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Proportionate mortality of Italian soccer players: Is amyotrophic lateral sclerosis an occupational disease?

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Abstract. *Objectives*: The objective of the study is to investigate the mortality experience of Italian soccer players and to discuss the findings in the light of possible long term effects of doping. *Methods*: Standardized proportionate mortality ratio (SPMR) and standardized proportionate cancer mortality ratio (SPCMR) were computed for 350 deceased subjects deriving from a list of about 24,000 active Italian soccer players from 1960 to 1996 in the three top leagues (A, B and C). *Results*: When considering SPMRs, there is a substantial adherence of observed to expected mortality, with the only exception of mortality for diseases of the nervous system (13 obs. vs. 6 exp.) mainly explained by an excess of amyotrophic lateral sclerosis (8 obs. vs 0.69 exp.). As far as SPCMRs are concerned, some digestive cancers (namely: colon cancer, liver cancer and pancreas cancer) show a doubled risk. *Conclusions*: A high risk for amyotrophic lateral sclerosis is observed among Italian soccer players. Epidemiological data on association between sport and Amyotrophic Lateral Sclerosis (ALS) are contrasting. On the basis of the overall available evidence we suggest a possible connection between dietary supplements or drugs used to enhance sporting performance and ALS pathogenesis. Further epidemiological studies are needed to confirm these specific mortality risks among soccer players.

Key words: Amyotrophic lateral sclerosis, Branched chain amino acids, Dietary supplements, Doping, Mortality, Soccer players

Introduction

Epidemiological studies on the long-term survival of professional athletes are very scarce [1–3]. In a cohort study performed on 2009 male athletes who had represented Finland in international competitions from 1920 to 1965 the standardized mortality ratio (SMR) for all causes, calculated in the 1971–1995 period with respect to the general population, was significantly lower than 1 (SMR = 0.74; 95% CI: 0.69–0.79) [1]. A specific analysis by cause of death showed a high statistically significant SMR for hypertension among power sports athletes (weightlifters, wrestlers, boxers and track and field throwers) (SMR = 2.63; 95% CI: 1.05–4.42) [1].

A further study conducted in Finland reported a high risk of death among competitive powerlifters suspected to have used anabolic agents. During a 12-year follow-up 8 deaths were observed among the 62 athletes in the study and 34 deaths in a reference group of 1094 subjects from the general population (standardized mortality ratio = 4.6; 95% CI: 2.04–10.45) [2]. The specific causes of death among the eight powerlifters were: suicide (n = 3), acute myocardial infarction (n = 3), hepatic coma (n = 1) and non Hodgkin's lymphoma (n = 1) [2].

Finally, a cohort of 1505 Polish athletes showed a low SMR for all causes in the period 1981–1998 (SMR = 0.42; 95% CI:0.35–0.50) [3].

In the present study the mortality patterns of about 24,000 Italian professional soccer players, active in the period 1960–1996, is analysed.

Objectives of the present study are:

(1) To present an experience of epidemiological survey of Italian soccer players arisen in the context of a public inquiry regarding possible long term effects of doping.
(2) To describe the results of the proportionate mortality analysis that was conducted.

Populations and methods

The present study was designed and conducted in the frame of an inquiry provided by an Italian Public Prosecutor to evaluate possible long term effects of doping.

A final set of about 24,000 soccer players was recruited by the use of a number of data sets. They consisted mainly of annual reports of active soccer players from 1960 to 1996 in the three top leagues (A, B and C). For each subject place and date of birth

were obtained, but incomplete information was available concerning their work histories. Poor data were found about:

(1) Age at start of sport activity.
(2) Age at entrance in professional activity.
(3) Age at each change of team and/or league.
(4) Age at each change of tactical role in the field.

We considered these items essential in determining the amount of a possible exposure, the length of the exposure, the age at first exposure and the time elapsed since first exposure. Therefore we regarded the classical SMR approach as inappropriate and we preferred to rely on the estimation of PMRs. Standardized proportionate mortality ratio (SPMRs) and standardized proportionate cancer mortality ratio (SPCMRs) represent the specific contribution of each cause of death to overall mortality and overall cancer mortality respectively [4, 5]. The rationale for selecting a PMR approach is that, while health status and causes of death could be ascertained for nearly all study subjects, information on dates of start and end of employment as a soccer player was not available thus precluding computation of person-years at risk [5].

