Journal of Alzheimer's Disease 55 (2017) 1123–1130
DOI 10.3233/JAD-160513
IOS Press

Serum SHBG Levels are not Associated with Longitudinal Cognitive Decline in Mild Cognitive Impairment

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Handling Associate Editor: Pankaj Mehta

Accepted 14 September 2016

Abstract.
Background: Prior studies have noted gender differences in cognition, imaging, and pathological markers in mild cognitive impairment (MCI) subjects. Sex hormone-binding globulin (SHBG), a major controlling factor in the proportion of bioavailable versus bound testosterone and estrogen, has been proposed to contribute to links between hormones and dementia, but has not yet been investigated fully in a prospective biomarker trial.
Objective: This study examined whether, among subjects with MCI, SHBG levels predict future rate of cognitive decline.
Methods: We examine the effect of gender on cognitive decline and factors modulating potential gender differences in 378 MCI subjects (134 females, 244 males) in the Alzheimer's Disease Neuroimaging Initiative-1 (ADNI-1), followed for up to 8 years (mean $\pm$ SE, 4.0 ± 0.1 years). Cognition was assessed using the ADAS-cog-11. Multivariate models examined the effect of gender covarying for age, ApoE4, baseline cognition, years of education, and SHBG levels.
Results: MCI women declined significantly faster than men in cognition over the follow up period. Baseline SHBG levels differed significantly between men and women ($p < 0.0001$), and by age in men, but not by ApoE4 status. In the multivariate models, SHBG levels were not a significant predictor of cognitive decline in men or women but ApoE4 status, baseline cognition, years of education, and female gender were.
Conclusion: SHBG levels did not influence the rate of cognitive decline in MCI. Further studies to confirm these findings and uncover other potential mechanisms of gender differences in the risk for AD may be warranted.

Keywords: Amyloid-β, apolipoprotein E4, secondary prevention, sex differences, sex hormone-binding globulin

INTRODUCTION

Previous research has suggested that women may progress faster than men in Alzheimer's disease (AD) [1–6]. Loss of estrogens at menopause is precipitous in women, whereas testosterone follows a more gradual age-related decline in men [7]. Loss of estrogens is associated with cognitive decline [8], and sex hormones in both men and women have been suggested to affect cognition in AD [6, 9–14]. Sex hormones, including both estrogen and

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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testosterone, have been suggested to promote the non-amyloidogenic alpha-secretase pathway, hence decreasing amyloid-β production [10]. Furthermore, estrogen appears to enhance plasticity and is important in the regulation of bioenergetics [15]. Hence, hormonal factors are important to consider in the understanding of the biology of AD.

It has been postulated that differences in hormones between men and women may be associated with observed differences in cognition and cognitive decline in AD. Plasma levels of estrogen have been noted to be lower in women with AD compared to age-matched controls [11]. Estrogen may regulate processes such as long-term potentiation, protect against cell death, inhibition of amyloid-β accumulation, and tau phosphorylation, and progesterone may be further involved in improvement of cognition via promotion of amyloid-β clearance [7]. In the examination of postmortem brain tissue from normal and AD subjects (N = 44), Rosario et al. found that brain levels of estrogens and androgens were lower in AD cases aged 80 years and older, and that there was an inverse relationship between testosterone levels and amyloid-β [12].

Sex hormone-binding globulin (SHBG) has been of interest to further investigate inconsistencies in these findings. SHBG, a major controlling factor in the balance of biologically active (free or unbound) versus bound testosterone and estrogen, is a protein secreted by the liver that is the major binding protein for sex hormones in plasma, preventing hormones from binding to the intracellular androgen or estrogen receptors [13]. It has been proposed that differences in levels of SHBG, resulting in changes in the balance between bound and bioactive hormones, may contribute to the inconsistent results pertaining to estrogen and testosterone in dementia [13]. SHBG appears to be associated with cognitive function in elderly men, with higher SHBG associated with worsened cognitive performance as well as greater cognitive decline [16].

