Title: Does Leisure Time Physical Activity Interact with and Mediate the Effect of Occupational Physical Activity on 20-Year Incidence of Acute Myocardial Infarction?

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AW conceived this study, performed all analyses, and wrote the manuscript. NK participated in study conception, provided guidance on analysis and interpretation of the result, and edited the manuscript. JK served as liaison with KIHD study data management at the University of Eastern Finland, provided access to data for this study, and reviewed the final manuscript. OAA provided statistical advice for model building and the interpretation of results, reviewed and edited the final manuscript draft, and supervised AW.

Competing Interest

None declared.

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Does Leisure Time Physical Activity Interact with and Mediate the Effect of Occupational Physical Activity on 20-Year Incidence of Acute Myocardial Infarction?

**ABSTRACT**

**Objectives:** To disentangle the interplay between occupational physical activity (OPA) and leisure-time physical activity (LTPA) in affecting cardiovascular health, this study aimed to examine (1) interactions between OPA and LTPA and their combined effect on 20-year incidence of acute myocardial infarction (AMI), and (2) the effect of OPA on AMI that is mediated through LTPA.

**Methods:** We analyzed data on 1891 men, aged 42-60 years at baseline, from the prospective Kuopio Ischemic Heart Disease Risk Factor Study. OPA was measured as relative aerobic strain (RAS), accounting for workers’ cardiorespiratory fitness. Averaged 12-month LTPA and potential confounders were assessed by questionnaires. Analyses were stratified by the presence of ischemic heart disease (IHD) at baseline.

**Results:** We found multiplicative but not additive interactions between OPA and LTPA among men with IHD. The multivariable Cox model, adjusted for age, education, smoking, alcohol consumption, psychosocial job factors, and participation in an unrelated drug trial, showed that high OPA positively predicted AMI at low LTPA levels for both men without and with IHD — HR 1.27 (95% CI: 0.96–1.68) and HR 1.59 (95% CI: 0.99–
1.68), respectively. The combination of high OPA and low LTPA constituted the group associated with the highest risk for AMI, irrespective of IHD status. LTPA was not independently predictive of AMI and did not mediate the impact of OPA on AMI.

**Conclusions:** LTPA interacted with OPA on the multiplicative scale only. LTPA did not mediate the effect of OPA on AMI.

**KEY TERMS**

occupational health; coronary heart disease; epidemiology; population based; effect modification; interaction; mediation; prospective study; relative aerobic workload; energy expenditure; physical activity
MAIN TEXT

INTRODUCTION

Sedentary lifestyle, or physical inactivity, is an established risk factor for cardiovascular disease (1–3). Accordingly, physical activity both at work and during leisure time have been recommended (4). While leisure-time physical activity (LTPA) has been well documented to promote health (5,6), the effect of occupational physical activity (OPA) is inconsistent (7). Without adjustment for LTPA, higher levels of OPA were reported to be protective against CVD in some studies (8,9), have no effect (10,11), or increase the CVD risk (12,13). When adjusting for LTPA, some studies showed that greater OPA is associated with progression of carotid atherosclerosis (14), and increased AMI incidence (15) or risk of IHD mortality (16).

One explanation for such inconsistencies could be that the effects of OPA depend on the level of LTPA (17,18) and possibly individual aerobic fitness (14,19). If interaction between OPA and LTPA exists, a model ignoring such interaction could, in some scenarios, result in cancellation of the effect of one variable across levels of another and yield a misleading average estimate of no effect. Another explanation could be that high and exhausting levels of OPA preclude workers from engaging in LTPA (20); thus, these workers cannot benefit from LTPA. Finally, OPA could directly affect CVD (21). Based on the negative correlation between OPA and LTPA observed in previous work (14) and
previous observations that LTPA participation was relatively low among blue-collar workers (22), we hypothesized that LTPA would both interact with OPA and mediate the effect of OPA on CVD. Therefore, following up on our previous work examining the relation between OPA and cardiovascular outcomes (14,23), we further assessed the modifying and mediating roles of LTPA on the pathway from OPA to 20-year incidence of AMI. We also explored the impact of LTPA on AMI at different levels of OPA. We conducted separate analyses for men with and without preexisting ischemic heart disease (IHD), as past studies suggested a heterogeneous OPA effect by IHD status (15).

More specifically, and separately for men with and without preexisting IHD at baseline, our study aimed to: (i) assess both multiplicative and additive interaction between OPA and LTPA, and their combined effect on 20-year incidence of AMI, and (ii) examine the potential mediating role of LTPA on the pathway from OPA to AMI, using causal mediation analysis that allowed for exposure-mediator interaction (24,25).

**METHODS**

**Study design, setting and population**

Participants were from the prospective Kuopio Ischemic Heart Disease Risk Factor (KIHD) Study, an age-stratified, random, population-based sample of Eastern Finnish men, residing in the city of Kuopio or its surrounding rural communities. Details of the study population are available elsewhere (15,26). Out of 3235 eligible men aged 42, 48,
54, or 60 years at baseline, 2682 (82.9%) men agreed to participate, with 553 men being excluded due to refusal (N=367) and no contact (N=186). All participants underwent baseline examinations and interviews between March 1984 and December 1989 and were passively followed by national hospitalization discharge and death registries until 2011. We excluded 791 participants who were not working at baseline or in the 12 months prior, resulting in a final study sample of 1891 participants with complete information on all the baseline covariates for the main analyses. All participants provided written informed consent. The University of Eastern Finland (former University of Kuopio) Research Ethics Committee, and the University of California, Los Angeles (UCLA) Institutional Review Board approved this study.

**Assessment of incidence of acute myocardial infarction**

As described previously (15), we ascertained first-time incident AMI (ICD-9 code 410) during follow-up via record linkage with national hospital discharge and death registries including the national AMI register established under the World Health Organizations “Monitoring of Trends and Determinants of Cardiovascular Diseases (MONICA)” project (27,28). A university-based cardiologist for this study confirmed hospital discharge diagnoses using other hospital records, lab results, and electrocardiograms. We censored the follow-up at December 31, 2011, or date of death whichever came first.

**Assessment of occupational physical activity**
We measured OPA as relative aerobic strain (RAS), the most predictive measurement for AMI among other OPA measures examined in the same study population (23). RAS (or relative aerobic workload) expresses the caloric demands of work as a percentage of the individual worker’s aerobic cardiorespiratory fitness or maximal work capacity (%VO$_{2\text{max}}$) (29). RAS takes into account both the absolute energy expenditure (EE) and the workers’ individual aerobic capacity. Detailed descriptions of the assessment of these variables can be found elsewhere (23,29). Based on work physiology and ergonomic principles, it is often the misfit between high job-related energy demands and low worker aerobic capacity, rather than a high absolute amount of EE alone, that will lead to elevated blood pressure and heart rate, two established risk factors for AMI (23,30). Also, OPA has been shown to be detrimental to workers with low cardiorespiratory fitness but not to those with high fitness level (31). Thus, we decided to use RAS as our OPA exposure measure in the main analyses.

Absolute EE at work (in kcal/day) was assessed from baseline interview data on time spent in various activities at work during a typical workday and reference data on the energy requirements (kcal/kg/hour) of these activities. EE in kcal for each reported activity was calculated by multiplying the duration (hours per day) by the respective intensity (MET) and body weight (kg) for each individual. EE per typical workday was the sum of EE for all activities.
Cardiorespiratory fitness (also known as aerobic capacity or VO$_2$max) was measured with a maximal, symptom-limited exercise-tolerance test on a bicycle ergometer as explained in detail elsewhere (32–34). VO$_2$max, in ml O$_2$ per kg per minute, was defined as the highest value or plateau in oxygen uptake during maximal symptom-limited bicycle ergometer and was standardized by body weight.

To avoid confusion in terminology, we used RAS or absolute EE when describing results from specific analyses or studies and used OPA as a general term for the entire occupational physical activity domain to facilitate discussion.

