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ORIGINAL RESEARCH

Effects of Leisure-Time and Transport-Related Physical Activities on the Risk of Incident and Recurrent Myocardial Infarction and Interaction With Traffic-Related Air Pollution: A Cohort Study

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***Background*—**Physical activity enhances the uptake of air pollutants, possibly reducing its beneficial effects. We examined the effects of leisure-time and transport-related physical activities on the risk of myocardial infarction (MI), and whether potential benefits on MI are reduced by exposure to traffic-related air pollution.

***Methods and Results*—**A group of 57 053 participants (50–65 years of age) from the Danish Diet, Cancer, and Health cohort reported physical activity at baseline (1993–1997) and were linked to registry data on hospital contacts and out-of-hospital deaths caused by MI, until December 2015. Nitrogen dioxide levels were estimated at participants' baseline residences. We used Cox regressions to associate participation in sports, cycling, walking, and gardening with incident and recurrent MI, and tested for interaction by nitrogen dioxide. Of 50 635 participants without MI at baseline, 2936 developed incident MI, and of 1233 participants with MI before baseline, 324 had recurring MI during follow-up. Mean nitrogen dioxide concentration was 18.7 $\mu g/m^3$ at baseline (1993–1997). We found inverse statistically significant associations between participation in sports (hazard ratio; 95% confidence interval: 0.85; 0.79–0.92), cycling (0.91; 0.84–0.98), gardening (0.87; 0.80–0.95), and incident MI, while the association with walking was statistically nonsignificant (0.95; 0.83–1.08). Recurrent MI was statistically nonsignificantly inversely associated with cycling (0.80; 0.63–1.02), walking (0.82, 0.57–1.16), and gardening (0.91; 0.71–1.18), and positively with sports (1.06; 0.83–1.35). There was no effect modification of the associations between physical activity and MI by nitrogen dioxide.

***Conclusions*—**Benefits of physical activity on both the incidence and the recurrence of MI are not reduced by exposure to high levels of air pollution. **(*J Am Heart Assoc*. 2018;7:e009554. DOI: 10.1161/JAHA.118.009554.)**

Key Words: air pollution • cardiovascular disease prevention • cardiovascular disease risk factors • exercise • interaction • myocardial infarction • nitrogen dioxide • physical exercise

Cardiovascular disease (CVD) remains the most common cause of death in Europe, accounting for 45% of all deaths.[1] Patients who have survived a myocardial infarction (MI) are at increased risk for recurrent ischemic events[2] and heart failure,[3] which stresses the importance of developing effective and safe primary and secondary prevention strategies.

There is extensive evidence that physical activity reduces the risk of incident CVD, including MI. A meta-analysis of 15 prospective cohort and case–control studies in 173 146

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Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/7/15/e009554/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- The long-term benefits of physical activity in preventing development of myocardial infarction (MI) outweigh the risks associated with exposure to air pollution.
- Physical activity can reduce the risk of MI, even at moderate intensity levels.
- Both leisure- and transport-related physical activities reduce the risk of both incident MI and the risk of MI recurrence in patients with MI history.
- Exposure to traffic-related air pollution increases the risk of both incident and recurrent MI.

What Are the Clinical Implications?

- Benefits of physical activity in reducing the risk of incident and recurrent MI are not reduced by exposure to air pollution, in cities with air pollution levels similar to Copenhagen.

participants showed that active commuting involving walking and cycling was associated with an overall 11% reduction in CVD risk.[4] Furthermore, exercise as a part of cardiac rehabilitation is a key component for secondary prevention of CVD and the recurrence of MI.[5,6] Physical activity can improve strength and cardiovascular fitness and induce beneficial changes in cardiometabolic risk factors that are independent of mere body weight reduction.[7] Mechanisms by which physical activity decreases the risk of CVD involve favorable changes in inflammatory status, hemostatic factors, insulin sensitivity, body fat, blood lipids and viscosity, blood pressure, coronary blood flow, decreases in myocardial oxygen demand and in adrenergic activity, and increases in vagal tone.[8–10] Furthermore, physical activities often go along with a favorable change of plasma vitamin D concentrations, which could be explained by higher sun exposure while exercising outdoors.

Outdoor air pollution is a major global risk factor for CVD. In 2015, it was estimated that exposure to air pollution, in terms of fine particulate matter, was responsible for 4.2 million deaths, representing 7.6% of total global deaths, with a majority of them caused by cardio- and cerebrovascular disease.[11] Exposure to outdoor air pollution is an established risk factor for CVD morbidity and mortality, including MI.[12–14] Inflammation and oxidative stress are suggested as principal underlying mechanisms for the detrimental effects of air pollution on the cardiovascular system.[15,16]

Physical activity increases the air pollution intake by increasing the inhaled dose of air pollutants because of the exercise-induced higher minute ventilation, and a higher deposition of the inhaled particles in the lungs.[17] Only a few studies examined whether exposure to air pollution during exercise attenuates the beneficial effects of physical activity on CVD.

Findings from the Danish Diet, Cancer, and Health cohort study of 52 000 participants showed that physical activity, in terms of cycling, gardening, and participation in sports, was associated with a 16% to 22% lower risk of all-cause and 18% to 22% lower risk of cardiovascular mortality, regardless of the nitrogen dioxide (NO_2; a surrogate for traffic-related air pollution) levels at the participants' residences.[18] Kubesch et al examined the interplay between physical activity and traffic-related air pollution in a crossover experimental study in 28 healthy participants in 4 exposure scenarios and found that cycling decreased systolic blood pressure despite high air-pollution exposure levels. On the other hand, the pollutant-associated increase in diastolic blood pressure was not attenuated after cycling.[19] Another recent experimental study in 119 healthy patients with chronic obstructive pulmonary disease and CVD compared the cardiopulmonary responses to walking in a traffic-polluted versus a recreational less-polluted area and concluded that the short-term exposure to air pollution inhibits the beneficial cardiopulmonary effects of physical activity.[20]

It therefore remains unclear whether beneficial effects of the physical activities on the cardiovascular system are reduced by exposure to traffic-related air pollution, and if so, under which conditions. To date no study has evaluated whether benefits of physical activities on incident and recurrent MI are modified by exposure to air pollution.

