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Physical activity and oxidized LDL, does intensity matter?

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ABSTRACT

Objectives: The aim of this study was to determine the pattern of the dose-response relationship between leisure time physical activity practice, considering its intensity, and serum oxidized LDL levels. We hypothesised that physical activity is inversely but non-linearly associated with oxidized LDL, and that only moderate or vigorous intensity physical activity practice is related to oxidized LDL levels.

Methods: Two population-based cross-sectional studies were designed within the framework of the REGICOR study (Registre Gironí del Cor, which stands for Girona Heart Register): 1,748 individuals recruited in the period 1994-96, and 3,056 in the period 1999-2002 (22 participated in both surveys). The main aim of these studies was to determine the prevalence of the main risk factors and determinants of cardiovascular diseases at the population level. Serum oxidized LDL was the dependent variable and light, moderate and vigorous leisure time physical activity were the independent variables. To assess the dose-response pattern of the association we used general additive models (GAM), if the non-linear pattern of the association was not significant, we explored the linear association using classical multiple linear regression analyses.

Results: The study was conducted in a sample of 2908 participants, of whom 1356 (46.6%) were men with a mean age of 50 years and 1552 (53.4%) were women with a mean age of 50.4 years. We observed a significant linear inverse relationship between vigorous-intensity physical activity and oxidized LDL levels in men, with no such relationship observed in women. Although we hypothesised that the non-linear component of the relationship between physical activity and oxidized LDL levels was relevant, we did not observe this pattern in our study.

Conclusions: Energy expenditure in vigorous intensity physical activity is linearly and inversely related to oxidized LDL levels. Lowering oxidized LDL levels could be one of the mechanisms that explain the beneficial effects of physical activity on cardiovascular health.

Keywords: physical activity, LDL cholesterol, oxidized LDL-cholesterol

RESUMEN

Objetivos: El objetivo de este estudio fue determinar el patrón de la relación dosis-respuesta entre la práctica de actividad física en el tiempo libre, considerando su intensidad, y los niveles séricos de LDL oxidada. Nuestra hipótesis fue que la actividad física se asocia de forma inversa pero no lineal con la LDL oxidada, y que sólo la práctica de actividad física de intensidad moderada o vigorosa se relaciona con los niveles de LDL oxidada.

Métodos: Se diseñaron dos estudios transversales de base poblacional en el marco del estudio REGICOR (Registro Gironí del Corazón): 1.748 individuos reclutados en el periodo 1994-96, y 3.056 en el periodo 1999-2002 (22 participaron en ambas encuestas). El objetivo principal de estos estudios era determinar la prevalencia de los principales factores de riesgo y determinantes de las enfermedades cardiovasculares a nivel poblacional. La variable dependiente fue la LDL oxidada sérica, y las variables independientes fueron la actividad física en el tiempo libre ligera, moderada y vigorosa. Para evaluar el patrón dosis-respuesta de la asociación se utilizaron modelos aditivos generales (GAM); si el patrón no lineal de la asociación no era significativo, exploramos la asociación lineal mediante análisis clásicos de regresión lineal múltiple.

Resultados: El estudio se realizó en una muestra de 2908 participantes, de los cuales 1356 (46,6%) eran hombres con una edad media de 50 años y 1552 (53,4%) eran mujeres con una edad media de 50,4 años. Observamos una relación lineal inversa significativa entre la actividad de intensidad vigorosa y los niveles de LDL oxidada en los hombres, no observando esta relación en las mujeres. Aunque nuestra hipótesis era que el componente no lineal de la relación entre la actividad física y los niveles de LDL oxidada era relevante, no observamos este patrón en nuestro estudio.

Conclusiones: El gasto energético en actividad física de intensidad vigorosa se relaciona lineal e inversamente con los niveles de LDL oxidada. La disminución de los niveles de LDL oxidada podría ser uno de los mecanismos que explique los efectos beneficiosos de la actividad física sobre la salud cardiovascular.

Palabras clave: actividad física, colesterol LDL, colesterol LDL oxidado

RESUM

Objectius: L'objectiu d'aquest estudi va ser determinar el patró de la relació dosi-resposta entre la pràctica d'activitat física al lleure, considerant-ne la intensitat, i els nivells sèrics de LDL oxidada. La nostra hipòtesi va ser que l'activitat física s'associa de manera inversa però no lineal amb la LDL oxidada i que només la pràctica d'activitat física d'intensitat moderada o vigorosa es relaciona amb els nivells de LDL oxidada.

