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Leisure physical exercise and creatine kinase activity. The Tromsø study

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Creatine kinase (CK) is an enzyme catalyzing energy reaction in muscle cells and has proven to modify cardiovascular risks. The influence of skeletal muscle activity on CK concentrations is a potential study confounder but is mainly reported in connection with sport activities. This study investigated the association between leisure physical exercise and CK and estimated the effect of physical exercise on the CK values. CK and leisure physical exercise defined as intensity, frequency, and duration subsets were measured in the population-based Tromsø study. Comparisons of CK at different exercise levels, multivariate analyses, and relative differences in CK between "never exercise" and "heavy exercise" (moderate or hard exercise ≥2 hours per week) subgroups were analyzed age- and sex-stratified in 12 796 men and women. CK increased significantly with higher levels of physical exercise intensity and frequency in both sexes analyzed by ANOVA. In a multivariate analysis, CK was independently associated with heavy exercise after adjusting for age, BMI, and blood pressure; OR 9.38 (95% CI 5.32-16.53), $P < .0001$ in men and OR 5.20 (95% CI 2.53-10.69), $P < .0001$ in women. The differences in CK between physically inactive and participants performing heavy exercise varied between 3.1% (women) and 6.4% (men) and was also larger in participants ≥50 years. In conclusion, CK was positively and independently associated with increasing leisure physical exercise in a general population. CK values associated with exercise were approximately twice as high in men than women, but exercise altered CK only modestly.

KEYWORDS

creatine kinase, exercise, general population, physical activity, sex

1 | INTRODUCTION

Creatine kinase (CK) is an enzyme largely located in skeletal muscle cells where it catalyzes energy reactions by moving phosphate from creatine and adenosine diphosphate to generate adenosine triphosphate (ATP) and creatine. Consequently, ATP becomes available for muscle contractions and other energy-demanding processes.[1] Muscular activity in relation to CK has been studied in many aspects. It is known that CK usually increases during both intense long-term exercise and eccentric muscular training.[2,3] The variation in CK response to physical exercise varies largely. A 74% CK increase was recorded 24 hours in male adolescent runners after performing a

21-km routine run.[2] Experimental studies have demonstrated different CK responses to eccentric exercise. In one study, comparisons of CK between 4 groups of participants performing different levels of eccentric exercise were indifferent.[4] Others reported increased CK after resistant exercise.[5] Different study designs may account for this, but several more factors including high and low CK responders to exercise,[6] CK levels at rest,[7] genetic variations,[8,9] and sex differences[10] may contribute to divergent results. Furthermore, a community study showed that incidentally elevated CK normalized in 70% of the subjects after a standardized control test.[11] A study comparing CK levels at rest with different exercise levels reflecting habitual training in the population will add to the knowledge about the CK-exercise relationship.

Population-based studies have reported CK to be associated with body mass index (BMI)[12,13] and blood pressure.[14] Further studies are needed to clarify the role of CK as a possible risk factor to develop cardiovascular diseases (CVD). An important part of this process is to investigate how potential confounders might influence the results. It is therefore a twofold motivation for this study. Mainly, to investigate associations between CK concentrations and leisure physical exercise, and secondly, to estimate the effect of leisure physical exercise on CK levels.

2 | MATERIALS AND METHODS

2.1 | Study population

The 6th Tromsø community Study was used to design the present one. The study was initiated in 1974, focusing originally on cardiovascular diseases. Inhabitants of the municipality of Tromsø, Norway, and samples from certain age groups of subjects participated in a previous survey (4th Tromsø study); 10% random sample from age groups 30-39, and all participants aged 40-49 and 60-87 years were selected for inclusion. The data were collected from October 2007 to 19 September 2008. In total, 12 984 mainly Causation (87.3% ethnic Norwegians, 1.6% Sami ethnicity, 1.3% Finnish origin, 2.2% of other ethnicities, and 7.6% without information about ethnicity) participated.[15] Written consent was obtained from all, and the Norwegian Committee for Medical and Health Research Ethics (REC) approved the study.

