Review of Psychology,
2007, Vol. 14, No. 1, 13-23 UDC 159.9

Association of high and low density serum cholesterol, cognitive performance and emotional well-being in menopausal women

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Decline in cognitive performance and changes in metabolism are characteristics of aging. The increased level of LDL in serum is associated with a higher risk to atherosclerosis that causes minor and major decline in cognitive functioning. On the other hand, HDL levels are associated with better preserved cognitive functioning in older age. The aim of the present study is to assess the association between levels of total serum cholesterol (TC), LDL, and HDL, as well as perceptual-motor, verbal, visuospatial and executive cognitive functions, and perception of menopausal state of health of menopausal women. A sample of 52 postmenopausal women was recruited from an outpatient gynecology clinic. The following measures and parameters were used: analysis of serum total LDL, and HDL cholesterol; standard neuropsychological testing of cognitive performance in perceptual- motor, verbal, visuospatial and executive domains, assessment of the perception of menopausal state of health. The results showed that perceptual motor speed was the highest at medium TC level. Higher TC and LDL levels were related to the reduction of verbal memory performance. The higher level of HDL was associated with increased working memory performance. Women with lower level of TC and LDL reported more health complaints occurring in menopause, while the highest level of HDL was related to the best perception of somatic state. These data demonstrate that verbal memory decline is associated with elevated levels of TC and LDL, and support the protective effects of increased plasma HDL in maintaining cognitive functions.

Key words: serum cholesterol, LDL; HDL; cognitive performance; emotional well being, menopause

The transition to menopause is a major hormonal event, associated with physical and psychosocial symptoms, and which may cause adverse changes in women's quality of life. Empirical and epidemiological studies demonstrate that endogenous estradiol concentration drops sharply after menopause. Changes in circulating hormone levels during menopause are associated with cognitive, physiological and gross motor performance difficulties and affect the emotional well-being of women. Estradiol effects on brain morphology are the following: higher levels of estradiol which inhibit the cell loss in the later life of postmenopausal women (Hogervorst, Williams, Budge, Ridel, & Jolles, 2000), a decrease of the effect of oxidative stress after brain trauma and the enhancement of the number of surviving neurons in the hippocampus (Behl, 1999). Beyond its impacts on direct neurophysiological pathways, estradiol affects brain morphology through lipid metabolical mechanisms. Reduction in circulating estrogen after menopause is accompanied by the changes in plasma levels of cholesterol and its fractions (Bittner, 2002). In menopause adverse changes in lipoprotein profiles occur, including the increase in total cholesterol (TC) and LDL cholesterol and decreases in HDL (Bittner, 2002). Cross-sectional studies consistently show more adverse lipoprotein patterns among postmenopausal than among premenopausal women (Bittner, 2002).

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Acknowledgements: This study was supported by OTKA T-60221.

Almost a quarter of the unesterified cholesterol present in the human body is contained in the brain, but whether behavior and cognitive functioning are affected by serum lipid levels is not clearly understood yet. Cholesterol is required for the formation and maintenance of cell membrane permeability and fluidity. In the brain, unesterified cholesterol is present in large quantities in the plasma membranes of glial and neuronal cells, and in the specialized membranes of myelin (Reiss, Keith, Rahman, Chan, Ghiso, & de Leon 2004). Recycling cholesterol in the brain, through esterification and utilizing apoE and LDL receptor transport may be important for neuron repair and growth (Dietschy & Turley, 2001). Longstanding hypercholesterolemia may lead to weakening of endothelial functions in cerebrovascular arterioles and capillaries and these changes may impair brain metabolism (Levine, Keaney, & Vita, 1995). Lipid/lipoprotein abnormalities have been implicated in the pathogenesis of ischemic cerebrovascular disease (CVD) (Demchuk, Hess, Brass, & Yatsu, 1999), but results are often contradictory regarding the predictive effect of serum cholesterol on the total stroke risk (Prospective Studies, Lancet, 1995). On the other hand, HDL proved to be a protective factor to atherosclerotic changes and CVD (Reiss et al., 2004). In a population based case-control study (Sacco, Benson, Kargman, Boden-Albala, Tuck, & Lin, 2001), increased HDL levels were associated with the reduced risk for ischemic stroke in the elderly. HDL plays a central role in the removal of cholesterol from cells, and in reversing cholesterol transport from the peripheral tissue to the liver (Reiss et al., 2004).

The status of the vascular system largely depends on the rate of lipoprotein (cholesterol, LDL, HDL) metabolism dysfunction and the progression of atherosclerosis. It also plays a pivotal role in the cognitive decline associated with atherosclerosis. A number of studies report that serum lipoprotein levels may be important predictors of cognitive functioning in aging. However, data demonstrating that dyslipidemia is associated with a higher risk of cognitive impairment are conflicting. Recent studies have shown elevated plasma concentrations of 24-hydroxycholesterol in patients with Alzheimer's disease (AD) and vascular dementia (Reiss et al., 2004), but other studies had the opposite results in the severe stage of AD (Papassotiropoulos, Lüthjohann, Bagli, Locatelli, Jessen, & Rao, 2000). Non-pathological late-life cognitive performance was not found to be related to blood lipid levels (Teunissen et al., 2003). Researches of age-related cognitive disorders, dementia and the vascular risk factors for cognitive impairment, increasingly focus attention on the role of cholesterol metabolism in the pathogenesis of these diseases.

