removed                               |
| GLAUCOMA          | Glaucoma ever                                    |
| GOITER            | Goiter ever                                      |
| GOITERNW          | Goiter now                                       |
| HEMOCCDT          | Date of last hemoccult test                      |
| HEMOCUL           | Hemoccult test ever                              |
| HIBLDCA           | High blood calcium                               |
| HICHLRPR          | High cholesterol requiring pills ever            |
| HIP55             | Hip fracture age 55 or older                     |
| HIPREP            | Hip replacement ever                             |
| HTNTRT            | Hypertension                                     |
| HYPT              | Hypertension ever                                |
| HYPTAGE           | Age told of hypertension                         |
| HYPTPILL          | Pills for hypertension ever                      |
| HYPTPILN          | Pills for hypertension now                       |
| INTESTRM          | Part of intestines removed ever                  |
| KIDNEYST          | Kidney or bladder stones ever                    |
| LUPUS             | Lupus ever                                       |
| MELN_F30          | Melanoma cancer ever                             |
| MIGRAINE          | Migraine headaches ever                          |
| MS                | MS ever                                           |
| NACOND            | None of listed medical conditions ever            |
| NACVD             | None of the listed CVD conditions ever            |
| NODULE            | Thyroid nodule ever                              |
| NODULENW          | Thyroid nodule now                               |
| NUMFALLS          | Times fell down last 12 months                   |
| OTHERCA           | Other cancers ever                               |
| Variable    | Label                                                      |
|-------------|------------------------------------------------------------|
| OTHJREP     | Other joint replacement ever                               |
| OVRTHY      | Overactive thyroid ever                                    |
| OVRTHYNW    | Overactive thyroid now                                     |
| PAD         | Peripheral arterial disease ever                           |
| PADANGGR    | Angiography for PAD ever                                   |
| PADANGP     | Angioplasty for PAD ever                                   |
| PADSURG     | Surgery to improve flow to legs for PAD                    |
| PANCREAT    | Pancreatitis ever                                          |
| PARKINS     | Parkinson's disease ever                                   |
| PCOLONRM    | Polyps of colon removed                                    |
| PTCA        | Angioplasty of coronary arteries ever                      |
| REVASC      | CABG/PTCA Ever                                             |
| RHEUMAT     | Rheumatoid arthritis ever                                  |
| SKINCA      | Skin cancer (not melanoma) ever                            |
| STOMULCR    | Stomach of duodenal ulcer ever                             |
| THYRCA55    | Thyroid cancer 55 or older                                 |
| THYROID     | Thyroid Cancer                                             |
| UNDTHY      | Underactive thyroid ever                                   |
| UNDTHYNW    | Underactive thyroid now                                    |

Form 31 Reproductive History (54)

| Variable    | Label                                                      |
|-------------|------------------------------------------------------------|
| AGEFBIR     | Age at First Birth                                         |
| ANYMENSA    | Age at last bleeding                                       |
| BOOPH       | Bilateral Oophorectomy                                     |
| BRSTAUG     | Operation to increase breast                               |
| BRSTAUGA    | How old at breast augmentation                             |
| BRSTBION    | How many breast biopsies                                   |
| BRSTDIS     | Breast Disease                                             |
| BRSTFDAQ    | How old when first breastfed                                |
| BRSTFDAL    | How old when last breastfed                                 |
| BRSTFDM     | How many months total                                      |
| BRSTFDMO    | Number of months breastfed                                 |
| BRSTFDN     | How many children breastfed                                 |
| BRSTFEED    | Breastfeed at least one month                              |
| BRSTIMP     | What type of implant                                        |
| BRSTOPOPOT  | Any other breast operations                                |
| BRSTPREM    | Removal of part of breast                                  |
| BRSTREM     | Removal of one or both breasts                             |
| BRSTREMO    | Other breast operation                                     |
| BRTHSTLN    | How many still births                                      |
| ECTPREG     | How many tubal pregnancies                                 |
| FULLTRMR    | Full term pregnancy ever                                   |
| GRAVID      | Number of Pregnancies                                      |
| Variable       | Label                                           |
|----------------|------------------------------------------------|
| MENARCHE       | Age at first period                            |
| MENOPSEA       | Age at last regular period                     |
| MENPSYAF       | Age at first hot flash                         |