**Assessment of leisure-time physical activity**

LTPA was measured using the KIHD 12-Month Leisure-Time Physical Activity History, a modified version of the Minnesota Leisure Time Physical Activity questionnaire (35), that included the 16 most common leisure time physical activities of middle-aged Finnish men (34,36). Respondents were asked to record the frequency, duration, and intensity of each of 16 activities performed for each of the 12 previous months. Conditioning (vigorous-intensity) LTPA included walking, jogging, cross-country skiing, bicycling, swimming, rowing, ball games, gymnastics, dancing, or weightlifting. We calculated the sum of these activities and obtained the average conditioning LTPA, expressed in minutes per week, in the previous year. Unless otherwise noted, we used LTPA to represent conditioning LTPA throughout the article.
Assessment of covariates

We included as confounders age, education, participation in an unrelated lipid-lowering drug trial (placebo group, treatment group, versus none), and baseline IHD. Education was categorized into: (i) some elementary school, (ii) elementary school completed, or elementary school plus some junior high school, (iii) junior high school completed, or junior high school plus some senior high school, and (iv) senior high school completed or beyond. A continuous smoking variable “pack-years” was calculated as the number of packs (20 cigarettes/pack) per day times the number of years smoked. Alcohol consumption (grams per week) accounted for the frequency of drinking and amount of drinks per occasion for each type of alcoholic beverage (beer, wine, spirits) for the last 12 months. Psychosocial job factors were measured using questionnaires that captured mental strain at work (11 items of psychological demands), social support at work (3 items), and stress from work deadlines. These factors have been associated with progression of atherosclerosis and an increased risk for myocardial infarction and mortality in this study population and showed satisfactory Cronbach’s α coefficients (37,38). We classified participants as having preexisting IHD at baseline if they (i) had a history of prior (before baseline) myocardial infarction or angina pectoris, (ii) currently used anti-angina medication, or (iii) had positive findings of angina according to the London School of Hygiene cardiovascular questionnaire (39).
Statistical analysis

We summarized the participants’ characteristics by their baseline IHD status.

Interaction analysis

We used Cox proportional hazard models (40) with adjustment for covariates listed in Table 1. We added an OPA × LTPA product term to assess the interaction between OPA and LTPA on the multiplicative scale. We also calculated the relative excess risk for interaction (RERI) as a measure of additive interaction (41): \( HR_{11} - HR_{10} - HR_{01} + 1 \), where \( HR_{11} \), \( HR_{10} \), and \( HR_{01} \) respectively represented the joint effect of OPA and LTPA, the main effect of OPA, and the main effect of LTPA. A positive value for RERI (i.e. > 0) would indicate that the combined effect of OPA and LTPA is greater than the sum of their separate effects assuming monotonic effects of both exposures (42). Variables were recoded jointly when necessary so that the reference combined category represented the lowest risk group (43). OPA was modeled as a binary indicator (RAS > 33% as high versus RAS ≤ 33% as low), based on the maximum level of 33% VO\(_{2}\)\(_{\text{max}}\) recommended for 8 hours of work (29,44). Similarly, LTPA was modeled as a binary indicator (LTPA≥ 75 minutes/week as high versus LTPA < 75 minutes/week as low) based on WHO global recommendations (45). We also performed the analyses using low OPA and high LTPA as the reference category for binary physical activity measures and compared different combinations of OPA and LTPA relative to this reference group as done in the existing literature. We reported the hazard ratio (HR) for AMI associated with a 1-unit increase in
OPA and its corresponding 95% confidence interval (CI) at different levels of LTPA and vice versa.

**Mediation analysis**

We assumed that baseline OPA level determined the baseline LTPA level based on the negative correlation observed between OPA and LTPA in the same cohort (14) and past literature (20,22), and that first-time incidence of AMI occurring during follow-up can be attributed to the OPA and LTPA levels measured at baseline. We invoked the stable unit treatment value assumption (SUTVA) (46), and assumptions of consistency, positivity, conditional exchangeability (no-uncontrolled-confounding) (47,48), and no selection bias and measurement error. Further discussions of these assumptions can be found elsewhere (49). We used recently proposed inverse-probability weighted (IPW) fitting of marginal structural models (MSMs) for causal mediation analysis (24) to estimate the marginal pure direct effect (PDE) of baseline OPA on AMI and the marginal total indirect effect (TIE) of baseline OPA via baseline LTPA (Figure 1). PDE was defined as the hazard ratio comparing high to low OPA levels while allowing LTPA to attain the natural value under the low OPA level. TIE was defined as the hazard ratio comparing two LTPA levels – the natural LTPA level under high OPA versus the natural LTPA level under low OPA – while setting OPA level to be high. Methodological details are in the appendix.

**Sensitivity analysis**
We conducted the following sensitivity analyses to check the robustness of our results for assessing interaction between OPA and LTPA. First, we repeated our analyses using both continuous and trichotomized measures for OPA and LTPA. Details of these measures are in the appendix. Second, we repeated our main analyses with additional adjustment for biological factors including blood glucose, plasma fibrinogen, body mass index, LDL-cholesterol, HDL-cholesterol, systolic blood pressure, lipid-lowering medication, and anti-hypertensive medication. Third, we used continuous absolute EE (500 kcal increase), centered at the population mean of 2111 kcal/day, as an alternative measure of OPA to assess the interaction between OPA and LTPA.

For assessing the mediating role of LTPA, we additionally included 4-year LTPA as a second mediator and examined the effect of OPA via pathways involving baseline LTPA, or 4-year LTPA, or neither. We further restricted our analytical sample to 455 men without baseline IHD and who had complete information on all variables. Detailed sample restriction criteria, methodology, effect definition, and implementation steps can be found elsewhere (25) and in the appendix.

All analyses were performed using Stata version 14 (StataCorp LP, College Station, Texas).
RESULTS

Characteristics of the study sample

The distribution of exposure variables and covariates by preexisting IHD status is listed in Table 1. Participants’ mean age at baseline was 51.5 years [standard deviation (SD): 5.0] for participants without IHD and 53.5 (SD: 3.9) for those with IHD. Over 70% of the participants completed elementary school but not junior high school. Participants with IHD had higher levels of RAS, absolute EE, and mental strain at work, smoked and drank more, and experienced more stress from work deadlines, and had a lower level of fitness than men without IHD. LTPA and social support at work were similar in these two subgroups.

Incidence of AMI

During an average of 19.56 years of follow-up (SD: 7.53; range: 0.01–27.76) and a total person-time of 36991 years, 495 first-time (after baseline) incident AMI occurred among 1891 study participants, yielding a yearly incidence rate of 1.34%. Among 1565 men without baseline IHD, 353 AMI occurred (yearly incidence 1.11%) whereas among 326 men with baseline IHD, 142 AMI occurred (yearly incidence 2.60%).

Interaction between binary OPA and binary LTPA in affecting AMI

Table 2 displays the associations between one PA domain and AMI at different levels of the other PA domain by preexisting IHD status and the joint association of both OPA and
LTPA with AMI, using the combination of low OPA and high LTPA as the reference.

For men without IHD, high OPA (RAS>33%) was only positively associated with AMI incidence among men with low LTPA and with age adjustment (HR: 1.34, 95% CI: 1.01–1.76) but this association attenuated after adjusting for other factors (HR: 1.27, 95% CI: 0.96–1.68). For men with IHD, high OPA positively predicted AMI at low LTPA (HR: 1.59, 95% CI: 0.99–2.57) but not at high LTPA (HR: 1.04, 95% CI: 0.61–1.79). For both IHD subgroups, high LTPA was weakly negatively associated with AMI at high but not at low OPA level. Compared to men with low OPA and high LTPA, men with high OPA and low LTPA had the highest risk for AMI, irrespective of IHD status (HR: 1.33, 95% CI: 0.99–1.78 for men without IHD; HR: 1.36, 95% CI: 0.84–2.18 for men with IHD).

Multiplicative interaction between OPA and LTPA was observed among men with IHD (ratio of HR: 0.65, \(P=0.240\)) but no additive interaction was observed for both subgroups.

Results from sensitivity analysis using continuous physical activity measures are presented in appendix Table A1. For men without IHD, higher OPA level—a 20% increase in RAS from a reference level of 23.5%—positively predicted AMI incidence at both LTPA of 0 minutes/week (HR: 1.45, 95% CI: 1.19–1.75) and at LTPA of 75 minutes/week (HR: 1.49, 95% CI: 1.28–1.75). Weaker but still substantial positive associations between OPA and AMI were found among men with IHD (HR: 1.25, 95% CI: 0.96–1.64 at LTPA of 0 minutes/week; HR: 1.32, 95% CI: 1.07–1.62 at LTPA of 75 minutes/week). We found no association between LTPA and AMI across levels of OPA.
and no multiplicative interaction between continuous OPA and LTPA. Detailed
descriptions for results from sensitivity analyses that (i) used trichotomized PA measures,
(ii) additionally adjusted for biological factors, and (iii) used absolute EE as OPA
measure are presented in the appendix (Tables A2a – A4).