The proportion of bioavailable hormones may be associated with cognition. In a cross-sectional study with 203 male subjects, Chu et al. found that mean serum bioavailable testosterone, but not total testosterone, were significantly lower in the subject group with amnestic mild cognitive impairment (MCI) [17]. In the OPTIMA study, only older men with AD (mean age 80 years) had significantly lower total testosterone; in younger men with AD (mean age 66 years), lower free testosterone and SHBG were observed, but total testosterone levels were not significantly lower [18]. In healthy postmenopausal women (N = 402) between the ages of 50 and 74, higher remaining circulating oestradiol levels were associated with a lower likelihood of cognitive impairment [19].

Several studies have examined the association between SHBG and cognitive impairment [13, 16, 17, 19–21]. SHBG appears to differ between normal individuals and individuals with AD. For instance, in a study of 576 women from the Washington Heights – Inwood Community Aging Project (WHICAP) cohort, significant differences were found only in levels of SHBG but not luteinizing hormone, follicle-stimulating hormone, testosterone, or DHEA, with SHBG levels 20% higher than that of controls [20]. In men and women from the WHICAP study (N = 731), higher levels of SHBG were associated with increased risk for AD and overall dementia [13]. Since SHBG decreases with age in normal postmenopausal women, it has been suggested that SHBG may be abnormally overproduced or upregulated in AD [20].

We have previously reported gender differences with the same dataset of subjects with MCI, who are at risk of AD [22]. In this present study, we also use data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a large biomarker study, to determine if SHBG is associated with 8-year rates of Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) decline in these subjects.

MATERIALS AND METHODS

Subjects

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. ADNI (ADNI ClinicalTrials.gov identifier: NCT00106899) is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, with subjects recruited from over 50 sites across the United States and Canada. ADNI-1 originally recruited 398 MCI subjects who then had the option to be followed in ADNI-2. Additional details are provided in the

ADNI-1 procedures manual [23, 24]. For up-to-date information, see http://www.adni-info.org.

All ADNI-1 MCI subjects with available baseline SHBG measurements were eligible for inclusion. The criteria for classification as MCI in ADNI-1 are as follows: subjective memory complaint, objective evidence of impaired memory calculated by scores of the Wechsler Memory Scale Logical Memory II adjusted for education, absence of significant confounding conditions such as current major depressive episode, normal, or near normal daily activities, absence of clinical dementia, an inclusive Mini-Mental State Examination (MMSE) score from 24–30, and a score of 0.5 on the global Clinical Dementia Rating. For a detailed list of all selection criteria, refer to the ADNI-1 procedures manual [24]. In addition, for subject inclusion, data for all the following parameters were required: baseline age, race, gender, and years of education; baseline MMSE score; ADAS-cog for at least two different time points, APOE genotyping results, and SHBG level at baseline. APOE allele genotyping of all subjects was completed using DNA extracted from peripheral blood cells, with details provided elsewhere [24]. In total, 378 MCI subjects from ADNI-1 were included. The term "baseline" is used to indicate data collected at the subject's first visit, which may be either screening or baseline. Additional details are provided in our previous manuscript [22] as well as in the ADNI-1 procedures manual.

Sex-hormone binding globulin data

Plasma samples from the ADNI cohort were analyzed with a 190-analyte multiplex immunoassay panel (Human Discovery Map, developed on the Luminex xMAP platform by Rules-Based Medicine: RBM). Plasma samples were obtained in the morning following an overnight fast. The ADNI Plasma QC Multiplex data, quality controlled and cleaned by the Biomarkers Consortium Project, was used for this analysis. For the SHBG assay (all units nmol/L), the lower assay limit was 1.4, the least detectable dose was 0.000936 nmol/L from the serum table, RBM low serum/plasma range is 18, and the RBM high plasma/serum range is 114. Additional details (regarding quality control, biological preparation, analysis, etc.) can be found in the study document [25].

Outcome measures

The ADAS-cog-11 is a 70-point scale with 11 tasks designed to assess severity of cognitive impairment; it is commonly used in MCI and AD trials. The 11 tasks comprising the ADAS-cog evaluate learning and memory, language production and comprehension, constructional and ideational praxis, and orientation [1]. Because the ADAS-cog is scored based on number of errors, higher scores indicate worse performance.