Objectives

The aim of this study was to determine the effects of leisure-time and transport-related physical activities on the risk of incident and recurrent MI in middle-aged men and women, and to examine whether these effects were modified by residential exposure to traffic-related air pollution.

Methods

Study Population

We used data from the Danish Diet, Cancer, and Health cohort with available information on physical activity and relevant confounders for MI. Between 1993 and 1997, a total of 160 725 people, 50 to 64 years of age, born in Denmark, living in Copenhagen or Aarhus, and free of cancer, were invited to participate in the cohort study. A total of 57 053 men (48%) and women (52%) were recruited.[21] The participants completed an extensive questionnaire on physical activity, diet, smoking, alcohol consumption, education, occupation, history of diseases and medication, reproductive

health, hormone therapy use, and other health-related information. In addition, participants' blood pressure, height, and weight were measured at the enrollment. Relevant Danish ethics committees and data protection agencies approved the study, and all participants provided written informed consent.

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The Danish Cancer Society owns all data related to the Diet, Cancer, and Health cohort, and the authors therefore cannot grant access. Access to dietary and lifestyle data as well as biological material from the Diet, Cancer, and Health cohort may be possible after approval from the board of the Diet, Cancer, and Health cohort.

Physical Activity Definition

In the Danish Diet, Cancer and Health cohort, physical activities information was collected by a self-administered, interviewer-checked questionnaire in which leisure-time and utilitarian (traveling to and from work, shopping, etc) physical activities were reported as hours per week (h/wk) spent on sports (exemplified as gymnastics, running, swimming, and badminton), cycling, gardening, walking, housework, and "do-it-yourself" activities. Information was collected separately for winter and summer of the previous year, and the 2 values were averaged, so that being active implies at least half an hour per week spent on a specific activity.

The validity of the physical activity–related items of the questionnaire used in this cohort was assessed in studies finding a high correlation between self-reported physical activity estimates with the accelerometer measurements of total metabolic equivalent in 182 participants[22] and with combined heart rate and movement-sensing measurements in 1941 participants.[23]

We focused on cycling, gardening, and walking, which are relevant for outdoor physical activities habitually taking place under exposure to outdoor air pollution in Denmark, as well as participation in sports, which could include both indoor and outdoor activities. Furthermore, the participants reported their level of physical activities at work at the time of enrollment defined as sedentary, standing, light, or heavy.[22]

NO_2 Exposure Estimation

The concentrations of the traffic-related pollutant NO_2 were estimated for the residential addresses of cohort participants using the Danish AirGIS dispersion modeling system.[24] AirGIS is based on a geographical information system, and provides estimates of traffic-related air pollution with temporal (1-year averages) and spatial (address-level) resolution, which have been validated, because a high correlation was found between AirGIS-estimated and measured NO_2 values.[25,26] The correlations between modeled and measured NO_2 concentrations at 204 locations in Copenhagen (1994–1995),[25] and in a busy street in Copenhagen (1995–2006),[26] were high (r=0.90 and 0.67, respectively). AirGIS has been used in earlier studies in this cohort, reporting associations of NO_2 with asthma and chronic obstructive pulmonary disease,[27] incident MI,[28] and overall and cause-specific mortality.[18]

We used the annual mean concentrations of NO_2 at residential addresses of each cohort participant as a proxy of average exposure to traffic-related air pollution in general, and during exercise. The mean NO_2 concentrations correspond to each participant's recruitment year and therewith to the same year for which participants reported physical activities. We defined an indicator of low (lower 25th percentile of exposure range: <14.3 $\mu g/m^3$), medium (≥ 14.3–21.0 $\mu g/m^3$), and high (upper 25th percentile of exposure range: ≥ 21.0 $\mu g/m^3$) exposure to NO_2.

Outcome Definition

Using the unique personal identification numbers, we linked the cohort data to the Central Population Registry[29] to obtain vital status data (death and emigration date), and the Danish National Patient Register,[30] to identify hospital contacts (emergency, outpatient, or inpatient) since 1978 using primary discharge diagnoses for MI according the *International Classification of Diseases, 10th revision* (*ICD-10*): code I21.[31] In addition, we linked the cohort data to the Danish Cause of Death register to include out-of-hospital deaths caused by MI, for those who did not have a record of hospital contact in the Danish National Patient Register. In addition, we checked our data set for primary discharge diagnosis for codes I22 and I23 (reinfarctions and acute complications related to a MI that occurred up to 28 days before) in order to identify potentially unregistered MI cases, and we did not find any additional MI cases.

Incident MI was defined as the date of first hospital contact or out-of-hospital death caused by MI between the cohort baseline and before December 31, 2015 in participants who did not have a hospital contact for MI before cohort baseline. In participants who had hospital contact for MI before baseline, MI recurrence was defined as first hospital contact for MI or out-of-hospital death caused by MI after cohort baseline and before December 31, 2015.

Statistical Analysis

We used Cox proportional hazards regression model with age as underlying time scale to examine the associations between the physical activities/NO_2 with MI (incident and recurrent) in separate models. The follow-up started on the date of

recruitment into the cohort (1993–1997) and ended at the date of first MI or first MI recurrence, date of emigration or death, or December 31, 2015, whichever came first.

First, we estimated the associations between MI (incident and recurrent) and participation in the different types of physical activities as a dichotomous variable (yes/no) in a crude model adjusted for age only (underlying time scale) and mutually for the other 3 physical activities. Second, we fit a fully adjusted model adjusting additionally for sex, occupational physical activity, diet (fruit, vegetable, fat, and fish intake), alcohol consumption, smoking (status, intensity, and duration), environmental tobacco smoke, marital status, education, and hormone replacement therapy use (as defined in Table 1). Next, we evaluated the effect of time spent on each of the physical activities, the total time of all 4 physical activities for each participant, and the total time spent on outdoor physical activities (cycling, walking, and gardening) (0.5–4 and >4 h/wk compared with <0.5 h/wk, respectively).

