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Amyotrophic lateral sclerosis among cross-country skiers in Sweden

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Abstract A highly increased risk of amyotrophic lateral sclerosis (ALS) has been suggested among professional athletes. We aimed to examine whether long distance cross-country skiers have also a higher risk of ALS and whether the increased risk was modified by skiing performance. We followed 212,246 cross-country skiers in the Swedish Vasaloppet cohort and a random selection of 508,176 general Swedes not participating in the Vasaloppet during 1989–2010. The associations between cross-country skiing as well as skiing performance (i.e., type of race, finishing time and number of races) and the consequent risk of ALS were estimated through hazard ratios (HRs) derived from Cox model. During the study, 39 cases of ALS were ascertained among the skiers. The fastest skiers (100–150 % of winner time) had more than fourfold risk of ALS (HR 4.31, 95 % confidence interval [CI] 1.78–10.4), as compared to skiers that finished at >180 % of winner time. Skiers who participated >4 races during this period had also a higher risk (HR 3.13, 95 % CI 1.37–7.17) than those participated only one race. When compared to the non-skiers, the fastest skiers still had a higher risk (HR 2.08, 95 % CI 1.12–3.84), as skiers who had >4 races (HR 1.88, 95 % CI 1.05–3.35), but those finishing at >180 % of winner time had a lower risk (HR 0.46, 95 % CI 0.24–0.87). In conclusion, long distance cross-country skiing is associated with a higher risk of ALS, but only among the best skiers; recreational skiers appear to have a largely reduced risk.

Keywords Amyotrophic lateral sclerosis · Cross-country ski · Physical activity · Longitudinal study

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Introduction

Highly elevated risk of amyotrophic lateral sclerosis (ALS) has been reported among professional football players [1–4]. Strenuous physical activity, repeated head injuries, use of illicit performance enhancing drugs, or environmental factors related to the football field have all been discussed as potential explanations for such risk elevations [1, 5]. Endogenous factors related to athleticism may also serve as potential explanations. For example, professional athletes are known to be exposed to high level metabolic stress [6] and ALS patients are known to demonstrate defects in energy metabolism [7]. More recently, chronic traumatic encephalopathy (CTE), a newly defined neurodegenerative disease that occurs following repeated head injuries, has been proposed as the underlying reason or the "correct" diagnosis for presumed ALS cases observed among professional athletes [8]. Post-mortem pathological

studies have, with some exceptions [9], also largely confirmed CTE among deceased athletes that had experienced repeated mild head injuries [8, 10]. Modifying factors for the risk of CTE related to athletics, boxing for example, may include high exposure to concussions, poor performance, and increased sparring [11, 12].

Given the fact that a wide variety of competitive sports, including wrestling, hockey, horse racing, skiing, and marathon running, may involve being exposed to some of the factors deemed as potential explanations for the highly increased ALS risk among Italian football players, it is interesting to assess whether ALS risk also differs among athletes of other sports. As a sport, cross-country skiing is very different from football since it does not involve much collision and thus less head injuries. Use of illicit performance enhancing drugs is presumably uncommon in cross-country skiing compared to professional football play as much less money is involved in the former (personal communication with Dr. Ulf Hållmarker). On the other hand, cross-country skiing is one of the most difficult endurance sports and burns the most calories per hour in execution as compared to many other competitive sports. At this end, we aimed to study the risk of ALS among a historical cohort of long distance cross-country skiers in Sweden, and further to assess the impact of potential modifying factors related to skiing performance on such risk.