Researches considering the contribution of serum lipoprotein levels to cognitive function in aging have yielded inconclusive results. Differences in data may reflect the varieties in the diagnostic criteria of cognitive impairment, methods and domains of cognitive testing, and the different duration of follow-up.

The Framingham Heart Study (Elias, Elias, D'Agostino, Sullivan, & Wolf, 2005) found significant positive linear associations between biennially assessed TC, and the 4 to 6 years' follow-up assessment of cognitive functioning of verbal fluency, attention/concentration, abstract reasoning, and composite scores in all the measured domains. Lower endogenous TC level (<200mg/dL) was related to poorer performance on cognitive measures. In an undergraduate sample Benton (1995) reported slower speed of mental processing and reaction times shown with lower level of TC in a choice decision task. Among monozygotic twin pairs persons with lower level of baseline TC exhibited perceptual-motor and visual attention performance level decline on the WAIS Digit Symbol Substitution Test over a 5-year period relative to the twins with higher baseline TC level (Swan, LaRue, Carmelli, Reed, & Fabsitz, 1992). Cognitive test performance on WAIS subscales reflecting crystallized intelligence (Information; Vocabulary Subscales) varied inversely with TC and LDL. Achievement on trials assessing fluid intelligence (Block Design) was the poorest at the lowest TC level and improved with an increasing level of TC (age = 41.7 y) (Muldoon, Ryan, Matthews, & Manuck, 1997.) Elevation in TC levels was found to be associated with better memory performance in healthy middle-aged women (Henderson, Guthrie, & Dennerstein, 2003).

Postmenopausal women in the highest LDL cholesterol quartile of the sample showed worse performance in Mini-Mental State Examination scores than participants belonging to the lowest quartile. Reduction in the LDL cholesterol level during 4 years tended to be related with lower odds of impairment. HDL cholesterol was not associated with cognition (Yaffe, Barrett-Connor, Lin, & Grady, 2002). Serum levels of cholesterol precursors (lathosterol and lanosterol) correlated negatively with performance on the Word Learning Test for verbal learning and memory both, in baseline tests and over the 6-year follow-up period, independent from age, education and sex (Teunissen et al., 2003). Plasma levels of HDL cholesterol, which declines in aging, had positive linear association with Mini Mental State Examination scores in centenarians (Ma, Muzumdar, Gabriely, Atzmon, & Barzilai, 2003). A large population-based study (Kivipelto et al., 2001) evaluating the impact of midlife vascular risk factors (elevated serum cholesterol level and blood pressure) on the subsequent development of mild cognitive impairment (MCI) in elderly found that midlife elevated cholesterol level ($\geq$ 6.5 mmol/L) was a significant risk factor for MCI. In conclusion, results from previous studies are controversial due to methodological differences and variations in examined age cohorts. Further conflicting data may be derived from differing psychosocial factors, namely mood and psychological well-being that presumably impose impact on cognitive performance.

Naturally occurring low cholesterol levels have been related to increased depression (Wardle, 1995; Brown, Salive, Harris, Simonsick, Guralnick, & Kohout, 1994; Horsten,

Wamala, Vingerhoest, Orth-Gomer, & 1997; Suarez, 1999), anxiety (Suarez, 1999) and lower levels of social support (Horsten et al., 1997) across different age groups (van Dam, Schiut, Schouten, Vader, & Pop, 1999). Results are inconsistent regarding gender differences and general health. Chen, Lu, Wu, and Chang (2001) reported that in a large nonclinical sample of women, low level of HDL-C (<35 mg/dL) was linked with heightened psychological distress manifest in depression, somatization, phobic anxiety, interpersonal sensitivity and hostile aggression, while TC levels below 160 mg/dL showed negative correlation to anxiety, and hostility**.** The reduction of lipid level through drug therapy was accompanied by increased depression in men (Beigel, Peleg, Assali, & Nachson, 1998). In obese women the relationship between lower TC level and negative mood was found to be age-specific and limited to the elderly (<60 years) (Troisi et al., 2001). Depression may have a biological link to low cholesterol by its association with altered central serotonergic function (Steegmans et al., 1996)

Relatively few studies have focused solely on menopausal and postmenopausal women (Dealberto, Ducimetiere, Mainard, & Alperovitch, 1993; Horsten et al., 1997; Brown, Giggey, Dennis, & Waldstein, 2004). Affective symptoms may occur during times of hormonal changes such as menopause. Decreased central serotonergic functioning has been related to the drop in estrogen during menopause (Meltzer, 1989) and may in part account for the increase of depression in this cohort. Besides the consequence of hormonal attenuation, menopause brings the challenge of accommodation to complex changes in family roles, partnership and life cycle, which may cause mood oscillations as well. Increased depressive symptoms were found among women with low cholesterol levels (<4.7 mmol/l) even after their adjustment to the menopausal status (Horsten et al., 1997). More frequent depressive symptoms were associated with lower cholesterol level among women not taking HRT (Brown et al., 2004).