We tested for effect modification of the associations between the 4 physical activities (yes/no) and incident and recurrent MI by exposure to NO_2 (low/medium/high) by introducing an interaction term into the model and using likelihood ratio tests. In addition, we performed an analysis stratified for the NO_2 concentrations (low/medium/high). Furthermore, we estimated the associations between incident and recurrent MI with NO_2, and we performed models assessing the associations between physical activities and MI under mutual adjustment for NO_2 exposure to provide additional information on potential effect modification between the 2 factors (results shown in Table S1).

As an additional analysis, we fitted a model adjusting additionally for body mass index, hypertension, hypercholesterolemia, diabetes mellitus, and stroke, which are potential biological mediators of the association between physical activities and MI (results shown in Table S2). Results are presented as hazard ratios with 95% confidence intervals, estimated with "stcox" using Stata 14 (StataCORP LP, TX).

Results

Cohort Characteristics

Of 57 053 cohort participants, 582 were excluded because of cancer diagnosis before baseline, 4410 because of missing NO_2 exposure assessment data or missing residential address at recruitment, and 193 because of missing information on potential confounder or effect modifier data, leaving 51 868 cohort participants for the study. Of these, 3260 incident or recurrent MI events (6.3%; 918 708 person years) were documented during a mean follow-up of 17.7 years between baseline (1993–1997) and December 31, 2015. Of 50 635 (97.6%) participants who did not have a history of MI at study baseline, 2936 participants developed incident MI during a mean follow-up of 17.8 years (902 192 person-years). Of 1233 (2.4%) participants with a history of MI before baseline, 324 had a recurrent MI during a mean follow-up of 14.4 years (16 515.88 person-years) (Table 1).

Mean age at baseline was 56.7 years, and 52.2% of the study participants were women. The mean body mass index was 26.0 kg/m^2 in the total cohort, and 27.1 kg/m^2 in participants who developed a MI. The majority (99.2%) of the study participants reported being involved in 1 of the 4 physical activities. Of all participants, 54% participated in sports, 68% cycled, 74% gardened, and 93% walked (Table 1). Cohort members who participated in physical activities spent on average 2.4 h/wk participating in sports, 3.2 h/wk cycling, 3.0 h/wk gardening, and 4.3 h/wk walking. Cohort participants who developed MI (incident or recurrent MI) during follow-up were slightly less physically active (98.6%; all 4 physical activities combined) than those who did not develop a MI (99.2%) (data not shown).

The mean concentration of NO_2 at residence was 18.7 $\mu g/m^3$ in the total cohort and 18.9 $\mu g/m^3$ in participants who developed a MI (incident or recurrent) during follow-up (Table 1). In this cohort, the cycling and walking levels at baseline were comparable for participants residing in areas with low (65%; 92%), medium (70%; 93%), and high (68%; 94%) NO_2 levels. In contrast, gardening was more common in participants living in areas with low NO_2 (85%) than in those in areas with medium (76%) and high (57%) NO_2 concentrations (data not shown).

Associations Between Physical Activities and MI

The crude model analysis showed a statistically significant inverse association with participation (yes/no) in sports (0.67; 0.63–0.73), cycling (0.84; 0.78–0.91), and walking (0.84; 0.74–0.96) with incident MI. These associations became weaker for sports (0.85; 0.79–0.92) and cycling (0.91; 0.84–0.98) in the fully adjusted model, while the inverse association between gardening and incident MI was strengthened (0.87; 0.80–0.95) (Table 2). Among participants with a history of MI at baseline, the crude (0.79; 0.63–0.99) and the fully adjusted analysis (0.80; 0.63–1.01) show an inverse association between cycling and recurrent MI, the latter without reaching statistical significance. We found statistically nonsignificant inverse associations between walking (0.82, 0.57–1.16) and gardening (0.91; 0.71–1.18) with recurrent MI, and a statistically nonsignificant positive association with participation in sports (1.06; 0.83–1.35) (Table 2). The inclusion of body mass index and comorbidities, such as hypertension and diabetes mellitus in the fully adjusted model, attenuated weakly the hazard ratios for the

Table 1. Characteristics of the Danish Diet, Cancer, and Health Cohort (n=51 868) at Cohort Baseline

	Total n=51 868	MI n=3260 (6.3%)
Participants without MI history before baseline, n (%)	50 635 (97.6)	2936 (90)
Participants with MI history before baseline, n (%)	1233 (2.4)	324 (9.9)
Baseline cohort covariates		
Mean (SD) age at cohort entry, y	56.7 (±4.4)	57.9 (±4.4)
Females, n (%)	27 200 (52.5)	994 (30.5)
Participation in sports, n (%)	28 170 (54.3)	1449 (44.5)
Cycling, n (%)	35 251 (68)	2031 (62.3)
Gardening, n (%)	38 146 (73.5)	2333 (71.6)
Walking, n (%)	48 262 (93.1)	2975 (91.3)
Mean (SD) h/wk participation in sports*	1.3 (±2.08)	1.1 (±2.0)
Mean (SD) h/wk cycling*	2.2 (±3.2)	2.0 (±3.2)
Mean (SD) h/wk gardening*	2.2 (±3.1)	2.5 (±3.5)
Mean (SD) h/wk walking*	4.1 (±4.6)	4.3 (±5.3)
Never smoked, n (%)	18 742 (36.1)	728.0 (22.3)
Previously smoked, n (%)	14 419 (27.8)	889 (27.3)
Currently smoking, n (%)	18 707 (36.1)	1643 (50.4)
Mean (SD) smoking duration, y	18.9 (±17.2)	26.0 (±17.1)
Mean (SD) smoking intensity, g/d	6.2 (±10.4)	9.6 (±12.2)
Environmental tobacco smoke, n (%)†	33 178 (64.0)	2397 (73.5)
Mean (SD) BMI, kg/m^2	26.0 (±4.1)	27.1 (±4.1)
Obesity (BMI ≥30 kg/m^2), n (%)	7.5 (14.4)	685 (21.0)
Sedentary work, n (%)	18 666 (36.0)	1019 (31.3)
Standing work, n (%)	8949 (17.3)	494 (15.2)
Manual work, n (%)	10 462 (20.2)	636 (19.5)
Heavy manual work, n (%)†	2386 (4.6)	202 (6.2)
Unemployed, n (%)	11 405 (22.0)	909 (27.9)
No further/professional education	7624 (14.7)	583 (17.9)
<3 y of further/professional education, n (%)	11 668 (22.5)	664 (20.4)
3 to 4 y of further/professional education, n (%)	21 099 (40.7)	1271 (39.0)
≥4 y of further/professional education, n (%)	11 477 (22.1)	742 (22.8)
Single, n (%)	3052 (5.9)	155 (4.8)
Married, n (%)	37 321 (72.0)	2344 (71.9)
Divorced, n (%)	8651 (16.7)	560 (17.2)
Widow/widower, n (%)	2844 (5.5)	201 (6.2)
Mean (SD) Fruit intake	181.6 (±148.9)	163.7 (±143.1)
Mean (SD) Vegetable intake	173.8 (±97.3)	158.6 (±94.2)
Mean (SD) Fish intake	43.2 (±26.5)	44.8 (±27.6)
Mean (SD) Fat intake	85.2 (±29.9)	89.6 (±31.4)
Mean (SD) Alcohol intake	20.5 (±21.7)	21.7 (±23.0)
Air pollution levels at baseline y (1993–1997)		
Mean SD (SD) NO_2	18.7 (±6.6)	18.9 (±6.6)