Materials and methods

The Vasaloppet cohort

Vasaloppet is a long-distance (90 km) cross-country skiing race in Sweden with both elite and recreational skiers as participants. In connection to the Vasaloppet, several other ski races are held, for participants who prefer to ski shorter distances (30 or 45 km) or who want to ski the full 90 km but without the competitive component and simply record their individual time to complete the race at an occasion when no winner is announced (Open Trail). The information on all participants including personal identification number (a unique identifier for all Swedish residents), year of race, type of race, and finishing time has been computerized by the Vasaloppet office from 1989. In the present analysis, we enrolled all participants who were living in Sweden (i.e., with a Swedish personal identification number) and had at least one registered skiing race, either Vasaloppet or any of the connecting races, during 1989–2010 (n = 212,250). Vasaloppet skiers on average have higher leisure time physical activity, smoke less, and have a healthier diet and lower mortality than the general Swedish population [13].

In the present study, the skiers were classified by races (Vasaloppet [90 km], Open Trail [90 km], Women's Vasa [30 km], or others), the best relative finishing time (% of winner time per year, race, and sex; 100–150, 151–180, or >180 %), and number of registered races (1, 2–4, or >4). Information on all registered races during 1989–2010 was used for these classifications. For the Vasaloppet, the winning time ranged from 3 h 39 min (1998) to 5 h 10 min (1989) during the study period. The cut-off values for finishing time and number of races were chosen to ensure that there was approximately same number of ALS cases per category. When classifying skiers by the race types, the most demanding type of races a skier ever participated in during 1989–2010 was counted. Vasaloppet was determined as the most demanding race, followed by others. We included all kinds of races when classifying skiers by best finishing time and number of races. Since races before 1989 were not registered they were not considered for these classifications. Those who had only suspended races during the study period were classified as a separate group called "suspended".

To study the health outcomes of the skiers as compared to the general Swedish population, for every racing year, a group of "non-skiers" (i.e., individuals that did not participate in the Vasaloppet cohort) were randomly selected from the Swedish Total Population Register and was frequency-matched to all the skiers of that year by age, sex, and region of residence. Since the skiers participated at a median of two racing years during the study, twice as many non-skiers were selected. Furthermore, given the fact that the non-skiers were randomly selected from the Swedish Total Population Register, repeated selection of a non-skiing individual for skiers from different racing years was possible. Finally, a total of 508,239 unique non-skiing individuals were selected for the Vasaloppet cohort and enrolled in the present analysis. Since male skiers participated on average more racing years than female skiers and non-skiers were selected per racing year, more non-skiers were selected for male skiers than for female skiers (Table 1).

Follow-up

Since 1964/1965, the Swedish Patient Register has been collecting information on hospital discharge records and the register became nationwide since 1987 [14]. Data included in this register are the personal identification numbers, all discharge diagnoses, and times of hospital admission and discharge. Accordingly, in our study, ALS was defined as a hospital admission with ALS either as the main or a secondary diagnosis at the time of discharge. Date of first ALS diagnosis was defined as the date of first admission for ALS as recorded in the Patient Register. Although the validity of ALS diagnosis using the Patient

Table 1 Characteristics of 212,246 long distance cross-country skiers in the Swedish Vasaloppet cohort and a random sample of 508,176 general Swedish population not participating in the Vasaloppet Cohort, 1989–2010

	All skiers		Non-skiers	
	N	%	N	%
Total	212,246	100	508,176	100
Sex				
Men	130,927	61.7	344,287	67.8
Women	81,319	38.3	163,889	32.2
Age at cohort entry, years				
<55	137,441	64.8	287,310	56.5
55–64	43,832	20.6	126,904	25.0
≥65	30,973	14.6	93,962	18.5
Year of cohort entry				
1989–2000	62,213	29.3	207,906	40.9
2000–2005	54,015	25.5	144,018	28.3
2006–2010	96,018	45.2	156,252	30.8
Race				
Vasaloppet	77,763	36.6		
Open trail	59,146	27.9		
Woman's Vasa	49,644	23.4		
Others	25,693	12.1		
Best finishing time (% of winner time)				
100–150	33,491	15.8		
151–180	48,212	22.7		
>180	118,742	56.0		
Suspended	11,801	5.6		
Number of races				
1	105,546	49.7		
2–4	74,705	35.2		
>4	31,995	15.1		