| MENPSYAL       | Age at last hot flash                          |
| MENPSYMP       | Hot flashes or night sweats                    |
| MENSREG        | Were periods regular                           |
| MENSREGA       | Age at first regular period                    |
| MENSWO1Y       | One year without period                        |
| MENSWOD        | Time between first and last period             |
| MISCARYN       | How many miscarriages                          |
| NEDLASP        | Needle aspiration ever                         |
| NOCNCEIV       | Tried becoming pregnant > 1 yr                 |
| NOCNCVDK       | Don't know reason                              |
| NOCNCVDR       | Saw doctor because you didn't                 |
| NOCNCVEN       | Endometriosis                                  |
| NOCNCVHR       | Hormones or ovulation                          |
| NOCNCVOT       | Other problem with you                         |
| NOCNCVPT       | Problem with partner                           |
| NOCNCVR        | Reason found for non-pregnancy                 |
| NOCNCVUT       | Tubes or uterus                                |
| NUMLIVER       | Number of Live Births                          |
| OOPH           | One or both ovaries removed                    |
| OOPHA          | Age when ovaries removed                       |
| PARITY         | Number of Term Pregnancies                     |
| PREG           | Ever been pregnant                             |
| PREG6M         | Ever have full-term pregnancy                  |
| PREG6MAF       | Age at first term pregnancy                    |
| PREG6MAL       | Age at last term pregnancy                     |
| PREG6MN        | How many times term pregnancy                  |
| PREGNUM        | How many times pregnant                        |
| TUBTIED        | Ever had tubes tied                            |
| TUBTIEDA       | Age when tubes tied                            |
| Form 32 Family History (79) | |

| Variable       | Label                                           |
|----------------|------------------------------------------------|
| BKBCKDAD       | Age father broke spine or back                  |
| BKBCKMOM       | Age mother broke spine or back                  |
| BKBONDAD       | Father broke a bone after age 40               |
| BKBONMOM       | Mother broke a bone after age 40                |
| BKBONREL       | Mom or dad broke bone after age 40              |
| BKHIPDAD       | Age father broke hip                            |
| BKHIPMOM       | Age mother broke hip                            |
| BKLARDAD       | Age father broke lower arm                      |
| BKLARMOM       | Age mother broke lower arm                      |
| Code     | Description                                      |
|----------|--------------------------------------------------|
| BKOTHAD  | Age father broke other than listed bone          |
| BKOTHMOM | Age mother broke other than listed bone           |
| BKUARDAD | Age father broke upper arm                       |
| BKUARMOM | Age mother broke upper arm                        |
| BRCDAD1  | Age daughter (1) had breast cancer               |
| BRCDAD2  | Age daughter (2) had breast cancer               |
| BRCDAD3  | Age daughter (3) had breast cancer               |
| BRCAFREL | Female relative had breast cancer                |
| BRCMAM   | Age mat. grandmother had breast cancer           |
| BRCMAP   | Age pat. grandmother had breast cancer           |
| BRAMOM   | Age mother had breast cancer                     |
| BRCASIS1 | Age sister (1) had breast cancer                 |
| BRCASIS2 | Age sister (2) had breast cancer                 |
| BRCASIS3 | Age sister (3) had breast cancer                 |
| BRONUM   | Number of brothers                               |
| BROTHER  | Have a brother who reached adulthood             |
| CANCFREL | Female relative had cancer                       |
| CANCMREL | Immediate male blood relative had cancer         |
| CERVREL  | Relative had cervical cancer                     |
| CERVRELN | Number of relatives had cervical cancer          |
| COLOBRO1 | Age brother (1) had colorectal cancer            |
| COLOBRO2 | Age brother (2) had colorectal cancer            |
| COLOBRO3 | Age brother (3) had colorectal cancer            |
| COLODAD  | Age father had colorectal cancer                 |
| COLODAU1 | Age daughter (1) had colorectal cancer           |
| COLODAU2 | Age daughter (2) had colorectal cancer           |
| COLOFREL | Female relative had colorectal cancer            |
| COLOMOM  | Age mother had colorectal cancer                 |
| COLOMREL | Male relative had colorectal cancer              |
| COOREL   | Male/Female relative had colorectal cancer       |
| COOSIS1  | Age sister (1) had colorectal cancer             |
| COOSIS2  | Age sister (2) had colorectal cancer             |
| COOSIS3  | Age sister (3) had colorectal cancer             |
| COOSON1  | Age son (1) had colorectal cancer                |
| COOSON2  | Age son (2) had colorectal cancer                |
| DADAGE   | Natural father's current age                     |
| DADALIVE | Natural father still alive                       |
| DADDIEDA | Age natural father died                          |
| DAUGHTER | Have a daughter who reached adulthood            |
| DAUNUM   | Number of daughters                              |
| DIABREL  | Relative had adult diabetes                      |
| DIABRELN | Number of relatives had adult diabetes           |
| ENDOREL  | Relative had endometrial cancer                  |
| ENDORELN | Number of relatives had endomet. cancer          |
| MIRO1    | Age brother (1) had MI                           |
| Variable | Label |
|----------|-------|