The mediating role of LTPA on the pathway from OPA to AMI

Table 3 depicts the pure direct effect (PDE) of OPA on AMI and the total indirect effect
via baseline LTPA, estimated using IPW fitting of MSMs. We observed similar effect
estimates from all methods that differed only in the way confounding was handled. For
men without IHD, the estimate for total effect (TE) of OPA on AMI was 1.31 (95% CI:
0.99–1.79) when marginalizing over all covariates and LTPA. The majority of the
positive association of OPA with AMI was attributable to pathways other than through
LTPA (PDE: 1.27, 95% CI: 0.93–1.74). The effect estimates for men with IHD were
similar to that among men without IHD.

Table A5 in the appendix depicts results from sensitivity analysis that used also LTPA
measured at 4-year follow-up and further decomposed the total effect into baseline LTPA
pathway-specific effect, 4-year LTPA pathway-specific effect, and natural direct effect
that is through neither baseline nor 4-year LTPA. In this restricted sample of men without
IHD, OPA was not associated with AMI overall (TE: 1.08, 95% CI: 0.58–2.02). Weak
positive natural direct effect (NDE: 1.22, 95% CI: 0.57–2.46) and weak negative indirect
effect via baseline LTPA (NIE\textsubscript{baseline}: 0.93, 95% CI: 0.69–1.21) were observed. Follow-up LTPA at 4 years did not mediate the effect of baseline OPA on AMI (NIE\textsubscript{4-year}: 0.96, 95% CI: 0.79–1.05).

DISCUSSION

This 20-year follow-up study examined the interaction between OPA and LTPA in affecting AMI incidence and whether LTPA mediated the effect of OPA on AMI among men with and without preexisting IHD. We found that high levels of OPA positively predicted AMI at low LTPA levels for both IHD subgroups. LTPA was not predictive of AMI after accounting for OPA in most combinations, although sensitivity analysis indicated that the effect of LTPA may be non-linear across levels of OPA and by IHD status. We found multiplicative but not additive interactions between OPA and LTPA among men with IHD. LTPA did not appear to mediate the effect of OPA on AMI.

Effects of OPA on AMI, accounting for LTPA

Our finding of the positive link between OPA and AMI, regardless of categorical or continuous physical activity measures being used, is in line with a previous study on OPA and AMI from the same cohort, despite slightly different covariate adjustment (14). Our study confirmed the previous finding that conditional on LTPA, a relative OPA measure (RAS) that accounts for individual cardiorespiratory fitness was more predictive of AMI than an absolute OPA measure (EE) (14,23). This finding is robust against the choice of
OPA measure and modeling schemes. It is consistent with an overall harmful effect of OPA on coronary heart disease (CHD) as recently synthesized based on five prospective cohort studies published in 2011, 2012, and the first quarter of 2013 (21) but not with two other prospective observational studies published earlier that suggest a protective effect (50) or no effect (51). All seven studies investigated the impact of OPA on health outcomes while simultaneously accounting for LTPA: one found a positive association with IHD mortality (16); one found a positive association with CHD incidence only among men with high LTPA levels but not among men with low LTPA levels (17); three found no associations with myocardial infarction (52) or CHD incidence (51,53); and two found negative associations with IHD incidence when additionally accounting for occupational heavy lifting (54), or with CHD incidence when additionally accounting for commuting physical activity (9). Adjusted for LTPA, one recent study reported elevated risk for CHD mortality (55). Additionally accounting for physical fitness, Holtermann and colleagues (56) found an increased risk of IHD mortality associated with high OPA in the least and moderately fit group, but not among the most fit men. Similarly, Clays et al. (19) reported a positive association between high OPA and mortality, and that association was particularly pronounced among workers with low physical fitness. Our study examined OPA effects with a commonly used absolute energy expenditure measure but also the preferred measure of relative aerobic strain (RAS) at work that took into account individual cardiorespiratory fitness, which, we believe, is crucial in studies examining the effect of different physical activity domains on cardiovascular health as
demonstrated in this paper and our previous report (14). The use of continuous versus broad categorical physical activity measures, difference in definition and categorization of these measures, and different study endpoints can also be reasons for the inconsistent findings in the current study as well as in the literature (15).

**Effects of LTPA, accounting for OPA**

Based on our analyses using dichotomized or continuous measures for physical activity, our study did not confirm the accumulated evidence on and the long-held belief in the cardio-protective effect of LTPA, at least not among working middle-aged men (21,57). Based on our sensitivity analysis of trichotomized physical activity measures, mixed results were found for the impact of high levels of LTPA: it appeared to decrease AMI risk for men at low OPA and with IHD, increase AMI risk for men at moderate OPA (regardless of IHD status, and up to 2.58-fold, 95% CI 1.03–6.45 among men with IHD), or have no effect on AMI at high OPA level. In fact, the evidence from the few previous studies that account for OPA is not consistent either: for workers with high OPA, high LTPA was found to be preventive in some studies (16,52) but harmful in others (17). A recent cluster randomized controlled trial also reported opposing health impacts of a 4-month aerobic exercise intervention among Danish cleaners. While the intervention increased cardiorespiratory fitness, lowered resting and sleeping heart rate, reduced inflammation markers, and reduced relative workload (measured as percent heart rate reserve which is equivalent to RAS), it also significantly increased systolic blood
pressure (58). These mixed findings cast doubt on whether the international physical activity recommendation for the public at large (45) is similarly applicable to working populations with high physical job demands or with preexisting CVD.

**Biological plausibility: OPA and LTPA elicit different physiological responses**

OPA and LTPA have different inherent characteristics. Mandatory OPA often has high frequency and long duration, involves activities such as heavy lifting, bending, pushing and pulling, monotonous and static postures with limited ability for pauses and restitution, and may not allow for adequate rest periods (15,59). Such long-term high cardiovascular workloads can cause atherosclerosis via a prolonged elevated heart rate that leads to increased intravascular turbulence, unfavorable wall shear stress, endothelial injury (60–63), and in turn inflammatory processes in the arterial walls (14), according to the hemodynamic-inflammatory theory of atherosclerosis (63). Another proposed physiological mechanism involves high OPA-induced elevation in systolic blood pressure over the day (during work, at home, and during sleep) (64), which is a strong predictor for cardiovascular events (65). In contrast, voluntary LTPA is usually of shorter duration compared to OPA, involves more dynamic movements, and is characterized by sufficient variation and time for restitution (59). Thus, people engaging in LTPA can achieve a training effect on the heart by performing relatively few and short but intensive bursts of momentarily exhausting conditioning physical activity in leisure (7). However, such activities are typically not performed during long hours of physically demanding work.
nor—due to exhaustion—after work. A recent study among Danish cleaners found that they spent most of their work being on their feet and on average worked 28% of the time, exceeding recommended maximum levels of RAS during work (>30%) that will lead to excessive exhaustion, but virtually never reached levels of RAS (>60%) that would confer any training benefit during or after work. After work, these cleaners spent most of their time sitting or lying down in order to recuperate from their exhausting work (20).