Follow-up

The ADNI MCI subjects were followed through ADNI-1 and then enrolled in ADNI-2. We compared ADAS-cog scores from baseline to end point (using most recent available scores at the time of our data extraction in late 2015). Study duration was up to 8 years, with a mean duration of 4.0 ± 0.1 years)

Statistical analyses

We compare SHBG levels in men versus women, as well as for different APOE ε4 status within those subject groups. We fit a 2 degree multivariate model for ADAS-cog rate of change per year for all 378 subjects using JMP Pro 11, using baseline age, gender, years of education, baseline MMSE, ApoE4 status, and baseline SHBG as predictors. Baseline SHBG was included as a predictor as a continuous variable in all multivariate models. The linear regression models were fit by the standard least squares method. We also show two plots of bivariate baseline SHBG versus ADAS rate of change per year (computed by dividing total value of ADAS-cog change from beginning to end of follow-up for each subject, by the number of years of follow-up), fit with a linear trendline. We used log transformed SHBG values for all analyses and figures, and findings are unchanged when the raw values are used.

RESULTS

Baseline characteristics (Table 1)

Baseline features of the sample are summarized in Table 1. The total number of subjects was 378. There are significant differences for mean baseline age (women are younger in this sample) and educational levels (with women having fewer years of education. There are no significant differences for baseline MMSE, baseline ADAS-cog, follow-up length, or %ApoE4 (one or more ApoE4 alleles).

Table 1
Baseline characteristics of ADNI-1 MCI sample

Variable	Male	Female	*p*-value
N	244	134	–
Age (SE)	75.45 (0.46)	73.52 (0.63)	**0.0133**
Years of education (SE)	15.83 (0.19)	15.19 (0.26)	0.0525
MMSE baseline (SE)	27.09 (0.11)	26.85 (0.15)	0.2187
ADAS-cog baseline (SE)	11.64 (0.29)	11.50 (0.39)	0.7715
Follow-up length (months) (SE)	48.13 (1.78)	46.30 (2.40)	0.5414
%ApoE4	53.69%	55.97%	0.6700
Mean SHBG (SE)	1.72 (0.01)	1.83 (0.02)	**<0.0001**

MCI, mild cognitive impairment; ADNI, Alzheimer's Disease Neuroimaging Initiative; *n*, number of subjects; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; %ApoE4, apolipoprotein E4; log-transformed SHBG value, sex hormone-binding globulin; SE, standard error. NOTE. For selection criteria details, refer to the text. Mean and SE shown in the table. Bold *p* values are statistically significant.

Effect of gender on SHBG levels

Men had a mean baseline SHBG of 56.4 ± 22.4 nmol/L, whereas women had a higher mean baseline SHBG of 75.4 ± 36.3 nmol/L. SHBG values ranged from 4.7 to 126 in men, and 16 to 266 in women. Covarying for age, mean baseline SHBG was significantly higher in women ($p < 0.0001$).

Effect of age on SHBG levels

Age was not significantly associated with baseline SHBG levels.

However, within genders, greater age was associated with higher SHBG in men ($p = 0.002$) but not women ($p = 0.78$).

Effect of APOE4 status on SHBG levels

Mean SHBG levels did not differ significantly by APOE4 status. Further, as shown in Fig. 1, within the male and female groups, SHBG did not also differ significantly by ApoE4 status.

Relationship between baseline ADAS-cog and SHBG levels

Baseline ADAS-cog and baseline SHBG were not significantly associated in men ($p = 0.12$) or women ($p = 0.53$).

Multivariate modeling of effect of SHBG levels on the change from baseline in ADAS-cog

The maximum follow-up duration was 8 years and mean follow-up was 4 ± 0.1 years. We examined the effect of SHBG on ADAS-cog decline after covarying for age, gender, education baseline cognition, and ApoE4. There were significant effects of gender ($p = 0.0011$), education ($p = 0.0046$), APOE ε4 status ($p = 0.0008$), and baseline MMSE ($p < 0.0001$), but not age on ADAS-cog change (Table 2). After covarying for these effects, baseline SHBG did not have a significant effect. Figure 2 depicts the non-significant univariate relationship between SHBG and ADAS-cog change by gender.