Register has not been specifically assessed, the Patient Register has been shown to have 85–95 % accuracy for the majority of chronic diseases [14] and hospital administrative databases have been largely accepted as a high quality source for ALS ascertainment in other European country [15]. Given its nationwide coverage since 1987, the Patient Register effectively includes almost all incident cases of ALS in patients who had ever been hospitalized either because of ALS specifically or for any other reason. The Swedish Causes of Death Register is based on death certificates and has nationwide coverage since 1911. Information available in this register includes personal identification numbers, date of death, underlying and contributory causes of death.

Through the unique personal identification numbers, follow-up of the Vasaloppet skiers was conducted through individual linkages to the Patient and Causes of Death Registers. A disease like ALS most likely prevents people from further participation in strenuous physical activity, and therefore follow-up of ALS occurrence was started from each skier's last registered race during 1989–2010, and ended at the time of first ALS diagnosis, death, or end of 2010, whichever came first. Individuals with potentially erroneous linkages, including four skiers with either an ALS diagnosis or death recorded before the last registered race were excluded, leaving 212,246 individuals in the final analyses.

The follow-up of non-skiers was also conducted through individual linkages to the Patient and Causes of Death Registers. Since the non-skiers might be repeatedly selected for different skiers from different racing years, we followed the non-skiers from the last time they were selected during 1989–2010. Repeated selection of non-skiers was uncommon and therefore vast majority of the non-skiers were followed from the first and only time when they were selected. As a result, non-skiers were on average younger at study entry and entered the follow-up in earlier calendar periods (Table 1). Similar to the skiers, the follow-up of the non-skiers terminated at the first diagnosis of ALS, death, or end of 2010, whichever came first. If a non-skier became a skier sometime after being selected, the follow-up was censored at the time of their race participation (n = 9722). March 1st was used as the date for individual years when follow-up started for the non-skiers. A total of 63 non-skiers were excluded due to prevalent ALS or erroneous linkage i.e., death before entry to the cohort, leaving 508,176 in the final analyses.

Statistical analysis

We first described the distribution of all skiers and non-skiers by sex, age at (<55, 55–64 and ≥65 years) and calendar period of (1989–2000, 2001–2005, and 2006–2010) cohort entry.

The association between skiing performance and ALS risk was assessed through Cox model. We first performed internal comparisons among the skiers to minimize the possibility of potential confounding from a better general health status, assuming that the skiers are different from the non-skiers in this respect, while such difference is non-existing or smaller among the skiers ("healthy skier effect"). We compared skiers who had participated at least once in the Vasaloppet (i.e., the most demanding race) to other skiers who participated in other types of races but never in the Vasaloppet. When assessing the roles of finishing time and number of races, we used the least well performing skiers (>180 % of winner time) and skiers who participated in only one race as the reference groups. When comparing the skiers with the non-skiers, we used all non-skiers as the reference group.

Attained age was used as the underlying time scale for all models. In the original analysis all models were further adjusted for sex and calendar period of cohort entry; in secondary models we also adjusted for education (≤9, >9 and ≤12, or >12 years of education), employment status (employed, not employed, or unknown), and region of residence (northern, central, or southern Sweden). Information on education, employment and region of residence was obtained from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA by Swedish acronym); this database has been collecting annually updated information on demographics and socioeconomic status in the entire Sweden since 1990. Information from the year of cohort entry was used for all individuals. Individuals with missing covariate information were classified into a separate group. Among the skiers, there were a total of 5876 with missing education (2.8 %), 7130 with missing employment status (3.4 %), and 5,631 with missing region of residence (2.6 %). Proportional hazard assumption was checked for all models and no clear sign of violation was suggested.

