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# Effects of leisure-time and occupational physical activities on 20-year incidence of acute myocardial infarction: mediation and interaction [1]

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*1 Appendix*

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**Contents of the appendix**

## 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≤23%, moderate: 23%≤RAS<33%, high: RAS>33%) and LTPA as trichotomized variable (low: LTPA<20 minutes/week, moderate: 20 minutes/week ≤LTPA<75 minutes/week, high: LTPA≥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 $W_{X_0} = P(X_0 = x_0)/P(X_0 = x_0|\mathbf{Z} = \mathbf{z})$ and $W_{M_0} = P(M_0 = m_0|X_0 = x_0{}^*, \mathbf{Z} = \mathbf{z})/P(M_0 = m_0|X_0 = x_0, \mathbf{Z} = \mathbf{z})$. Finally, we ran a marginal structural Cox model (MSCM), weighted by $W$, on $X_0$, $X_0{}^*$, and $X_0 \cdot X_0{}^*$. The exponenttiated 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 [$P(X_0 = x_0|\mathbf{Z} = \mathbf{z})$ and $P(M_0 = m_0|X_0 = x_0, \mathbf{Z} = \mathbf{z}]$ 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 ($NIE_{4\text{-year}}$) 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[a], 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)** | |
|---|---|---|---|---|---|
| **LTPA level** | **OPA level** | **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 |
| | 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 |
| | 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) |
| **OPA level** | **LTPA level** | | | | |
| RAS=23.5% | 0 minute/week | Reference | Reference | Reference | Reference |
| | 75 minutes/week | 0.96 (0.88–1.04) | 0.98 (0.90–1.07) | 0.95 (0.82–1.09) | 0.95 (0.82–1.10) |
| RAS=43.5% | 0 minute/week | Reference | Reference | Reference | Reference |
| | 75 minutes/week | 0.99 (0.91–1.08) | 1.01 (0.93–1.10) | 0.99 (0.88–1.11) | 1.00 (0.89–1.12) |
| *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 × 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[a] 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).

| | | Men without IHD (N=1565) | | | Men with IHD (N=326) | | |
|---|---|---|---|---|---|---|---|
| **LTPA level** | **OPA level** | **N** | **HR (95% CI)** | ***P* for interaction[b]** | **N** | **HR (95% CI)** | ***P* for interaction[b]** |
| 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** | | | | | | |
| 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[a] 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).

| | | **Men without IHD (N=1565)[b]** | | | **Men with IHD (N=326)[c]** | | |
|---|---|---|---|---|---|---|---|
| **LTPA level** | **OPA level** | **N** | **HR (95% CI)** | **RERI (95% CI)[d]** | **N** | **HR (95% CI)** | **RERI (95% CI)** |
| | Low | 63 | 1.29 (0.63–2.67) | -- | 5 | 3.77 (0.93–15.35) | -- |
| Low | 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) | -- |
| | Low | 151 | Reference | -- | 11 | 3.92 (1.20–12.78) | -0.38 (-6.05–5.30) |
| Moderate | 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) |
| | Low | 323 | 1.28 (0.78–2.13) | -- | 28 | 1.12 (0.36–3.46) | -4.23 (-10.44–1.98) |
| High | 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[a] 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,[b] 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)** |
|---|---|---|---|
| **LTPA level** | **OPA level** | **HR (95% CI)** | **HR (95% CI)** |
| Low | Low | Reference | Reference |
| | High | 1.14 (0.86–1.51) | 1.43 (0.87–2.33) |
| High | Low | Reference | Reference |
| | High | 0.91 (0.62–1.33) | 0.89 (0.51–1.53) |
| **OPA level** | **LTPA level** | | |
| Low | Low | Reference | Reference |
| | High | 1.02 (0.78–1.34) | 1.32 (0.76–2.30) |
| High | Low | Reference | Reference |
| | 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** | | | |
| 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)≤33%; high OPA: RAS>33%; low LTPA: <75 minutes/week; high LTPA: ≥75 minutes/week.

[c] *P* value for the RAS × LTPA product term.

