Published in final edited form as:
Dement Geriatr Cogn Disord. 2014 ; 38(0): 300–309. doi:10.1159/000361043.

Total Cholesterol and Neuropsychiatric Symptoms in Alzheimer's Disease: the Impact of Level and Gender

James R. Hall[a,b], **April R. Wiechmann**[a,b], **Leigh A. Johnson**[a,c], **Melissa Edwards**[d], **Robert C. Barber**[a,e], **Rebecca Cunningham**[a,e], **Meharvan Singh**[a,e], **Sid E. O'Bryant**[a,c], and **the Texas Alzheimer's Research and Care Consortium**

[a] Institute of Aging and Alzheimer's Disease Research, University of North Texas Health Science Center, Fort Worth, Texas, USA

[b] Department of Psychiatry and Behavioral Health, University of North Texas Health Science Center, Fort Worth, Texas, USA

[c] Department of Internal Medicine, University of North Texas Health Science Center, Fort Worth, Texas, USA

[d] Department of Psychology, University of North Texas, Denton, Texas, USA

[e] Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, Texas, USA

Abstract

Background—Neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) are a major factor in nursing home placement and a primary cause of stress for caregivers. Elevated cholesterol has been linked to psychiatric disorders and has been shown to be a risk factor for AD and to impact disease progression. The present study investigated the relationship been cholesterol and NPS in AD.

Methods—Data on cholesterol and NPS from 220 individuals (144 females, 76 males) with mild to moderate AD from the TARCC (Texas Alzheimer's Research and Care Consortium) cohort was analyzed. Total number of NPS, symptoms of hyperactivity, psychosis, affect and apathy were evaluated. Groups based on total cholesterol (TC) above and below 200 were compared on NPS. The impact of gender was also assessed.

Results—Individuals with high TC had lower MMSE and significantly more NPS and more symptoms of psychosis. When stratified by gender males with high TC had significantly more NPS than high TC females or low TC males or females.

Discussion—The role of elevated cholesterol in the occurrence of NPS in AD appears gender and symptom specific. Cross validation of these findings has implications for interventions especially for males with high TC.

Correspondence to: James R. Hall, PhD, Department of Psychiatry, University of North Texas Health Science Center, 3500 Camp Bowie Blvd., Fort Worth, Texas, USA 76107; 817-735-2326; Fax 817-735-0615; james.hall@unthsc.edu.

Competing Interests: The authors have no competing interests to report.

Keywords

Cholesterol; Neuropsychiatric Symptoms; Alzheimer's Disease

Introduction

The findings on the relationship of total cholesterol to Alzheimer's disease (AD) have been inconsistent. High cholesterol during midlife has been found to increase the risk for AD [1-3] as well as impact disease progression in the elderly [4-6]. Recent work has provided evidence linking altered cholesterol metabolism and hypercholesterolemia to amyloid plaque formation and tau hyperphosporylation [7]. Even mild hypercholesterolemia has been linked to AD pathology [8]. However other studies have found an association between higher cholesterol in late life and reduced risk for dementia [9, 10]. The Honolulu-Asia Aging Study found that cholesterol levels decline before the onset of dementia [11]. Still others have found significantly lower levels of total cholesterol (TC) in a community dwelling sample of demented elderly [12] and others have found no relationship between cholesterol and the risk for cognitive decline in the elderly [13].

Although there is no consensus on the role of cholesterol in the development of dementia, a large body of experimental and epidemiological research continues to focus on this potentially modifiable risk. The link between cholesterol and neuropsychiatric symptoms (NPS) in AD has not been extensively investigated. Woods et al. [14] suggested that disturbances in the cholesterol system may be a significant factor in the development of psychiatric disorders such as schizophrenia, autistic spectrum disorders and depression as well as AD. The mechanism through which serum cholesterol affects brain cholesterol and brain pathology is unclear at this time [15, 16]. It has been argued that high cholesterol triggers an inflammatory cascade that influences amyloid beta production [17]. Neuroinflammation has also been linked to a number of psychiatric disorders such as depression, schizophrenia and bipolar disorder [18]. The impact of cholesterol on inflammatory processes may be one possible pathway by which high serum cholesterol may affect the occurrence of neuropsychiatric symptoms in AD.

Prior work by our group [19]) has studied the relationship between inflammatory and clinical vascular risk biomarkers and the occurrence of NPS in mild to moderate AD. Regression analyses found total serum cholesterol to be a significant predictor of NPS but this relationship held only for males. We also found that APOEε4 status was not a significant factor in this relationship as cholesterol was a significant predictor for both male carriers and non-carriers [20]. The present study was conducted to investigate the extent to which level of cholesterol is the primary determinant of the relationship between serum cholesterol and NPS. Additionally, we sought to investigate the role of gender in this relationship. Total cholesterol of ≥200 has been widely used as a clinical cut-off [21] for the diagnosis of borderline high cholesterol. In the current study, individuals diagnosed with mild-moderate AD were separated into two groups based on total serum cholesterol level and the impact of cholesterol on the occurrence of NPS was assessed.

