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Physical fitness is associated with lower inflammation, even in individuals with high cholesterol — An alternative to statin therapy?

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Summary
Background: High cholesterol, leukocytes (LEUK) and erythrocyte sedimentation rate (ESR) are associated with cardiovascular diseases.
Design: Cross sectional study of 10,000 healthy young men.
Methods: About 10,167 men were analyzed for the association of cholesterol concentrations and erythrocyte sedimentation rate with fitness (assessed by achieved physical working capacity at a heart rate of 170 beats per min = PWC170). Physical fitness was categorized as low (<2.5 W/kg; $n = 2755$) medium (2.5—2.8 W/kg; $n = 3783$) and good (>2.8 W/kg; $n = 3629$). Cholesterol was categorized as elevated cholesterol (>200 mg/dl) and normal cholesterol concentration (<200 mg/dl).
Results: Men with elevated cholesterol compared to men with normal cholesterol concentrations had significantly higher LEUK (6.34 ± 1.47 vs. 6.17 ± 1.44; $p < 0.001$) and ESR (2.86 ± 3.06 vs. 2.44 ± 2.43; $p < 0.001$). When stratified by physical fitness, this effect was present in men with low physical fitness (LEUK 6.48 ± 1.51 vs. 6.27 ± 1.44; $p = 0.001$; ESR 3.32 ± 3.78 vs. 2.72 ± 3.03, $p < 0.001$) and medium physical fitness (LEUK 6.38 ± 1.44 vs. 6.16 ± 1.43, $p < 0.001$; ESR 2.77 ± 3.04 vs. 2.40 ± 2.36, $p < 0.001$), but not in men with good physical fitness.

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Conclusion: Cholesterol greater than 200 mg/dl was associated with elevated leukocytes and erythrocyte sedimentation rates, suggestive of a higher burden of inflammation. In young men with good physical fitness, this association was not present, indicating that physical fitness might be effective in preventing cardiovascular diseases by reducing the cholesterol mediated triggering of inflammation.

Introduction

Cardiovascular diseases, particularly coronary artery disease (CAD) with myocardial infarction (MI), account for a large portion of the burden of diseases in the western world. The pathogenesis of CAD is multifactorial. One important risk factor for CAD and MI is hypercholesterolemia [1]. Inflammation seems to play a key role in triggering atherosclerotic pathogenesis [2,3]. Several studies have pointed out that markers of inflammation are associated with atherosclerosis [4,5]. In general, a high pro-inflammatory state seems to predispose individuals to develop cardiovascular diseases. There is evidence that the established inflammatory markers leukocyte count (LEUK) [6,7] and erythrocyte sedimentation rate (ESR) [8,9] are associated with unfavorable cardiovascular outcomes.

Furthermore, there is a link between hypercholesterolemia and inflammation. A recently published study [10] showed in patients with an acute coronary syndrome treated with statins, that those with low C-reactive protein levels had a significantly better outcome than those with higher C-reactive protein levels. This effect was seen with different levels of cholesterol concentrations and reflects the complex association of inflammation and hypercholesterolemia. Reduction of inflammation in hypercholesterolemia might therefore be a therapeutic goal in both primary and secondary prevention of CAD and MI.

Physical fitness is known to result in a more favorable cardiovascular risk profile [11,12]. There is substantial evidence that high physical fitness identifies individuals at lower risk for manifest CHD [13,14]. On the other hand, obesity and metabolic syndrome are associated with higher inflammatory markers [15]. Physical fitness seems to be inversely associated with inflammation [16,17].

The aim of our study was to analyze the association of hypercholesterolemia and inflammation with physical fitness since there is little known about the modulation of inflammation and cholesterol by physical fitness. The a priori null-hypothesis was that the association of cholesterol and inflammation is not affected by physical fitness.

Methods

Subjects

The study population was procured between 1977 and 2004. All participants had an aero medical disposition according to the German military standard. Inclusion criteria were absence of any disease or alcohol addiction, complete lipid analysis and a heart rate attained under workload conditions of 170 beats per minute. The study population was procured after authorization by the local advisory boards (Contract No. 7/01045), and written informed consent was obtained. The study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the ethical committee of the Bavarian Physicians Chamber. Adhering to the ethical committee requirements, all data and blood samples were anonymized.