**Combined effects of OPA and LTPA**

When assessing the combined effect of both OPA and LTPA, we found men with high OPA and low LTPA had the highest risk for AMI. This is in line with the above theory on the different health impact of OPA versus LTPA, and the Belgian Physical Fitness Study (19). However, using similar cutoff points to divide low versus moderate or high LTPA for men without preexisting IHD, our result did not support the finding by another Belgian study that showed an almost four times increased incidence of coronary events comparing men with high OPA and high LTPA to men with low OPA and high LTPA (17). Instead, we found that men with high OPA and low LTPA had the highest risk for AMI (HR: 1.36, 95% CI: 0.98–1.89), which is consistent with our main result. A recent study in Israel found that employees who performed moderate-hard OPA (self-reported) and no LTPA had the greatest risk for all-cause mortality (55). The combination of low OPA and low LTPA, averaging over levels of commuting physical activity, was associated with the highest risk for heart failure among Finnish men (66). Given these
mixed findings in the literature, the question of whether workers with high OPA would benefit from being highly physically active during leisure time (59), remains open. Aside from this uncertainty, the need for rest of workers in physically demanding work may prevent them from engaging in such LTPA regardless. In fact, our study showed that high OPA (RAS) at baseline predicted lower LTPA during 4-year follow-up (adjusted OR: 0.56, 95% CI: 0.44–0.70 among men without IHD; adjusted OR: 0.51, 95% CI: 0.32–0.83 among men with IHD). Therefore, it may be necessary, instead, to lower physical work demands for these workers, allow for longer rest periods, or redesign work tasks so that exhausting effects are minimized and some training effects included.

**Lessons learned from sensitivity analyses and implications for future studies**

By comparing results from main and sensitivity analyses, we found patterns of the effects of physical activity domains on AMI that may be worth considering in future studies.

First, the impact of OPA on AMI within a specific level of LTPA appeared non-linear. Based on our analysis using continuous physical activity measures, quadratic terms for OPA measures may not capture such non-linearity (results not shown). Second, how OPA is related to AMI (i.e. the shape of the relation) may differ across different levels of LTPA. These two points also apply to the relation between LTPA and AMI by levels of OPA. Third, results from analyses that use dichotomized physical activity measures may also depend on the cut-off points chosen for the categorization. To further complicate matters, the pattern seems to differ by preexisting IHD status as well.
Impact of OPA and LTPA among workers with preexisting CVD

Few studies examined the interplay between OPA, LTPA, and fitness on cardiovascular outcomes among workers with preexisting CVD. One study among Copenhagen men with preexisting CVD (67) found no association between moderate or high OPA and IHD mortality and a positive but uncertain association between high OPA and all-cause mortality. We observed a greater impact of OPA (RAS) on AMI at low compared to high LTPA levels among men with IHD. Importantly, both studies failed to find negative associations between LTPA and cardiovascular outcomes. Compared to their counterparts free of IHD at baseline, these men had higher OPA levels (in terms of both absolute energy expenditure and relative aerobic strain) but lower levels of cardiorespiratory fitness. They may be more likely to experience an overloading associated with job-related heavy and especially static work on their cardiovascular system (68) and thus experienced a more detrimental health impact of high OPA than men without preexisting CVD as well as no benefit from LTPA. The uncertainty of the positive association between OPA and AMI could be attributed to the small sample size. However, we cannot rule out the possibility that these employees who remained working, despite their preexisting conditions, were also a selected, relatively healthy group, biasing results towards no association.

Effects of OPA on AMI, mediated by LTPA
Despite the fact that high OPA (RAS) negatively predicted high LTPA at baseline in our sample (adjusted OR: 0.56, 95% CI: 0.44–0.70 among men without IHD; adjusted OR: 0.51, 95% CI: 0.32–0.83 among men with IHD), our hypothesized mediating pathway from OPA to AMI via LTPA was not supported. This is probably due to the absence of an independent effect of LTPA on AMI after accounting for OPA and OPA-LTPA interaction.

In the current study, socioeconomic status as captured by education, cumulative measures for smoking and alcohol consumption, and psychosocial job factors are considered potential confounders and were adjusted for but biological factors were not. Different from physical activity measures that can be considered rather stable behaviors and are reflective of their activity levels for the past year or even a longer period of time before baseline interview, highly variable biological measures such as blood pressure and blood glucose assessed during baseline examination need to be considered mostly reflective of this moment in time and may have been influenced by past LTPA behavior. Therefore, biological factors were conceptualized as mediating variables on the pathways from OPA or LTPA to AMI and not adjusted for in the main analyses. Supplemental analysis with additional adjustment for these factors showed that the positive OPA-AMI association at low LTPA attenuated, suggesting indeed possible mediation by these factors. However, among men with IHD, the positive OPA-AMI associations persisted, despite the widened
confidence intervals. Future studies can examine the possible mediating role of both LTPA and these biological factors (69,70).

**Strengths and limitations**

The main strengths of our study include the prospective design, the representative sample of the population in Kuopio, long and complete register-based follow-up, and adequate covariate adjustment. Also, the use of a validated detailed occupational interview combined with objective measures of cardiorespiratory fitness in our main exposure variable (RAS) produced a better assessment of OPA compared to broad OPA categories or absolute EE obtained from most population-based surveys used in previous cohort studies. The assessment of LTPA accounted for the seasonal variability of LTPA among Finnish men by averaging LTPA over a 12-month period. Different analytic strategies were implemented to disentangle the impact of OPA and LTPA on AMI. The strategies included: accounting for cardiorespiratory fitness, using a priori cutoff-points based on recommended and established guidelines for OPA and LTPA, and conducting several sensitivity analyses including different modeling schemes and measures of physical activity domains. Finally, this is, to our best knowledge, the first study that used causal mediation analysis to examine the possible mediating pathway from OPA to AMI via LTPA.
Several limitations need to be addressed. Misclassification of OPA may be possible due to self-reporting rather than direct observations on type and duration of work activities and because energy expenditure assessment did not include upper extremity work or the handling of external loads. EE also did not account for the amount of static work and ambient temperature, leading to a possibly conservative measure of the actual amount of energy expended at work (14). Also, due to the lack of repeated cardiorespiratory fitness assessment at 4 years, we cannot compute a repeated RAS measure and further examine the change in RAS over time, leading to possible exposure misclassification. However, examination of repeated measures for absolute EE in this cohort revealed a relatively high correlation between baseline and 4-year absolute EE (correlation coefficient: 0.77). Due to the lack of 4-year RAS, our mediation analysis for estimating the path-specific effect of OPA on AMI via 4-year LTPA could be subject to uncontrolled exposure (OPA) induced mediator-outcome (LTPA–AMI) confounding. Future work will involve conducting sensitivity analysis to check these results against the presence of such uncontrolled OPA-induced LTPA-to-AMI confounding that can introduce collider-stratification bias in the target OPA-to-AMI relation (25,49).

Conclusion

Our study contributes to clarifying the unsettled complex roles of OPA, LTPA, and hence fitness in predicting AMI with and without preexisting conditions. We found that the impact of one physical activity domain on AMI depended on the level of the other
physical activity domain on the multiplicative scale but not the additive scale, when accounting for individual fitness. Our hypothesized mediating pathway from OPA to AMI via LTPA was not supported due to the absence of an independent effect of LTPA on AMI after accounting for OPA and OPA-LTPA interaction. Our results reaffirmed the need to develop physical activity recommendations that distinguish between OPA and LTPA (71), and take into account individual worker health status, aerobic fitness, and physical demands of the job when designing strategies for CVD prevention for working populations (15).
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### Table 1: Characteristics of the study sample and distribution of exposure and covariates by preexisting ischemic heart disease (IHD) status, Kuopio Ischemic Heart Disease Risk Factor Study, 1984-2011 (N=1891).