Materials and Methods

Participants

The sample was drawn from the individuals enrolled in the longitudinal research cohort of the Texas Alzheimer's Research Care and Consortium (TARCC) who had complete serum biomarker panel, were genotyped for APOEε4 status and had a completed Neuropsychiatric Inventory (NPI) interview. TARCC is a longitudinal multi-site study of a cohort of AD, Mild Cognitive Impairment and normal controls where each participant undergoes an annual evaluation that includes a medical examination, interview, neuropsychological testing, and blood draw. AD patients met consensus-based diagnosis for probable AD based on NINCDS-ADRDA criteria [22]. The final sample of 220 consisted of 144 females and 76 males meeting the diagnostic criteria for AD. As part of the evaluation the MMSE, a screening measure of cognitive functioning was administered. A global dementia rating (CDR-Global) based on interview data was determined along with the CDR Sum of Boxes (CDR-SB), which is a measure of functional impairment where higher scores indicate greater impairment. The mean age of the sample was 77.55 (*SD*=8.416) with an average education of 14.11 years (*SD*= 3.203), a mean MMSE of 19.09 (*SD*= 6.202), a mean CDR-Global score of 1.35 (*SD*= .766) and a mean CDR-SB of 7.95 (*SD*= 4.413). Genotyping revealed that 59% of the sample was APOEε4 carriers and 41% were non-carriers. The total years of education was determined from the patient's self-report of completed years of education. Institutional Review Board approval was obtained at each TARCC site and written informed consent was obtained from all participants and/or caregivers.

Methods

As part of the TARCC evaluation, the NPI-Q was administered to family members or caregivers with direct knowledge of participant's behavior. The NPI-Q is a brief informant-based assessment of NPS that has been shown to be valid and reliable [23]. The informant reports the presence of twelve NPS and rated their severity on a 1-3 scale from mild to severe. As in our previous research [19, 20], we utilized the four factors found by Aalten and colleagues [24]. This factor structure was based on a total NPI score (sum of each item multiplied by its severity score); however, we chose to utilize only the total number of NPS as our focus was on the occurrence of the symptoms not the perceived severity. The four NPI factors include the hyperactivity factor composed of the NPI items of agitation, disinhibition, irritability, aberrant motor behavior and euphoria; the psychosis factor which includes delusions, hallucinations and night-time behavior disturbances; the affective symptoms factor made up of depression and anxiety items; and the apathy factor which includes the apathy ,appetite and eating abnormalities items. Data were recorded for the presence of each of the 12 NPS and these items were summed to produce a score for the total number of symptoms. The number of symptoms reported for each factor were summed and made up the score for each factor.

Biomarkers

The TARCC research platform used the Rules Based Medicine multiplexed immunoassay Multi-Analyte Profile (humanMAP) which is able to simultaneously assay over 152 serum-based biomarkers. This platform has been utilized in the development of blood-based

algorithms for the detection of Alzheimer's [25] and the development of test specific blood-based algorithms of cognitive impairment [26]. For the current study total cholesterol was the biomarker of interest as our earlier work found that components of HDL, LDL and triglycerides individually were not significant predictors of NPS. Baseline lipid profiles and homocysteine levels of the participants were obtained through collaboration with the Atherosclerosis Clinical Research Laboratory at Baylor College of Medicine.

Assays

Non-fasting samples were collected with 10mL serum-separating (tiger-top) vacutainers tubes at the time of interview. Samples were allowed to clot at room temperature for 30 minutes in a vertical position before being centrifuged at 1300 × g for 10 minutes. Next, 1mL aliquots were pipetted into polypropylene cryovial tubes and placed in −20° C (non-frost free) or −80° C freezers until shipment to TARCC Biobank. Total processing time (stick to freezer) was two hours or less. Baseline lipid profiles and homocysteine levels of the participants were obtained through the Atherosclerosis Clinical Research Laboratory at Baylor College of Medicine. Lipids were measured in serum using an AU400e automated chemistry analyzer (Olympus America, Center Valley, PA).

Data Analysis

Participants with total serum cholesterol >200 were defined as belonging to the high TC group. Those with serum cholesterol ≤were sorted in the low TC group. Categorical data were analyzed with Chi square goodness of fit test and differences on demographic variables, NPI scores and Cholesterol were analyzed by t-tests and Multivariate Analysis of Variance. Odds Ratios for the presence and absence of NPS were calculated.

