

Longer Duration of Hormonal Contraceptive Use Predicts Better Cognitive Outcomes Later in Life

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Abstract

Background: The cognitive effects of postmenopausal hormone therapy (HT) have been studied extensively, but little is known about the relationship between premenopausal hormone use and cognition. Hormonal contraceptive use vs. nonuse may be a potential factor influencing cognitive processes in midlife. The aim of this study is to explore the effect of modification of hormone milieu through use of hormonal contraception in premenopausal women and midlife cognitive function.

Methods: Subjects were 261 cognitively normal women, aged 40–65 (mean $\mu=52$), enrolled in the Wisconsin Registry for Alzheimer's Prevention. All women completed the Women's Health History Questionnaire and a self-report health history questionnaire and were administered a battery of neuropsychologic tests. Cognitive results were analyzed using summary scores for the domains of Verbal Ability, Visuo-spatial Ability, Working Memory, Verbal Learning & Memory, and Speed & Flexibility derived using a confirmatory factor analysis.

Results: Hormonal contraceptive ever users performed significantly better than never users in the domains of Visuo-spatial Ability ($\mu=0.75$, 95% confidence interval [CI] 0.23-1.28, $p=0.005$) and Speed & Flexibility ($\mu=0.52$, 95% CI -0.16 -1.04, $p=0.007$), with duration-dependent increases in performance, especially in ever users with ≥ 15 years of use.

Conclusions: These data provide preliminary evidence that hormonal contraceptive use may influence cognitive outcomes, even years after use is discontinued. Hormonal contraceptive users scored better in domains of Visuo-spatial Ability and Speed & Flexibility than never users, with a duration-dependent trend. Further research is needed to explore the use of hormonal contraceptives to prevent or delay cognitive decline and to clarify the physiologic basis of this phenomenon.

Introduction

IN OUR AGING POPULATION, the incidence of Alzheimer's disease (AD) and dementia is increasing.^{1,2} The social and economic burden these diseases place on the healthcare system, patients, and family members makes them a significant public health concern.³ There is an urgent need for research focused on earlier recognition and prevention of these degenerative diseases in addition to continued efforts to develop new treatment strategies.

Some research has shown that hormone therapy (HT), specifically estrogen, can have a protective effect against the onset of dementia in women, depending on the type of therapy and age at the onset of use.⁴⁻⁶ However, a Cochrane review found that there is little evidence that estrogen or combined estrogen and progestin therapy protects against a decline in overall cognitive functioning of healthy older postmenopausal women.⁷ A substudy of the Women's Health

Initiative (WHI) looked at the effects of postmenopausal HT on a variety of outcomes, including cognition. In subjects receiving conjugated equine estrogens (CEE) plus progestin, an almost doubled risk of all-cause dementia was shown.^{8,9} Given that all the women enrolled in the WHI study were ≥ 65 years of age, some researchers have speculated that there is a critical period during menopause characterized by a relatively rapid estrogen decline, during which therapy must be applied in order to see cognitive benefits.¹⁰⁻¹²

Studies have begun to look at the link between premenopausal hormone use and cognition, specifically the use of hormonal contraceptives.^{13,14} Hormonal contraceptive use allows for the study of premenopausal women exposed to controlled levels of exogenous hormones, in contrast to those whose hormone levels vary naturally across the menstrual cycle. The various generations of contraceptive HTs employed different dosages and combinations of hormones.¹⁵ Little is known about the cognitive effects of these hormones,

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and further research is needed to explore the association between the history of hormonal contraceptive use and cognitive functioning in midlife and old age. Other factors that need to be evaluated include family history and apolipoprotein E4 (ApoE4) status and how these variables play a part in cognitive decline along with concurrent or past hormone use.

In this study, we sought to characterize the cognitive effect of manipulating ovulation through exogenous hormone exposure in women by modification of estrogen and progesterone levels. We hypothesized that this performance was duration dependent, with longer duration being correlated with better performance.