| ALC12DR  | Drank 12 alcoholic beverages ever |
| ALCNOW   | Still drink alcohol |
| ALCOHOL  | Alcohol intake |
| ALCQUIT  | Reasons quit drinking alcohol |
| ALCSWK   | Alcohol servings per week |
| AVWKEXP  | Energy expend from avg walking |
| CIGSDAY  | Smoke, cigs/day |
| COFFEE   | Drink coffee each day |
| CUPREG   | Number of regular cups of coffee, day |
| DBDIET34 | Diabetic or ADA diet |
| FBDIET34 | High-fiber diet |
| FFWKEXP  | Energy expend fr walking fairly fast |
| HAREXP   | Energy expenditure from hard exercise |
| HRDEX    | Times per week of very hard exercise |
| HRDEX18  | Very hard exercise 3 times/wk at age 18 |
| HRDEX35  | Very hard exercise 3 times/wk at age 35 |
### Variable Definitions

| Variable | Label |
|----------|-------|
| HRDEX50 | Very hard exercise 3 times/wk at age 50 |
| HRDEXMIN | Duration per time of very hard exercise |
| LACTDIET | Lactose-free (no milk/dairy foods) diet |
| LCALDIET | Low calorie diet |
| LEPITOT | Recr. phys activity per week >= 20 Min |
| LFATDIET | Low-fat or low cholesterol diet |
| LMSEPI | Mod-stren activity >20 min/week (categorical) |
| LSLTDIET | Low salt (low sodium) diet |
| MILDEX | Times per week of mild exercise |
| MILDEXMIN | Duration per time of mild exercise |
| MODEX | Times per week of moderate exercise |
| MODEXMIN | Duration per time of moderate exercise |
| MODEXP | Energy expend from moderate exercise |
| MSEPIWK | Mod. to strenuous phys activity per week |
| MSMINWK | Minutes of mod-stren activity per week |
| OTHDIET | Other than listed special diet |
| QSMOKAGE | Age quit smoking regularly |
| QSMOKHP | Quit smoking because of health problems |
| SEPIWK | Strenuous activity episodes per week |
| SMINWK | Minutes of stren. phys activity per week |
| SMOKAGE | Age started smoking cigarettes regularly |
| SMOWEVR | Smoked at least 100 cigarettes ever |
| SMOKING | Smoking status |
| SMOKNOW | Smoke cigarettes now |
| SMOKWGT | Smoked to lose weight |
| SMOKYRS | Years a regular smoker |
| TEPIWK | Recreational phys activity per week |
| TEXPWK | Total MET-hours per week |
| TMINWK | Minutes of recr. phys activity per week |
| VFWKEXP | Energy expend from walking very fast |
| WALK | Times walk for > 10 min |
| WALKEXP | MET-hours per week from walking |
| WALKMIN | Duration of walks when >10 min |
| WALKSPD | Walking speed when walking for >10 min |
| WGTADULT | Weight during adult life, lbs |
| XLMSEPI | Mod-stren activity > 20 min/week |
| YOYO10LB | Number times weight went up/down >10 lbs |

### Form 37 Thoughts and Feelings (216)

| Variable | Label |
|----------|-------|
| ACHES | General aches and pains |
| ACTDLY | Activities of Daily Living Construct |
| AMBEMOT | Ambivalence over Emotional Expressiveness |
| ANNOYED   | Becoming easily annoyed or irritable  |
|----------|--------------------------------------|
| ANXIOUS  | Feeling nervous, anxious, on edge    |
| APPRVNEG | Fear others will not approve if negative |
| BACKSLP  | Trouble getting back to sleep       |
| BADLUCK  | Think people make bad luck for sympathy |
| BADSEX   | People guilty of bad sexual behavior |
| BATHING  | Bathing or dressing yourself         |
| BENDING  | Bending, kneeling, stooping           |
| BIRD     | Bird                                 |
| BLOATING | Bloating or gas                       |
| BODPAIN  | How much body pain                    |
| BOTHER   | After anger bothered for a long time  |
| CALM     | Felt calm and peaceful                |
| CAREGIV1 | Care Giving Construct #1 (0,1 scoring) |
| CAREGIV2 | Care Giving Construct #2 (0-5+ scoring) |
| CAT      | Cat                                  |
| CGHINCON | Leak urine when cough, laugh          |
| CHILCON  | Major conflict with children          |
| CLUB     | Attend clubs/lodges/groups last month |
| CLUMSY   | Clumsiness                           |
| COERC    | Number of people who try to coerce    |
| CONCEN   | Difficulty concentrating              |
| CONSTIP  | Constipation                         |
| COUGH    | Coughing or wheezing                  |
| COUNTGD  | Rarely count on good things happening |
| CRYSPELL | You had crying spells                 |
| DIAPER   | Leak protect/Diaper, Attends          |
| DIARRHEA | Diarrhea                              |
| DISAPPN  | Express disappointment                |
| DIVORCE  | Have a divorce or break-up            |
| DIZZY    | Dizziness                             |
| DOG      | Dog                                  |
| DRESS    | Can you dress and undress self        |
| DWNDUMPS | Felt down in dumps                    |
| EAT      | Can you eat                           |
| EMOLIMIT | Role Limitations Due to Emotional Problem |
| EMOWELL  | Emotional Well-being                  |
| ENERFAT  | Energy/Fatigue                        |
| ENERGY   | Had lots of energy                    |
| ENJLIF   | You enjoyed life                      |
| EXCLUDE  | Number of people who exclude you      |
| EXPECTBST| Usually expect the best               |
| EXPERTS  | Experts often no better than I        |
| FALLSLP  | Fall asleep during quiet activity     |
| FELTBLUE | Felt downhearted and blue             |
| Code    | Description                                      |
|---------|--------------------------------------------------|
| FELTDEP | You felt depressed                               |
| FELTSAD | You felt sad                                     |
| FISH    | Fish                                             |
| FORGET  | Forgetfulness                                    |
| FRIENDIE| Did a close friend die                           |
| FRNDIV  | Close friend had a divorce                       |
| FRNDSUSE| Make friends because friends are useful          |
| FRNJOB  | Close friend lost job                            |
