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Using predictors of hormone therapy use to model the healthy user bias: how does healthy user status influence cognitive effects of hormone therapy?

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Abstract

Objective: This study investigated the phenomenon known as the healthy user bias by equating hormone therapy (HT) use (past or current) with healthy user status.

Methods: Data from the Survey of Midlife in the United States were used to identify the predictors of HT use. The unique Survey of Midlife in the United States data include psychological, demographic, health-related, and behavioral variables as well as history of HT use. Predictors of HT use were combined to derive propensity scores, describing the likelihood that a woman was an HT user, based on her psychological, demographic, physical, and behavioral profile (ie, likelihood of being a healthy user) as opposed to her actual use of HT. Finally, cognitive performance on an executive function test was examined in women stratified by propensity score.

Results: Using a multiple logistic regression model, nine variables emerged as predictors of HT use. The nine variables were used to estimate the propensity or conditional probability of using HT for each subject; resultant propensity scores were ranked and divided into tertiles. Women in the highest tertile demonstrated shorter median response latencies on a test of executive function than did women who did not use HT.

Conclusions: From an array of psychological, medical, and behavioral variables, nine emerged as predictors of HT use. If validated, these features may serve as a means of estimating the phenomenon known as healthy user bias. Moreover, these data suggest that the degree to which a woman fits a model of a healthy user may influence cognitive response to HT.

Key Words: Hormone therapy – Healthy user – Cognition – Menopause – Selection bias – Executive functioning.

Before the publication of findings from two Women's Health Initiative (WHI) ancillary studies, the WHI Memory Study[1-4] (WHIMS) and the WHI Study of Cognitive Aging[5] (WHISCA), it was widely believed that hormone therapy (HT) use could reduce a woman's risk of dementia by 50%.[6-8] This belief was predicated, in large part, on observational data from longitudinal case-control and cohort studies. In contrast, data from the large randomized controlled WHIMS and WHI Study of Cognitive Aging trials revealed adverse cognitive effects and increased risk of dementia for women age 65 years and older who were administered a widely used form of oral HT, conjugated equine estrogens. The phenomenon referred to as the healthy user bias was frequently cited as an explanation for the dramatic reversal in findings (eg, Barrett-Conner et al,[9] Prentice et al[10]). Specifically, the healthy user bias purports that women who use HT during the menopausal transition are systematically different (ie, healthier) than women who do not use HT; moreover, it is the fundamental differences between HT users and nonusers, not the exposure to HT, that results in HT's seemingly beneficial health effects, such as fewer cardiovascular risk factors and a reduced risk of dementia found in observational studies.

Although healthy user bias is thought to be a serious threat to study validity, contributing to past misconceptions about HT, it is only loosely and inconsistently operationalized as a research construct. The difficulty in defining healthy user bias may lie in the fact that the sources of bias are multifactorial. For example, behavioral features, such as exercising, not

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smoking, and regularly consulting with a medical provider and psychological features such as optimism, sense of control, and proactive behaviors are all alleged to be characteristics of a "healthy user." Another source of selection bias pertaining to healthy users is differences in access to HT, such that only healthy women who regularly visit a physician would be prescribed HT, whereas women in poor health, those already taking several medications, or those with a shortened life expectancy may be less likely to be prescribed a potentially protective medication. These features, along with the demographic characteristics of being well educated and in higher socioeconomic strata, culminate in a multifaceted picture of the healthy user, who is allegedly more engaged, physically fit, articulate, adherent to medical advice, and psychologically well than her nonuser counterpart.

Data from the Survey of Midlife in the United States (MIDUS) include psychological, behavioral, and demographic variables, as well as data on HT use from a large population-based sample. In combination, the data provide a unique opportunity to examine the multiple components theoretically associated with the healthy user construct. Using this comprehensive dataset, we characterized healthy user bias as it applies to women opting to use HT. In other words, the use of HT was equated with the healthy user phenomenon. In doing so, we attempted to define the demographic, personality, and behavioral characteristics of the healthy user by optimally identifying relevant predictors of HT use from a large pool of potential predictors. Variables predicting HT use (ie, healthy user status) were used in a subsequent analysis to develop a propensity score. The propensity score would then represent the likelihood of being a healthy user, regardless of whether a woman was actually using HT. We examined the cognitive performance of women after stratifying for healthy user status. Overall, we hypothesized that the characteristics indentified as predictors of HT use would coincide with the characteristics traditionally portrayed as features of healthy users. Moreover, we predicted that even after accounting for the healthier user status, the cognitive effects related to the use versus nonuse of HT would be evident.