Finally, for ALS patients identified through the follow-up, we further linked them to the Causes of Death Register to ascertain vital status before the end of 2010. Given the specific interest of CTE in the studied association, either as a potential differential diagnosis for ALS or a mediating factor between athletics and ALS, we further linked the ALS patients to the Patient Register to ascertain their hospital admission history for head injuries before ALS diagnosis, as repeated head injuries have been shown as an established risk factor for CTE [10]. Head injuries included were concussion, fractured skull, traumatic intracranial hemorrhage and cerebral contusion.

All analyses were conducted using the SAS software 9.3 (SAS Institute, North Carolina, USA). This study was approved by the Ethical Review Board in Uppsala, Sweden.

Results

A total of 39 ALS cases were identified among the skiers (six women and 33 men; crude incidence rate = 2.57 per 100,000 person-years). After adjustment for age, sex and calendar period of cohort entry, skiers with the fastest finishing time (100–150 % of winner time) had 4.31-fold risk of ALS (95 % confidence interval [CI] 1.78–10.4) and skiers with 151–180 % of winner time had 2.70-fold risk of ALS (95 % CI 1.14–6.35), compared to those with >180 % of winner time. Individuals who registered but never completed a race also had a 3.38-fold risk of ALS (95 % CI 1.21–9.46), compared to skiers with >180 % of winner time. Having participated in >4 races was associated with a 3.13-fold risk of ALS (95 % CI 1.37–7.17), compared to those who only participated once (Table 2). Furthermore, skiers that participated in >4 races and had the fastest finishing time had >12-fold risk of ALS (hazard ratio [HR] 12.2, 95 % CI 2.30–64.6, no of ALS cases = 5), compared to skiers that participated in only one race and with >180 % of winner time (no of ALS cases = 2). Models further adjusted for education, employment and region of residence did not yield largely different results (Table 2).

A total of 150 ALS cases were identified among the non-skiers (31 women and 119 men; crude incidence rate = 3.38 per 100,000 person-years). Compared to the non-skiers, the fastest skiers (HR 2.08, 95 % CI 1.12–3.84) and skiers with >4 races (HR 1.88, 95 % CI 1.05–3.35) both had a higher risk of ALS, whereas the skiers with >180 % of winner time had a clearly decreased risk of ALS (HR 0.46, 95 % CI 0.24–0.87) (Table 3). These associations did not differ between men and women and did not change after adjustments for education, employment and region of residence (data not shown).

Among the 39 ALS cases of the skiers, 32 had died at the end of the study including 27 with ALS and five with other chronic diseases as the underlying cause of death. Among the 150 ALS cases of the non-skiers, 120 had died at the end of study including 111 with ALS and nine with other chronic diseases as the underlying cause of death. The suspended skiers had around 10 years' lower median age at diagnosis compared to other groups, and they also had the highest mortality rate after diagnosis (Table 4). In contrary, the fastest skiers had the lowest mortality rate after diagnosis. Finally, we identified one skier and seven non-skiers who had been hospitalized at least once for head injuries before the diagnosis of ALS (Table 4).

Discussion

In this large historical cohort of long distance cross-country skiers in Sweden, we found that as compared to the least well performing skiers, the best performing skiers had a highly increased risk of ALS later in life. The least well performing skiers, on the other hand, had a largely decreased risk of ALS, when comparing to the general Swedish population not participating in the Vasaloppet Cohort.

Although multiple previous studies have demonstrated highly increased risk of ALS among football players [1–4], other athletes [16], and individuals with vigorous physical activity [17], inconsistent results have also been reported [18–21]. Our study was the first to address the risk of ALS among long distance cross-country skiers. Findings from different competitive sports may provide evidence to establish or refute suspected risk factors linking these sport activities and ALS.

