Pressler A[1]

A Run a Day Keeps Lipids at Bay? Regular Exercise as a Treatment of Dyslipidaemias

Der Fettstoffwechselstörung davonlaufen? Körperliches Training als Behandlungsoption bei Dyslipidämien

REVIEW

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Summary

- **Problem:** Dyslipidaemia and physical inactivity are leading risk factors for the development of atherosclerotic disease, accounting annually for approximately 5.8 million deaths worldwide. A lipid-lowering effect of exercise is commonly assumed, but, in contrast to multi-modal lifestyle interventions, the particular effect of exercise on lipid profiles is less-well established.
- **Methods:** Systematic literature search for epidemiological and randomized trials, reviews and meta-analyses evaluating the particular effects of high fitness or exercise interventions on changes in lipid levels.
- **Results:** A higher fitness assessed by exercise testing is moderately associated with favourable HDL-cholesterol and triglyceride, but not LDL levels. This is confirmed by findings from randomized trials and meta-analyses, but effects are not consistently observed. Moderate aerobic exercise is preferred over resistance or high-intensity interval exercise. Besides absolute lipid values, exercise favourably influences atherogenic lipid subfractions. The combination of statins with exercise improves clinical outcomes; thus, statins should not be withheld if indicated according to guidelines.
- **Discussion:** The effect of exercise on lipid levels is at best moderate, with small improvements in HDL and triglyceride, but not LDL levels. Nonetheless, dyslipidaemia is rarely observed as a single risk factor, and exercise remains a cornerstone of multimodal lifestyle interventions to favourably modify cardiovascular risk.

KEY WORDS:
Fitness, Exercise, Dyslipidaemia, LDL, Statins

Zusammenfassung

- **Problem:** Dyslipidämien und Inaktivität sind führende Risikofaktoren in der Pathophysiologie der Arteriosklerose und werden für ca. 5,8 Millionen jährliche Todesfälle weltweit verantwortlich gemacht. Ein lipidsenkender Effekt durch körperliches Training als Bestandteil multimodaler Lebensstilintervention wird allgemein angenommen; die Datenlage für Sport als alleinige Interventionsmaßnahme ist dagegen weniger eindeutig.
- **Methoden:** Systematische Literaturrecherche nach epidemiologischen und randomisierten Studien, Übersichtsarbeiten und Metaanalysen, die den alleinigen Effekt einer hohen Fitness oder eines körperlichen Trainings auf Blutfette thematisieren.
- **Ergebnisse:** Eine hohe Fitness, ermittelt anhand eines Ergometertests, ist mit höheren HDL- und niedrigeren Triglyzerid-, nicht aber günstigeren LDL-Werten assoziiert. Dies bestätigt sich in der Mehrheit randomisierter Studien und Metaanalysen, wird aber nicht durchgehend beobachtet. Moderates Ausdauertraining ist dem Kraft- oder hochintensivem Intervalltraining vorzuziehen. Neben Veränderungen der absoluten Lipidwerte kann Training auch atherogene Lipid-Subfraktionen günstig beeinflussen. Unabhängig von singulären, in der Summe seltenen Nebenwirkungen wie Muskelschmerzen ergänzt eine Statintherapie nach epidemiologischen Daten positive Trainingseffekte und sollte daher bei bestehender Indikation nicht vorenthalten werden.
- **Diskussion:** Körperliches Training hat einen bestenfalls moderaten Effekt auf Blutfette und verbessert hauptsächlich HDL- und Triglyzerid-, nicht aber LDL-Werte. Da die überwiegende Mehrheit der Patienten allerdings eine Kombination mehrerer Risikofaktoren aufweist, bleibt regelmäßiges Training ein unverzichtbarer Bestandteil multimodaler Lebensstilinterventionen zur Optimierung des kardiovaskulären Risikoprofils.

SCHLÜSSELWÖRTER:
Fitness, körperliches Training, Dyslipidämien, LDL, Statine

Introduction

Dyslipidaemias represent a leading risk factor for cardiovascular disease, and appropriate treatment of elevated lipid levels targeting recommended goals is a key component of risk modification in both primary and secondary prevention. According to the World Health Organisation, elevated cholesterol levels are a major risk factor for heart disease and stroke, estimated to cause 4.5% of all annual deaths worldwide (49). In addition, insufficient physical activity is estimated to be the fourth leading risk factor for mortality, accounting for 3.2 million annual deaths worldwide.

Thus, both lowering lipid levels and increasing physical activity represent valuable treatment goals, and it will not be challenged by many that both modalities are favourably associated with each other. ›

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However, exercise is usually offered as part of multi-modal lifestyle interventions including nutritional advice, whereas little is known on the independent effects of exercise on lipid levels. Therefore, the present article intends to summarize the current evidence on the contribution of exercise as a single intervention to improvements in lipid profiles, with respect to primary and secondary prevention of cardiovascular disease.

What Do Current Guidelines Advice?

According to the significance of appropriate lipid management, guidelines are updated in close intervals, with the current recommendations of the European Society of Cardiology in association with either the European Atherosclerosis Society (4) (EAS; focusing on dyslipidaemia) and the European Association of Cardiovascular Prevention and Rehabilitation (36) (focusing on prevention) having been published in 2016.

Both guidelines almost exclusively focus on Low-density-lipoprotein-cholesterol (LDL) as the primary treatment target, in line with the latest guidelines from the American Heart Association (43). Although the favourable epidemiological effect of elevated High-density-lipoprotein-cholesterol (HDL) levels on mortality is still acknowledged, recent efforts to reduce mortality risk by actively elevating HDL levels using various agents have mostly failed, despite substantial increases induced by these drugs (14).