|                                      | Men without IHD (N = 1565) | Men with IHD (N = 326) |
|-------------------------------------|-----------------------------|------------------------|
|                                      | Mean | SD  | N  | %  | Mean | SD  | N  | %  |
| **Occupational physical activity (OPA)** |      |     |    |    |      |     |    |    |
| Relative aerobic strain (%)          | 29.7 | 12.1 | 38.5 | 16.4 |
| Binary relative aerobic strain (>33%) |      |     | 490 | 31.3 |      |     | 179 | 54.9 |
| Absolute energy expenditure (kcal/day) | 2078 | 875 | 2272 | 970 |
| **Leisure-time physical activity (LTPA)** |      |     |    |    |      |     |    |    |
| Conditioning LTPA (minutes/week)     | 105  | 117 | 109 | 145 |
| Binary conditioning LTPA (≥75 minutes/week) | 742  | 47.4 | 143 | 43.9 |
| **Cardiorespiratory fitness (VO\(_2\)max, O\(_2\)/kg/minute)** | 32.8 | 7.0  | 27.5 | 6.9  |
| **Covariates**                       |      |     |    |    |      |     |    |    |
| Age at baseline (years)              | 51.5 | 5.1  | 53.5 | 3.9  |
| Age group                            |      |     |    |    |      |     |    |    |
| 42 years old                         | 292  | 18.7 | 17  | 5.2  |
| 48 years old                         | 274  | 17.5 | 47  | 14.4 |
| 54 years old                         | 916  | 58.5 | 233 | 71.5 |
| 60 years old                         | 83   | 5.3  | 29  | 8.9  |
| Participation in lipid-lowering drug trial |      |     |    |    |      |     |    |    |
| Placebo group                        | 135  | 8.6  | 28  | 8.6  |
| Treatment group                      | 136  | 8.7  | 27  | 8.3  |
| Education                            |      |     |    |    |      |     |    |    |
| Some elementary school               | 113  | 7.2  | 41  | 12.6 |
| Elementary school completed/some junior high school | 1144 | 73.1 | 251 | 77.0 |
| Junior high school completed/ some senior high school | 150  | 9.6  | 28  | 8.6  |
| Senior high school completed or beyond | 158  | 10.1 | 6   | 1.8  |
| Behavioral factors                   |      |     |    |    |      |     |    |    |
| Smoking (pack-years)                 | 7.1  | 14.5 | 10.5 | 17.4 |
| Alcohol consumption (g/week)         | 71.5 | 111.8| 88.3 | 196.4|
Psychosocial job factors

|                                          | a          | b          |
|-----------------------------------------|------------|------------|
| Mental strain at work index*a           | 11.5       | 6.3        |
| Social support at work score*b          | 6.5        | 2.5        |
| Stress from work deadlines              | 357        | 22.8       |

|                                          | a          | b          |
|-----------------------------------------|------------|------------|
|                                          | 13.4       | 7.1        |
|                                          | 6.5        | 2.4        |
|                                          | 105        | 32.2       |

*a Higher score means experiencing more mental strain.

*b Higher score means less social support.
Table 2 Hazard ratios (HR) and 95% confidence intervals (95% CI) for the main effect and joint effect of occupational physical activity (OPA) and leisure-time physical activity (LTPA) on 20-year incidence of acute myocardial infarction (N=495) when both domains of physical activity were modeled as binary variables,\textsuperscript{a} by preexisting ischemic heart disease (IHD) status, Kuopio Ischemic Heart Disease Risk Factor Study, 1984–2011 (N=1891).

| LTPA level | OPA level | N   | Age-adjusted | Fully-adjusted\textsuperscript{b} | N   | Age-adjusted | Fully-adjusted\textsuperscript{b} |
|------------|-----------|-----|--------------|-------------------------------|-----|--------------|-------------------------------|
|            |           |     | HR           | 95% CI                        |     | HR           | 95% CI                        |
| Low        | Low       | 571 | Reference    | Reference                     | 80  | Reference    | Reference                     |
| High       | Low       | 171 | 1.20         | 0.83–1.74                     | 63  | 0.97         | 0.58–1.63                     |
|            | High      | 504 | 1.17         | 0.90–1.52                     | 67  | 0.84         | 0.50–1.42                     |
| High       | Low       | 319 | 1.57         | 1.19–2.07                     | 116 | 1.28         | 0.83–1.99                     |

\textit{P} for multiplicative interaction\textsuperscript{c} 0.649 0.543 0.205 0.240

| Combinations of OPA and LTPA, using the lowest risk group as reference |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Low OPA and high LTPA           | 0.19            | -0.37–0.75      | 0.18            | -0.32–0.69      |
| High OPA and high LTPA          |                  |                 |                 |                 |
| Low OPA and low LTPA            |                  |                 |                 |                 |
| High OPA and low LTPA           |                  |                 |                 |                 |

\textsuperscript{a}Low OPA: relative aerobic strain (RAS)≤33%; high OPA: RAS>33%; low LTPA: <75 minutes/week; high LTPA: ≥75 minutes/week.

\textsuperscript{b}Model adjusted for age, education, participation in an unrelated clinical trial, smoking, alcohol consumption, mental strain at work, social support at work, and stress from work deadlines.

\textsuperscript{c}P value for the OPA × LTPA product term.

\textsuperscript{d}RERIs were measures for additive interaction. For men without IHD, RERIs were calculated as HR\textsubscript{high OPA, low LTPA} − HR\textsubscript{high OPA, high LTPA} − HR\textsubscript{low OPA, low LTPA} + 1. For men with IHD, RERIs were calculated as HR\textsubscript{high OPA, high LTPA} − HR\textsubscript{high OPA, low LTPA} − HR\textsubscript{low OPA, high LTPA} + 1, using low OPA and low LTPA as the reference group.
### Table 3

Hazard ratios (HR) and 95% confidence intervals (95% CI) for the pure direct effect (PDE) and total indirect effect (TIE) of occupational physical activity as measured by binary relative aerobic strain (with leisure-time physical activity as mediator) on 20-year incidence of acute myocardial infarction (N=495) for all men, stratified by preexisting ischemic heart disease (IHD) status, and estimated using inverse-probability weighted (IPW) fitting of marginal structural models (MSMs)\(^a\), in the Kuopio Ischemic Heart Disease Risk Factor Study, 1984-2011 (N=1891).

| Method                      | Men without IHD (N=1565) | Men with IHD (N=326) |
|-----------------------------|--------------------------|----------------------|
|                             | HR\(^b\) | 95% CI       | HR\(^b\) | 95% CI       |
| MSM\(^c\)                   |           |              |           |              |
| PDE                         | 1.27     | 0.93–1.74   | 1.28     | 0.88–1.90   |
| TIE                         | 1.04     | 0.88–1.22   | 1.04     | 0.88–1.27   |
| Total effect                | 1.31     | 0.99–1.79   | 1.33     | 0.97–1.85   |
| **Conditional MSM\(^d\)**  |           |              |           |              |
| PDE                         | 1.20     | 0.96–1.55   | 1.28     | 0.87–1.93   |
| TIE                         | 1.02     | 0.90–1.15   | 1.05     | 0.90–1.24   |
| Total effect                | 1.22     | 1.02–1.54   | 1.35     | 0.96–1.91   |
| **Doubly robust MSM\(^e\)**|           |              |           |              |
| PDE                         | 1.23     | 0.93–1.67   | 1.30     | 0.88–1.95   |
| TIE                         | 1.04     | 0.90–1.21   | 1.04     | 0.89–1.24   |
| Total effect                | 1.28     | 0.98–1.70   | 1.34     | 0.97–1.92   |
| **Conditional total effect\(^f\)** | 1.22 | 0.97–1.53 | 1.34 | 0.94–1.91 |

---

\(^a\) Occupational physical activity was measured by binary relative aerobic strain (RAS) indicator (RAS > 33% versus RAS ≤ 33%) and leisure-time physical activity was dichotomized (≥ 75 minutes/week versus < 75 minutes/week). Covariates included age, education, participation in an unrelated clinical trial, smoking, alcohol consumption, mental strain at work, social support at work, and stress from work deadlines.

\(^b\) Bias-corrected and accelerated 95% confidence intervals (CIs) were obtained using 1000 bootstrap samples.

\(^c\) IPW was created based on a weight for OPA (dealing with confounding) and a weight for LTPA (decomposing effect).

\(^d\) IPW was created based on a weight for LTPA (decomposing effect) only. Conditional MSM included covariates to control for confounding.

\(^e\) IPW was created based on a weight for OPA (dealing with confounding) and a weight for LTPA (decomposing effect). In the final MSM, covariates were adjusted for.

\(^f\) Cox proportional hazard model included OPA, age, education, participation in an unrelated clinical trial, smoking, alcohol consumption, mental strain at work, social support at work, and stress from work deadlines.
**FIGURES**

![Graphical presentation](image)

**Figure 1** Graphical presentation (solid black lines) of pure direct effect (a) and total indirect effect (b) of occupational physical activity (OPA) on acute myocardial infarction (AMI), with mediator leisure-time physical activity (LTPA).
Appendix

Title: Does Leisure Time Physical Activity Interact with and Mediate the Effect of Occupational Physical Activity on 20-Year Incidence of Acute Myocardial Infarction?

