Published in final edited form as:
Am J Geriatr Psychiatry. 2015 March ; 23(3): 253–260. doi:10.1016/j.jagp.2013.02.003.

Sex Hormone Binding Globulin and Verbal Memory in Older Men

Yoichiro Takayanagi, M.D., Ph.D., **Adam P. Spira, Ph.D.**, **Roger S. McIntyre, M.D., FRCPC**, and **William W. Eaton, Ph.D.**
Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States (YT, APS and WWE); Department of Psychiatry, University of Toronto, Toronto, ON, Canada (RSM)

Abstract

Background—Cognitive function in older adults may be affected by multiple factors such as sex hormone levels, metabolic disturbances and neuropsychiatric illness. However, relatively few studies have tested the associations between these factors and cognitive function in a single sample. A cross-sectional analysis was conducted to examine the association between sex hormones, metabolic parameters, and psychiatric diagnoses with verbal memory in non-demented older men.

Methods—Participants included 112 men (mean age = 61.3 years) from the Baltimore Epidemiologic Catchment Area Follow-Up Study who completed measures of blood sex hormone levels, metabolic parameters (e.g. lipid profiles), and verbal memory.

Results—Higher levels of serum sex hormone binding globulin (SHBG) were associated with lower delayed verbal memory scores [standardized coefficients (beta) = −0.19, t = −2.07, df = 1, 105, p = 0.04)], and higher body mass index (BMI) was associated with better immediate (beta = 0.21, t = 2.41, df = 1,105, p = 0.02) and delayed (beta = 0.22, t = 2.46, df = 1,105, p = 0.02) verbal memory performance following adjustment for age, education, and psychiatric disorders. There was an inverse correlation between SHBG levels and BMI (Pearson's r = −0.37, n = 112, p < 0.001). Estimated free testosterone levels revealed curvilinear associations with verbal memory performance.

Conclusion—Our data suggest that higher SHBG levels are associated with worse verbal memory, whereas a higher BMI is associated with better verbal memory in older men. Higher SHBG levels due to lower adiposity may be a risk factor for cognitive dysfunction. The mechanisms linking SHBG to cognitive function have yet to be elucidated.

Correspondence: Yoichiro Takayanagi M.D., Ph.D., Johns Hopkins Bloomberg School of Public Health, 624 North Broadway, Baltimore, MD 21212, United States, Phone: 410 614 2410 Fax: 410 614 7469, y-takayanagi@sky.707.to.

Conflict of interest
No disclosures to report

INTRODUCTION

Human cognitive performance is affected by factors such as age and educational attainment. In addition, recent studies suggest that physical conditions (e.g., sex hormone imbalances,[1, 2] metabolic disturbances,[3] psychiatric disorders[4–7]) may have a substantial impact on cognitive performance.

Evidence derived from animal models suggests that testosterone may have a neuroprotective effect and prevent cognitive decline.[8, 9] Hence, age-related declines in testosterone levels [2] may be linked to cognitive decline in men. However, research evaluating the association between the bioavailability of endogenous testosterone and levels of free testosterone (FT) with cognitive function in men provides mixed results.[2] Sex hormone binding globulin (SHBG) is a testosterone transport protein that affects circulating levels of FT. Few studies have tested the relationship between serum SHBG levels and cognitive function; however a recent study identified a negative correlation between SHBG levels and cognition in elderly men.[10] Similarly, a separate study demonstrated that older men and women with higher levels of SHBG had an elevated risk for developing Alzheimer's disease (AD).[11]

Metabolic syndrome has been defined as a clustering of clinical and biochemical risk factors including central obesity, dyslipidemia, hypertension, and insulin resistance which increase the risk for developing type 2 diabetes and cardiovascular disease.[12] The relationship between metabolic syndrome and cognition has been extensively studied. Moreover, obesity, [13] hypertension, [14] and type-2 diabetes [15] have been linked to cognitive impairment. To date, relatively few studies that have assessed the association between cognitive function with both sex hormones and metabolic parameters in older men; even fewer studies have used structured psychiatric interviews to measure the extent of psychopathology. However, use of appropriate assessment measures evaluating psychopathology is paramount in this line of research because psychiatric illness may confound the association between hormones and/or metabolic parameters with cognitive outcomes. Our study evaluated the association of testosterone, SHBG, and metabolic parameters with memory performance in older men from the Baltimore Epidemiologic Catchment Area study.