| FRQINCON| How often leaked urine                           |
| FULLPEP | Did you feel full of pep                         |
| FUN     | Someone to something fun with                    |
| GENHEL  | In general, health is                            |
| GENHLTH | General Health Construct                         |
| GOODADV | Someone to give good advice                      |
| GOODTIME| Someone to have a good time with                 |
| HAPPY   | Have you been happy                              |
| HEADACHE| Headaches or migraines                           |
| HEARLOSS| Hearing loss                                     |
| HEARTBRN| Heartburn                                        |
| HEARTAC | Heart racing or skipping beats                   |
| HLPCHORS| Someone to help with daily chores                |
| HLPPROB | Someone to help understand a problem            |
| HLPICKT | Helping sick family/friend                       |
| HLTHC1Y | Compare health to 1 year ago                     |
| HLTHEXCL| My health is excellent                          |
| HLTHWORS| I expect health to get worse                     |
| HLTHYANY| I am as healthy as anybody                       |
| HONEST  | Most people are honest due to fear               |
| HOPEFUL | Always hopeful about future                      |
| HOSTIL  | Hostility Construct                              |
| HOTFLASH| Hot flashes                                      |
| HRSSLP  | How many hours of sleep                          |
| HUNGRY  | Increased appetite                               |
| INCONDIS| How much does leakage bother                     |
| INCONLMT| leak limit activities                            |
| INCONT  | Ever leaked urine                                |
| INOUTBED| Can you get in and out of bed                    |
| INTSOC  | Phys or emotional probs interfere                |
| INTSOC2 | Physical or emotional problem                    |
| JNTPAIN | Joint pain or stiffness                          |
| KNWANGRY| Usually people around know when angry           |
| LEAKAMT | How much urine you lose                          |
| LESSACCE| Emot/Accomplished less                           |
| LESSACCP| Phys/Accomplished less                           |
| Abbreviation  | Description                                                  |
|---------------|--------------------------------------------------------------|
| LESSCARE      | Emot/Worked less carefully                                   |
| LESSKNDP      | Phys/limited kind of work                                     |
| LESSWRKE      | Emot/cut down on time spent                                  |
| LESSWRKP      | Phys/cut down on time spent                                  |
| LFEVENT1      | Life Event Construct #1 (0,1 scoring)                        |
| LFEVENT2      | Life Event Construct #2 (0-3 scoring)                        |
| LIE           | Most people would lie to get ahead                           |
| LIFEQUAL      | Rate quality of life                                         |
| LIFTGROC      | Lifting or carrying groceries                                |
| LISTEN        | Someone to listen when need to talk                          |
| LIVALN        | Live alone                                                   |
| LIVALOR       | Living Alone                                                 |
| LIVCHILD      | Live with children                                           |
| LIVFRNDS      | Live with friends                                            |
| LIVOTH        | Live with other than listed                                  |
| LIVPRT        | Live with husband/partner                                    |
| LIVREL        | Live with relatives                                          |
| LIVSIBL       | Live with brother/sister                                     |
| LOVE          | Someone to love you/make you feel wanted                     |
| LOWBACKP      | Low back pain                                                |
| MAJACC        | Major accident or disaster                                   |
| MARRIED       | Currently married or intimate                                |
| MEDSLEEP      | take medication for sleep                                    |
| MENS PAD      | Leak Protection/Menstrual pad                                |
| MINIPAD       | Leak Protect/Mini-pad, tissue                                |
| MODACT        | Moderate activities                                          |
| MONPROB       | Major problems with money                                    |
| MOODSWNG      | Mood swings                                                  |
| MOREGOOD      | Expect more good things than bad                             |
| MSCLACHE      | Muscle tension aches or soreness                             |
| NAP           | Did you nap during the day                                   |
| NAUSEA        | Nausea                                                       |
| NECKPAIN      | Neck pain                                                    |
| NEGEMOT       | Negative Emotional Expressiveness (NEE)                      |
| NERVES        | Number of people who get on nerves                           |
| NERVOUS       | Have you been a very nervous person                          |
| NIGHTSWT      | Night sweats                                                 |
| NOCARE        | No one cares what happens to you                              |
| NOCONCEN      | Trouble concentrating on things, reading                     |
| NOHELP        | People inwardly don’t like to help                           |
| NOHUNGER      | Decreased appetite                                           |
| NOINCON       | No longer leak urine                                         |