Materials and Methods

Study population

Institutional Review Board approval was obtained to do a cross-sectional review of 261 female subjects in the Wisconsin Registry for Alzheimer's Prevention (WRAP) database through the Wisconsin Alzheimer's Institute. Inclusionary criteria for the database required documented positive or negative parental history of AD. Subjects who met the parental history requirement for AD were between the ages of 40 and 65 and had a parent diagnosed with AD, either autopsy confirmed or verified through medical record review by a multidisciplinary diagnostic consensus conference. Patients enrolled without the parental history requirement were between the ages of 40 and 65 and had a mother who survived to age ≥ 75 and a father who survived to age ≥ 70 without evidence of dementia. All participants were volunteers who provided informed consent for study enrollment as well as cognitive testing.

Each participant completed an entry assessment that included neuropsychologic testing, ApoE genotyping (Athena Diagnostics, Worcester MA, and Atwood Lab, Madison, WI), and a health history questionnaire assessing demographics; medical and psychiatric status; self-reported history of cardiovascular, neurologic, psychiatric, and other major medical disorders; current medications; selected lifestyle variables (exercise, tobacco, and alcohol use); and depressive symptoms (20-item Center for Epidemiologic Studies-Depression scale [CES-D]).¹⁶ The content of the health history questionnaire was based on the questionnaire used in the WHI Memory Study.¹⁷ Potential participants were excluded if they had incomplete data on cognitive tests or hormonal contraceptive use or if they self-reported (1) stroke or probable dementia, (2) multiple sclerosis, (3) epilepsy/seizures, (4) meningitis, or (5) Parkinson disease. These criteria were intended to exclude conditions affecting cognition. To verify that patients with cognitive impairment were excluded, cognitive testing data were reviewed by the study investigators. All patients spoke fluent English.

Hormonal contraceptive use

Hormonal contraceptive use history and duration of use were obtained from the health history questionnaire, and users were categorized as ever users and never users.

Cognitive testing

Each WRAP participant completed neuropsychologic assessment at entry into the study. Patients completed a battery

of 17 cognitive tests designed to test a broad range of specific cognitive functions and affect. Patients were evaluated on an individual basis by a trained psychometrician. Tests included the Wechsler Abbreviated Scale of Intelligence, (WASI)¹⁸ Boston Naming Test,¹⁹ Controlled Oral Word Fluency,²⁰ Benton's Judgment of Line Orientation,²⁰ Wide Range Achievement Test-3rd ed. (WRAT-3)²¹ Auditory Verbal Learning Test,²² Wisconsin Card Sort-64,²³ Wechsler Adult Intelligence Scale (WAIS-3) Working Memory,²⁴ Trail Making Tests A and B,²⁵ and the Stroop Color Word Test.²⁶

Analysis

Outcomes of the cognitive testing were summarized into a five-factor structure. This structure compiles all administered tests by loading significantly high on a single factor (loading varied, in absolute value, from 0.09 to 0.95) (Fig. 1). The strength of the factor loadings suggested that each of the subscales effectively measured its respective construct. The magnitude of the correlations between the factors (0.26–0.55) indicated a high level of interconnectedness among measures. The confirmatory factor analysis accounts for 65.5% of the total variance among tests. This allowed the WRAP neuropsychologic test battery to be sorted into five multitest domains labeled Verbal Ability, Visuo-spatial Ability, Working Memory, Verbal Learning & Memory, and Speed & Flexibility. The confirmatory factor analysis allows a global measure of five factor domains to be used to represent a common trait of potential clinical relevance in studying cognitive aging.²⁷

Comparability of hormonal contraceptive ever users vs. never users was assessed based on age at screening, race, years of education, socioeconomic status (SES), depression, parental history of AD, self-rated health, hysterectomy, HT use, ApoE4 status, and parity using analysis of variance (ANOVA) models for continuous variables and chi-square analyses for categorical variables.

