Physical activity paradox: could inflammation be a key factor?

Joshua Buron Feinberg [1,2], Anne Møller [3], Volkert Siersma [3], Helle Bruunsgaard [4,5], Ole Steen Mortensen [1,6]

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[1]Department of Occupational and Social Medicine, Holbaek Hospital, Holbaek, Denmark
[2]Faculty of Health Sciences, Institute of Regional Health, University of Southern Denmark, Odense, Denmark
[3]Department of Public Health, The Research Unit for General Practice and Section of General Practice, University of Copenhagen, Copenhagen, Denmark
[4]Department of Clinical Immunology, Rigshospitalet, Copenhagen, Denmark
[5]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[6]Section of Social Medicine, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

Correspondence to
Dr Joshua Buron Feinberg, Department of Occupational and Social Medicine, Holbaek Hospital, Holbaek 4300, Denmark; wtv945@alumni.ku.dk

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ABSTRACT

Objective The aim of this study was to test the extent to which physical activity performed during work and leisure is associated with systemic inflammation.

Methods Data regarding job history and high-sensitivity C reactive protein (hs-CRP) levels, as well as potential confounders, came from the Copenhagen Aging and Midlife Biobank. The participants' self-reported job history was combined with a job exposure matrix to give a more valid assessment of cumulated occupational physical activity compared with conventional self-reported activity. Occupational physical activity was measured as cumulative ton-years (lifting 1000 kg each day for a year). Current leisure time physical activity was self-reported into four different categories. We analysed the association between occupational physical activity, current leisure time physical activity and hs-CRP level in a multivariable linear regression model with adjustment for age, sex, smoking history, number of chronic diseases, body mass index and alcohol.

Results In unadjusted analysis, higher occupational physical activity was associated with increased hs-CRP levels, while higher leisure time physical activity was associated with lower hs-CRP levels. In adjusted analysis, lower leisure time physical activity resulted in 12% higher hs-CRP levels while higher occupational physical activities showed a 6% increase in hs-CRP. When we analysed occupational and leisure time physical activity as continuous variables, only leisure time physical activity affected hs-CRP.

Conclusion This study indicates that the relationship between physical activity and hs-CRP depends on the setting of physical activity, with lower hs-CRP related to leisure time physical activity and higher hs-CRP related to occupational physical activity. The results suggest that systemic inflammation may explain the physical activity paradox.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The benefits of physical activity appear to depend on the context: whether it happens during ones occupation or leisure time. Occupational physical activity has been associated with an increased risk of coronary heart disease and mortality. Multiple hypotheses have been proposed to explain the mechanisms behind this physical activity paradox.

WHAT THIS STUDY ADDS

⇒ Lower leisure time physical activity and higher occupational physical activity are associated with increased high-sensitivity C reactive protein levels. This study supports that systemic inflammation may be one of the mechanisms behind the physical activity paradox.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study makes it prudent to further study the role of systemic inflammation in the context of the physical activity paradox.

INTRODUCTION

High occupational physical activity has been shown to be associated with as much as a 25% increase in risk for coronary heart disease and mortality compared with low occupational physical activity, even after adjustments for confounders (most commonly smoking, alcohol drinking, body mass index (BMI) and education level).[1–7] The opposite holds true for leisure time physical activity where both moderate and high leisure time physical activity are associated with a lower risk of coronary heart disease.[2 5] The literature, however, is not in agreement with regard to the relative importance of leisure time physical activity and occupational time physical activity for the development of cardiovascular disease and mortality, which may also depend on how the activity is measured.[1 2] Still, the fact that the health benefits of physical activity seem to depend on whether activity happens in connection with work or leisure is called 'the physical activity paradox'.[2 8]