Both initiation and intensity of LDL-lowering treatment are based on individual risk profiles, depending on the presence of other risk factors or atherosclerotic disease (table 1), with a target of <70mg/dl being still the current recommendation for very high-risk patients. However, targeting even lower LDL levels (up to 30mg/dl) by adding agents such as ezetimibe (3) or evolocumab has recently been shown to further improve clinical outcomes (42). Further outcome studies evaluating these (8) and other new treatment modalities (2, 38) are eagerly awaited as they will probably have significant impact on future recommendations.

Exercise is mentioned within the sections on non-pharmacological treatment options, but is largely embedded into the evidence for combined effects of multi-modal lifestyle interventions. Nonetheless, single evidence grades for exercise are provided in the EAS guidelines, with the highest evidence for increasing HDL (+++A), followed by reducing triglycerides (TG; ++A); instead, lowering LDL by exercise is less well established (LDL; +B) (4). The following paragraphs summarize the background of these evidence grades, which have been derived fom different scientific approaches.

The Epidemiological Perspective: "Fitness" and Lipid Levels

The "classic" epidemiological association of low LDL and high HDL levels with reduced mortality is still undoubtedly accepted. Regarding exercise, substantial evidence for the associations with lipid profiles can as well be derived from epidemiological observations. Nonetheless, the limitations of this approach have to be kept in mind, as exercise behaviours are measured indirectly (e.g. by questionnaires), results may statistically be confounded, and causality is often equivocal.

A very common approach has been to link the maximum workload attained during a single exercise test (commonly termed "fitness") to long-term mortality outcomes. Using this method, a landmark study by Myers et al. in 6,213 men (age 59±11 years (y)) has observed a significantly reduced mortality risk in the subgroup with the highest fitness as compared to the lowest fitness group, independent of a total cholesterol (TC) level >220mg (32). Similarly, in 5,721 women (52±8y) a higher fitness was associated with reduced mortality after adjustment for the Framingham Risk Score, which includes TC and HDL levels (10). These findings indicate that a high "fitness" as asessed by exercise testing appears to mitigate the unfavourable effects of elevated cholesterol levels in both middle-aged men and women.

A recent study has investigated the impact of fitness on the age-related longitudinal changes of lipid levels over the life course (35). In 11,418 healthy males (44±9y), a higher fitness level was associated with a delayed development of abnormal lipid profiles as compared to participants with low fitness. In 3,148 men (42±8y) undergoing preventive examinations at two different time points, both a loss in fitness and a gain in fatness (body mass index (BMI)) were associated with the development of hypercholesterolemia (27). In contrast, improving fitness was independently associated with a 30% lower risk for hypercholesterolemia. Thus, gaining fitness is apparently linked to improved lipid levels, independent of fatness changes.

In 27,158 asymptomatic females in the Women´s Health Study (55±7y), the amount of physical activity was assessed by questionnaire (31). A significantly lower proportion of women classified as "active" had HDL values <50mg/dl as compared to inactive women, independent of BMI category. In addition, normal-weight, active women were significantly less likely to show LDL levels >130mg compared to their sedentary counterparts, but this was not confirmed in the other BMI categories.

Epidemiological studies conducted in the 1990s provided evidence on the amount of endurance exercise required to improve lipid profiles. In 8,283 male recreational runners (45±10y), weekly running distances obtained by questionnaire were linked to individual lipid profiles (46). Runners with a weekly distance of >80km showed significantly higher HDL and lower TG levels compared to those running <16km. Differences in LDL levels were less pronounced. Similar findings were obtained with respect to increases in HDL in a cohort 1,837 female runners (45). These observations are of some interest, but few patients will be convinced of the benefits of running >80km/week. In addition, recent data did not show additional mortality benefits with increasing running distances per week (26), indicating that epidemiological associations based on evaluations at single time points do not always transfer into improved clinical outcomes.

Overall, findings from epidemiological studies indicate several positive associations between high fitness or physical activity level and favourable lipid profiles, mostly pertaining to improved HDL and TG levels, whereas the evidence for LDL is less clear. Although mortality risk is reduced in subjects with higher baseline fitness, a potential mediation of this association by exercise-induced lipid profile improvements cannot be derived from this data.

Randomized and Observational Trials

Few randomized controlled trials (RCT) of sufficient quality have focused on lipid levels as primary outcome of exercise interventions; they are by far more often assessed as secondary variables, lacking adequate statistical power. The latter are therefore preferably summarized in meta-analyses, presented in the subsequent section. Others have focused on the effect of specific types of exercise on lipid levels and are also presented in a later section.

In a RCT conducted in the early 1980s, 81 men (30-55y) were randomized to a regular, moderate running program (70-85% peak oxygen uptake (VO_2peak)) over 1 year or to a non-

Table 1

Treatment goals for lowering LDL levels according to risk factor constellation (modified from the European Society of Cardiology 2016 guidelines on dyslipidaemia and cardiovascular disease prevention (4, 30)). The SCORE system estimates the 10-year cumulative risk of a first fatal atherosclerotic event, based on traditional risk factors (age, gender, smoking, cholesterol, systolic blood pressure). Evidence grades are: Class/Level. CVD, cardiovascular disease; GFR, glomerular filtration rate; LDL, low-density-lipoprotein-cholesterol; SCORE, systematic coronary risk estimation.

