Biomédica 2018;38:496-506
doi: https://doi.org/10.7705/biomedica.v38i4.4262

ARTÍCULO ORIGINAL

Effects of exercise on the cognition of older women treated with lovastatin

Edgardo Molina-Sotomayor[1], Rocío Arreguín-Moreno[2], Fernando Rodríguez-Rodríguez[3], Francisco Pradas[4], Juan Antonio León[4], José Antonio González-Jurado[5]

[1] Departamento de Educación Física, Universidad Metropolitana de Ciencias de la Educación, Santiago de Chile, Chile
[2] Departamento de Psicología y Ciencias de la Comunicación, Universidad de Sonora, Hermosillo, México
[3] Grupo IRyS, Escuela de Educación Física, Pontificia Universidad Católica de Valparaíso, Valparaíso, Chile
[4] Departamento de Expresión Musical, Plástica y Corporal, Universidad de Zaragoza, Zaragoza, España
[5] Facultad de Ciencias del Deporte, Universidad Pablo de Olavide, Sevilla, España

Introduction: The deterioration of cognition is highly predominant in older adults.
Objective: The aim of this study was to analyze the effects of a walking program on the cognition and blood concentration of lipids in women over 60 years of age who were being treated with lovastatin.
Materials and methods: Participants were distributed in two groups: An exercise group (EG, n=45) with aerobic training and an inactive sedentary group (SG, n=22). The cognitive state of the subjects was assessed through the Spanish *Mini-Cog Test* version of the MMSE; lipoproteins were quantified using a lipid profile test, and the cardiorespiratory fitness was measured using the six-minute walking test (6MWT).
Results: EG showed a significant increase ($p<0.05$) in cardiorespiratory fitness and in HDL-C concentrations. Furthermore, the results from the cognition tests showed a large effect size in spatial orientation and in and calculation. The decrease in LDL-C was not significant ($p>0.05$).
Conclusion: A controlled and progressive walking program for older women treated with Lovastatin may induce a boost of brain activity linked to HDL-C, which could delay cognitive impairment.

Key words: Exercise; cognition; dyslipidemia; hydroxymethylglutaryl-CoA reductase inhibitors; mental health; aging.
doi: https://doi.org/10.7705/biomedica.v38i4.4262

Efectos del ejercicio físico sobre la cognición en mujeres mayores tratadas con lovastatina

Introducción. El deterioro cognitivo tiene una gran incidencia en el adulto mayor.
Objetivo. El principal objetivo de este estudio fue analizar los efectos sobre la cognición y la concentración de lípidos de un programa de caminatas en mujeres mayores de 60 años tratadas con lovastatina.
Materiales y métodos. Las participantes se distribuyeron en dos grupos: uno con ejercicio (EG, n=45) sometido a entrenamiento aeróbico y otro inactivo o sedentario (SG, n=22). El estado cognitivo se evaluó mediante la versión en español del *Mini-Mental Test*. Los niveles de lipoproteínas se midieron con una prueba de perfil lipídico y la aptitud cardiorrespiratoria se valoró con la prueba de caminata de 6 minutos (*Six-Minute Walking Test*, 6MWT).
Resultados. El grupo con ejercicio mostró una mejora significativa ($p<0,05$) de la aptitud cardiorrespiratoria y de las concentraciones de colesterol HDL. Además, en la prueba de cognición se observó un efecto de gran tamaño en la orientación espacial, en la atención y en el cálculo. La reducción del colesterol LDL no fue significativa.
Conclusión. Un programa de entrenamiento progresivo y supervisado para mujeres mayores tratadas con lovastatina, podría mejorar la actividad cerebral relacionada con el colesterol HDL, lo cual podría retrasar el deterioro cognitivo.
Palabras clave: ejercicio; cognición; dislipidemias; inhibidores de hidroximetilglutaril-CoA reductasa; salud mental; envejecimiento.
doi: https://doi.org/10.7705/biomedica.v38i4.4262

Contribución de los autores:
All authors contributed to the idea and the design of the study, the data analysis and interpretation, and to the manuscript drafting.

A sedentary lifestyle is a determining factor for the appearance of dyslipidemia, which is associated with the development of atherosclerotic diseases (1,2). Recent studies have reported on the effects of supervised exercise on the improvement of blood pressure (3,4), the decrease in LDL-C (5,6), and the increase in HDL-C (7,8). The efficiency of cardiorespiratory fitness training has also been demonstrated, as it drives beneficial changes in the levels of serum lipoproteins in women and obese men (9).

Several studies have reported the beneficial effects of regular and systematic exercise to maintain normal lipid levels, to increase HDL-C concentrations, (10) and to prevent atheroma plaque formation reducing LDL-C (11). In this sense, it has been previously shown that the length and type the training program seem to be essential elements of the effect on plasma lipoproteins (12-14). However, despite all the physiological and enzymatic changes caused by training, the mechanisms by which exercise reduces atherogenic risk are still unknown (15). Apparently, its beneficial effects on the reduction of high plasma cholesterol (16,17) depend upon the characteristics of exercise training (18), which demands more research on the effects of the type and intensity of exercise for the reduction of blood lipids (Wells JR. Medium-intensity rhythmic exercise and high-intensity resistance exercise reduces fasting plasma cholesterol/HDL ratio. 37th Congress of IUPS (Birmingham, UK) (2013), Proc. 37th IUPS, PCC236).

Statin treatments have also been shown to have a beneficial effect on the reduction of total cholesterol and LDL-C and on the prevention of arterial diseases and ischemic cerebrovascular accidents (19), thus becoming a cornerstone for the treatment of dyslipidemia (20,21). While some researchers have found mild adverse effects on cognition (22), others studies have reported a beneficial effect of statins on cognitive function (23-25), and others could not prove its beneficial effect on cognitive function in elders (26,27). Therefore, firm conclusions regarding whether statin use affects cognition function and dementia remain elusive.

Corresponding author:
José Antonio González-Jurado, Facultad de Ciencias del Deporte, Universidad Pablo de Olavide, Carretera de Utrera km 1, CP: 41013, Sevilla, España
Telephone: (+34) 651 517 571
jagonjur@upo.es

Concern exists that statins may be a causative factor for cognitive problems; however, this adverse effect appears to be rare and likely represents a yet-to-be-defined vulnerability in susceptible individuals (28).