METHODS

Sample

The Baltimore Epidemiologic Catchment Area (ECA) Follow-Up Study is an ongoing, longitudinal, population-based cohort of adults originally interviewed in 1981 (N = 3481) and followed-up in 1982 (N = 2768), 1993 (N = 1920), and 2004 (N = 1071). The ECA was designed to collect data on the prevalence and incidence of psychiatric illness in an adult community sample according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition-Revised (DSM-III-R) criteria, as well as the use of, and need, for psychiatric services by individuals with psychiatric illness. Methods for the Baltimore ECA Follow-Up Study have been described in detail elsewhere.[16] We used data from Wave 4 (2003–2004), in which a sample of blood was requested from each of the 1071 respondents. The characteristics of the 683 who agreed to donate a blood sample are reported by Mezuk et al.[17]

Although the ECA wave 4 consists of 1071 participants, we selected individuals who met following criteria: (1) male gender (397/1071, 37%), (2) 50 years and older (282/397, 71%), (3) completed verbal memory assessment described below (244/282, 87%), (4) completed Mini-Mental State Examination[18](MMSE) and scored ≥27 (205/244, 84%), (5) their BMI assessed (183/205, 89%), and (6) donated blood at the interview (112/183, 61%), resulting a final sample size of 112. Compared with the 959 participants excluded from our analysis, the 112 participants included were older (61.3 years old vs. 58.6 years old; $t = 2.08$, $df = 1069$, $p = 0.04$), more likely to be white (78% vs. 60%; $\chi^2 = 13.3$, $df = 1$, $p < 0.01$), had more education (13.1 years vs. 12.4 years; $t = 2.58$, $df = 1069$, $p = 0.01$), and had a similar BMI (29.2 vs. 30.0; $t = -0.98$, $df = 940$, $p = 0.3$). We used a relatively high MMSE cut-point in an attempt to exclude subjects with mild cognitive impairment (MCI) or dementia; the conventional cut-point (≥24) would likely permit the inclusion of more participants with clinical levels of cognitive impairment, especially among the highly educated.[19] The study was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board. All participants provided written informed consent.

Assessment of cognitive function

Verbal memory was assessed by a modified version of the Rey Verbal Learning Test.[20] Detailed procedures of verbal memory assessment have been described elsewhere.[21] Briefly, participants listened to 20 common words, and were asked to recall them immediately in any order. After 20 minutes, they were asked to recall the same list again. The total number of words recalled at each time point served as measures of immediate and delayed recall, respectively.

Hormonal and other biochemical assays

Blood specimens were collected in participants' homes and delivered to the Johns Hopkins Cell Center to be centrifuged and separated into 1mL aliquots within 12 hours of collection. Aliquots were stored at −80°C for approximately 12 months before being transferred to the Johns Hopkins General Clinical Research Center Laboratory at the Johns Hopkins Bayview Medical Center for analysis. Samples were analyzed by laboratory technicians blinded to any information about the subject from the interview. Testosterone levels were measured using Human Testosterone RIA kits (Diagnostic Systems Laboratories, Inc). Sex Hormone Binding Globulin levels were analyzed with SHBG IRMA kits (Diagnostic Systems Laboratories, Inc). To calculate FT level, we used the Nanjee-Wheeler equation, which estimates FT using total testosterone and SHBG values.[22] Hemoglobin A1C (HbA1C), total cholesterol, and HDL cholesterol levels were also measured (Analyzer, Medical Computer Systems). Respective intra- and inter-assay coefficients of variation were 6.5% and 7.5% for SHBG, 5.2% and 6.9% for total testosterone level, 1.4% and 2.3% for HbA1C, and 3.1% and 3.7% for serum lipids. The sensitivities of assays were 0.1nmol/L for SHBG, 0.02 ng/ml for total testosterone, <1% for HbA1C, and 0.8% for serum lipids.

Assessment of obesity, diabetes and blood pressure

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Participants were considered diabetic if they hadanHbA1c ≥6.5% or used any anti-diabetic medications. Assessment of anti-diabetic drugs was based on participant

report. During the interview, blood pressure was measured twice with an OMRON model HEM-711 automatic blood pressure monitor with several minutes between each assessment in a seated position. The average of the two scores was calculated.