2.2 | Measurements

After the phlebotomy, serum CK was analyzed within 6 hours in an automated clinical chemistry analyzer (Modular P, Roche) by photometry, using an enzymatic method (CK-NAC, Roche Diagnostics, Mannheim, Germany) with an analytic variation coefficient ≤1.6%. The standard cut-off limits for CK used were those developed by the Nordic Reference Interval Project (NORIP): Men 18-50 years (50-400 U/L); Men ≥50 years (40-280 U/L); Women (35-210 U/L).[16] CK ≥ 1000 U/L was detected in 7 men and 16 women were regarded as outliers and excluded. All the analyses were done at the Department of Clinical Biochemistry, University Hospital of North Norway. According to the standard procedure in the Tromsø study, height and weight were measured wearing light clothing without shoes to the nearest 0.1 cm and 0.1 kg using an automatic device, and BMI calculated as weight (kg) divided by height squared (m^2). Information on diabetes, use of lipid-lowering drugs, and coronary heart disease was obtained from standard questionnaires in the Tromsø study. Coronary heart disease was registered as a case when participants reported previous heart attack. Diabetes was defined as $HbA_{1c} \geq 6.5\%$ or use of antidiabetic drugs. An automatic device (Dinamap Vital Signs Monitor 1846; Critikon Inc, Tampa, FL) was used to record blood pressure. After 2 minutes rest in a sitting position, 3 readings were taken on the upper right arm at 1-minute intervals. Of them was the average of the 2 last readings used in the analyses. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication.

2.3 | Outcome assessment

Endpoints were obtained from a self-administered questionnaire. Leisure physical activity was recorded in the following way:

1. Light activity (not sweating or out of breath). How has your physical activity in leisure time been during the last year? Think of your weekly average for the year. Time spent going to work counts as leisure time (hours per week).
2. Vigorous physical activity (sweating⁄out of breath). How has your physical activity in leisure time been during the last year? Think of your weekly average for the year. Time spent going to work counts as leisure time (hours per week).

Physical exercise assessed by intensity, frequency, and duration via questionnaire is previously validated[17] and addressed in the following way:

1. Exercise intensity: If you exercise; how hard do you exercise? (a) I take it easy without becoming breathless and sweaty (easy), (b) I push myself so hard that I

become breathless and sweaty (moderate), (c) I push myself to near exhaustion (hard)
2. Exercise frequency: If you exercise; how frequent do you exercise? (a) Never, (b) Less than once a week, (c) Once a week, (d) 2-3 times a week, (e) Almost every day
3. Exercise duration: If you exercise; for how long do you exercise? (a) <15 minutes, (b) 15-29 minutes, (c) 30-60 minutes, (d)> 60 minutes

Combining information about frequency and duration of exercise, "hours of leisure time physical exercise per week" was calculated. The frequency response option "2-3 times a week" was counted as 2.5 and "almost every day" as 6 days per week. Options of exercise durations <15, 15-29, 30-60, and >60 minutes were counted as 10, 25, 45, and 75 minutes. The study population was categorized into three groups: Physical inactive (n = 752), participants performing leisure physical exercise 0.1-1.9 hours per week (n = 8284), and ≥2 hours per week (n = 3534). Moderate or hard exercise ≥2 hours per week was defined as "heavy exercise" (n = 2144). These categories were combined since the group of participants performing hard exercise was small (n = 376).

2.4 | Statistical analysis

Distribution of endpoint variables was evaluated by inspection of histograms, and calculation of kurtosis and skewness. The histograms showed right-sided skewness of CK values for both men and women. Likewise, serum CK showed non-Gaussian distribution (men: skewness 2.7, kurtosis 11.9 and women: skewness 3.7, kurtosis 25.4). Subsequent analyses of log CK (men: skewness 0.4, kurtosis 0.5; women: skewness 0.5, kurtosis 1.2) and inspection of histograms showed normal distribution of CK. Log CK was therefore used in the analyses.

