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The independent and joint associations of physical activity and body mass index with myocardial infarction: The Tromsø Study

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Abstract

Physical activity and overweight are associated with myocardial infarction (MI). However, their joint association with MI remains unclear. Our objective was to examine the independent and joint association between leisure-time physical activity (LTPA), body mass index (BMI) and MI. This prospective cohort study included 16572 men and women (47.5% women) aged 20-54 years who took part in the second Tromsø Study. At baseline in 1979-80 LTPA was assessed by questionnaire. Data on MI was collected and adjudicated through hospital and causes of death registries between 1979 and 2013. Cox proportional hazards models were used to examine the independent and joint associations between LTPA, BMI and MI. The final sample included 16104 individuals. During a median follow up of 34 years, 1613 incident cases of MI were recorded. Physical inactivity and elevated BMI were both independently associated with MI (p for trend 0.02 and < 0.001). In joint analyses, normal weight, inactive individuals had a 20% higher risk of MI compared to their active counterparts (hazard ratio (HR) 1.20 (1.02-1.41). The highest risk of MI was seen in obese, inactive individuals when compared to normal weight, active individuals (HR 3.20 (2.30-4.44)). The risk of MI increased with increasing BMI regardless of the activity level. HRs were lower for active compared to inactive individuals within the same BMI category. The findings suggest that LTPA and BMI are independently associated with risk of MI. LTPA seems to attenuate but not eliminate the risk of MI associated with excess bodyweight.

Introduction

The incidence and mortality rates of coronary heart disease (CHD) have declined in Western countries in recent years [1,2]. This trend is also seen in the Norwegian population, with a 24% decrease in the incidence rate for acute myocardial infarction (MI) among those 45 years or older between 2001-2009 [3]. The decrease in CHD incidence rates are mainly explained by favorable changes in cardiovascular disease (CVD) risk factors such as decreasing smoking prevalence, systolic blood pressure and total cholesterol values [2,4,5], and possibly a favorable increase in leisure time physical activity (LTPA) [2,5].

LTPA is an important protective factor for the development of CHD with a risk reduction of about 20-30% in active compared to inactive individuals [6,7]. Excess bodyweight on the contrary has shown to increase the risk for CHD and in particular MI by 20-60% in overweight and obese individuals respectively, compared with those of normal weight [8-10]. Most studies examining the joint effects of physical activity and body mass index (BMI) on CVD and CHD have reported that physical activity attenuated but did not fully eliminate the increased CVD risk associated with overweight and obesity [11-16]. However, one recent study showed that overweight and obese active individuals do not have an elevated CVD risk when compared to normal weight, active individuals [17]. Most previous studies were conducted in single sex only [11-13,15], and examined either the associations of physical activity and obesity with CVD [12,16,17] or CHD [11,13-15]. The exposure of interest in earlier research was LTPA [11-13,15,17] or a combination of occupational and leisure-time physical activity [14,16].

The aim of this study was therefore to assess the relationship between LTPA, BMI and MI in both sexes. We examined whether the association between LTPA and MI risk differs across BMI categories and if LTPA can counteract the potential excess risk of MI associated with overweight and obesity.

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Methods

Study population

The data were derived from the Tromsø Study, a population-based, prospective cohort study with repeated surveys (Tromsø 1-7, 1974-2016). The study design and data collection are described elsewhere [18]. For the present study, data from 16572 men and women aged 20-54 years who took part in the second Tromsø Study survey in 1979-1980 (participation rate 74%) were included.

After excluding individuals with incomplete data on BMI, LTPA, daily smoking, blood pressure treatment, self-reported diabetes (n = 412) and subjects with prevalent MI at baseline (n = 56), the final sample included 8235 men (51.1%) and 7869 women (48.9%). The Tromsø study is approved by the Norwegian Data Inspectorate and the Regional Committee of Research Ethics.