Mètodes: Es van dissenyar dos estudis transversals de base poblacional en el marc de l'estudi REGICOR (Registre Gironí del Cor): 1.748 individus reclutats en el període 1994-96, i 3.056 en el període 1999-2002 (22 van participar en les dues enquestes). L'objectiu principal d'aquests estudis era determinar la prevalença dels factors de risc principals i determinants de les malalties cardiovasculars a nivell poblacional. La variable dependent va ser la LDL oxidada sèrica, i les variables independents van ser l'activitat física al lleure lleugera, moderada i vigorosa. Per avaluar el patró dosi-resposta de l'associació es van fer servir models additius generals (GAM); si el patró no lineal de l'associació no era significatiu, vam explorar l'associació lineal mitjançant anàlisis clàssiques de regressió lineal múltiple.

Resultats: L'estudi es va fer en una mostra de 2908 participants, dels quals 1356 (46,6%) eren homes amb una edat mitjana de 50 anys i 1552 (53,4%) eren dones amb una edat mitjana de 50,4 anys. Vam observar una relació lineal inversa significativa entre l'activitat física d'intensitat vigorosa i els nivells de LDL oxidada als homes, no observant aquesta relació a les dones. Tot i que la nostra hipòtesi era que el component no lineal de la relació entre l'activitat física i els nivells de LDL oxidada era rellevant, no vam observar aquest patró al nostre estudi.

Conclusions: La despesa energètica en activitat física d'intensitat vigorosa es relaciona linealment i inversament amb els nivells de LDL oxidada. La disminució dels nivells de LDL oxidada podria ser un dels mecanismes que expliqui els efectes beneficiosos de l'AF sobre la salut cardiovascular.

Paraules clau: activitat física, colesterol LDL, colesterol LDL oxidada

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality worldwide, accounting for approximately one in three deaths (1). Atherosclerosis, a chronic, progressive inflammatory process that develops in the arterial wall, is the main pathogenic mechanism responsible for CVD (2). Atherosclerosis is estimated to be responsible for 9.5% of deaths worldwide and 14.5% of the global burden of disease (1).

Atherosclerotic plaque formation is caused by the accumulation of lipids, mainly low-density lipoprotein (LDL) cholesterol, and inflammatory cells in the arterial wall. There is strong evidence that oxidation of LDL cholesterol particles plays a key role in the pathogenesis of atherosclerosis (3). The oxidised LDL particle (ox-LDL) has a high affinity for monocyte/macrophage scavenger receptors (CD36, SRA) that favour its entry and the formation of foam cells. The accumulation of these cholesterol-laden cells in the subendothelial space triggers an exaggerated immune response and the production of proinflammatory cytokines, which cause damage to the arterial wall (2).

Physical activity (PA) is a protective factor for cardiovascular disease, and it is estimated that 6% of premature deaths worldwide could be prevented if the population were sufficiently physically active (4). Although PA has beneficial effects on multiple cardiovascular risk factors, including hypertension, dyslipidaemia, diabetes mellitus and obesity, the mechanisms by which it produces all its beneficial health effects are not fully defined (5). It has been suggested that during PA practice, free radical production increases, generating greater oxidative stress, but also that regular PA practice improves the body's antioxidant capacity. This increased antioxidant capacity could protect LDL particles, reduce the level of ox-LDL, and prevent the progression of atherosclerosis. Several studies have examined the relationship between PA and acute oxidative stress, as well as the effects of physical activity programmes on biomarkers of oxidative stress (6–9). Most of these studies have involved interventions in controlled populations and small sample sizes. In addition, there is a lack of studies analysing the dose-response pattern of PA and biomarkers of oxidative stress, considering the intensity of PA in the general population. The aim of this study was to determine the pattern of the dose-response relationship between leisure time PA (LTPA) practice, considering its intensity, and serum ox-LDL levels. We hypothesised that PA is inversely but non-linearly associated with ox-LDL, and that only moderate or vigorous intensity PA practice is related to ox-LDL levels.