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1. **Description of sensitivity analyses using alternative modeling schemes for OPA (RAS) and LTPA**

We further modeled OPA (RAS) as continuous variable (1 unit representing a 20% increase in RAS) centered at a level of 23.5% and LTPA as continuous variable (1 unit representing a 75 minutes/week increase). A quadratic term for the continuous RAS measure was not significant at \( P=0.1 \) level and did not improve model fit. Thus, the hazard function was modeled in a linear form for this measure. Table A1 presents the results from this sensitivity analysis.

Additionally, we modeled OPA as trichotomized variable (low: RAS\( \leq \)23%, moderate: \(23%<\text{RAS}<33\%\), high: \( \text{RAS}>33\%\)) and LTPA as trichotomized variable (low: LTPA<20 minutes/week, moderate: 20 minutes/week \( \leq \)LTPA<75 minutes/week, high: LTPA\( \geq \)75 minutes/week). Table A2a and A2b present the results from this sensitivity analysis.

2. **Description of inverse-probability weighted (IPW) fitting of marginal structural models (MSM) for causal mediation analysis applied in the main analysis**

Let \( X_0, M_0, \) and \( Z \) denote baseline OPA, baseline LTPA, and the set of covariates sufficient for confounding control. For binary OPA and LTPA, the steps are as follows. First, we created two copies of the original data set and included an additional variable \( X_0^* \). \( X_0^* \) was set to the actual value of OPA (i.e., \( X_0^* = X_0 \)) for the first copy and was set to the opposite of the actual value of OPA (i.e., \( X_0^* = 1 - X_0 \)). Then, in order to achieve both confounding control and effect decomposition, two sets of weights were computed: \( W_{X_0} \) and \( W_{M_0} \). We modeled baseline OPA as a function of covariates and modeled baseline LTPA as a function of baseline OPA and covariates. The weight for each individual was calculated as:
\[ W = W_{X_0} \cdot W_{M_0} \] where \[ W_{X_0} = P(X_0 = x_0)/P(X_0 = x_0 | Z = z) \] and \[ W_{M_0} = P(M_0 = m_0 | X_0 = x_0^*, Z = z)/P(M_0 = m_0 | X_0 = x_0, Z = z). \] Finally, we ran a marginal structural Cox model (MSCM), weighted by \( W \), on \( X_0, X_0^* \), and \( X_0 \cdot X_0^* \). The exponentiated coefficient for \( X_0 \) was taken as the point estimate for PDE whereas the exponent of the linear combination of coefficients for both \( X_0^* \), and \( X_0 \cdot X_0^* \) was taken as the point estimate for TIE. Bias-corrected and accelerated 95% CIs were obtained based on 1000 bootstrap samples randomly selected from the original data with replacement.

To avoid unstable estimates due to extreme values of \( W_{X_0} \), we also ran (1) a conditional MSCM, weighted by \( W_{M_0} \) and with adjustment for covariates, and (2) a doubly robust (DR) MSCM, weighted by \( W \) and with adjustment for covariates. The latter has DR property because we would obtain unbiased estimates for PDE and TIE as long as either the exposure model or the final Cox model for the outcome was correctly specified. For continuous exposure and mediator, this approach became less ideal because this method requires substituting the probabilities \( [P(X_0 = x_0 | Z = z) \) and \( P(M_0 = m_0 | X_0 = x_0, Z = z) \) in the weights by probability densities, which may yield unstable weights (1). In the current study, only binary OPA and LTPA were examined in the mediation context. We further assumed that our models for the exposure and the mediator were correctly specified.

3. Description for sensitivity analysis of mediation by LTPA

Sample restriction

Of the total cohort of 2682 participants, a sub-cohort of men (N=1229) was actively followed at 4 and 11 years by examinations and questionnaire. Only 1038 participated at 4-year follow-up,
after excluding 191 men due to death (N=35), severe illness (N=12), migration (N=5), no address (N=2), refusal (N=107), no contact (N=29) and other reason (N=1). We further excluded men who had retired (N=486) or had first-time AMI incidence after baseline (N=5) before 4-year follow-up, or had first-time AMI incidence within 1 year after the 4-year follow-up (N=1), or had missing data on key variables (N=41), leaving a sample of 505 men. Data involving 4-year follow-up on the sub-cohort were only used in the sensitivity analyses. Due to small number of men with IHD (N=50), we limited our analysis to men without IHD (N=455).

**Method description**

Due to the lack of 4-year repeated measurement of cardiorespiratory fitness, an important co-determinant of the health impact of OPA, mediating effect via 4-year OPA was not examined in the current study. With 4-year LTPA as an additional mediator, the PDE examined in the main analysis where only baseline LTPA was considered as the mediator was further decomposed into the pathway effect of OPA on AMI that was through 4-year LTPA (NIE\textsubscript{4-year}) only and the natural direct effect of OPA that was through neither baseline nor 4-year LTPA (NDE) (Figure A1). To account for differential censoring by exposure, covariates and the outcome, we used inverse probability of censoring weights (IPCW) to reweight the sample in the final MSM so that censoring was statistically made to appear as a random event conditional on exposure, covariates, and the outcome.

**Incidence of AMI for the restricted sample of 455 men without IHD**
For the restricted sample of 455 men without preexisting IHD that has the start of follow-up as the survey date of 4-year follow up, 71 first-time incidence AMI occurred during an average of 16.96 years of follow-up (SD: 4.79; range: 1.01-20.81) and a total person-time of 7716 years.

Appendix Table A5 depicted the results from this sensitivity analysis.

4. Results from sensitivity analyses

(i) Using trichotomized PA measures

Results from sensitivity analysis using trichotomized PA measures are presented in Tables A2a and A2b. Moderate (23%≤RAS<33%) and high (RAS>33%) OPA, compared to low (RAS≤23%) OPA, were positively associated with AMI at moderate (20≤LTPA<75 minutes/week) and high (≥75 minutes/week) LTPA levels among men without IHD (with the highest HR associated with moderate OPA of 2.35, 95% CI: 1.43–3.85 at moderate level of LTPA) and at high level of LTPA among men with IHD (with highest HR associated with moderate OPA of 2.31, 95% CI: 0.97–5.48). LTPA was less predictive than OPA but high LTPA appeared protective for men with IHD and low OPA (HR 0.30, 95% CI: 0.07–1.20) while moderate and high levels of LTPA increased AMI risk for all men at moderate OPA (up to 2.58–fold associated with high LTPA, 95% CI: 1.03–6.45, among men with IHD), and possibly for men at high OPA and with IHD (HR associated with moderate LTPA: 1.54, 95% CI: 0.89–2.66).

The combined effect of moderate OPA and moderate LTPA was greater than the product of their separate effects among men without IHD. The combined effect of high OPA and moderate LTPA was greater than the product of their separate effects among men with IHD. When using
the low OPA and moderate LTPA as the general reference (low risk) group for men without IHD, those with moderate OPA and moderate LTPA had the highest risk for AMI (HR: 2.35, 95% CI: 1.43–3.85). For men with IHD, those with low OPA and moderate LTPA had the highest risk for AMI (HR: 3.92, 95% CI: 1.20–12.78), when compared to their respective moderate OPA and low LTPA (<20 minutes/week) reference (low risk) group. Negative (i.e., the combined effect of two PA measures being smaller than the sum of their separate effects) but uncertain additive interactions were found (1) comparing moderate OPA and low LTPA to low OPA and moderate LTPA among men without IHD, and (2) comparing low OPA and high LTPA to moderate OPA and low LTPA among men with IHD.

(ii) Additionally adjusting for biological factors

Results from sensitivity analysis that additionally adjusted for biological factors are presented in Table A3. Neither RAS nor LTPA predict AMI, although high OPA shows a considerable albeit statistically uncertain high AMI risk for men with IHD and low LTPA (HR 1.43, 95% CI 0.87–2.33). We did not observe multiplicative or additive interactions between RAS and LTPA.