Descriptive data are presented as mean and standard deviations (SD) or numbers and frequencies. Student´s t test was used to calculate differences between means and chi-square test to compare frequencies of data between sexes. ANOVA was used to test differences between means of CK in exercise subgroups. By multiple regression analysis, possible confounders (ie, variables included in the Tromsø study known to affect CK) were tested and adjusted for with log CK as the dependent variable and age, BMI, and systolic and diastolic blood pressure as independent variables. Also, creatinine and use of lipid-lowering drugs were analyzed in association with CK. All comparisons were performed separately in men and women. Two-sided $P < .05$ was considered statistically significant. All analyses were conducted using SPSS software (Statistical Package for Social Science INC, Chicago, Illinois, USA), version 25.

3 | RESULTS

Clinical characteristics of the subjects are described in Table 1. Men had higher frequency of reported CVD and CVD risk factors (Table 1). Furthermore, more men than women used lipid-lowering drugs (Table 1), but the CK levels were not elevated in these subgroups (data not shown). Categories of leisure time physical exercise intensity, frequency, and duration are displayed in Table 2. Men were more often physical inactive than women, but these subgroups are relatively small (Table 2). On the other hand, 51.6% men trained at moderate or hard intensity compared to 44.2% in women ($P < .0001$). Women trained more often (≥ 2 hours per week), while men trained longer each time (Table 2). CK correlated positively with BMI in both sexes, but positively with systolic and diastolic blood pressure in women only (data not shown). Also, CK correlated positively with creatinine in men ($r = .047$; $P < .0001$) and women ($r = .113$; $P < .0001$).

Tables 3 and 4 show associations between CK and exercise intensity and frequency. The increase in CK concentrations from lowest to highest subgroups of exercise performances was highly significant for both sexes. Additionally, the differences between each level of exercise intensity were all significant (Table 3). Covariates showed invariable associations with exercise intensity and frequency. Decreasing BMI values in association with increasing exercise levels were significant except for men in the intensity category (Tables 3 and 4). CK associated positively with moderate or hard exercise ≥2 hours per week after adjusting for age, BMI, and blood pressure (Table 5). CK was independently associated with heavy exercise after adjusting for age, BMI, and blood pressure; OR 9.38 (95% CI 5.32-16.53), $P < .0001$ in men and OR 5.20 (95% CI 2.53-10.69), $P < .0001$ in women (Table 5). When including creatinine in the model [men: OR (95% CI) = 1.00 (0.99-1.01), $P = .76$; women: 0.99 (0.98-1.00), $P = .99$], the statistical outcome remained unchanged (data not shown). Table 6 shows differences in CK values between groups performing exercise activities at different levels and physical inactive. The CK differences between participants performing heavy exercise (moderate or hard exercise ≥2 hours per week) were 6.4% in men and 3.1% in women and were lower in participants <50 years of age in both sexes (Table 6).

4 | DISCUSSION

This study demonstrated a significant and independent association between CK and leisure physical activity in the general population. The relative change in exercise related CK concentrations ranged from 3.1% in women to 6.4% in men using physical inactive groups as references. The associations were also significant between inactivity and lowest

TABLE 1 Clinical characteristics of the participants presented as mean (SD) or numbers (%)