The primary comparison of interest was group (users and never users of hormonal contraceptives) differences on five cognitive factors. Secondary comparisons of interest were differences on the five cognitive factors between users and never users based on duration of hormonal contraceptive use using a grouping variable. Differences between groups were assessed using the two-sample multivariate analysis of covariance (MANCOVA) models. This statistic examines group differences on all dependent variables (differences on five cognitive factors) simultaneously to reduce the risk of false positive results that is associated with performing a series of univariate analyses of covariance (ANCOVA). The grouping variable was never vs. ever use of hormonal contraceptives. Age at study enrollment, years of education, and SES, all known modifiers of cognitive performance, were entered into the model as covariates. Ever users were dichotomized into three groups based on duration of exposure (<5 years, 5 to <15 years, 15+ years). A *post-hoc* pairwise comparison MANCOVA was performed to determine if there was a difference in effect based on duration of use.

Because not all women in our study were postmenopausal, not all of them qualified for HT use. Therefore, a subanalysis of postmenopausal women with known HT status was conducted to look for confounding effects of this endogenous

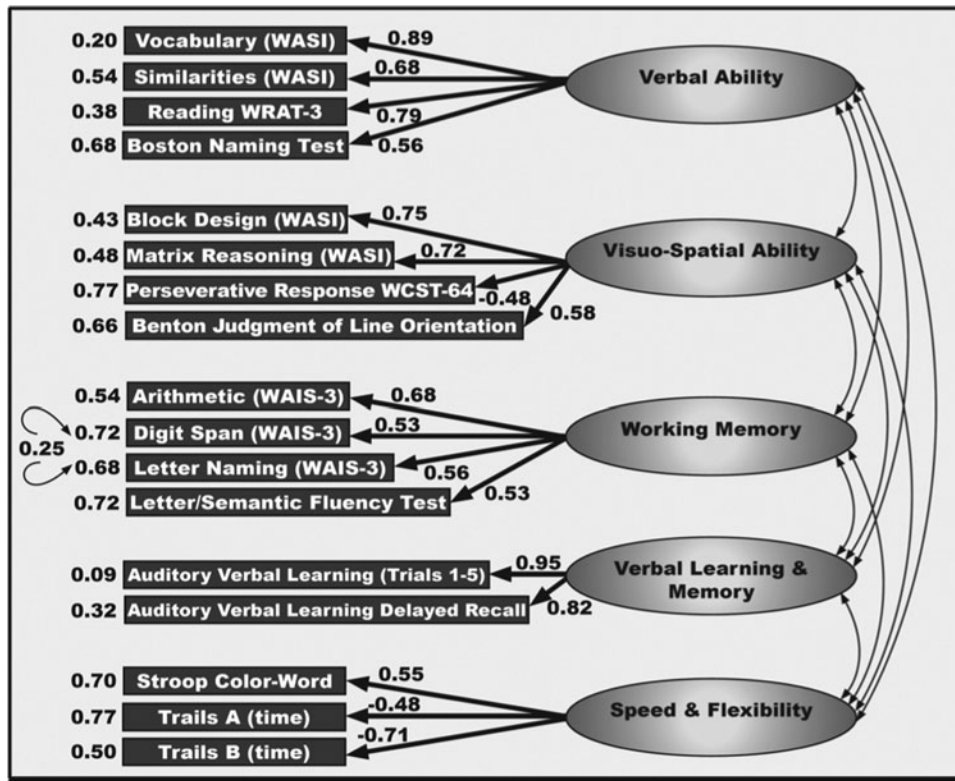


FIG. 1. Confirmatory factor analysis of cognitive variables obtained with the Wisconsin Registry for Alzheimer’s Prevention (WRAP) neuropsychologic battery, using the full sample. Fit indices are as follows: root mean square error of approximation (RMSEA)=0.07, normed fit index (NFI)=0.94, comparative fit index (CFI)=0.96, and goodness of fit index (GFI)=0.91. Model tested with subgroups: Males vs. females; young (age 30–54) vs. old (55–67); parental history positive vs. parental history negative; parental history and apolipoprotein E4 (ApoE4)+ vs. parental history negative and ApoE4–. In all cases, fit indices were in acceptable ranges. WASI, Wechsler Adult Intelligence Scale, 3rd ed.; WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sort Test-64; WRAT-3, Wide Range Achievement Test, 3rd ed.