METHODS

Participants

Data were obtained from the second wave of MIDUS data collection (MIDUS 2). The participants in this large population-based survey with metropolitan oversampling of noninstitutionalized, English-speaking adults are now aged 35 to 86 years. The intent of the MIDUS project is to investigate patterns, predictors, and consequences of midlife development using a comprehensive array of physical, psychological, and social indicators. The second wave of data collection, MIDUS 2, occurred between January 2004 and January 2006 and included a telephone interview, two self-administered questionnaires mailed, and cognitive testing by telephone. Details of methods used to ensure maximum follow-up are provided in an online manual.[11] From the original MIDUS sample (N = 7,108), 4,963 participants completed the telephone interview, resulting in a longitudinal retention rate of 70% (75% response rate when adjusted for mortality). Of the telephone respondents, 81% (n = 4,032), returned the two self-administered questionnaires and 85% (n = 4,205) completed the 45-minute telephone cognitive testing. Altogether, a variety of data were collected, including information on demographics, psychological and physical health status, cognition, lifestyle choices, attitudes, and health-related behaviors. Further information on the MIDUS 2 sample and study methods is available at the study's data Web site.[12]

Groups: report of menopause status and HT exposure

The study analyses presented here included only postmenopausal women with complete menopause status and HT exposure data. Although the MIDUS 2 study was not specifically designed to assess women's history of HT use, the responses on self-administered questionnaires were used to determine women's menopause status and exposure to HT. If a respondent indicated that she had stopped menstruating in the last year, she was asked to select a reason from a list of choices (eg, menopause or hysterectomy) and to provide the approximate year of her last menstrual period. To clarify perimenopause status, the women were asked about the regularity of their menstrual periods and whether they experienced menopausal symptoms. Women next reported their current or past use of HT. If they had used HT, they indicated their reasons for taking the medication using a list of options and provided the dates of initiation and (if applicable) discontinuation of the medications. These data were systematically interrogated to ensure that women were accurately categorized, such that any inconsistencies in the participants' reports were identified and clarified through a review of their responses in total.

Based on their responses, postmenopausal women were categorized into three main groups: Never Users (n = 782), Past Users (n = 506), or Current Users (n = 315). Figure 1 describes the subject selection process. The exclusion of study participants with missing data (described in Fig. 1) resulted in a final analytical sample size of 1,189 for the multivariate logistic analyses.

Measures

Variables were selected for possible inclusion in the model predicting HT use if previous published analyses (1) included a variable as a confounder or covariate in analyses (eg, body mass index, smoking, vitamin use, or diabetes[13]) or (2) revealed the variable to be predictive of HT use (eg, level of exercise[14] or socioeconomic status[15]). In addition, some variables were included based on a well-justified but hypothesized relationship to the healthy user phenomenon (eg, psychological well being). We intended the first stage of variable selection to be highly inclusive. All variables considered for inclusion are listed below and described in detail in Supplementary Table A (See Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A14). Of note, for the present study, our primary interest was to identify variables predicting HT use, not to obtain estimates of the population values for