METHODS

Study design and population

Two population-based cross-sectional studies were designed within the framework of the REGICOR study (Registre Gironí del Cor, which stands for Girona Heart Register): 1,748 individuals recruited in the period 1994-96, and 3,056 in the period 1999-2002 (22 participated in both surveys). The main aim of these studies was to determine the prevalence of the main risk factors and determinants of CVD at the population level. Participants were initially selected by a 2-phase random sampling. In the first phase, populations were selected; in the second, the same number of men and women stratified by 10-year age groups were selected from the most recent census (1991 and 1999, respectively). Selected participants were contacted by a letter informing them of the aims of the study and the tests to be performed. Inclusion criteria required that participants were aged 25 to 74 years, had lived in the referral area for at least 6 months, were free of terminal diseases, and were not institutionalized. The participation rate was above 71%. All participants were duly informed and signed their consent. The local ethics committee approved the study.

Assessment of leisure-time physical activity

Leisure time PA was collected using the Minnesota LTPA Questionnaire, validated for the Spanish adult population (10,11). This questionnaire assesses leisure and active commuting domains and frequency, duration, and intensity dimensions. Briefly, from a list of 64 activities, participants mark those they have practiced during the year prior to the visit, and a trained interviewer collects information related to the frequency of practice and the duration of each session. Each PA is assigned an intensity based on metabolic equivalents of task (MET) (12).

Total energy expenditure in PA (T-EEPA) was estimated in MET·min/week, and further classified as light-intensity PA (EE Light PA) if PA required ≤ 4 METs (such as low-paced walking), moderate-intensity (EE Moderate PA) if PA required 4.5 to 5.5 METs (such as brisk walking), and vigorous-intensity (EE Vigorous PA) if PA required ≥ 6 METs (such as jogging). Thus, for each participant: T-EEPA = EE light PA + EE moderate PA + EE vigorous PA.

EEPA was grouped in strata of 100 METs·min/week from 0-99 to ≥ 2,000 METs·min/week to increase the consistency of the exposure (0-99, 100-199, 200-299, …. ≥2,000 METs·min/week). Participants reporting a T-EEPA = 0 METs·min/week and greater than 12,000 METs·min/week, as well as those with an EE light PA,

EE moderate PA, or EE vigorous PA greater than 5,000, 6.000 and 10,000 METs·min/week, respectively, were excluded. Thus, the final sample consisted of 2908 participants.

LDL oxidations analyses

Biological samples from the participants were obtained in the baseline visit after 10 h fasting, coded, frozen, shipped to a central laboratory, and conserved at 80 ºC until the assay. To guarantee the technical quality of the assays, no previous freeze-thaw cycles were permitted.

Serum ox-LDL was determined in a random sample of 2,908 participants out of the unique 4.782. Serum ox-LDL was determined by an ELISA sandwich procedure using the murine monoclonal antibody mAB-4E6 as capture antibody and a peroxidase conjugated antibody against oxidized ApoB bound to the solid phase (oxLDL, Mercodia AB, Uppsala, Sweden). The inter-serial coefficient of variation was 9.98%.

Other variables

Examinations were performed by trained nurses and interviewers using standardized and validated questionnaires and measurement methods, as previously described (13). Smoking, alcohol intake, educational level and previous CVD were self-reported on standard questionnaires. Hypertension was considered when previously diagnosed by a physician, under treatment, or with values of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.

Participants were asked to fast for at least 10 hours before their appointment at the health examination site. Fasting blood samples were taken and total cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose concentrations were determined by enzymatic methods (Roche Diagnostics, Basel, Switzerland) in a Cobas Mira Plus autoanalyzer (Roche Diagnostics, Basel, Switzerland). Low-density lipoprotein cholesterol levels were estimated using the Friedewald equation when triglycerides were <300 mg/dL. Quality control was performed with the External Quality Assessment-WHO Lipid Program (WHO, Prague, Czech Republic) and Monitrol-Quality Control Program (Baxter Diagnostics, Dudingen, Switzerland). Diabetes was defined if previously diagnosed, under treatment, or with fasting glucose values ≥ 126 mg/dL.

