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Original Research Paper

Physical activity is associated with a decreased multiple sclerosis risk: The EnvIMS study

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Abstract

Background: The lifestyle factors smoking and obesity have been associated with the risk of multiple sclerosis (MS). Physical activity (PA) may also be of importance.

Objective: To examine the association between PA and MS risk in Italy, Norway, and Sweden and to evaluate the possible influence by established risk factors.

Methods: In this case–control study, 1904 cases and 3694 controls were asked to report their average weekly amounts of light and vigorous PA during adolescence on a scale ranging from none to more than 3 hours activity. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) and adjusted for potential confounders.

Results: Vigorous PA was inversely associated with MS risk in the pooled analysis (p-trend < 0.001) with an age- and sex-adjusted OR of 0.74 (95% CI: 0.63–0.87) when comparing the highest and lowest levels. Adjusting for outdoor activity, infectious mononucleosis, body size, and smoking yielded similar results. The association was present in all countries and was not affected by exclusion of patients with early disease onset. Light PA was not associated with the risk of MS.

Conclusion: Our findings suggest that vigorous PA can modify the risk of developing MS independent of established risk factors.

Keywords: Multiple sclerosis, epidemiology, case–control study, risk factors, physical activity, exercise

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) likely caused by an interaction between environmental and genetic risk factors.[1] Infectious mononucleosis (IM) and lifestyle factors such as low levels of vitamin D, little sun exposure, cigarette smoking, and being overweight have been associated with an increased risk of MS,[2–4] with adolescence and early adulthood likely critical periods for exposure.[5]

Physical activity (PA) is another modifiable lifestyle factor that may be of etiological importance. In the general population, regular PA has been associated with reduced all-cause mortality[6] and lower risk of various chronic conditions such as cardiovascular diseases, type 2 diabetes mellitus, certain cancers, and dementia.[7,8] In MS patients, different types of exercise therapies have favorable effects on muscle strength, exercise tolerance functions, mobility, and fatigue.[9,10] Furthermore, cardiorespiratory fitness may even preserve gray matter volume and white matter integrity.[11]

Less is known about the potential role of PA as a risk modifier in MS. Two prospective cohort studies recently observed that future male MS cases had lower physical performance scores at age 18–19 years compared to controls,[12,13] even after adjusting for body mass index (BMI), suggesting a possible protective role of PA on MS risk. However, it is not known whether these findings can be generalized to women or to populations in other geographical areas or if other risk factors could confound the results. A recent study among American female nurses that analyzed PA at various ages observed an inverse association between total PA in adulthood and MS risk. However, the association in this study was no longer significant after excluding the first 6 years of follow-up, indicating that lower levels of PA could be a consequence of early MS-symptoms rather than a risk factor for MS, that is, reverse causality.[14] Thus,

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the current evidence for an impact of PA on MS risk remains inconclusive.

We therefore analyzed data from a large multinational case–control study to examine the role of PA on MS risk and to assess whether established risk factors or reverse causality could explain a possible association.

Materials and methods

Study design

A detailed overview of the study design and the methodology has been reported elsewhere.[15] In short, the Environmental Risk Factors In MS (EnvIMS) study is a population-based multinational case–control study designed to examine the contribution of relevant environmental factors and lifestyle behaviors on MS risk in different well-defined geographical areas in Europe (Italy, Norway, Sweden, and Serbia) and in Canada. The majority of data were collected between 2009 and 2013. The cases were recruited from national or local MS registries/databases in Europe and from neurological clinics in Canada. Only adult MS cases (⩾18 years) diagnosed according to the McDonald criteria[16] or the Poser criteria[17] with disease duration of 10 years or less were included in the study. Four times as many controls frequency-matched on sex, age, and area were drawn from the general population. At the time of analysis included in this study, complete data from Serbia and Canada were not available.

A self-administered postal questionnaire (the EnvIMS-Q) identical for cases and controls was designed for this study to inquire about age-specific exposures during childhood, adolescence, and young adulthood until age 30 years.[18] It included questions about outdoor activity, infections, diet and dietary supplements, smoking habits, body size, PA, and occupational and hormonal factors. The EnvIMS-Q has been translated into relevant languages and has been evaluated for acceptability, feasibility, cross-cultural validity, and reliability.[18]

Study population

Data from Italy, Norway, and Sweden were available for the current analyses. The response rates were in general higher among cases than controls with similar response rates in Norway (cases 70% and controls 36%) and Sweden (cases 68%, controls 37%), but lower in Italy (cases 42%, controls 21%). In total, our study population comprised 3694 controls (1717 from Norway, 1333 from Italy, and 644 from Sweden) and 1904 cases (953 from Norway, 707 from Italy, and 244 from Sweden).

