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Longevity and causes of mortality in elite athletes

Juliana Antero

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PARIS DESCARTES UNIVERSITY
DOCTORAL SCHOOL OF PUBLIC HEALTH – EDSP

LONGEVITY AND CAUSES OF MORTALITY IN ELITE ATHLETES

Juliana Antero-Jacquemin

16th November 2015

Jury:

Mme. Claudine Berr	(Rapporteur)	Directeur de recherche, <i>Montpellier</i>
Mme. Martine Duclos	(Rapporteur)	PU-PH, <i>Clermont Ferrand</i>
Mr. Jean Bouyer	(Examineur)	Directeur de recherche, <i>Paris</i>
Mme. Emmanuelle Cambois	(Examineur)	Directeur de recherche, <i>Paris</i>
Mr. Alejandro Lucia	(Examineur)	Directeur de recherche, <i>Madrid</i>
Mr. Aurélien Latouche	(Co-directeur)	Professeur des universités, <i>Paris</i>
Mr. Jean-François Toussaint	(Directeur)	PU-PH, <i>Paris</i>



UNIVERSITE PARIS DESCARTES
ECOLE DE SANTE PUBLIQUE – EDSP

LONGEVITE ET CAUSES DE MORTALITE DE L'ELITE SPORTIVE

Juliana Antero-Jacquemin

Le 16 novembre 2015

Jury:

Mme. Claudine Berr	(Rapporteur)	Directeur de recherche, <i>Montpellier</i>
Mme. Martine Duclos	(Rapporteur)	PU-PH, <i>Clermont Ferrand</i>
Mr. Jean Bouyer	(Examineur)	Directeur de recherche, <i>Paris</i>
Mme. Emmanuelle Cambois	(Examineur)	Directeur de recherche, <i>Paris</i>
Mr. Alejandro Lucia	(Examineur)	Directeur de recherche, <i>Madrid</i>
Mr. Aurélien Latouche	(Co-directeur)	Professeur des universités, <i>Paris</i>
Mr. Jean-François Toussaint	(Directeur)	PU-PH, <i>Paris</i>



I. ABSTRACT

Background and objectives: along their careers, elite athletes are subjected to specific constraints that distinguish them from the general population. Such constraints, related to the high intensity of their physical activity, their overexposure to injuries or particular lifestyle, may have long-term consequences on the athletes' health, and ultimately on their longevity. Thus, the main goals of the present study are the following: 1) to describe and analyze elite athletes' longevity and specific causes of mortality in comparison with the general population and according to the type of effort they performed; and 2) to investigate their lifespan trends in comparison with the longest-lived humans in order to apprehend the current scenario of human longevity trends.

Methods: we collected data on the biography and the athletic performances of all the French athletes who participated in the Olympic Games (OG) from 1912 to 2012 (n = 4708), and all the French cyclists who participated in the Tour de France (TDF) from 1947 to 2012 (n=786). Then, we verified their vital statuses through the National Registry of Identification of Physical Persons (RNIPP). For the deceased athletes, we obtained the causes of their deaths through the Centre for epidemiology on medical causes of death (CépiDc). We compared the athletes' overall and specific mortality (according to the main chapters of the International Classification of Disease) with the French civilian life tables using Standardized Mortality Ratio (SMR) and the Kaplan-Meier methods. We adapted and applied the life years-lost method under the competing risk model to quantify differences on longevity due to major causes of death according to the athletes' type of effort. Furthermore, we collected data on worldwide deceased Olympians participating in the OG from 1896 to 2012 (n=19 012) and on worldwide supercentenarians (>110 years) deceased between 1900 and 2013 (n= 1 205) in order to analyze their lifespan trends using a density analysis tool (total number of life durations per birth date).

Findings and conclusion: French elite athletes show consistently lower mortality (\approx 40-50% lower) in comparison with their compatriots, whether female or male Olympians, or professional cyclists, mostly related with a lower cardiovascular (\approx 40-60% lower) and cancer mortality (\approx 45% lower). No excess mortality was observed in elite athletes for any of the specific causes of death we studied. French Olympians' lower mortality results in an average of seven years of life saved in relation to the general population. This gain partitioned according to specific causes of deaths shows that cardiovascular longevity benefit is associated with the type of sports practiced during the Olympic career, favoring combined type of effort over very short- or very long-duration effort. In relation to cancer mortality, all types of effort studied were associated with better longevity. Despite their survival advantage, no Olympian in the world, up to date, has ever reached the status of a supercentenarian, as the longest-lived was 106 years old. The common lifespan trends between Olympians and supercentenarians indicate similar mortality pressures over both populations that increase with age, a scenario that is better explained by a biological "barrier" limiting further progression. The supercentenarians' density trends show a current stagnation of the human longevity.