In this regard, it seems clear that there is a relationship between cognitive disturbance and increased concentrations of serum low-density lipoproteins (29-31); also, low levels of HDL-C seem to be linked to poor cognitive function (32,33).

It has been shown that exercise could reduce the risk of cognitive decline in older people (34,35), and although a systematic review concluded that there is no solid evidence that exercise improves cognition in older adults, some studies have also reported the need for further research with exercise to confirm its effect on cognition (36,37). Accordingly, a preventive effect on cognitive decline has been attributed to exercise (38), since it improves frontal lobe activity (39) and brain plasticity (40) favoring cognitive performance and executive function in adults (41). Moreover, it has been shown that exercise activates numerous molecular and cellular signals involved in multiple processes of the central nervous system (42) with large benefits for mental health and against depressive states (43), which also calls for further research to confirm its effects on cognition (37).

Likewise, low concentrations of HDL-C combined with inflammatory states are considered as predicting factors of a poor general cognitive performance and a decrease in information processing speed (44). On the other hand, an increase of HDL-C concentrations has been observed as a response to an exercise program of aerobic resistance (45) along with an adequate diet (46), where low concentrations of HDL-C were associated with memory decline, which is the first stage of mild cognitive decline (47), coronary diseases, and long-term depressive symptoms (48).

A recent study reported that the combination of statins and exercise appears to be associated with significant improvement in the cognition of patients with coronary artery disease and mild pre-existing cognitive dysfunction (49).

The associations between plasma lipids and cognition and the underlying mechanism, as well as the relationship between statins and cognitive function, are complex and currently not fully understood.

Therefore, more research will provide insights into the causes and interdependencies of cognitive impairment and dementia (28).

The purpose of this study was to analyze the effects of progressive walk-based cardiorespiratory exercise on cognitive function and the serum levels of HDL-C and LDL-C, in older women on antilipemic treatment with lovastatin.

Materials and methods

We conducted a quasi-experimental, non-probabilistic prospective study in a two-group pre-test-post-test design. The sample (n=67) was composed of older adult women who were patients of the health center "*La Estrella"* at the commune of Pudahuel (Chile). These women were diagnosed with dyslipidemia and were following a lovastatin treatment (20 mg/day). The sample size was calculated with a 5 % alpha and a 95% confidence level. The women were randomly assigned to the exercise group (EG, n=45) with (X±SD) 67.8 ± 5.0 years of age and the sedentary group (SG, n=22) with (X±SD) 71.9 ± 5.4 years of age. The women in both groups showed a level of education that allowed them to read and write without help.

The biochemical profile to determine LDL-C and HDL-C concentrations was performed from 10 ml blood samples extracted from each subject after 12 hours fasting. Cognitive decline was assessed through the Mini-Cog Test Spanish version (50) based on the Mini-Mental State Examination (MMSE) (51), with a total score of three points. The cut-off for cognitive decline is 24/25 for the sum of the domains of temporal and spatial orientation, fixation-immediate recall, attention-calculation, delayed recall, and language (52).

The six-minute walking test (6MWT) was used to assess cardiorespiratory performance (VO_2 max). It showed good validity and reliability at estimating maximum aerobic capacity in subjects with different pathologies (53-56) and accuracy at predicting maximum cardiorespiratory function in the healthy population (57) and assessing health-related physical fitness (58). It was applied before and after the intervention in homogenous groups of five people at a 400 m flat track.

The following inclusion criteria were considered: (i) Women between 60 and 80 years of age participating in the cardiovascular program of the health center "*La Estrella*" with their clinical tests updated; (ii) medical clearance compatible with the requirements of the cardiovascular training; (iii) patients diagnosed with dyslipidemia and treated with lovastatin (20 mg/day); (iv) pharmacological treatment length between 13 and 15 months; (v) MMSE score ≤24 points, i.e., "mild cognitive decline"; (vi) patients with reading and writing skills, and (vii) signed informed consent approved by the board of the health center and the Universidad Metropolitana de Ciencias de la Educación in Santiago de Chile.

The exclusion criteria considered were: (i) Depressive patients with medication; (ii) patients with pathologic conditions incompatible with exercise; (iii) patients without the basic educational level, and (iv) patients with severe pathologies during the study.

The cardiorespiratory training consisted of a progressive walk on a horizontal plane, throughout a period of 16 consecutive weeks distributed in three sessions per week one hour per session, with two active rest periods of 5 minutes.

The progressive walk training program included these phases: A 10-minute warm-up for joint mobility and general and specific flexibility. The following chart shows the main characteristics of the program:

	Mesocycle 1				Mesocycle 2			
Weeks	1	2	3	4	5	6	7	8
$\%VO_2$max.	45	45	50	45	50	45	50	60
Km/hour	2.7	2.7	3.3	2.7	3.3	2.7	3.3	4.3
	Mesocycle 3				Mesocycle 4			
Weeks	9	10	11	12	13	14	15	16
$\%VO_2$max.	45	50	60	50	60	45	50	60
Km/hour	2.7	3.3	4.3	3.3	4.3	2.7	3.3	4.3

The cool-down routine was done for 10 minutes including general and specific flexibility.

Data analysis

The statistical processing of data was performed using the IBM SPSS 20™ software. The normality was tested with the Shapiro-Wilk test and the homoscedasticity with the Levene test. The two groups were compared using the Student´s t-test if they met the conditions of normality and equal variances, and the Mann-Whitney´s U-test was used otherwise. The Student´s t-test or the Wilcoxon test were used to compare paired data according to their normality. The effect size was calculated according to the Cohen´s equation (59). Regression and correlation among the variables of interest were calculated based on the regression curve and the correlation coefficient, respectively.

Ethical considerations

The project was approved by the Ethical Committee of the *Universidad Pablo de Olavide* in Seville and all the procedures met the indications of the Declaration of Helsinki approved by the World Medical Association (60).