Continued

Table 1. Continued

	Total n=51 868	MI n=3260 (6.3%)
Low 25th percentile (<14.3 μg/m^3), *n* (%)	12 863 (24.8)	293 (23.8)
Medium (14.3–21.0 μg/m^3), *n* (%)	26 129 (50.4)	631 (51.2)
High (>21.0 μg/m^3), *n* (%)	12 876 (24.8)	309 (25.1)

BMI indicates body mass index; MI, myocardial infarction; NO_2, nitrogen dioxide.
*Duration of participation in physical activities for participants.
†Indicator of exposure to smoke in the home and/or at work for at least 4 h/d.

associations between physical activities and incident and recurrent MI (Table S2).

Association Between the Time Spent With Physical Activities and MI

In participants without a history of MI at baseline, the participation in sports 0.5 to 4 and >4 h/wk reduced the risk for incident MI by 14% and 18%, respectively (0.86; 0.79–0.93, and 0.82; 0.70–0.96), compared with no participation in sports (<0.5 h/wk). Cycling for >4 h/wk was inversely associated with incident MI (0.86; 0.77–0.97) as compared with cycling <0.5 h/wk. We found an inverse association with gardening 0.5 to 4 h/wk (0.87; 0.79–0.95) and >4 h/wk (0.89; 0.79–0.95), compared with gardening <0.5 h/wk. In participants with MI history at baseline, we found an inverse association with cycling 0.5 to 4 h/wk (0.69; 0.53–0.89) as compared with cycling <0.5 h/wk, showing a 31% risk reduction of recurrent MI. The combined analysis of the 4 physical activities and recurrent MI showed an inverse association with 0.5 to 4 h/wk (0.47; 0.24–0.89) and >4 h/wk (0.42; 0.23–0.78), compared with <0.5 h/wk participation in all 4 activities combined. More than 4 h/wk participation in outdoor physical activities (cycling, walking, and gardening combined) was inversely associated (0.50; 0.28–0.88) with recurrent MI, compared with <0.5 h/wk participation in outdoor activities combined (Table 3).

Table 2. Association Between Participation in PAs (Yes/No) and MI

	Crude Model*	Fully Adjusted Model†
	HR (95% CI)	
Incident MI (n=2936) in 50 635 participants without a history of MI before baseline		
Sports (n=27 672)	0.67 (0.63–0.73)	0.85 (0.79–0.92)
Cycling (n=34 529)	0.84 (0.78–0.91)	0.91 (0.84–0.98)
Walking (n=47 142)	0.84 (0.74–0.96)	0.95 (0.83–1.08)
Gardening (n=37 298)	0.94 (0.87–1.02)	0.87 (0.80–0.95)
Recurrent MI (n=324) in 1233 participants with a history of MI before baseline		
Sports (n=498)	0.97 (0.77–1.22)	1.06 (0.83–1.35)
Cycling (n=722)	0.79 (0.63–0.99)	0.80 (0.63–1.01)
Walking (n=1120)	0.78 (0.55–1.10)	0.82 (0.57–1.16)
Gardening (n=848)	0.98 (0.78–1.25)	0.91 (0.71–1.18)

CI indicates confidence interval; HR, hazard ratio; MI, myocardial infarction; PAs, physical activities.
*Adjusted mutually for the other 3 PAs.
†Adjusted for sex, smoking (status, intensity, and years smoked), environmental tobacco smoke, education, PAs at work, diet (fruit, vegetable, fat, and fish intake), alcohol consumption, marital status, and mutually for the other 3 PAs.

Association Between NO_2 and MI

As compared with residing in areas with low NO_2 (<14.3 μg/m^3), residing in areas with high NO_2 concentrations (>20.9 μg/m^3) was positively associated with incident MI in both the crude (1.19; 1.07–1.32) and the fully adjusted (1.17; 1.05–1.30) analysis. In participants with history of MI at baseline, residing in areas with high NO_2 levels was positively associated with the risk of recurrent MI in the fully adjusted analyses (1.39; 1.01–1.93) (Table S3).

Interaction Between Physical Activities and NO_2

We found no statistically significant effect modification of the association between incident or recurrent MI with participation in physical activities by residential NO_2 at the time of enrollment in the study (Table 4). In addition, the effects of physical activities were independent of NO_2 in the adjusted model (Table S1).