The physical activity paradox may be explained by six mechanisms (with some overlap) that each can be tested and possibly refuted as the possible explanations for the physical activity paradox.[8] (1) Occupational physical activity is of too low intensity/too long duration, not granting the cardiopulmonary fitness benefits seen with leisure time physical activity; (2) occupational physical activity increases the average 24-hour heart rate which is known to be an independent risk factor for developing heart disease; (3) occupational physical activity includes more heavy and static activity than leisure time physical activity which elevates the average 24-hour blood pressure, which in turn increases the risk of cardiovascular disease; (4) occupational physical activity does not leave enough time for recovery; (5) occupational physical activity is less worker-controlled leading to scenarios that are detrimental to the worker's health, such as improper clothing with respect to the environment, dehydration, injuries and mental stress; (6) occupational physical activity increases the levels of inflammation. This

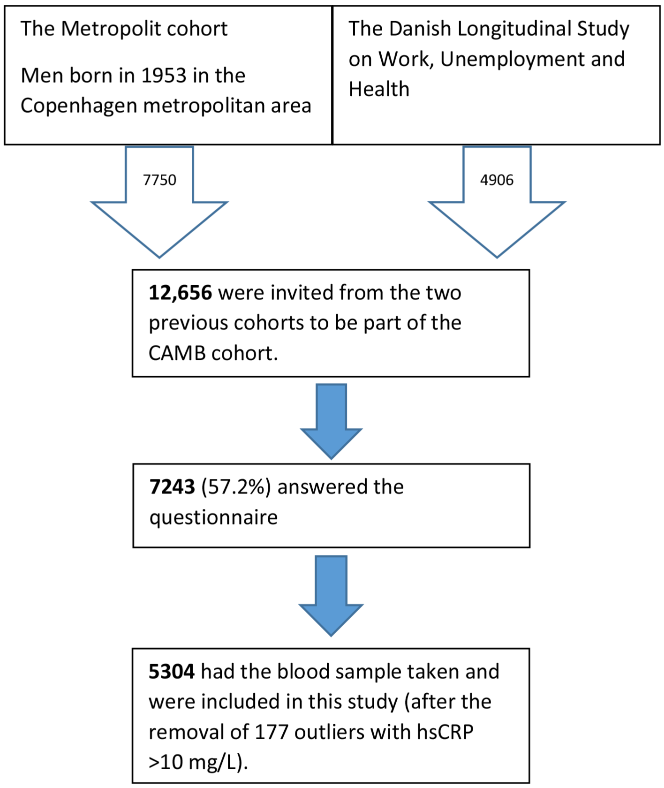

Figure 1. Flow chart of participants and cohorts used from the Copenhagen Aging and Midlife Biobank. CAMB, Copenhagen Aging and Midlife Biobank; hsCRP, high-sensitivity C reactive protein.

last suggested mechanism is the focus of the current study and is further explained below.

It seems plausible that high occupational physical activity many days in a row does not allow for sufficient recovery time to initiate the proper cellular response that would lower the resting inflammation.[9 10] Instead, occupational physical activity may lead to higher sustained levels of inflammation increasing the risk of atherosclerosis and other cardiovascular diseases.[1 8] Mechanisms 4 and 6 are somewhat overlapping, but mechanism 6 focuses on the inflammation being the driver of the paradox.

Systemic inflammation is conventionally thought of as occurring in the setting of acute disease, where it activates the immune system to fight off infection.[11] However, sustained systemic inflammation also appears to play a key part in the development of several diseases such as diabetes, atrial fibrillation and atherosclerosis.[11 12] An especially well-documented biomarker for this association is C reactive protein (CRP), which serves as a downstream marker of the inflammatory response which may, for example, lead to the formation of atherosclerotic plaques.[13] Other more upstream key biomarkers in the inflammatory response are tumour necrosis factor (TNF)-alpha, interleukin (IL)-6 and IL-1.[13]

The way the inflammatory response may be activated appears to depend on the type of event that activates the inflammatory response.[11] In the setting of acute disease, several proinflammatory cytokines are released, some of the most well-known are TNF-alpha, IL-6 and IL-1.[11] In contrast, it appears that TNF-alpha is not released as part of a non-classical inflammatory response after leisure time physical activity while IL-6 is released in both kinds of inflammatory responses. Leisure time physical activity also appears to act by activating an anti-inflammatory response both directly through IL-6, IL-10 and indirectly by having an effect on fat distribution and endothelial function.[14] Leisure time physical activity may also have a modulating effect on toll-like receptors, which normally are thought to play a role in the acute inflammatory response.[14]

If a difference in inflammatory response precipitates the physical activity paradox, it remains to be seen whether the adverse effects of high occupational physical activity can be mitigated by higher levels of leisure time physical activity.[9 10]

The aim of this study is to test the extent to which physical activity performed during work and leisure is associated with systemic inflammation.