Exposures and confounding factors

In the EnvIMS-Q, the participants were asked how many hours they spent on average on PA each week from age 13 until 19 years. The intensity of PA was categorized into "light PA," which was defined as activity without increased respiratory rate or perspiration, and "vigorous PA," which was defined as activity increasing the respiratory rate and resulting in perspiration. The participants reported the number of hours of light PA and vigorous PA on a 4-point scale ("none," "less than 1," "1–2," and "3 or more" hours per week). As very few participants reported the lowest level of activity ("none"), we combined category 1 and 2.

Other potential confounders reported in the EnvIMS-Q were smoking (ever-never), IM (ever-never), outdoor activity during summer (rated as "seldom," "moderate," "often," and "almost all the time"), and body size at age 15 years (defined by nine body silhouettes on Stunkard's[19] figure rating scale where we combined body sizes 6–9 representing overweight due to low numbers in the extreme groups).

To include information on exposure to PA and outdoor activity during the same age interval in the models, we created a variable that combined summer outdoor activity from age 13–15 and 16–18 years in Norway and Sweden and from age 11–15 and 16–20 years in Italy. In the Norwegian and Swedish EnvIMS-Q, the age intervals were matched to the educational system to facilitate recall, while for the Italian EnvIMS-Q it was decided to use fixed 5-year intervals instead. The values in the original variables (ranging from 1, "seldom," to 4, "almost all the time") were added and the new variable took value "1" if the sum was 1–2, "2" if the sum was 3–4, "3" if the sum was 5–6, and "4" if the sum was 7–8. In Norway, we had additional information about vitamin D3 supplementation through a frequency-rated intake of cod liver oil in adolescence (13–19 years) during winter when the sun-induced vitamin D production at this latitude is negligible.[20] Further details on the description of the exposures are reported elsewhere.[18]

Statistical analyses

The statistical analyses were performed with the statistical software IBM SPSS, version 23. We merged the datasets for each country to make both pooled and country-specific analyses. We also stratified the pooled data on sex to examine any sex differences. The

characteristics of the study population were expressed as frequencies, means, and proportions of relevant exposures within each category of light and vigorous PA.

We used logistic regression to estimate odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for the effect of PA on MS risk. PA was modeled as a categorical variable using category 1 (less than 1 hour PA) as reference level. All analyses were adjusted for age (categorical variable: "18–39 years," "40–49 years," "50–59 years," "60 years and above") and sex. *p*-value for trend was calculated by including PA as a continuous variable in the model. We further adjusted for level of outdoor activity during adolescence, IM, smoking, and body size at age 15 years as previously described. In Norway, we also adjusted for the intake of various amounts of cod liver oil during winter. Since outdoor activity and IM were not equally distributed across strata of PA, we first included these in one model and then also included smoking and body size in a second model. We introduced an interaction term in the regression model to test for interaction on the multiplicative scale between sex and PA.

All controls were given a randomly distributed index age based on the distribution of age at onset for the cases. Exposures that took place after the index age/age at onset were not considered as exposure. Participants with missing values on PA or relevant covariates were excluded from the analyses. In addition, we excluded participants with an index age of 20 years or less as outdoor activity in Italy covered the whole period from age 11 until 20 years. We finally did a sensitivity analysis among participants with an index age of more than 30 years to examine whether the association between PA and the risk of MS was influenced by the time between exposure and onset of disease, which could suggest reverse causality.

Ethical considerations and approvals

Responding and returning the EnvIMS-Q was considered as implied consent. The participants were de-identified using a numerical code on the questionnaires.

The EnvIMS study was approved by regional ethical committees in Norway, Italy, and Sweden.[15]

Results

The pooled population characteristics and how other relevant exposures are distributed across the categories of light and vigorous PA are shown in Table 1. There were more participants in the active groups, and women were less active than men. Smoking and IM were more frequently reported among cases. The proportion of participants reporting IM and high level of outdoor activity increased with increasing amounts of light and vigorous PA. A large body size was infrequently reported in all groups and was inversely related to the level of PA. Participants who had missing data on PA had similar baseline characteristics compared to the other participants who reported on PA, but there were a higher proportion of men among the non-responders of light PA and a lower proportion of men among the non-responders of vigorous PA.