Characterization

Lifestyle factors were assessed by standardized questionnaires as previously described [18].

Laboratory parameters

After a minimum of eight hours of fasting, including abstinence from smoking, blood samples were taken from the cubital vein by means of the BD Vacutainer® under standardized conditions, between 7.00 h and 8.00 h a.m. Immediately afterwards, laboratory testing was performed. Study participants were usually not on flying duty (with potential exposure to increased cosmic radiation) for at least 12 to 24 h before venipuncture. The laboratory fulfills internal and external quality standards as required by the German Medical Association guidelines. All system changes and technical modifications throughout the study-period were validated by interlaboratory tests, and changes in measurements or normal values were adapted post hoc to ensure comparability of values.

Cholesterol

Quantitative analysis of total cholesterol concentration in blood serum was performed with Cobas

Integra® analysis systems (Roche, Grenzach-Wyhlen, Germany) and predecessor models by enzymatic, colorimetric testing with cholesterol esterase, cholesterol oxidase, and 4-aminoantipyrine.

Triglycerides

Cobas Integra® was also applied for the determination of triglycerides (TG) in blood serum following a standardized enzymatic, colorimetric method with glycerolphosphate oxidase and 4-aminophenazone.

Erythrocyte sedimentation rate (ESR)

ESR levels [mm] were detected visually in a standardized fashion at 60 and 120 min after venipuncture and instant tube calibration (Sedivette, Sarstedt, Nümbrech, Germany) by trained personnel.

Leukocytes (LEUK)

Standardized venipuncture for EDTA whole blood samples was performed between 7.00 AM and 8.00 AM and blood counts were measured within 3 h by fully automated flow cytometry and cytochemistry (peroxidase activity) of a Technicon H*3® hematology analyzer and predecessor model (Bayer, Leverkusen, Germany).

Physical fitness/physical working capacity (PWC170)

Physical fitness, determined by physical working capacity at a HR of 170 bpm (PWC 170) was assessed by standard cycle ergometry (Ergometer Ergoline® and predecessor model, Arcon Systems, Starnberg, Germany) in a 45° sitting position and expressed as the achieved performance (watts, [W]) per kilogram of body weight [kg] at an actual HR of 170 bpm). Ergometric power was increased every three minutes by steps of 50 W, starting from 100 W up to the point of physical exhaustion or commonly accepted termination criteria. Ergometric performance was monitored by continuous ECG, HR, and BP recordings and supervised by an experienced physician.

Statistics

Statistical evaluation was performed using SPSS for Windows® Version 12.0. Since the variables were normally distributed, univariate analysis of variance (ANOVA) was applied. A double-sided *p*-value <0.05 was considered to be significant. Quantitative data were given as mean values with ± standard deviation; qualitative data were expressed as frequencies. The null-hypothesis was that men with different fitness (as independent variables) and high concentrations of cholesterol (as a further independent variable) do not have different levels of leukocytes or erythrocyte sedimentation rates. After univariate analysis a multivariate regression analysis was performed.

Results

Characteristics of the study population

As given in Table 1, the study population represents a young and healthy male population with an overall prevalence of elevated cholesterol (>200 mg/dl) of 18% ($n = 1879$) and an average acceptable level of physical fitness (2.7 W/kg).

Relation of physical fitness, inflammation, and cholesterol in highest and lowest groups of physical fitness

Table 2 gives the characteristics of highest and lowest physical fitness levels (upper and lower 10%), of lowest physical fitness further stratified by high (>200 mg/dl) and low (<200 mg/dl) cholesterol concentration, as well as highest fitness further stratified by high and low cholesterol concentration. LEUK, ESR, cholesterol and triglyceride concentrations were all significantly reduced in the group of highest physical fitness compared to lowest physical fitness levels ($p < 0.05$). This was also true in the lowest physical fitness subgroup with low cholesterol concentrations compared to high cholesterol concentrations. In the highest physical fitness subgroup with low cholesterol concentrations, LEUK and ESR were not significantly different from those with high cholesterol concentrations ($p > 0.70$).