The analysis stratified by different levels of residential NO_2 exposure showed inverse associations between sport and incident MI in medium and high residential NO_2 exposure (0.87;0.78–0.97; and 0.79; 0.68–0.92), and cycling in medium residential NO_2 exposure (0.85; 0.76–0.95). Cycling was also inversely associated with recurrent MI in higher residential NO_2 exposure (0.54; 0.34–0.86) only (Table 5).

Discussion

Summary

The results of this cohort study support existing evidence that physical activity can reduce the risk of MI, even at moderate

Table 3. Association Between Times Spent on PAs and MI

	Sport*	Cycling*	Walking*	Gardening*	All PAs†	Outdoor PAs‡
	HR (95% CI)					
Incident MI (n=2936) in 50 635 participants without a history of MI before baseline						
	n=27 672	n=34 529	n=47 142	n=37 298	n=50 242	n=50 042
<0.5 h/wk	1.0	1.0	1.0	1.0	1.0	1.0
0.5 to 4 h/wk	0.86 (0.79–0.93)	0.93 (0.86–1.01)	0.95 (0.83–1.09)	0.87 (0.79–0.95)	0.77 (0.55–1.08)	0.81 (0.61–1.09)
>4 h/wk	0.82 (0.70–0.96)	0.86 (0.77–0.97)	0.96 (0.83–1.11)	0.89 (0.79–0.99)	0.72 (0.51–1.01)	0.76 (0.57–1.02)
Recurrent MI (n=324) in 1233 participants with a history of MI before baseline						
	n=498	n=722	n=1120	n=848	n=1212	n=1205
<0.5 h/wk	1.0	1.0	1.0	1.0	1.0	1.0
0.5 to 4 h/wk	1.03 (0.80–1.32)	0.69 (0.53–0.89)	0.90 (0.62–1.30)	0.89 (0.68–1.17)	0.47 (0.24–0.89)	0.55 (0.30–1.00)
>4 h/wk	1.15 (0.69–1.89)	1.14 (0.83–1.57)	0.72 (0.49–1.06)	1.05 (0.76–1.44)	0.42 (0.23–0.78)	0.50 (0.28–0.88)

CI indicates confidence interval; HR, hazard ratio; MI, myocardial infarction; PAs, physical activities.
*Adjusted for sex, smoking (status, intensity, years smoked), environmental tobacco smoke, occupational smoke, education, PAs at work, diet (fruit, vegetable, fat, and fish intake), alcohol consumption, marital status, and mutually for other 3 PAs.
†Combined time spent on sport, cycling, walking, and gardening; adjusted for sex, smoking (status, intensity, years smoked), environmental tobacco smoke, occupational smoke, education, PAs at work, diet (fruit, vegetable, fat, and fish intake), alcohol consumption, and marital status.
‡Combined time spent cycling, walking, and gardening; adjusted for sex, smoking (status, intensity, years smoked), environmental tobacco smoke, occupational smoke, education, PAs at work, diet (fruit, vegetable, fat, and fish intake), alcohol consumption, and marital status.

intensity levels. We found that all physical activities (sports, cycling, and gardening) with the exception of walking were associated with a significantly reduced (9%–15%) risk of incident MI. In patients with MI, with the exception of sports, all physical activities (cycling, walking, and gardening) were nonstatistically significantly associated with a 9% to 20% reduction in risk of recurrent MI. We found statistically significant associations with moderate (0.5–4 h/wk) cycling, reducing the risk of recurrent MI by 31%, a 58% reduction for >4 h/wk participation in all physical activities combined, and 50% for outdoor physical activities only, all compared with no participation in physical activities. Exposure to traffic-related air pollution, assessed as NO_2 at the participants' residences, was associated with increased risk of both incident MI and recurrent MI. We present a novel finding of no effect modification of the association between physical activities and MI by residential NO_2.

Effects of Physical Activities on MI Incidence and Recurrence

We found a 15% lower rate of incident MI hospital contacts in cohort members who participated in sports and 9% risk reduction associated with cycling. These results are in agreement with recent studies reporting an 8% to 35% lower risk of MI associated with physical activities.[4,9,32,33]

Generally, we did not find a dose–response relationship between time spent on physical activities and incident MI or recurrent MI. A Swedish study showed a 31% reduced risk for incident MI associated with high versus low leisure-time physical activities.[34] Earlier studies with data on high- and moderate-intensity exercise among CVD patients found that both intensity levels decreased CVD risk, but also pointed to the knowledge gap regarding the right intensity and amount of physical activity in secondary prevention of CVD.[35–37]

We primarily compare the participation in physical activities with no participation in physical activities (<0.5 h/wk), which also involves sedentary participants. Generally, in a comparison with a sedentary population, it should be considered that sedentary or close to sedentary participants are more likely to be a particular group with potentially lower health status or a generally less healthy lifestyle, which may lead to an overestimation of the health-promoting effects of physical inactivity if not taken into account.[38]

Interaction Between Physical Activities and NO_2

Our results complement recent findings by Roswall et al in this cohort, showing that long-term exposure to NO_2 was associated with increased risk of incident MI.[28] We found that high (>20.9 $\mu g/m^3$) as compared with low (<14.3 $\mu g/m^3$) residential NO_2 exposure was associated with 17% increased risk of incident MI, in agreement with Roswall et al, and 39% increased risk for recurrent MI, which is a novel finding. The findings in this cohort agree with previous evidence showing that exposure to outdoor air pollution increases risk of CVD morbidity and mortality.[12–14,39]

Table 4. Effect Modification of Association* Between Participation in PAs and MI by Annual Mean Level of NO_2 at Cohort Baseline