| NOPRTCT       | Leak Protect/No protection                                   |
| NOTMYWAY      | Hardly ever expect things to go my way                       |
| OPTIMISM      | Optimism Construct                                           |
| ORDERS         | Take orders from someone who knew less |
|---------------|----------------------------------------|
| OTHINCON      | When leak urine, Other                 |
| OTHPET         | Other pet                              |
| OTHPRTCT      | Leaking urine protection, Other        |
| PAIN           | Pain Construct                         |
| PAININT        | How much did pain interfere            |
| PANIC          | Having an anxiety attack -- feel fear or panic |
| PEOPDIS       | You felt people disliked you           |
| PET            | Lived with a pet in home               |
| PETDIE         | Did a pet die                          |
| PHYAB          | You were physically abused             |
| PHYLIMIT       | Role Limitations Due to Physical Health|
| PHYSFUN        | Physical Functioning Construct         |
| PSHTDEP        | Shortened CES-D/DIS Screening Instrument|
| QUALSLP       | Typical night's sleep                  |
| RELGTIME       | Times attend religious service/church  |
| RELSTRN       | Religion gives strength and comfort    |
| RESPECT        | People demand more respect than give   |
| RESTLSIT       | Feeling restless so hard to sit still  |
| RESTSLP       | Your sleep was restless                |
| SAD2WK         | Felt sad for two weeks                 |
| SAD2YRS        | Felt sad two or more years             |
| SADMUCH        | Felt sad much of past year             |
| SATFROSX       | Satisfied with sex frequency           |
| SATLIFE        | Satisfied with quality of life         |
| SATSEX         | How satisfied sexually                 |
| SCENEPUB       | If angered, cause scene in public place|
| SEX            | Who you have had sex with              |
| SEX45          | Description of adult sexual orientation|
| SEXACTIV       | Sexual activity in last year           |
| SEXWORRY       | Sexual activity affect health           |
| SHARE          | Someone to share private worries/fears |
| SHOWER         | Can you take a bath or shower          |
| SICKEASY       | I get sick easier                      |
| SKINDRY        | Skin dryness or scaling                |
| SLPDSTRB       | Sleep Disturbance Construct            |
| SLPINCON       | Leak when I am sleeping                |
| SNORE          | Did you snore                          |
| SOCFUNC        | Social Functioning                     |
| SOCSTRN        | Social Strain Construct                |
| SOCSUPP        | Social Support Construct               |
| SPOUSDIE       | Did your spouse die                    |
| SPOUSILL       | Did your spouse have a serious illness |
| STAIR          | Climbing one flight of stairs          |
| STAIRS         | Climbing several flights               |
| STAYSLP         | Trouble falling asleep or staying asleep                             |
|----------------|---------------------------------------------------------------------|
| SUPPRESS       | Usually suppress anger                                               |
| SWELLHND       | Swelling of hands or feet                                            |
| SYMPTOM        | Symptom Construct                                                    |
| TAKEDR         | Someone can take to the doctor                                       |
| TELLFEEL       | Tell from facial expressions how feeling                             |
| TIRED          | Did you feel tired                                                   |
| TIRED2         | Feeling tired                                                        |
| TIREASY        | Getting tired very easily                                            |
| TOINCON        | Leak when can’t get to toilet                                        |
| TOO MUCH       | Number of people who ask too much                                    |
| TRBSEE         | Trouble with vision                                                  |
| TRBSLEEP       | Did you have trouble sleeping                                       |
| TREMORS        | Tremors                                                              |
| TRUSTNO        | Safer to trust nobody                                                |
| TRUTH          | Argue to convince people of truth                                    |
| UNFAIR         | Most people are unfair to gain profit                                |
| UPEARLY        | Wake up earlier than planned                                         |
| UPSTOM         | Upset stomach or belly pain                                          |
| URINPAIN       | Pain/burning while urinating                                         |
| VAGDIS         | Vaginal or genital discharge                                         |
| VAGDRY         | Vaginal or genital dryness                                           |
| VAGITCH        | Vaginal or genital irritation                                         |
| VORBAB         | You were verbally abused                                              |
| VIGACT         | Vigorous activities                                                  |
| WAKENIGHT      | Did you wake up several times                                        |
| WALK1BLK       | Walking one block                                                    |
| WALK1M         | Walking more than one mile                                           |
| WALKBLKS       | Walking several blocks                                               |
| WELBEING       | Rate current sense of well-being                                    |