Table 2 Incidence rates and hazard ratios of amyotrophic lateral sclerosis among 212,246 long distance cross-country skiers in the Swedish Vasaloppet cohort during 1989–2010

	N	Person-years	Incidence rate, per 100,000 person-years	Hazard ratio (95 % confidence interval)[a]	Hazard ratio (95 % confidence interval)[b]
Race					
Vasaloppet	21	578,458	3.63	1.74 (0.89–3.44)	1.65 (0.84–3.28)
Others	18	938,909	1.92	1.00	1.00
Best finishing time (% of winner time)					
100–150	11	187,557	5.86	4.31 (1.78–10.4)	4.18 (1.70–10.3)
151–180	12	311,220	3.86	2.70 (1.14–6.35)	2.66 (1.13–6.30)
>180	10	886,275	1.13	1.00	1.00
Suspended	6	132,316	4.53	3.38 (1.21–9.46)	3.27 (1.16–9.16)
Number of races					
1	12	860,717	1.39	1.00	1.00
2–4	14	512,634	2.73	1.50 (0.69–3.25)	1.46 (0.68–3.18)
>4	13	144,017	9.03	3.13 (1.37–7.17)	3.02 (1.31–6.95)

[a] Attained age was used as the time scale, and models were adjusted for sex and calendar period for cohort entry

[b] Models were further adjusted for employment status, education level and region of residence

Table 3 Hazard ratios of amyotrophic lateral sclerosis, comparing 212,246 long distance cross-country skiers of the Swedish Vasaloppet cohort to 508,176 general Swedish population not participating in the Vasaloppet Cohort, 1989–2010

	N	Hazard ratio (95 % confidence interval)[a]
Non-skiers	150	1.00
Skiers	39	0.98 (0.69–1.39)
Race		
Vasaloppet	21	1.38 (0.87–2.20)
Others	18	0.72 (0.44–1.19)
Best finishing time (% of winner time)		
100–150	11	2.08 (1.12–3.84)
151–180	12	1.29 (0.72–2.33)
>180	10	0.46 (0.24–0.87)
Suspended	6	1.69 (0.74–3.82)
Number of races		
1	12	0.65 (0.36–1.17)
2–4	14	0.97 (0.56–1.68)
>4	13	1.88 (1.05–3.35)

[a] Attained age was used as the time scale, and models were adjusted for sex and calendar period for cohort entry

Chronic traumatic encephalopathy (CTE), as a differential diagnosis of ALS, a mediating factor between repeated head injuries related to collision sports and ALS, or a distinct event in parallel with ALS, is one attractive explanation for a high ALS risk among professional athletes and perhaps also US military veterans [22–24]. As the diagnosis of CTE is largely based on post-mortem pathological findings, it is impossible to disentangle the temporality of CTE respective to ALS [25]. Although it is possible that the cross-country skiers experience higher rate of head injuries than average while training for endurance, long distance cross-country ski is in general not known for high risk of head trauma. Indeed in our data, the skiers had very low risk of hospitalization for head injuries before ALS diagnosis (one of 39 patients) and the rate appeared to be lower than that of the non-skiers (seven of 150).

A survey of 12,241 Vasaloppet participants in 2006 found that, among skiers with the fastest finishing time (100–150 %), around 47 % were training for more than 5 h per week at age 20 and >38 % at age 40, which were significantly higher than those of the less well performing skiers. On the other hand, the Vasaloppet skiers, regardless of finishing time, had higher physical training level than the general Swedish population [26]. Factors related to the different levels of physical exercise in cross-country skiing may explain the different ALS risks observed between the best and least well skiers. For example, endurance exercise promotes oxidative metabolism and enhance motor neuron degeneration; while moderate exercise protects the neuromuscular system [27].

Other environmental or lifestyle factors related to cross-country skiing such as use of performance enhancing drugs may also need to be explored. Doping control of the skiers is performed in about ten skiers randomly chosen per Vasaloppet and five skiers in the Women's Vasa; although some skiers were detected with high hemoglobin values, no skiers had been detected with high androgen steroids or erythropoietin (personal communication with Dr. Hållmarker).