hormone application. A Bonferroni correction was used to maintain the familywise error rate. Finally, potential interaction effects resulting from the participant variables of parental history of AD and ApoE4 status were assessed by including the appropriate interaction term in the model in two secondary analyses. Parental history and ApoE4 status were included in the model as an additional grouping variable in separate MANCOVA analyses. A Bonferroni correction was used to maintain the familywise error rate.

Analyses were conducted using SPSS for Mac (version 17.0, release 17.0.2, SPSS Inc., Chicago, IL). A nominal two-sided *p* value of 0.05 was regarded as statistically significant.

Results

Characteristics of hormonal contraceptive users and never users are shown in Table 1. The average age of the 262 women was 52.4 years (standard deviation [SD] 6.2 years). ANOVA comparisons showed that subjects at screening were of comparable age (*p*=0.11), race/ethnicity (*p*=0.89), years of education (*p*=0.19), SES (*p*=0.47), history of depression (*p*=0.58), and self-reported health status (*p*=0.88). There were no differences in variables affecting hormone levels, such as hysterectomy (*p*=0.83) and history of HT use (*p*=0.79). Distribution of the ApoE4 allele and parental history of AD were comparable in users and never users (*p*=0.21 and 0.90, respectively). Significantly fewer hormonal contraceptive ever users than never users had a history of pregnancy (*p*=0.002). Prevalence of underlying health characteristics/behaviors (heart disease, hypertension, hypercholesterolemia, diabetes mellitus, depression, self-rated health, smoking, and alcohol use) also did not differ across groups (data not shown) (all *p*>0.10).

There was a significant group difference between users and never users in history of pregnancy, and this factor was included in the adjusted model. Age at study enrollment, years of education, and SES were also included in adjusted MANCOVA analysis, as these factors have all been associated with cognitive performance in prior studies. As reported in Table 2, there were significant differences in cognitive performance across the model associated with hormonal contraceptive use (*p*=0.029, MANCOVA). Hormonal contraceptive ever users had higher scores than nonusers in Speed & Flexibility ($\mu_D=0.52$, 95% confidence interval [CI] -0.16-1.04, *p*=0.007) and in Visuo-spatial Ability ($\mu_D=0.75$, 95% CI 0.23-1.28, *p*=0.005). Scores were similar between ever users and never users in Verbal Ability ($\mu_D=0.44$, 95% CI -0.16-1.04, *p*=0.007), Working Memory ($\mu_D=0.40$, 95% CI 0.15-0.95, *p*=0.15), and Verbal Learning & Memory ($\mu_D=0.01$, 95% CI -0.51-0.53, *p*=0.97). (μ_D =mean of the differences.)

A secondary analysis (*n*=259) was performed to look for main effect differences in cognitive outcomes based on length of time of hormonal contraceptive use according to four categories (never user, <5 years of use, 5 to <15 years of use, 15+ years of use) (Table 3). Cognitive performance increased as a function of use-duration of hormonal contraceptives but was not significant across all five domains (*p*=0.096, MANCOVA). A pattern of cognitive performance could be discerned from this analysis, however, especially in the domains of Speed & Flexibility and Visuo-spatial Ability. In *post-hoc* pairwise comparisons, ever users with the most hormonal contraceptive exposure (15+ years) performed the best against never users in the domain of Speed & Flexibility ($\mu_D=0.68$, 95% CI 0.39-0.96, *p*=0.02) vs. those with <5 years of use ($\mu_D=0.48$, 95% CI 0.25-0.73, *p*=0.16) and 5 to <15 years of use ($\mu_D=0.54$, 95% CI 0.33-0.74, *p*=0.07). There was also a trend toward