The potential effect of changing lipid profiles during menopause on cognitive performance and psychological well-being are supported by several studies. Elevated lipid levels proved to be risk factors not only because of adverse cardiovascular and atherosclerotic processes, but through vascular damage, for cognitive impairments. In order to preserve physical and mental health in aging it is advisable to control the lipid levels, but to date it is not clear which domains of cognitive functioning are most influenced by cholesterol. In addition lipid lowering prevention trials increase the risk of negative mood, i.e. depression and anxiety (Wardle, 1995). Consequently, setting the optimal cholesterol level after menopause is important for the preservation of mental health including both psychological well-being and the prevention of cognitive decline.

The purpose of the present study was to explore the effect of serum total, LDL and HDL cholesterol levels to different domains of cognitive performance and emotional well-being in postmenopausal women. The study investigated which cognitive domains are the most vulnerable to fluctuation serum lipid levels in order to investigate the possible areas of prevention for cognitive impairment in aging. It was hypothesized that increased levels of total cholesterol and LDL cholesterol support perceptual-motor and visuospatial functions and link with lower depression and anxiety, and are associated with verbal memory and the decline of executive functions. In addition, increased HDL level was supposed to be associated with better preserved cognitive functioning.

METHODS

Participants

52 volunteer postmenopausal women (age: 51.96 ± 5.78 years, range 42-66) participated in the study (see Table 1). They were recruited from an outpatient gynecology clinic. The participants had reached menopause at the mean of 8.63

Table 1
Descriptive statistics of the sample with total serum cholesterol, HDL cholesterol and LDL cholesterol

	M	*SD*	Min	Max	Low	Medium	High
Age	51.96	5.78	42	66			
Education	13.98	2.80	8	18	1-8 year	9-12 year	13-18 year
BMI	26.72	3.73	21	39			
Cholesterol	5.88 mmol/l	1.03	2.39	8.68	2.39-5.41 mmol/l *n*=16	5.52-6.03 mmol/l *n*=18	6.04-8.68 mmol/l *n*=18
LDL	3.21 mmol/l	1.23	0.90	6.33	0.90-2.62 mmol/l *n*=17	2.63-3.61 mmol/l *n*=17	3.62-6.33 mmol/l *n*=18
HDl	1.43 mmol/l	0.31	0.85	2.18	0.85-1.30 mmol/l *n*=17	1.1-1.60 mmol/l *n*=17	1.61-2.18 mmol/l *n*=18

± 2.31 years before entering the study (range: 1 to 15). Six of the 52 participants (11%) reached menopause because of uterectomy in the age between 41 and 59 (mean age during the time of the study was 54.16±5.95 years, range 45-61). The uterectomysed group differed neither in their mean age (*t(50)* = 1.29; n.s.), nor in the time of the last menstruation (39.5 ± 24.96 vs. 40.68 ± 47.03 months; *t(45)* = 0.52; n.s.) from women who reached menopause naturally. None of the women were currently on hormonal replacement therapy. Years of formal education ranged from primary school to university level (13.98 ± 2.80 ranges 8-18). Mean BMI was 26.72 ± 3.73, range 21-39.

Women with current occurrence or past history of psychiatric and neurological disorders, cardiovascular, renal or hepatic diseases were excluded from the study. The local Committee of Medical Ethics approved to the study protocol. All participants provided written informed consent.

Procedure and Instruments

Lipid analyzes. Fasting blood sample for lipid analyzes was collected in the medical laboratory of the outpatient clinic. HDL, LDL, and cholesterol from serum were defined by a standard method (in mmol/l).

Assessment of cognitive functions and mood. Participants were screened for demographic, health, and life style information. Cognitive performance measure and mood, emotional and menopausal symptom assessment was accomplished in two settings for 7 days consecutively.

Assessment of cognitive functions

Cognitive functioning was assessed by standard neuropsychological tests in four domains: (a) perceptual–motor functions (perceptual-motor speed and visuospatial attention); (b) visuospatial short term memory; (c) verbal abilities: fluency, short term and working memory and learning; and (d) executive functions.

Perceptual motor functions:

Trail making Test Part A, B (Reitan & Wolfson, 1985; Mitrushina, Boone, & D' Elia, 1995.). Part A contains a page with scattered circled numbers from 1 to 25, and participants are instructed to connect the numbers with lines in ascending order as quickly as possible. Part B is a page with circled numbers from 1 to 13 and letters from A to L. Participants are instructed to connect the numbers and letters with lines in order, alternating between numbers and letters. The Trail Making Test assesses attention, visual scanning, and the speed of eye-hand coordination, as well as information processing. In addition, Part B assesses an executive function, the ability to alternate between sets of stimuli. The two obtained scores reflect the total time in seconds needed to complete each task. Reliability coefficients vary considerably, with most of them above 0.60, but several in the 0.80. s (see Lezak, 2004).