Results

Table 1 presents the demographic characteristics of the sample split by gender and cholesterol level. The female sample was significantly older than the male sample $F(1, 219) = 11.842$, $p = .001$). There were no significant differences observed between males and females on years of education, MMSE, CDR Global or CDR-SB. Females had significantly higher levels of total cholesterol ($M = 220.78$, $SD = 49.343$) than males ($M = 189.24$, $SD = 40.692$, $t(218) = 4.761$, $p \leq .0001$). Significantly more females than males had total cholesterol above 200 ($X^2(1) = 14.091$, $p = .0002$). Females in the high total cholesterol group (High TC) had significantly higher levels of cholesterol ($M = 243.41$, $SD = 41.335$) than the males in High TC group ($M = 227.24$, $SD = 26.686$, $t(133) = 2.104$, $p = .0373$). There was no difference between APOEε4 carriers and non-carriers in cholesterol level ($X^2(1) = 1.739$, $p = .187$). When analyzed by gender, no differences between were found APOEε4 carriers and non-carriers for cholesterol level for either males ($X^2(1) = .020$, $p = .888$) or females ($X^2(1) = .529$, $p = .469$).

The High TC and the Low TC groups did not differ significantly on age or education. The MMSE score for the High TC group was significantly lower than the Low TC group ($t(218) = 3.425$, $p = .000$). The CDR Global, ($t(218) = 2.939$, $p = .004$) and CDR-SB ($t(218) = 3.064$, $p = .003$) scores were both significantly higher in the High TC group indicating

greater impairment. Analysis of variance revealed that individuals with total cholesterol ≥ 200 were reported to have significantly more total NPS than those with total cholesterol ≤ 199 $F(1, 218) = 3.90$, $p = .007$) and had more reported symptoms of psychosis $F(1, 218) = 8.046$, $p = .005$). The two groups did not differ on reported symptoms of hyperactivity, apathy, or affective symptoms.

Table 2 presents the NPS by gender and cholesterol level. Males did not differ from Females on any of the NPI variables. A significant main effect for cholesterol level was found for total number of NPS $F(1, 216) = 7.426$, $p = .007$), hyperactive symptoms F (1,216) = 4.346, $p = .038$), and psychosis symptoms $F(1,216) = 10.863$, $p = .001$). A significant gender X cholesterol interaction was found for total NPS $F(1,216) = 4.546$, $p = .034$), psychosis symptoms $F(1,216) = 3.934$, $p = .049$) and affective symptoms F (1,216) = 6.024, $p = .015$).

To clarify these findings, the relationship between gender and cholesterol level was investigated. Analyses comparing High TC females with High TC males found that the females had significantly higher MMSE than the males ($t(131) = 2.210$, $p = .028$), but the two groups did not differ on CDR Global score ($p = .745$) or CDR-SB ($p = .4515$). Low TC females had significantly lower MMSE scores than Low TC males ($t(85) = 2.996$, $p = .004$) and significantly higher CDR-SB than Low TC males ($t(85) = 2.875$, $p = .005$) although the Low TC groups did not differ on CDR Global ($p = .092$). When analyzing the female sample alone there were no differences between the High TC group and the Low TC group on total number of NPS or any of the symptom factors. Nor were differences found for MMSE, CDR-Global, or CDR-SB. Analyses comparing High TC males and Low TC males revealed a different relationship. The MMSE scores were significantly different ($t(74) = 4.638$, $p = .0001$) with High TC males having a mean MMSE of 15.85 ($SD = 7.459$) and Low TC males having a mean MMSE of 22.54 ($SD = 5.114$). There was a significant difference between the groups for CDR-Global score ($t(74)= 2.519$, $p = .014$) and on CDR-SB. High TC males had a mean CDR-SB of 9.17 ($SD = 4.410$) compared to Low TC males having a mean of 5.52 ($SD = 4.039$) $t(74) = 3.709$, $p = .0004$). The males in the High TC group had significantly more total NPS ($t(74) = 2.855$, $p = .006$), more psychosis symptoms ($t(74) = 3.245$, $p = .002$) and significantly more affective symptoms ($t(74) = 2.322$, $p = .023$). There was a trend for males with cholesterol above 200 to have more symptoms of hyperactivity ($p = .080$) and more symptoms of apathy ($p = .067$) but these differences did not reach statistical significance.

Table 3 presents the Odds Ratios (OR) for the presence and absence of NPS for cholesterol ≥200. For the overall sample, only symptoms of psychosis ($p = .034$) and hyperactivity ($p = .017$) were significantly related to cholesterol level. Individuals with High TC were 1.8 and 2 times more likely, respectively, to have one or more symptoms of psychosis and hyperactivity than those with lower cholesterol. The OR for affective symptoms and symptoms of apathy suggests that the occurrence of these symptoms is not closely tied to cholesterol level when the total sample is considered.