| WORNOUT        | Did you feel worn out                                                |
| WRKDIFFP       | Phys/difficulty perform work                                          |
| WRONG          | Expect something that can will go wrong                               |

Form 43 Hormone Use (44)

| Variable   | Label                                      |
|------------|--------------------------------------------|
| DES        | DES (diethylstilbestrol) use ever          |
| DESAGEMAX  | Age stopped DES                            |
| DESAGEMIN  | Age started DES                            |
| DESTIME    | DES Duration (years)                       |
| DMPA       | DMPA (depo-provera) use ever               |
| DMPAFREQ   | DMPA frequency of use                      |
| DMPAGEMAX  | Age last used DMPA                         |
| DMPAGEMIN  | Age first used DMPA                        |
| Variable     | Label                                      |
|--------------|--------------------------------------------|
| DMPATIME     | DMPA duration (years)                      |
| DMPAUOM      | DMPA frequency UOM                         |
| ESTR         | Estratest use                              |
| ESTRMAX      | Age last used estratest                    |
| ESTRMIN      | Age first used estratest                   |
| ESTRSTAT     | Estratest usage status                     |
| ESTRTIME     | Estratest duration                         |
| OC           | Oral contraceptive use ever                |
| OCAGEMAX     | Age last used OC                           |
| OCAGEMIN     | Age first used OC                          |
| OCBPREG      | OC use before first term pregnancy         |
| OCBPTIME     | OC use before first term preg duration (years) |
| OCTIME       | OC duration (years)                        |
| PCYCLE       | Progesterone cycle during last PERT use    |
| TEST         | Testosterone or other male hormone use     |
| TESTMAX      | Age last used testosterone                 |
| TESTMIN      | Age first used testosterone                |
| TESTSTAT     | Testosterone or other male hormone status  |
| TESTTIME     | Testosterone or other male hormone duration|
| TOTE         | Unopposed estrogen use ever                |
| TOTECAT      | Unopposed estrogen duration by category     |
| TOTEMAX      | Age last used unopposed estrogen            |
| TOTEMIN      | Age first used unopposed estrogen           |
| TOTESTAT     | Unopposed estrogen usage status             |
| TOTETIME     | Lifetime unopposed estrogen duration        |
| TOTH         | HRT use ever                               |
| TOTHCAT      | HRT duration by category                   |
| TOTHMAX      | Age last used HRT                          |
| TOTHMIN      | Age first used HRT                         |
| TOTHSTAT     | HRT usage status                           |
| TOTHTIME     | Lifetime HRT duration                      |
| TOTP         | Estrogen + progesterone use ever           |
| TOTPMAX      | Age last used estrogen + progesterone      |
| TOTPMIN      | Age first used estrogen + progesterone     |
| TOTPSTAT     | Estrogen + progesterone usage status       |
| TOTPTIME     | Lifetime estrogen + progest duration        |

Form 45 Current Supplements  (55)

| Variable   | Label                                      |
|------------|--------------------------------------------|
| F45BETA    | Supplemental Beta-carotene, mcg            |
| F45BIOT    | Supplemental Biotin, mcg                   |
| F45CALC    | Supplemental Calcium, mg                   |
| F45CHROM   | Supplemental Chromium, mcg                 |
| F45COMBP   | Any Combination Pill                      |
| Code   | Description                          |
|--------|--------------------------------------|
| F45COPP| Supplemental Copper, mg               |
| F45FOLIC| Supplemental Folic Acid, mcg          |
| F45IRON| Supplemental Iron, mg                 |
| F45MAGN| Supplemental Magnesium, mg            |
| F45MANG| Supplemental Manganese, mg            |
| F45MOLYB| Supplemental Molybdenum, mcg        |
| F45MULTI| Multivitamin without Minerals        |
| F45MVMIN| Multivitamin with Minerals          |
| F45NIAC| Supplemental Niacin, mg              |
| F45OTHCM| Other Comb Pill (not multivit/stress) |
| F45PANTO| Supplemental Pantothenic Acid, mg    |
| F45PHOS| Supplemental Phosphorus, mg           |
| F45POTAS| Supplemental Potassium, mg            |
| F45RETN| Supplemental Retinol, mcg            |
| F45SELEN| Supplemental Selenium, mcg          |
| F45STRES| Stress Formula Pills                  |
| F45VITA| Supplemental Vitamin A, mcg RE        |
| F45VITB1| Supplemental Vitamin B1 (Thiamine), mg |
| F45VITB2| Supplemental Vitamin B2 (Thiamine), mg |
| F45VITB6| Supplemental Vitamin B6, mg          |
| F45VITC| Supplemental Vitamin C, mg            |
| F45VITD| Supplemental Vitamin D, mcg           |
| F45VITE| Supplemental Alpha-tocopherol, IU    |
| F45VTB12| Supplemental Vitamin B12, mcg        |
| F45ZINC| Supplemental Zinc, mg                |
| TKBIOT| F45 Taking biotin from single sup    |
| TKCALC| F45 Taking calcium from single sup   |
| TKCHROM| F45 Taking chromium from single sup  |
| TKCOPP| F45 Taking copper from single sup    |
| TKFOLIC| F45 Taking folic acid from single sup |
| TKIRON| F45 Taking iron from single sup      |
| TKMAGN| F45 Taking magnesium from single sup |
| TKMANG| F45 Taking manganese from single sup |
| TKMOLYB| F45 Taking molybdenum from single sup |
| TKNIAC| F45 Taking niacin from single sup    |
| TKPANTO| F45 Taking pantoth. acid from single sup |
| TKPHOS| F45 Taking phosphorus from single sup |
| TKPOTAS| F45 Taking potassium from single sup |
| TKRETN| F45 Taking retinol from single sup   |