RISK CATEGORY	DEFINED BY:	LDL TREATMENT GOAL	EVIDENCE GRADE
Very high risk	Any of the following: - Documented CVD, clinical or unequivocal on imaging. This includes previous myocardial infarction, acute coronary syndrome, coronary revascularisation, coronary artery bypass graft surgery, and other arterial revascularization procedures, stroke and transient ischemic attack, peripheral artery disease, and significant plaque on coronary angiography or carotid ultrasound. - Diabetes with target organ damage (proteinuria, smoking, hypertension, dyslipidaemia) - Severe chronic kidney disease (GFR <30ml/min/1.73m²) - A calculated SCORE ≥10% for 10-year risk of fatal CVD	<70mg/dl (1.8mmol/l) or reduction of at least 50% if baseline LDL is between 70-135mg/dl (1.8-3.5mmol/l)	IB
High risk	- Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension - Most other people with diabetes - Moderate chronic kidney disease (GFR 30-59 ml/min/1.73m²) - A calculated SCORE ≥ 5% and < 10% for 10-year risk of fatal CVD	<100mg/dl (2.6mmol/l) or reduction of at least 50% if baseline LDL is between 100-200mg/dl (2.6-5.2mmol/l)	IB
Moderate risk	SCORE is ≥1% and <5% for 10-year risk of CVD	<115mg/dl (3.0mmol/l) should be considered	IIaC
Low risk	SCORE is <1% for 10-year risk of CVD		

exercising control group (48). Although lipid profiles in runners improved in absolute terms, group differences were not significant. Only runners with weekly distances >13km showed significant increases in HDL. Similar to the epidemiological observations mentioned above, running distance per week was significantly associated with improved HDL and LDL levels.

In the observational HERITAGE Family study, 675 participants from black and white families (17-65y) underwent 20 weeks of moderate aerobic exercise training on cycle ergometers (75% VO_2peak) (28). A modest, but significant increase in HDL in males and females and a significant reduction of TG in males was observed; other lipid levels remained unchanged. Interestingly, the lipid response to exercise correlated significantly within family members (40), indicating a contribution of genetic factors to the extent of exercise-induced effects.

Summarizing these findings, the effect of prolonged moderate-intensity aerobic exercise interventions on lipid levels was rather disappointing. Again, HDL and TG appeared to be the primary target of exercise, whereas LDL remained largely unaffected.

Meta-Analyses

Several meta-analyses have summarized the specific effects of exercise interventions on lipid levels, either assessed as primary or secondary outcomes.

Kodama et al. summarized 25 RCT with 1,404 participants (23-75y) evaluating the effect of aerobic exercise interventions with a minimum duration of 8 weeks particularly on HDL (21). They observed a mean, statistically significant increase of 2.53mg/dl, but a minimum of 120 min of exercise per week was necessary to induce these changes. The effect was most pronounced in subjects with a BMI <28kg/m² and a TC >220mg/dl, and the duration of exercise sessions was a strong predictor of HDL increase. Kelley et al. summarized studies focusing on aerobic exercise interventions (≥8 weeks) particularly in overweight and obese individuals (18). In 13 RCT with 613 participants (31-63y), only TG was significantly reduced by 16% with no changes in TC, HDL and LDL levels. In 1260 patients with coronary artery disease (50-67y), Kelley et al. found 10 RCT of sufficient quality, evaluating the effect of aerobic exercise interventions (≥4 weeks) on lipid levels (16). They reported modest, but significant improvements in HDL (+3.7±1.3mg/dl) and TG (-19.3±5.4mg/dl), with no changes in TC and LDL levels.

Findings from these meta-analyses very much reflect those of larger single RCT in confirming HDL and TG as primary targets of exercise interventions in both primary and secondary prevention, consistent with the evidence grades provided in the above-mentioned guidelines.

Which Type of Exercise?

The vast majority of studies has implemented interventions based on moderate aerobic exercise at intensities ranging from 60-85% VO_2peak. However, resistance training (RT) or high-intensity interval training (HIIT) may represent alternative approaches in selected patients, and several studies have evaluated their particular effects on lipid levels.

Kelley et al. performed a meta-analyses of 29 RCT in 1,329 participants applying exclusively RT interventions (≥ 4 weeks) in adult populations (20-75y) and measuring changes in lipid levels as outcomes (15). Interestingly, they found significant improvements in TC (-2.7%), LDL (-4.6%) and TG (-6.4%) levels, but not in HDL levels. These findings were not confirmed by a meta-analysis in patients with type 2 diabetes, summarizing 34 RCT with either aerobic or resistance exercise alone or combined (5). RT showed no effect on lipid levels; a significant TG reduction was observed only when it was combined with aerobic exercise. None of the intervention modalities resulted in significant changes in HDL and LDL levels.

A landmark study evaluating the effect of amount vs. intensity of exercise on a variety of lipid parameters was conducted by Kraus et al. (23). A total of 84 sedentary, overweight-to-obese, dyslipidemic men and women (51±8y) were randomized to 3 subgroups differing by pre-defined amounts and intensities of exercise, or to a non-exercising control group. After 8 months of training, a significant increase in HDL was observed only in the group performing high amount and high intensity exercise. No overall effects on TC and LDL were observed. Summarizing the absolute group-effects on all investigated lipoprotein parameters, there was a clear association with the amount, but not with the intensity of exercise. Similarly, Tjonna et al. compared moderate exercise with HIIT in patients with the Metabolic Syndrome, and significant improvements in HDL levels were only seen in the moderate exercise group (44). Accordingly, in a review on RCT applying HIIT interventions (≥8 weeks), only 3 of 14 studies reported significant increases in HDL levels, with no overall effect on any other lipid parameters (19). ›

In summary, moderate aerobic exercise appears superior to RT or HIIT, with the amount rather than the intensity of exercise being more effective in improving HDL and TC levels. In other words, when selectively intending to improve lipid levels, performing long bouts of moderate, dynamic exercise should be preferred over short, intensive bouts, including RT. No consistent effect is reported on LDL levels, again reflecting the lower evidence grade pertaining to this parameter in current guidelines.