Subsequently, vital status was ascertained of each subject included in the study through the national tax office: those subjects who had paid their taxes in 1996 were considered alive at the date 31 December 1996. For all the others, the last year of contribution was registered; the following year was considered as the possible year of death. For each subject in this second group the respective municipality of birth was contacted to know his vital status. A total of 375 male subjects were identified that were deceased in the period 1960–1996. Each cause of death, derived from municipal death registries, was coded accordingly to the ICD revision at the date of death. For 25 subjects the cause of death resulted unknown. Standardizations were performed using national death rates, specific for sex, age class, cause and calendar period. Confidence intervals were computed assuming a Poisson distribution of the number of events.

For all computations the OCMAP program was used [6].

Table 1. Observed deaths by age and calendar period

Age class	Calendar period					
	1960–1974	1975–1979	1980–1984	1985–1989	1990–1996	Total
15–19	0	0	1	0	1	2
20–24	1	6	2	2	8	19
25–29	1	5	5	4	7	22
30–34	0	6	4	5	6	21
35–39	1	5	5	5	9	25
40–44	0	2	7	6	13	28
45–49	0	3	9	12	16	40
50–54	0	3	5	6	24	38
55–59	0	4	7	9	32	52
60–64	1	0	4	8	30	43
65–69	0	1	2	4	13	20
70–74	0	0	1	4	22	27
75–79	0	0	1	0	7	8
80–84	0	0	1	0	4	5
85+	0	0	0	0	0	0
Total	4	35	54	65	192	350

Results

Table 1 shows the distribution of deaths by age and calendar period. The mean age at death was 50.8 years (SD = 15.2).

Table 2 shows the substantial adherence of observed to expected mortality, with the only exception

Table 2. Observed and expected deaths by cause

Cause of death	Obs.	Expected	SPMR	95% CI
All causes	350	350.00	100	–
Infectious diseases	1	2.50	40	6–264
Malignant neoplasms	126	112.78	111	97–128
Immunity disorders[a]	10	6.08	165	93–291
Diseases of the nervous system	13	6.05	215	127–364
Motor neuron disease[b]	8	0.69	1158	672–1998
Other diseases	5	5.36	93	30–218
Diseases of the circulatory system	77	93.02	83	69–100
Diseases of the respiratory system	4	12.65	32	13–78
Diseases of the digestive system	22	28.89	76	51–113
Diseases of the genitourinary system	2	3.04	66	17–259
Ill-defined conditions	15	2.08	720	468–1107
Other diseases	9	12.80	70	32–133
Violences	71	65.46	109	90–130

[a]All the 10 cases are AIDS.
[b]All the 8 cases are amyotrophic lateral sclerosis (ALS).

Table 3. Cancer deaths by anatomic site and/or type of neoplasm

Anatomic site and/or type of neoplasm	Obs.	Exp.	SPCMR	95% CI
All malignancies	126	126.00	100	–
Digestive organs	49	40.10	122	97–154
Oesophagus	3	3.22	93	31–284
Stomach	13	10.76	121	64–207
Intestine and rectum	13	9.53	136	73–203
Colon and rectosigmoid junctions	13	5.99	217	116–371
Liver and intrahepatic bile ducts	9	8.01	112	60–211
Liver (primary)	9	4.81	187	100–351
Gallbladder and extrahepatic bile ducts	1	1.08	92	13–649
Pancreas	10	4.99	201	111–364
Respiratory organs	38	45.25	84	65–108
Trachea, bronchus and lung	33	39.55	83	63–110
Genitourinary organs	14	10.91	128	78–210
Lymphatic and haematopoietic tissue	16	11.30	141	91–222
Linfosarcoma and reticulosarcoma	6	3.48	172	80–374
Hodgkin's disease	1	1.55	64	10–430
Leukaemias	9	5.08	177	96–328
Other sites	9	5.82	155	71–294

of mortality for diseases of the nervous system (13 obs. vs. 6 exp.).