Results

Table 1 shows the mean values and standard deviations obtained before and after the intervention, as well as the differences between the pre-tests and post-tests in both groups. It also shows the statistical significance values of the intragroup comparisons (paired data) for the means between pre- and post-tests and the effect size of such intervention. SG showed a slight non-significant decrease (p=0.518) in the distance walked at the end of the experiment with the 6MWT; however, EG showed a remarkable and statistically significant increase (p<0.05) at the end of the intervention. It also presents the changes produced in cognition in both groups, showing a significant increase (p<0.05) and a large effect size in the MMSE scores in EG, whereas SG did not show significant changes (p=0.564) between pre-test and post-test. With respect to HDL-C levels, there was a statistically significant decrease in SG (p<0.05), while EG showed significant increases in HDL-C plasma concentration (p<0.05). Finally, this table also shows the results obtained from LDL-C levels, with non-significant decreases and a small effect size in both groups.

Table 2 shows the intragroup differences of the cognitive dimensions assessed by the MMSE, with a large effect size (p<0.05) in spatial orientation, attention, and calculation and a moderate effect in temporal orientation, fixation, recall, and language in EG. In contrast, SG showed no significant differences in the measurements analyzed.

Figure 1 shows the percentages of change between pre-test and post-test comparing such changes between groups. Except for LDL-C concentrations, there were statistically significant differences (p<0.001) in the rest of the variables between SG and EG.

Table 1. Intragroup differences of the variables studied

	Exercise group (n=45)					
	Pre (Mean ± SD)	**Post (Mean ± SD)**	**Change (Mean ± SD)**	**p value***	**Effect size§**	**Magnitude**
MMSE (score)	23.9 ± 2.1	27 ± 1.9	3.2 ± 2.3	0.000	1.67	Large
HDL-C (mg/dl)	49.8 ± 7.5	55.2 ± 10.1	5.4 ± 6.1	0.000	0.53	Medium
LDL-C (mg/dl)	130 ± 29.5	127 ± 28.8	-3.3 ± 33.6	0.509	0.11	Small
6MWT (meters)	547 ± 42.3	572 ± 43.6	25.1 ± 27.9	0.000	0.58	Medium
	Sedentary group (n=22)					
	Pre (Mean ± SD)	**Post (Mean ± SD)**	**Change (Mean ± SD)**	**p value***	**Effect size§**	**Magnitude**
MMSE (score)	23.5 ± 1.7	23.7±2.1	0.3 ± 1.8	0.564	0.13	Small
HDL-C (mg/dl)	52.4 ± 11.2	47.5 ± 12.1	-4.9 ± 3.6	0.000	0.4	Medium
LDL-C (mg/dl)	140 ± 25.7	135 ± 26	-5 ± 15.2	0.137	0.2	Small
6MWT (meters)	406 ± 62.9	401 ± 77.4	-5 ± 35.4	0.518	0.06	Small

MMSE: Mini-Mental State Examination; HDL-C: HDL-Cholesterol; LDL-C: LDL-Cholesterol; 6MWT: The six-minutes walking test
*: Student’s t test or Wilcoxon Significant: p<0.05
§: Effect size (Cohen 1988)

Table 2. Intragroup differences in the cognitive dimensions of the MMSE1

	Pre (Mean ± SD)	Post (Mean ± SD)	Change (Mean ± SD)	p value*	Effect size§	Magnitude
Exercise group (n=45)						
Temporal Orientation	4.49 ± 0.55	4.76 ± 0.43	0.27 ± 0.45	0.001	0.61	Medium
Spatial Orientation	4.49 ± 0.66	4.82 ± 0.39	0.33 ± 0.64	0.002	0.86	Large
Fixation	2.67 ± 0.52	2.89 ± 0.32	0.22 ± 0.52	0.008	0.70	Medium
Attention and Calculation	2.42 ± 1.22	3.69 ± 1.36	1.27 ± 1.36	0.000	0.93	Large
Recall	2.42 ± 0.62	2.69 ± 0.47	0.27 ± 0.62	0.008	0.57	Medium
Language	7.38 ± 1.27	8.13 ± 0.99	0.76 ± 1.32	0.001	0.76	Medium
MMSE	23.9 ± 2.1	27 ± 1.9	3.2 ± 2.3	0.000	1.68	Large
Sedentary group (n=22)						
	Pre (Mean ± SD)	**Post (Mean ± SD)**	**Change (Mean ± SD)**	**p value***	**Effect size§**	**Magnitude**
Temporal orientation	4.55 ± 0.67	4.73 ± 0.55	0.18 ± 0.80	0.271	0.33	Small
Spatial orientation	4.91 ± 0.29	4.91 ± 0.29	0.00 ± 0.44	1.000	0.00	
Fixation	2.91 ± 0.29	2.95 ± 0.21	0.05 ± 0.38	0.564	0.21	Small
Attention and calculation	1.36 ± 1.40	1.09 ± 1.41	-0.27 ± 1.49	0.382	-0.19	Small
Recall	2.64 ± 0.58	2.64 ± 0.58	0.00 ± 0.76	1.000	0.00	
Language	7.09 ± 1.02	7.41 ± 1.26	0.32 ± 0.89	0.100	0.25	Small
MMSE	23.5 ± 1.74	23.7 ± 2.05	0.27 ± 1.78	0.564	0.13	Small

[1]MMSE: Mini-Mental State Examination
*: Student's t-test or Wilcoxon Significant: p<0.05
§: Effect size (Cohen 1988)

Figure 2 shows the association of the results obtained after the intervention between the variables "fitness expressed in distance walked in 6 minutes" and the MMSE scores in EG and SG.SG showed a negative correlation (r=-0.08; R^2=0.007) with a wide scatter of the data with respect to the regression line. However, EG at the end of the study showed a positive although weak correlation (r=0.22; R^2=0.049). In both cases, the results were not significant.

Figure 3 shows the results obtained in the linear regression analysis between the final results of the 6MWT and the HDL-C (mg/dl).