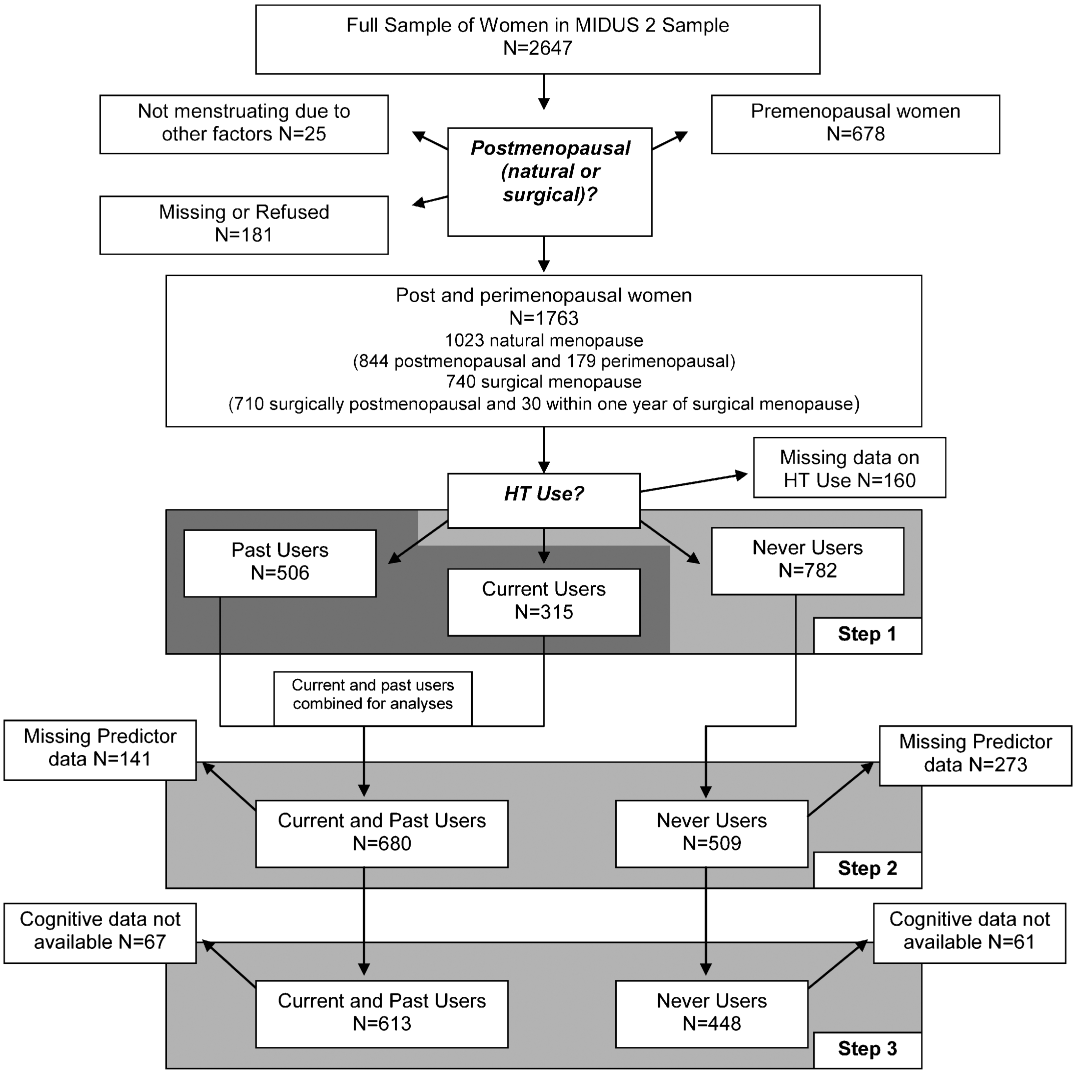

FIG. 1. Selection of participants included in the current analyses. The sample is from MIDUS 2 data set, which includes approximately 70% of MIDUS 1 participants. In step 1 of analysis, 49 potential predictors were tested individually for univariate association with HT use (n = 1,603). In step 2, 26 predictors surviving univariate analysis were entered in combination into multiple logistic regression models to predict HT use (n = 1,189). Based on resultant model HT use propensity scores, meant-to-quantificate healthy user traits were derived for every subject. The participants were grouped into tertiles, representing the degree to which participants resembled an HT user (ie, a "healthy user"). In step 3, the cognitive abilities of the three tertiles of women were examined. MIDUS, Survey of Midlife in the United States; HT, hormone therapy.

these variables. Therefore, our analyses did not use case weights to correct for differential selection probabilities and nonresponse.

Demographic and anthropometric variables

Demographic data included age, marital status, highest level of education completed, self-identify ethnicity (Hispanic vs non-Hispanic), and race. For analyses, white and Asian participants were combined and compared with black/African American, Native American, and self-described "Other" racial category. Socioeconomic status was estimated using a log-transformed reported household annual income (log income). Anthropometric data included body mass index and waist-to-hip ratios. Further details regarding these variables are provided in Supplementary Table A (see Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A14).

Psychological and personality variables

A range of variables measuring psychological and personality characteristics, either empirically or theoretically linked to healthy user bias were selected for inclusion in the model predicting HT use. Each is described in Supplementary Table A (See Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A14). Briefly, these variables evaluated a participant's perceived control over her health (health locus of control [HLOC]; HLOC-Self and HLOC-Others),[16] her sense of agency or perceived control,[17] self-described level of conscientiousness,[17] optimism,[18] and self-esteem.[19] In addition, six variables from the Psychological Well-Being Scale[20] were included: Autonomy, Environmental Mastery, Personal Growth, Positive Relations, Purpose in Life, and Self-Acceptance. Although there is correlation between the six Psychological Well-Being scales, factor analyses demonstrate that they measure distinct constructs.[20,21] Moreover, the scales differentially associate with biological processes.[22]

Mood, level of satisfaction, and self-evaluation of health

Mood and outlook characteristics of participants were considered in the model. Described in Supplementary Table A (See Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A14), the specific variables included positive and negative affect subscales from the Positive and Negative Affect Schedule,[23] depression and anxiety scores from the Composite International Diagnostic Interview–Short Form,[24] a rating of overall life satisfaction,[25] and a single item assessing self-evaluated physical health that has been shown to be a robust predictor of health outcomes.[26]

Health-related behaviors

Several variables assessing health-related behaviors were selected to evaluate the degree to which women engaged in health maintenance activities. These included a participant's use of vitamins and supplements; her access to or utilization of routine medical, dental, and optical care; her physical and mental activity; and her use of cigarettes and alcohol. Methods describing how each variable was derived are provided in Supplementary Table A (See Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A14).

Physical health and medical history

Indicators of current physical and past medical history were investigated as possible predictors of HT use (ie, healthy use bias). Details on how these were derived are provided in Supplementary Table A (See Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A14). Specifically, women's answers to questions about two common chronic conditions (high blood pressure and diabetes) were included in the model, along with the number of hospitalizations in the last year; the number of medications; an estimate of physical disability due to health; and history of stroke, myocardial infarction, head injury, or cancer.