The pooled data showed that vigorous PA of more than 3 hours/week was associated with a reduced risk of MS with an age- and sex-adjusted OR of 0.74 (95% CI: 0.63–0.87) compared to the lowest amounts of PA (Table 2). Adjusting for the other risk factors gave only minor changes to this risk estimate. The results suggested a dose–response relationship between the amount of vigorous PA and the risk of MS (*p* for trend: <0.001). We did not find any association between the amount of light PA and the risk of MS, neither in the age- and sex-adjusted analyses nor in the multivariable-adjusted analyses.

The analyses for each country showed the same trend toward a protective effect of the highest levels of vigorous PA ranging from age- and sex-adjusted OR 0.59 (95% CI: 0.39–0.90) in Sweden to OR 0.79 (95% CI: 0.60–1.05) in Italy (Table 3). The point estimates remained similar after adjusting for relevant other exposures, although the *p*-trends in Norway and Sweden did not reach statistical significance. Additional adjustment for the intake of cod liver oil during winter in the Norwegian data had no impact on the results (data not shown).

In the pooled data, we found a significant association among women (multivariable-adjusted OR 0,68, 95% CI: 0.54–0.85), but not among men (multivariable-adjusted OR 0.81, 95% CI: 0.55–1.19) for the highest versus the lowest levels of PA (Table 4). However, the difference was not significant (*p* for effect modification = 0.58). In a sensitivity analysis, we observed that the effect estimate for more than 3 hours of vigorous PA remained similar when excluding participants with an index age of 30 years or less (age- and sex-adjusted OR 0.79, 95% CI: 0.65–0.96, *p*-trend: 0.012) compared to the analysis including all participants (OR 0.74, 95% CI: 0.63–0.87, *p*-trend: <0.001).

Discussion

In this large case–control study, we found an inverse association between vigorous PA during adolescence

Table 1. Baseline characteristics according to amount of light and vigorous physical activity in the study population.

Physical activity, amount/week	<1 hour		1–2 hours		⩾ 3 hours		Missing	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Light physical activity								
Number, *n*	162	295	263	545	1086	2025	282	614
Age at study, mean	44.0	43.9	43.9	45.4	43.4	44.4	44.0	44.9
Female, %	75.9	80.3	75.3	79.1	67.8	72.5	55.7	63.4
Smoking before onset, %	50.3	47.5	67.2	48.0	58.2	45.0	65.9	48.4
IM before onset, %	10.9	3.6	14.0	6.4	15.5	8.0	15.4	6.6
High level of outdoor activity,[a] %	59.2	60.3	56.5	62.8	77.8	81.1	83.8	86.5
Large body size at age 15,[b] %	7.0	7.2	4.5	5.1	4.0	3.5	3.1	1.8
Vigorous physical activity								
Number, *n*	404	682	488	948	636	1347	265	502
Age at study, mean	43.1	45.1	43.7	43.5	42.9	43.9	46.3	47.7
Female, %	78.7	83.0	72.1	75.8	53.6	61.4	76.6	82.5
Smoking before onset, %	59.2	47.2	58.8	45.3	62.2	46.9	58.5	44.9
IM before onset, %	10.7	4.5	16.9	7.8	18.2	8.6	8.8	5.3
High level of outdoor activity,[a] %	57.9	62.6	69.7	74.0	88.6	88.5	69.8	74.0
Large body size at age 15,[b] %	5.7	4.5	3.1	4.5	3.6	2.7	5.5	4.2

IM: infectious mononucleosis.
[a]Defined as two highest levels of outdoor activity.
[b]Defined as body size 6–9 on Stunkard's figure rating scale (body mass index > 27).

Table 2. Odds ratio (OR) for multiple sclerosis according to average amount of light and vigorous physical activity per week during adolescence (age 13–19).

	Cases/controls	OR (95% CI)			
		Age- and sex-adjusted	Multivariable[a]	Multivariable[b]	Multivariable[c]
Light physical activity[d]					
<1 hour/week	162/295	Ref.	Ref.	Ref.	Ref.
1–2 hours/week	263/545	0.88 (0.69–1.12)	0.93 (0.72–1.19)	0.91 (0.69–1.20)	0.89 (0.67–1.20)
⩾3 hours/week	1086/2025	0.96 (0.78–1.18)	1.05 (0.84–1.31)	0.98 (0.78–1.25)	0.96 (0.74–1.24)
p-trend		0.91	0.33	0.79	0.97
Vigorous physical activity[e]					
<1 hour/week	404/682	Ref.	Ref.	Ref.	Ref.
1–2 hours/week	488/948	0.85 (0.72–1.00)	0.85 (0.72–1.01)	0.83 (0.69–1.00)	0.82 (0.67–0.99)
⩾3 hours/week	636/1347	0.74 (0.63–0.87)	0.79 (0.66–0.93)	0.74 (0.62–0.89)	0.72 (0.59–0.87)
p-trend		<0.001	0.006	0.001	0.001