TABLE 1. BASELINE CHARACTERISTICS OF FEMALE WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION STUDY PARTICIPANTS

Characteristic	Hormonal contraceptive ever users (n=227)	Hormonal contraceptive never users (n=34)	p value ^a (2-sided)
Age at screening, mean (SD)	52.6 (6.0)	50.8 (7.4)	0.11 ^b
Race/ethnicity, n (%)			0.89
American Indian	1 (0.4)	0 (0.0)	
Black	2 (0.9)	0 (0.0)	
White	223 (98.2)	34 (100.0)	
Hispanic	1 (0.4)	0 (0.0)	
Years of education, mean (SD)	15.9 (2.6)	16.5 (2.8)	0.19 ^b
SES, n (%)			0.47
≤ \$19,000	5 (2.2)	0 (0.0)	
\$20,000–\$39,000	19 (8.4)	6 (17.6)	
\$40,000–\$59,000	53 (23.3)	8 (23.5)	
\$60,000–\$79,000	42 (18.5)	8 (20.6)	
> \$80,000	100 (44.1)	13 (38.2)	
Not reported	8 (3.5)	0 (0.0)	
Depression, n (%)	55 (24.2)	6 (17.6)	0.58
Self-rated health, mean (SD) ^c	3.9 (0.8)	3.8 (0.8)	0.88 ^b
Hysterectomy, n (%)	48 (21.1)	5 (14.7)	0.38
Postmenopausal, n (%)	177 (78.0)	22 (64.7)	0.69
HT use, n (%) ^d			0.69
Ever	112 (63.3)	11 (50.0)	
Never	59 (33.3)	11 (50.0)	
Don't know	6 (3.3)	0 (0.0)	
ApoE4, n (%)			0.21
Yes	139 (61.2)	17 (50.0)	
No	88 (38.8)	17 (50.0)	
Parent with AD, n(%)	206 (90.7)	31 (91.2)	0.90
Parity, n (%)	204 (89.9)	33 (97.1)	0.002

^aBased on chi-square tests (categorical variables) or *t* tests (continuous variables).

^bEqual variance assumed based on Levene's test for equality of variances.

^cBased on 5-point scale of self-reported health.

^dPostmenopausal women only, *n* = 199.

AD, Alzheimer's disease; ApoE4, Apolipoprotein E e4 allele; HT, hormone therapy; SD, standard deviation; SES, socioeconomic status.

better performance in subjects with 15+ years of use in the domain of Visuo-spatial Ability ($\mu_D=0.51$, 95% CI 0.11-0.92, $p=0.054$).

To look for a potential confounding effect of HT use, a subanalysis of cognitive scores in perimenopausal and postmenopausal subjects was conducted (*n* = 199) (Table 4). There was no significant difference in performance across all five domains between hormonal contraceptive users and never

users ($p=0.101$, MANCOVA). However, hormonal contraceptive users continued to score significantly higher in the domains of Visuo-spatial Ability ($\mu_D=0.79$, 95% CI 0.10-0.91, $p=0.03$) and Speed & Flexibility ($\mu_D=0.59$, 95% CI 0.10-1.07, $p=0.02$). There were no significant differences in the domains of Verbal Ability ($\mu_D=0.35$, 95% CI -0.40-1.09, $p=0.36$), Working Memory ($\mu_D=0.27$, 95% CI 0.43-0.80, $p=0.45$), and Verbal Learning & Memory ($\mu_D=0.03$, 95% CI -0.66-0.72, $p=0.90$).