Table 4 Characteristics of amyotrophic lateral sclerosis cases according to their best relative finishing time

	Skiers, by best finishing time (% of winner time)				Non-skiers
	100–150	151–180	>180	Suspended	
No of cases	11	12	10	6	150
Age at cohort entry, years[a]	56 (55–63)	56 (54–63)	62 (57–66)	40 (39–54)	55 (49–62)
Age at diagnosis, years[a]	64 (62–72)	63 (58–68)	64 (59–69)	54 (47–58)	62 (56–69)
N of deceased cases	7	10	10	5	120
Mortality, per person-year	0.23	0.39	0.60	0.70	0.54
N of cases with severe head injury before diagnosis[b]	0	0	1	0	7

[a] Median age (interquartile range)

[b] Any hospitalization with head injury as one of the discharge diagnoses since 1981, including concussion, fractured skull, traumatic intracranial hemorrhage and cerebral contusion

Our study highlights the importance of taking into account potential effect modifying factors while studying the associations between sports and ALS. Given the strikingly different results observed for the best and recreational skiers in our study, pooling all skiers together as one exposure group would only provide a null association (HR 0.98). Our findings are also in line with previous findings on a highly increased risk of ALS among professional football players [1–4], while not among individuals who played football in high school [20]. Similar results have been recently reported from a large European case-control study which showed a 49 % risk of ALS for organized sport (defined as "any sport practiced for at least 1 year by joining a given sport association and participation to official competitions"), while a 59 % higher risk of ALS, although not statistically significant, for professional sport (defined as "any sport practiced for at least 1 year, intended as the main occupation") [28].

Worth noting in our study is that the skiers who never completed any race during the study period had ALS diagnosed on average 10 years earlier and had also a higher mortality after diagnosis, than both other skiers and non-skiers. Therefore, this group of patients appeared to have a fast developing disease, as younger people are in general at a lower risk of ALS and younger ALS patients are known to have a better survival [29]. Prodromal symptoms of ALS, such as muscle twitches or cramps, may have been exaggerated during the skiing race and prevented these individuals to complete the race. However, given the fact that the time interval between the last registered race and ALS diagnosis did not differ largely between the suspended skiers and other skiers, these prodromal symptoms, if truly causing the suspension, did not lead to an ALS diagnosis immediately after the race. Another interesting finding is that although the fastest skiers had a >2-fold risk of ALS than the non-skiers, they had the lowest rate of death after diagnosis as compared to the less well performing skiers and non-skiers. If our findings on the different ALS risks among the best skiers and recreational skiers are true, one speculative explanation may be that after ALS diagnosis, the best skiers reduced their physical exercise level from extraneous to moderate, while moderate physical activity in turns slowed down the motor neuron degeneration. Given the small number of ALS cases identified, however, chance findings of these differences can never to be ruled out completely.

Our study has a few great strengths, including its large sample size, the prospectively and independently collected data on exposure and outcome, detailed and accurate data on skiing performance as well as a long and complete follow-up. A further strength relates to the possibility of performing both an internal comparison among the skiers and an external comparison between the skiers and non-Vasaloppet-skiers. A few limitations should also be addressed. Given the register-based nature, detailed clinical data on ALS was not available in the present study, precluding the possibility to assess the associations for different subgroups of ALS (e.g., bulbar versus limb onset). We ascertained ALS patients through the hospital discharge records alone; leaving possibly a small number of cases cared only at outpatient setting not identified [30]. Furthermore, although no difference in previous hospitalizations for head injuries were noted between ALS cases among skiers and non-skiers as shown for all Swedish ALS patients [31], no information on milder injuries was available. However, since it is well recognized that athletes rarely seek medical care for mild concussions [12], a complete assessment of such history may only be available through an interview with the patients or proxies.

In conclusion, we found that long distance cross-country skiing was associated with a higher risk of ALS, but only among the best skiers; recreational skiers appeared to have a largely reduced risk.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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