Relation of inflammatory markers with cholesterol

LEUK and ESR were significantly associated ($F = 126$; $p < 0.0001$). ESR ($F = 41$; $p < 0.0001$) and LEUK ($F = 15$; $p < 0.0001$) were significantly associated with cholesterol. In a multivariate regression analysis, the association between ESR and cholesterol was significant in men with low physical fitness, while an association was absent in men with high physical fitness. This regression analysis is presented in Table 3.

Table 1 Main characteristics of the study population (mean ± SD).

N	10,167
Age (years)	21 ± 4
Height (cm)	180 ± 6
Weight (kg)	73 ± 7
BMI (kg/m^2)	22.5 ± 2.3
Smokers (*n* (%))	2588 (26%)
Cigarettes per day (in smokers)	11 ± 6
Regular alcohol consumption (*n* (%))	3459 (34%)
Alcohol (l/week)	0.63 ± 1.36
Systolic blood pressure (mm Hg)	130 ± 12
Diastolic blood pressure (mm Hg)	79 ± 7
PWC_{170} (W/kg)	2.7 ± 4.3
Leukocytes (G/l)	6.2 ± 1.4
Erythrocyte Sedimentation Rate (mm/h)	2.5 ± 2.6
Cholesterol (mg/dl)	173 ± 33
Triglyceride (mg/dl)	80 ± 41
Elevated Cholesterol (⩾200 mg/dl)	1879 (18%)

Table 2 Differences in lipids and inflammatory markers in men with very low and very high levels of high physical fitness (A). Difference in lipids and inflammatory markers in men with cholesterol above or below 200 mg/dl stratified by very low and very high levels of physical fitness (B).

A	Very low Physical fitness (lowest 10%)	Very high Physical fitness (upper 10%)
N	912	964
Leukocytes (G/l)	6.4 ± 1.4	6.2 ± 1.4*
Erythrocyte sedimentation rate (mm/h)	3.2 ± 3.6	2.3 ± 2.0*
Cholesterol (mg/dl)	178 ± 35	167 ± 31*
Triglycerides (mg/dl)	87 ± 48	74 ± 33*
Elevated cholesterol (>200 mg/dl)	209 (23%)	139 (14%)*
B	Very low Physical fitness Lowest 10% and Cholesterol <200 mg/dl	Very low Physical fitness lowest 10% and Cholesterol >200 mg/dl
N	703	209
Leukocytes (G/l)	6.3 ± 1.4	6.6 ± 1.5*
Erythrocyte sedimentation rate (mm/h)	3.0 ± 3.4	3.7 ± 4.4*
Cholesterol (mg/dl)	164 ± 21	225 ± 28*
Triglycerides (mg/dl)	78 ± 36	120 ± 86*
	Very high Physical fitness upper 10% and cholesterol <200 mg/dl	Very high Physical fitness upper 10% and cholesterol >200 mg/dl
N	825	139
Leukocytes (G/l)	6.1 ± 1.4	6.1 ± 1.4 n.s.
Erythrocyte sedimentation rate (mm/h)	2.3 ± 2.1	2.3 ± 1.8 n.s.
Cholesterol (mg/dl)	158 ± 23	220 ± 20*
Triglycerides (mg/dl)	70 ± 29	95 ± 43*

* $p < 0.05$; n.s. = not significant (here $p > 0.70$).

Relation of physical fitness and inflammation

Fig. 1 illustrates the association of fitness and inflammatory markers LEUK and ESR. Stratified into tertiles of PWC170 (1st representing lower physical fitness (<2.5 W/kg), 2nd medium and 3rd higher physical fitness (>2.8 W/kg)), it is shown that the leukocyte count is inversely associated with fitness

Table 3 Multivariate regression analysis for the inflammatory marker erythrocyte sedimentation rate (ESR).