Statistical analysis

Quantitative variables are described as mean (standard deviation) or median (interquartile range) based on their distribution. Categorial variables are described as counts and percentages. To assess the association between quantitative variables the Spearman correlation was used. ANOVA was used to

identify differences in the distribution of quantitative variables among groups, and Chi-squared to identify differences in the proportion of categorical variables among groups.

Serum ox-LDL was the dependent variable and light, moderate and vigorous LTPA were the independent variables. To assess the dose-response pattern of the association we used general additive models (GAM), including the variables of light, moderate and vigorous intensity PA as smooth terms in the linear predictor of ox-LDL to account for non-linear patterns of effect. We used the gam package. If the non-linear pattern of the association was not significant, we explored the linear association using classical multiple linear regression analyses. We tested for the assumptions of normality and homoscedasticity of residuals. Three models were defined a priori: 1) which included light LTPA, moderate LTPA and vigorous LTPA; 2) further adjusted for age and sex; 3) additionally adjusted for LDL-cholesterol, HDL-cholesterol, smoking, and diabetes. The analyses were additionally stratified by sex to explore potential differences between men and women. A p-value < 0.05 was considered as statistically significant. SPSS and R were used in the statistical analysis.

Ethical aspects

This work was carried out according to the declaration of Helsinki (1964 last revision 2013) for biomedical research, and current legislation for data protection (EU Data Protection Regulation of April 27, 2016 (2016 /679) and Spanish legislation LOPD 3/2018 of December 5). This research project was presented, reviewed, and approved by the PSMAR Clinical Research Ethics Committee (CEIC) and all the participants signed an informed consent.

RESULTS

The study was conducted in a sample of 2908 participants, of whom 1356 (46.6%) were men with a mean age of 50 years and 1552 (53.4%) were women with a mean age of 50.4 years. The main clinical and demographic characteristics of the overall sample and stratified by sex are presented in table 1. Serum ox-LDL, triglycerides, glycaemia, systolic (SBT) and diastolic (DBT) blood pressure were significantly lower in women, while body mass index (BMI), HDL cholesterol and heart rate were higher in women.

In relation to physical activity, the energy expenditure in moderate, vigorous, and total PA was significantly lower in women than in men ($p<0.001$).

Table 1

Clinical characteristics and energy expenditure in physical activity overall and stratified by gender.

	All N=2908	Men N=1356	Women N=1552	N	P-value
Age [c]	50.5 (13.6)	50.7 (13.8)	50.4(13.3)	2908	0.538
Body mass index [a] (kg/m^2) [c]	26.9 (4.4)	27.2 (3.9)	26.7 (4.8)	2896	**0.0018**
Personal history of hypercholesterolemia [e]: n (%)	701 (24.1)	336 (24.8)	365 (23.5)	2904	0.304
Personal history of diabetes [e]: n (%)	270 (9.29)	146 (10.8)	124 (7.99)	2906	**0.010**
Personal history of hypertension [e]: n (%)	704 (24.2)	331 (24.4)	373 (24.0)	2908	0.813
Smoking [e]: n (%)	649 (22.3)	388 (28.6)	261 (16.8)	2907	**<0.001**
Heart rate [c]	70.4 (36.5)	66.9 (11.8)	73.5 (48.5)	2888	**<0.001**
Systolic blood pressure [b] (mmHg) [c]	129.9 (20.9)	134.2 (19.2)	126.1 (21.6)	2904	**<0.001**
Diastolic blood pressure [b] (mmHg) [c]	78.2 (10.7)	80.7(10.3)	76.1 (10.7)	2890	**<0.001**
LDL oxidada (U/L) [d]	49.7 [36.0;66.5]	52.5[38.1;69.8]	47.0 [34.7;63.3]	2908	**<0.001**
Cholesterol total (mg/dl) [c]	222.3 (43.3)	221.0 (41.9)	223.3 (44.4)	2882	0.147
HDL cholesterol (mg/dl) [c]	52.1 (13.2)	47.2(11.5)	56.4 (13.2)	2856	**<0.001**
LDL cholesterol (mg/dl) [c]	149 (38.8)	149.9(37.6)	148.2(39.8)	2748	0.248
Triglycerides (mg/dl) [d]	92 [68.2;127]	104 [76;142]	82 [63;112]	2878	**<0.001**
Glycaemia (mg/dl) [d]	99 [92;108]	101 [95;111]	96 [89;104]	2876	**<0.001**
Total EEPA (MET·min/week) [d]	1344 [644;2356]	1650.5[782;3006]	1160.0 [533;1896]	2908	**<0.001**
EE Light PA (MET·min/week) [d]	343 [2;928]	357 [19.5;980]	322 [0;835]	2908	**0.0525**
EE Moderate PA(MET·min/week) [d]	143 [0;588.2]	234.5 [0;877]	86.0 [0;427]	2908	**<0.001**
EE Vigorous PA (MET·min/week) [d]	261 [105;712.2]	288 [105;894]	227 [96.2;588.5]	2908	**<0.001**

