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Cognitive Benefits of Hormone Therapy: Cardiovascular Factors and Healthy User Bias

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Abstract

Objective—The Women's Health Initiative study (WHI) and its ancillary Memory Study (WHIMS) revealed increased rates of cardiovascular risk, cognitive decline and dementia with opposed conjugated equine estrogens (CEE). As a result, previously accepted observational data suggesting cardiovascular and cognitive benefits and reduced risk for dementia with hormone therapy (HT) were largely attributed to 'healthy-user' bias. The present observational, community-based, case-controlled study examined the 'healthy-user' bias theory by comparing cognitive task performance in two groups of postmenopausal women, who were either HT users or non-users.

Design—Participants were 213 non-demented, postmenopausal women residing in the community and in assisted-living facilities who completed a self-report health questionnaire and underwent a one hour cognitive test battery. To study the independent contribution of variables in the prediction of cognitive performance, we employed a series of hierarchical regression models adding terms in three stages. The first stage included only HT, the second stage added demographics, and the last stage added alcohol, depression and a cardiovascular risk factor (CVRF) composite derived from a confirmatory factor analysis. The CVRF composite consisted of: stroke, diabetes, hypertension, and hypercholesterolemia.

Results—Although independent samples t-tests revealed no statistically significant differences in the CVRF composite and its individual components between the two groups, HT users tended to possess fewer CVRF than non-users. Conversely, HT users were younger and more educated than non-users. HT users outperformed non-users on 7/9 cognitive variables. The full regression model controlling for CVRF, demographic variables, and mood showed HT users outperformed non-users on measures of verbal memory and abstract reasoning.

Conclusions—While there is some evidence HT users possess fewer preexisting CVRF than non-users, the observed positive association between HT and cognition is not completely explained by this trend.

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Keywords

Hormone Therapy; Estrogen; Healthy User Bias; Cardiovascular Risk; Cognition; Alzheimer's disease

Introduction

Basic science, observational and clinical research has suggested that hormone therapy (HT) may prevent cognitive decline associated with Alzheimer's disease (AD) in postmenopausal women [1,2] (see Miller et al. [3] Hogervorst et al. [4,5] Fillit [6], and Rossouw [7]) for reviews. In contrast, the Women's Health Initiative (WHI) and the Women's Health Initiative Memory Study (WHIMS) revealed increased, though not significant, rates of cardiovascular risk factors (CVRF) [8] and more frequent diagnoses of probable dementia among HT users, raising serious concerns about the long-term safety of both opposed and unopposed conjugated equine estrogen (CEE) [2,9]. Based on these results, prior observational and epidemiological reports linking perimenopausal HT to substantial cognitive benefits and improved CVRFs were attributed to the 'healthy-user' bias [10]. The 'healthy-user' bias rests on the premise that women who elect to undergo HT are more aware of their overall health than non–users, prompting HT users to be more proactive than non-users in regard to their healthcare. Thus, HT users are more likely to have a better CVRF profile at baseline, which then results in a preexisting cognitive advantage.

Many clinical and observational studies have reported women taking HT tend to exhibit more favorable demographic and CVRF characteristics than non - users. For instance, some studies have reported HT users are more highly educated and have a higher socioeconomic status than women who elect not to undergo HT [11]. Some of these studies also report HT users exhibit better levels of CVRF before HT administration and are less likely to be diabetic than women not taking HT [12]. Additionally, the 'healthy - user' bias postulates that HT users evidence cognitive benefits because these women are healthier, and thus, their overall health influences cognition as opposed to neuromodulatory effects of HT [11,13].