Keywords: elite athletes, mortality, physical activity, years-lost, years-saved, human longevity trends, limit, epidemiology

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« Si j'ai vu plus loin,
c'est parce que je me suis juché
sur les épaules de géants »

~Isaac Newton

Te agradeço meu **Deus**, porque de Ti, por ti e para Ti são todas as coisas.

--~--

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COMMON ABBREVIATIONS

CépiDc = Centre for epidemiology on medical causes of death

CV = cardiovascular

INSEE = National Institute of Statistics and Economical Studies

OG = Olympic Games

RNIPP = National Registry of Identification of Physical Persons

SMR = Standardized Mortality Ratio

TDF = Tour de France

IV. THE THESIS IN 3 PAGES

Physical activity is recommended worldwide because of its health benefits and its major impact on reducing populations' mortality. However, the relationship between dose of physical activity and health benefits is not well established: the impact of intense training on one's health, and particularly on the cardiovascular system, is currently debated. The population of elite athletes, consisting in participants to the world's most important competitions, is subjected to training loads 5-10 times higher than the recommendations, with potential impacts on their health. The constraints increase due to the intensity and the exposure time during training and competitions, submitting the athletes to recurrent injuries and accidents. To these constraints is added a particular lifestyle aiming to optimize their performance, ranging from healthy behaviors to the use of doping substances that are potentially harmful to one's health. Such constraints may provoke specific benefits and risks to the athletes' general health, and impact on their mortality.

The main objective of this thesis is thus to investigate the longevity and causes of mortality in elite athletes. The interest of focusing the investigation on this population also relies on their characteristic as outliers, occupying the far end of a distribution curve of human physiological capacities, possibly providing new approaches to understand human longevity trends.

We performed an exhaustive data collection of the biographies and athletic performances of all the athletes worldwide who participated in the Olympic Games (OG) since 1896 and of all the French athletes who participated in the Tour de France (TDF) since 1947, totalizing more than 20 000 athletes. Then, we verified the vital statuses of over 5 000 French athletes through the National Registry of Identification of Physical Persons (RNIPP). For the athletes concerned, we obtained their causes of death through the Centre for epidemiology on medical causes of death (CépiDc).

For a descriptive approach of athletes' mortality in comparison with the general population, we relied on the differential mortality analysis, using the "Standardized Mortality Ratio" (SMR) and the Kaplan-Meier methods.

Our first results show that the French elite athletes have a 50% lower overall mortality and a significantly lower mortality due to cardiovascular disease, cancer and external causes of death. Similarly, we found that sportswomen, who had not been assessed in comparable studies before, have a survival advantage just as important as that found among men¹. Similar analyzes were extended to two other cohorts that were more homogeneous in terms of sports physiology.

The first one focused on elite rowers. The scientific literature describes their type of training as a possible source of cardiac alterations. Our analyses, based on a century of follow-up, reveal on the contrary a significant reduction on rowers' overall and also cardiovascular mortality².

The second one, formed by professional cyclists from the TDF, was of particular interest because of the high physiological demand of such a sports event, associated with numerous cases of doping confessions. Yet, similarly to previous cohorts, cyclists show 41% lower overall mortality, with lower risk of death from cardiovascular diseases and cancers, although the risk of accidental deaths was slightly higher during the cyclists' career³.

To investigate the impact of sport's physiological constraints on specific causes of death, we had to use new methods. Contrary to the majority of cohorts for which the survival analysis methods have been conceived, elite athletes outlive the reference population. We relied on the competing risk model for a survival approach coherent with the specificity of our cohort. For the first time, it was possible to estimate the number of years of life saved among elite athletes: they save on average 7 years of life compared to the general population; from which approximately 2 years are saved from cardiovascular diseases, 2 from cancers, and 3 from all other causes⁴.

However, such advantage is heterogeneous among the athletes. We show an association between the type of effort (differentiated according to the duration of effort performed in the Games) and the number of years of life saved from cardiovascular diseases, revealing a possible optimal relationship between the type of physical exertion and its health benefits, for which the greater benefits demonstrated concern events combining different types of physical activity. In addition, preliminary results suggest that high exposure to a particularly inauspicious environment may compromise the extent of longevity benefits observed in athletes, raising new hypotheses to be tested.

Thus, our research shows that elite athletes' longevity is overall better than that of the general population, but dependent on the characteristics of each sport, impacting differently specific mortalities, notably the cardiovascular, or external causes of death, according to the sports' constraints^{5,6}.