Bold values indicate statistical significance ($p<0.05$).

Abbreviations: HDL: high-density lipoprotein; LDL: low-density lipoprotein; Total EEPA: Total energy expenditure in physical activity; EE Light PA = Energy expenditure in light-intensity physical activities (2-4 METs); EE Moderate PA = Energy expenditure in moderate-intensity physical activities (4.5-5.5 METs); EE Vigorous PA =Energy expenditure in high-intensity physical activities (6-12 METs).

[a] Body mass index was calculated using weight in kilograms divided by the square of the height in meters.

[b] Calculated based on two readings.

[c] Mean (standard deviation), p-value estimated with the Student t-test.

[d] Median [percentile 25; percentile 75], p-value estimated with the Mann–Whitney U test.

[e] P-value estimated with by the $\chi 2$ test.

In the bivariate correlation analysis (Table 2), ox-LDL was significantly positively correlated with EE light PA, total cholesterol, LDL cholesterol, triglycerides, glycaemia, age, SBT, DBT and BMI, and negatively correlated with HDL cholesterol and EE vigorous PA.

Table 2

Relationship between clinical and demographic characteristics, total EEPA, EE Light PA, EE Moderate PA, EE Vigorous PA, and oxidized LDL.

	LDL-ox		
	N	r	P-value
Age	2908	0.167	**<0.001**
Body mass index [a] (kg/m^2)			
Systolic blood pressure [b] (mmHg)	2904	0.154	**<0.001**
Diastolic blood pressure [b] (mmHg)	2890	0.118	**<0.001**
Triglycerides (mg/dl)	2878	0.285	**<0.001**
Total cholesterol total (mg/dl)	2882	0.375	**<0.001**
HDL cholesterol (mg/dl)	2856	-0.126	**<0.001**
LDL cholesterol (mg/dl)	2748	0.394	**<0.001**
Glycaemia (mg/dl)	2876	0.132	**<0.001**
Total EEPA (MET·min/week)	2908	0.028	0.129
EE Light PA (MET·min/week)	2908	0.045	**0.016**
EE Moderate PA (MET·min/week)	2908	0.033	0.077
EE Vigorous PA (MET·min/week)	2908	-0.068	**<0.001**

Bold values indicate statistical significance ($p<0.05$).

Abbreviations: HDL: high-density lipoprotein; LDL: low-density lipoprotein; Total EEPA: Total energy expenditure in physical activity; EE Light: PA Energy expenditure in light-intensity physical activities (2-4 METs); EE Moderate PA: Energy expenditure in moderate-intensity physical activities (4.5-5.5 METs); EE Vigorous PA: Energy expenditure in high-intensity physical activities (6-12 METs).

[a] Body mass index was calculated using weight in kilograms divided by the square of the height in meters.

[b] Calculated based on two readings.

r, Spearman's correlation coefficient.

Figure 1 presents the results of the two non-parametric regression models (general additive models) with ox-LDL as linear predictor and total EEPA as smoothed term in a first model, and EE Light PA, EE Moderate PA, and EE Vigorous PA as smoothed terms in a second model. No significant non-linear relationship was found between EEPA (total, light, moderate or vigorous) and ox-LDL levels. Therefore, a multiple linear regression analysis was performed to explore a possible linear association.