Although many studies make reference to the 'healthy-user' bias, few studies have directly investigated this issue and reports are conflicting. Matthews et al. conducted the first prospective, epidemiological study designed to address the 'healthy-user' bias hypothesis [14]. Matthews reported that women electing to use HT were better educated and had a healthier CVRF profile prior to HT treatment than women who subsequently did not use HT during the menopausal transition. Their results support the hypothesis that at least a portion of the apparent benefit associated with HT is due to preexisting characteristics of women who choose to undergo treatment. Other investigators argue that baseline differences in CVRF cannot explain the apparent beneficial neuromodulatory effects of HT. Barrett-Connor (1991) suggested cross-sectional differences in CVRF, such as total cholesterol, triglycerides and smoking, are not apparent when HT users and non-users are compared 15 years prior to HT administration [11]. Grodstein reported that there is little evidence for the 'healthy-user' bias hypothesis in studies examining the relation between HT and CVRF, cancer, osteoporosis, and venous thromboembolism [15]. Most recently, an observational study by Lokkegaard examining risk of myocardial infarction (MI) as a result of HT use concluded that, while there was not an overall relationship between MI and HT use, HT users aged 60 – 69 years exhibited a decreased risk of MI compared to HT non-users [16]. Thus, although the 'healthy-user' bias may not fully explain differences between HT users and non-users in observational studies, it is possible that studies investigating HT are susceptible to these biases.

The current case-control, observational study investigated the relationship between cognitive task performance and HT in a sample of postmenopausal women after controlling for mood, demographic variables, and health measures central to the 'healthy-user' bias. Given the non-randomized design, we employed we employed a series of hierarchical regression models adding terms in three stages to remove the possible correlation between the HT status indicator or "treatment" variable and the error term.

Methods

Participants

Participants consisted of 213 postmenopausal women ranging in age from 51 to 93 years (M=77.61, SD=8.44) with an average education of 14 years and an average MMSE score of 28.17. Participants took part in a free community dementia screening service called the Midwest INitiative for Dementia Screening (MINDS) Project, organized by the Wisconsin Comprehensive Memory Program (WCMP) at the University of Wisconsin-Madison. The MINDS population was comprised of older, assisted - living and community dwelling adults residing in southern Wisconsin, within a 140-mile radius of UW-Madison. Participants were recruited through flyers and advertisements posted throughout eight community centers and assisted-living facilities. Though not intended to provide a medical diagnosis, MINDS was designed to identify patients with dementia - related cognitive impairments and provide recommendations to participants' primary care physicians regarding specific methods to definitively diagnose such impairments.

Cognitive Tasks

The current observational study was a between - subjects design, and each participant was tested once. All cognitive test administrators were blind to participant information regarding medications and CVRF. Testing procedures were identical for all participants regardless of CVRF status or HT use. Cognitive tasks were selected based on prior evidence demonstrating sensitivity to fluctuating sex hormone levels and their ability to detect cognitive impairment.

The cognitive battery included tests assessing global cognition (Modified Mini-Mental State Examination (3MS) [17]), abstract reasoning (Cognistat Memory and Similarities Subscales [18]), verbal fluency [19], verbal memory (Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List [20]), and attention (Stroop Task [21]). Additionally, the Geriatric Depression Scale (GDS) was administered to assess potential association between HT and depression [22]. Cognitive tasks were administered by trained research coordinators.

Hormone Therapy and Cardiovascular Questionnaire

HT status was used to define two comparison groups: HT users vs. non - HT users. Information regarding current and past HT use, CVRF, and demographic information was collected using a self-administered health questionnaire. Questions concerning CVRF and HT status were dichotomous, asking for a 'yes' or 'no' response. Participants were directly asked about CVRF, including heart attack, cardiac arrest, atrial fibrillation, angioplasty, endarterectomy, stent, heart or neck bypass surgery, pacemaker, congestive heart failure, stroke, diabetes, hypertension, high cholesterol, and smoking. Specifically, CVRF questions read as follows: "Do you have, or in the past have you had, any of the following conditions or procedures" and HT questions read "Are you currently, or have you ever been on HT?" Current and former HT users were combined for analyses. Alcohol consumption was assessed based on the number of drinks consumed per week. Demographic questions such as current age and years of completed formal education had an open-ended format.

Outcome Measures and Predictor Variables

In all analyses, HT status was the predictor of interest. The cognitive outcome measures included scores on Cognistat similarities and memory tests, the total CERAD delayed recall score, total percent retention on the CERAD retention task and total CERAD score, the 3MS, and the number of items correctly identified on the 'color' and 'color–word' conditions of the Stroop task. The verbal fluency score was the number of exemplars in the category 'animals' produced in 60 seconds. For all tests, a higher score denotes better cognitive function. Covariates included demographic variables (age and education), GDS depression score, alcohol consumption, and the cardiovascular risk index described below.