Variable	*t*-Value	*p*-Value
In 1st Tertile of PWC170 n = 2755		
Age	4.18	0.001
Cholesterol	2.84	0.005
PWC170	−5.06	0.001
Leukocytes	7.71	0.001
BMI	−0.26	0.794
In 3rd Tertile of PWC170 n = 3629		
Age	1.59	0.110
Cholesterol	−0.36	0.717
PWC170	0.02	0.984
Leukocytes	4.67	0.001
BMI	0.34	0.733

level (ANOVA $p < 0.001$). Likewise ESR shows a significant association in men with higher physical fitness having a reduced erythrocyte sedimentation rate. Thus, men with good physical fitness had lower levels of both LEUK and ESR, i.e. lower inflammatory markers.

Relation of cholesterol and inflammation

Fig. 2 demonstrates the relation between cholesterol and inflammatory markers LEUK and ESR. As depicted in Fig. 2, with cholesterol concentrations being grouped into quintiles, men with an elevated cholesterol concentration above 200 mg/dl (5th quintile) had significantly higher leukocyte levels and higher erythrocyte sedimentation rates than men with cholesterol concentrations less than 200 mg/dl (1st to 4th quintile), both $p < 0.001$. Thus, men with elevated cholesterol (>200 mg/dl) had higher levels of LEUK and ESR, i.e. higher markers of inflammation.

Relation of cholesterol and inflammation with physical fitness

Men with elevated cholesterol compared to men with normal cholesterol concentration had significantly higher LEUK (6.34 ± 1.47 vs. 6.17 ± 1.44; $p < 0.001$) and ESR (2.86 ± 3.06 vs. 2.44 ± 2.43; $p < 0.001$). When stratified for physical fitness by tertiles of PWC170, men with normal cholesterol concentrations (<200 mg/dl) compared to men with elevated cholesterol (>=200 mg/dl) showed a significantly higher LEUK and ESR with the lowest level of (1st tertile) physical fitness (LEUK 6.48 ± 1.51 vs. 6.27 ± 1.44; $p = 0.001$; ESR 3.32 ± 3.78 vs. 2.72 ± 3.03, $p < 0.001$), and medium (2nd tertile) level of physical fitness (LEUK 6.38 ± 1.44 vs. 6.16 ± 1.43, $p < 0.001$; ESR