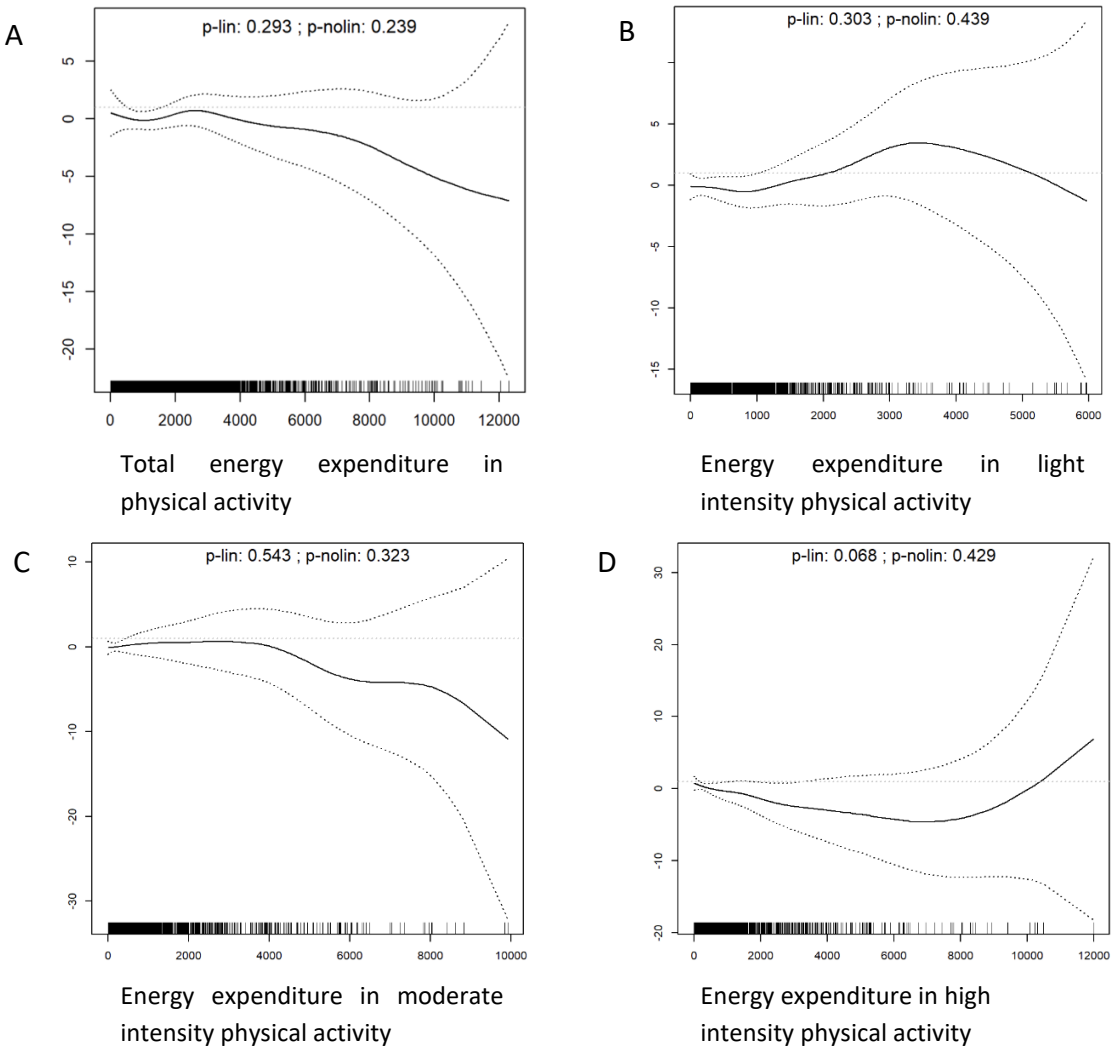

Fig. 1. Dose–response association pattern for energy expenditure in physical activity and LDL-ox: total energy expenditure (panel A), energy expenditure in light-intensity physical activity (panel B), energy expenditure in moderate-intensity physical activity (panel C), and energy expenditure in high-intensity physical activity (panel D).