Wechsler Symbol Digit Subtest (Weschler, 1939). In this WAIS subtest, participants are requested to copy symbols marked by numbers into cells that are indexed with numbers. Time limit is 90s. The Symbol Digit test measures the speed of eye-hand coordination and information processing, as well as selective attention. We used raw scores that reflect the number of correctly copied symbols. Psychometric properties of the Hungarian version of the WAIS proved to be good (see: Kun & Szegedi, 1996).

Rey-Osterreith Complex Figure Test – drawing and 3 minutes delayed recall (Rey, 1941; Lezak, 2004). Rey Osterreith Complex Figure test is composed of a complex figure constructed from 18 simple geometrical shapes (lines, rectangles, triangles, circles). First, participants are instructed to copy the figure as precisely as possible, and to recall and draw it 3 minutes later as precisely as they can. The test assesses the graphomotor coordination and visuospatial memory. Interscorer reliability for the Rey-figure tends to be high- above .95 (see Lezak, 2004).

Verbal functions:

Addenbrook's verbal fluency test (Hungarian version, Stachó, Ivándy, & Dudás, 2001): letter and category fluency. In this verbal fluency task participants are asked to list as many words as they can: a) beginning with a certain letter; and b) belonging to a semantic category (names of animals) in 1 minute time. Psychometric properties and internal consistency of the Addenbrook's test proved to be good (Cronbach-alpha is .78; Mathuranath, Nestor, Berrios, Rakowitz, & Hodges, 2000).

Wechsler Digit Span subtest (Wechsler, 1939). Digit Span (DS) has two subtests assessing immediate recall of numerical lists forward or backward. Forward recall assesses short-term memory capacity, backward recall measures working memory capacity (Wechsler, 1939). Psychometric properties of the Hungarian version of the WAIS proved to be good (see: Kun & Szegedi, 1996).

AVLT - Rey Auditory Verbal Learning Test (Rey, 1941; Mitrushina et al., 1995). AVLT has been extensively used to evaluate the ability to acquire and retain new verbal information. The test assesses serial learning using 15 common nouns. It provides a simple measure of immediate recall, assesses learning over successive trials, and identifies incorrect memory mechanisms caused by interference and confabulation. The administration procedure includes five successive presentations of the original list of 15 nouns followed by free recall on each trial; a following interference trial involving the presentation and free recall of another list of 15 words; a post interference free recall of the original list; and a 30 minutes delayed free recall of the original list. The AVLT has good reliability scores (see Lezak, 2004). We

used three categories to measure performance: (I) TOT- total number of recalled words in each list (I.-VII.); (II) PE- number of perseverative errors, when the participant recalls the same word repeatedly (this type of error represents a tendency to perseverate, which is a fine deficit of self-monitoring mechanisms.); and (III) CO - number of correctly recalled words.

Executive functions:

WCST Wisconsin Card Sorting Test (Grant & Berg, 1948). WCST was originally developed to assess abstract reasoning ability and the ability to shift cognitive strategies in response to changing environmental contingencies. Thus it is considered as a measure of executive functions (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). WTSC requires organized searching, strategic planning, utilizing environmental feedback to shift cognitive sets, flexible responding and modulating impulsive responding. These cognitive functions are major elements of executive functions and working memory (Tranel, Anderson, & Benton, 1994). Participants have to deduce a rule for sorting cards, which can be sorted by color, shape, or number, and have to switch between sorting rules, based on feedback of correct or incorrect response. Performance on WCST is related to the physiological activation of the dorsolateral prefrontal cortex that is involved in the control of central executive functions and working memory (Berman et al., 1995). Cronbach-alpha coefficients for WCST subscores are moderately good, ranging from .53 to .72 (Heaton et al., 1993).

Emotional and menopausal symptom assessment questionnaires:

Women's Health Questionnaire (Hunter, 1992). WHQ is a 37 item questionnaire providing a rapid assessment of several separate domains of physical and emotional functioning of middle-aged women. Responses are recorded on a four point Likert-scale. WHQ contains 9 subscales: depression (WHQ-D), somatization (WHQ-S, memory (WHQ-M), vasomotor symptoms (WHQ-V), anxiety (WHQ-A), sex problems (WHQ-Sex), sleeping problems (WHQ-Sleep), menstrual problems (WHQ-Mens.), attractivity subscales (WHQ-Att.). The psychometric properties of the WHQ are being computed using a large data base. Provisional multi-trait analysis suggests that the internal reliability of the subscales is reasonably good. Cronbach alpha levels were as follows: depressed mood (.7), anxiety (.77), somatic symptoms (.76), vasomotor symptoms (.84), sleep problems (.73); for menstrual problems and sexual problems the coefficients were lower, being .64 and .59 respectively (Hunter, 2003.)