We also examined the effect of SHBG on ADAS-cog change separately in men and women using multivariate models, and in both analyses there was no significant effect of SHBG.

We also analyzed the effect of baseline SHBG on ADAS-cog change from baseline to year 3, to test whether SHBG may have had shorter-term effects. The additional 3-year analyses of SHBG versus 3-year ADAS-cog change revealed the same finding as the 8-year analyses. The average follow-up for the 8-year analyses is 4 years because of the attrition in the latter years. We did the 3-year analyses to verify that the larger attrition after this period did not affect the final result. These results suggest that a slope analysis using all possible data points would not have resulted in a different finding. There was no significant SHBG effect in this analysis either.

DISCUSSION

This study found that baseline SHBG does not have an effect on rate of cognitive decline as measured by ADAS-cog in men and women with MCI. Age, baseline cognition, education, and ApoE4 (which has substantial correlation with risk for amyloid-β positive status) were adjusted for in the models. Overall, our findings could not confirm the hypothesis that

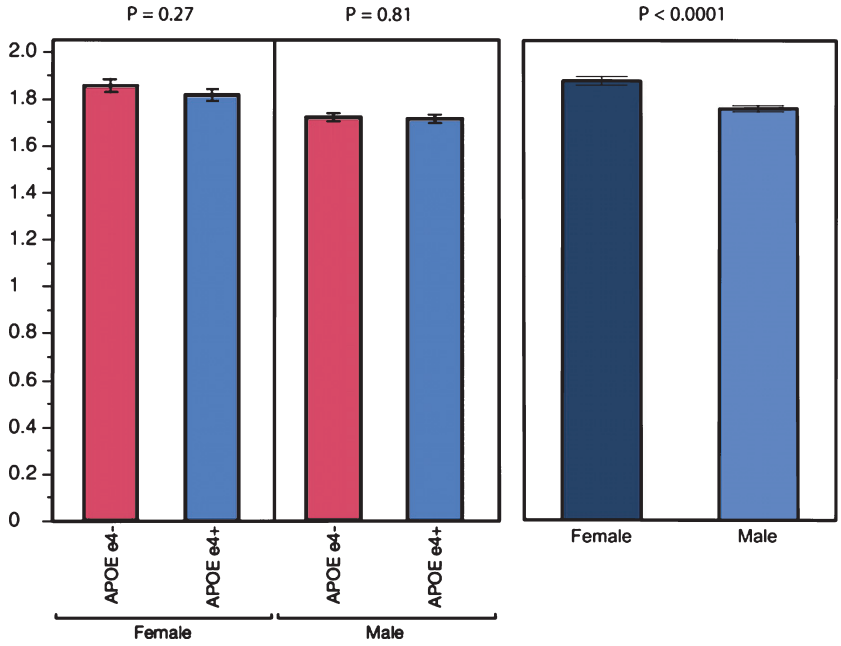

Fig. 1. Baseline SHBG levels in MCI by gender and APOE ε4 status. *P*-values are for SHBG levels by APOE ε4 status within male and female groups are presented. Baseline SHBG did not differ significantly by APOE ε4 status within these groups. Overall, SHBG levels were significantly higher in women than men. Baseline SHBG values are log-transformed.

Table 2
Multivariate model for ADAS-cog rate of change per year

Term	Value	SE	*p*-value
Baseline rate	9.09	3.96	**0.0223**
Age	0.01	0.03	0.6957
Gender	0.68	0.21	**0.0011**
Years of education	0.18	0.06	**0.0046**
APOE ε4 status	1.28	0.38	**0.0008**
Baseline MMSE	–0.43	0.11	**<0.0001**
Baseline SHBG	0.48	0.96	0.6166

ADAS-cog, Alzheimer's disease assessment scale-cognitive subscale; ApoE4, apolipoprotein E4; MMSE, Mini-Mental State Examination; SHBG, sex-hormone binding globulin. NOTE. Values are model coefficients. Units are ADAS-cog score change per year. Women had greater rates of decline than men. Positive changes in ADAS-cog scores indicate worsening. Bold *p* values are statistically significant. All 378 subjects are included in this analysis.

levels of bound sex hormones have an additive impact upon rate of cognitive decline in subjects at risk for AD.