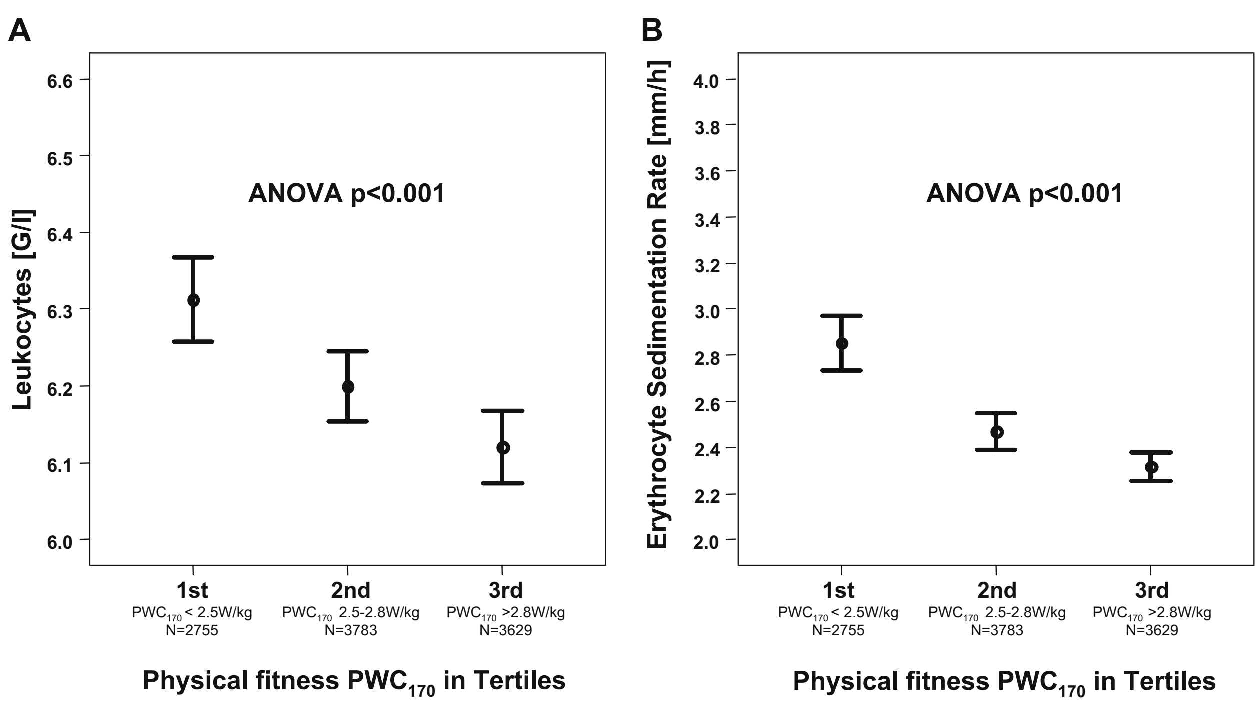

Figure 1 The association of physical fitness with leukocyte count (A) and erythrocyte sedimentation rate (B). *Note:* Physical fitness was assessed by achieved physical working capacity at a heart rate of 170 beats per min (PWC_{170}) and categorized as low (PWC_{170} <2.5 W/kg; $n = 2755$) medium (PWC_{170} 2.5—2.8 W/kg; $n = 3783$) and good (PWC_{170} > 2.8 W/kg; $n = 3629$).