	Low NO_2 <14.3 μg/m^3	Medium NO_2 14.3 to 21.0 μg/m^3	High NO_2 ≥21.0 μg/m^3	
	HR (95% CI)			*P* Value for Interaction With NO_2
Incident MI (n=2936) in 50 635 participants without a history of MI before baseline				
	n=12 570	n=25 498	n=12 567	
Sports				0.6089
No	1.00	1.10 (0.97–1.25)	1.22 (1.06–1.41)	
Yes	0.91 (0.78–1.07)	0.93 (0.77–1.11)	0.91 (0.74–1.11)	
Cycling				0.1656
No	1.00	1.19 (1.02–1.38)	1.23 (1.04–1.46)	
Yes	1.01 (0.87–1.19)	0.84 (0.69–1.01)	0.91 (0.74–1.13)	
Walking				0.5895
No	1.00	1.20 (0.88–1.64)	1.38 (0.97–1.97)	
Yes	1.05 (0.81–1.37)	0.87 (0.63–1.20)	0.83 (0.57–1.21)	
Gardening				0.6743
No	1.00	1.16 (0.93–1.46)	1.24 (0.99–1.56)	
Yes	0.97 (0.78–1.21)	0.90 (0.70–1.15)	0.93 (0.72–1.21	
Recurrent MI (n=324) in 1233 participants with a history of MI before baseline				
	n=293	n=631	n=309	
Sports				0.8327
No	1.00	1.05 (0.73–1.50)	1.19 (0.79–1.80)	
Yes	0.82 (0.49–1.35)	1.31 (0.73–2.36)	1.49 (0.77–2.86)	
Cycling				0.8698
No	1.00	1.05 (0.70–1.57)	1.47 (0.94–2.30)	
Yes	0.74 (0.46–1.19)	1.21 (0.69–2.13)	0.90 (0.48–1.70)	
Walking				0.5899
No	1.00	1.12 (0.54–2.32)	0.67 (0.23–1.93)	
Yes	0.67 (0.35–1.26)	1.04 (0.47–2.31)	2.25 (0.74–6.87)	
Gardening				0.052
No	1.00	1.26 (0.70–2.26)	0.99 (0.53–1.86)	
Yes	0.86 (0.48–1.55)	0.88 (0.45–1.72)	1.71 (0.83–3.54)	

CI indicates confidence interval; HR, hazard ratio; MI, myocardial infarction; NO_2, nitrogen dioxide; PAs, physical activities.
*Adjusted for sex, smoking (status, intensity, and years smoked), environmental tobacco smoke, occupational smoke, education, PAs at work, diet (fruit, vegetable, fat, and fish intake), alcohol consumption, marital status, and mutually for 3 other PAs.

There was no evidence of modification of the associations between physical activities and incident or recurrent MI by NO_2 at residence (Table 4). This table also shows that the risk of MI increased with increasing levels of NO_2, in participants who were not physically active, while the benefits of physical activity remained in all 3 NO_2 level groups (Table 4). Similar patterns were observed in the stratified analyses (Table 5), which showed that physical activity reduced the incident MI risk in all 3 groups of NO_2 (low/medium/high), while in participants with a history of MI, the risk for MI recurrence was inversely associated with some (sports, gardening, and walking), but not all physical activities. In high residential NO_2 concentrations, only cycling was strongly protective. This may suggest an increased susceptibility of patients with MI (in contrast to participants without MI history) to the exposure to traffic-related air pollution during physical activity. However, these results need to be interpreted with caution, because of the small number of cases and inconsistent results across different activities in the group of participants with a history of MI.

Table 5. Association* Between Participation in PAs and MI, Stratified by NO_2 Annual Mean Concentrations at Participants' Residences

	Low NO_2 <14.3 μg/m^3	Medium NO_2 14.3 to 21.0 μg/m^3	High NO_2 ≥21.0 μg/m^3
	HR (95% CI)		
Incident MI (n=2936) in 50 635 participants without a history of MI before baseline			
	n=12 570	n=25 498	n=12 567
Sports	0.92 (0.78–1.08)	0.87 (0.78–0.97)	0.79 (0.68–0.92)
Cycling	0.99 (0.84–1.17)	0.85 (0.76–0.95)	0.93 (0.80–1.07)
Walking	1.01 (0.77–1.33)	0.93 (0.77–1.12)	0.86 (0.66–1.12)
Gardening	0.96 (0.76–1.20)	0.89 (0.78–1.00)	0.89 (0.77–1.03)
Recurrent MI (324) in 1233 participants with a history of MI before baseline			
	n=293	n=631	n=309
Sports	0.89 (0.51–1.58)	1.19 (0.84–1.69)	1.33 (0.85–2.07)
Cycling	0.88 80.52–1.50)	0.93 (0.66–1.30)	0.54 (0.34–0.86)
Walking	0.63 (0.31–1.29)	0.69 (0.43–1.13)	1.49 (0.57–3.92)
Gardening	1.10 (0.57–2.09)	0.74 (0.52–1.06)	1.58 (0.98–2.54)

CI indicates confidence interval; HR, hazard ratio; MI, myocardial infarction; NO_2, nitrogen dioxide; PAs, physical activities.
*Adjusted for sex, smoking (status, intensity, and years smoked), environmental tobacco smoke, education, PAs at work, diet (fruit, vegetable, fat, and fish intake), alcohol consumption, marital status, and mutually for 3 other PAs.

Our finding of a long-term, preventive effect of physical activities on CVD morbidity and mortality, independent from the exposure to traffic-related air pollution, complements recent results by Kubesch et al, who, in an human experimental study of the interaction between short-term exposure to traffic-related air pollution and physical activity in Barcelona, Spain, found no evidence of interaction with NO_X (a generic term for nitrogen oxides relevant for traffic-related air pollution), and furthermore, confirmed that cycling both in locations with high and low traffic-related air pollution lowered systolic blood pressure, albeit to a lesser extent after high traffic-related air pollution exposure.[19] The authors also found that the pollutant-associated diastolic blood pressure increases were not attenuated by physical activity. Sinharay et al showed reduced beneficial changes in indices of arterial stiffness in healthy and ischemic heart disease participants after walking in streets with high compared with low concentrations of traffic-related air pollution.[20] However, the air pollution exposures in the above experimental studies taking place in Barcelona and London were substantially higher levels than those in our study. Finally, the results of our study corroborate recent findings from this cohort on beneficial long-term effects of physical activities in reducing risk of premature overall and CVD mortality, in areas with low and high levels of traffic-related air pollution in Denmark.[18]