(iii) Using absolute EE as OPA measure

Table A4 depicts results from using absolute EE as OPA measure. High absolute EE was associated with AMI only at LTPA level of 75 minutes/week (HR: 1.06, 95% CI: 1.00–1.13) but not at a lower LTPA level for men without IHD and was not associated with AMI across LTPA levels among men with IHD. LTPA did not predict AMI or interact with EE at the multiplicative scale.
5. Appendix Tables: Results from sensitivity analyses

1. Use a continuous OPA measure (RAS) and a continuous LTPA measure

Table A1 Hazard ratios (HR) and 95% confidence intervals (95% CI) for the effect of occupational physical activity (OPA) and leisure-time physical activity (LTPA) on 20-year incidence of acute myocardial infarction (N=495) when both domains of physical activity were modeled as continuous variables, by preexisting ischemic heart disease (IHD) status, Kuopio Ischemic Heart Disease Risk Factor Study, 1984-2011 (N=1891).

| LTPA level | OPA level | Men without IHD (N=1565) | Men with IHD (N=326) |
|------------|-----------|--------------------------|-----------------------|
|            |           | Age-adjusted HR (95% CI) | Fully-adjusted\(^b\) HR (95% CI) | Age-adjusted HR (95% CI) | Fully-adjusted\(^b\) HR (95% CI) |
| 0 minute/week | RAS=23.5%  | Reference                 | Reference              | Reference               | Reference               |
| 0 minute/week | RAS=43.5%  | 1.45 (1.21–1.74)          | 1.45 (1.19–1.75)       | 1.20 (0.93–1.55)        | 1.25 (0.96–1.64)        |
| 75 minutes/week | RAS=23.5% | Reference                 | Reference              | Reference               | Reference               |
| 75 minutes/week | RAS=43.5% | 1.50 (1.30–1.74)          | 1.49 (1.28–1.75)       | 1.26 (1.04–1.52)        | 1.32 (1.07–1.62)        |

\(P\) for multiplicative interaction\(^c\) 0.362  0.458  0.571  0.494

\(^a\) Effect estimates associated with 1-unit increase for one domain of physical activity were presented at two specific values of the other domain of physical activity. RAS: relative aerobic strain.

\(^b\) Model adjusted for age, education, participation in an unrelated clinical trial, smoking, alcohol consumption, mental strain at work, social support at work, and stress from work deadlines.

\(^c\) \(P\) value for the OPA \(\times\) LTPA product term.
2. Use a trichotomized OPA measure (RAS) and a trichotomized LTPA measure

2a. Effect estimates for one domain of PA across levels of the other domain of PA

Table A2a Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the main effect and joint effect of occupational physical activity (OPA) and leisure-time physical activity (LTPA) on 20-year incidence of acute myocardial infarction (N=495) when both domains of physical activity were modeled as trichotomized variables, by preexisting ischemic heart disease (IHD) status, Kuopio Ischemic Heart Disease Risk Factor Study, 1984-2011 (N=1891).

| LTPA level       | OPA level | Men without IHD (N=1565) | Men with IHD (N=326) |
|------------------|-----------|--------------------------|----------------------|
|                  |           | N | HR (95% CI) | P for interaction | N | HR (95% CI) | P for interaction |
| Low (LTPA<20 minutes/week) | Low      | 63 | Reference | -- | 5 | Reference | -- |
|                  | Moderate  | 111 | 1.11 (0.53–2.29) | -- | 21 | 0.27 (0.07–1.08) | -- |
|                  | High      | 153 | 1.71 (0.88–3.31) | -- | 54 | 0.56 (0.17–1.87) | -- |
| Moderate (20 minutes/week ≤LTPA<75 minutes/week) | Low      | 151 | Reference | -- | 11 | Reference | -- |
|                  | Moderate  | 179 | 2.35 (1.43–3.85) | 0.093 | 30 | 0.39 (0.14–1.11) | 0.668 |
|                  | High      | 166 | 1.91 (1.14–3.20) | 0.595 | 62 | 0.83 (0.33–2.09) | 0.011 |
| High (LTPA≥75 minutes/week) | Low      | 323 | Reference | -- | 28 | Reference | -- |
|                  | Moderate  | 248 | 1.38 (0.94–2.02) | 0.796 | 52 | 2.31 (0.97–5.48) | 0.614 |
|                  | High      | 171 | 1.31 (0.85–2.02) | 0.509 | 63 | 1.84 (0.77–4.37) | 0.118 |

| OPA level       | LTPA level | Men without IHD (N=1565) | Men with IHD (N=326) |
|------------------|-------------|--------------------------|----------------------|
|                  |             | N | HR (95% CI) | P for interaction | N | HR (95% CI) | P for interaction |
| Low (RAS≤23%)    | Low         | -- | Reference | -- | Reference | -- |
|                  | Moderate    | -- | 0.77 (0.37–1.60) | -- | 1.04 (0.25–4.37) | -- |
|                  | High        | -- | 0.99 (0.52–1.91) | -- | 0.30 (0.07–1.20) | -- |
| Moderate (23%<RAS≤33%) | Low     | -- | Reference | -- | Reference | -- |
|                  | Moderate    | -- | 1.64 (1.00–2.70) | -- | 1.53 (0.55–4.25) | -- |
|                  | High        | -- | 1.24 (0.75–2.04) | -- | 2.58 (1.03–6.45) | -- |
| High (RAS>33%)   | Low         | -- | Reference | -- | Reference | -- |
|                  | Moderate    | -- | 0.86 (0.57–1.30) | -- | 1.54 (0.89–2.66) | -- |
|                  | High        | -- | 0.76 (0.50–1.17) | -- | 0.98 (0.55–1.72) | -- |

a Model adjusted for age, education, participation in an unrelated clinical trial, smoking, alcohol consumption, mental strain at work, social support at work, and stress from work deadlines. RAS: relative aerobic strain.

b P values for the product term between the corresponding OPA and LTPA categories.
2b. Joint effect estimates of OPA and LTPA on AMI

Table A2b Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the main effect and joint effect of occupational physical activity (OPA) and leisure-time physical activity (LTPA) on 20-year incidence of acute myocardial infarction (N=495) when both domains of physical activity were modeled as binary variables, by preexisting ischemic heart disease (IHD) status, Kuopio Ischemic Heart Disease Risk Factor Study, 1984-2011 (N=1891).

| LTPA level | OPA level | Men without IHD (N=1565)b | | Men with IHD (N=326)c | |
|------------|-----------|---------------------------|------------------------|---------------------------|------------------------|
|            |           | N  | HR (95% CI) | RERI (95% CI)d | N  | HR (95% CI) | RERI (95% CI) |
| Low        | Low       | 63 | 1.29 (0.63–2.67) | -- | 5 | 3.77 (0.93–15.35) | -- |
|            | Moderate  | 111 | 1.43 (0.79–2.60) | -1.21 (-2.69–0.27) | 21 | Reference | -- |
|            | High      | 153 | 2.21 (1.32–3.69) | 0.01 (-1.21–1.23) | 54 | 2.11 (0.85–5.19) | -- |
| Moderate   | Low       | 151 | Reference | -- | 11 | 3.92 (1.20–12.78) | -0.38 (-6.05–5.30) |
|            | Moderate  | 179 | 2.35 (1.43–3.85) | -- | 30 | 1.53 (0.55–4.25) | -- |
|            | High      | 166 | 1.91 (1.14–3.20) | -- | 62 | 3.24 (1.34–7.83) | 0.61 (-1.15–2.36) |
| High       | Low       | 323 | 1.28 (0.78–2.13) | -- | 28 | 1.12 (0.36–3.46) | -4.23 (-10.44–1.98) |
|            | Moderate  | 248 | 1.77 (1.08–2.91) | -0.86 (-2.01–0.29) | 52 | 2.58 (1.03–6.45) | -- |
|            | High      | 171 | 1.69 (1.00–2.86) | -0.50 (-1.57–0.56) | 63 | 2.05 (0.83–5.05) | -1.63 (-4.26–1.00) |

- **a** Model adjusted for age, education, participation in an unrelated clinical trial, smoking, alcohol consumption, mental strain at work, social support at work, and stress from work deadlines.
- **OPA levels**: low (RAS≤23%), moderate (23%<RAS≤33%), high (RAS>33%).
- **LTPA levels**: low (LTPA<20 minutes/week), moderate (20 minutes/week ≤ LTPA<75 minutes/week), high (LTPA≥75 minutes/week).
- **b** P=0.093 for the product term between moderate OPA and moderate LTPA. P values for other product terms are above 0.20.
- **c** P=0.011 for the product term between high OPA and moderate LTPA. P=0.118 for the product term between high OPA and high LTPA. P values for other product terms are above 0.20.
- **d** RERIs were measures for additive interaction and were calculated as \( HR_{\text{index OPA, index LTPA}} - HR_{\text{index OPA, reference LTPA}} - HR_{\text{reference OPA, index LTPA}} + 1 \).
3. Additional adjustment for biological factors