Procedures

Assisted living facilities located in the vicinity of the University of Wisconsin were contacted and interested facilities hosted a large-scale, educational lecture for residents and older individuals residing in the community. The educational lectures were designed to raise awareness of AD and Mild Cognitive Impairment (MCI) symptoms and stress the need for early diagnosis and treatment. Immediately following the educational lecture, participants could sign–up for a voluntary, free–of–charge, neuropsychological assessment.

One to three days after the educational lecture, participants returned to the designated testing center to take part in the neuropsychological testing session. After giving informed consent, all cognitive tasks were administered to participants in private screening rooms.

Following the testing session, a clinical neuropsychologist specializing in dementia reviewed the participant's test results to determine the patient's degree of cognitive functioning, as compared to standardized age and education norms for each test [23]. The clinician met with each participant to explain test results and clarify that although test results were not equivalent to a diagnosis, they were an indicator as to whether further evaluation should be considered.

Analyses

To assess the influence of CVRF on cognitive performance, we computed a composite CVRF index incorporating all reported risk factor indicators. To study the dimensionality of four dichotomously-scored (1=Yes; 0=No) cardiovascular risk measures (stroke, hypertension, cholesterol, and diabetes), a confirmatory factor analysis (CFA) was performed. A matrix of tetrachoric correlations was submitted to analysis and a robust unweighted least-squares estimator was used to obtain a solution. As expected, a one-factor solution produced a good overall model fit (χ^2 =2.50, p =0.29). The root mean squared error (RMSEA), which should be less or equal to 0.05 for a good fit, was 0.025. The factor loadings were all statistically significant and ranged from 0.38 (stroke) to 0.70 (cholesterol). The estimated values of the factor score for individuals produced by the CFA solution was used as the cardiovascular risk predictor in all regression models. All CFA analyses were conducted using the LISREL program [24].

As a preliminary step, the data was inspected and regression diagnostics performed to check serious departures from normality and model violation assumptions. Next, we conducted independent samples t - tests to compare HT users and non-users for demographic characteristics, CVRF index, depression, alcohol consumption, and cognitive task performance. Finally, to examine the effect of HT use on cognitive performance and the additional contribution of demographics and morbidity to the model, a series of simultaneous hierarchical regression models were fitted adding predictors in the following three stages: (1) HT status; (2) HT, age, and education, and (3) HT status, age, education, cardiovascular risk, depression, and alcohol consumption. Significance tests were conducted using a 0.05 alpha

level. The statistical analyses performed in this step were conducted using Stata (Stata Statistical Software: release 8.0).

Results

A summary of the independent samples t - test results comparing HT users and non - users for demographic characteristics, CVRF and MMSE is presented in Table 1. Average age across all participants was 77.6 years and average education 14.2 years. Mean GDS scores were well within the non-depressed range (M = 2.28, S.D. = 2.35). HT users and non-users did not differ significantly on the CVRF index, although there was a trend for HT users to self-report fewer CVRF overall. HT users reported lower prevalence of stroke, hypertension, high cholesterol, and diabetes. An equally low occurrence of smoking was reported from both groups, while more HT users than non-users reported current alcohol use. Conversely, HT users and non - users differed significantly on measures of age (t = -2.35, p = 0.02) and education (t = 3.60, p = 0.001), such that HT users were younger and more educated than non-users.

Table 2 shows the results of the estimated hierarchical regression equations modeling the relation between cognitive task performance and HT while controlling for demographics, mood, alcohol consumption, and CVRF index variables entered into the model in three stages. The first stage shows that HT users outperformed non-users on 7 of 9 cognitive measures. The cognitive subscales favored HT users for each of the 5 cognitive domains assessed in the current study (verbal memory, verbal fluency, abstract reasoning, attention, and global cognition). HT made the largest contribution to the prediction model that included Cognistat Similarities (R^2 = 9%) and CERAD retention (R^2 = 4.1%) as outcomes.