Is Increased Physical Activity already Sufficient?

Increased physical activity (PA) is favourably associated with reduced mortality (25), but few studies have focused on its particular effect on lipid levels, further limited by sometimes diffuse differentiations between "exercise" and "physical activity" particularly in epidemiological approaches. In the Women´s Health Study mentioned above, beneficial lipid profiles contributed approximately 20% to the cardiovascular risk reduction associated with increased PA (30). In the CARDIA study on 12,364 middle-aged adults, walking or cycling to work (assessed by questionnaire) was linked to improved TG levels in men, with no effect on other lipids and in women (9). In contrast, when comparing 33,060 runners with 15,945 walkers from the National runners´ and walkers´ health cohorts (51±11y), the amount of risk reduction for incident hypercholesterolemia was similar among groups of similar energy expenditures (47). Regarding sedentary behaviour, in 8,800 Australian adults (53±14y), a television viewing time of <2 hours per day was associated with more favourable lipid profiles compared to ≥2 hours, although absolute differences were small (7).

In randomized approaches, following a PA counseling intervention in 179 type 2 diabetic subjects (62±1y), lipid profiles overall improved alongside weekly increases in energy expenditure; statistical significance was reached when values corresponding to 2.5 hours of walking were exceeded (6). In contrast, a meta-analysis of 25 RCT evaluating effects of >8 weeks of walking on lipid levels in 1,176 adults (49±14y), only LDL was significantly reduced (-5.5±2.2mg/dl) (17). Interestingly, according to a recent meta-analysis (34), performing >12 weeks of Tai Chi resulted in significantly lower TG levels (-16.8mg/dl) compared to controls, without affecting other lipid parameters.

Overall, findings are inconsistent with respect to single lipid parameters, but results from PA studies suggest that ´something is better than nothing`. Thus, patients should be motivated to increase their PA habits, but should be informed that effects will be more pronounced with more vigorous activities.

Quality, not Quantity? Exercise Effects on Particle Structure

High HDL and low LDL levels are epidemiologically associated with reduced mortality, thus improving the quantity of these parameters has been the traditional focus of exercise intervention studies. However, changes in their "quality", namely particle size and structure, have also been linked to an increased risk for developing atherosclerotic disease. Regarding LDL subfractions, this particularly pertains to the proportion of particles of small density, whereas risk appears reduced with increasing LDL particle size. In the study by Kraus et al. on amount and intensity of exercise presented above (23), no changes in total LDL levels, but significant reductions of small dense particles and increases in particle size were observed, indicating beneficial exercise effects on a molecular level. Similarly, a significantly lower proportion of LDL small dense subfractions were reported in fit vs. unfit hypercholesterolemic men (as assessed by exercise testing) (12).

Regarding HDL, recent research has also focused on functional components rather than simply measuring absolute levels. In the population-based Dallas Heart Study, HDL efflux capacity (the ability of HDL to accept cholesterol from macrophages), but not baseline HDL level was inversely associated with incident cardiovascular events after adjustment for baseline risk factors (41). Furthermore, in the JUPITER-trial on the effects of rosuvastatin in primary prevention, HDL particle number rather than absolute HDL levels was the strongest predictor of incident cardiovascular disease, independent of medication (20). These parameters have not specifically been targeted in exercise intervention studies so far. However, Adams et al. have focused on another important, but less known functional property of HDL, the ability to promote endothelial function by stimulating the production of nitric oxide in vascular endothelial cells (1). This function was shown to be impaired in heart failure patients as compared to healthy controls, but was restored after 12 weeks of aerobic exercise training, which was, in turn, clinically linked to improved flow-mediated dilatation.

Apart from these preliminary observations, a key clinical problem remains unresolved. As mentioned above, drug-induced massive HDL increases have not consistently resulted in a reduction of cardiovascular events as compared to placebo. Thus, at this point of time, it is equivocal whether the comparably small increases in HDL levels induced by exercise will transfer into any clinical significance at all.

Exercise, Lipoprotein(a) and Familial Hypercholesterolemia

Although Lp(a) significantly contributes to the development of coronary and valvular heart disease, data on associations with exercise or fitness levels is scarce. When comparing the most active with the inactive group of females in the Women´s Health Study already cited above, Lp(a) as part of a set of "novel" lipids showed only a small contribution (15.5%) to overall risk reduction (30). In an observational study on diabetic men (55±8y), higher fitness as assessed by exercise testing was associated with significantly lower levels of Lp(a), but no clinical outcomes were reported (13). Regarding familial hypercholesterolemia (FAH), some affected patients may have been included in the studies mentioned so far, but no exercise intervention study has specifically targeted this particular cohort. However, in an observational study on 639 patients with heterozyguous FAH free of cardiovascular disease at baseline, decreased exercise capacity assessed by exercise testing significantly predicted incident coronary events during follow-up (37). In summary, both the evidence for the effect of regular exercise on elevated Lp(a) levels and in FAH is low, and future research is required before definitive conclusions are permitted.

Statins and Exercise – an Unfavourable Combination?