OR: odds ratio; CI: confidence interval.
[a]Further adjusted for frequency of outdoor activity.
[b]Further adjusted for infectious mononucleosis.
[c]Further adjusted for smoking and body size.
[d]Defined as physical activity that did not increase breathing rate or caused perspiration.
[e]Defined as physical activity that increased breathing rate and caused perspiration.

and MS risk. A similar effect was seen in different geographical areas, and there was no significant effect modification by sex. Neither other established risk factors nor reverse causality, that is, physical inactivity being due to prodromal symptoms of MS, could explain our findings.

Our results are in line with a recent prospective cohort study of young 19-year-old men registered in the Norwegian military conscription database who underwent a 3000 m maximal endurance running test during their conscription examination. In this study, lower aerobic fitness was significantly associated with a

Table 3. Odds ratio (OR) for multiple sclerosis according to average amount of vigorous physical activity[a] per week during adolescence (age 13–19) in Italy, Norway and Sweden.

	Cases/ controls	OR (95% CI)			
		Age- and sex-adjusted	Multivariable[b]	Multivariable[c]	Multivariable[d]
Italy					
<1 hour/week	195/320	Ref.	Ref.	Ref.	Ref.
1–2 hours/week	127/288	0.70 (0.53–0.92)	0.69 (0.52–0.93)	0.68 (0.49–0.93)	0.63 (0.44–0.89)
⩾3 hours/week	162/311	0.79 (0.60–1.05)	0.83 (0.62–1.11)	0.72 (0.52–1.00)	0.71 (0.50–1.01)
p-trend		0.09	0.21	0.05	0.05
Norway					
<1 hour/week	153/243	Ref.	Ref.	Ref.	Ref.
1–2 hours/week	286/470	0.96 (0.74–1.23)	0.97 (0.74–1.26)	0.97 (0.73–1.28)	1.03 (0.77–1.38)
⩾3 hours/week	390/791	0.73 (0.57–0.93)	0.78 (0.60–1.01)	0.78 (0.59–1.03)	0.82 (0.61–1.10)
p-trend		0.002	0.03	0.04	0.09
Sweden					
<1 hour/week	56/119	Ref.	Ref.	Ref.	Ref.
1–2 hours/week	75/190	0.74 (0.49–1.14)	0.72 (0.46–1.12)	0.67 (0.40–1.10)	0.76 (0.45–1.27)
⩾3 hours/week	84/245	0.59 (0.39–0.90)	0.61 (0.38–0.97)	0.62 (0.37–1.03)	0.68 (0.40–1.15)
p-trend		0.02	0.04	0.09	0.16

OR: odds ratio; CI: confidence interval.
[a]Defined as physical activity that increased breathing rate and caused perspiration.
[b]Further adjusted for frequency of outdoor activity.
[c]Further adjusted for infectious mononucleosis.
[d]Further adjusted for smoking, body size.

Table 4. Odds ratio (OR) for multiple sclerosis according to average amount of vigorous physical activity per week during adolescence (age 13–19) and stratified by sex.

	Cases/controls	OR (95% CI)	
		Age-adjusted	Multivariable[a]
Men			
<1 hour/week	86/116	Ref.	Ref.
1–2 hours/week	136/229	0.80 (0.57–1.14)	0.80 (0.52–1.22)
⩾3 hours/week	295/520	0.77 (0.56–1.05)	0.81 (0.55–1.19)
p-trend		0.13	0.37
Women			
<1 hour/week	318/566	Ref.	Ref.
1–2 hours/week	352/719	0.87 (0.72–1.05)	0.83 (0.67–1.03)
⩾3 hours/week	341/827	0.72 (0.60–0.87)	0.68 (0.54–0.85)
p-trend		0.001	0.001

OR: odds ratio; CI: confidence interval.
[a]Adjusted for age, frequency of outdoor activity, infectious mononucleosis, smoking and body size at age 15.

higher MS risk. Adjusting for BMI or excluding those with examination closest to the first symptom did not change the results in any meaningful way.[12] Similarly, a Swedish cohort study, which also included young men who were eligible for military service, observed that a physical working capacity score generated from a cycle ergometer test was inversely related to MS risk, even after adjusting for BMI.[13]

Unlike these studies, we could examine the association in both men and women and test whether there were any differences between the groups. We only

observed a significant association in women, which could indicate that the effect of PA on MS risk varies by sex. However, as results from prospective studies support an association in men and as we did not observe any significant interaction between sex and PA, a true difference is less likely.