The second set of analyses in Table 2 show that, as expected, demographics were strongly related to cognitive performance across all tasks. The proportion of variance in all the cognitive outcomes accounted for by the demographic variables (R^2 change) was statistically significant varying from 6.5% (with CERAD retention as outcome) to 18.4 % (STROOP color test as outcome).

Finally, after entering all covariates into the model, HT users and non - users remained significantly different on two cognitive outcome variables, the Cognistat similarities and CERAD retention, again favoring HT users. Adding CVRF and mood variables accounted for a smaller proportion of the total variability in the dependent measures. That is, R^2 change values ranged from an non-significant 1% (MMSE as outcome) to a statistically significant change of 13.3% with STROOP color-word as the outcome measure. The CVRF index was strongly related to both Stroop task measures, suggesting a link between cardiovascular health and improved attention. Alcohol use was also positively related to better cognitive task performance on 4 of 9 tasks, which is consistent with prior literature reporting individuals who consume moderate amounts of alcohol outperform non drinkers. Although there was not a statistically significant mean difference between HT users and non-users, GDS score was significantly associated with 5 of 9 cognitive task measures, indicating depression is positively correlated to poorer cognitive performance.

Discussion

A number of mid - life risk factors have been proposed as targets for early AD and dementia intervention. While controversial, a potentially modifiable, mid-life risk factor for women is the rapid loss of endogenous sex hormones occurring during the menopausal transition. Prior to the publication of the WHI study, it was widely believed that HT could significantly reduce a woman's risk for dementia. Supportive data derived from both basic science and

epidemiological evidence indicating HT could reduce the risk of AD by up to 50% (See[4,6, 11] [25,26] for reviews).

Despite this body of evidence, several investigators have suggested that cognitive performance differences between HT users and non - users can be attributed to the 'healthy-user bias' [12]. In other words, women who elect to take HT might be less likely to develop AD, not because of postmenopausal HT exposure, but because they have healthier preexisting lifestyles and fewer CVRF than non-users and thus, HT users will naturally outperform non-users on cognitive tasks. The main conclusion of the current observational, case-controlled study is that HT users and non-users differed significantly on cognitive measures associated with HT use after controlling for both demographics and CVRF. Benefits were observed on measures of abstract reasoning and verbal memory, both favoring HT users. These results challenge the opinion that observational data revealing cognitive benefits and reduced risk for dementia associated with HT use were solely attributable to the 'healthy-user' bias.

Current results support a wealth of basic science, observational and clinical research reporting improved cognitive performance with HT administration. Results are also consistent with our laboratory's previous reports that HT can favorably alter AD symptoms, such as improved cognitive functioning and increased hippocampal activation [27,28]. While there was not a statistically significant difference between HT users and non - users on CVRF at baseline, there was a between-group difference in education and age. This result is consistent with previous reports and may suggest that demographic factors such as age, education, and socioeconomic status might be more likely to influence the relationship between HT and cognition than CVRF [29,30]. Future research pertaining to the 'healthy-user' bias should differentiate between direct and indirect health measures, particularly in studies utilizing cognitive testing. The potential influence of demographic variables such as education and age on cognitive performance is likely different than the influence of CVRF such as cholesterol and blood pressure and merits separate consideration. Additionally, as suggested by Sherwin (2003), the 'healthy-user' bias is particularly problematic in studies of cognitive function and aging, because younger age and higher educational levels are themselves independent predictors of cognitive aging, and their effects could easily be confounded with a possible hormonal influence on cognition.

The current study does not support the 'healthy-user' bias hypothesis, in that the difference in cognitive task performance between HT users and non – users was entirely explained by preexisting CVRFs. However, results did suggest that some between group variability was influenced by demographic variables and CVRF. While this is likely a factor in virtually all observational drug studies, it is possible that CVRF play a unique role in the cognitive performance benefits associated with HT. While overwhelming evidence is not available from this study, we posit the potential influence of CVRF on cognitive task performance can occur as a result of HT, not only necessarily because of preexisting, between-group differences, and these affects could subsequently influence cognitive task performance.