Psychiatric assessment

Trained interviewers administered the Diagnostic Interview Schedule (DIS), [23] a structured interview that yields psychiatric diagnoses based on DSM-III-R criteria.[24] Lifetime history of the following three psychiatric illnesses was evaluated and used for the present analysis: major depressive disorder (MDD) alcohol abuse or dependence, and substance abuse or dependence (excluding alcohol abuse or dependence).

Statistical Analysis

First, we calculated descriptive statistics to characterize our sample and examined simple correlations among demographics, immediate/delayed memory scores, sex hormones and metabolic parameters (e.g., BMI, total testosterone, FT, SHBG, total cholesterol, HDL cholesterol, hypertension, and diabetes) by calculating Pearson's r. To evaluate the association of sex hormones, metabolic syndrome parameters, and psychiatric disorders with immediate and delayed verbal memories, we first performed a series of nine linear regression analyses adjusting for age and years of education (Model 1), each with BMI, total testosterone, FT, SHBG, total cholesterol, HDL cholesterol, systolic/diastolic blood pressure, or diabetes as the primary predictor. Next, we repeated these analyses, and adjusted for three dichotomous variables simultaneously to each model (Model 2) representing whether a history was present for the following three categories of psychiatric disorders: (1) substance abuse or dependence, (2) alcohol abuse or dependence and (3) major depressive disorder. We also conducted these multivariate linear regression analyses using the subjects selected by a conventional cut-off score for the MMSE (i.e., MMSE score ≥24, sample size = 124). As previous papers have shown curvilinear associations of FT with cognition (reviewed by Holland et al., 2011) [2] we conducted additional linear regression analyses using curvilinear variables (squared total testosterone or squared FT) as an independent variable alongside with a non-squared variable (total testosterone or FT) without other covariates.

All statistical analyses were conducted using SPSS version 19. Statistical significance was set at $p<0.05$ (two-tailed).

RESULTS

On average, participants were 61.3 ± 9.9 years old (Table 1). Approximately 22% were non-white with 13.1 ± 2.6 years of education. Participants' mean MMSE, immediate and delayed verbal memory scores were 29.0 ± 1, 6.9 ± 2.7 and 5.5 ± 2.7, respectively. They had a mean BMI of 29.2 ± 5.9, total cholesterol of 190.7 ± 38.4 mg/dl, HDL cholesterol of 48.8 ± 14.9 mg/dl, total testosterone of 2.8 ± 1.5 nmol/L, estimated FT of 0.17 ± 0.1 nmol/L, and SHBG of 71.2 ± 41 nmol/L. Of the 112 participants, 10 (9%) had a history of substance abuse or dependence, 18 (16%) had a history of alcohol abuse or dependence, and 8 (7%) had a

history of major depressive disorder. Two participants met either the DSM-III criteria for schizophrenia or bipolar disorder at the wave interview in 1982.

In the simple correlations among cognition, sex hormones and metabolic parameters, SHBG levels were inversely associated with BMI ($r = -0.37$, $n = 112$, $p < 0.001$) and FT ($r = -0.36$, $n = 112$, $p < 0.001$) and positively correlated with HDL cholesterol ($r = 0.21$, $n = 112$, $p = 0.026$). Total testosterone negatively correlated with BMI ($r = -0.30$, $n = 112$, $p = 0.002$) and the diagnosis of diabetes ($r = -0.20$, $n = 112$, $p = 0.036$). However, a positive association between total testosterone and HDL cholesterol ($r = 0.23$, $n = 112$, $p = 0.016$) was observed. Higher BMI was associated with higher likelihood of having a diagnosis diabetes ($r = 0.23$, $n = 112$, $p = 0.016$); however, BMI negatively correlated with HDL cholesterol ($r = -0.30$, $n = 112$, $p = 0.002$) There were significant correlations between total testosterone and substance abuse/dependence ($r = 0.19$, $n = 112$, $p = 0.044$), BMI and alcohol abuse/dependence ($r = -0.21$, $n = 112$, $p = 0.03$), HDL cholesterol and alcohol abuse/dependence ($r = 0.24$, $n = 112$, $p = 0.01$). The full correlation matrix is shown in supplemental table 1.