Cognitive variables

The Brief Test of Adult Cognition by Telephone, having been found to demonstrate sound psychometric properties and to offer data equivalent to those obtained using face-to-face data collection, was administered to MIDUS 2 participants.[27] The battery consists of tests from five cognitive domains sensitive to age and illness-associated changes in cognition, including measures of verbal memory, working memory, executive function, reasoning, and processing speed. Although combined summary scores were available, we selected the only speeded executive function task to examine the potential effects of HT on cognition. As reported previously, evidence suggests that the cognitive effects of HT are not global but are rather domain specific.[28]

Therefore, the most challenging and only timed task administered was selected for analyses. The Stop and Go Switch Task (SGST) assesses the ability of participants to switch between two conditional tasks. Under the Normal response condition, participants were to say "go" in response to an examiner reading the word "green" and "stop" in response to the word "red." Conversely, under the Reverse condition, they were instructed to provide the opposite response: say "stop" to the word "green" and "go" to the word "red." Two single-task sets were administered initially, with the first being a Normal response condition and the second a Reverse response condition. A third set was administered with the conditions switching between Normal and Reverse at random intervals, referred to as a Mixed-Task set.

Four variables from the SGST test were selected for analyses: (1) median reaction time (RT) under the Normal condition (Normal RT), (2) median reaction time under the Reverse condition (Reverse RT), (3) median reaction time for Mixed-Tasks items wherein a condition switch occurred (Normal to Reverse or Reverse to Normal; referred to here as Mixed-Switch RT), and (4) median RT from the Mixed-Task trial wherein a condition switch did not occur (Mixed-Nonswitch RT). For each of the last two variables, Mixed-Switch RT and Mixed-Nonswitch RT, additional variables characterizing aspects of performance within each task were available for follow-up analyses. These included (1) the median reaction time from Normal and Reverse condition trials occurring immediately after a condition switch occurred (Mixed-Switch Normal Switch RT and Mixed-Switch Reverse-Switch RT) and (2) median RTs from Normal and Reverse condition occurring without a switch in conditions (Mixed-Switch Normal Nonswitch RT and Mixed-Switch Reverse Nonswitch RT).

Statistical methods

Based on previous publications investigating the association between HT use and cognitive outcomes, 48 variables were selected as possible predictors of HT use (ie, potential qualities of a healthy user). As a first step in reducing the number of variables included in the analyses (step 1), each of the 48 potential predictors was examined individually for its univariate association with HT use (Never vs Past or Current Use). χ^2 tests were used to determine the statistical significance of the association between categorical variables and HT use. Univariate logistic regression models predicting HT use were selected to examine the statistical association between continuous predictors and HT use.

In the next stage of analysis, the P values associated with each univariate test were ranked, and variables with a significance level of $P \leq 0.10$ were selected for inclusion in multivariate logistic regression models to predict HT use (step 2), with the goal being to reduce the number of variables without overly limiting the number of potential predictors. Given the potential effect of multicollinearity on parameter estimation, we examined the strength of the associations among all pairs of candidate predictors using Pearson product-moment correlations. The magnitude of the correlations ranged from 0.002 to 0.764. To minimize multicollinearity effects and efficiently manage the large number of predictors in the model, we used SAS PROC SCADGLIM version 1.1