The determination of the OR for the occurrence of total NPS was effected by the very small number of individuals who had no reported NPS. Given that the vast majority of individuals in the sample were reported to exhibit at least one NPS regardless of cholesterol level,

analyses were conducted based on comparing individuals with three or fewer symptoms (the approximate median number of NPS for the sample) and those reported to have four or more symptoms. The likelihood of having four or more symptoms was 2.173 (95% CI 1.253-3.767, p = .007) times greater for the High TC group.

The role of elevated cholesterol appears gender and symptom specific. When comparing High TC males to High TC females, males were 2.66 (95% CI 1.142-6.243, p= .027) times more likely than females to have 4 or more NPS. High TC males were 2.78 (95% CI 1.023-7.544, p= .045) times more likely to have hyperactive symptoms; 2.34 (95% CI 1.001-5.453, p= .049) times more likely to have affective symptoms and 2.58 (95% CI 1.052-6.216, p= .038) times more likely to have symptoms of apathy than High TC females. There was not a significant difference in the likelihood of having psychosis symptoms. When looking at each gender separately, for males having elevated total cholesterol significantly increased the likelihood of having symptoms of psychosis almost 4 times and of having apathy symptoms over 3 times compared to males with lower cholesterol. Although not reaching significance, there was a trend suggesting a relationship between High TC in males and the occurrence of hyperactive and affective symptoms. The likelihood of High TC males having four or more NPS was 4.5 times greater (95% CI 1.681-12.045, p = .002) than for the Low TC group. For females, only symptoms of hyperactivity were significantly related to elevated cholesterol and increased the likelihood of having one or more symptoms of hyperactivity by 2.25 times (p = .029) compared to Low TC females. Neither symptoms of psychosis nor affective symptoms nor symptoms of apathy were significantly related to high cholesterol for this group. The likelihood of High TC females having four or more NPS was not significantly different than the Low TC females (OR= 1.452 95% CI .7125-2.958, p = .303).

Analysis of the individual NPI symptoms revealed a significant main effect for TC level for symptoms of delusions (F(1,216) = 6.098, p= .014), motor symptoms (F(1,216) = 10.131, p=.002) and sleep related symptoms (F(1,216) = 5.231, p= .023). There was a significant effect for gender only for the irritability symptoms (F(1,216) = 7.111, p= .008)where significantly more symptoms were reported for males than females. Significant level by gender interactions were found for anxiety symptoms (F(1,216) = 6.543, p= .011), apathy (F(1,216) = 4.947, p= .027) and sleep related symptoms (F(1,216) = 4.067, p= .045). Post-hoc analyses of the impact of cholesterol level on specific symptoms revealed no significant differences between High and Low TC females on any of the items. Compared to Low TC males, High TC males were reported to have significantly more delusions (t(74) = 2.735, p= .008); more anxiety symptoms (t(74) = 2.502, p= .015); more symptoms of motor disturbances (t(74) = 2.851, p= .006) and more sleep related symptoms (t(74) = 3.152, p= .002). Table 4 presents the Odds Ratios for each of the NPI items for the male sample. High TC males were over 5 times more likely to have reported symptoms of motor disturbances and delusions than low TC males. Anxiety symptoms and sleep related symptoms were over 3 times more likely.

Discussion

NPS in AD increase caregiver stress [27, 28] and increase the likelihood of nursing home placement [29]. Many of the available pharmacological interventions for these symptoms are either potentially harmful or unproven [30]. Discovering the characteristics of individuals who are more likely to exhibit NPS could lead to the development of interventions to reduce their occurrence. The current findings provide support for serum cholesterol playing a significant role in the number and type of NPS in AD. The results suggest that borderline to high levels of total serum cholesterol are associated with NPS and that there are significant differences in the occurrence of NPS based on level of cholesterol.

In our study, the High TC group scored significantly lower on MMSE and scored higher on measures assessing stage of decline and functional impairment where higher indicates greater decline. Elevated serum cholesterol has been shown to influence the rate of disease progression [31]. NPS in AD have been shown to slightly increase over the course of the disease [32] and to be relatively persistent [33, 34]. NPS, especially hallucinations and apathy [35], are also related to global functional impairment over time. It could be argued that our finding of greater global impairment and higher number of NPS for High TC reflects disease severity as much as any specific effect of cholesterol.

This position fails to account for the significant gender differences found in the relationship of cholesterol to NPS. In our study the effect of cholesterol on the occurrence of NPS is greatly influenced by gender. Although High TC females had higher MMSE scores than High TC males, the two groups did not differ on stage of decline or level of functional impairment. Females in our sample had significantly higher cholesterol and a significantly higher percentage of had TC above 200, yet females and males did not differ on the occurrence of NPS. The High and Low TC females did not differ on any of the NPS variables. The differences found in NPS for cholesterol level appears to be driven by the High TC males. This group had significantly more total NPS and symptoms of psychosis and affective symptoms than the Low TC males.