TABLE 2. EVER USE OF HORMONAL CONTRACEPTIVES AND COGNITIVE OUTCOMES IN FEMALE WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION STUDY PARTICIPANTS

Cognitive domain	Hormonal contraceptive users (n=227) Mean (SE) ^a	Hormonal contraceptive never users (n=34) Mean (SE) ^a	Difference between users and never users Mean (95% CI) ^{a,b}	p Value ^{a,b} (MANCOVA = 0.029)
Verbal Ability	0.46 (0.11)	0.01 (0.28)	0.44 (-0.16-1.04)	0.15
Visuo-spatial Ability	0.48 (0.10)	-0.38 (0.25)	0.75 (0.23-1.28)	0.005
Working Memory	0.28 (0.10)	-0.12 (0.26)	0.40 (-0.15-0.95)	0.15
Verbal Learning & Memory	0.43 (0.10)	0.42 (0.25)	0.01 (-0.51-0.53)	0.97
Speed & Flexibility	0.51 (0.07)	-0.01 (0.18)	0.52 (0.14-0.90)	0.007

^aAdjusted for age at intake, SES, years of education, and parity.

^bA Bonferroni adjustment was adopted for multiple comparisons.

CI, confidence interval; MANCOVA, multivariate analysis of covariance; SE, Standard Error.

TABLE 3. HORMONAL CONTRACEPTIVES AND COGNITIVE OUTCOMES ACCORDING TO YEARS OF USE IN FEMALE WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION STUDY PARTICIPANTS

Cognitive domain	Duration of use (years)	Score Mean (95% CI) ^{a,b}	p value ^{a,b} (Overall p=0.096)
Verbal Ability	Never user (n=34)	-0.09 (-0.65-0.46)	0.16
	<5 (n=69)	0.64 (0.27-1.02)	
	5-<15 (n=99)	0.33 (0.02-0.65)	
	15+ (n=51)	0.50 (0.06-0.93)	
Visuo-spatial Ability	Never user	-0.35 (-0.86 to 0.16)	0.05
	<5	0.41 (0.06-0.75)	
	5-<15	0.30 (0.00-0.59)	
	15+	0.51 (0.11-0.92)	
Working Memory	Never user	-0.09 (-0.61-0.45)	0.38
	<5	0.13 (-0.23-0.49)	
	5 to <15	0.27 (-0.03-0.57)	
	15+	0.48 (0.06-0.90)	
Verbal Learning & Memory	Never user	0.49 (0.00-0.99)	0.48
	<5	0.63 (0.29-0.96)	
	5-<15	0.34 (0.05-0.62)	
	15+	0.27 (-0.13-0.67)	
Speed & Flexibility	Never user	-0.01 (-0.37-0.35)	0.03
	<5	0.48 (0.24-0.73)	
	5-<15	0.54 (0.33-0.74)	
	15+	0.68 (0.39-0.96)	

^aAdjusted for age at intake, SES, years of education, and parity.
^bA Bonferroni adjustment was adopted for multiple comparisons.

In order to determine if an interaction was present between family history of AD and hormonal contraceptive use, an interaction term was included in the model. Parental history did account for some of the effect of history of hormonal contraceptive use in the model. The impact of hormonal contraceptive use on cognitive performance differed based on parental history of AD ($p=0.022$, MANCOVA). Although there was no significant difference in Working Memory performance between never and ever users, the mean difference in Working Memory between users and never users was greater in women with no parental history of AD ($\mu_D=2.67$) than in women with a parental history of AD ($\mu_D=0.19$, $p=0.01$). Analysis was limited by the small sample size ($n=3$) in parental history-negative never users. Differences in other domains between users and never users did not differ based on parental history of AD (Verbal Ability, $p=0.25$; Visuo-spatial Ability, $p=0.44$; Verbal Learning & Memory, $p=0.78$). There was, however, a trend suggesting that hormonal contraceptive users with a parental history of AD performed

better than those without a parental history of AD in the domain of Speed & Flexibility ($p=0.08$).

Because it is a known risk factor for AD, ApoE4 status was also included in the model to determine possible interaction with hormonal contraceptive use; no interaction was found between ApoE4 and hormonal contraceptive use ($p=0.68$, MANCOVA). Hormonal contraceptive use did not appear to differentially affect cognition in women depending on their ApoE4 status.