METHODS

Participants

The current cross-sectional study uses data from the Copenhagen Aging and Midlife Biobank (CAMB) cohort.[15] CAMB was established in 2009 and was based on inviting participants from three existing Danish cohorts to answer questionnaires and perform tests. We only used data from two of the cohorts: 'The Danish Longitudinal Study on Work, Unemployment and Health' (DALWUH) and the 'the Metropolit Cohort' (MP).[15–17] The DALWUH cohort originally consisted of 7125 men and women who were randomly selected with an age between 40 and 50 years before 1 October 1999. The response rate was 69%. The MP originally comprised of 11.532 boys born in 1953 in the Copenhagen metropolitan area. Ninety-four per cent of the boys in the Copenhagen metropolitan area in the year of 1953 were included. The third cohort, The Copenhagen Perinatal Cohort, included mostly information on the prenatal, natal and postnatal period. The data collection in CAMB took place between April 2009 and March 2011. In total, 12 656 middle-aged men and women from DALWUH, and men from MP, were invited to take part in the CAMB cohort (figure 1—flow chart). Of the 12 656 invited, a total of 7243 participants answered the questionnaire (40%). Five thousand five hundred and seventy-six attended the physical examination, and 5304 had blood sample taken including the inflammatory marker: high-sensitivity CRP (hs-CRP).[15]

An attrition analysis showed that those who completed both the questionnaire and tests were more employed (90.0% vs 75.3%), and had a higher education level (40.2% had tertiary education vs 23.8% of non-responders).[15]

Exposure and outcome

Occupational physical activity was based on self-reported job history combined with data from a job exposure matrix.[18] The job exposure matrix was constructed based on expert opinion from five experts. Experts were presented a job group, which contained multiple job titles assumed to have the same exposure pattern. Experts were instructed to give their opinion on the amount of heavy lifting pr. day and the variation in lifting across the job group. Any disagreement on mean exposure was resolved by discussion. The CAMB questionnaire contained information on the length of service for the five longest held occupations held by each participant. The job history was coded according to the 1988 revision of the Danish Version of the International Standard Classification of Occupations register. We used the codes to retrieve information from a job exposure matrix.[18 19] The choice was made to combine the self-reported job history with a job matrix due to low reliability of self-reported occupational physical activity in a study by Møller *et al*.[19] Occupational physical activity was measured by heavy lifting reported as ton-years (lifting a 100 kg/day for a year).

We retrieved information on current leisure time physical activity from the CAMB questionnaire as self-reported physical activity per week (7 days). The questionnaire did not specify a time period for participants to consider so this was up for each participants' own interpretation. Participants were on average 54.4 years old and in the later part of their working career. Participants reported one of four different levels of leisure time physical activity: competitive sport regularly and several times a week; physical training or heavy house or garden work at least 4 hours per week; go for walks, biking or other kinds of light exercise at least 4 hours per week or; read, watch television or have other sedentary activities.[20–22]

We reconfigured the level of both occupational physical activity and leisure time physical activity into two categories (high and low), making it possible to define four groups of varying occupational and leisure time physical activity. The divisional line for occupational physical activity was 10 ton years, hence the low group had less than 10 ton years and the high group had more. For leisure time physical activity participants who answered they were sedentary or did light physical activity were combined, and the participants who did medium or hard leisure time physical activity were combined.

Outcome was hs-CRP measured in mg/L as a surrogate measure for systemic chronic inflammation.