TABLE 1. *Participant characteristics by hormone therapy exposure*

Variables	Never user		Past user		Current user		Combined past and current users		Significance: never users vs past or current users:
	N		N		N		N		*P*
Demographic and anthropometric variables									
Age, mean (SD), y	782	59.8 (11.2)	506	62.7 (9.1)	315	59.5 (9.4)	821	61.5 (9.3)	0.01
Education, high school degree or higher, n (%)	782	704 (90.0)	505	472 (93.5)	314	285 (90.8)	819	757 (92.4)	0.40
Marital status, married, n (%)	781	455 (58.2)	506	319 (63.0)	315	220 (69.8)	821	539 (65.7)	0.01
Annual household income, mean (SD), thousands	782	65.7 (51.5)	506	69.0 (51.7)	314	73.3 (53.5)	820	70.7 (52.4)	0.06
Race, nonwhite, n (%)	777	77 (9.9)	505	27 (5.3)	314	18 (5.7)	819	45 (5.5)	<0.01
Body mass index, mean (SD), kg/m^2	740	28.1 (6.7)	475	27.7 (6.2)	295	27.1 (5.1)	770	27.4 (5.8)	0.04
Waist-to-hip ratio, mean (SD)	713	0.9 (0.1)	468	0.8 (0.1)	291	0.8 (0.1)	759	0.8 (0.1)	0.01
Psychological and personality variables									
Optimism, total of responses,[a] mean (SD)	779	22.8 (5.1)	502	23.7 (4.8)	314	23.7 (4.9)	816	23.7 (4.8)	<0.01
Self-esteem, total responses,[a] mean (SD)	779	36.7 (7.7)	501	38.0 (7.4)	315	37.9 (7.5)	816	37.9 (7.4)	<0.01
Autonomy,[b] total responses,[a] mean (SD)	781	37.0 (7.3)	505	36.2 (7.2)	315	36.1 (7.1)	816	36.2 (7.1)	0.03
Environmental mastery,[b] total responses,[a] mean (SD)	781	37.6 (7.8)	505	38.2 (7.6)	315	38.3 (7.9)	816	38.2 (7.7)	0.10
Personal growth,[b] total responses,[a] mean (SD)	781	38.3 (7.3)	505	39.2 (6.6)	315	39.1 (7.3)	816	39.2 (6.9)	0.02
Positive relations,[b] total responses,[a] mean (SD)	781	41.2 (7.1)	505	42.2 (6.4)	315	41.8 (6.9)	816	42.0 (6.6)	0.02
Purpose in life,[b] total responses,[a] mean (SD)	781	37.7 (7.2)	505	38.8 (6.8)	315	38.9 (7.0)	816	38.8 (6.9)	<0.01
Self-acceptance,[b] total of responses,[a] mean (SD)	781	37.5 (8.8)	505	38.3 (8.2)	315	38.4 (8.2)	816	38.4 (8.2)	0.05
Mood, level of satisfaction, and self-evaluation variables									
Life satisfaction, response,[a] mean (SD)	782	7.6 (1.7)	506	7.7 (1.6)	315	7.8 (1.6)	821	7.8 (1.6)	0.04
Self-rated health, rating health as good or higher, n (%)	782	646 (82.6)	506	432 (85.4)	315	270 (85.7)	821	702 (85.5)	0.10
Health-related behaviors									
Reports regular use of multivitamins, n (%)	782	420 (53.7)	506	346 (68.4)	315	219 (69.5)	821	565 (68.8)	<0.01
Reports regular use of Vitamin C, n (%)	782	195 (24.9)	506	168 (21.5)	315	90 (28.6)	821	258 (31.4)	<0.01
Reports regular use of calcium, n (%)	782	315 (40.3)	506	310 (61.3)	315	185 (58.7)	821	495 (60.3)	<0.01
Reporting 1-2 physical exams per year, n (%)	584	321 (55.0)	483	308 (63.8)	283	179 (63.3)	766	487 (63.6)	<0.01
Reporting 1-2 dental exams per year, n(%)	566	341 (60.2)	466	332 (71.2)	276	201 (72.8)	742	533 (71.8)	<0.01
Reporting 1-2 eye exams per year, n (%)	557	301 (54.0)	459	287 (62.5)	265	165 (62.3)	724	452 (62.4)	<0.01
Frequency of mental activities, score,[a] mean (SD)	762	16.6 (5.3)	494	17.5 (5.0)	306	17.2 (5.1)	800	17.4 (5.0)	<0.01
Reporting light to moderate alcohol use, n (%)	746	593 (79.5)	492	418 (85.0)	308	253 (82.1)	800	671 (83.9)	0.04
Physical health and medical history									
With experience or has received treatment of diabetes, n (%)	782	91 (11.6)	506	50 (9.9)	315	17 (5.4)	821	67 (8.2)	0.02
Physical limitations, score,[a] mean (SD)	742	18.2 (8.3)	487	18.7 (8.4)	306	19.1 (8.8)	793	18.9 (8.5)	0.10
No. prescription medications, mean (SD)	748	1.7 (1.9)	486	2.1 (1.7)	308	2.8 (1.7)	794	2.3 (1.7)	<0.01

Table includes 26 variables considered to be potential predictors of HT use. For categorical variables, *P* values were derived using regression models predicting HT use (never user vs past or current user); χ^2 models were used for categorical variables. Age and education for the groups are also provided.
HT, hormone therapy.
[a]Higher scores indicate higher levels of the variable being measured.
[b]Scale from the Psychological Well-Being Inventory.

(http://methodology.psu.edu) as a variable selection method for the multiple-logistic (or generalized linear) model.[29] This automated variable selection procedure uses a penalized likelihood approach known as the smoothly clipped absolute deviation (SCAD) estimator to adjust the likelihood function. The SCAD penalty is the preferred selection process in the presence of collinearity and highly dimensional data compared with other penalized regression approaches such as the least absolute shrinkage and selection operator and ridge regression.[30] The Bayesian information criterion was used as a criterion for final model selection.[31] We also examined model sensitivity, specificity, and receiver operating characteristic curves to interpret results.

Finally, using the prediction model derived in step 2, we estimated the propensity or conditional probability of using HT for each subject given a vector of relevant covariates. The resultant propensity scores (ie, probabilities were ranging from 0 to 1) were ranked and subdivided into tertiles. In an exploratory analysis, the cognitive performance for women in each of the tertiles was examined by regressing cognitive scores on HT use status while covarying for age and education level (step 3).

RESULTS

Of the 1,603 postmenopausal or perimenopausal women included in step 1 analysis, 982 (61.3%) had undergone or were currently experiencing natural menopause. Conversely, 621 (38.7%) women reported undergoing surgical menopause. The mean age of the women included in the step 1 analysis was 60.7 (SD, 10.3) years. All but 8.7% of the participants completed at least a high school education. In general, the participants exhibited low levels of depression and anxiety symptoms, rated their health as good to excellent, and viewed themselves as conscientious and optimistic. Table 1 provides a summary of the sample characteristics in HT users, including the groups past and current users and never users.