Discussion

Through analysis of a cognitively healthy, middle-aged group of women, we aimed to elucidate the effects of hormonal contraceptive use on cognitive outcomes, comparing women who had no history of hormonal contraceptive use (never users) to two groups of past users of hormonal contraceptives. Specifically, we compared cognitive outcomes between groups of women with three duration levels of

TABLE 4. USE OF POSTMENOPAUSAL HORMONE THERAPY AND COGNITIVE OUTCOMES IN FEMALE WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION STUDY PARTICIPANTS

Cognitive domain	Hormonal contraceptive users ^a (n=177) Mean (SE)	Hormonal contraceptive never users ^a (n=22) Mean (SE)	Mean difference (Users - never users) ^a	p value ^a (Overall p=0.101)
Verbal Ability	0.53 (0.12)	0.18 (0.36)	0.35	0.36
Visuo-spatial Ability	0.25 (0.11)	-0.53 (0.33)	0.79	0.03
Working Memory	0.15 (0.12)	-0.12 (0.34)	0.27	0.45
Verbal Learning & Memory	0.30 (0.12)	0.27 (0.33)	0.03	0.90
Speed & Flexibility	0.34 (0.08)	-0.24 (0.23)	0.59	0.02

^aAdjusted for age at intake, SES, years of education, parity, and HT use; Bonferroni for multiple comparisons.

exposure. We also explored the data for possible interactions between hormonal contraceptive use and risk factors for AD, such as parental history and presence of a genetic risk factor for AD, the ApoE4 allele, both potential modifiers of cognitive outcomes.

When adjusting for age, SES, parity, and years of education, hormonal contraceptive use was found to be associated with significantly better performance in the cognitive domains of Visuo-spatial Ability and Speed & Flexibility. This association was supported by the finding that the effect was dose dependent. Surprisingly, even those users with very brief exposures (< 5 years) outperformed never users. The same effect was still present in a secondary analysis of perimenopausal and postmenopausal women with a history of HT use.

An interaction was found between parental history of AD and hormonal contraceptive use. Performance in the domain of Working Memory between ever users and never users was better in women with no parental history of AD than in women with a parental history of AD. There was no differential effect of hormonal contraceptive use depending on ApoE4 status. However, the analysis of interactions between AD risk factors and cognition was limited by small sample size. These results are only preliminary findings and are presented to prompt further research.

Our finding that hormone contraceptive use has a duration-dependent effect on cognitive performance has important clinical relevance. In developed countries, many women have an extensive history of exogenous hormone exposure.²⁸ Hormonal contraceptive use is often started at a young age for everything from acne control to alleviation of premenstrual symptoms. Considering HT along with hormone contraceptives, a woman could potentially have upward of 40 years of exogenous hormone exposure. The implications of this modification of the hormonal milieu are not well understood. Moreover, subtle group differences in cognition related to hormone exposure earlier in life may play out in a meaningful way later in life. In other words, our study population is relatively young; small differences in cognitive performance at this age may portend marked changes decades later if the trajectory continues. Likewise, subtle changes in cognitive reserve could influence age of onset.^{29,30} Finally, possible protective effects of early life exogenous hormone use could protect cognitive reserve in an older woman.

Our results suggesting that hormonal contraceptive use affects Speed & Flexibility are consistent with other findings that estrogen modulates and even improves this area of function.³¹⁻³³ Speed & Flexibility has been labeled a female-specific task, meaning women tend to outperform men in this area. Women perform better on female-oriented tasks when estrogen levels are high, for example, during the midluteal stage of the menstrual cycle.³⁴ Women taking hormonal contraceptives have controlled levels of estrogen that are higher than the body's normal levels, meaning that improved performance in this domain is biologically plausible.