RESULTS

Findings of neuropsychological and symptom assessment in connection with cholesterol level

ANOVA showed no differences in age ($F(2, 30) = 1.30$; n.s.) and educational level ($F(2, 86) = 1.86$; n.s.) among the groups of women in the high, medium, and low cholesterol tertiles. Assessment of cognitive functioning in the perceptual-motor domain revealed significant difference only in WAIS Symbol Digit scores (shown in Table 2). A conducted Tukey post hoc test indicated higher perceptual-motor speed in Symbol Digit coding in the medium cholesterol level tertile compared to the low cholesterol level tertile Trail making test performance showed no other differences between different cholesterol level groups.

As can be seen from Table 2 and Figure 1, the analysis of AVLT records confirmed a significant decrease in AVLT trials II, III, IV, V, delayed recall in trial VII, and the total number of recalled words from all trials (AVLT ∑TOT) in the high cholesterol level group. Verbal learning capacity (AVLT II.-V.) and verbal retention reflected in the delayed recall (AVLT VII.) were poorer in the high cholesterol level group. Perseverative tendencies showed a significant correlation with the medium level of TC. Participants in the medium cholesterol level tertile made more perseverative error than participants belonging to the low and high tertiles of cholesterol levels. Verbal learning capacity measured by the number of correctly recalled words proved to be increased in the group of medium cholesterol level tertile compared to the group of high levels of serum cholesterol. In the delayed condition, participants in the medium cholesterol level group also recalled more correct words (AVLT CO VII).

Women with medium levels of cholesterol reported more expressed somatic and sleeping complaints (shown in Table 2) than participants with lower and higher cholesterol levels. Participants who had either lower or higher levels of cholesterol, considered their health-related quality of life to be better in terms of somatic, menopausal and sleeping complaints.

Findings of neuropsychological and symptom assessment in connection with low-density lipoprotein

ANOVA revealed that individuals with high level of LDL showed reduced verbal learning capacity performance in the AVLT trial IV and recalled fewer words correctly in AVLT trials IV and VI compared to participants with medium or low level of LDL (see Table 3).

Low levels LDL was associated with poorer performance in the rule abstraction (Learning to Learn) subtests of WCST. Post hoc test revealed that in the measures of abstract reasoning participants in the medium tertile differed

Table 2
Results of cognitive assessment and m enopausal symptom assessment in relation to serum cholesterol levels

	Low		Medium		High		Statistics			
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*df*	*p*	*Tukey*
Trail-Making A (sec)	129.0	36	102.0	42	127.5	38	1.66	2	n.s	
Trail-Making B (sec)	50.64	25	51.59	20	50.35	18	0.02	2	n.s	
WAIS Symbol Digit	50.8	8.88	62.0	10.09	54.6	8.27	6.36	2	<.05	l-m
Rey-Osterreith recall	15.80	6.2	15.26	5.4	13.68	7.2	0.66	2	n.s.	
AVLT Total sum	84.25	12.20	94.70	9.43	74.11	15.27	11.46	2	<.05	m-h
AVLT Pers. Err. sum	6.93	3.85	12.35	5.97	5.47	4.21	9.69	2	<.05	l-m m-h
AVLT Cor. Res. sum	71.87	9.99	78.70	8.66	67.47	14.31	4.28	2	<.05	m-h
WHQ-Depression	0.31	0.42	0.29	0.12	0.36	0.25	0.36	2	n.s.	
WHQ-Somatization	0.36	0.28	0.47	0.45	0.44	0.29	0.60	2	n.s.	
WHQ-S15	0.46	0.51	0.88	0.34	0.56	0.51	3.28	2	<.05	m-h
WHQ-Sleep29	0.77	0.43	0.20	0.41	0.40	0.50	2.61	2	<.05	l-m
WHQ-Memory	0.55	0.48	0.54	0.36	0.68	0.42	0.63	2	n.s	
WHQ- Vasomotor	0.53	0.35	0.56	0.47	0.65	0.51	0.27	2	n.s.	
WHQ-Anxiety	0.40	0.23	0.39	0.27	0.43	0.36	0.11	2	n.s.	
WHQ-Sex	0.48	0.32	0.47	0.33	0.60	0.49	0.33	2	n.s.	
WHQ-Menopausal	0.15	0.08	0.31	0.15	0.23	0.10	2.01	2	n.s.	

Note. AVLT Total sum: the total number of all recalled words form list. I. to VII. Of the Auditory Verbal Learning Test; AVLT Pers. Err.sum: the total number of all perseverative repetitions form list. I. to VII. of the Auditory Verbal Learning Test; AVLT Corr. Res. Sum: the total number of all correctly recalled words form list. I. to VII. of the Auditory Verbal Learning Test; WHQ-S15: item 15th of the somatization subscale of the WHQ; WHQ-Sleep29: item 29th of the sleep problems subscale of the WHQ.

Tukey-test: l-low levels of cholesterol; m-medium level of cholesterol; h-high level of cholesterol; l-m: significant difference between low and medium level groups.