Table 3 presents the results of multiple linear regression analysis in three different models: model 1, unadjusted; model 2, adjusted for age and sex; and model 3, adjusted for age, sex, LDL cholesterol, HDL cholesterol, smoking and personal history of diabetes. In the first model, significant direct associations are observed for light (p=0.003) and moderate activity (p=0.015), and inverse for vigorous activity (p=0.001). In the second model, the significant negative association (p=0.051) between vigorous activity and ox-LDL levels remained. In the third model, no significant associations were found. When we stratified the analysis by sex, in women, the first model revealed significant positive associations for light (p=0.002) and

moderate activity (p=0.015), and negative associations for vigorous activity (p=0.013). However, in the second and third models, no significant associations were found. In the case of men, in all three models, the significant negative association remained for vigorous activity (p=0.001, p=0.021 and p=0.049 respectively). Each increase of 100 MET-min/week was associated with a decrease in ox-LDL of 0.19 U/L in the fully adjusted model.

Table 3
Multiple linear regression models of the association between physical activity practice and oxidized LDL levels.

	Model 1 [a]			Model 2 [a]			Model 3 [a]		
Global sample	β	EE	P-value	β	EE	P-value	β	EE	P-value
EE Light PA (Δ 100 MET·min/week)	0.22	0.07	**0.003**	0.08	0.07	0.307	0.07	0.07	0.302
EE Moderate PA (Δ 100 MET·min/week)	0.18	0.07	**0.015**	0.02	0.08	0.791	0.02	0.07	0.736
EE Vigorous PA (Δ 100 MET·min/week)	-0.24	0.07	**0.001**	-0.15	0.08	**0.051**	-0.12	0.07	0.079
Women									
EE Light PA (Δ 100 MET·min/week)	0.33	0.10	**0.002**	0.19	0.10	0.065	0.15	0.09	0.124
EE Moderate PA (Δ 100 MET·min/week)	0.29	0.12	**0.015**	0.22	0.12	0.058	0.18	0.11	0.094
EE Vigorous PA (Δ 100 MET·min/week)	-0.28	0.11	**0.013**	-0.06	0.11	0.588	-0.05	0.11	0.639
Men									
EE Light PA (Δ 100 MET·min/week)	0.08	0.10	0.424	0.00	0.11	0.988	-0.00	0.10	0.982
EE Moderate PA (Δ 100 MET·min/week)	0.00	0.10	0.993	-0.06	0.10	0.518	-0.07	0.09	0.433
EE Vigorous PA (Δ 100 MET·min/week)	-0.32	0.10	**0.001**	-0.24	0.10	**0.021**	-0.19	0.09	**0.049**

Bold values indicate statistical significance (p<0.05).
Abbreviations: EE Light: PA Energy expenditure in light-intensity physical activities (MET·min/week); EE Moderate PA (2-4 MET·min/week); Energy expenditure in moderate-intensity physical activities (4.5-5.5 MET·min/week); EE Vigorous PA: Energy expenditure in high-intensity physical activities (6-12 MET·min/week).
β coefficient.
[a] Model 1: Included EE light PA, EE Moderate PA, and EE vigorous PA; Model 2: Adjusted for age and gender; Model 3: Adjusted for age, gender, LDL cholesterol, HDL cholesterol, smoking habits, and personal history of diabetes.

DISCUSSION

In this population-based observational study, we observed a significant linear inverse relationship between vigorous-intensity PA and ox-LDL levels in men, with no such relationship observed in women.

Physical activity is associated with a lower risk of cardiovascular disease (4). This relationship follows a non-linear pattern, with a large benefit at low doses of PA and a subsequent plateauing (14,15). Although we hypothesised that the non-linear component of the relationship between PA and ox-LDL levels would be relevant, we did not observe this pattern in our study.

One of the most important findings of our study is that the association between vigorous PA and lower ox-LDL levels was only observed in men. These results are consistent with several studies showing sex differences in the impact of PA on lipid profile. A relatively weak association between PA and lipid risk factors has been seen in young women, with a much stronger association in men of similar age (16). In another Finnish cohort study in young women, the only lipid parameter that showed an association with PA was triglycerides (17). Therefore, these results suggest that there may be a sex difference in the relationship between PA and lipid profile. This may be biologically explained by a hormonal protection in women of childbearing age. Elevated oestrogen levels may have favourable effects on the lipid profile by various mechanisms, such as the reduction of free radicals through their antioxidant effect, thereby decreasing ox-LDL levels (18–20).