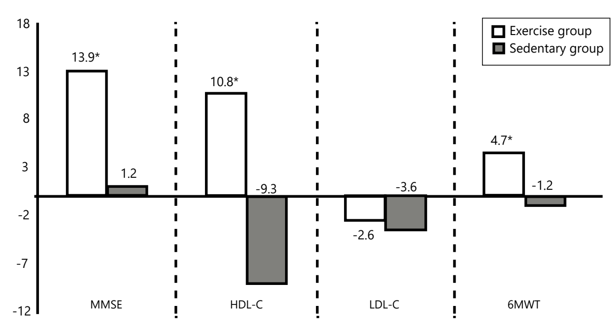

Figure 1. Intergroup comparisons and percent change
* p<0.001 Mann-Whitney U test

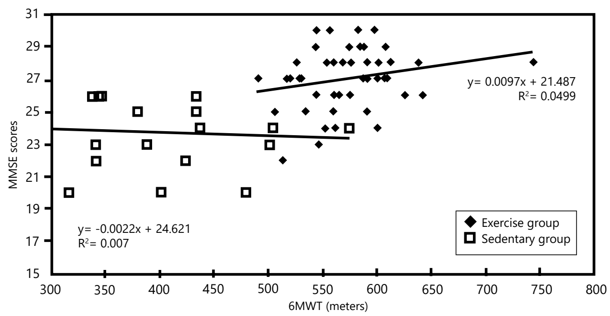

Figure 2. Post-intervention linear regression analysis between 6MWT and MMSE. No significant correlation was found in any of the groups (p>0.05)

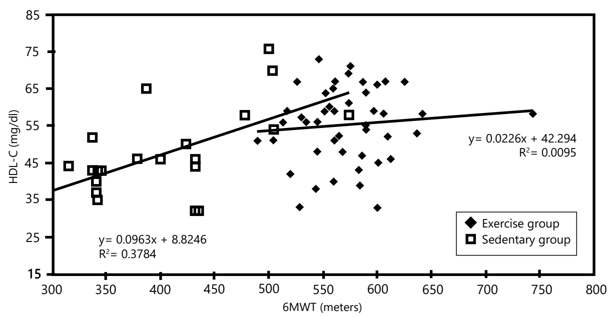

Figure 3. Post-intervention linear regression analysis between 6MWT and HDL-C. We found no significant correlation in the exercise group (p>0.05) and a significant correlation in the sedentary group (p<0.05)

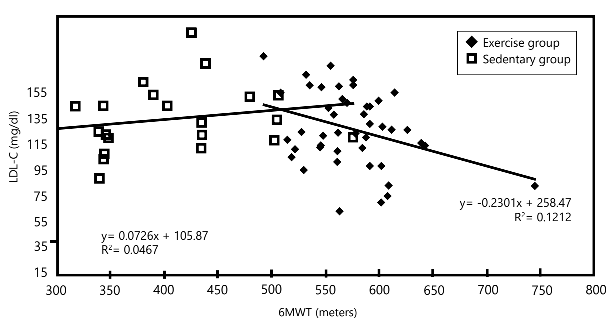

Figure 4. Post-intervention linear regression analysis between 6MWT and HDL-C. No significant correlation in the sedentary group (p>0.05) and significant correlation in the exercise group (p<0.05)

The association between these two variables at the end of the study in SG showed statistical significance (r=0.61; R^2=0.37). However, the results of EG showed a weak (r=0.09; R^2=0.009), non-significant correlation.

Figure 4 shows that the scatter between cardiorespiratory performance (6MWT) and LDL-C concentrations after the intervention presented a positive, weak correlation (r=0.21; R^2=0.046) in SG that was not significant (p>0.05); in turn, EG showed a negative correlation coefficient (r=-0.34; R^2=0.12) that was statistically significant (p<0.05).

Discussion

The aim of this study was to analyze the effects of systematized exercise on cognitive decline and plasma lipoproteins concentrations. At the beginning of the study, the presence of mild cognitive impairment was verified in the two groups studied; however, at the end of the intervention, EG showed a normal cognitive state with a significant increase (p<0.05) in the comparison between the MMSE pre- and post-tests. SG did not show significant changes in cognition (table 1). Thus, the differences between groups in the percentages of change were statistically significant for this variable (p<0.001) (figure 1). Therefore, the group that combined a training program with a lovastatin treatment (EG) obtained a beneficial effect on mild cognitive decline with a large effect size in the increase of MMSE scores. These results are consistent with the study by Sparks, et al. (61), who reported that MMSE performance decreased significantly with time in those subjects that did not take any lipid reducing drug. They also observed a significant correlation between MMSE and HDL in subjects treated with statins, although the existing evidence to prove the role of physical activity in the improvement of cognition in older adults is limited (36).

The absence of changes in MMSE in SG could be associated with mild cognitive decline, considered as a precursor of cognitive decline, which in turn compromises one or more higher mental functions (62,63). In this sense, it has been reported that some statins have differentiated effects on brain function: they can deteriorate cognition or either have a neutral or beneficial effect. However, some findings reported in the literature contrast with the effects related to statins. A slight decrease in cognitive decline has been observed in older people (64) while another study reports on the differentiated effects on brain function (65), which suggest that further research is required to confirm or refute the possible effects of statins on cognitive function.

Delving into this argument, in this study no significant differences were found (p>0.05) for SG, neither in the MMSE scores nor in any of its measurements, whereas EG showed statistically significant differences (p<0.05) in six dimensions of the MMSE (table 2), with a large effect size in spatial orientation and attention and in calculation, and a moderate effect size for temporal orientation, fixation, recall, and language. Thereby, the lovastatin treatment combined with an improved level of cardiorespiratory fitness seems to induce a protective effect on cognition in older women, which is in line with other studies reporting that physical activities like walking may help improve cognitive function in patients with vascular cognitive impairment of subcortical origin (66), or with studies which state that greater cardiorespiratory fitness is strongly related to global cognitive function, attention/executive function, information processing speed, problem solving, and inhibition (67,68). It has also been demonstrated that exercise with moderate intensity improves cognitive function by influencing certain regions of the brain, like the prefrontal area and the hippocampus, increasing memory and executive function mainly through aerobic or cardiorespiratory exercise (69). In combination with the treatment with statins, exercise could have beneficial effects on blood lipid levels and, thus, on brain functions (70), although in this study no significant relationship was found between the total distance walked and the general MMSE score (figure 2). Even though physical activity has been associated with neurological improvements, other mechanisms could also be involved, like neurogenesis, synaptogenesis or changes in the levels of inflammatory markers (68), variables that were not monitored in this study.