Depending on the risk profiles, many patients will be candidates for both exercise interventions and statin treatment. Kokkinos et al. investigated the combined effect of fitness (exercise test) and statin therapy in a population of 10,043 men (59±11y) with and without cardiovascular disease (22). A total of 2,318 deaths were noted during a follow-up of 10 years, and both high fitness and statin therapy were independently associated with reduced mortality. If both modalities were present, risk

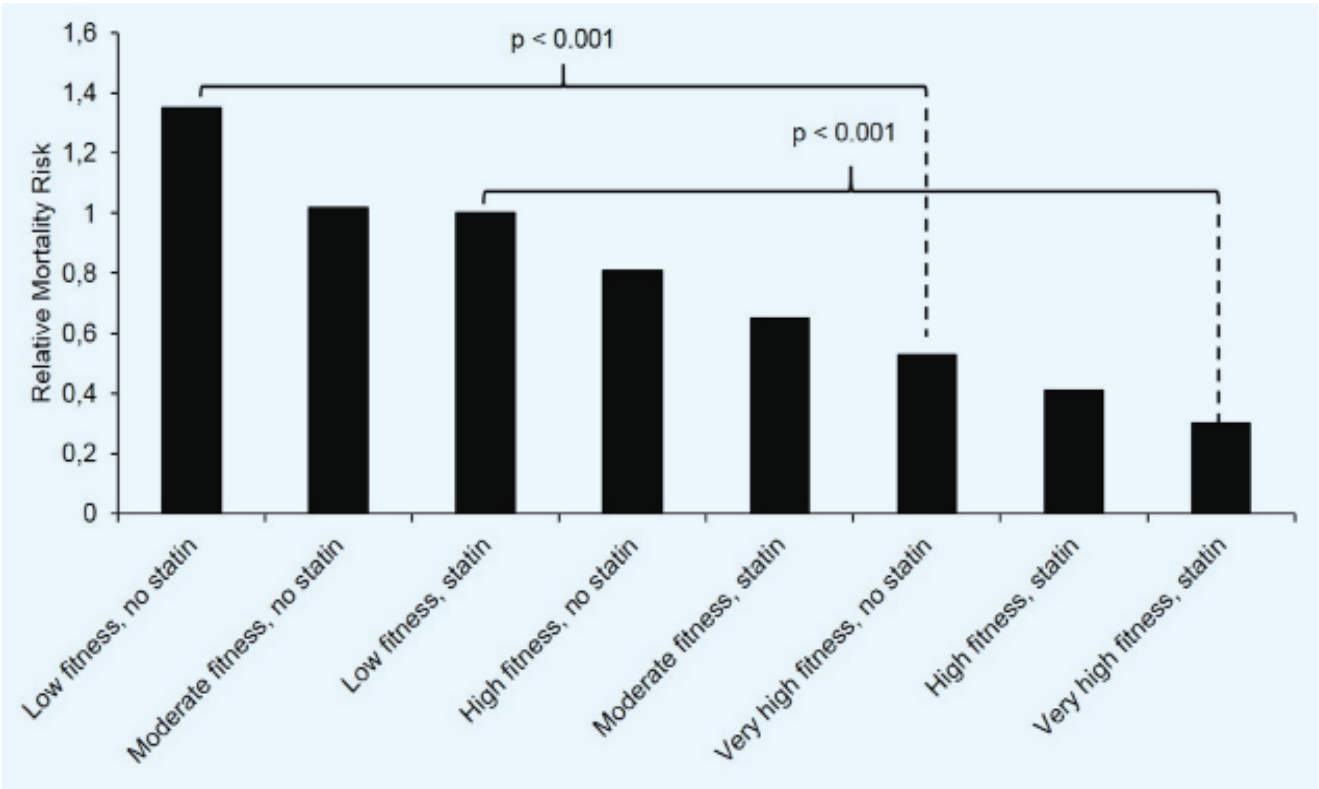

Figure 1

Schematic illustration of the associations between statin intake and fitness level as assessed by exercise testing. Highly significant reductions in all-cause mortality risk were observed between least vs. highly fit patients both with and without statin treatment. Being highly fit and taking statins showed the highest benefit (modified from (18)).

reduction was more than doubled, indicating an exponential beneficial effect of combining exercise and statins at least from an epidemiological perspective (fig. 1). In a cardiac rehabilitation setting, no differences in changes in VO_2peak after 3 months of exercise training were observed between patients with (n=968) or without (n=233) statin treatment (39).

In contrast, in a RCT in patients with the Metabolic Syndrome, 37 participants (43±11y) were randomized to 12 weeks of aerobic exercise alone or to exercise and simvastatin 40mg (29). VO_2peak increased significantly in the exercise-only group, but was blunted in the combined group, indicating an unfavourable interaction between statins and exercise in this small population. Moreover, among patients there is an increasing scepticism regarding the initiation and value of statin therapy, unfortunately supported by many media reports in recent years (33). This often pertains to side effects such as myalgia, a clinical problem that indeed requires attention in individual cases, but the prevalence of which is much lower than anticipated (11, 24).

In summary, statin therapy may attenuate the effects induced by regular exercise in single cases, but the overall evidence suggests neutral or even beneficial effcts of combining both treatments. It is therefore not justified to withhold statin treatment (if indicated according to current guidelines) in patients exercising regularly, or vice versa.

Conclusion

Summarizing the current evidence, effects of regular exercise on lipid levels are at best modest, and many studies have yielded rather disappointing results. Long bouts of moderate aerobic exercise are preferred over resistance or high-intensity interval exercise. Small improvements in HDL and TG are most frequently observed, the clinical significance of which remains to be established. LDL is rarely affected in absolute terms, but exercise-induced reductions of atherogenic small dense subfractions indicate that future research should additionally focus on changes in lipid quality rather than quantity. Elevated LDL levels should be treated according to current guidelines, which in many cases will include early-onset statin therapy. Apart from individual side effects pertaining to symptoms of myalgia, the overall evidence supports a favourable effect of combining exercise and statin therapy.

Finally, as stated in the introduction, the present article focuses on the effects of exercise on lipid levels as a single intervention. Since in many patients abnormal lipid profiles are part of a combination of various risk factors, exercise training as a key component of multi-modal lifestyle interventions remains a cornerstone of non-pharmacological therapies and should be implemented into treatment strategies whereever possible.