Variables	Men (n = 5969)	Women (n = 6827)	*P*
Age (years)	57.4 (12.3)	57.4 (13.0)	1.0
BMI (kg/m^2)	27.3 (3.8)	26.6 (4.7)	<.0001
Obesity (BMI ≥ 30 kg/m^2)	1234 (20.7)	1397 (20.5)	.69
Diabetes mellitus	327 (5.5)	306 (4.5)	.01
Use of lipid-lowering drugs	992 (16.6)	845 (12.4)	<.0001
Systolic BP (mm Hg)	137.8 (20.4)	133.8 (25.0)	<.0001
Diastolic BP (mm Hg)	81.1 (10.2)	74.9 (10.2)	<.0001
Hypertension	2083 (34.6)	1949 (28.6)	<.0001
Coronary heart disease	482 (8.1)	199 (2.9)	<.0001
S-creatinine (μmol/L)	78.7 (15.9)	62.7 (12.5)	<.0001
S-CK (U/L)	147.8 (96.2) (IQR12.0-981.0)	98.6 (60.1) (IQR10.0-871.0)	<.0001
Log CK (U/L)	2.10 (0.23)	1.94 (0.20)	<.0001
High CK[a]	319 (5.3)	276 (4.0)	<.0001

Abbreviations: BMI, body mass index; BP, blood pressure; CK, creatine kinase.

[a]Reference limits for normal CK: Men <50 y: 50-400 U/L, men ≥50 y: 40-280 U/L, women: 35-210 U/L.

TABLE 2 Domains of leisure time physical exercise. Numbers (%)

Leisure time physical exercise intensity	Men (n = 5969)	Women (n = 6827)	*P*
Inactive	397 (6.7)	355 (5.2)	.001
Easy (not breathless and sweaty)	2360 (39.5)	3105 (45.5)	<.0001
Moderate (breathless and sweaty)	2837 (47.5)	2884 (42.2)	<.0001
Hard (near exhaustion)	242 (4.1)	134 (2.0)	<.0001
Missing	133 (2.2)	349 (5.1)	
Leisure time physical exercise per week (hours)			
0.1-1.9	3966 (66.4)	4318 (63.2)	.001
≥2	1523 (25.5)	2011 (29.5)	<.0001
Missing	83 (1.4)	143 (2.1)	
Heavy exercise (moderate or hard ≥2 h per week)	1019 (17.1)	1125 (16.5)	.014
Exercise duration (min)			
<15	242 (4.1)	182 (2.7)	<.0001
15-29	709 (11.9)	819 (12.0)	.76
30-60	2895 (48.5)	3745 (54.9)	<.0001
>60	1388 (23.2)	1210 (17.7)	<.0001
Missing	735 (12.3)	871 (12.7)	<.0001

exercise levels indicating also low exercise activity to be associated with increased CK. The significances persisted after adjusting for age, BMI, and blood pressure in both sexes. Leisure physical activity does not seem to bias CK values substantially.

There is a known relationship between CK and physical exercise, but there exists no standard on how CK responds to specific muscular activities. Knowledge about this relationship is evident from both human and animal studies. A 10- to 20-fold CK increase or more is common in long distance runners and athletes performing eccentric sport activities.[18] Upper CK references were three times higher in football players and swimmers compared to inactive and twice as high for moderately active athletes.[19] In line with this "dose-response" observation, a substantially lower difference in CK activity at rest between inactive and active leisure physical trainers was observed in the presented study. Thus, a small but significant CK increase along with increasing exercise

TABLE 3 CK and covariates in categories of exercise intensity

Exercise intensity					
	Inactive	**Easy[a]**	**Moderate[b]**	**Hard[c]**	***P* for trend**
N (men)	397	2360	2837	242	
Age (years)	60.3 (12.7)	60.5 (12.1)	54.9 (11.4)	49.0 (10.2)	<.0001
BMI (kg/m^2)	27.9 (4.4)	27.3 (3.8)	27.2 (3.6)	26.9 (3.6)	.31
Systolic BP (mm Hg)	138.5 (21.2)	139.6 (21.2)	136.3 (19.4)	131.3 (18.5)	<.0001
Diastolic BP (mm Hg)	80.6 (10.3)	81.0 (10.3)	81.3 (10.0)	79.2 (10.8)	.01
Log CK (U/L)	2.05 (0.23)	2.10 (0.23)	2.14 (0.24)	2.22 (0.20)	<.0001[d]
N (women)	355	3105	2884	134	
Age (years)	66.8 (13.8)	60.6 (12.3)	52.1 (11.1)	47.6 (10.6)	<.0001
BMI (kg/m^2)	27.7 (5.4)	26.7 (4.7)	26.2 (4.5)	25.0 (3.9)	<.0001
Systolic BP (mm Hg)	141.3 (26.3)	137.5 (25.8)	127.6 (22.3)	120.8 (20.2)	<.0001
Diastolic BP (mm Hg)	74.7 (10.7)	75.5 (10.3)	74.4 (9.9)	71.7 (8.8)	<.0001
Log CK (U/L)	1.91 (0.20)	1.94 (0.20)	1.98 (0.20)	2.04 (0.27)	<.0001[d]