Measurements

Assessment of LTPA and BMI

At baseline in 1979-1980, LTPA was self-reported using a validated questionnaire [19] that was first introduced by Saltin and Grimby in 1968 and participants were categorized into four physical activity categories. I (inactive): reading, watching TV, or other sedentary activity; II (moderately active): walking, cycling, or other forms of exercise at least 4 h/week; III (highly active): participation in recreational sports, heavy gardening, etc. at least 4 h/week; IV (vigorously active): participation in hard training or sports competitions regularly several times a week.

Height and weight were measured to the nearest centimeter and half-kilogram without shoes and with light clothing. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). For the combined BMI/LTPA categories, normal-weight was defined as BMI < $25kg/m^2$, overweight as BMI 25-<$30kg/m^2$ and obesity as BMI ≥ $30kg/m^2$. Individuals in activity categories II, III and IV were classified as physically active according to physical activity recommendations [20], whereas individuals in category I were classified as inactive.

Assessment of covariates

Information about covariates was collected at baseline by self-report and physical examinations at the study site by trained technicians. Self-reported data on current smoking (yes/no), diabetes (yes/no), years of education (No. of years including primary and secondary school) and blood pressure treatment (yes/no) were derived from the questionnaire. Blood pressure was measured with a mercury sphygmomanometer and stethoscope using standard procedures, and total cholesterol was derived from non-fasting blood samples analyzed by standard methods at the Department of Laboratory Medicine of the University Hospital of North Norway.

Assessment of MI

The outcome in this study was first-ever MI that occurred between the baseline examination in 1979-1980 and the end of follow-up 31 December 2013. The following diagnostic codes in the discharge diagnosis register at the University Hospital of North Norway, the only hospital serving the area of Tromsø, were included to identify all possible incident MI cases: International Classification of Diseases (ICD) 8 codes 410-414; ICD 9 codes 410-414 and ICD 10 codes I20-I25. When appropriate, discharge letters from other hospitals were collected as well. To identify fatal out-of-hospital cases of MI as well as deaths that occurred outside Tromsø, the Tromsø Study participant list was linked with the National Cause of Death Registry at the Norwegian Institute of Public Health. Death certificates for those with an underlying or contributing diagnosis of CVD or sudden death were retrieved and additional information from autopsy records and records from general practitioners, ambulance services and nursing homes was collected. Thereafter, cases were validated by reviewing the medical records and death certificates by trained physicians from an independent end-point committee [5]. Information on migration was obtained through the Population Registry of Norway.

Each participant contributed person-time from the baseline examination in 1979-80 until the date of the first MI, migration, death or end of follow-up 31 December 2013, whichever came first.

Statistical analyses

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between independent and joint BMI/LTPA categories and the risk of MI. To determine the associations between BMI and MI, and between LTPA and MI, normal-weight and inactive individuals, respectively, were used as the reference category. For the joint BMI/LTPA analyses, individuals were grouped into six categories and normal-weight active individuals were used as the reference category. Three different models were used in the Cox regression analyses. Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, daily smoking and BMI in the LTPA model and LTPA in the BMI model. In an additional model, systolic and diastolic blood pressure, total cholesterol, and self-reported diabetes and hypertension treatment were added as covariates (Model 3). Since these variables might be considered as intermediate factors in the causal pathway of BMI/LTPA and MI, model 2 was used as the main model. Possible interactions between BMI and LTPA were evaluated by adding multiplicative interaction terms to the models. To examine the associations between LTPA and MI in different weight groups, individuals were stratified into three BMI groups (normal-weight, overweight, obese). Interactions between sex and BMI group, and sex and LTPA level were tested in all models and no significant modification by sex was observed. Similarly, there was no indication of a BMI by LTPA interaction in any of the models (data not shown).

In sensitivity analyses we additionally adjusted models 2 and 3 for years of education as a proxy for socio-economic status in individuals with valid data on education (n=14002), and the results were virtually unchanged (data not shown). To reduce the chance of reverse causation, we conducted a sensitivity analysis where individuals with MI within the first two years of follow-up were excluded (n=38), with virtually unchanged results.