Table 1 shows a significant decrease in HDL-C blood levels (p<0.05) in SG. This suggests that the treatment with lovastatin on its own did not increase HDL-C concentration, which is consistent with other studies reporting that statins do not alter the relationship between HDL-C and the level of cardiovascular risk (71). On the other hand, EG showed the opposite inclination, with a significant increase (p<0.05) in the levels of HDL-C and a medium effect size (table 1), which is in line with other studies reporting that statins could reduce the risk of cerebrovascular accidents (72), although in this case, the differential element was the exercise program carried out by the group.

Likewise, a positive relationship was found between cardiorespiratory fitness (6MWT) and HDL-C concentrations in both groups (figure 3). However, this correlation was statistically significant only in SG (p<0.05), i.e., those subjects with better cardiorespiratory fitness showed greater levels of HDL-C. Although it has been reported that cardiorespiratory exercise increases HDL-C concentrations (73), in the present study there was a weak, non-significant correlation (p>0.05) between physical performance and HDL-C concentrations in the group that carried out the exercise program (figure 3). Similar results have been found in a study reporting that a form of statin (simvastatin) attenuates the increase of cardiorespiratory fitness and the mitochondrial content in muscles when it is combined with exercise in patients under the risk of metabolic syndrome (74). Although the data of the correlations appear to be in contradiction, when the percentages of change between groups (figure 1) for the concentrations of HDL-C were compared, a significant difference (p<0.001) was observed between SG and EG, with a decrease of 9.3% and an increase of 10.8%, respectively.

With respect to the results obtained for LDL-C concentrations, table 1 shows a non-significant decrease (p>0.05) in SG with a small effect size. These results are in contrast with studies in which the use of statins produced significant reductions of LDL-C without severe side effects (75). Likewise, the differences in EG were not significant (p=0.509), even though it has been reported in patients with coronary disease that statin treatment combined with exercise resulted in the significant improvement of the arterial wall stiffness (76). After comparing the changes between groups, no significant differences were found in this variable (figure 1). In this sense, EG showed a statistically significant negative correlation (p<0.05) between cardiorespiratory fitness and LDL-C, whereas the correlation between the same variables was positive for SG, although not significant (p>0.05) (figure 4). These opposite trends between groups could be explained by the effect attributed to the lovastatin treatment on LDL-C, which may be due to the low dosage. In seventy-five studies related to coronary disease and the reducing effect of statins on cholesterol and its differentiated effects, it has been reported that a daily dose of 40-80 mg of lovastatin could decrease LDL-C by 30-40%, and 10-20 mg of lovastatin could decrease LDL-C by 20-30% (77), or it could be due to the effect attributed to the exercise program in EG (78).

Finally, regarding cardiorespiratory fitness, a non-significant decrease (p=0.518) was observed for SG in the distance walked (6MWT) after the intervention, whereas the distance walked by EG increased significantly (p<0.05), with a moderate effect size (table 1). On the other hand, the differences in the percentages of change in 6MWT between groups (figure 1) were significant (p<0.05). This could be related to a reduction in the risk of dementia due to the direct relationship between brain functionality and integrity (79).

The results obtained in the present study support the beneficial effects of a monitored walk exercise of moderate intensity performed regularly and systematically and combined with the intake of 20 mg of lovastatin on a better prognosis of cognitive performance associated with the increase in the concentrations of high-density lipoproteins in the sample studied.

Furthermore, these findings reveal that sedentary older women, even with the intake of lovastatin, are more vulnerable to atherogenic damage due to the low concentrations of HDL-C and to the exiguous decreases of LDL-C. Likewise, a positive correlation has been observed between the improvements in cardiorespiratory fitness and the levels of HDL-C in the population studied.

Regarding limitations, only participants from a single health center were selected, which lowers the generalizability of these findings. This correlation was more evident in the sedentary group than in the active group, which shows that it is necessary to modify the present research design to elucidate the selective effects of lovastatin and aerobic exercise in older dyslipidemic adults. In addition, an important number of participants from the sedentary group dropped out, probably because in this group the monitoring of the exercise program was not carried out.

Conflicts of interest

The authors confirm that there are no known conflicts of interest associated with this article.

Financing

This study was funded by the research division of *Universidad Metropolitana de Ciencias de la Educación* (Santiago de Chile).

References

1. **Allison MA, Jensky NE, Marshall SJ, Bertoni AG, Cushman M.** Sedentary behavior and adiposity-associated inflammation: The multi-ethnic study of atherosclerosis. Am J Prev Med. 2012;42:8-13. https://doi.org/10.1016/j.amepre.2011.09.023
2. **Koh Y, Ben-Ezra V, Biggerstaff KD, Nichols DL.** Responses of blood lipids and lipoproteins to extended-release niacin and exercise in sedentary postmenopausal women. J Gerontol A Biol Sci Med Sci. 2010;65:924-32. https://doi.org/10.1093/gerona/glq097
3. **Jong-Hwan P, Masashi M, Masaki T, Noriaki K, Harumi H, Hyun-Shik K, *et al.*** Low-volume walking program improves cardiovascular-related health in older adults. J Sports Sci Med. 2014;13:624-31.
4. **van den Kommer TN, Dik MG, Comijs HC, Jonker C, Deeg DJH.** The role of lipoproteins and inflammation in cognitive decline: Do they interact? Neurobiol Aging. 2012;33:196.e1-96.e12. https://doi.org/10.1016/j.neurobiolaging.2010.05.024
5. **Lucio Mazini Filho M, Gama de Matos D, Minelli Rodrigues B, Jose Aidar F, Rezende de Oliveira Venturini G, da Silva Salgueiro R, *et al.*** The effects of 16 weeks of exercise on metabolic parameters, blood pressure, body mass index and functional autonomy in elderly women. Int Spotmed J. 2013;14:86-93.
6. **Sang-Ho L, Byoung-Do S, Sang-Mi C.** The effect of walking exercise on physical fitness and serum lipids in obese middle-aged women: Pilot study. J Phys Ther Sci. 2013;25:1533-6. https://doi.org/10.1589/jpts.25.1533
7. **Kosmidou KV, Douda HT, Eleftheriadou AI, Volaklis KA, Tokmakidis SP.** The effect of a 3-year combined exercise program on body composition and lipid profile in elderly women. Archives of Hellenic Medicine. 2014;31:191-9.
8. **Hayashino Y, Jackson JL, Fukumori N, Nakamura F, Fukuhara S.** Effects of supervised exercise on lipid profiles and blood pressure control in people with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. Diabetes Res Clin Pract. 2012;98:349-60. https://doi.org/10.1016/j.diabres.2012.10.004
9. **Greene NP, Martin SE, Crouse SF.** Acute exercise and training alter blood lipid and lipoprotein profiles differently in overweight and obese men and women. Obesity. 2012;20:1618-27. https://doi.org/10.1038/oby.2012.65
10. **Macoris Colombo C, Michel de Macedo R, Morita Fernandes-Silva M, Moro Caporal A, Emilia Stinghen A, Roberto Costantini C, *et al.*** Short-term effects of moderate intensity physical activity in patients with metabolic syndrome. Einstein (Sao Paulo). 2013;11:324-30. http://dx.doi. org/10.1590/S1679-45082013000300011
11. **Lippi G, Schena F, Salvagno GL, Montagnana M, Ballestrieri F, Guidi GC.** Comparison of the lipid profile and lipoprotein(a) between sedentary and highly trained subjects. Clin Chem Lab Med. 2006;44:322-6. https://doi.org/10.1515/CCLM.2006.056
12. **Kodama S, Tanaka S, Saito K, Shu M, Sone Y, Onitake F, *et al.*** Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: A meta-analysis. Arch Intern Med. 2007;167:999-1008. https://doi.org/10.1001/archinte.167.10.999
13. **Wooten JS, Biggerstaff KD, Ben-Ezra V.** A single 1-h session of moderate-intensity aerobic exercise does not modify lipids and lipoproteins in normolipidemic obese women. Appl Physiol Nutr Metab. 2011;36:715-22. https://doi.org/110.1139/h11-090