Univariate analyses conducted with 48 candidate variables suggested that 26 characteristics of the sample were predictive of HT use when examined alone (step 1). Table 1 summarizes each of the 26 variables, as well as the age and educational status of participants, including variable sample sizes, prevalence (for categorical variables), means (for continuous variables), and the *P* values obtained in the univariate tests. Supplementary Table B (Supplemental Digital Content 2, http://links.lww.com/MENO/A15) lists the same information for the 22 variables not selected as predictors of HT use (ie, *P* of univariate analyses > 0.10). Notably, the age of users (current and past) differed from that of nonusers. Although the difference was statistically significant, this variable was not included in predictor models because it was thought to reflect a cohort difference. Specifically, older women were more likely to be past users as opposed to current or never users probably because women well past menopause were encouraged to discontinue HT after the WHI findings were published.

When the 26 candidate predictors were entered into a multiple logistic regression model predicting HT use, using the SCAD variable selection approach, the best model (Bayesian information criterion, 1,262) produced nine statically significant predictors of group membership (Never User vs Past or Current User). Table 2 lists the variables surviving step 2 analysis. Overall, the area under the curve obtained when the nine variables listed in Table 2 were used to predict HT use (Never vs Past or Current) was 0.73.

Finally, cognitive variables measuring speeded executive function were examined in combination with HT propensity scores. Women's likelihood of using HT was characterized as either a low, medium, or high propensity to be an HT user (ie, a healthy user). Women in the low and middle ranges demonstrated no significant difference in their performance on the SGST variables. However, women in the highest tertile (ie, women embodying the healthy user characteristics) demonstrated shorter median response latencies on the SGST Mixed-Switch trials than did women who did not use HT. Table 3 lists the median response times and *P* values for cognitive task comparison between HT users and never users in the highest stratum of propensity scores. A follow-up comparison of the type of switch task that occurred revealed that past or current users of HT were faster than never users on tasks requiring them to switch from the Reverse condition to the Normal condition. Their performance when switching from the Normal condition to the Reverse condition was not different based on HT use.

DISCUSSION

From a list of candidate variables describing a variety of psychological, behavioral, mood, and health status characteristics, nine participant features emerged as predictors of HT use. Specifically, HT users were more likely to be white or Asian, had higher incomes, had lower waist-to-hip ratios, received regular physical exams (1-2 per year), were likely to use

TABLE 2. *Nine variables predicting hormone therapy use*

Variable	β	SE	*P*	Odds ratio
Demographic and anthropometric variables				
Race				
White and Asian groups combined (R)				
African American	−1.26	0.39	<0.01	0.29
Other	0.00	0.34	1.00	1.00
Waist-to-hip ratio	−2.36	0.85	0.01	0.09
Annual household income	0.22	0.07	<0.01	1.24
Psychological and personality variables				
Self-esteem	0.03	0.01	<0.01	1.03
Autonomy	−0.04	0.01	<0.01	0.97
Mood, level of satisfaction, and self-evaluation variables				
Health-related behaviors				
Reports regular use of calcium	0.78	0.13	<0.01	2.18
No. physical exams per year				
0 routine visits/y (R)				
1-2 routine visits/y	0.83	0.21	<0.01	2.29
3 routine visits/y or more	0.74	0.23	<0.01	2.09
Physical health and medical history				
Diabetes, experience or treated for condition	−1.00	0.22	<0.01	0.37
No. prescription medications	0.36	0.05	<0.01	1.44
Constant	−1.65	1.20	0.17	0.19

Twenty-six variables were entered in multiple logistic regression models predicting HT use (never vs past or current). Using SAS PROC SCADGLIM Version 1.1 (http://methodology.psu.edu) as a variable selection method, nine variables were associated with HT use. These variables were used to derive propensity scores.
R, Reference category of the variable; HT, hormone therapy.

TABLE 3. *Results of the regressions of cognitive task performance (SGST) on HT use for the upper tertile of propensity to be an HT user/healthy user (ie, women possessing characteristics of HT users)*

	β	SE	t	P
A. Four global performance scores				
Median reaction time under the Normal condition (Normal RT)				
Constant	0.891	0.332	2.680	0.008
Age	0.008	0.005	1.642	0.101
Education	0.002	0.018	0.110	0.913
HT use	**−0.181**	**0.102**	**−1.782**	**0.085**
Median reaction time under the Reverse condition (Reverse RT)				
Constant	0.856	0.088	9.684	<0.001
Age	0.004	0.001	2.972	0.003
Education	−0.012	0.005	−2.650	0.008
HT Use	**−0.028**	**0.027**	**−1.030**	**0.304**
Median reaction time from the Mixed-Task trial wherein a condition switch did not occur (Mixed-Nonswitch RT)				
Constant	0.877	0.080	10.930	<0.001
Age	0.004	0.001	3.372	0.001
Education	−0.012	0.004	−2.833	0.005
HT Use	**−0.026**	**0.025**	**−1.042**	**0.298**
Median reaction time for Mixed-Tasks items wherein a condition switch occurred (Mixed-Switch Normal to Reverse or Mixed-Switch Reverse to Normal)				
Constant	0.917	0.178	5.140	<0.001
Age	0.009	0.003	3.573	<0.001
Education	−0.013	0.009	−1.320	0.188
HT Use	**−0.132**	**0.055**	**−2.416**	**0.016**
B. Subsets of performance scores for Mixed-Task switch tasks				
Median reaction time for Mixed-Tasks items wherein the condition switched from Reverse to Normal (Mixed-Switch Normal switch RT)				
Constant	0.812	0.261	3.114	0.002
Age	0.014	0.004	3.650	<0.001
Education	−0.004	0.014	−0.299	0.765
HT Use	**−0.198**	**0.079**	**−2.492**	**0.030**
Median reaction time for Mixed-Tasks items wherein the condition switched from Normal to Reverse (Mixed-Switch Reverse switch RT)				
Constant	0.661	0.061	10.837	<0.001
Age	0.004	0.001	5.117	<0.001
Education	−0.007	0.003	−2.273	0.024
HT Use	**−0.022**	**0.019**	**−1.161**	**0.246**