Strengths and Limitations

The main strength of our study includes the use of the objective definition of MI incidence and recurrence based on the hospital contact data from the Danish National Patient Register, a nationwide validated register[31] of routinely collected data on all hospital contacts in Denmark since 1978, with no loss to follow-up, as well as MI-related out-of-hospital deaths from the Danish Cause of Death Register. Validation studies of MI diagnoses from the Danish National Patient Register, as compared with medical records and discharge summaries, found high validity and positive predictive value between 90% and 100%.[31] Furthermore, we benefited from the large prospective cohort with well-defined data on MI-related confounders and physical activity. Our data on physical activities included differentiated information on the physical activities level at work that we could adjust for in our analysis. Another major strength of this study is the setting in 2 urban areas in Denmark, where prevalence of cycling was high (68%), and includes both leisure and utilitarian cycling. Moreover, information and differential bias in relation to exposure can be considered minimal in this study, since MI events, vital status, and information on residential addresses used for modeling NO_2 exposure concentrations are obtained objectively from reliable population registers.

A weakness of the study is the long follow-up time without updated information, neither on the participants' residences and therewith on changes in their residential NO_2 exposures, nor on changes of participants' physical activity habits or risk factors for MI, which might have changed from the time of reporting at enrollment in the study. Another weakness of the study is the use of NO_2 levels at baseline residence as a proxy

of traffic-related air pollution level exposure during the investigated physical activities. This proxy is probably reasonable for gardening, which is assumed to take place at the baseline residence, where NO_2 levels are modeled, but less reasonable for walking, cycling, and sports. The exact location where physical activities took place is not known, and resulting exposure misclassification of the investigated effect modifier may explain lack of interaction between physical activities and NO_2 in this study. Moreover, we used NO_2 as a proxy for traffic-related air pollution since there is a lack of data on other pollutants. The exposure to particulate matter, ozone, and carbon monoxide while exercising was previously discussed as a risk factor, especially in patients with CVD.[40] Although NO_2 is a good proxy of traffic-related air pollution, the results of this study for NO_2 cannot be generalized to other pollutants, and more data with particulate matter and ozone are needed. Furthermore, we assume potential air pollution exposure misclassification because of different levels of exposure between work and residential NO_2 exposure concentrations. Generally, people spent a considerable time of their life at work away from their residences. The NO_2 exposures at the participants' work addresses potentially differ from the concentration we estimated for the residences of our cohort participants. In this cohort, only ≈21% of the participants reported being unemployed and therefore, the real NO_2 exposures of the major part of our cohort participants may vary from the estimated NO_2 exposure. However, considering the age of the cohort participants at recruitment (50–65 years), several of whom retired during follow-up, we can assume that walking and cycling occurred in close proximity to their residences.

Physical activity "dose" is a combination of the duration, intensity, and frequency of activity.[41] We lacked detailed information on physical activities intensities, which is a weakness of this study when it comes to the development of strategies concerning the appropriate dose of physical activities for the prevention of incident, and in particular for the prevention of MI recurrence. Furthermore, the nonspecific nature of participation in sports is variable, and whether it pertained to indoor or outdoor activity limits our results. Also, we lacked data on the health history status of participants with MI before baseline and cannot distinguish MI patients by disease severity. For that reason, we cannot determine whether physical activities are generally beneficial for all patients with MI regardless of their health impairment or only for those with less severe health impairment after MI.

Another weakness of the study is the possibility that the nonsignificant interaction between NO_2 and physical activity was explained by the reverse association between air pollution and physical activity, meaning that people chose not to participate in physical activity on days with higher levels of air pollution.[42,43]

Finally, we cannot exclude some degree of potential reverse causality, meaning that cohort participants with some kind of unrecognized or recognized health condition at baseline were already less engaged in physical activities because of their condition. Also, we cannot exclude an overestimation of the benefits of the physical activities presented in this cohort, since participants of the Diet, Cancer, and Health cohort were potentially healthier than the general Danish population, because of their better education and higher income than nonparticipants.[22]

Our results add new evidence to the literature on the protective effect of physical activities and the time spent on these activities on MI incidence and recurrence. Our results support that physical activity, even at low and moderate levels, and even outdoor activities such as cycling and gardening, are effective in the prevention of MI among middle-aged women and men. Our finding that long-term benefits of physical activities on MI incidence and recurrence are not statistically significantly modified by exposure to higher levels of NO_2 is novel. Our results strengthen and complement a growing number of health impact assessment studies, supporting the evidence that health benefits because of increased physical activities levels generally outweigh the risks related to increases in inhaled air pollution doses during physical activity.[44] However, given the limitations of our study, we cannot exclude potentially higher net effects of physical activities, when predominantly performed in low air pollution. We therefore recommend, particularly to the more susceptible populations, eluding increased air pollutant uptake by simple measures such as avoiding active commuting or exercising along busy main roads, and instead to choose alternative less polluted side roads, parks and green areas, etc.

Conclusion

We found that physical activity has preventive effects on both the incidence and the recurrence of MI. The beneficial effects of physical activities on incident and recurrent MI are independent of the exposure to NO_2, and are not reduced in those living in areas with high residential NO_2 levels. Thus, we can conclude that the long-term benefits of physical activity in preventing the development of MI in healthy, middle-aged participants, and possibly as effective disease control in patients with prior MI, can outweigh the risks associated with enhanced residential exposure to traffic-related air pollution during physical activity.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Association between annual mean level of NO_2 at cohort baseline, physical activities (yes/no), and myocardial infarction, in a mutually adjusted model.