The odds of having multiple NPS and symptoms of hyperactivity, apathy and affective symptoms were significantly higher for High TC males compared to High TC females and Low TC males. In our sample, High TC males were over 2 times more likely to have symptoms of hyperactivity (OR= 2.78, p= .045), affective symptoms (OR=2.34, p= .049) and symptoms of apathy (OR= 2.35, p= .048) when compared with the rest of the total sample regardless of gender or cholesterol group.

There are a number of limitations that may affect the generalizability of the findings. The size of the sample was relatively small although the cohort is well characterized as an AD cohort. Analyzing by gender and grouping by cholesterol level further reduced sample size. The study is cross-sectional and conclusions would be strengthened by looking longitudinally at the impact of high cholesterol. Additionally, the cholesterol measurements were made on non-fasting samples and as such may not be representative of the actual circulating level. The initial TARCC protocol did not include collection of data on the use of statins and other cholesterol lowering medications nor on the intitation or discontinuation of

these medications. This is an important limitation and may have introduced a confound. This information is being collected in ongoing cross-validation study, which will allow us to assess the impact of statin use. It is interesting to note that in general statin use among elderly women is significantly lower than among elderly males [36]. However, even in the absence of knowledge about medications, individuals with total cholesterol ≥200 at the time of the assessment showed a significantly different pattern of NPS.

The current findings are suggestive of the importance of understanding the role of cholesterol and gender in the occurrence of NPS in AD. The mechanism by which high cholesterol appears to differentially impact Males in the occurrence of NPS is unclear and beyond the scope of the current research. Cross validating these finding in larger samples has significant implications for possible treatment interventions to reduce the occurrence of NPS in AD

Acknowledgments

Research reported in this publication was supported by the National Institute on Aging of the National Institutes of Health under Award Numbers R01AG039389 and P30AG12300. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This study was made possible by the Texas Alzheimer's Research and Care Consortium (TARCC) funded by the state of Texas through the Texas Council on Alzheimer's Disease and Related Disorders. The funders had no role in study design, data collection, analysis, decision to publish, or preparation of the manuscript. Investigators from the Texas Alzheimer's Research and Care Consortium: Baylor College of Medicine: Rachelle Doody, MD, PhD, Susan Roundtree, MD , Valory Pavlik, PhD, Wen Chan, PhD, Paul Massman, PhD, Eveleen Darby, Tracey Evans; Texas Tech University Health Science Center: Benjamin Williams, MD, Gregory Schrimsher, PhD, Andrew Dentino, MD, Ronnie Orozco,; University of North Texas Health Science Center: Thomas Fairchild, PhD, Janice Knebl, DO, Douglas Mains, Lisa Alvarez; University of Texas Southwestern Medical Center: Perrie Adams, PhD, Roger Rosenberg, MD, Myron Weiner, MD, Mary Quiceno, MD, Joan Reisch, PhD, Ryan Huebinger, PhD, Guanghua Xiao, PhD, Doris Svetlik, Amy Werry, Janet Smith; University of Texas Health Science Center – San Antonio: Donald Royall, MD, Raymond Palmer, PhD, Marsha Polk.

References

1. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 2001; 322:1447–51. [PubMed: 11408299]
2. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, Helkala EL, Tuomilehto J, Soininen H, Nissinen A. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005; 62:1556–60. [PubMed: 16216938]
3. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005; 64:277–81. [PubMed: 15668425]
4. Reiss AB, Siller KA, Rahman MM, CHAN ES, Ghiso J, de Leon MJ. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol. 2004; 61:705–14. [PubMed: 15148148]
5. Shobab LA, Hsiung GY, Feldman HH. Cholesterol in Alzheimer's disease. Lancet Neurol. 2005; 4:841–52. [PubMed: 16297842]
6. Panza F, D'Introno A, Colacicco AM, Capurso C, Pichichero G, Capurso SA, Capurso A, Solfrizzi V. Lipid metabolism in cognitive decline and dementia. Brain Res Rev. 2006; 51:275–92. [PubMed: 16410024]
7. Gamba P, Testa G, Sottero B, Gargiulo S, Poli G, Leonarduzzi G. The link between altered cholesterol metabolism and Alzheimer's disease. Ann N Y Acad Sci. 2012; 1259:54–64. doi: 10.1111/j.1749-6632.2012.06513.x. [PubMed: 22758637]
8. Pappolla MA, Bryant-Thomas TK, Herbert D, Pacheco J, Fabra Garcia M, Manjon M, Girones X, Henry TL, Matsubara E, Zambon D, Wolozin B, Sano M, Cruz-Sanchez FF, Thal LJ, Petanceska

SS, Refolo LM. Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. Neurology. 2003; 61:199–205. [PubMed: 12874399]