In our study, we were also able to adjust for a number of relevant exposures that could be related to both PA and the risk of MS. We found that outdoor activity during summer and IM co-varied with the amount of PA. Previous research has demonstrated a likely protective effect of outdoor activity[4] while IM has been associated with an increased MS risk.[21] However, adjusting for these potential confounders did not have any major impact on the results, nor did smoking and body size. This makes it unlikely that other established risk factors can fully explain our findings.

A prospective study among female nurses in the United States observed an inverse association between self-reported levels of PA in adulthood and MS risk.[14] However, the risk was diminished in a sensitivity analysis excluding cases with a diagnosis of MS during the first 6 years of follow-up, interpreted as lower PA being an early sign of MS rather than representing a risk factor for the disease. In our study, we did not observe any meaningful difference in the estimates when excluding those with disease onset as much as 10 years after the exposure period. While our findings could be more sensitive to bias due to the retrospective design, they are consistent with the prospective study among Norwegian military recruits on PA and MS risk, where the effect estimates remained similar after excluding men with disease onset within 10 years after the physical examination and testing.[12] In addition to the prospective design, this study also benefited from objective measures of physical fitness, rather than relying on self-reported levels of PA.

An association between vigorous PA and MS may be related to immunological pathways relevant to MS pathogenesis. Although a session of strenuous exercise leads to an inflammatory acute phase response with increased C-reactive protein (CRP) and pro-inflammatory cytokines,[22] regular PA over time seems to reduce the baseline levels of CRP and other inflammatory markers and increase the percentage of immunosuppressive regulatory T-cells.[22–24]

An acute bout of exercise also activates the hypothalamo-pituitary-adrenal axis with the subsequent release of cortisol and catecholamines (norepinephrine and epinephrine).[25] Cortisol may inhibit the activation of pro-inflammatory T helper 1 (Th1) cells through suppression of interleukin (IL)-12 and tissue necrosis factor alpha (TNFα), while catecholamines may promote an anti-inflammatory Th2 response by suppressing IL-12 and stimulating IL-10 production.[26,27] As the immunopathogenesis in MS is partly driven by autoreactive Th1 and Th17 cells,[28] one might speculate whether an exercise-induced Th2 shift can prevent autoimmune activation of the adapted immune cells.

The possible immunomodulatory effects of PA seem to be dependent on the frequency, amounts, and level of intensity. Studies have shown that individuals who exercise more frequently, longer, and burn more calories during one session have lower baseline CRP levels compared to less active individuals.[29] Furthermore, the threshold intensity to achieve a significant increase in the cortisol levels has been found to be around 60% of maximal oxygen consumption.[30] This is compatible with our findings of no effect of light PA and a dose-dependent inverse relationship between vigorous PA and the risk of MS.

Our study has some limitations. It has a retrospective, self-reported design with an inherent risk of recall bias. Nevertheless, recall bias may be less likely since PA is not among the established risk factors for MS. Another problem with the retrospective design is lower accuracy when answering the questions. We have tried to increase the level of accuracy by encouraging the participants to ask a close relative if their own memory on a question was scarce. The lower response rate among controls may also affect the results in our material, introducing the possibility of selection bias. However, our results regarding PA and MS risk are consistent across the participating countries and with prospective studies not relying on self-reported information, which make it unlikely that our findings can be fully explained by recall or selection bias. In addition, environmental factors most consistently associated with MS risk in prospective cohorts have been replicated in previous studies using data from the EnvIMS study,[4,31] providing some evidence for the cases and controls being representative of the source population.

Our scale defining the weekly amount of PA does not include higher amounts than "more than 3 hours," and we were thus unable to examine whether the dose–response curve between vigorous PA and the risk of MS continues with higher weekly levels of PA. It also prevents us from considering whether the World Health Organization (WHO)-recommended daily dose of 60 minutes of moderate to vigorous PA for youth could be associated with an even lower risk of MS.[32] Finally, the EnvIMS-Q did not include further

questions on specific types of PA, and we could therefore not examine whether the association varied with mode of training. Still, our results could indicate that the possible beneficial effects of PA on MS risk are closer related to intensity and duration than to the specific type.

In summary, we have shown that higher amounts of vigorous PA during adolescence is inversely associated with the risk of MS across different European countries which cannot be explained by currently established risk factors or reverse causality.

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