Blood samples were collected without participants fasting, and stored at −80°C. Within 2 years, hs-CRP was analysed with a high sensitive assay (Tina quant, Roche Diagnostics GmbH, Mannheim, Germany) using latex-entrenched immune-turbidimetry analysis (Roche/Hitachi automatic instrument COBAS).[23 24]

CRP outliers (>10 mg/L) were excluded to account for high CRP values that could be related to prevalent disease. A total of 177 outliers were removed. The outliers had a similar age (54.0 years vs 54.5 years), similar alcohol consumption (12.0 units vs 11.9 units), higher BMI (28.3 vs 25.9), had smoked more (20.8 pack years vs 15.6 pack years), had more occupational physical activity (14.0 ton years vs 9.5 ton years) and more sedentary leisure time physical activity (21% vs 9%).

Covariates

We hypothesised that the inflammatory response measured as hs-CRP is dependent on whether physical activity happens during work or leisure. We considered the following potential confounders: age as a continuous variable, sex as a binary variable, smoking history measured as pack-years (1 pack year=20 cigarettes/day in a year) as a continuous variable, alcohol consumption measured as the number of units (1 unit=8 g of pure alcohol) of alcohol per week as a continuous variable; and BMI measured in kg/m^2 as a continuous variable. Chronic diseases were categorised in 0, 1 or ≥2 number of chronic diseases. The self-reported chronic diseases we considered of relevance were asthma, diabetes, hypertension, angina pectoris, stroke, myocardial infarction, bronchitis, emphysema, rheumatoid arthritis, osteoarthritis, cancer, anxiety, depression/other psychiatric diseases and back pain. These diseases were chosen, as the diseases or their treatment were specifically registered for the cohorts and were judged to potentially influence the CRP levels.

The categorisation of social class into six groups in table 1 was based on the article by Christensen *et al*.[25] We here briefly summarise the different classes: social class I: 4 years of university training, for example, government advisor; social class II: 3 years of theoretical training such as nurse, primary school teacher; social class III: 1.5 years of theoretical training, for example, accountant; social class IV: up to 1 year of theoretical training, for example, sales assistant; social class V: manual jobs without much training, for example, construction worker; social class VI: economically inactive such as the unemployed.

Statistical analysis

The association between each of the two types of physical activity and the average level of hs-CRP was assessed in multivariable linear regression models in which hs-CRP was log10-transformed. This transformation gives multiplicative effects between the categories of physical activity—that is, how many times the hs-CRP increases on average if the physical activity changes from low to high—if the regression coefficients are transformed back to original hs-CRP scale; it is these back-transformed coefficients that are reported in text and tables. We analysed each of the two types of physical activity separately (performing additional analyses where the other type was used as extra adjustment). The analyses were performed unadjusted and adjusted for potential confounders: age, sex, BMI, units of alcohol consumed each week, number of chronic diseases and smoking history.

We conducted all analyses using SAS software (Statistical Analysis Software 9.4, SAS Institute, Cary, North Carolina, USA).

We performed two post-hoc analyses. We performed a stratified analysis according to social class as well as performed our linear regression treating both occupational physical activity and leisure time physical activity as a continuous outcome instead of a dichotomous outcome. They are presented in online supplemental file 1.

RESULTS

A summary of the main characteristics of the population included in the study is presented in table 1. The average age of the participants was 54 years and 68.7% of participants were men. The average duration of working life was 29.3 years and the average lifting measured as ton years was 9.46 (SD 19.16, min 0 max 174.8). Most participants did light physical leisure exercise (57.8%) followed by medium/hard (32.9%) and sedentary (9.3%). The mean BMI was 25.9 kg/m^2 (SD 4.01, min 14.28, max 56.61), the mean cumulative smoking burden was 15.65 pack years (SD 22.41, min 0 max 525), the mean amount of alcohol pr. week was 11.95 units (SD 12.37, min 0 max 160).

In unadjusted analysis, hs-CRP increased with higher levels of occupational physical activity, with hs-CRP increasing with 23% when going from low occupational physical activity to high occupational physical activity (table 2). We found the opposite was true for leisure time physical activity where comparing high leisure time physical activity to low leisure time physical activity resulted in a 27% increase in hs-CRP.

In adjusted analyses, the increase in hs-CRP attributable to lower leisure-time physical activity was 12%. Higher occupational physical activity increased hs-CRP with 6%. The 6% increase with higher occupational physical activity was not statistically significant when the model also contained leisure time physical activity (p=0.0657), but the magnitude of effect was similar (column 3 of table 2).