Table A3 Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for the main effect and joint effect of occupational physical activity (OPA) and leisure-time physical activity (LTPA) on 20-year incidence of acute myocardial infarction (N=495) when both domains of physical activity were modeled as binary variables, by preexisting ischemic heart disease (IHD) status, Kuopio Ischemic Heart Disease Risk Factor Study, 1984-2011 (N=1891).

| LTPA level | OPA level | Men without IHD (N=1565) HR (95% CI) | Men with IHD (N=326) HR (95% CI) |
|------------|-----------|--------------------------------------|----------------------------------|
| Low        | Low       | Reference                            | Reference                        |
| High       | Low       | 1.14 (0.86–1.51)                     | 1.43 (0.87–2.33)                 |
| High       | High      | 0.91 (0.62–1.33)                     | 0.89 (0.51–1.53)                 |
| OPA level  | LTPA level|                                      |                                  |
| Low        | Low       | Reference                            | Reference                        |
| High       | Low       | 1.02 (0.78–1.34)                     | 1.32 (0.76–2.30)                 |
| High       | High      | 0.81 (0.56–1.19)                     | 0.82 (0.51–1.33)                 |

\(P\) for multiplicative interaction\( ^c\)  
0.334 0.197

Combination of OPA and LTPA, using low OPA and high LTPA as the reference

| OPA and LTPA | Men without IHD (N=1565) HR (95% CI) | Men with IHD (N=326) HR (95% CI) |
|--------------|--------------------------------------|----------------------------------|
| Low OPA and high LTPA | Reference                            | Reference                        |
| High OPA and high LTPA | 0.91 (0.62–1.33)                     | 0.89 (0.51–1.53)                 |
| Low OPA and low LTPA | 0.98 (0.75–1.28)                     | 0.76 (0.43–1.31)                 |
| High OPA and low LTPA | 1.12 (0.84–1.50)                     | 1.08 (0.66–1.77)                 |

RERI\( ^d\)  
0.23 (-0.21–0.67) -0.58 (-1.58–0.42)

\( ^a\) Model adjusted for age, education, participation in an unrelated clinical trial, smoking, alcohol consumption, mental strain at work, social support at work, stress from work deadlines and biological factors including blood glucose, plasma fibrinogen, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, body mass index, systolic blood pressure, and taking lipid- or blood-pressure-lowering medication during follow-up as listed in Krause et al. (2)

\( ^b\) Low OPA: relative aerobic strain (RAS)\( \leq 33\%\); high OPA: RAS>33%; low LTPA: <75 minutes/week; high LTPA: \(\geq\)75 minutes/week.

\( ^c\) \(P\) value for the RAS \(\times\) LTPA product term.

\( ^d\) RERIs were measures for additive interaction. For men without IHD, RERIs were calculated as HR(high OPA, low LTPA) − HR(low OPA, low LTPA) + 1. For men with IHD, RERIs were calculated as HR(high OPA, high LTPA) − HR(low OPA, low LTPA) + 1, using low OPA and low LTPA as the reference group.
4. Use of absolute energy expenditure (EE) during work as OPA measure (continuous in kcal/workday)

Table A4 Hazard ratios (HR) and 95% confidence intervals (95% CI) for the main effect and joint effect of occupational physical activity (OPA), measured as continuous absolute energy expenditure, and continuous leisure-time physical activity (LTPA) on 20-year incidence of acute myocardial infarction (N=495), by preexisting ischemic heart disease (IHD) status, Kuopio Ischemic Heart Disease Risk Factor Study, 1984-2011 (N=1891).

| LTPA level | OPA level | Age-adjusted HR (95% CI) | Fully-adjusted<sup>a</sup> HR (95% CI) | Men without IHD (N=1565) | Men with IHD (N=326) |
|------------|-----------|--------------------------|----------------------------------------|--------------------------|----------------------|
| 0 minute/week | Absolute EE = 2111 kcal/day | Reference | Reference | Reference | Reference |
| 75 minutes/week | Absolute EE = 2111 kcal/day | 1.04 (0.96–1.12) | 1.04 (0.96–1.12) | Reference | Reference |
| 0 minute/week | Absolute EE = 2611 kcal/day | Reference | Reference | Reference | Reference |
| 75 minutes/week | Absolute EE = 2611 kcal/day | 1.07 (1.01–1.13) | 1.06 (1.00–1.13) | Reference | Reference |

| OPA level | LTPA level | Age-adjusted HR (95% CI) | Fully-adjusted<sup>a</sup> HR (95% CI) |
|-----------|-----------|--------------------------|----------------------------------------|
| Absolute EE = 2111 kcal/day | 0 minute/week | Reference | Reference |
| 75 minutes/week | 0.95 (0.89–1.03) | 0.98 (0.91–1.06) | Reference | Reference |
| Absolute EE = 2611 kcal/day | 0 minute/week | Reference | Reference |
| 75 minutes/week | 0.98 (0.90–1.07) | 1.01 (0.92–1.09) | Reference | Reference |

P for multiplicative interaction<sup>b</sup> 0.220 0.297 0.333 0.193

<sup>a</sup>Model adjusted for age, education, participation in an unrelated clinical trial, smoking, alcohol consumption, mental strain at work, social support at work, and stress from work deadlines.
<sup>b</sup>P value for the RAS × LTPA product term.
5. Sensitivity analysis for mediation of LTPA

Table A5 Hazard ratios (HR) and 95% confidence intervals (95% CI) for the natural direct effect (NDE), natural indirect effect via baseline (NIE_{Baseline}) and 4-year (NIE_{4-year}) leisure-time physical activity of baseline occupational physical activity as measured by binary relative aerobic strain on 20-year incidence of acute myocardial infarction (N=71) among men without preexisting ischemic heart disease using inverse-probability weighted (IPW) fitting of marginal structural models (MSM)^a, Kuopio Ischemic Heart Disease Risk Factor Study, 1984-2011 (N=455).

| Method          | HR (95% CI) |
|-----------------|-------------|
| **MSM^c**       |             |
| NDE             | 0.97 (0.48–1.84) |
| NIE_{Baseline}  | 0.79 (0.57–1.10) |
| NIE_{4-year}    | 1.00 (0.87–1.08) |
| Total effect    | 0.77 (0.41–1.37) |
| **Conditional MSM^d** |             |
| NDE             | 1.22 (0.57–2.46) |
| NIE_{Baseline}  | 0.93 (0.69–1.21) |
| NIE_{4-year}    | 0.96 (0.79–1.05) |
| Total effect    | 1.08 (0.58–2.02) |
| **Doubly robust MSM^e** |           |
| NDE             | 1.04 (0.45–2.04) |
| NIE_{Baseline}  | 0.92 (0.68–1.20) |
| NIE_{4-year}    | 0.97 (0.82–1.05) |
| Total effect    | 0.91 (0.46–1.69) |

aOccupational physical activity was measured by binary relative aerobic strain (RAS) indicator (RAS>33% versus RAS≤33%) and leisure-time physical activity was dichotomized (≥75 minutes/week versus <75 minutes/week). Covariates included age, education, participation in an unrelated clinical trial, smoking, alcohol consumption, mental strain at work, social support at work, and stress from work deadlines.

bBias-corrected and accelerated 95% confidence intervals (CIs) were obtained using 1000 bootstrap samples.

cIPW was created based on a weight for OPA (dealing with confounding) and a weight for LTPA (decomposing effect).

dIPW was created based on a weight for LTPA (decomposing effect) only. Conditional MSM included covariates to control for confounding.

eIPW was created based on a weight for OPA (dealing with confounding) and a weight for LTPA (decomposing effect). In the final MSM, covariates were adjusted for.
Appendix Figures

Figure A1 Graphical presentation (solid black lines) of natural direct effect (a), natural indirect effect via baseline leisure-time physical activity (LTPA) (b), and natural indirect effect via 4-year LTPA only (c) of occupational physical activity (OPA) on acute myocardial infarction (AMI). Subscript 0 represents baseline measure and 1 represents 4-year measure.
Reference

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