Tables 2 and 3 represent the results of the series of linear regression analyses for immediate memory and delayed memory, respectively. BMI predicted a better immediate verbal memory after controlling for age and years of education (beta = 0.20, t = 2.48, df = 1,108, p = 0.015) and this remained significant even consider psychiatric diagnoses (beta = 0.21, t = 2.41, df = 1,105, p = 0.018). BMI and SHBG were associated with delayed verbal memory after adjustment for age and years of education (beta = 0.20, t = 2.37, df = 1,108, and p = 0.02 for BMI; beta = −0.18, t = −2.01, df = 1,108 and p = 0.047 for SHBG). After further adjustment for psychiatric diagnoses, BMI and SHBG remained significantly associated with delayed verbal memory (beta = 0.22, t = 2.46, df = 1,105, and p = 0.016 for BMI; beta = −0.19, t = −2.07, df = 1,105 and p = 0.041 for SHBG).

When we limited analyses to participants with a conventional cut-off score for the MMSE (i.e., MMSE score ≥ 24, sample size = 124), similar results were obtained for regression models which included BMI (beta = 0.18, t = 2.26, df = 1,117 and p = 0.03 for immediate recall in the fully adjusted model; beta = 0.18, t = 2.18, df = 1,117, and p = 0.03 for delayed recall in the fully adjusted model) and SHBG levels (beta = −0.16, t = −1.86, df = 1,117, and p = 0.05 for delayed recall, in the fully adjusted model).

In the additional linear regression analyses using curvilinear variables, although squared total testosterone did not predicted memory, squared FT predicted both immediate (beta = −0.58, t = −2.80, df = 1,109, and p = 0.006) and delayed (beta = −0.52, t = −2.50, df = 1,109, and p = 0.14) verbal memories.

As a sensitivity analysis, we further added the linear regression analyses that excluded participants with a history of cancer, since these individuals are likely to have lower BMI and may have confounded the results. We identified 10 subjects with a history of cancer. After their removal from the sample, higher BMI still predicted better scores of immediate recall (beta = 0.282, t = 3.39, df = 1,98, and p = 0.001 for model 1; beta = 0.298, t = 3.39, df

= 1,95, and p = 0.001 for model 2) and delayed recall (beta = 0.273, t = 3.15, df = 1,98, and p = 0.002 for model 1; beta = 0.300, t = 3.32, df = 1,95, and p = 0.001 for model 2).

DISCUSSION

In this study, we found that SHBG levels and BMI were associated with cognitive function in non-demented older men. While higher BMI was associated with better verbal memory, higher SHBG levels correlated with poorer verbal memory. Our data also suggest a curvilinear correlation between FT and verbal memory. Despite past research supporting inverse associations between cognitive function and diabetes or hypertension, [14, 15] we failed to detect these negative associations.

A few prior studies have tested the association between serum SHBG levels and cognition or risk of dementia. Yaffe et al.[25] reported that SHBG levels were inversely associated with cognitive function (e.g. MMSE, Trails B, and Digit Symbol), but were no longer significant after adjustment for age and education. Lessove-Schlaggar et al.[26] did not find a correlation between SHBG and cognition. Recently, LeBlanc et al.[10] reported a negative correlation of SHBG levels with cognition using the Trails B and global cognitive function tests. Moreover, they reported that higher SHBG levels were associated with an increased risk of cognitive decline. Finally Muller et al [11] reported that higher levels of SHBG were associated with an increased risk for Alzheimer's disease. Our data provides further evidence supporting the inverse association between higher SHBG levels and cognitive function in men.