Conflict of Interest

The author has no conflict of interest.

References

(1) **ADAMS V, BESLER C, FISCHER T, RIWANTO M, NOACK F, HÖLLRIEGEL R, OBERBACH A, JEHMLICH N, VOLKER U, WINZER EB, LENK K, HAMBRECHT R, SCHULER G, LINKE A, LANDMESSER U, ERBS S.** Exercise training in patients with chronic heart failure promotes restoration of high-density lipoprotein functional properties. Circ Res. 2013; 113: 1345-1355. doi:10.1161/CIRCRESAHA.113.301684

(2) **BLOM DJ, AVERNA MR, MEAGHER EA, DU TOIT THERON H, SIRTORI CR, HEGELE RA, SHAH PK, GAUDET D, STEFANUTTI C, VIGNA GB, LARREY D, BLOEDON LT, FOULDS P, RADER DJ, CUCHEL M.** Long-Term Efficacy and Safety of the Microsomal Triglyceride Transfer Protein Inhibitor Lomitapide in Patients With Homozygous Familial Hypercholesterolemia. Circulation. 2017; 136: 332-335. doi:10.1161/CIRCULATIONAHA.117.028208

(3) **CANNON CP, BLAZING MA, GIUGLIANO RP, MCCAGG A, WHITE JA, THEROUX P, DARIUS H, LEWIS BS, OPHUIS TO, JUKEMA JW, DE FERRARI GM, RUZYLLO W, DE LUCCA P, IM K, BOHULA EA, REIST C, WIVIOTT SD, TERSHAKOVEC AM, MUSLINER TA, BRAUNWALD E, CALIFF RM; IMPROVE-IT INVESTIGATORS.** Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015; 372: 2387-2397. doi:10.1056/NEJMoa1410489

(4) **CATAPANO AL, GRAHAM I, DE BACKER G, WIKLUND O, CHAPMAN MJ, DREXEL H, HOES AW, JENNINGS CS, LANDMESSER U, PEDERSEN TR, REINER Z, RICCARDI G, TASKINEN MR, TOKGOZOGLU L, VERSCHUREN WM, VLACHOPOULOS C, WOOD DA, ZAMORANO JL.** 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2016; 37: 2999-3058. doi:10.1093/eurheartj/ehw272

(5) **CHUDYK A, PETRELLA RJ.** Effects of exercise on cardiovascular risk factors in type 2 diabetes: a meta-analysis. Diabetes Care. 2011; 34: 1228-1237. doi:10.2337/dc10-1881

(6) **DI LORETO C, FANELLI C, LUCIDI P, MURDOLO G, DE CICCO A, PARLANTI N, RANCHELLI A, FATONE C, TAGLIONI C, SANTEUSANIO F, DE FEO P.** Make your diabetic patients walk: long-term impact of different amounts of physical activity on type 2 diabetes. Diabetes Care. 2005; 28: 1295-1302. doi:10.2337/diacare.28.6.1295

(7) **DUNSTAN DW, BARR EL, HEALY GN, SALMON J, SHAW JE, BALKAU B, MAGLIANO DJ, CAMERON AJ, ZIMMET PZ, OWEN N.** Television viewing time and mortality: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Circulation. 2010; 121: 384-391. doi:10.1161/CIRCULATIONAHA.109.894824

(8) **GIUGLIANO RP, SABATINE MS.** Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? J Am Coll Cardiol. 2015; 65: 2638-2651. doi:10.1016/j.jacc.2015.05.001

(9) **GORDON-LARSEN P, BOONE-HEINONEN J, SIDNEY S, STERNFELD B, JACOBS DR JR, LEWIS CE.** Active commuting and cardiovascular disease risk: the CARDIA study. Arch Intern Med. 2009; 169: 1216-1223. doi:10.1001/archinternmed.2009.163

(10) **GULATI M, PANDEY DK, ARNSDORF MF, LAUDERDALE DS, THISTED RA, WICKLUND RH, AL-HANI AJ, BLACK HR.** Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation. 2003; 108: 1554-1559. doi:10.1161/01.CIR.0000091080.57509.E9

(11) **GUPTA A, THOMPSON D, WHITEHOUSE A, COLLIER T, DAHLOF B, POULTER N, COLLINS R, SEVER P; ON BEHALF OF THE ASCOT INVESTIGATORS.** Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet. 2017; 389: 2473-2481. doi:10.1016/S0140-6736(17)31075-9

(12) **HALLE M, BERG A, KÖNIG D, KEUL J, BAUMSTARK MW.** Differences in the concentration and composition of low-density lipoprotein subfraction particles between sedentary and trained hypercholesterolemic men. Metabolism. 1997; 46: 186-191. doi:10.1016/S0026-0495(97)90300-0

(13) **JAE SY, HEFFERNAN KS, LEE MK, FERNHALL B, PARK WH.** Relation of cardiorespiratory fitness to inflammatory markers, fibrinolytic factors, and lipoprotein(a) in patients with type 2 diabetes mellitus. Am J Cardiol. 2008; 102: 700-703. doi:10.1016/j.amjcard.2008.05.012

(14) **KEENE D, PRICE C, SHUN-SHIN MJ, FRANCIS DP.** Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. BMJ. 2014; 349: g4379. doi:10.1136/bmj.g4379

(15) **KELLEY GA, KELLEY KS.** Impact of progressive resistance training on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. Prev Med. 2009; 48: 9-19. doi:10.1016/j.ypmed.2008.10.010

(16) **KELLEY GA, KELLEY KS, FRANKLIN B.** Aerobic exercise and lipids and lipoproteins in patients with cardiovascular disease: a meta-analysis of randomized controlled trials. J Cardiopulm Rehabil. 2006; 26: 131-139. doi:10.1097/00008483-200605000-00002