An interaction between occupational and leisure time physical activity on hs-CRP was not statistically significant (p=0.98). The estimated effect of the combined types of physical activity also shows that this may be accurately calculated as the product of the individual effects.

We also performed the above analyses treating both occupational physical activity and leisure time physical activity

Table 1 Characteristics of the study population

	Whole population	High occupational physical activity	Low occupational physical activity	P value	High leisure time physical activity	Low leisure time physical activity	P value
Age (years), mean (SD)	54.4 (3.9)	54.8 (3.8)	54.3 (3.9)	<0.0001	54.2 (3.8)	54.5 (3.9)	=0.01
Men	3644 (68.7%)	1077 (79.13%)	2479 (64.83%)		1284 (74.74%)	2301 (65.69%)	
Women	1660 (31.3%)	284 (20.87%)	1345 (35.17%)	<0.0001	434 (25.26%)	1202 (34.31%)	<0.0001
Social Class 1	823 (16.0%)	28 (2.08%)	795 (20.97%)		328 (19.29%)	496 (14.31%)	
Social Class 2	1354 (26.35%)	160 (11.89%)	1194 (31.49%)		482 (28.35%)	871 (25.14%)	
Social Class 3	1220 (23.74%)	362 (26.89%)	858 (22.63%)		420 (24.71%)	799 (23.06%)	
Social Class 4	835 (16.25%)	338 (25.11%)	497 (13.11%)		266 (15.65%)	575 (16.59%)	
Social Class 5	434 (8.45%)	278 (20.65%)	156 (4.11%)		115 (6.76%)	318 (9.18%)	
Social Class 6	472 (9.19%)	180 (13.37%)	292 (7.70%)	<0.0001	89 (5.24%)	406 (11.72%)	<0.0001
BMI (<18.5)	47 (0.92%)	11 (0.82%)	36 (0.95%)		10 (0.59%)	38 (1.10%)	
BMI (18.5–25)	2241 (43.77%)	445 (33%)	1796 (47.51%)		856 (50.15%)	1409 (40.88%)	
BMI (25–<30)	2166 (42.30%)	644 (48.06%)	1522 (40.26%)		696 (40.77%)	1477 (42.85%)	
BMI (>30)	666 (13.01%)	240 (17.91%)	426 (11.27%)	<0.0001	145 (8.49%)	523 (15.17%)	<0.0001
0 units alcohol/week	563 (10.97%)	188 (13.99%)	375 (9.90%)		136 (7.99%)	435 (12.56%)	
1–14/21 units alcohol/week	3652 (71.16%)	874 (65.03%)	2778 (73.34%)		1316 (77.32%)	2357 (68.06%)	
14/21–35 units alcohol/week	694 (13.53%)	185 (13.76%)	509 (13.44%)		209 (12.28%)	485 (14.01%)	
>35 units alcohol/week	223 (4.35%)	97 (7.22%)	126 (3.33%)	<0.0001	41 (2.41%)	186 (5.37%)	<0.0001
Smokers*	1164 (22.48%)	434 (31.94%)	730 (19.11%)		257 (14.97%)	924 (26.41%)	
Non-smokers	4015 (77.52%)	925 (68.06%)	3090 (80.89%)	<0.0001	1460 (85.03%)	2575 (73.59%)	<0.0001
0 chronic disease	1792 (34.2%)	378 (27.77%)	1400 (36.63%)		1098 (31.36%)	684 (39.81%)	
1 chronic disease	1792 (34.2%)	448 (32.92%)	1323 (34.62%)		1165 (33.28%)	620 (36.09%)	
2+ chronic disease	1663 (31.7%)	535 (39.31%)	1099 (28.75%)	<0.0001	1238 (35.36%)	414 (24.10%)	<0.0001
Armed forces occupations	52 (1%)	–	–		–	–	
Managers	472 (9%)	–	–		–	–	
Professionals	630 (12%)	–	–		–	–	
Technicians and associate professionals	1050 (20%)	–	–		–	–	
Clerical support workers	787 (15%)	–	–		–	–	
Service and sales workers	630 (12%)	–	–		–	–	
Skilled agricultural, forestry and fishery workers	52 (1%)	–	–		–	–	
Craft and related trades workers	892 (17%)	–	–		–	–	
Plant and machine operators, and assemblers	157 (3%)	–	–		–	–	
Elementary occupations	367 (7%)	–	–		–	–	
No stated occupation	157 (3%)	–	–		–	–	