Our results conflict with those from previous studies which showed an inverse association between BMI and cognitive function.[27] However, there is a notion that adiposity may predict a better survival and/or outcome for older adults in select illnesses.[28–30] In fact, there are studies which demonstrated that lower BMI in late life (75 years) predicted cognitive decline,[31] or alternatively that higher BMI in late life (75 years) was protective against developing dementia.[32] As in prior research, [33] we found a negative association between BMI and SHBG levels (i.e. higher BMI correlated with lower SHBG levels). Moreover, lower SHBG levels predicted better verbal memory in this study. Hence, the positive association between BMI and verbal memory might be mediated in part by SHBG (when both variables were included in the equation neither were statistically significant predictors). These data suggest that SHBG is a key molecule in the "obesity paradox" for cognitive decline in older men. It has been suggested that SHBG may have neuroendocrine functions [34]; however, the roles of SHBG in the brain are still unclear and further investigation is required to address these contradicting associations. One possible hypothesis considers the involvement of leptin. Gomez et al.[35] reported a negative relationship between serum SHBG levels and leptin levels. Moreover, two recent large-scale studies reported a positive correlation between serum leptin levels and cognitive function in older persons (mean age = 79 years old), [36] and younger people (mean age = 36 years old).[37] The inverse correlation of SHBG levels with cognitive function found in this study might have been mediated by the positive impact of leptin on cognitive function. Meanwhile, higher SHBG level might be both favorable and harmful for physical health in older men, since previous studies have shown negative associations of SHBG levels and insulin resistance (or type 2

diabetes), metabolic syndrome, or cardiovascular disease mortality, [38–40] whereas a positive correlation of SHBG levels and osteoporosis has been also reported (reviewed by Hoppe et al.). [41]

We demonstrated a curvilinear association of FT with verbal memory, consistent with past literatures (reviewed by Holland et al.).[42] This supports the notion that there is an "optimal FT level range" with regard to better cognition among older men.

Our study has several limitations. First, it lacked the measurement of estradiol levels, although the effects of this hormone in men are arguable.[43] Second, only MMSE and verbal memory were available in this study. Since past studies have demonstrated the association between SHBG levels and executive function/overall cognitive performance, [10, 25] future studies should include broader neurocognitive domains. Third, since data regarding anti-diabetic and blood pressure lowering medications were from participant report, there may have been a risk for recall bias. Fourth, due to the relatively modest sample size of this study, the number of participants who had histories of psychiatric disorders was small and therefore we may not have had the sufficient statistical power in terms of elucidating the relationships between cognition and psychiatric illness. Finally, psychotropic/anti-epileptic drugs or thyroid status may have altered sex hormone levels [44] or cognition, [45–47] but we were unable to consider these effects in this study.

Conclusion

Our data suggest a negative impact of SHBG levels on cognitive function in older men. Metabolic disturbances (excluding obesity), and psychiatric illness were not associated with cognition in this study. The underlying mechanisms linking SHBG to cognition require further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study is supported by an NIH grant (DA 026652 to WWE)

References

1. Etgen T, Bickel H, Forstl H. Metabolic and endocrine factors in mild cognitive impairment. Ageing Res Rev. 2010; 9(3):280–288. [PubMed: 20109582]
2. Holland J, Bandelow S, Hogervorst E. Testosterone levels and cognition in elderly men: A review. Maturitas. 2011; 69(4):322–337. [PubMed: 21696899]
3. Yaffe K. Metabolic syndrome and cognitive disorders: Is the sum greater than its parts? Alzheimer Dis Assoc Disord. 2007; 21(2):167–171. [PubMed: 17545744]
4. Scheurich A. Neuropsychological functioning and alcohol dependence. Curr Opin Psychiatry. 2005; 18(3):319–323. [PubMed: 16639156]
5. Beveridge TJ, Gill KE, Hanlon CA, Porrino LJ. Review. parallel studies of cocaine-related neural and cognitive impairment in humans and monkeys. Philos Trans R Soc Lond B Biol Sci. 2008; 363(1507):3257–3266. [PubMed: 18640916]

6. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med. 2011; 5(1):1–8. [PubMed: 21321675]
7. Hasselbalch BJ, Knorr U, Kessing LV. Cognitive impairment in the remitted state of unipolar depressive disorder: A systematic review. J Affect Disord. 2011; 134(1–3):20–31. [PubMed: 21163534]
8. Leranth C, Petnehazy O, MacLusky NJ. Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. J Neurosci. 2003; 23(5):1588–1592. [PubMed: 12629162]
9. Meydan S, Kus I, Tas U, et al. Effects of testosterone on orchiectomy-induced oxidative damage in the rat hippocampus. J Chem Neuroanat. 2010; 40(4):281–285. [PubMed: 20696235]
10. LeBlanc ES, Wang PY, Janowsky JS, et al. Association between sex steroids and cognition in elderly men. Clin Endocrinol (Oxf). 2010; 72(3):393–403. [PubMed: 19744108]
11. Muller M, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Sex hormone binding globulin and incident alzheimer's disease in elderly men and women. Neurobiol Aging. 2010; 31(10):1758–1765. [PubMed: 19022535]
12. Grundy SM, Brewer HB Jr, Cleeman JI, et al. Definition of metabolic syndrome: Report of the national heart, lung, and blood Institute/American heart association conference on scientific issues related to definition. Circulation. 2004; 109(3):433–438. [PubMed: 14744958]
13. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and alzheimer disease. Arch Neurol. 2005; 62(10):1556–1560. [PubMed: 16216938]
14. Novak V, Hajjar I. The relationship between blood pressure and cognitive function. Nat Rev Cardiol. 2010; 7(12):686–698. [PubMed: 20978471]
15. Strachan MW, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. Nat Rev Endocrinol. 2011; 7(2):108–114. [PubMed: 21263438]
16. Eaton WW, Kalaydjian A, Scharfstein DO, Mezuk B, Ding Y. Prevalence and incidence of depressive disorder: The baltimore ECA follow-up, 1981–2004. Acta Psychiatr Scand. 2007; 116(3):182–188. [PubMed: 17655559]
17. Mezuk B, Eaton WW, Zandi P. Participant characteristics that influence consent for genetic research in a population-based survey: The baltimore epidemiologic catchment area follow-up. Community Genet. 2008; 11(3):171–178. [PubMed: 18376114]
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12(3):189–198. [PubMed: 1202204]
19. O'Bryant SE, Humphreys JD, Smith GE, et al. Detecting dementia with the mini-mental state examination in highly educated individuals. Arch Neurol. 2008; 65(7):963–967. [PubMed: 18625866]
20. Lezak, MD. Neuropsychological Assessment. NY: Oxford University Press; 1976.
21. Cornoni-Huntley J, Ostfeld AM, Taylor JO, et al. Established populations for epidemiologic studies of the elderly: Study design and methodology. Aging (Milano). 1993; 5(1):27–37. [PubMed: 8481423]
22. Nanjee MN, Wheeler MJ. Plasma free testosterone--is an index sufficient? Ann Clin Biochem. 1985; 22 (Pt 4):387–390. [PubMed: 4041156]
23. Robins, L. NIMH Diagnostic Interview Schedule: Version III Revised (DIS-III-R). St. Louis: Washington University School of Medicine; 1989.
24. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3. Washington DC: 1987. Revised
25. Yaffe K, Lui LY, Zmuda J, Cauley J. Sex hormones and cognitive function in older men. J Am Geriatr Soc. 2002; 50(4):707–712. [PubMed: 11982672]
26. Lessov-Schlaggar CN, Reed T, Swan GE, et al. Association of sex steroid hormones with brain morphology and cognition in healthy elderly men. Neurology. 2005; 65(10):1591–1596. [PubMed: 16301487]
27. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: A 27 year longitudinal population based study. BMJ. 2005; 330(7504):1360. [PubMed: 15863436]