A body of epidemiological and clinical research shows that in addition to cognitive benefits, HT imparts multiple cardiovascular benefits including increased HDL and decreased LDL cholesterol and reduced risk factors for atherosclerosis. The salutary effects of HT have also been implicated in protecting arterial wall function [31] and lowering blood pressure [31]. Thus, while differential preexisting health trends may exist between HT users and non-users, our data show the presence of preexisting CVRF does not explain the beneficial HT–cognition relationship. Further, to the extent that CVRF do affect cognition, it is difficult to differentiate between the effects of preexisting vs. coexisting, HT-induced effects in observational studies.

Present findings are not the result of an experimental design. The women in our study were not randomly assigned to treatment groups. However, the sample consisted of postmenopausal

women residing both in the community and in assisted-living facilities, which is a comprehensive sample of individuals likely to utilize the memory screening service. The current study does not differentiate between different types of HT or approximate duration of HT use. Additionally, proximity of HT administration to the menopausal transition is an important factor [32,33] not accounted for in this study, so we are not able to remark on this factor's potential effect. Also, because we were not able to differentiate between past vs. current HT users in the analyses, it is possible that the cognitive and vascular benefits of HT were diluted.

As this data was collected as part of a free community screening, HT use and CVRF measurements were based on self-assessments versus medical history reports and therefore cannot be corroborated. While self reports are less reliable than medical records [34], participants were likely able to accurately report history of HT use and disease. First, although our participants were older (average age 77.6 years) and some were residing in assisted living facilities, the average MMSE Score was 28.17 and did not differ between HT users and non-users, suggesting that 'dementia bias' (the underreporting of hormone therapy use in women with dementia) [35]] did not play a more significant role in our cohort than in other studies utilizing the self-report method. Furthermore, our data show that even participants who exhibit cognitive impairment (those women more likely to be HT non-users) were able to report vascular disease, such that they reported more risk factors than cognitively healthy participants (the majority of who are HT users). Education has been positively associated with the accuracy of self-reported chronic diseases, which may be particularly relevant to the current study because our sample is highly educated [36,37]. Moreover, recent reports, including those conducted with the WHIMS [38], support the use of self-report measures to ascertain ever estrogen exposure and medical reports in postmenopausal women [32,33].

Further research examining the influence of HT on cognition is needed to clarify the association between AD and menopausal HT. Studies assessing the impact of demographics and CVRF, both at baseline and after administration of study medication are also needed. On-going research projects are exploring the cognitive effects of HT at the menopausal transition and the impact of CVRF. The Kronos Early Estrogen Prevention Study (KEEPS) will be the first randomized clinical trial to evaluate the relationship between estrogen-induced changes in cognition and markers of heart disease, atherosclerosis, lipid metabolism, and thromboembolic disease in perimenopausal women. Furthermore the Kronos Early Estrogen Prevention Cognitive and Affective Study (KEEPS-CA), an ancillary study of the parent KEEPS, will characterize the differential effects of CEE and transdermal 17β estradiol on cognitive task performance and affect in perimenopausal women. Findings from the KEEPS and KEEPS-CA studies will provide critical information related to a number of issues raised by the WHI and will provide data central to the 'healthy-user bias' hypothesis by evaluating the cognitive implications of preexisting health conditions.

Acknowledgments

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Table 1

Independent Samples T-Test

Outcome Variables	Total (213)		HT Users (N=102)		Controls (N=111)		
	Mean	SD	Mean	SD	Mean	SD	t
Age	77.61	8.44	76.22	7.93	78.9	8.72	-2.35[*]
Education	14.23	3	14.98	2.93	13.54	2.9	3.60[**]
GDS	2.28	2.35	1.98	2.01	2.55	2.61	-1.78
Alcohol	0.32	0.47	0.36	0.48	0.29	0.46	1.16
Cholesterol	0.39	0.49	0.38	0.49	0.41	0.49	-0.34
Stroke	0.15	0.35	0.13	0.34	0.16	0.37	-0.72
Hypertension	0.51	0.50	0.46	0.50	0.55	0.50	-1.29
Diabetes	0.10	0.31	0.10	0.30	0.11	0.31	-0.24
Smoking	0.02	0.14	0.02	0.14	0.02	0.13	0.09
Cardiovascular Risk Index	0.01	0.24	-0.01	0.25	0.03	0.23	-1.07
MMSE	28.17	2.09	28.35	.20	28.00	0.19	1.51