(17) **KELLEY GA, KELLEY KS, TRAN ZV.** Walking, lipids, and lipoproteins: a meta-analysis of randomized controlled trials. Prev Med. 2004; 38: 651-661. doi:10.1016/j.ypmed.2003.12.012

(18) **KELLEY GA, KELLEY KS, VU TRAN Z.** Aerobic exercise, lipids and lipoproteins in overweight and obese adults: a meta-analysis of randomized controlled trials. Int J Obes. 2005; 29: 881-893. doi:10.1038/sj.ijo.0802959

(19) **KESSLER HS, SISSON SB, SHORT KR.** The potential for high-intensity interval training to reduce cardiometabolic disease risk. Sports Med. 2012; 42: 489-509. doi:10.2165/11630910-000000000-00000

(20) **KHERA AV, DEMLER OV, ADELMAN SJ, COLLINS HL, GLYNN RJ, RIDKER PM, RADER DJ, MORA S.** Cholesterol efflux capacity, high-density lipoprotein particle number, and incident cardiovascular events: an analysis from the JUPITER trial (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). Circulation. 2017; 135: 2494-2504. doi:10.1161/CIRCULATIONAHA.116.025678

(21) **KODAMA S, TANAKA S, SAITO K, SHU M, SONE Y, ONITAKE F, SUZUKI E, SHIMANO H, YAMAMOTO S, KONDO K, OHASHI Y, YAMADA N, SONE H.** Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. Arch Intern Med. 2007; 167: 999-1008. doi:10.1001/archinte.167.10.999

(22) **KOKKINOS PF, FASELIS C, MYERS J, PANAGIOTAKOS D, DOUMAS M.** Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study. Lancet. 2013; 381: 394-399. doi:10.1016/S0140-6736(12)61426-3

(23) **KRAUS WE, HOUMARD JA, DUSCHA BD, KNETZGER KJ, WHARTON MB, MCCARTNEY JS, BALES CW, HENES S, SAMSA GP, OTVOS JD, KULKARNI KR, SLENTZ CA.** Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med. 2002; 347: 1483-1492. doi:10.1056/NEJMoa020194

(24) **LAUFS U, SCHARNAGL H, HALLE M, WINDLER E, ENDRES M, MÄRZ W.** Treatment Options for Statin-Associated Muscle Symptoms. Dtsch Arztebl Int. 2015; 112: 748-755. doi:10.3238/arztebl.2015.0748

(25) **LEAR SA, HU W, RANGARAJAN S, GASEVIC D, LEONG D, IQBAL R, CASANOVA A, SWAMINATHAN S, ANJANA RM, KUMAR R, ROSENGREN A, WEI L, YANG W, CHUANGSHI W, HUAXING L, NAIR S, DIAZ R, SWIDON H, GUPTA R, MOHAMMADIFARD N, LOPEZ-JARAMILLO P, OGUZ A, ZATONSKA K, SERON P, AVEZUM A, POIRIER P, TEO K, YUSUF S.** The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. Lancet. 2017 [Epub ahead of print]. doi:10.1016/S0140-6736(17)31634-3

(26) **LEE DC, PATE RR, LAVIE CJ, SUI X, CHURCH TS, BLAIR SN.** Leisure-time running reduces all-cause and cardiovascular mortality risk. J Am Coll Cardiol. 2014; 64: 472-481. doi:10.1016/j.jacc.2014.04.058

(27) **LEE DC, SUI X, CHURCH TS, LAVIE CJ, JACKSON AS, BLAIR SN.** Changes in fitness and fatness on the development of cardiovascular disease risk factors hypertension, metabolic syndrome, and hypercholesterolemia. J Am Coll Cardiol. 2012; 59: 665-672. doi:10.1016/j.jacc.2011.11.013

(28) **LEON AS, RICE T, MANDEL S, DESPRES JP, BERGERON J, GAGNON J, RAO DC, SKINNER JS, WILMORE JH, BOUCHARD C.** Blood lipid response to 20 weeks of supervised exercise in a large biracial population: the HERITAGE Family Study. Metabolism. 2000; 49: 513-520. doi:10.1016/S0026-0495(00)80018-9

(29) **MIKUS CR, BOYLE LJ, BORENGASSER SJ, OBERLIN DJ, NAPLES SP, FLETCHER J, MEERS GM, RUEBEL M, LAUGHLIN MH, DELLSPERGER KC, FADEL PJ, THYFAULT JP.** Simvastatin impairs exercise training adaptations. J Am Coll Cardiol. 2013; 62: 709-714. doi:10.1016/j.jacc.2013.02.074

(30) **MORA S, COOK N, BURING JE, RIDKER PM, LEE IM.** Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. Circulation. 2007; 116: 2110-2118. doi:10.1161/CIRCULATIONAHA.107.729939

(31) **MORA S, LEE IM, BURING JE, RIDKER PM.** Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women. JAMA. 2006; 295: 1412-1419. doi:10.1001/jama.295.12.1412

(32) **MYERS J, PRAKASH M, FROELICHER V, DO D, PARTINGTON S, ATWOOD JE.** Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002; 346: 793-801. doi:10.1056/NEJMoa011858

(33) **NIELSEN SF, NORDESTGAARD BG.** Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. Eur Heart J. 2016; 37: 908-916. doi:10.1093/eurheartj/ehv641

(34) **PAN XH, MAHEMUTI A, ZHANG XH, WANG YP, HU P, JIANG JB, XIANG MX, LIU G, WANG JA.** Effect of Tai Chi exercise on blood lipid profiles: a meta-analysis of randomized controlled trials. J Zhejiang Univ Sci B. 2016; 17: 640-648. doi:10.1631/jzus.B1600052