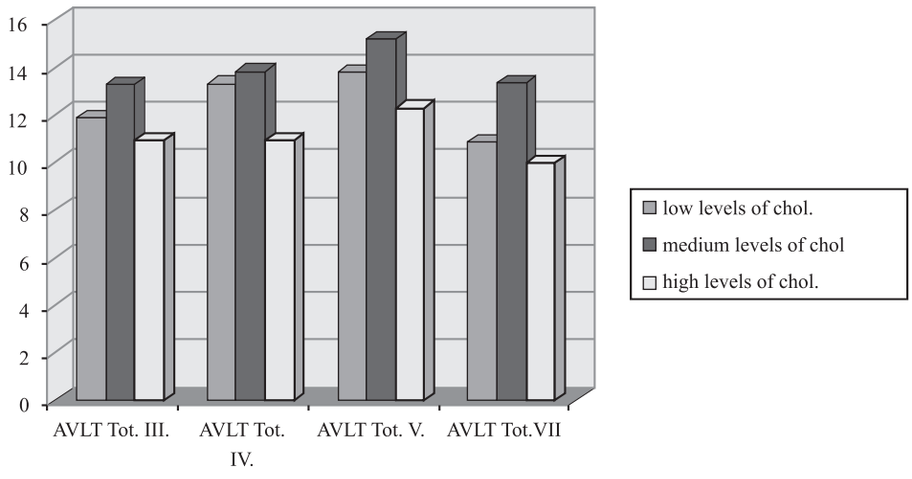

Figure 1. Verbal learning performance measured by AVLT in relation to serum cholesterol levels

Note. AVLT Total III.:the number of all recalled words form list. III. of the Auditory Verbal Learning Test; AVLT Total IV.: the number of all recalled words form list. IV. of the Auditory Verbal Learning Test; AVLT Total V.: the number of all recalled words form list. V. of the Auditory Verbal Learning Test; AVLT Total VII.: the number of all recalled words form list. VII. of the Auditory Verbal Learning Test.

Table 3
Result of cognitive assessment and menopausal symptom assessment in relation to serum LDL levels

	Low		Medium		High		Statistics			
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*df*	*p*	*Tukey*
AVLT total words IV	12.82	2.53	13.82	1.55	11.53	3.08	3.68	2	< .05	m-h
AVLT cor. words IV	11.47	1.87	11.76	1.25	10.23	1.85	3.94	2	<.05	m-h
AVLT cor. words VI	10.11	2.11	10.64	2.54	7.76	2.90	1.66	2	<.05	l-h m-h
WISC Learning to Learn	-15.74	13.64	-5.06	8.89	-7.50	11.03	3.61	2	<.05	l-m
WHQ-V27	0.71	0.46	0.27	0.45	0.63	0.50	3.65	2	<.05	l-m
WHQ-Mens. sum	0.33	0.23	0.08	0.13	0.32	0.23	6.86	2	<.05	m-h

Note. AVLT Total words IV.: the total number of all recalled words from list. IV. of the Auditory Verbal Learning Test.; AVLT Corr. Words IV.: the total number of all correctly recalled words form list. IV. of the Auditory Verbal Learning Test.; AVLT Corr. Words Vi.: the total number of all correctly recalled words form list. VI. of the Auditory Verbal Learning Test.; WISC Learning to Learn: the Learning to Learn subscores of the WISC.; WHQ-V27: item 27th of the vasomotor subscale of the WHQ.; WHQ-Mens. Sum: summarized scores of menopausal symptoms of the menstrual problems subscale of the WHQ.

Tukey-test: l- low levels of LDL; m-medium level of LDL; h-high level of LDL; l-m: significant difference between low and medium level groups.

Table 4
Results of cognitive assessment and menopausal symptom assessment in relation to serum HDL levels

	Low		Medium		High		Statistics			
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*df*	*p*	*Tukey*
Educational level	13.69	2.02	12.65	2.29	15.18	1.59	6.16	2	<.05	m-h
Trail Making A (sec)	139	10.5	116	18.2	102	15.9	2.41	2	n.s.	
Trail Making B (sec)	52.67	9.9	48.29	11.2	51.94	15.5	0.27	2	n.s.	
WAIS Symbol Digit	57.53	8.2	55.76	7.6	55.0	9.2	0.25	2	n.s.	
Rey-Osterreith recall	14.88	8.2	13.56	8.45	16.28	7.6	1.03	2	n.s.	
WAIS Digit Span fw	6.44	0.85	5.76	0.68	6.29	0.08	1.62	2	n.s	
WAIS Digit Span bw	4.56	0.81	3.88	0.78	4.59	0.79	4.25	2	<.05	m-h
WAIS Digit Span sum	11.00	0.76	9.65	0.89	10.88	0.91	3.31	2	n.s.	
Verbal Fluency summa	12.25	0.65	11.76	0.72	12.29	0.74	0.74	2	n.s.	
WHQ-Depression	0.40	0.54	0.32	0.29	0.26	0.45	1.27	2	n.s.	
WHQ-Somatization	0.54	0.22	0.45	0.29	0.31	0.23	3.10	2	<.05	l-h
WHQ-S35	0.67	0.49	0.53	0.51	0.25	0.44	4.48	2	<.05	l-m-h
WHQ Sleep	0.60	0.42	0.52	0.49	0.47	0.33	0.48	2	n.s.	
WHQ-Memory	0.64	0.29	0.58	0.32	0.57	0.44	0.15	2	n.s.	
WHQ- Vasomotor	0.65	0.35	0.59	0.39	0.53	0.42	0.25	2	n.s	
WHQ-Anxiety	0.50	0.42	0.40	0.35	0.34	0.31	1.10	2	n.s.	
WHQ-Sex	0.64	0.42	0.48	0.35	0.45	0.27	0.47	2	n.s	
WHQ-Menopausal	0.17	0.05	0.24	0.19	0.28	0.18	0.81	2	n.s.	