[*] p < 0.05;

[**] p < 0.01

Table 2

Hierarchical Regression Models Predicting Performance

Predictor	Cognistat Memory			Cognistat Similarities			Retention CERAD			Total Learning CERAD			CERAD Delayed Recall		
	B	SE	R² Change	B	SE	R² Change	B	SE	R² Change	B	SE	R² Change	B	SE	R² Change
Intercept	8.820	.261		6.757	.145		66.260	2.756		18.883	.428		5.198	.234	
HT	.719	.376	0.02	.949**	.209	0.09	11.952**	3.982	0.041	1.372*	.619	0.023	.988**	.337	0.039
Intercept	14.772	1.761	.128**	5.613	.990	.097**	134.024	19.270	.065**	29.534	2.944	.096**	12.117	1.586	.116**
HT	.131	.371		.657**	.209		8.922*	4.066		.630	.621		.574	.335	
Age	-.110**	.022		-.015	.012		-.925**	.237		-.169**	.036		-.104**	.020	
Education	.203**	.062		.174**	.035		.383	.679		.200	.104		.094	.056	
Intercept	15.016	1.705	.071**	5.703	.986	.025	132.559	19.204	.026	30.056	2.814	.094**	12.151	1.558	.048**
HT	-.047	.361		.598**	.209		8.338*	4.062		.293	.595		.452	.330	
Age	-.105**	.021		-.013	.012		-.922**	.236		-.161**	.035		-.101**	.019	
Education	.182**	.061		.165**	.035		.460	.685		.192	.100		.084	.056	
GDS	-.247**	.074		-.079	.043		-.811	.829		-.544**	.121		-.159*	.067	
alcohol	.809*	.367		.267	.212		6.593	4.132		1.133	.605		.819*	.335	
cardio risk	-.665	.724		-.370	.418		13.364	8.148		.612	1.194		.172	.661	
Full Model R²			22%			21%			13%			21%			20%
f²			0.28			0.27			0.15			0.27			0.25

Predictor	STROOP Color			STROOP Color-Word			Fluency			MMSE		
	B	SE	R² Change	B	SE	R² Change	B	SE	R² Change	B	SE	R² Change
Intercept	59.811	1.524		27.423	1.049		16.685	.529		27.829	.195	
HT	3.013	2.202	0.01	4.233**	1.516	0.036	1.629	.764*	0.021	.710*	.283	0.029

Predictor	Cognistat Memory			Cognistat Similarities			Retention CERAD			Total Learning CERAD			CERAD Delayed Recall		
	B	SE	R² Change	B	SE	R² Change	B	SE	R² Change	B	SE	R² Change	B	SE	R² Change
Intercept	116.776	9.962	.184**	55.681			7.124		.117**	31.735	3.517	.153**	30.902	1.359	.077**
HT	-.262	2.102		2.180			1.503			.396	.742		.353	.287	
Age	-.843**	.123		-.457**			.088			-.256	.043**		-.062**	.017	
Education	.705*	.351		.575*			.251			.380	.124**		.133**	.048	
Intercept	119.074	9.395	.106**	56.789			6.616		.133**	31.838	3.501	.026	30.950	1.367	.010
HT	-1.391	1.987		1.358			1.399			.235	.741		.314	.289	
Age	-.797**	.115		-.420**			.081			-.248	.043**		-.061**	.017	
Education	.471	.335		.364			.236			.328	.125**		.138**	.049	
GDS	-1.439**	.406		-.875**			.286			-.131	.151		-.074	.059	
alcohol	4.244*	2.021		4.716**			1.423			1.265	.753		.109	.294	
cardio risk	-13.013**	3.986		-10.733**			2.807			-2.490	1.485		.499	.580	
Full Model R²	30%			30%			29%			20%			12%		
f²	0.43			0.43			0.40			0.25			0.13		

**
$p < 0.01$;

*
$p < 0.05$