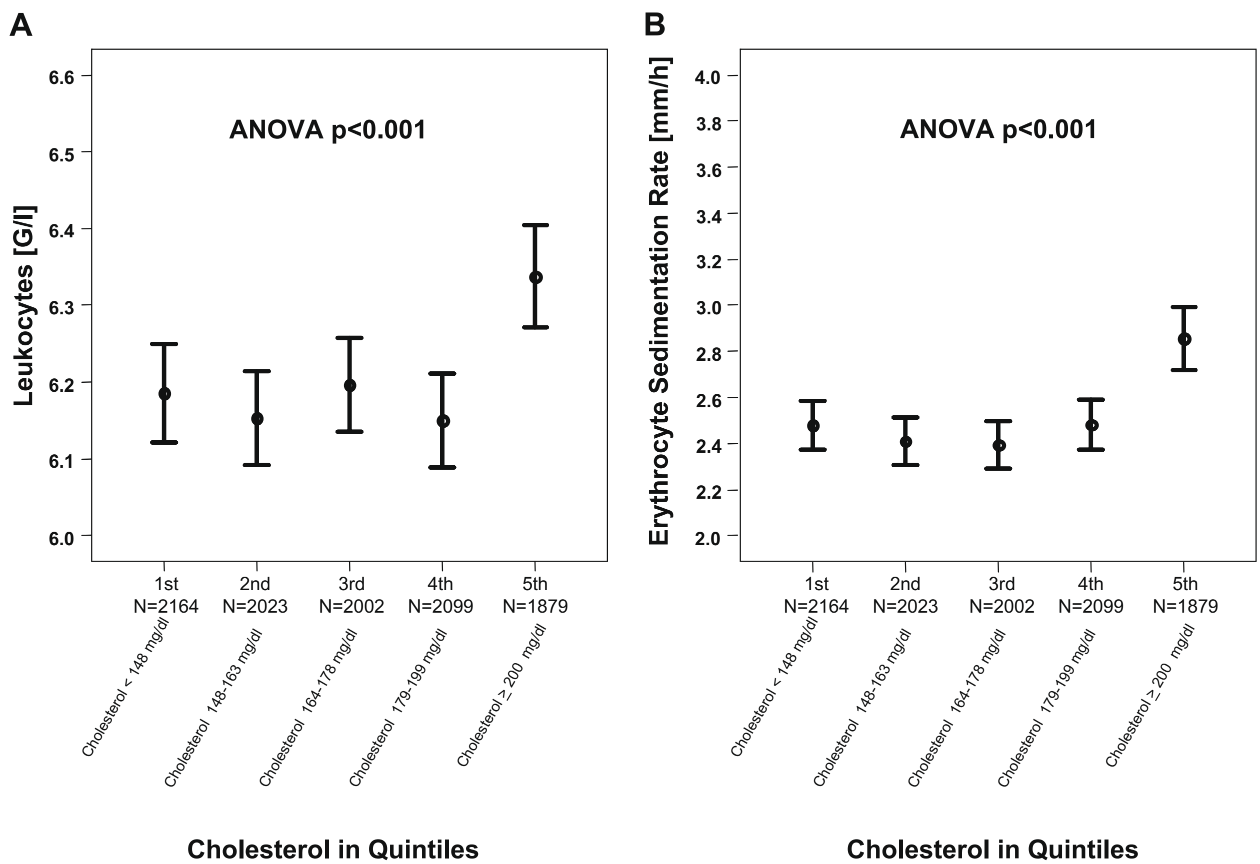

Figure 2 The association of cholesterol levels (by quintiles; 5th quintile being cholesterol concentration of >200 mg/dl) with leukocyte count (A) as well as erythrocyte sedimentation rate (B).

2.77 ± 3.04 vs. 2.40 ± 2.36, $p < 0.001$), but not with the highest level of physical fitness (3rd tertile). This finding indicates that good physical fitness is associated with lower levels of inflammatory markers independent of cholesterol concentration. Fig. 3 demonstrates that men with good physical fitness showed no difference in inflammatory markers regardless of high or low cholesterol concentration. Men with low physical fitness and high cholesterol had higher inflammatory makers than men with low physical fitness and low cholesterol.

Discussion

Cardiovascular diseases account for the majority of deaths in the western world [19]. Beside hypercholesterolemia, inflammation plays a key role in the pathogenesis of atherosclerosis [2,3,20,21]. Atheromas consist of lipids and inflammatory cells. The main problem is plaque instability and rupture causing acute MI [21]. This rupture seems to be driven by immune cells [22,23].

It is further known that cholesterol lowering statin therapy leads to a significant reduction of inflammation [10,24]. This effect might account for a great proportion of the reduction of cardiovascular mortality. Therefore, reducing inflammation appears to be an important goal in preventing CAD and MI. Next to novel inflammatory makers such as high sensitivity CRP, IL-6 or serum amyloid-A, which were not available throughout the entire long-term observational study period, established markers like LEUK and ESR can also be used to measure the inflammatory burden and cardiovascular risk of an individual [4—7,25]. The advantage of LEUK and ESR is their access and stability in comparison to other inflammatory markers, for example interleukins.

In this study we analyzed the association of cholesterol and LEUK/ESR in over 10,000 individuals in relation to physical fitness (PWC170). As expected, high cholesterol concentration (>200 mg/dl) was associated with a significantly higher burden of inflammation and a high level of fitness was associated with a lower burden of inflammation. While it is known, that good physical fitness is associated with low inflammation [16,17], interestingly, the