9. Reitz C, Tang MX, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol. 2004; 61:705–14. [PubMed: 15148148]
10. Mielke MM, Zandi PP, Sjögren M. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology. 2005; 64:1689–95. [PubMed: 15911792]
11. Stewart R, White LR, Xue QL, Launer LJ. Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol. 2007; 64:103–7. [PubMed: 17210816]
12. Zuliani G, Cavalieri M, Galvani M, Volpato S, Cherubini A, Bandinelli S, Corsi AM, Lauretani F, Guralnik JM, Fellin R, Ferrucci L. Relationship between low levels of high-density lipoprotein cholesterol and dementia in the elderly. The InChianti study. J Gerontol A Biol Sci Med Sci. 2010; 65:559–64. doi: 10.1093/gerona/glq026. Epub 2010 Mar 18. [PubMed: 20299544]
13. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. Am J Geriatr Psychiatry. May. 2008; 16(5):343–54. doi: 10.1097/JGP.0b013e31816b72d4. [PubMed: 18448847]
14. Woods AG, Sokolowska I, Taurines R, Gerlach M, Dudley E, Thome J, Darie CC. Potential biomarkers in psychiatry: focus on the cholesterol system. J Cell Mol Med. 2012; 16(6):1184–95. doi: 10.1111/j.1582-4934.2012.01543.x. [PubMed: 22304330]
15. Mathew A, Yoshida Y, Maekawa T, Kumar DS. Alzheimer's disease: Cholesterol a menace? Brain Res Bull. 2011; 86:1–12. doi: 10.1016/j.brainresbull.2011.06.006. [PubMed: 21741455]
16. Sánchez-Ferro A, Benito-León J, Mitchell AJ, Bermejo-Pareja F. A review of the potential therapeutic role of statins in the treatment of Alzheimer's disease: current research and opinion. Neuropsychiatr Dis Treat. 2013; 9:55–63. doi: 10.2147/NDT.S29105. Epub 2013 Jan 4. [PubMed: 23319866]
17. Niranjan R. Molecular basis of etiological implications in Alzheimer's disease: focus on neuroinflammation. Mol Neurobiol. 2013; 48:412–28. doi: 10.1007/s12035-013-8428-4. [PubMed: 23420079]
18. Najjar S, Pearlman DM, Hirsch S, Friedman K, Strange J, Reidy J, Khoukaz M, Ferrell RB, Devinsky O, Najjar A, Zagzag D. Brain Biopsy Findings Link Major Depressive Disorder to Neuroinflammation, Oxidative Stress, and Neurovascular Dysfunction: A Case Report. Biol Psychiatry. Sep 13.2013 doi:pii: S0006-3223(13)00741-5.10.1016/j.biopsych.2013.07.041. [Epub ahead of print].
19. Hall JR, Wiechmann AR, Johnson LA, Edwards M, Barber RC, Winter AS, Singh M, O'Bryant SE. The relationship of biomarkers of Cardiovascular Risk, Systemic Inflammation and Microvascular Pathology to Neuropsychiatric Symptoms in Alzheimer's Disease. Journal of Alzheimer's Disease. 2013; 35:363–371. doi: 10.3233/JAD-122359.
20. Hall JR, Wiechmann AR, Johnson LA, Edwards ME, Barber RC, Cunningham R, Singh M, O'Bryant SE. The Impact of APOE Status on Relationship of Biomarkers of Vascular Risk and Systemic Inflammation to Neuropsychiatric Symptoms in Alzheimer's Disease. Journal of Alzheimer's Disease. in press.
21. American Heart Association. [November 2013] What your cholesterol levels mean. Dec 10. 2012 Available at http://www.heart.org/HEARTORG/Conditions/Cholesterol/AboutCholesterol/What-Your-Cholesterol-Levels-Mean_UCM_305562_Article.jsp.
22. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology. 1984; 34:939–944. [PubMed: 6610841]
23. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, Lopez OL, DeKosky ST. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci. 2000; 12:233–239. [PubMed: 11001602]
24. Aalten P, Verhey FR, Boziki M, Bullock R, Byrne EJ, Camus V, Caputo M, Collins D, De Deyn PP, Elina K, Frisoni G, Girtler N, Holmes C, Hurt C, Marriott A, Mecocci P, Nobili F, Ousset PJ, Reynish E, Salmon E, Tsolaki M, Vellas B, Robert PH. Neuropsychiatric syndromes in dementia.