Proportional hazard assumptions were examined for each model and were not violated. All analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). The first author M.R. and senior author B.M. had full access to all the data in the study and take responsibility for its integrity and the data analysis.

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Results

Baseline characteristics

In total, 7869 women (48.9%) and 8235 men (51.1%) were included in the analyses. During a median follow-up of 34.1 years (33.8 and 34.2 years for the 25th and the 75th percentile, respectively; 499196 person-years), 344 women (aged 40.6y, SD 6.5) and 1269 men (aged 41.6y, SD 8.8) had an incident MI. The overall incidence of MI was 3.18/1000 person-years, 1.35/1000 person-years in women and 5.18/1000 person-years in men (Table 1). Descriptive data are presented in Table 1.

LTPA and MI

In general, we observed an inverse relationship between LTPA and risk of MI (Table 2). In Model 1 (adjusted for age and sex), moderately and highly active individuals had 23% and 29% reduced risk of MI [HRs 0.77, 95% CI 0.68-0.87 and 0.71, 95% CI 0.62-0.83] compared with the inactive group. The MI risk among individuals who reported vigorous activity was halved compared with the inactive group [HR 0.44, 95% CI 0.29-0.65]. Adding smoking and BMI to the model (Model 2) attenuated these associations, although the associations were still statistically significant in the moderate and vigorous activity group. In the additional model (Model 3), the associations were further weakened but moderately active individuals still showed a significantly reduced risk of MI compared to inactive individuals [HR 0.87, 95% CI 0.77-0.99].

BMI and MI

The risk of MI increased monotonically with elevated BMI, by 19%, 21% and 12% for every two units of BMI increment in Model 1, 2, and 3 [HR 1.19, 95% CI 1.16-1.23; HR 1.21, 95% CI 1.18-1.25 and HR 1.12, 95% CI 1.09-1.16] (Table 2). When individuals where categorized into BMI groups, those in the overweight and obese groups had an elevated risk for MI with the highest risk in the obese group [HR 2.53 95% CI 2.10-3.05; HR 2.70 95% CI 2.24-3.26] in Model 1 and Model 2, respectively. In the additional model (Model 3), the HRs were attenuated although still statistically significant. The MI risk in overweight and obese individuals was 29% and 88% higher compared to normal-weight individuals [HRs 1.29, 95% CI 1.16-1.44 and 1.88, 95% CI 1.55-2.28].

Joint associations of LTPA and BMI with MI

In Model 1, the risk of MI was 37% higher in normal weight, inactive individuals than in their active counterparts [HR 1.37, 95% CI 1.16-1.61] (Table 3). When adjusting for covariates (Models 2 and 3), the risk increase was attenuated, although statistically significant [HRs 1.20, 95% CI 1.02-1.41 and 1.17, 95% CI 1.00 -1.38]. The highest risk of MI was seen in obese, inactive individuals, with a 3-fold risk compared to normal-weight, active individuals in Model 2 [HR 3.20, 95% CI 2.30-4.44]. Irrespective of the activity level, the risk of MI increased with increasing BMI (Table 3). However, the risk estimates were lower for active individuals compared to inactive individuals within the same weight category.

The risk of MI was higher in inactive than active individuals across BMI groups (Table 4). This was observed in crude and adjusted models in the normal-weight group, whereas the association in multivariable models was non-significant in overweight and obese individuals.

Discussion

In this cohort of young and middle-aged individuals followed for 34 years, both elevated BMI and leisure-time physical inactivity were independently associated with an increased risk of MI in a dose-response manner. Active individuals in the same weight category showed lower risk estimates than their inactive counterparts. However, the magnitude of association seems to be stronger for obesity compared to physical inactivity. Being obese and inactive was associated with the highest risk of MI and LTPA seems to attenuate but not eliminate the risk for MI associated with overweight and obesity.