Abbreviations: BP, blood pressure; CK, creatine kinase.

The trends analyzed by ANOVA were significant between all categories for both sexes.

[a]Easy, not breathless and sweaty

[b]Moderate, breathless and sweaty

[c]Hard, near exhaustion

TABLE 4 CK and covariates in categories of exercise frequency (hours per week)

Exercise frequency				
	Inactive	**0.1-1.9 h**	**≥2 h**	***P* for trend**
N (men)	397	3966	1523	
Age (years)	60.3 (12.7)	56.6 (12.0)	58.4 (12.5)	<.0001
BMI (kg/m^2)	27.9 (4.4)	27.4 (3.8)	26.7 (3.4)	<.0001
Systolic BP (mm Hg)	138.5 (21.2)	137.3 (20.1)	138.4 (20.9)	.12
Diastolic BP (mm Hg)	80.6 (10.3)	81.2 (10.2)	80.7 (10.3)	.19
Log CK (U/L)	2.03 (0.25)	2.10 (0.23)	2.13 (0.23)	<.0001[a]
N (women)	355	4318	2011	
Age (years)	66.8 (13.8)	56.5 (12.6)	56.9 (12.4)	<.0001
BMI (kg/m^2)	27.7 (5.4)	26.9 (4.8)	25.6 (4.1)	<.0001
Systolic BP (mm Hg)	141.3 (26.3)	133.1 (24.7)	132.5 (24.7)	<.0001
Diastolic BP (mm Hg)	74.7 (10.7)	74.9 (10.1)	75.0 (10.2)	.91
Log CK (U/L)	1.91 (0.23)	1.93 (0.20)	1.96 (0.20)	<.0001[b]

Abbreviations: BP, blood pressure; CK, creatine kinase.

[a]The trends analyzed by ANOVA were significant between all categories.

[b]The trends analyzed by ANOVA was significant between "inactive" and "≥ 2 h" exercise per week.

TABLE 5 Adjusted odds ratio (OR) with 95% confidence interval (CI) for CK associated with moderate or hard exercise ≥2 h per week

	OR (95% CI)	*P* value
N (men)	1019	
Log CK (U/L)	9.38 (5.32-16.53)	<.0001
Age (years)	0.97 (0.96-0.98)	<.0001
BMI (kg/m^2)	0.90 (0.87-0.93)	<.0001
Systolic blood pressure (mm Hg)	1.00 (0.99-1.01)	.39
Diastolic blood pressure (mm Hg)	1.01 (1.00-1.03)	.33
N (women)	1121	
Log CK (U/L)	5.20 (2.53-10.69)	<.0001
Age (years)	0.91 (0.90-0.93)	<.0001
BMI (kg/m^2)	0.91 1(0.89-0.94)	<.0001
Systolic blood pressure (mm Hg)	1.00 (0.99-1.01)	.98
Diastolic blood pressure (mm Hg)	1.02 (1.00-1.03)	.07

Abbreviation: CK, creatine kinase.

levels including easily active individuals was evident in this "leisure physical activity" designed study.