Likewise, long-term aerobic exercise decreases susceptibility to LDL particle oxidation and oxidative stress in men but aerobic exercise over a shorter period favours LDL particle oxidation. In contrast, oxidative stress from aerobic exercise does not seem to negatively affect LDL oxidation in women, with LDL oxidation being independent of physical activity (21). These possible explanations are also consistent with the triglyceride and ox-LDL levels of the women in our sample, which are significantly lower than those of the men, while HDL cholesterol values are higher. Finally, this difference between men and women could be since women in our study perform less total, light, moderate and vigorous PA than men, which could limit the statistical power of our study.

Our results are consistent with those observed in the literature. Several experimental studies have examined the relationship between PA and ox-LDL levels. They have demonstrated the benefit of PA on the reduction of ox-LDL levels in a very wide range of people studied, both for differences in age, presence of cardiovascular pathologies, obesity or type of activity performed (9,22–24). There is also evidence from intervention (25) and observational studies (26) in which subjects with lower levels of fitness and training volumes have higher ox-LDL levels.

Regarding the intensity of PA, in contrast to our findings, in a population-based study with 1820 participants and a 10-year follow-up (27), no significant association was found between ox-LDL levels and the different categories of PA. On the other hand, moderate-intensity exercise has been shown to be more effective in reducing susceptibility to long-term oxidative damage compared to high-intensity exercise in subjects following a high-fat diet (28). Furthermore, the ATTICA population-based study suggests that moderate, not intense, PA reduces the risk of diabetes by more than 50% through the reduction of oxidative stress (29). In the same vein, several articles suggest that intense PA stimulates free radical production by increasing oxidative stress levels while moderate PA protects monocytes from suppression of antioxidant capacity (30,31). In contrast, several articles indicate that, although high-intensity exercise results in a temporary increase in oxidative stress markers, there is no persistence of these markers over time. This is probably because chronic training induces adaptations of the antioxidant defence system (6,32).

The mechanisms explaining this reduction in ox-LDL levels in relation to vigorous or intense PA may be several. Firstly, the reduction in the levels of LDL particles themselves (33), although in our study the relationship remained independent when adjusting for LDL levels. Another mechanism may be related to the higher resistance, lower susceptibility, of LDL particles to oxidation (6,34). On the other hand, regular PA may increase endogenous antioxidant mechanisms, such as antioxidant enzymes (6,35) or the antioxidant capacity of HDL particles (36).

From a public health perspective, vigorous PA is associated with larger reductions on all-cause mortality risk than PA of lower intensity (37). However, the regular practice of intense vigorous activity is unfeasible in many cases for a large part of the general population. There is therefore an emerging strategy, known as intermittent lifestyle physical activity (VILPA), in which intermittent vigorous activity is performed during the day for short periods of time, making it more accessible to the general population. This strategy has been shown to be associated with a 26-30% reduction in all-cause and cancer mortality risk and a 32-34% reduction in CVD mortality risk (38).

Our study has some limitations. PA was assessed using a questionnaire that, although validated for the Spanish population, may introduce an information bias in the measurement of the exposure variable of interest. The low variability in the practice of PA, especially in women, may limit the statistical power to identify statistically significant associations. On the other hand, some strengths are also identified. The main ones being the population base and the sample size of the study.

CONCLUSIONS

This study provides further support to the existing scientific literature regarding the relationship between physical activity and ox-LDL levels. Our results are consistent with an inverse and linear relationship between vigorous PA and ox-LDL, specifically in men. Lowering ox-LDL levels could be one of the mechanisms that explain the beneficial effects of PA on cardiovascular health.

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ABBREVIATIONS

CVD	cardiovascular disease
MET	metabolic equivalents of task
HDL	high-density lipoprotein
LDL	low-density lipoprotein
Ox-LDL	oxidized low density lipoprotein
PA	physical activity
LTPA	leisure-time physical activity
EEPA	energy expenditure in physical activity
T-EEPA	total energy expenditure in physical activity
EE Light PA	energy expenditure in light physical activity
EE Moderate PA	energy expenditure in moderate physical activity
EE Vigorous PA	energy expenditure in vigorous physical activity
SBT	systolic blood pressure
SDT	diastolic blood pressure
BMI	body mass index
VILPA	vigorous intermittent lifestyle physical activity

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