Possible mechanisms

Previous studies have shown that the relationship between obesity and CHD is substantially mediated by traditional CVD risk factors, mainly blood pressure, cholesterol and blood glucose, explaining about half of the increased risk associated with high BMI [21]. In this study, the risk estimates for the association between BMI and MI were attenuated following adjustment for CVD risk factors, particularly in the obese group.

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Similarly, adjusting for traditional CVD risk factors such as blood pressure, total cholesterol levels, and diabetes status attenuated the association between LTPA and MI. This may partially be explained by the mediating effects of these factors on the association between physical inactivity with increased risk of MI corroborating previous findings [22]. Others have suggested that the pronounced risk reduction in active compared with inactive individuals may include enhanced endothelial function and a positive impact on the autonomic nervous system, such as improved peripheral baroreflex function [23].

Both the association between LTPA and MI and the association between BMI and MI seem to be largely mediated by CVD risk factors (blood pressure, total cholesterol, diabetes status), and adjustment for these factors might reflect over-adjustment, as indicated by the attenuated risk estimates in Model 3.

Comparison with other studies

The association between increased physical activity and a decreased risk of MI observed in our study is consistent with findings from several previous studies [15,22,24], and the associations between overweight and obesity with risk of MI have been reported previously [16,25].

Our findings regarding the joint association between LTPA, BMI and MI are consistent with those of several observational studies. In a 20-year follow-up of 88 393 women in the Nurses' Health Study [13], high levels of adiposity and physical inactivity independently predicted increased risk of CHD. The highest CHD risk was seen in obese and inactive women, with a more than 3-fold risk of CHD compared with the normal-weight active group. In agreement with the present study, LTPA attenuated but did not eliminate the adverse effects of overweight on CHD risk [13]. These results were recently supported by data from the Nurses' Health Study II [11], suggesting that LTPA was protective against CHD across BMI categories. Further, results from the Women's Health Study, [15] indicate similar findings, including independent associations between self-reported LTPA and BMI with CHD risk. However, the reported risk estimates for obese inactive women were lower than in our study. This may be explained by the shorter follow-up time and a different assessment of LTPA as well as the inclusion of

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percutaneous transluminal coronary angioplasty and coronary artery bypass graft in the outcome definition [15]. Carlsson et al. [12] examined the associations between repeated measurements of BMI and self-reported LTPA in the ULSAM-study with risk of CVD and reported similar results as those we report here. Furthermore, our findings are in contrast to studies that identified the obesity paradox. In our study, individuals with a higher BMI also had a higher risk of MI, while active individuals had a lower risk of MI than inactive individuals independent of their BMI. Taken together, it seems that LTPA attenuates but does not fully eliminate the increased risk of adiposity associated with MI. This suggests that public health initiatives should strive to reduce obesity and simultaneously increase physical activity in populations optimally reducing the risk of MI and other CVD. It should be emphasized that physical activity is important also in the obese and should be encouraged.

Strengths and limitations

The study has several strengths, including the prospective design with a long follow-up period of 34 years, rigorous outcome ascertainment, a large number of MI cases, a population-based sample and minimal loss to follow-up.

A limitation of the present study is that we did not use updated information on the exposure variables. This might lead to some misclassification due to changes in LTPA and BMI during follow-up.

Self-reported physical activity is prone to misclassification error. However, due to the prospective design of the present study, reported physical activity level is not biased by future disease status, and misclassification of physical activity will most likely be non-differential. Furthermore, Emaus et al. [26] observed overestimation of physical activity by self-report in the participants of the Tromsø study, which will most likely lead to underestimation of the true association between LTPA and MI.

The stronger magnitude of associations observed between BMI compared to LTPA and MI may be explained by the differences in measurement precision of the two exposure variables[27]. Height and weight were measured objectively by trained technicians, whereas LTPA was self-reported and therefore more likely to be affected by random measurement error.