Results from the European Alzheimer Disease Consortium: Part I. Dement Geriatr Cogn Disord. 2007; 24:457–463. [PubMed: 17986816]

25. O'Bryant S, Xiao G, Barber R, Reisch J, Hall J, Cullum CM, Doody R, Fairchild T, Adams P, Wilhelmsen K, Diaz-Arrastia R. A Blood-Based Algorithm for the Detection of Alzheimer's Disease. Dementia and Related Cognitive Disorders. 2011; 32:55–62.
26. O'Bryant S, Xiao G, Barber R, Cullum M, Weiner M, Hall JR, Grammas P, Diaz-Arrastia R. Molecular Neuropsychology: Creation of Test-Specific Blood Biomarker Algorithms. Dementia & Geriatric Cognitive Disorders. 2014; 37:45–57. [PubMed: 24107792]
27. Allegri RF, Sarasola D, Serrano CM, Taragano FE, Arizaga RL, Butman J, Loñ L. Neuropsychiatric symptoms as a predictor of caregiver burden in Alzheimer's disease. Neuropsychiatr Dis Treat. 2006; 2:105–110. [PubMed: 19412452]
28. Okura T, Langa KM. Caregiver burden and neuropsychiatric symptoms in older adults with cognitive impairment: The Aging, Demographics, and Memory Study (ADAMS). Alzheimer Dis Assoc Disord. 2011; 25:116–121. [PubMed: 21192239]
29. Tun SM, Murman DL, Long HL, Colenda CC, von Eye A. Predictive validity of neuropsychiatric subgroups on nursing home placement and survival in patients with Alzheimer disease. Am J Geriatr Psychiatry. 2007; 15:314–27. [PubMed: 17384314]
30. Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, Cedarbaum J, Brashear R, Miller DS. Neuropsychiatric symptoms in Alzheimer's disease. Alzheimers Dement. 2011; 7:532–539. doi: 10.1016/j.jalz.2011.05.2410. [PubMed: 21889116]
31. Samtani MN, Farnum M, Lobanov V, Yang E, Raghavan N, Dibernardo A, Narayan V. An improved model for disease progression in patients from the Alzheimer's Disease Neuroimaging Initiative. J Clin Pharmacol. 2012; 52:629–644. doi: 10.1177/0091270011405497. [PubMed: 21659625]
32. Chow TW, Fridhandler JD, Binns MA, Lee A, Merrilees J, Rosen HJ, Ketelle R, Miller BL. Trajectories of behavioral disturbance in dementia. J Alzheimers Dis. 2012; 31:143–9. doi: 10.3233/JAD-2012-111916. [PubMed: 22531424]
33. Vilalta-Franch J, López-Pousa S, Calvó-Perxas L, Garre-Olmo J. Psychosis of Alzheimer disease: prevalence, incidence, persistence, risk factors, and mortality. Am J Geriatr Psychiatry. 2013; 21:1135–43. doi: 10.1016/j.jagp.2013.01.051. Epub 2013 Feb 6. [PubMed: 23567368]
34. Vilalta-Franch J, Calvó-Perxas L, Garre-Olmo J, Turró-Garriga O, López-Pousa S. Apathy syndrome in Alzheimer's disease epidemiology: prevalence, incidence, persistence, and risk and mortality factors. J Alzheimers Dis. 2013; 33:535–43. doi: 10.3233/JAD-2012-120913. [PubMed: 23001707]
35. Wadsworth LP, Lorius N, Donovan NJ, Locascio JJ, Rentz DM, Johnson KA, Sperling RA, Marshall GA. Neuropsychiatric symptoms and global functional impairment along the Alzheimer's continuum. Dement Geriatr Cogn Disord. 2012; 34:96–111. [PubMed: 22922821]
36. Bhattacharjee S, Findley PA, Sambamoorthi U. Understanding gender differences in statin use among elderly Medicare beneficiaries: an application of decomposition technique. Drugs Aging. 2012; 29(12):971–80. doi: 10.1007/s40266-012-0032-1. [PubMed: 23160960]

Table 1

Sample Characteristics by Gender and Cholesterol Level

	Total Sample		**Male**			**Female**		
	TC ≥200 *N* = 133	**TC ≤199 *N* = 87**	**Total Sample *N* = 76**	**TC ≥200 *N* = 33**	**TC≤199 *N* = 43**	**Total Sample *N* = 144**	**TC ≥200 *N* = 100**	**TC ≤199 *N* = 44**
Age Mean (*SD*)	78.38 (8.8)	76.78 (0.7)	75.31 (8.4)	74.24 (8.8)	76.17 (8.1)	78.73 (8.1)	77.65 (8.6)	81.11 (6.3)
Education Mean (*SD*)	14.31 (3.3)	13.81 (2.9)	14.49 (3.2)	14.52 (3.2)	14.46 (3.0)	13.91 (3.1)	14.24 (3.2)	13.20 (2.8)
MMSE Mean (*SD*)	17.96 (6.4)	20.82 (5.3)	19.55 (7.0)	15.85 (7.4)	22.54 (5.1)	18.85 (5.7)	18.68 (5.9)	19.23 (5.1)
CDR-Global Mean (*SD*)	1.45 (0.7)	1.15 (0.7)	1.25 (0.7)	1.42 (0.7)	0.99 (0.7)	1.43 (1.0)	1.48 (1.1)	1.31 (0.9)
CDR-SB Mean (*SD*)	8.67 (4.3)	6.84 (4.3)	7.15 (4.5)	9.17 (4.4)	5.52 (4.0)	8.37 (4.2)	8.51 (4.3)	8.07 (4.2)
APOEε4 Status (%) Carriers/Non-Carriers	62%/38%	49%/51%	44%/56%	49%/51%	43%/57%	65%/35%	67%/33%	60%/40%