The interest in identifying the risks and benefits of sports practice among the elite may have public health implications: the benefits allow strengthening the preventive character of sports, while the risks justify protective measures to be implemented. These findings must be interpreted in light of the distinctions between the general population and the elite: the athletes are selected due to their predisposition to training and submitted to particular lifestyles.

In order to extrapolate the analysis of sports elite to better understand trends in human longevity, we conducted one more research. Knowing that athletes live longer

than the general population, we compared their lifespan trends to those of all verified supercentenarians (living over 110 years) in the 20th century⁷. The parallel between such cohorts relies on the fact that both are highly selected in terms of survival.

For this analysis, we developed a specific methodological tool comparing secular trends in longevity of 19 012 Olympic athletes and 1205 supercentenarians. Our results reveal common trends between both cohorts, indicating similar mortality pressures increasing with age. The observed stagnation of human maximal longevity strengthens arguments of a biological barrier limiting further progression⁸.

Through all this work, we wish to contribute to various scientific fields: to sports medicine and physiology, through a better understanding of sport's effects and its health benefits; to public health and epidemiology, through the development of specific methods and the potential transposition of the findings to the general population.

LIST OF PUBLICATIONS

PEER-REVIEWED PAPERS AND BOOK CHAPTERS PUBLISHED OUT OF THIS THESIS:

1. **J Antero-Jacquemin**, G Rey, A Marc, F Dor, A Haïda, A Marck, G Berthelot, A Calmat, A Latouche, JF Toussaint. Mortality in Female and Male French Olympians: A 1948-2013 Cohort Study. *Am J Sports Med.* 2015
2. **J Antero-Jacquemin**, F D Desgorces, F Dor, A Sedeaud, A H, P Le Van, JF Toussaint. Row for your life: a century of mortality follow-up of French olympic rowers. *PLoS ONE.* 2014;9:e113362.
3. E Marijon, M Tafflet, **J Antero-Jacquemin**, N El Helou, G Berthelot, D S Celermajer, W Bougouin, N Combes, O Hermine, JP Empana, G Rey, JF Toussaint, X Jouven. Mortality of French participants in the Tour de France (1947–2012). *Eur Heart J.* 2013;eht347
4. **J Antero-Jacquemin**, M Pohar, G Rey, JF Toussaint, A Latouche. Years-saved from cardiovascular death in elite athletes: efforts too short or too long are not too good. [Ongoing work]
5. **J Antero-Jacquemin**, G Berthelot, A Calmat, A Latouche, JF Toussaint. Mortalité de l'élite sportive française. In, THEVENOM, André. 2015. Le sport est-il un médicament?. Sauramps médical, France
6. S Vergès, **J Antero-Jacquemin**, T Cattigni, S Doutreleau, P Flore, M Guinot, C Hausswirth, R Lepers, V Martin, A Paria, S Perrey, S Ratel, J Schipman, A Sedeaud, JF Toussaint. Activité physique : supplice ou délice ? INSERM. Le muscadier 2015, Paris, France.
7. **J Antero-Jacquemin**, G Berthelot, A Marck, P Noirez, A Latouche, JF Toussaint. Learning From Leaders: Life-span Trends in Olympians and Supercentenarians. *J Gerontol A Biol Sci Med Sci.* 2014
8. **J Antero-Jacquemin** J, JF Toussaint. Y a t-il une limite à l'augmentation de la durée de vie humaine ? *Revue Gériatrie et Société* [Under review].