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There is inconsistent evidence as to whether BMI, waist-to-hip ratio (WHR) or waist-circumference (WC) is the superior indicator of obesity. While a widely recognized case-control study showed a stronger relation between WHR and MI [28], a more recent collaborative analysis of 58 cohort studies refuted these results and showed a similar association of BMI, WHR and WC with CVD risk [29]. Furthermore, the long-term reproducibility of BMI was higher than that of WHR or WC [29]. Thus, although BMI might slightly underestimate the association of obesity and MI, BMI seems to be a valid indicator of overweight and obesity in large population-based studies.

Finally, we cannot exclude the possibility that our observations are influenced by unmeasured confounders (e.g. diet and genotype).

Conclusion

This prospective cohort study suggests an independent association between BMI and LTPA with incident MI. LTPA reduced the risk of MI in both normal-weight and overweight individuals, but did not fully eliminate the increased risk of MI associated with overweight and obesity. These findings underline the importance of public health interventions targeted at weight loss and increasing LTPA to reduce the incidence of MI and other cardiovascular diseases.

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Tables:

TABLE 1: Baseline characteristics and incidence of MI by BMI-LTPA categories.

The Tromsø Study 1979-2013

n = 16104	normal weight / active	normal weight / inactive	overweight / active	overweight / inactive	obese / active	obese / inactive
n (% of all)	9390 (58.3)	2340 (14.5)	3003 (18.6)	841 (5.2)	395 (2.5)	135 (0.8)
Men (%)	45.6	42.1	69.3	71.7	52.9	57.8
Age (years)	33.2 (8.5)	32.8 (8.4)	37.4 (8.7)	37.5 (8.8)	39.0 (8.5)	38.5 (8.3)
Body height (cm)	170.4 (9.2)	169.5 (9.0)	172.2 (9.1)	172.3 (9.1)	169.1 (9.7)	169.7 (11.1)
Body weight (kg)	64.2 (9.4)	62.9 (9.5)	79.2 (9.0)	79.9 (9.2)	92.8 (11.7)	96.3 (14.7)
BMI (kg/m2)	22.0 (1.8)	21.8 (1.9)	26.7 (1.3)	26.8 (1.4)	32.4 (2.5)	33.4 (3.6)
Systolic blood-pressure (mmHg)	123.8 (13.5)	123.4 (13.5)	130.9 (15.0)	130.8 (14.1)	135.9 (15.8)	136.5 (17.5)
Diastolic blood-pressure (mmHg)	78.5 (9.8)	78.3 (10.1)	84.1 (10.5)	84.6 (10.4)	89.6 (10.8)	89.9 (10.6)
Total cholesterol (mmol/l)	5.6 (1.2)	5.7 (1.2)	6.3 (1.2)	6.3 (1.3)	6.6 (1.4)	6.9 (1.2)
Incidence (cases/1000py)	2.2	2.6	5.5	6.6	8.3	10.6
Smoking in % (n)	47.4 (4448)	62.4 (1461)	43.1 (1294)	54.7 (460)	40.3 (159)	53.3 (72)
Treatment for hypertension, % (n)	0.9 (81)	1.0 (24)	3.0 (89)	3.2 (27)	7.8 (31)	10.4 (14)
Diabetes, % (n)	0.2 (22)	0.3 (8)	0.5 (14)	0.2 (2)	1.5 (6)	0.0 (0)

Data are presented as mean (SD) or % (n).

Table 2: Risk of MI in relation to LTPA and BMI. The Tromsø Study 1979-2013.

Data are Hazard Ratios (95% CI).