Table 3 shows the distribution of cancer deaths by anatomic site and/or type of neoplasm. Generally, observed figures are in good agreement with expectations, though colon cancer, liver cancer and pancreas cancer show a doubled risk.

Surprisingly, 8 out of 13 deaths for diseases of the nervous system, are due to motor neuron disease. In particular, all the cases were diagnosed as amyotrophic lateral sclerosis (ALS). Correspondingly an expected figure equal to 0.69 was found, thus leading to a SPMR equal to 1158 (95% CI: 672–1998).

Table 4 shows the distribution of ALS deaths by age and calendar period.

Age at death was less than 39 in 3 subjects (out of 8) and less than 59 in 6 subjects (out of 8).

If we consider these same aspects in the Italian population in the period 1980–1996, we see that 14.6% of the deaths occur before the age of 39 and 32.1% of the deaths occur before the age of 59.

Table 4. ALS deaths by age and calendar period

Age class	Calendar period				
	1960–1979	1980–1984	1985–1989	1990–1996	Total
15–34	0	0	0	0	0
35–39	0	1	1	1	3
40–54	0	0	0	0	0
55–59	0	0	1	2	3
60–69	0	0	0	0	0
70–74	0	0	1	0	1
75–79	0	1	0	0	1
80+	0	0	0	0	0
Total	0	2	3	3	8

Discussion

The validity of PMR studies requires that the deaths included in the study are representative of all the deaths identifiable in the hypothetical corresponding cohort study; this condition was fulfilled. Also, the discrepancy between observed and expected figures should concern a cause of death for which the 'healthy worker effect' (a reduced mortality observed in occupational cohorts due to selection procedures combined with differential permanence at work of diseased subjects [7]), does not appear to be likely. The latter point requires a further comment. The 1healthy worker effect' has been consistently shown to affect overall mortality, cardiovascular and respiratory diseases, while contrasting evidence exists for cancer mortality and no suggestions are available for neurologic diseases, namely for ALS [8–13].

Athletes can hardly be considered a random sample of some general population given the health selection that athletes undergo. As a consequence, the mortality patterns of this group of professional soccer players show a low proportional mortality for cardiovascular, infectious and respiratory diseases. The contribution of mortality for cancers to overall mortality does not exceeds the expected as well; however, if some sites of the digestive tract are considered, some increases appear. No hypotheses are given with this respect; however anabolic agents are in relation with hepatic hyperplasia and association between chronic assumption and liver cancers has been reported among athletes [14].

Quite surprisingly, a greatly increased contribution to overall mortality appears when considering the cause 'motor neuron disease'.

In Italy, the total number of ALS deaths in the1960–1996 period (n = 3379) is the 0.07% of all deaths (n = 4,848,555); in our data set the ALS deaths are the 2.29%.

Regarding the high number of ALS deaths observed in the present study (n = 8), a SPMR estimation of 1158 for ALS is thus indicative of an underlying ten-fold increased mortality rate for this disease among soccer players. Interestingly enough, after the end of the follow-up period (1996), some more 16 ALS deaths have been reported. The latter finding indirectly corroborates the indication of an increased occurrence of ALS in this population. Other relevant clinical point is the early onset of the ALS disease in most cases.

ALS is a rare devastating neurodegenerative disease of unknown etiology characterized by a loss of motoneurons in the spinal cord, brainstem and motor cortex [15].

High frequency of ALS has been reported in some Western Pacific Islands and Asia including the Kii Peninsula of Japan, Irian Jaya on the island of New Guinea and Guam in the Marianas. The estimate incidence of ALS was between 50 and 100 times higher than in the rest of the world. Several possible epidemiological explanations are given for these clusters [15–19]. On the other hand, clinical and experimental evidences show that especially glutamatergic transmission is implicated in the ALS pathogenesis [20].

Known risk factors for ALS

The specific relation between sport and ALS has been considered with contrasting results. Two studies show a statistical significant association between subjects who achieved a sporting award during the university period or who participated in active sports and ALS onset [21, 22]. Conversely, three studies fail to show any statistical relation between athletics and ALS [23–25].