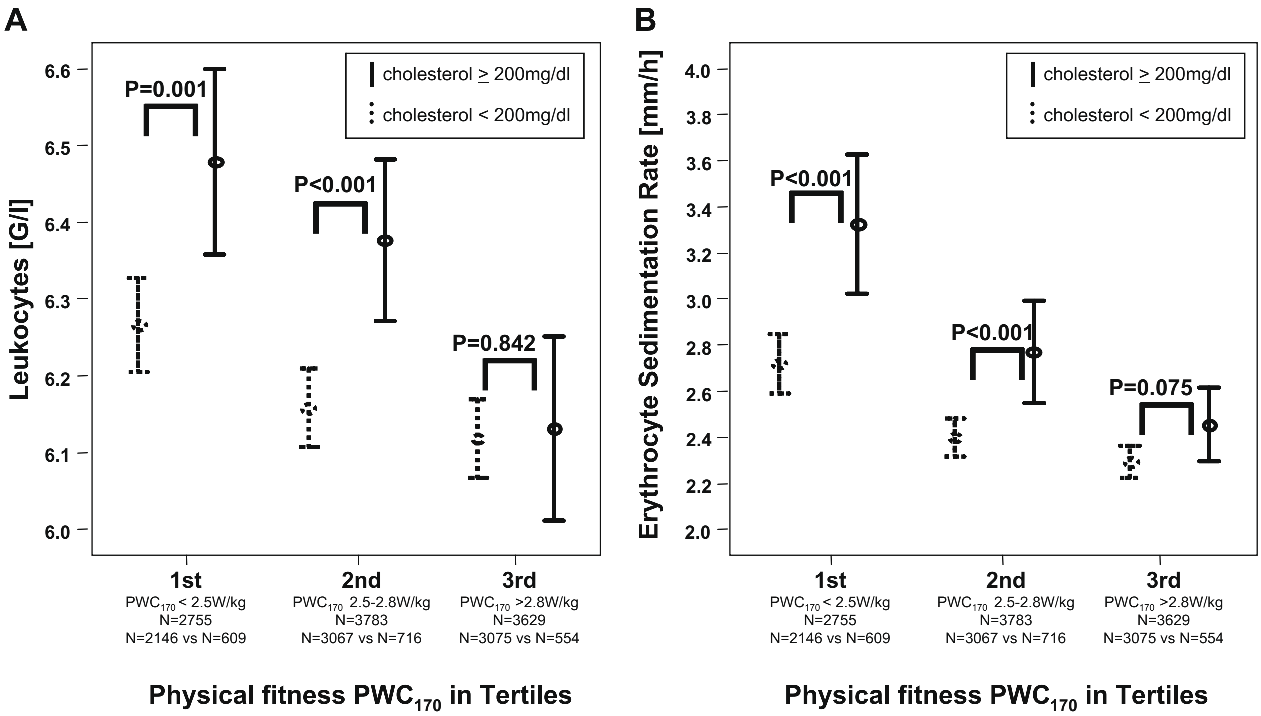

Figure 3 The association of physical fitness, elevated cholesterol (>200 mg/dl) and leukocyte count (A) as well as erythrocyte sedimentation rate (B). *Note:* cholesterol was categorized as elevated (>200 mg/dl; n = 1879) and normal (<200 mg/dl; n = 8288).

association of elevated cholesterol and high inflammation was absent in men with good physical fitness in contrast to men with low physical fitness in our study.

In light of a recently published study [26] our findings might further outline that physical fitness could be an alternative to statin treatment, which is known for its anti-inflammatory effects, in primary prevention of atherosclerosis. Furthermore, while inflammation seems to impair reverse cholesterol transport in vivo [27], physical fitness might reduce inflammation and thus optimize reverse cholesterol transport. Thus, good physical fitness may be able to abolish the induction of inflammation by high cholesterol. Therefore, good physical fitness might reduce cardiovascular risk particularly by reducing cholesterol-mediated inflammation.

The limitation of our study is its cross-sectional character and the inclusion of healthy subjects without cardiovascular endpoints. However, the strength of our study is the high number and homogenous characterization of young male individuals.

In summary, our study highlights the potential for physical fitness to help prevent cardiovascular diseases. Further studies are warranted focusing on the potential benefit of physical activity with statin therapy rather than mono-pharmacotherapy in primary and secondary prevention of CAD and MI.

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References

[1] Stammler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? JAMA 1986;256:2823—8.

[2] Ross R. Atherosclerosis — an inflammatory disease. New Engl J Med 1999;340(2):115—26.

[3] Paoletti R, Gotto Jr AM, Hajjar DP. Inflammation in atherosclerosis and implications for therapy. Circulation 2004;109:III20—=0?>III26.

[4] Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. Lancet 1998;351:88—92.