Women in the highest tertile were likely to be white or Asian, have lower waist-to-hip ratios and higher household income, report higher self-esteem but lower sense of autonomy, use calcium supplements regularly, take more prescription medications, and get regular physical exams and were less likely to have diabetes compared with women in lower propensity score tertiles.
Bolded values highlight the comparison of interest.
Part A shows the results of regressions on four parameters of SGST performance.
Part B describes the results for regression on two subsets of trials for the Mixed-Switch conditions.
SGST, Stop and Go Switch Task; RT, reaction time; HT, hormone therapy.

calcium supplements, and were less likely to have diabetes than women who never used HT. HT users reported slightly more use of prescription medications than nonusers (mean of two to three medications compared with 1.7 in nonusers). In addition, HT users in our study exhibited higher self-esteem and reported a small but significantly lower level of autonomy than nonusers.

HT use, more than the use of other medications, has been proposed as a marker for the phenotype referred to as the healthy user (eg, Barrett-Conner et al,[9] Prentice et al[10]). For this reason, being an HT user was equated in this study with being a healthy user. These analyses were motivated by concerns that any association between HT use and cognitive function in postmenopausal women may be artifacts of the healthy user bias (ie, HT users are reported to be psychologically and physically healthier and to have better access to preventative care and are more likely to engage in healthy behaviors than nonusers); as such, the superior cognitive performance of HT users was attributed to selection bias rather than the direct effects of HT use. In contrast, our results suggest that women possessing the characteristics of a "healthy user" who used HT demonstrated an advantage on an executive functioning task over similar women who never used HT. If confirmed, these data suggest that HT confers beneficial cognitive effects but only for women in optimal health.

A number of previous studies have examined how HT users differ from nonusers. For example, women who used HT in the Nurses' Health Study were at lower risk for cardiovascular events (ie, myocardial infarction and death due to coronary heart disease). However, they were also thinner, ate healthier diets, engaged in more exercise, and used less alcohol than women who did not use HT.[32] Other studies specifically examined how HT users and nonusers differed, consistently reporting that women prescribed HT at menopause were less obese, more physically active, and better educated and, in contrast with the Nurses' Health Study findings, were more likely to use alcohol.[33,34] Also influencing the likelihood of being an HT user was age, type of menopause (surgical vs natural), and the diagnosis of osteoporosis, with users being younger and more likely to have experienced surgical menopause and to carry a diagnosis of osteoporosis.[33] Similar relationships between HT use and demographic and behavioral characteristics emerge when European cohorts were examined. Although less commonly prescribed in European countries, HT use was positively associated with education, socioeconomic status, nulliparity or lower birth rates, nonimmigrant status, lower body mass index, better diet, regular exercise, surgical menopause, and osteoporosis.[35-37] Interestingly, the characteristics of user and nonusers did not appear to change markedly after the publication of data suggesting HT was potentially harmful for cardiovascular health.[38]

The emerging story that women who were prescribed HT were systematically different than never users led Matthews et al[39] to ask whether users were indeed healthier than nonusers. In other words, a selection bias occurs in HT prescription practices, such that women using HT fit a profile of a healthy user. Unlike other studies describing the HT user, Matthews et al[39] were able to include both health and psychological factors in their investigation and found that HT users exhibited healthier cardiovascular risk profiles before HT use, described themselves as possessing type A personality features, and were more likely to be aware of and to express their emotions, motives, and symptoms of stress.

Although a number of studies examined characteristics of HT users, none had access to the wide array of psychological, personality, demographic, and health status variables available in the MIDUS data set. Given the richness of the MIDUS data, we may be able to more fully characterize the healthy user bias by examining a greater variety of potential characteristics of HT users than past studies examining a more limited set of predictors.