Recently, in a large case–control study, a statistically significant association to ALS was observed for slimness (OR = 2.21; 95% CI: 1.40–3.47) and varsity athletics (OR = 1.70; 95% CI: 1.04–2.76) [26]. Longstreth et al. suppose that vigorous physical activity might increase the exposure to environmental toxins for motoneurons [27].

Some epidemiological studies on risk factors for ALS evaluated the relationship between ALS and body mass before the diagnosis of the disease. Slim subjects seem to experience higher ALS risks [23, 24]. Contrasting findings have been reported regarding the association between vigorous physical activity and ALS [23, 25]. Other epidemiological case–control studies show a relationship between physical trauma or limb injury and ALS; unfortunately, these factors are associated to vigorous physical activity as well: therefore a confounding relation should be carefully evaluated [21, 24, 25].

Hypothetical relation between dietary supplements or drugs and ALS

Apart from the above discussion on epidemiological risk factors for ALS, no data regarding doping and ALS are given in the literature. Dietary supplements and many different drugs are used in attempts to enhance sporting performance. In particular, some hypotheses might be advanced considering that a high consumption of dietary supplements containing branched chain amino acids (BCAA) and a chronic misuse of anti-inflammatory drugs might play a key role in the ethiopathogenesis of ALS among susceptible athletes [28, 29].

Creatine monohydrate is a dietary supplement used especially by athletes to improve their muscular performance [30]. It can enhance cellular energy transduction and has a crucial role in the physiology of central nervous system. The metabolism of creatine and creatine kinase is regulated by a number of enzymatic complexes like the arginin:glycine amidinotransferase and the guanidinoacetate-methyltransferase [31]. The oral administration of creatine monohydrate (15 mg/die) for 1 month showed to influence the *in vivo* ratios of some metabolites (N-acetylaspartate, creatine plus phosphocreatine, choline, glutamate and glutamine) of motor cortex in both ALS patients and healthy controls [32].

In transgenic murine model of ALS, creatine monohydrate improves motor performance, and survival of motor neurons, while reducing oxidative stress [33].

BCAAs (leucine, isoleucine and valine) supplementation is frequently used among athletes to stimulate the muscular protein synthesis, to improve both mental and physical performances, and to accelerate the body's recovery after particularly intense and prolonged sport activities.

After skeletal muscles, brain is the organ with the highest activity of two key enzymes in the catabolism of BCAAs [34]. Recently, a relationship between cerebral metabolism of BCAAs and glutamate has been proposed. The 'glutamate-glutamine' and the 'leucine-glutamate' cycles would function in tandem to regulate the glutamatergic metabolism [35].

GH is usually assumed by athletes in association to anabolic steroids to increase their sporting performance [36]. GH and its chief mediator, the insulin-like growth factor (IGF-1) are involved in the development of the nervous system and have a trophic effect on survival of the motoneurons [37].

In the last years creatine monohydrate, BCAAs and synthetic human GH have been used in different clinical trials on ALS patients in order to delay the

progression of the disease [38–41]. While the placebo-controlled trials did not find any beneficial effect of creatine monohydrate and GH on survival and progression of the disease in ALS patients [38, 39], a large Italian clinical trial with BCAAs was interrupted because there was an excess mortality in BCAAs treated ALS patients [40].

When considering drugs, some attention should be devoted to the chronic misuse of anti-inflammatory products among soccer players, as they could influence the glutamatergic metabolism and induce a pathological inhibition of astrocytic activity [29].

Conclusions

Epidemiological data on association between sport and ALS are contrasting. On the basis of the overall available evidence we suggest a possible connection between dietary supplements and/or drugs used to enhance sporting performance and ALS pathogenesis.

The critical question is which long-term effects should be expected after a sudden interruption of a prolonged over-stimulation of such complex and closely biological systems that are involved both in the metabolism of drugs and dietary supplementations and ALS pathogenesis.

In conclusion, the present study seems to show a high risk for ALS among soccer players. However further epidemiological studies are needed in order to confirm these specific mortality risks. Detailed professional and clinical histories of ALS soccer players might be of considerable value in the interpretation of this unexpected and mysterious cluster of cases.

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