The anticipated mechanism is damage to the muscle cell sarcolemma with subsequent release of CK to the circulation,[20] but exercise-induced rice in CK may also reflect pharmacokinetic properties of the compound.[21] Furthermore, inflammation may facilitate release of CK to the circulation, especially during muscular exertion.[22] Animal studies have shown altered energy metabolism in trained rats by changing CK isoenzyme composition and enzymatic activity especially in fast twitch glycogenic dependent muscle in which CK concentrations are supposed to be higher.[23,24] One documented training effect in humans is reduced CK response after initially performing one bout of exercise. The bout effect may persist for up to 6 months.[25] Consequently, training may hypothetically protect muscles from damage and subsequent CK leakage.[26] It is also shown that repeated submaximal eccentric exercise bouts are equivalent with one maximal bout.[27] This may support the view that training effect is obtained also by easy and moderate exercise, more commonly performed in leisure time. Furthermore, repeated bouts of exercise reduced basic CK levels especially in the younger.[28] Lower CK levels in adolescents compared to adults after strenuous exercise are further indicative of an age-dependent skeletal muscle protection.[29] Accordingly, differences in CK activity between exercisers and inactive in the present study were lower in individuals <50 years compared to groups ≥50 years. Whether young individuals are less susceptible to sarcolemma disruption due to age-related differences in repeated bout effect is a presumed mechanism but is only a matter of speculation in this study.

There is a sex difference in Δ CK between inactive and heave exercise groups in this population as the data indicated men to be twice as high CK responders to exercise than women. This is in line with studies on CK response to sport activities,[18] and reference values was twofold higher in 483 athletic men than 245 women in a study where samples was obtained during active training and competition periods.[19] This difference is not obviously explained by a relatively more muscle mass fraction in men than women, as CK was unrelated to muscle mass in an exercise study.[30] Estrogen is reported to exert a protective effect on the muscle cell membrane due to antioxidative properties,[31] but studies on how estrogen interacts with CK are conflicting in the literature.[32,33] Furthermore, the CK responses to exercise vary with ovulatory status in a complex way.[34] Anecdotally, increased CK

TABLE 6 Log CK in participants performing exercise at different levels and Δ log CK between heavy exercise and inactive groups. Mean (SD) or numbers (%)

	Men (n = 5969)	Women (n = 6827)	*P*
Log CK (U/L) in exercise subgroups			
Inactive	2.03 (0.25) (n = 397)	1.91 (0.23) (n = 355)	<.0001
Exercise ≥2 h per week	2.13 (0.23) (n = 1523)	1.96 (0.20) (n = 2011)	<.0001
Hard intensity exercise	2.17 (0.24) (n = 242)	1.97 (0.21) (n = 134)	<.0001
Moderate or hard exercise ≥2 h per week	2.16 (0.23) (n = 1019)	1.97 (0.20) (n = 1125)	<.0001
Δ log CK (U/L) between heavy exercise and inactive groups (%)			
Total group	6.4	3.1	<.0001
<50 y	4.8	2.2	<.0001
≥50 y	6.4	3.6	<.0001

Note: Heavy exercise, moderate or hard exercise ≥ 2 h per week.

Abbreviation: CK, creatine kinase.

normalized during pregnancy but reappeared after delivery in a woman with persistent hyperCKemia.[35]

Limitations of the study mainly refer to the observation study design which enables conclusion about causality, use of exercise questions rather than objective measures of physical activity as outcomes and lack of specific information about training forms. Contrary, a large population cohort provides valid associations between CK activity at rest and exercise subgroups. Furthermore, drug-related increase in CK might have been overlooked due to incomplete drug lists in the dataset.

5 | PERSPECTIVE

This study demonstrated that CK associated significantly with all levels of exercise intensity and duration in men and women in the population-based Tromsø study. With an approximately 5% difference (higher in men and lower in women) in CK levels between heavy training and physical inactive, leisure physical exercise is not expected to be a major confounder in population-based studies. In clinical practice, other causes than leisure physical activity should therefore be searched for in the process of diagnosing individuals with elevated CK.

CONFLICT OF INTEREST

There is no conflict of interest related to the study.

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