Overall, the findings of the present analyses portray a similar profile of HT users as that of Matthews et al.[39] For example, compared with nonusers, women in the MIDUS study who used HT had higher incomes, were more likely white or Asian, had lower waist-to-hip ratios, and reported higher self-esteem. Consistent with their being healthy, HT users in our study received regular physical exams (one to two per year), were likely to use calcium supplements, and were less likely to have diabetes than women who never used HT. Perhaps because of their regular medical care, HT users reported more use of prescription medications than nonusers. Another finding contrasted earlier reports; specifically, HT users in our study reported a small but significantly lower level of autonomy than nonusers. These data were collected shortly after the publication of the WHI findings,[40] and the time periods of HT use or nonuse reported by respondents straddle the dates of the WHI publications. The finding that women prescribed HT describe themselves as less autonomous than nonusers may reflect a reaction to shifts in public perception of HT, such that women describing themselves as autonomous addressed their menopausal transition by opting not to use HT.

Another aspect of the current study involved using the nine variables predictive of HT use to develop healthy user propensity scores for each subject. In doing so, we were able to characterize the propensity of individual women to be HT users or healthy users, regardless of whether they used or did not use HT. Per our theory, women with high propensity scores possess more of the qualities of a healthy user than do women with low propensity scores. An exploratory analysis, comparing cognitive performance on a demanding executive function task suggested that only women possessing more qualities of the healthier user may demonstrate cognitive differences based on their HT exposure. Specifically, the difference in performance was noted on the SGST. Women were instructed that they were to provide either concordant (normal) or discordant (reverse) responses to the stimuli “Stop” and “Go,” saying either “red” to stop or “green” to stop depending on the instructions (normal vs reverse). In sets that required women to switch between the normal and reverse conditions (mixed-task), women who were past or current users of HT responded faster than nonusers when a switch occurred. The advantage in speed appeared to occur when the switch involved moving from the more difficult condition (reverse switch) to the easier condition (normal switch).

The current study’s limitations need to be acknowledged. First, it may be inaccurate to equate the healthy user with an HT user. Although related, the two concepts probably diverge in some regards. For example, HT use would describe only female healthy users, and it may not apply to non-US and non-European populations or to selected subgroups within these primarily white affluent cultures, where medical care is relatively easily accessible. Importantly, this cross-sectional analysis does not imply a causal relationship between HT use and healthy user variables, only an association. Another limitation was the large number of participants who were missing data for one or more of the 26 variables included in the propensity models (step 2 of analyses; Fig. 1). More than 400 women were excluded for this reason, most of whom were never users. This would also limit the generalizability of our models and may have reduced the power to detect the relationships between the variables and HT use. There may be biases introduced by selection of only a subset of the MIDUS sample (ie, women for whom menopause status and HT use were available). Finally, the analysis of cognitive data was considered exploratory, and *P* values were not corrected for multiple comparisons. This increases the risk for type I error, such that the suggestion of cognitive benefits with HT may be inaccurate, reflecting spurious or random findings.

Still, the present study may help clarify the contradictory findings regarding HT use, cognitive function, and risk for dementia. As noted, it was once widely believed that HT use could reduce a woman’s risk for dementia by up to 50%.[6-8] In sharp contrast, the findings from WHIMS[1-4] suggested cognitive harm and increased risk for dementia. To clarify the contradiction, some proposed a theoretical “critical window” during which HT needed to be applied in order to be protective (eg, Resnick and Henderson,[41] Sherwin[42]). Specifically, in observational studies, most use of HT occurred at or shortly after menopause, as opposed to initiating use after a decade or more of no exposure to hormones (endogenous or exogenous), as was the case for many WHI participants. As per the critical window hypothesis, use outside the critical time frame around menopause could have no effect or could in fact be harmful. The data from the present study suggest an additional explanation. Specifically, the beneficial effects of HT may be sufficiently small, such that illnesses like diabetes and lifelong exposure to stress and poverty overwhelm any potential benefit of HT medications. On the other hand, for women in good health, whose socioeconomic status and psychological health are optimized, HT may confer some cognitive benefits.

There is less equivocation about the biological effects of endogenous hormones compared with exogenous HT. For example, cardiac event rates are low in premenopausal women; however, the rates rise dramatically after menopause.[43] Similarly, an earlier age of menopause is associated with increased risk of dementia in women with Down syndrome.[44] The confusion regarding exogenous hormones administered as HT highlights the pressing need to reconcile the contradictory science regarding the neurobiological and cognitive effects of menopausal HT. In the meantime, dramatic reversals followed by continued equivocation in scientific opinions have left women confused and mistrustful about any reports on the neurobiological effects of HT. The present study offers insight as to how the healthy user bias might be defined and how these intrinsic differences between HT users and nonusers could influence the potential cognitive benefits of HT. Continued exploration of the healthy user bias and other key differences between observational and clinical trial data (eg, when in relation to menopause did HT exposure occur) is needed to address and overcome the inconsistencies in findings.

CONCLUSIONS

The present study offers insights into the nature of the healthy user bias and how this influential factor may have contributed to past misconceptions about HT. By equating the concepts of HT user and healthy user, this study offers a means to estimate a person's propensity to be a healthy user. These data suggest that the degree to which a person fits a model of healthier user status may influence cognitive response to HT.

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