28. Freedman DM, Ron E, Ballard-Barbash R, Doody MM, Linet MS. Body mass index and all-cause mortality in a nationwide US cohort. Int J Obes (Lond). 2006; 30(5):822–829. [PubMed: 16404410]
29. Curtis JP, Selter JG, Wang Y, et al. The obesity paradox: Body mass index and outcomes in patients with heart failure. Arch Intern Med. 2005; 165(1):55–61. [PubMed: 15642875]
30. Beddhu S, Ramkumar N, Samore MH. The paradox of the "body mass index paradox" in dialysis patients: Associations of adiposity with inflammation. Am J Clin Nutr. 2005; 82(4):909–10. [PubMed: 16210724]
31. Cronk BB, Johnson DK, Burns JM. Alzheimer's Disease Neuroimaging Initiative. Body mass index and cognitive decline in mild cognitive impairment. Alzheimer Dis Assoc Disord. 2010; 24(2):126–130. [PubMed: 19571736]
32. Atti AR, Palmer K, Volpato S, Winblad B, De Ronchi D, Fratiglioni L. Late-life body mass index and dementia incidence: Nine-year follow-up data from the kungsholmen project. J Am Geriatr Soc. 2008; 56(1):111–116. [PubMed: 18028342]
33. Caldwell JD, Jirikowski GF. Sex hormone binding globulin and aging. Horm Metab Res. 2009; 41(3):173–182. [PubMed: 18956301]
34. Herbert Z, Gothe S, Caldwell JD, et al. Identification of sex hormone-binding globulin in the human hypothalamus. Neuroendocrinology. 2005; 81(5):287–293. [PubMed: 16155373]
35. Gomez JM, Maravall FJ, Gomez N, Navarro MA, Soler J. Determinants of sex hormone-binding globulin concentrations in a cross-sectional study of healthy men randomly selected. J Nutr Health Aging. 2007; 11(1):60–64. [PubMed: 17315082]
36. Holden KF, Lindquist K, Tylavsky FA, et al. Serum leptin level and cognition in the elderly: Findings from the health ABC study. Neurobiol Aging. 2009; 30(9):1483–1489. [PubMed: 18358569]
37. Beydoun MA, Beydoun HA, Shroff MR, Kitner-Triolo MH, Zonderman AB. Serum leptin, thyroxine and thyroid-stimulating hormone levels interact to affect cognitive function among US adults: Evidence from a large representative survey. Neurobiol Aging. 2011; 33(8):1730–1743. [PubMed: 21763035]
38. Lakshman KM, Bhasin S, Araujo AB. Sex hormone-binding globulin as an independent predictor of incident type 2 diabetes mellitus in men. J Gerontol A Biol Sci Med Sci. 2010; 65(5):503–509. [PubMed: 20106959]
39. Muller M, Grobbee DE, den Tonkelaar I, Lamberts SW, van der Schouw YT. Endogenous sex hormones and metabolic syndrome in aging men. J Clin Endocrinol Metab. 2005; 90(5):2618–2623. [PubMed: 15687322]
40. Kalme T, Seppala M, Qiao Q, et al. Sex hormone-binding globulin and insulin-like growth factor-binding protein-1 as indicators of metabolic syndrome, cardiovascular risk, and mortality in elderly men. J Clin Endocrinol Metab. 2005; 90(3):1550–1556. [PubMed: 15613437]
41. Hoppe E, Bouvard B, Royer M, Audran M, Legrand E. Sex hormone-binding globulin in osteoporosis. Joint Bone Spine. 2010; 77(4):306–312.10.1016/j.jbspin.2010.03.011 [PubMed: 20452803]
42. Holland J, Bandelow S, Hogervorst E. Testosterone levels and cognition in elderly men: A review. Maturitas. 2011; 69(4):322–337. [PubMed: 21696899]
43. Janicki SC, Schupf N. Hormonal influences on cognition and risk for alzheimer's disease. Curr Neurol Neurosci Rep. 2010; 10(5):359–366. [PubMed: 20535591]
44. Hogervorst E, Bandelow S, Combrinck M, Smith AD. Low free testosterone is an independent risk factor for alzheimer's disease. Exp Gerontol. 2004; 39(11–12):1633–1639. [PubMed: 15582279]
45. Quinlan P, Nordlund A, Lind K, Gustafson D, Edman A, Wallin A. Thyroid hormones are associated with poorer cognition in mild cognitive impairment. Dement Geriatr Cogn Disord. 2010; 30(3):205–211. [PubMed: 20798541]
46. Hamed SA. The aspects and mechanisms of cognitive alterations in epilepsy: The role of antiepileptic medications. CNS Neurosci Ther. 2009; 15(2):134–156. [PubMed: 19254331]
47. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: A meta-analysis. CNS Drugs. 2004; 18(1):37–48. [PubMed: 14731058]

Table 1

Clinical variables of subjects (N=112)

Age, mean (SD), years	61.3 (9.9)
White, n (%)	87 (78)
Education, mean (SD), years	13.1 (2.6)
Body mass index, mean (SD)	29.2 (5.9)
Total cholesterol (mg/dl), mean (SD)	190.7(38.4)
HDL cholesterol (mg/dl), mean (SD)	48.8 (14.9)
Systolic blood pressure (mmHg), mean (SD)	142.6 (23.0)
Diastolic blood pressure (mmHg), mean (SD)	83.9 (11.7)
Diabetes (%)	18 (16)
Total testosterone (nmol/L), mean (SD)	2.8 (1.5)
FT (nmol/L), mean (SD)	0.17 (0.10)
SHBG (nmol/L), mean (SD)	71.2 (41.0)
History of substance abuse or dependence (%)	10 (9)
History of alcohol abuse or dependence (%)	18 (16)
History of MDD (%)	8 (7)
MMSE score, mean (SD)	29.0 (1.0)
Immediate recall score, mean (SD)	6.9 (2.7)
Delayed recall score, mean (SD)	5.5 (2.7)

FT, estimated free testosterone; MDD, major depressive disorder; MMSE, Mini Metal State Examination; SHBG, sex hormone binding globulin.