14. **Boardley D, Fahlman M, Topp R, Morgan AL, McNevin N.** The impact of exercise training on blood lipids in older adults. Am J Geriatr Cardiol. 2007;16:30-5.

15. **Čaparevič Z, Kostič N, Čelič V, Čosič Z, Marina D, Ilič S, *et al.*** Effects of acute exercise on atherogenic lipids in untreated mild hypertensive patients. Vojnosanit Pregl. 2009;66:313-8.

16. **Tjønna AE, Lee SJ, Rognmo Ø, Stølen TO, Bye A, Haram PM, *et al.*** Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: A pilot study. Circulation. 2008;118:346-54. https://doi.org/10.1161/CIRCULATIONAHA.108.772822

17. **Martins RA, Veríssimo MT, Coelho e Silva MJ, Cumming SP, Teixeira AM.** Effects of aerobic and strength-based training on metabolic health indicators in older adults. Lipids Health Dis. 2010;9:76. https://doi.org/10.1186/1476-511X-9-76

18. **Bateman LA, Slentz CA, Willis LH, Shields AT, Piner LW, Bales CW, *et al.*** Comparison of aerobic versus resistance exercise training effects on metabolic syndrome (from the Studies of a Targeted Risk Reduction Intervention Through Defined Exercise - STRRIDE-AT/RT). Am J Cardiol. 2011; 108:838-44. https://doi.org/10.1016/j.amjcard. 2011.04.037

19. **Poolsup N, Suksomboon N, Wongyaowarat K, Rungkanchananon B, Niyomrat P, Kongsuwan S.** Metaanalysis of the comparative efficacy and safety of pitavastatin and atorvastatin in patients with dyslipidaemia. J Clin Pharm Ther. 2012;37:166-72. https://doi.org/10.1111/j.1365-2710.2011.01274.x

20. **Semple SJ.** Statin therapy, myopathy and exercise--a case report. Lipids Health Dis. 2012;11:40. https://doi.org/10.1186/1476-511X-11-40

21. **Davignon J.** Pleiotropic effects of pitavastatin. Br J Clin Pharmacol. 2012;73:518-35. https://doi.org/10.1111/j.1365-2125.2011.04139.x

22. **Benito-León J, Louis ED, Vega S, Bermejo-Pareja F.** Statins and cognitive functioning in the elderly: A population-based study. J Alzheimers Dis. 2010;21:95-102. https://doi.org/10.3233/JAD-2010-100180

23. **Ghodke R, Tour N, Devi K.** Effects of statins and cholesterol on memory functions in mice. Metab Brain Dis. 2012;27:443-51. https://doi.org/10.1007/s11011-012-9343-5

24. **Carlsson CM, Gleason CE, Hess TM, Moreland KA, Blazel HM, Koscik RL, *et al.*** Effects of simvastatin on cerebrospinal fluid biomarkers and cognition in middle-aged adults at risk for Alzheimer's disease. J Alzheimers Dis. 2008;13:187-97. https://doi.org/10.3233/JAD-2008-13209

25. **Smith KB, Kang P, Sabbagh MN.** The effect of statins on rate of cognitive decline in mild cognitive impairment. Alzheimers Dement (N Y). 2017;3:149-56. https://doi.org/10.1016/j.trci.2017.01.001

26. **van Vliet P.** Cholesterol and late-life cognitive decline. J Alzheimers Dis. 2012;30(Suppl.2):S147-62. https://doi.org/10.3233/JAD-2011-111028

27. **Bunt CW, Hogan AJ.** The effect of statins on dementia and cognitive decline. Am Fam Physician. 2017;95:151-2.

28. **Li R, Wang TJ, Lyu PY, Liu Y, Chen WH, Fan MY, *et al.*** Effects of plasma lipids and statins on cognitive function. Chin Med J. 2018;131:471-6. https://doi.org/10.4103/0366-6999.225062

29. **Reynolds CA, Gatz M, Prince JA, Berg S, Pedersen NL.** Serum lipid levels and cognitive change in late life. J Am Geriatr Soc. 2010;58:501-9. https://doi.org/10.1111/j.1532-5415.2010.02739.x

30. **Parnowski T, Kałua B.** Global cardio - metabolic risk in pati-ents with cognitive dysfunction. Archives of Psychiatry & Psychotherapy. 2012;14:15-9.