| TKSELEN| F45 Taking selenium from single sup  |
| TKVITA| F45 Taking vitamin A from single sup  |
| TKVITB1| F45 Taking vitamin B1 from single sup |
| TKVITB12| F45 Taking vitamin B12 from single sup |
| TKVITB2| F45 Taking vitamin B2 from single sup |
| TKVITB6| F45 Taking vitamin B6 from single sup |
| Variable   | Label                                                   |
|------------|---------------------------------------------------------|
| TKVITC     | F45 Taking vitamin C from single sup                    |
| TKVITED    | F45 Taking vitamin D from single sup                    |
| TKVITE     | F45 Taking alpha-toco from single sup                   |
| TKZINC     | F45 Taking zinc from single sup                         |

Form 60 Energy (139)

| Variable     | Label                                                   |
|--------------|---------------------------------------------------------|
| F60ACARO     | Dietary Alpha-Carotene (mcg)                           |
| F60ADSGR     | Dietary Added Sugars (g)                               |
| F60ALAN      | Dietary Alanine (g)                                    |
| F60ALCWK     | Alcohol servings per week                              |
| F60ANMPR     | Dietary Animal Protein (g)                             |
| F60ARGIN     | Dietary Arginine (g)                                   |
| F60ASH       | Dietary Ash (g)                                        |
| F60ASPRT     | Dietary Aspartic Acid (g)                              |
| F60ATOUCO    | Dietary Alpha-Tocopherol (mg)                          |
| F60BCRYP     | Dietary Beta-Cryptoxanthin (mcg)                       |
| F60BTOCO     | Dietary Beta-Tocopherol (mg)                           |
| F60BETA      | Dietary Beta-Carotene (mcg)                            |
| F60BIOCHN    | Dietary Biochanin A (mg)                               |
| F60CALC      | Dietary Calcium (mg)                                   |
| F60CBPCT     | Percent Calories from Carbohydrates                    |
| F60CHOLS     | Dietary Cholesterol (mg)                               |
| F60COPPR     | Dietary Copper (mg)                                    |
| F60CUMST     | Dietary Coumestrol (mg)                                |
| F60CYNSTN    | Dietary Cystine (g)                                    |
| F60DAIDZ     | Dietary Daidzein (mg)                                  |
| F60DIETGA    | Dietary Glycemic Index (using available carbs)         |
| F60DIETGI    | Dietary Glycemic Index (using total carbs)             |
| F60DTOCO     | Dietary Delta-Tocopherol (mg)                          |
| F60ENRGY     | Dietary Energy (kcal)                                  |
| F60ENRGYJ    | Dietary Energy (joules)                                |
| F60FRUIT     | Daily Fruit Consumption (med portion)                  |
| F60FIBER     | Dietary Fiber (g)                                      |
| F60FLEQ      | Dietary Folate Equivalents (mcg)                       |
| F60FLNAT     | Dietary Natural Folate (food folate) (mcg)             |
| F60FLSYN     | Dietary Synthetic Folate (folic acid) (mcg)            |
| F60FOL1      | Dietary Folacin (mcg)                                  |
| F60FRMNT     | Dietary Formononetin (mg)                              |
| F60FRUCT     | Dietary Fructose (g)                                   |
| Code    | Description                                      |
|---------|--------------------------------------------------|
| F60FTPCT| Percent Calories from Fat                       |
| F60GALAC| Dietary Galactose (g)                            |
| F60GLAC | Dietary Glycemic Load Based on Available Carb    |
| F60GLUC | Dietary Glucose (g)                              |
| F60GLUT | Dietary Glutamic Acid (g)                        |
| F60GLYC | Dietary Glycine (g)                              |
| F60GLYCTN | Dietary Glycitein (mg)                          |
| F60GNISTN | Dietary Genistein (mg)                        |
| F60GRAMS| Dietary Gram Amount                              |
| F60GTLCD| Dietary Glycemic Load Based on Total Carb        |
| F60GTOCO| Dietary Gamma-Tocopherol (mg)                    |
| F60HISTD| Dietary Histidine (g)                            |
| F60INSFB| Insoluble Dietary Fiber (g)                      |
| F60IRON | Dietary Iron (mg)                                |
| F60ISOLE| Dietary Isoleucine (g)                           |
| F60LACT | Dietary Lactose (g)                              |
| F60LEUCCN| Dietary Leucine (g)                             |
| F60LUTZX| Dietary Lutein+Zeaxanthin (mcg)                 |
| F60LYCOC| Dietary Lycopene (mcg)                           |
| F60LYSIN| Dietary Lysine (g)                               |
| F60MAGN | Dietary Magnesium (mg)                           |
| F60MALT | Dietary Maltose (g)                              |
| F60MANGN| Dietary Manganese (mg)                           |
| F60METH | Dietary 3-Methylhistidine (mg)                   |
| F60METHN| Dietary Methionine (g)                           |
| F60MF141| Dietary MFA 14:1 (g)                             |
| F60MF161| Dietary MFA 16:1 (g)                             |
| F60MF181| Dietary MFA 18:1, Oleic Acid (g)                 |
| F60MF201| Dietary MFA 20:1 (g)                             |
| F60MF221| Dietary MFA 22:1 (g)                             |
| F60MFAC | Dietary Total MFA (g)                            |
| F60MFPCD| Percent Calories from MFA                       |
| F60NATOC| Dietary Natural Alpha-Tocopherol (mg)            |
| F60NIACN| Dietary Niacin (mg)                              |
| F60NICNEQ| Dietary Niacin Equivalents (mg)                  |
| F60OMGAC3| Dietary Omega 3 (g)                              |
| F60OMGAE6| Dietary Omega 6 FA (g)                           |