Table 2

Associations between standardized immediate memory score and metabolic parameters/sex hormones[a]

	Models1[b]								Models2[c]							
	Variable values				Model values				Variable values				Model values			
Predictors[#]	Beta[##]	t	df	p	R^2	F	df	p	Beta[##]	t	df	p	R^2	F	df	p
SHBG	−0.13	−1.53	1,108	0.129					−0.14	−1.54	1,105	0.126				
TT	−0.12	−1.42	1,108	0.158					−0.13	−1.47	1,105	0.144				
FT	−0.07	−0.71	1,108	0.479					−0.07	−0.73	1,105	0.467				
BMI	0.20	2.48	1,108	0.015	0.27	14.90	3,108	<0.01	0.21	2.41	1,105	0.018	0.25	7.00	6,105	<0.01
Total cholesterol	0.02	0.27	1,108	0.789					0.03	0.28	1,105	0.777				
HDL cholesterol	−0.04	−0.51	1,108	0.608					−0.04	−0.47	1,105	0.637				
Systolic BP	−0.05	−0.60	1,108	0.551					−0.05	−0.63	1,105	0.533				
Diastolic BP	0.01	0.13	1,108	0.900					0.01	0.11	1,105	0.914				
Diabetes	0.08	0.94	1,108	0.349					0.08	0.94	1,105	0.350				

[a] Accessed by multiple linear regression analysis

[b] Adjusted for age and years of education

[c] Adjusted for age, years of education, diagnoses of psychiatric disorders (Substance abuse/dependence, alcohol abuse/dependence, and major depressive disorder)

BMI, body mass index; BP, blood pressure; FT, free testosterone; NS, not statistically significant; SHBG, sex hormone binding globulin; TT, Total testosterone

[#] Linear regression analyses were conducted separately for each predictor (i.e., total 9 equations for each model).

[##] Standardized coefficients

Table 3

Associations between standardized delayed memory score and metabolic parameters/sex hormones[a]

	Models1[b]								Models2[c]							
	Variable values				Model values				Variable values				Model values			
Predictors[#]	Beta[##]	t	df	p	R^2	F	df	p	Beta[##]	t	df	p	R^2	F	df	p
SHBG	−0.18	−2.01	1,108	0.047	0.21	10.66	3,108	<0.01	−0.19	−2.07	1,105	0.041	0.20	5.49	6,105	<0.01
TT	−0.04	−0.40	1,108	0.689					−0.05	−0.48	1,105	0.633				
FT	0.05	0.51	1,108	0.613					0.05	0.47	1,105	0.641				
BMI	0.20	2.37	1,108	0.020	0.22	11.32	3,108	<0.01	0.22	2.46	1,105	0.016	0.21	5.85	6,105	<0.01
Total cholesterol	0.06	0.67	1,108	0.503					0.05	0.58	1,105	0.561				
HDL cholesterol	−0.07	−0.76	1,108	0.449					−0.07	−0.75	1,105	0.455				
Systolic BP	−0.01	−0.10	1,108	0.918					−0.01	−0.07	1,105	0.943				
Diastolic BP	0.08	0.85	1,108	0.400					0.08	0.82	1,105	0.417				
Diabetes	0.12	0.34	1,108	0.183					0.13	1.37	1,105	0.173				

[a] Accessed by multiple linear regression analysis

[b] Adjusted for age and years of education

[c] Adjusted for age, years of education, diagnoses of psychiatric disorders (Substance abuse/dependence, alcohol abuse/dependence, and major depressive disorder)

BMI, body mass index; BP, blood pressure; FT, free testosterone; NS, not statistically significant; SHBG, sex hormone binding globulin; TT, Total testosterone

[#] Linear regression analyses were conducted separately for each predictor (i.e., total 9 equations for each model).

[##] Standardized coefficients