TC = Total Cholesterol; MMSE= Mini Mental Status Exam; CDR= Clinical Dementia Rating; CDR-SB Clinical Dementia Rating Sum of Boxes

Table 2

Neuropsychiatric Symptoms by Gender and Cholesterol Level

	NPI Total	Hyperactive	Psychosis	Affective	Apathy
Total Sample *N* = 220	*M* = 3.98 *SD* = 2.63	*M* = 1.49 *SD* = 1.32	*M* = .75 *SD* = .83	*M* = .87 *SD* = .80	*M* = .82 *SD* = .75
Cholesterol ≥200 *N* = 133	*M* = 4.26 *SD* = 2.60	*M* = 1.60 *SD* = 1.28	*M* = .87 *SD* = .81	*M* = .89 *SD* = .81	*M* = .85 *SD* = .75
Cholesterol ≤199 *N*= 87	*M* = 3.56 *SD* = 2.65	*M* = 1.32 *SD* = 1.38	*M* = .55 *SD* = .67	*M* = .85 *SD* = .79	*M* = .77 *SD* = .74
Male Total *N* = 76	*M* = 4.20 *SD* = 2.93	*M* = 1.67 *SD* = 1.34	*M* = .74 *SD* = .89	*M* = .87 *SD* = .7544	*M* = .84 *SD* = .78
Cholesterol ≥200 *N* = 33	*M* = 5.24 *SD* = 2.96	*M* = 1.97 *SD* = 1.33	*M* = 1.09 *SD* = 1.01	*M* = 1.09 *SD* = .77	*M* = 1.03 *SD* = .73
Cholesterol ≤199 *N* = 43	*M* = 3.40 *SD* = 2.67	*M* = 1.44 *SD* = 1.32	*M* = .47 *SD* = .67	*M* = .70 *SD* = .71	*M* = .70 *SD* = .80
Female Total *N* = 144	*M* = 3.86 *SD* = 2.47	*M* = 1.40 *SD* = 1.31	*M* = .75 *SD* = .81	*M* = .88 *SD* = .83	*M* = .81 *SD* = .73
Cholesterol ≥200 *N* = 100	*M* = 3.93 *SD* = 2.40	*M* = 1.48 *SD* = 1.24	*M* = .80 *SD* = .84	*M* = .82 *SD* = .82	*M* = .79 *SD* = .76
Cholesterol ≤199 *N* = 44	*M* = 3.71 *SD* = 2.66	*M* = 1.21 *SD* = 1.44	*M* = .64 *SD* = .72	*M* = 1.00 *SD* = .84	*M* = .84 *SD* = .68

NPI = Neuropsychiatric Inventory

Table 3

Odds Ratios for the Occurrence of NPS for High Cholesterol (≥ 200) compared to Low Cholesterol (≤199)

	Total Sample		Male		Female	
	OR (95% CI)	**P-value**	**OR(95% CI)**	**P-Value**	**OR(95% CI)**	**P-Value**
NPS Total	1.24(1.12-3.63)	0.657	2.03(0.37-11.24)	0.405	0.84(0.21-3.33)	0.806
Hyperactive	2.02(1.04-3.10)	0.017	2.70(0.85-8.50)	0.082	2.25(1.07-4.72)	0.029
Psychosis	1.80(1.04-3.10)	0.034	3.88(1.47-10.20)	0.004	1.16(0.05-2.36)	0.679
Affective	1.23(0.69-2.17)	0.472	2.47(0.91-6.71)	0.071	0.65(0.31-1.37)	0.265
Apathy	1.06(0.60-1.86)	0.823	3.27(1.20-8.86)	0.017	0.67(0.31-1.42)	0.296

NPS = Neuropsychiatric Symptoms

Table 4

Odds Ratios Comparing AD Males Total Cholesterol ≤199 and ≥200 for NPI Items

Behavior	Odds Ratio	95% Confidence Interval	P-Value
Hallucinations	2.166	0.558-8.417	.256
Irritability	1.385	0.547-3.512	.491
Motor Activity	5.138	1.708-15.464	.002*
Agitation	1.792	0.650-4.063	.212
Delusions	5.797	1.446-23.238	.007*
Depression	1.588	0.632-3.989	.323
Anxiety	3.186	1.238-8.205	.014*
Elation	0.629	0.108-3.662	.604
Apathy	2.239	0.884-5.671	.086
Disinhibition	1.066	0.414-2.749	.896
Night time	3.551	1.369-9.222	.008*
Appetite	1.756	0.695-4.439	.231