The strengths of our study include a relatively large baseline at-risk sample (378 MCI subjects recruited nationally) with a relatively long follow-up duration (mean 4 years), as well as the employment of specific clinical criteria for amnestic MCI with standardized data collection across multiple sites. Further, MCI subjects recruited in ADNI-1 had a more traditional form of MCI (late MCI) with well-established memory criteria. We did not exclude subjects who progressed to AD dementia. All data points on subjects who had available measurements for baseline SHBG and entered the study as MCI in ADNI-1 were analyzed. Subjects newly recruited in ADNI-Go or ADNI-2 with early MCI were not included because they lacked sufficient long-term follow-up. Though there were fewer women than men in the sample, and attrition biases are possible, baseline MMSE and follow-up duration were comparable between males and females.

There are some potential limitations of this study. One is that ADNI MCI subjects may be more representative of MCI subjects recruited at research centers or those who have been enrolled into secondary prevention trials, and not necessarily representative of the population as a whole. Finally, other biomarkers or genes aside from APOE4 were not examined since we focused primarily on testing the relationship between SHBG and cognition and since cerebrospinal fluid data were available only in about a third of ADNI-1 subjects. Testosterone was not a main goal of the ADNI study and hence was not measured using a sensitive assay but through a platform with suboptimal reproducibility. Hence, we could not analyze testosterone for our study. We agree that