Note. WAIS Digit Span fw: row scores of WAIS Digit Span forward trial; WAIS Digit Span bw: row scores of WAIS Digit Span backward trial; WAIS Digit Span sum: sum of row scores of WAIS Digit Span forward and backward trial; WHQ-S35: item 35th of the somatization subscale of the WHQ.

Tukey-test: l- low levels of HDL; m-medium level of HDL; h-high level of HDL; l-m: significant difference between low and medium level groups.

significantly from participants with low level of LDL. No other differences on WCST variables were found among high, medium, and low level of LDL groups.

Fewer vasomotor complaints (WHQ-27) were reported in the group of medium level of LDL compared to the low level group. Women belonging to either groups of high or low levels of LDL experience more menopausal symptoms on WHQ-Mens scale, than participants in the medium level range.

Findings of neuropsychological and symptom assessment in connection with high-density lipoprotein

The results of ANOVA computed on neuropsychological test scores indicated significant difference only in WAIS Digit Span Backward between HDL groups (Table 4). A post hoc test revealed that participants with increased HDL level showed significantly better working memory performance measured by WAIS Digit Span raw score than individuals with medium HDL level. To ascertain that educational level differences between the medium and high cholesterol level tertile had no confounding effect on the association of HDL levels with working memory performance, we conducted ANOVA on WAIS scores among groups of different educational levels. Results showed no relation of educational level to WAIS results ($F(2,30) = 2.26$; n.s.). Women in the low HLD cholesterol level tertile reported in the WHQ Somatisation Scale expressed more somatic symptoms accompanying menopause than individuals in the high level tertile (see Table 4).

DISCUSSION

In the present study of postmenopausal women, the varieties of effects of total, LDL and HDL cholesterol on different domains of cognitive performance and emotional well-being were shown. In accordance with our expectations, and consistent with previous studies (Swan et al., 1992; Benton, 1995), our results demonstrated a declination in fine perceptual-motor skills, graphomotor speed and visual attention measured by WAIS Symbol Digit Subtest, in the group with the lowest level of total cholesterol. The group with medium level of TC performed better in the WAIS Symbol Digit Subtest than the group with low levels of TC, as reflected in higher speed of visual information processing and reaction times. These results are in accordance with the findings of Benton (1995) and Swan (1992). However, lipoprotein fraction had no impact on visuospatial memory performance.

One of the most significant findings presented here indicate that high levels of serum TC and LDL cholesterol are related to exhibited verbal memory problems. The adverse effect of the increased TC and LDL on verbal learning capacity and retention appeared in both immediate and delayed recall performances. Compared to LDL a stronger effect of TC on verbal memory performance was experienced. The present results tend to corroborate the findings of Teunissen et al. (2003) who reported a negative correlation of serum levels of cholesterol precursors (lathosterol and lanosterol) with verbal learning and memory in both, baseline tests and over the 6-year follow-up period, but our results were consistent with other studies (Reitz, Luschinger, Tang, Manly, & Mayeux, 2005).

A detailed analysis of verbal learning performance reflecting the ratio of perseverative errors, correct responses and total recall showed that better achievement in the group of medium TC and LDL level compared to high level groups. This means a quantitative, not a qualitative enhancement of verbal learning capacity, because both, the number of correct responses and of perseverative errors, increased at lower serum lipid levels.

An opposite impact of HDL was found on working memory; and the highest level of HDL was associated with the improved working memory performance. Our finding, that higher levels of HDL strengthen a basic cognitive function, i.e. working memory, confirmed evidences that support the beneficial effects of elevated level of HDL on the cognitive performance in aging (Ma et al., 2003; Atzmon, Gabriely, Greiner, Davidson, Schechter, & Barzilai, 2002). The protective influence of HDL to atherosclerotic changes (Reiss et al., 2004) may play an important role in the preservation of frontal lobe mediated executive functions, such as working memory in aging.

The analysis of the results of higher executive function test WCST revealed that rule abstraction scores (Learning to Learn) increased in the group with a medium level of LDL compared to the low level groups. *Learning to Learn* scores show the extent of participant's ability to recognize and maintain the general rule of sorting across consecutive categories (Heaton et al., 1993). This result is in accordance with previous findings about the association of lower cholesterol level with reduced executive functions in terms of speed of mental processing and attention concentration (Benton, 1995; Yaffe et al., 2002; Elias et al., 2005). However, because of the calculation method of Learning to Learn scores, this result should be interpreted with caution.