*Smokers were grouped into currently active smokers and non-active smokers, including previous smokers.
BMI, body mass index.

as continuous variables. The results were somewhat similar, although occupational physical activity seemed to influence hs-CRP less in this analyses (online supplemental sTable 1). R^2 was the same whether occupational physical activity and leisure time physical activity were considered as continuous variables or were transformed into a dichotomous variable.

We also performed the analyses stratified for social class. Results were similar for each strata (online supplemental sTable 2).

DISCUSSION

Main results

In this study, we observed that high leisure time physical activity was associated with a lower inflammatory response, that is, lower hs-CRP levels, and high occupational physical activity was associated with high inflammatory response, that is, higher hs-CRP levels; the latter association was weaker after adjusting for known confounders. When analysing both occupational physical activity and leisure time physical activity as continuous variableeisure time physical activity seemed to be more strongly associated with hs-CRP whereas occupational physical activity did not seem to influence hs-CRP.

Our results strengthen one of the six hypotheses that occupational physical activity generates a different physiological response compared with leisure physical activity.[8] The impact on hs-CRP for occupational physical activity seems to be weaker compared with leisure physical activity. Our results do not explain why there is this difference in the hs-CRP response depending on whether one is physical active in leisure time or during work time, but our study supports the theory that systemic chronic inflammation could ultimately lead to this difference in cardiovascular risk.[2]

We tested one of the six possible explanations previously hypothesised to explain the physical activity paradox.[8] The results of this study should be reviewed together with any studies examining the other hypotheses. We suggest that such an

Table 2 Results of analyses

	Hs-CRP (mg/L)		Unadjusted		Adjusted for potential confounders		Adjusted for potential confounders and the other PA	
	Median (IQR)	Mean (SD)	Factor increase in average hs-CRP (95% CI)*	P value	Factor increase in average hs-CRP (95% CI)	P value	Factor increase in average hs-CRP (95% CI)	P value
Model for occupational physical activity								
Low occupational physical activity	1.0 (0.5–2.1)	1.7 (1.8)	Ref		Ref		Ref	
High occupational physical activity	1.3 (0.7–2.6)	2.0 (2.0)	1.23 (1.16 to 1.31)	<0.0001	1.06 (1.00 to 1.12)	0.0477	1.06 (1.00 to 1.12)	0.0657
Model for leisure time physical activity								
Low leisure time physical activity	1.2 (0.6–2.4)	1.9 (1.9)	1.27 (1.21 to 1.35)	<0.0001	1.12 (1.06 to 1.18)	<0.0001	1.12 (1.06 to 1.18)	<0.0001
High leisure time physical activity	0.9 (0.5–1.8)	1.5 (1.6)	Ref		Ref		Ref	

The four top rows with results show results with leisure time physical activity and occupational physical activity as individual variables in a linear regression.
*Because we log transformed the hs-CRP, the results are measured as factor increase which can be transformed into a percentage increase. For example, going from high leisure time physical activity to low leisure time physical activity in the unadjusted analysis resulted in a factor increase of 1.27 which means a 27% increase in hs-CRP level with this change of leisure time physical activity level. Since the change is relative this means the change is dependent on the initial level of hs-CRP.
hs-CRP, high-sensitivity C reactive protein; PA, physical activity.

article should set up a framework to further guide the research concerning the paradox moving forward ultimately leading to interventions that can improve health. Future studies may look for the molecular mechanisms acting to induce an elevated CRP response. Factors to consider may be the length of the exposure and the work–rest cycle. It may, for example, be that the normal work–rest cycle of a normal working week results in too short a resting period which leads to a sustained inflammatory response.[26] It may also be worth considering whether the type of activity plays a role: occupational physical activity is more static whereas leisure time physical activity is more dynamic. Further subjects of interest are the technical aspects of measurement issues including considerations on how to make the measurement of physical exposure more objective.[27 28]