LTPA level	n	MI events	Model 1	Model 2	Model 3
Low	3316	388	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Moderate	8963	837	0.77 (0.68-0.87)	0.87 (0.77-0.98)	0.87 (0.77-0.99)
High	3278	362	0.71 (0.62-0.83)	0.88 (0.76-1.02)	0.91 (0.79-1.06)
Vigorous	547	26	0.44 (0.29-0.65)	0.63 (0.42-0.95)	0.70 (0.47-1.05)
P for trend			< 0.001	0.02	0.10
Per physical activity category			0.83 (0.77-0.89)	0.92 (0.86-0.99)	0.94 (0.88-1.01)
BMI category					
Underweight	402	10	0.83 (0.44-1.56)	0.73 (0.39-1.36)	0.80 (0.42-1.49)
Normal weight	11328	825	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Overweight	3844	647	1.47 (1.33-1.64)	1.54 (1.39-1.72)	1.29 (1.16-1.44)
Obese	530	131	2.53 (2.10-3.05)	2.70 (2.24-3.26)	1.88 (1.55-2.28)
P for trend			< 0.001	< 0.001	< 0.001
BMI per 2 kg/m²			1.19 (1.16-1.23)	1.21 (1.18-1.25)	1.12 (1.09-1.16)

Effect estimates are presented as HR (95% CI), n=16104, Model 1: adjusted for age and sex, , Model 2: adjusted for age, sex, BMI/LTPA and daily smoking, Model 3: adjusted for age, sex, BMI/LTPA, systolic blood pressure, diastolic blood pressure, total cholesterol, diabetes, hypertension treatment and daily smoking

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Table 3: Joint associations of LTPA and BMI on MI risk. The Tromsø Study 1979-2013

BMI-LTPA category	n	MI events	Model 1	Model 2	Model 3
Normal weight/active	9390	643	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Normal weight/inactive	2340	192	1.37 (1.16-1.61)	1.20 (1.02-1.41)	1.17 (1.00-1.38)
Overweight/active	3003	489	1.50 (1.33-1.69)	1.58 (1.40-1.78)	1.31 (1.16-1.48)
Overweight/inactive	841	158	1.87 (1.57-2.23)	1.77 (1.49-2.11)	1.45 (1.22-1.74)
Obese/active	395	93	2.51 (2.01-3.12)	2.74 (2.20-3.41)	1.92 (1.54-2.40)
Obese/inactive	135	38	3.34 (2.40-4.63)	3.20 (2.30-4.44)	2.10 (1.51-2.92)
P for trend			< 0.001	< 0.001	< 0.001

Effect estimates are presented as HR (95% CI), n=16104, Model 1: adjusted for age and sex, , Model 2: adjusted for age, sex and daily smoking, Model 3: adjusted for age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol, diabetes, hypertension treatment and daily smoking

Table 4: Risk of MI in relation to LTPA stratified by BMI groups. The Tromsø Study 1979-2013

LTPA level	n	MI events	Model 1	Model 2	Model 3
Normalweight	11730	835			
Active	9390	643	1.00 (ref)	1.00 (ref)	1.00 (ref)
Inactive	2340	192	1.38 (1.18-1.62)	1.19 (1.01-1.40)	1.17(1.00 -1.37)
Overweight	3844	647			
Active	3003	489	1.00 (ref.)	1.00 (ref)	1.00 (ref)
Inactive	841	158	1.24 (1.03-1.48)	1.13 (0.94-1.36)	1.11 (0.93-1.34)
Obese	530	131			
Active	395	93	1.00 (ref.)	1.00 (ref)	1.00 (ref)
Inactive	135	38	1.30 (0.89-1.90)	1.19 (0.81-1.75)	1.10 (0.75-1.62)

Effect estimates are presented as HR (95% CI), n=16104, Model 1: adjusted for age and sex, , Model 2: adjusted for age, sex and daily smoking, Model 3: adjusted for age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol, diabetes, hypertension treatment and daily smoking

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Highlights

- Low physical activity (PA) and high BMI independently linked to heart attack risk

- Lower heart attack risk in active than inactive individuals within each BMI category

- PA attenuates, but does not eliminate risk of heart attack associated with high BMI