[d] RERIs were measures for additive interaction. For men without IHD, RERIs were calculated as $HR_{\text{high OPA, low LTPA}} - HR_{\text{high OPA, high LTPA}} - HR_{\text{low OPA, low LTPA}} + 1$. For men with IHD, RERIs were calculated as $HR_{\text{high OPA, high LTPA}} - HR_{\text{high OPA, low LTPA}} - HR_{\text{low OPA, high LTPA}} + 1$, 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).

| | | **Men without IHD (N=1565)** | | **Men with IHD (N=326)** | |
|---|---|---|---|---|---|
| **LTPA level** | **OPA level** | **Age-adjusted HR (95% CI)** | **Fully-adjusted[a] HR (95% CI)** | **Age-adjusted HR (95% CI)** | **Fully-adjusted[a] HR (95% CI)** |
| 0 minute/week | Absolute EE = 2111 kcal/day | Reference | Reference | Reference | Reference |
| | Absolute EE = 2611 kcal/day | 1.04 (0.96–1.12) | 1.04 (0.96–1.12) | 0.95 (0.85–1.07) | 0.96 (0.86–1.08) |
| 75 minutes/week | Absolute EE = 2111 kcal/day | Reference | Reference | Reference | Reference |
| | Absolute EE = 2611 kcal/day | 1.07 (1.01–1.13) | 1.06 (1.00–1.13) | 0.98 (0.90–1.08) | 1.00 (0.91–1.09) |
| **OPA level** | **LTPA level** | | | | |
| Absolute EE = 2111 kcal/day | 0 minute/week | Reference | Reference | Reference | Reference |
| | 75 minutes/week | 0.95 (0.89–1.03) | 0.98 (0.91–1.06) | 0.95 (0.86–1.06) | 0.96 (0.86–1.07) |
| Absolute EE = 2611 kcal/day | 0 minute/week | Reference | Reference | Reference | Reference |
| | 75 minutes/week | 0.98 (0.90–1.07) | 1.01 (0.92–1.09) | 0.98 (0.87–1.10) | 0.99 (0.89–1.11) |
| *P* for multiplicative interaction[b] | | 0.220 | 0.297 | 0.333 | 0.193 |

[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.

[b] *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 ($NIE_{4\text{-}year}$ ) 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)[b] |
|---|---|
| **MSM[c]** | |
| NDE | 0.97 (0.48–1.84) |
| $NIE_{baseline}$ | 0.79 (0.57–1.10) |
| $NIE_{4\text{-}year}$ | 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) |
| $NIE_{4\text{-}year}$ | 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) |
| $NIE_{4\text{-}year}$ | 0.97 (0.82–1.05) |
| Total effect | 0.91 (0.46–1.69) |

[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.

**Appendix Figures**

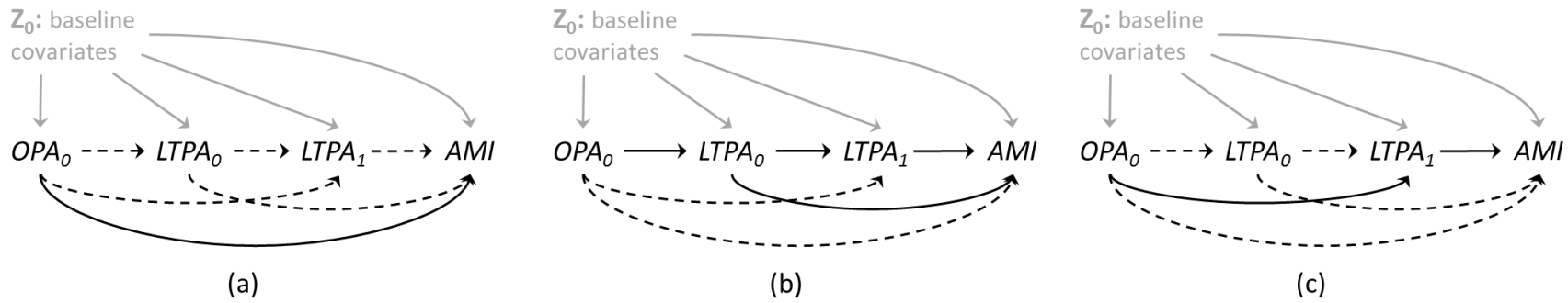


**Figure A1** Graphical presentation (solid black lines) of natural direct effect (a), natural indirect effect via baseline leisure-time physical activity (LTPA) (b), and natural indirect effect via 4-year LTPA only (c) of occupational physical activity (OPA) on acute myocardial infarction (AMI). Subscript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

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