Although exact mechanisms are unknown, the presence of estrogen receptors in the basal forebrain cholinergic nuclei has led to suggestions that interactions with the cholinergic system are involved.^{35,36} In addition, estrogen has been shown to increase the density of hippocampal cell connections in animal models.^{37,38} The location of estrogen receptors near nerve growth factor in the brain may imply that estrogen facilitates neurotrophic responses.³⁹ Detailed discussion of

other potential mechanisms of the effects of estrogen on cognition is beyond the scope of this article. Comprehensive reviews can be referenced for further information on this topic.⁴⁰⁻⁴²

Our finding that hormonal contraceptive ever users outperform never users in the domain of Visuo-spatial Ability is surprising. Better performance on visuo-spatial tasks has been associated with androgenic hormones and has been labeled a male-oriented task.⁴³ The androgen receptor is expressed in various brain regions, including the cerebral cortex, amygdala, and hypothalamus.⁴⁴ Studies of genetically male individuals born with complete androgen insensitivity syndrome, which is characterized by nonfunctional androgen receptors, have found that these individuals have impaired visuo-spatial cognition.^{45,46} This suggests that androgen receptor activation may influence visuo-spatial cognitive differences between males and females. Although estrogen levels are similar in all types of hormonal contraceptives, levels of progesterone vary depending on the preparation used. New research has found that preparations of hormonal contraceptives with the most androgenic activity are associated with the strongest performance on visuo-spatial tasks.⁴⁷ In addition, a study looking at HT with estrogen alone and HT including progestin found that both are positively associated with visuo-spatial performance.⁴⁸ Detailed information on the types of hormonal contraceptive preparations our subjects used was not available, but it is possible that better performance in the domain of Visuo-spatial ability could be related to the progestin in these preparations. This exposure to exogenous progestins makes better performance in the domain of Visuo-spatial ability plausible. Further research is warranted to explore these findings.

The present study's strength is its relevance and timeliness. However, it is important to acknowledge limitations so they can be addressed and their impact can be minimized. As with any cross-sectional study, if an association is found during analysis, it is impossible to determine a causal relationship. Given the limitations in suggesting a temporal relationship between exposure and outcome, this study may be useful in providing directions for future research in the form of prospective cohort studies or case-control studies that will better establish etiologic relationships and clarify questions about the efficacy of formulations, dosages, and durations of use. Although we controlled statistically for the effects of several important demographic characteristics (age at study onset, SES, parity, history or HT use, and years of education) in our analyses, other unknown or unmeasured characteristics may have contributed to our results. Cohort effects and user biases may also play a role in this study. However, our finding that duration of use significantly impacts cognitive outcomes helps to strengthen our conclusion that hormonal contraceptive use and not cohort effects is responsible for these outcomes.

Because participants for this study were volunteers, the generalizability of our database to the overall Wisconsin population may be a concern. Additionally, the WRAP database itself is inherently biased in that it is not population based. Research has shown that people who volunteer for a health study tend to be better educated, to have better SES, and to be in better overall health than those who do not participate.⁴⁹ This may be a particularly influential confounding factor for an AD study. History of hormonal contraceptive use was gathered by self-report, leading to the potential for recall

bias. In a previous study, however, self-report of contraceptive use was shown to be a valid and accurate data collection method.⁵⁰

Lack of data on the type of hormonal contraceptive preparation used prevented us from determining if the type of hormonal preparation impacted cognition in ever users. In future research, tools to aid recall, such as pictures of different preparation types or multiple choice answers, may aid in collection of these data.

Conclusions

The relationship between hormonal contraceptive use and cognition at midlife is not well understood. Consequently, there are notable gaps in existing research. Our study examined the cognitive effects associated with hormonal contraceptive use in women with and without a history of parental AD. Our analysis indicated that hormonal contraceptive use may have a protective cognitive effect even years after use is discontinued. This is especially true in subjects with a longer duration of use. This result, however, should be interpreted with caution, given the cross-sectional study design and limited sample size. We believe our findings form the basis for further research in larger and more focused clinical studies about differences between types of hormonal preparation used that look for cause and effect relationships of this phenomenon.

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Disclosure Statement

The authors have no conflicts of interest to report.

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