[5] Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. New Engl J Med 2000;342: 836—43.
[6] Friedman GD, Klatsky AL, Siegelaub AB. The leukocyte count as a predictor of myocardial infarction. New Engl J Med 1974;290:1275—8.
[7] Madjid M, Awan I, Willerson JT, Casscells SW. Leukocyte count and coronary heart disease: implications for risk assessment. J Am Coll Cardiol 2004;44:1945—56.
[8] Froom P, Margaliot S, Caine Y, Benbassat J. Significance of erythrocyte sedimentation rate in young adults. Am J Clin Pathol 1984;82:198—200.
[9] Timmer JR, Ottervanger JP, Hoorntje JC, Boer MJ, Suryapranata H, Hof AW, et al. The Zwolle myocardial infarction study group. Prognostic value of erythrocyte sedimentation rate in ST segment elevation myocardial infarction: interaction with hyperglycaemia. J Int Med 2005;257:423—9.
[10] Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. Pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 (PROVE IT-TIMI 22) investigators. C-reactive protein levels and outcomes after statin therapy. New Engl J Med 2005;352:20—8.
[11] Boreham C, Twisk J, Neville C, Savage M, Murray L, Gallagher A. Associations between physical fitness and activity patterns during adolescence and cardiovascular risk factors in young adulthood: the Northern Ireland young hearts project. Int J Sports Med 2002;23(Suppl. 1):S22—6.
[12] Gibbons LW, Blair SN, Cooper KH, Smith M. Association between coronary heart disease risk factors and physical fitness in healthy adult women. Circulation 1983;67:977—83.
[13] LaMonte MJ, Fitzgerald SJ, Levine BD, Church TS, Kampert JB, Nichaman MZ, et al. Coronary artery calcium, exercise tolerance, and CHD events in asymptomatic men. Atherosclerosis 2006;189(1):157—62.
[14] Church TS, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Arch Int Med 2005;165:2114—20.
[15] Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999;282(22):2131—5.
[16] Church TS, Barlow CE, Earnest CP, Kampert JB, Priest EL, Blair SN. Associations between cardiorespiratory fitness and C-reactive protein in men. Arterioscler Thromb Vasc Biol 2002;22:1869—76.
[17] Aronson D, Sheikh-Ahmad M, Avizohar O, Kerner A, Sella R, Bartha P, et al. C-reactive protein is inversely related to physical fitness in middle-aged subjects. Atherosclerosis 2004;176:173—9.
[18] Ortlepp JR, Metrikat J, Vesper K, Mevissen V, Schmitz F, Albrecht M, et al. The interleukin 6 promoter polymorphism is associated with elevated leukocytes and reduced physical fitness in young healthy smokers. J Mol Med 2003;81: 578—84.
[19] Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 1997;349:1436—42.
[20] Zouridakis E, Avanzas P, Arroyo-Espliguero R, Fredericks S, Kaski JC. Markers of inflammation and rapid coronary artery disease progression in patients with stable angina pectoris. Circulation 2004;110:1747—53 [Epub 2004 Sep 20].
[21] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. New Engl J Med 2005;352:1685—95.
[22] Dirksen MT, Van der Wal AC, van den Berg FM, van der Loos CM, Becker. Distribution of inflammatory cells in atherosclerotic plaques relates to the direction of flow. Circulation 1998;98:2000—3.
[23] van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 1994;89:36—44.
[24] Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Reversal of atherosclerosis with aggressive lipid lowering (REVERSAL) investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. New Engl J Med 2005;352:29—38.
[25] Margolis KL, Manson JE, Greenland P, Rodabaugh RJ, Bray PF, Safford M, et al. Women's health initiative research group. Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the women's health initiative observational study. Arch Int Med 2005;165:500—8.
[26] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto Jr AM, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New Engl J Med 2008;359:2195—207.
[27] McGillicuddy FC, a Moya M, Hinkle CC, Joshi MR, Chiquoine EH, Billheimer JT, et al. Inflammation impairs reverse cholesterol transport in vivo. Circulation 2009;119(8): 1135—45.