31. **Meusel LA, Anderson ND, Parrott MD, Yuen W, Tchistiakova E, MacIntosh BJ, *et al.*** Brain function is linked to LDL cholesterol in older adults with cardiovascular risk. J Am Geriatr Soc. 2017;65:e51-5. https://doi.org/110.1111/jgs.14663

32. **McGrowder D, Riley C, Morrison EY, Gordon L.** The role of high-density lipoproteins in reducing the risk of vascular diseases, neurogenerative disorders, and cancer. Cholesterol. 2011:2011:496925. https://doi.org/10.1155/2011/496925

33. **Packard CJ, Westendorp RG, Stott DJ, Caslake MJ, Murray HM, Shepherd J, *et al.*** Association between apolipoprotein E4 and cognitive decline in elderly adults. J Am Geriatr Soc. 2007;55:1777-85. https://doi.org/10.1111/j.1532-5415.2007.01415.x

34. **Langlois F, Vu TT, Chassé K, Dupuis G, Kergoat M-J, Bherer L.** Benefits of physical exercise training on cognition and quality of life in frail older adults. J Gerontol B Psychol Sci Soc Sci. 2013;68:400-4. https://doi.org/10.1093/geronb/gbs069

35. **Yoon JE, Lee SM, Lim HS, Kim TH, Jeon JK, Mun MH.** The effects of cognitive activity combined with active extremity exercise on balance, walking activity, memory level and quality of life of an older adult sample with dementia. J Phys Ther Sci. 2013;25:1601-4. https://doi.org/10.1589/jpts.25.1601

36. **Snowden M, Steinman L, Mochan K, Grodstein F, Prohaska TR, Thurman DJ, *et al.*** Effect of exercise on cognitive performance in community-dwelling older adults: Review of intervention trials and recommendations for public health practice and research. J Am Geriatr Soc. 2011;59:704-16. https://doi.org/10.1111/j.1532-5415.2011.03323.x

37. **Briken S, Gold SM, Patra S, Vettorazzi E, Harbs D, Tallner A, *et al.*** Effects of exercise on fitness and cognition in progressive MS: A randomized, controlled pilot trial. Mult Scler. 2014;20:382-90. https://doi.org/10.1177/1352458513507358

38. **Meeusen R**. Exercise, nutrition and the brain. Sports Med. 2014;44(Suppl.1):47-56. https://doi.org/10.1007/s40279-014-0150-5

39. **Andrade LP, Gobbi LT, Coelho FG, Christofoletti G, Riani Costa JL, Stella F.** Benefits of multimodal exercise intervention for postural control and frontal cognitive functions in individuals with Alzheimer's disease: A controlled trial. J Am Geriatr Soc. 2013;61:1919-26. https://doi.org/10.1111/jgs.12531

40. **Mang CS, Campbell KL, Ross CJ, Boyd LA.** Promoting neuroplasticity for motor rehabilitation after stroke: Considering the effects of aerobic exercise and genetic variation on brain-derived neurotrophic factor. Phys Ther. 2013;93:1707-16. https://doi.org/10.2522/ptj.20130053

41. **Masley S, Roetzheim R, Gualtieri T.** Aerobic exercise enhances cognitive flexibility. J Clin Psychol Med Settings. 2009;16:186-93. https://doi.org/10.1007/s10880-009-9159-6.

42. **Stroth SK.** Aerobic endurance exercise benefits memory and affect in young adults. Neuropsychol Rehabil. 2009;19:223-43. https://doi.org/10.1080/09602010802091183

43. **Donaghy ME.** Exercise can seriously improve your mental health: Fact or fiction? Adv Physiother. 2007;9:76-88. https://doi.org/10.1080/14038190701395838

44. **van den Kommer TN, Dik MG, Comijs HC, Jonker C, Deeg DJ.** Role of lipoproteins and inflammation in cognitive decline: Do they interact? Neurobiol Aging. 2012;33:196.e1-12. https://doi.org/10.1016/j.neurobiolaging.2010.05.024

45. **Varady KA, Bhutani S, Klempel MC, Kroeger CM.** Comparison of effects of diet versus exercise weight loss regimens on LDL and HDL particle size in obese adults. Lipids Health Dis. 2011;10:119-23. https://doi.org/10.1186/1476-511X-10-119

46. **Kelley GA, Kelley KS, Roberts S, Haskell W.** Combined effects of aerobic exercise and diet on lipids and lipoproteins in overweight and obese adults: A meta-analysis. J Obes. 2012;2012:985902. https://doi.org/10.1155/2012/985902

47. **Crisby M, Bronge L, Wahlund LO.** Low levels of high density lipoprotein increase the severity of cerebral white matter changes: Implications for prevention and treatment of cerebrovascular diseases. Curr Alzheimer Res. 2010;7:534-39. https://doi.org/10.2174/156720510792231694

48. **Lehto SM, Niskanen L, Tolmunen T, Hintikka J, Viinamäki H, Heiskanen T, *et al.*** Low serum HDL-cholesterol levels are associated with long symptom duration in patients with major depressive disorder. Psychiatry Clin Neurosci. 2010;64:279-83. https://doi.org/10.1111/j.1440-1819.2010.02079.x

49. **Toyama K, Sugiyama S, Oka H, Hamada M, Iwasaki Y, Horio E, *et al.*** A pilot study: The beneficial effects of combined statin-exercise therapy on cognitive function in patients with coronary artery disease and mild cognitive decline. Intern Med. 2017;56:641-9. https://doi.org/10.2169/internalmedicine.56.7703

50. **Beaman SRd, Beaman PE, García-Peña C, Villa MA, Heres J, Córdova A, *et al.*** Validation of a modified version of the Mini-Mental State Examination (MMSE) in Spanish. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2004;11:1-11.

51. **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;12:189-98. https://doi.org/10.1016/0022-3956(75)90026-6

52. **Lourenço RA, Veras RP.** Mini-mental state examination: Psychometric characteristics in elderly outpatients. Rev Saúde Pública. 2006;40:712-9. https://doi.org/10.1590/S0034-89102006000500023

53. **Mossberg KA, Fortini E**. Responsiveness and validity of the six-minute walk test in individuals with traumatic brain injury. Phys Ther. 2012;92:726-33. https://doi.org/10.2522/ptj.20110157

54. **Larsson UE, Reynisdottir S.** The six-minute walk test in outpatients with obesity: Reproducibility and known group validity. Physiother Res Int. 2008;13:84-93. https://doi.org/10.1002/pri.398

55. **Pollentier B, Irons SL, Benedetto CM, DiBenedetto A, Loton D, Seyler RD, *et al.*** Examination of the six minute walk test to determine functional capacity in people with chronic heart failure: A systematic review. Cardiopulm Phys Ther J. 2010;21:13-21.