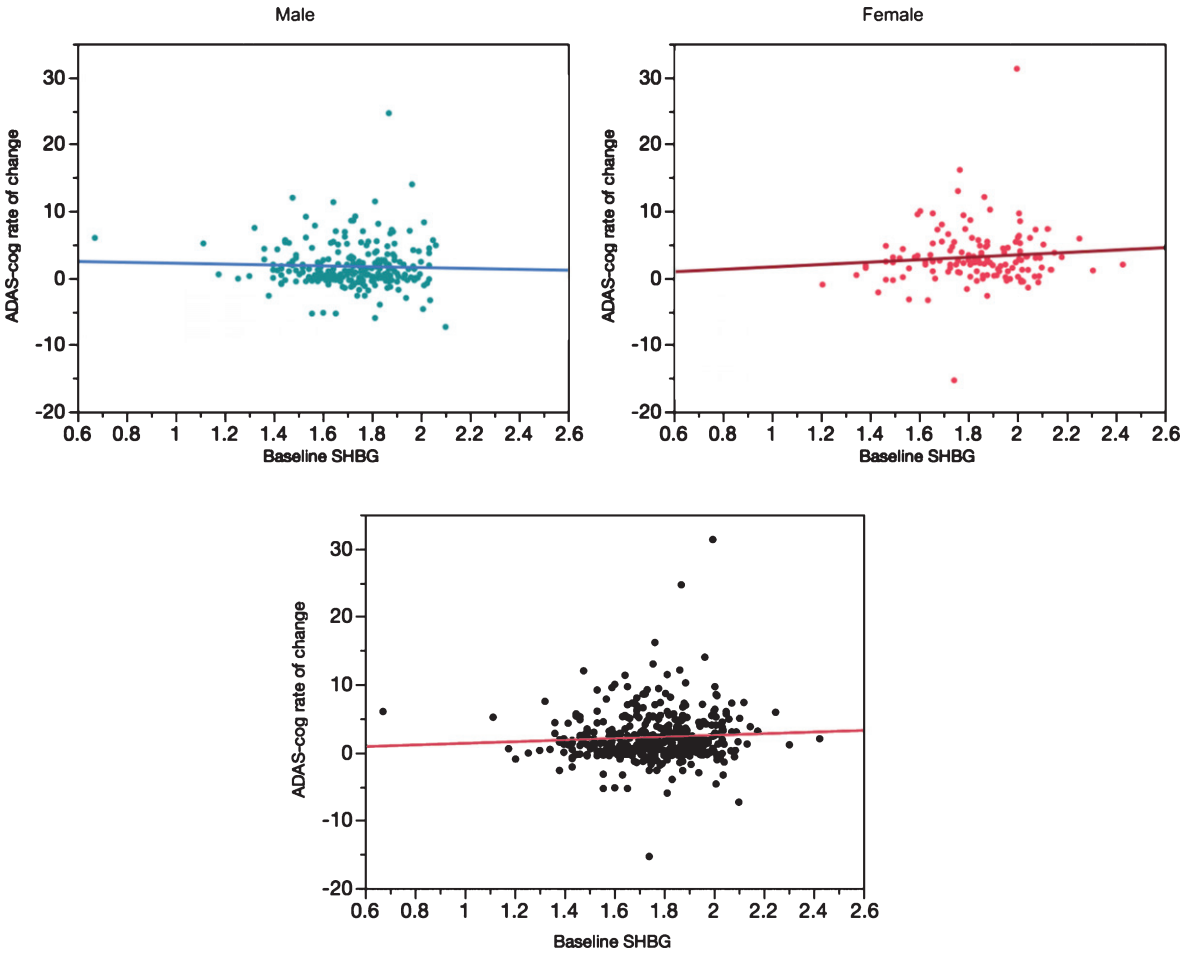

Fig. 2. Bivariate fit of baseline SHBG and longitudinal ADAS-cog decline. Slopes are –0.66 and +1.81 in male and female subjects, respectively. In all subjects, the slope is 1.20. Slopes were not significant. Units for ADAS-cog rate of change are points per year. Baseline SHBG values are log-transformed.

future studies could consider this variable to add value to the SHBG interpretation. We also did not examine various cognitive domains, only examining an overall measure of cognitive performance (ADAS-11 total composite score); since different domains of memory may be differentially affected by hormone levels [26], our study may not have been able to adequately assess these more-subtle differences. Our analyses do not exclude the possibility that SHBG may still be related to specific cognitive subdomains even though the relationship to total ADAS-cog score was not significant. Prior studies have noted SHBG links to global cognition (e.g., MMSE) as well as verbal memory scores. In our sample of MCI subjects, the total ADAS score was primarily driven by verbal memory score deficits. Thus, examining whether SHBG influenced specific cognitive domains would be a study of future interest. Furthermore, SHBG levels can fluctuate depending on various factors, such as time of day and age [27]. Though all ADNI subjects were generally medically healthy with normal physical exams and stable normal liver function at entry when SHBG was measured, there is the possibility that normal variations in liver function may affect SHBG levels. Also, it has been suggested that there may be an optimal level of SHBG [13]; as such, it is not straightforward to determine a linear correlation between SHBG and cognition. SHBG binds both testosterone and estradiol, and the interconversion of testosterone and estradiol has been suggested to have implications in AD [26, 28]. Hence, future studies could potentially examine levels of individual hormones as well as SHBG in cognitive decline in at-risk subjects. Lastly, there are other

hormones that may be regulated by SHBG in a less-direct manner [18, 21], including luteinizing hormone and progesterone. There may also be unknown genes that affect SHBG regulation; for instance, the hypothalamic–pituitary–gonadal axis is implicated in AD [9]. Hence our findings must be interpreted within this context.

Regardless, SHBG should still be considered in order to determine if our findings can be replicated [29]. Increased levels of SHBG (which binds to sex steroids and reduces their bioactivity) have been linked to increased risk of dementia in both men and women, perhaps due to SHBG binding and inhibiting action on respective receptors of sex steroids [20]. With some studies noting an inverse correlation between cognition and SHBG, it may be important for SHBG to be more widely included as a measure, alongside other biomarkers and plasma markers, in studies of hormone therapy or clinical trials. In this regard, the ADNI-2 study with complete amyloid PET and cerebrospinal fluid data on all subjects offers a rich dataset to further explore the interactions between genes, hormones, biomarkers, and AD progression.

In conclusion, our results indicate that there appears to be no effect of SHBG on rate of cognitive decline in women and men with MCI. Further studies are warranted to better understand the inconsistency of findings on hormones and cognition in existing literature.

ACKNOWLEDGMENTS

K.A.L. and this publication, through the Wrenn Clinical Research Scholars program gift to Duke University Medical Center, were supported by the Karen L. Wrenn Family trust.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/16-0513r2).

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