(35) **PARK YM, SUI X, LIU J, ZHOU H, KOKKINOS PF, LAVIE CJ, HARDIN JW, BLAIR SN.** The effect of cardiorespiratory fitness on age-related lipids and lipoproteins. J Am Coll Cardiol. 2015; 65: 2091-2100. doi:10.1016/j.jacc.2015.03.517

(36) **PIEPOLI MF, HOES AW, AGEWALL S, ALBUS C, BROTONS C, CATAPANO AL, COONEY MT, CORRA U, COSYNS B, DEATON C, GRAHAM I, HALL MS, HOBBS FD, LOCHEN ML, LOLLGEN H, MARQUES-VIDAL P, PERK J, PRESCOTT E, REDON J, RICHTER DJ, SATTAR N, SMULDERS Y, TIBERI M, VAN DER WORP HB, VAN DIS I, VERSCHUREN WM.** 2016 European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts), developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016; 37: 2315-2381. doi:10.1093/eurheartj/ehw106

(37) **PITSAVOS CH, CHRYSOHOOU C, PANAGIOTAKOS DB, KOKKINOS P, SKOUMAS J, PAPAIOANNOU I, MICHAELIDES AP, SINGH S, STEFANADIS CI.** Exercise capacity and heart rate recovery as predictors of coronary heart disease events, in patients with heterozygous Familial Hypercholesterolemia. Atherosclerosis. 2004; 173: 345-350. doi:10.1016/j.atherosclerosis.2003.12.027

(38) **RAY KK, LANDMESSER U, LEITER LA, KALLEND D, DUFOUR R, KARAKAS M, HALL T, TROQUAY RP, TURNER T, VISSEREN FL, WIJNGAARD P, WRIGHT RS, KASTELEIN JJ.** Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. N Engl J Med. 2017; 376: 1430-1440. doi:10.1056/NEJMoa1615758

(39) **RENGO JL, SAVAGE PD, TOTH MJ, ADES PA.** Statin therapy does not attenuate exercise training response in cardiac rehabilitation. J Am Coll Cardiol. 2014; 63: 2050-2051. doi:10.1016/j.jacc.2014.02.554

(40) **RICE T, DESPRES JP, PERUSSE L, HONG Y, PROVINCE MA, BERGERON J, GAGNON J, LEON AS, SKINNER JS, WILMORE JH, BOUCHARD C, RAO DC.** Familial aggregation of blood lipid response to exercise training in the health, risk factors, exercise training, and genetics (HERITAGE) Family Study. Circulation. 2002; 105: 1904-1908. doi:10.1161/01.CIR.0000014969.85364.9F

(41) **ROHATGI A, KHERA A, BERRY JD, GIVENS EG, AYERS CR, WEDIN KE, NEELAND IJ, YUHANNA IS, RADER DR, DE LEMOS JA, SHAUL PW.** HDL cholesterol efflux capacity and incident cardiovascular events. N Engl J Med. 2014; 371: 2383-2393. doi:10.1056/NEJMoa1409065

(42) **SABATINE MS, GIUGLIANO RP, KEECH AC, HONARPOUR N, WIVIOTT SD, MURPHY SA, KUDER JF, WANG H, LIU T, WASSERMAN SM, SEVER PS, PEDERSEN TR; FOR THE FOURIER STEERING COMMITTEE AND INVESTIGATORS.** Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017; 376: 1713-1722. doi:10.1056/NEJMoa1615664

(43) **STONE NJ, ROBINSON JG, LICHTENSTEIN AH, BAIREY MERZ CN, BLUM CB, ECKEL RH, GOLDBERG AC, GORDON D, LEVY D, LLOYD-JONES DM, MCBRIDE P, SCHWARTZ JS, SHERO ST, SMITH SC JR, WATSON K, WILSON PW.** 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014; 63: 2889-2934. doi:10.1016/j.jacc.2013.11.002

(44) **TJONNA AE, LEE SJ, ROGNMO O, STOLEN TO, BYE A, HARAM PM, LOENNECHEN JP, AL-SHARE QY, SKOGVOLL E, SLORDAHL SA, KEMI OJ, NAJJAR SM, WISLOFF U.** Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. Circulation. 2008; 118: 346-354. doi:10.1161/CIRCULATIONAHA.108.772822

(45) **WILLIAMS PT.** High-density lipoprotein cholesterol and other risk factors for coronary heart disease in female runners. N Engl J Med. 1996; 334: 1298-1304. doi:10.1056/NEJM199605163342004

(46) **WILLIAMS PT.** Relationship of distance run per week to coronary heart disease risk factors in 8283 male runners. The National Runners' Health Study. Arch Intern Med. 1997; 157: 191-198. doi:10.1001/archinte.1997.00440230063008

(47) **WILLIAMS PT, THOMPSON PD.** Walking versus running for hypertension, cholesterol, and diabetes mellitus risk reduction. Arterioscler Thromb Vasc Biol. 2013; 33: 1085-1091. doi:10.1161/ATVBAHA.112.300878

(48) **WOOD PD, HASKELL WL, BLAIR SN, WILLIAMS PT, KRAUSS RM, LINDGREN FT, ALBERS JJ, HO PH, FARQUHAR JW.** Increased exercise level and plasma lipoprotein concentrations: a one-year, randomized, controlled study in sedentary, middle-aged men. Metabolism. 1983; 32: 31-39. doi:10.1016/0026-0495(83)90152-X

(49) **WORLD HEALTH ORGANIZATION.** Global status report on noncummicable diseases 2010. Geneva: World Health Organization 2011.