56. **Fowler RM, Jenkins SC, Maiorana AJ, Gain KR, O'Driscoll G, Gabbay E.** Measurement properties of the 6-min walk test in individuals with exercise-induced pulmonary arterial hypertension. Intern Med J. 2011;41:679-87. https://doi.org/10.1111/j.1445-5994.2011.02501.x

57. **Laskin JJ, Bundy S, Moore H, Swanson M, Thies H, Blair M.** Using a treadmill for the six minute walk test: Reliability and validity. J Cardiopulm Rehabil Prev. 2007;27:407-10. https://doi.org/10.1097/01.HCR.0000300270.45881.d0

58. **Tveter AT, Dagfinrud H, Moseng T, Holm I.** Measuring health-related physical fitness in physiotherapy practice: Reliability, validity, and feasibility of clinical field tests and a patient-reported measure. J Orthop Sports Phys Ther. 2014;44:206-16. https://doi.org/10.2519/jospt.2014.5042

59. **Cohen J.** Statistical Power Analysis for the Behavioral Sciences. Second edition. Hillsdale, NJ: L. Erlbaum Associates; 1988. p. 20-27

60. **World Medical Association.** Declaration of Helsinki - Ethical principles for medical research involving human subjects. World Med J. 2013;59:199-202.

61. **Sparks DL, Kryscio RJ, Connor DJ, Sabbagh MN, Sparks LM, Lin Y, *et al.*** Cholesterol and cognitive performance in normal controls and the influence of elective statin use after conversion to mild cognitive impairment: Results in a clinical trial cohort. Neurodegener Dis. 2010;7:183-6. https://doi.org/10.1159/000295660

62. **Petersen RC.** Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004;256:183-94. https://doi.org/10.1111/j.1365-2796.2004.01388.x

63. **Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, *et al.*** Mild cognitive impairment - Beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004;256:240-6. https://doi.org/10.1111/j.1365-2796.2004.01380.x

64. **Bernick C, Katz R, Smith NL, Rapp S, Bhadelia R, Carlson M, *et al.*** Statins and cognitive function in the elderly: The Cardiovascular Health Study. Neurology. 2005;65:1388-94. https://doi.org/10.1212/01.wnl.0000182897.18229.ec

65. **Rojas-Fernández CH, Cameron J-CF.** Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. Ann Pharmacother. 2012;46:549-57. https://doi.org/10.1345/aph.1Q620

66. **Ihara M, Okamoto Y, Hase Y, Takahashi R.** Association of physical activity with the visuospatial/executive functions of the montreal cognitive assessment in patients with vascular cognitive impairment. J Stroke Cerebrovasc Dis. 2013;22:e146-e51. https://doi.org/10.1016/j.jstrokecerebrovasdis.2012.10.007

67. **Barnes DE, Yaffe K, Satariano WA, Tager IB.** A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. J Am Geriatr Soc. 2003;51:459-65. https://doi.org/10.1046/j.1532-5415.2003.51153.x

68. **Cherry BJ, Zettel-Watson L, Chang JC, Shimizu R, Rutledge DN, Jones CJ.** Positive associations between physical and cognitive performance measures in fibromyalgia. Arch Phys Med Rehabil. 2012;93:62-71. https://doi.org/10.1016/j.apmr.2011.08.006

69. **Wilbur J, Márquez DX, Fogg L, Wilson RS, Staffileno BA, Hoyem RL, *et al.*** The relationship between physical activity and cognition in older latinos. J Gerontol B Psychol Sci Soc Sci. 2012;67:525-34. https://doi.org/10.1093/geronb/gbr137

70. **Kelly RB.** Diet and exercise in the management of hyperlipidemia. Am Fam Physician. 2010;81:1097-102.

71. **Jafri H, Alsheikh-Ali AA, Karas RH.** Meta-analysis: Statin therapy does not alter the association between low levels of high-density lipoprotein cholesterol and increased cardiovascular risk. Ann Intern Med. 2010;153:800-8. https://doi.org/10.7326/0003-4819-153-12-201012210-00006

72. **Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP.** Dyslipidemia as a risk factor for ischemic stroke. Curr Top Med Chem. 2009;9:1291-7. https://doi.org/10.2174/156802609789869628

73. **Kelley GA, Kelley KS.** Aerobic exercise and HDL2-C: A meta-analysis of randomized controlled trials. Atherosclerosis. 2006;184:207-15. https://doi.org/10.1016/j.atherosclerosis.2005.04.005

74. **Mikus CR, Boyle LJ, Borengasser SJ, Oberlin DJ, Naples SP, Fletcher J, *et al.*** Simvastatin impairs exercise training adaptations. J Am Coll Cardiol. 2013;62:709-14. https://doi.org/10.1016/j.jacc.2013.02.074

75. **Feuerstein JS, Bjerke WS.** Powdered red yeast rice and plant stanols and sterols to lower cholesterol. J Diet Suppl. 2012;9:110-5. https://doi.org/10.3109/19390211.2012.682645

76. **Toyama K, Sugiyama S, Oka H, Iwasaki Y, Sumida H, Tanaka T, *et al.*** Combination treatment of rosuvastatin or atorvastatin, with regular exercise improves arterial wall stiffness in patients with coronary artery disease. PLoS One. 2012;7:e41369. https://doi.org/10.1371/journal.pone.0041369

77. **Weng TC, Yang YHK, Lin SJ, Tai SH.** A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther. 2010;35:139-51. https://doi.org/10.1111/j.1365-2710.2009.01085.x

78. **Hagner W, Hagner-Derengowska M, Wiacek M, Zubrzycki IZ.** Changes in level of VO_2max, blood lipids, and waist circumference in the response to moderate endurance training as a function of ovarian aging. Menopause. 2009;16:1009-13. https://doi.org/10.1097/gme.0b013e31819c0924

79. **Weinstein A, Erickson K.** Healthy body equals healthy mind. Generations. 2011;35:92-8.