	Crude* model	**Fully adjusted† model**
	HR (95% CI)	HR (95% CI)
Incident MI (n =2,936) in 50,635 participants without a history of MI before baseline		
NO_2	1.09 (1.04-1.15)	1.08 (1.03-1.14)
Sports	0.68 (0.63-0.73)	0.86 (0.79-0.93)
Cycling	0.83 (0.77-0.90)	0.90 (0.84-0.98)
Walking	0.83 (0.73-0.95)	0.94 (0.82-1.07)
Gardening	0.97 (0.90-1.06)	0.89 (0.82-0.98)
Outdoor PAs‡	0.66 (0.50-0.88)	0.77 (0.58-1.03)
Recurrent MI (n =324) in 1,233 participants with a history of MI before baseline		
NO_2	1.14 (0.97-1.34)	1.18 (1.00-1.39)
Sports	0.98 (0.78-1.23)	1.06 (0.84-1.35)
Cycling	0.78 (0.62-0.98)	0.79 (0.62-1.00)
Walking	0.77 (0.55-1.09)	0.80 (0.56-1.14)
Gardening	1.03 (0.81-1.32)	0.96 (0.75-1.25)
Outdoor PAs‡	0.50 (0.29-0.88)	0.52 (0.30-0.91)

NO_2 – Nitrogen Dioxide; MI – Myocardial infarction; HR - hazard ratio; CI - Confidence Interval

* Adjusted mutually for other three physical activities and residential annual mean NO_2 exposure.

† Assessed in a separate model; Adjusted for sex, smoking (status, intensity, years smoked) , environmental tobacco smoke, education, physical activities at work, diet (fruit, vegetable, fat, and fish intake), alcohol consumption, marital status, and mutually for other three physical activities, and residential annual mean NO_2 exposure.

‡ Combined time spent cycling, walking, and gardening; adjusted for sex, smoking (status, intensity, years smoked) , environmental tobacco smoke, occupational smoke, education, physical activities at work, diet (fruit, vegetable, fat, and fish intake), alcohol consumption, marital status.

Table S2. Association between participation (yes/no) in physical activities and myocardial infarction.

	Crude* **model**	**Fully Adjusted† model**	**Fully Adjusted† model** Additional adjustment for BMI‡	**Fully Adjusted† model** Additional adjustment for BMI & Co-morbidities§	**Fully Adjusted† model** Without adjustment for Education	**Fully Adjusted† model** **Females**	**Fully Adjusted† model** **Males**
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Incident MI (n =2,936) in 50,635 participants without a history of MI before baseline							
Sports	0.67 (0.63-0.73)	0.85 (0.79-0.92)	0.89 (0.82-0.96)	0.92 (0.85-0.99)	0.84 (0.78-0.91)	0.83 (0.72-0.95)	0.87 (0.79-0.96)
Cycling	0.84 (0.78-0.91)	0.91 (0.84-0.98)	0.93 (0.86-1.00)	0.94 (0.87-1.02)	0.91 (0.84-0.98)	0.88 (0.76-1.01)	0.92 (0.84-1.01)
Walking	0.84 (0.74-0.96)	0.95 (0.83-1.08)	0.96 (0.84-1.09)	0.95 (0.83-1.08)	0.94 (0.82-1.07)	0.87 (0.68-1.12)	0.97 (0.83-1.13)
Gardening	0.94 (0.87-1.02)	0.87 (0.80-0.95)	0.89 (0.82-0.97)	0.91 (0.83-0.99)	0.86 (0.79-0.94)	0.98 (0.85-1.12)	0.83 (0.75-0.93)
Recurrent MI (n =324) in 1,233 participants with a history of MI before baseline							
Sports	0.97 (0.77-1.22)	1.06 (0.83-1.35)	1.07 (0.84-1.36)	1.06 (0.84-1.35)	1.05 (0.83-1.33)	1.68 (0.96-2.91)	1.00 (0.76-1.31)
Cycling	0.79 (0.63-0.99)	0.80 (0.63-1.01)	0.79 (0.63-1.00)	0.80 (0.63-1.01)	0.80 (0.63-1.01)	0.47 (0.27-0.82)	0.92 (0.71-1.21)
Walking	0.78 (0.55-1.10)	0.82 (0.57-1.16)	0.85 (0.60-1.20)	0.85 (0.60-1.21)	0.81 (0.57-1.15)	0.55 (0.25-1.22)	0.84 (0.56-1.26)
Gardening	0.98 (0.78-1.25)	0.91(0.71-1.18)	0.91 (0.71-1.17)	0.92 (0.71-1.19)	0.90 (0.70-1.16)	0.90 (0.51-1.59)	0.91 (0.68-1.22)

MI – Myocardial infarction; HR - hazard ratio; CI - confidence interval;

* Adjusted mutually for the other physical activities;

† Adjusted for sex, smoking (status, intensity, years smoked) , environmental tobacco smoke, education, physical activities at work, diet (fruit, vegetable, fat, and fish intake), alcohol consumption, marital status, and mutually for other three physical activities.

‡ Additional adjustment for BMI ("Underweight = <18.5 //Normal weight = 18.5–24.9 //Overweight = 25–29.9 //Obesity = BMI of 30 or greater")

§ Additional adjustment for BMI and self-reported co-morbidities (stroke, hypertension, high cholesterol, and diabetes mellitus type II)

Table S3. Association of annual mean level of NO_2 at cohort baseline and myocardial infarction.

	Crude model	**Fully adjusted† model**
	HR (95% CI)	HR (95% CI)
Incident MI (n =2,851) in 50,635 participants without a history of MI before baseline		
Low NO_2 (< 14.3 µg/m^3)	1.0	1.0
Medium NO_2 (14.3-20.9 µg/m^3)	1.06 (0.97-1.16)	1.06 (0.97-1.17)
High NO_2 (> 20.9 µg/m^3)	1.19 (1.07-1.32)	1.17 (1.05-1.30)
Recurrent MI (n =324) in 1,233 participants with a history of MI before baseline		
Low NO_2 (< 14.3 µg/m^3)	1.0	1.0
Medium NO_2 (14.3-20.9 µg/m^3)	1.11 (0.84-1.47)	1.16 (0.88-1.54)
High NO_2 (> 21.0 µg/m^3)	1.29 (0.94-1.78)	1.39 (1.01-1.93)

MI – Myocardial infarction; HR hazard ratio; CI confidence interval;

*Adjusted for sex, smoking (status, intensity, years smoked), environmental tobacco smoke, occupational smoke, education, physical activities at work, diet (fruit, vegetable, fat, and fish intake), alcohol consumption, marital status, and for commute and leisure time physical activities.