| F60OXALC| Dietary Oxalic Acid (mg)                         |
| F60PANTO | Dietary Pantothenic Acid (mg)                    |
| F60PECT | Dietary Pectins (g)                              |
| F60PF182| Dietary PFA 18:2, Linoleic Acid (g)              |
| F60PF183| Dietary PFA 18:3, Linolenic Acid (g)             |
| F60PF184| Dietary PFA 18:4 (g)                             |
| F60PF204| Dietary PFA 20:4 (g)                             |
| F60PF205| Dietary PFA 20:5, EPA (g)                        |
| Code     | Description                                      |
|----------|--------------------------------------------------|
| F60PF225 | Dietary PFA 22:5 (g)                             |
| F60PF226 | Dietary PFA 22:6, dha (g)                        |
| F60PFA   | Dietary Total PFA (g)                            |
| F60PFPCT | Percent Calories from PFA                       |
| F60PHNYL | Dietary Phenylalanine (g)                        |
| F60PHOS  | Dietary Phosphorous (mg)                         |
| F60PHYTC | Dietary Phytic Acid (mg)                         |
| F60POTAS | Dietary Potassium (mg)                           |
| F60PROLN | Dietary Proline (g)                              |
| F60PROT  | Dietary Protein (g)                              |
| F60PRPCT | Percent Calories from Protein                    |
| F60RETIN | Dietary Retinol (mcg)                            |
| F60RIBO  | Dietary Riboflavin (mg)                          |
| F60SELEN | Dietary Selenium (mcg)                           |
| F60SERIN | Dietary Serine (g)                               |
| F60SF100 | Dietary SFA 10:0 (g)                             |
| F60SF120 | Dietary SFA 12:0 (g)                             |
| F60SF140 | Dietary SFA 14:0 (g)                             |
| F60SF160 | Dietary SFA 16:0, Palmitic Acid (g)              |
| F60SF170 | Dietary SFA 17:0 (g)                             |
| F60SF180 | Dietary SFA 18:0, Stearic Acid (g)               |
| F60SF200 | Dietary SFA 20:0 (g)                             |
| F60SF220 | Dietary SFA 22:0 (g)                             |
| F60SF40  | Dietary SFA 4:0 (g)                              |
| F60SF60  | Dietary SFA 6:0 (g)                              |
| F60SF80  | Dietary SFA 8:0 (g)                              |
| F60SFA   | Dietary Total SFA (g)                            |
| F60SFPCT | Percent Calories from SFA                        |
| F60SODUM | Dietary Sodium (mg)                              |
| F60SOLFB | Water Soluble Dietary Fiber (g)                  |
| F60STOCO | Dietary Synthetic Alpha-Tocopherol (mg)          |
| F60STRCH | Dietary Starch (g)                               |
| F60SUCR  | Dietary Sucrose (g)                              |
| F60TF161 | Dietary Trans Fatty Acid, 161T (g)               |
| F60TF181 | Dietary Trans Fatty Acid, 181T (g)               |
| F60TF182 | Dietary Trans Fatty Acid, 182T (g)               |
| F60TFTOT | Dietary Total Trans Fatty Acid (g)               |
| F60THIAM | Dietary Thiamin (mg)                             |
| F60THREO | Dietary Threonine (g)                            |
| F60TRYPT | Dietary Tryptophan (g)                           |
| F60TSUGR | Dietary Total Sugars (g)                         |
| F60TYROS | Dietary Tyrosine (g)                             |
| F60VALIN | Dietary Valine (g)                               |
| F60VB12  | Dietary Vitamin B12 (mcg)                        |
| F60VEG   | Daily Vegetable Consumption (med portion)        |
| Variable  | Label                              |
|-----------|-----------------------------------|
| BMICX     | BMI Categorical                   |
| BMIX      | BMIX                              |
| DIAS      | Diastolic BP                      |
| DIASBP1   | Diastolic blood pressure (1st reading) |
| DIASBP2   | Diastolic blood pressure (2nd reading) |
| DIASTOL   | Diastolic BP                      |
| group21   | Antineoplastics                   |
| group24   | Estrogens                         |
| group24930| Estrogen & Progestin              |
| group26   | Progestins                        |
| group28   | THYROID                           |
| group32   | ANTIANGINAL AGENTS                |
| group33   | BETA BLOCKERS                     |
| group34   | CALCIUM BLOCKERS                  |
| group35   | ANTIARRHYTHMIC                    |
| group36   | ANTIHYPERTENSIVE                  |
| group37   | DIURETICS                         |
| group38   | PRESSORS                          |
| group39   | Antihyperlipidemic                |
| group40   | MISC. CARDIOVASCULAR              |
| group57   | Antianxiety Agents                |
| group58   | Antidepressants                   |
| group59   | Antipsychotics                    |
| group60   | Hypnotics                         |
| group64   | ANALGESICS - NONNARCOTIC          |
| group65   | ANALGESICS - NARCOTIC             |
| group72   | ANTICONVULSANT                    |
| HEMATOCR  | Hematocrit (%)                    |
| HEIGHTX   | Height cm                         |
| Code    | Description                          |
|---------|--------------------------------------|
| HIPX    | Hip circumference cm                 |
| PLATELET| Platelet count (Kcell/ml)            |
| PULSE30 | Resting pulse in 30 seconds          |
| SYST    | Systolic BP                          |
| SYSTBP1 | Systolic blood pressure (1st reading)|
| SYSTBP2 | Systolic blood pressure (2nd reading)|
| SYSTOL  | Systolic BP                          |
| WAISTX  | Waist circumference cm               |
| WBC     | White blood cell (Kcell/ml)          |
| WEIGHTX | Weight kg                            |
| WHEXPECT| Waist and Hip measurement expected   |
| WHRX    | Waist hip ratio                      |