Strength and limitations

In this present study, we used a job exposure matrix instead of self-reported exposure, which should increase the validity of this assessment. Combining this with a detailed, self-reported job history used in CAMB, the accuracy of the exposure variable for occupational physical activity should have greatly improved. However, there is still a risk of misclassification of the occupational physical activity, as exposure is based on job title, but we expect this on average will have little influence. The agreement in the job exposure matrix was moderate (kappa=0.49) for heavy lifting, hence it could still be improved.[18] Heavy lifting was used as surrogate for occupational physical activity; however, one could use other measures of occupational physical activity as well. Analyses of the Job Exposure Matrix have shown that job types normally defined as jobs with high physical activity include heavy lifting.[18] However, although perhaps better than self-reported exposure, ideally an objective way of assessing exposure would have been preferred. The use of a job exposure matrix also introduced another possible bias: the job matrix assumes a homogeneous exposure according to job title and this assumption may be false.[18] Choosing ton-years as our exposure variable as the surrogate for physical activity during work, we captured both intensity and duration of physical exposure in one outcome. This, however, is ultimately also a weakness of the study, as the study may consider intensive physical exposure over a short period and less intensive physical exposure over a longer period as the same exposure.

Leisure physical activity was self-reported and sought to capture the leisure physical activity during 1 week at the time of answering which was on average in the later part of their working career. The questionnaire did not specify the time period for this activity, for example, over the last 3 months. In contrast, the occupational physical activity questions sought to capture the cumulative exposure. This is a limitation when interpreting our results. A better measure of cumulative leisure physical activity would have been preferred, but previous work has shown low validity of self-reports of cumulative exposures according to occupational physical activity. Therefore, a cohort study as mentioned above, including data on leisure time physical activity would be preferred in future studies.

We chose to categorise physical activity in groups to increase the understanding of the study. However, through the review process, we were suggested to study the effect also with continuous variables. There are similarities in the findings, but also discrepancies. This discrepancies must be considered when interpreting the study.

Our study only assessed hs-CRP as a surrogate measure of systemic chronic inflammation. Our study may therefore not provide a complete picture of the inflammatory response. Future studies may want to assess other markers of systemic inflammation. Furthermore, we did not have access to data about the use of medication such as non-steroidal anti-inflammatory drugs that could influence the level of hs-CRP and we did not adjust for acute inflammatory events. This may lead to some residual confounding despite removing outliers with hs-CRP >10 mg/L.

We considered also adjusting for social class in our analyses, but were concerned that this would eliminate part of the effect that we were to assess. Social class is often for a large part defined from one's occupation; low social class typically implies manual work, that is, an occupation with high physical activity. Including social class would adjust out a potential pathway from occupational physical activity to systemic inflammation which is part of the association of interest.

Our study included a large number of participants, which was a strength. However, our study was at risk of attrition bias from two sources. First, attrition analysis from the CAMB-study have shown that non-responders differed from responders with respect to health and social factors. This may impact the generalisability of our results. Second, some participants who answered the questionnaire did not complete the measurement of hs-CRP.[15 29] It may be that the participants without a blood sample taken would have higher hs-CRP.

Conclusion

This study indicates that the relationship between physical activity and hs-CRP depends on the setting of physical activity, with lower hs-CRP associated with leisure time physical activity and higher hs-CRP associated with occupational physical activity. The results suggest that systemic inflammation may explain the physical activity paradox.

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Contributors OSM and AM conceived the study. JBF wrote the initial draft. AM and JBF performed the analysis with assistance from VS. VS provided overall statistical advice. All authors revised the manuscript and approved the final version. JBF serves as the guarantor.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Request are made to the PI of CAMB. More information is available from https://camb.ku.dk/.

ORCID iD

Joshua Buron Feinberg http://orcid.org/0000-0003-1975-9300

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