There are conflicting data showing that dyslipidemia is related to a higher risk of cognitive impairment (Kivipelto et al., 2001; Yaffe et al., 2002; Teunissen et al., 2003). Results in this study are inconsistent with a set of previous studies (Reitz et al., 2005), that found zero or negative association between TC, LDL and cognitive performance (Elias et al., 2005; Henderson et al., 2003; Swan et al., 1992). These contradictions may arise from differences in methodology, varieties of methods and the different domains of cognitive functioning, the mean age of the sample, and the duration of follow up. Studies finding negative association between cognitive performance and serum lipoprotein level seemed to have failed to make the differentiation of lipoprotein fractions of cholesterol, LDL and HDL and measured only TC

level and assessed different areas of cognition (Elias et al., 2005; Henderson et al., 2003; Muldoon et al., 1997), which may explain conflicting results. Previous researches that measured TC LDL and HDL separately and assessed verbal memory found either the lack of association between levels of plasma lipids and verbal memory (Reitz et al., 2005; Teunissen et al., 2003;), or results similar to our findings (Muldoon et al., 2000).

Our present findings suggest that reduced level of TC and LDL have different effects on different cognitive functions; low TC and LDL mildly impair perceptual-motor and executive functions but support the preservation of verbal memory performance. These apparent contradictions may have biological plausibility. Neuronal cells require cholesterol for normal metabolic processes (Muldoon, Flory, & Ryan, 2001), for the microviscosity of cell membranes and signal transduction (Golier, Marzuk, Leon, Weiner, & Tardiff, 1995)**.** The interaction between plasma cholesterol concentrations, cholesterol present in the cell membrane, and serotonergic activity is complex and may account for negative cognitive effects of low cholesterol level. The relationship between low serum cholesterol concentrations and impulsive behavior (Manuck, Flory, McCaffery, Matthews, Mann, & Muldoon, 1998) has turned attention towards the role of cholesterol in serotonin metabolism (Steegmans et. al, 1996) and it is possible that adverse modulating effect of low TC on serotonergic activity may extend to the role of serotonin in cognitive processes as well. Serotonin dysregulation may have an impact on the adverse modulation of prefrontal lobe mediated response selection and inhibitory processes (Clark, Cools, & Robbins, 2004) which are the key components in graphomotor coordination, and visual attention measured by WAIS Digit Symbols Substitution Subtest and executive function assessed by WISC.

The assessment of life satisfaction and state of health demonstrated that there is no relationship between the sense of life satisfaction, general health perception and serum lipid profiles. Contrary to our expectation, the present findings did not confirm the association of negative emotionality (i.e. elevated anxiety and depression scores) with decreased level of cholesterol and LDL. The possible explanations may be derived from the relatively good health and socioeconomic condition of the present sample, and from the lack of direct assessment of mood.

Detailed assessment of women's perceived health state indicated that participants who had the lowest levels of TC and LDL reported the most somatic complaints reflected in the number of vasomotor menopausal symptoms and sleeping disorders, while individuals with high level of HDL reported the best physical state - an important factor of well-being. Because negative affectivity, in terms of depression and anxiety, is often accompanied y somatization and focusing on somatic signs (Van Diest, De Peuter, Eertmans, Bogaerts, Victoir, & Van den Bergh, 2005; Costa & McCrae, 1987; Watson & Pennebaker, 1989), and the link between low levels of TC and LDL to negative mood states is well established (Wardle, 1995; Chen et al., 2001), a more precise assessment of mood would have been necessary to evaluate the mediating pathways between the sharpened perceived health complaints and lipoprotein levels in the present sample. In relation to the present findings it is presumable that beyond psychological effects of mood on health state perception, lipoprotein fractions directly influence women's somatic state through atherosclerotic processes. Previous research confirmed the protective role of HDL in atherosclerotic changes. Consequently, women with high levels of HDL are supposed to have better condition of health than those with low level of HDL.

Although attempts of lowering lipid levels intend to reduce risk factors for cognitive impairments (Yaffe et al., 2002) findings in the present sample concerning the perceptual-motor and executive function decline and the negative perception of health state show the possibility of beneficial and possibly adverse effects of low serum TC and LDL levels. Decreased TC and LDL may impair executive functions by their relation to impulsivity and inhibitory problems, and through their relation with serotonergic dysregulation could increase the risk for negative mood.

The limitation of the present study was the relatively small sample size, which was further divided along the cholesterol tertiles and has diminished statistical power. A detailed analysis of mood and psychological well-being would have made it possible to examine the multiple effects of TC LDL and HDL levels, mood and cognitive performance. Hopefully, the results and limitations of the present study will be taken into consideration in further researches designed to elucidate the mechanisms underlying the relationships between serum lipoprotein levels and cognitive performance, as well as psychological well-being in postmenopausal women.

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