CONFERENCE CONTRIBUTIONS

- European Society of Cardiology Congress, September 2013, Amsterdam, Netherlands. X Jouven, M Tafflet, E Marijon, J Antero-Jacquemin, N El Helou, G Berthelot, N Combes, W Bougouin, D S Celermajer, G Rey, JF Toussaint. Abstract: Longevity and Causes of Death in Elite French Cyclists from the Tour de France.
- 61st Annual meeting of the American College of Sports Medicine, Mai 2014, Orlando, USA. J Antero-Jacquemin, A Latouche, F Dor, G Berthelot, A Marc, L Marquet, A Haida, A Calmat, G Rey, JF Toussaint. Abstract : Overall mortality reduced by half among French Olympic athletes.
- 36th Annual Conference of the International Society for Clinical Biostatistics (ISCB2015), August 23-27, 2015 in Utrecht, Netherlands. M Perme, J Antero-Jacquemin, JF Toussaint, A Latouche. Abstract: Analyzing relative survival of groups that outlive the population – the French olympians study.
- 8th Congrès de Physiologie, de Pharmacologie et de Thérapeutique, April 2013, Angers, France. J Antero-Jacquemin, A Latouche, M Tafflet, F Dor, A Marc, LA Marquet, P LeVan, G Berthelot, A Calmat, Toussaint JF. Oral presentation: French Olympic medalists' longevity: a follow up since the first Olympiad.
- 8th Symposium de l'IRMES, September 2013, Strasbourg, France. J Antero-Jacquemin, A Latouche, M Tafflet, F Dor, A Marc, LA Marquet, P LeVan, G Berthelot, A Calmat, Toussaint JF. Oral presentation: French Olympic medalists' longevity: a follow up since the first Olympiad.
- Journées Pierre de Coubertin : Le sport est-il un médicament?, November, 2013, Lille, France. J Antero-Jacquemin, G Rey, G Berthelot, A Calmat, A Latouche, JF Toussaint. Invited seminar: Mortalité de l'élite sportive française.
- 10th Journée Médicale de l'INSEP, December 2013, Paris, France. J Antero-Jacquemin, G Rey, G Berthelot, A Calmat, A Latouche, JF Toussaint. Invited seminar: Mortalité de l'élite sportive française.
- 9th Symposium de l'IRMES, September 2014, Paris, France. J Antero-Jacquemin, F Desgorces, F Dor, A Sedeaud, A Haïda, P Le Van, JF Toussaint. Oral presentation: *Un siècle de suivi de la mortalité des rameurs olympiques français.*
- 34th Congrès National de la Société Française de Médecine, de l'Exercice et du Sport, September 2014, Paris, France. J Antero-Jacquemin, A Latouche, F Dor, A Marc, LA Marquet, A Haida, JF Toussaint. Oral presentation: *Mortalité des athlètes olympiques français.*

Objectif santé 2014, November 2014, Nice, France. J Antero-Jacquemin. Invited seminar:
La longévité n'augmentera plus, c'est sur ?

1st Symposium Performance & Vieillesse, May 2015, Paris, France. J Antero-Jacquemin, A Latouche, G Rey, F Dor, G Berthelot, A Marck, A Calmat, P Le van, JF Toussaint. Invited seminar: Longevity and causes of death in elite athletes.

Séminaire du Centre d'Epidemiologie sur les causes Médicales de Décès (CépiDc), June 2015, Kremlin Bicentre, France. J Antero-Jacquemin, A Latouche, G Rey, F Dor, M Perme, G Berthelot, A Marck, A Marc, JF Toussaint. Invited seminar : Approche épidémiologique de la longévité et causes de décès de l'élite sportive.

10th Symposium de l'IRMES, September 2015, Orleans, France. J Antero-Jacquemin, M Perme, G Rey, G Saulière, JF Toussaint, A Latouche. Invited seminar: Bénéfices cardiovasculaires chez les athlètes olympiques : années de vie gagnées selon leur type d'effort.

Congrès de l'Association des chercheurs en activités physiques et sportives, October 2015, Nantes, France. J Antero-Jacquemin, A Latouche, G Rey, A Marck, G Saulière, JF Toussaint. Invited seminar: Sport et longévité.

Objectif santé 2015, November 2015, Monaco. J Antero-Jacquemin. Invited seminar: La longévité n'augmentera plus, c'est sur ?

OTHER PUBLICATIONS

PEER-REVIEWED PAPERS

- J Antero-Jacquemin**, P Santos, P A Garcia, R C Dias, et J M D Dias. Isokinetic muscle function comparison of lower limbs among elderly fallers and non-fallers. *Fisioterapia e Pesquisa* 19 (1): 39-44, 2012.
- A Haïda, F Dor, M Guillaume, L Quinquis, A Marc, LA Marquet, **J Antero-Jacquemin**, et al. Environment and Scheduling Effects on Sprint and Middle Distance Running Performances. *PLoS One* 8 (11): e79548, 2013.
- A Marc, A Sedeaud, M Guillaume, M Rizk, J Schipman, **J Antero-Jacquemin**, et al. Marathon Progress: Demography, Morphology and Environment. *Journal of Sports Sciences* 32 (6): 524-32, 2014.
- T R Souza, H L Fonseca, AC A Vaz, **J Antero**, C S Marinho, S T Fonseca. Between-Day Reliability of a Cluster-Based Method for Multisegment Kinematic Analysis of the Foot-Ankle Complex. *Journal of the American Podiatric Medical Association* 104 (6): 601-9, 2014.
- G Berthelot, A Sedeaud, A Marck, **J Antero-Jacquemin**, J Schipman, G Saulière, et al. Has Athletic Performance Reached its Peak? *Sports Medicine*, 2015 <http://doi.org/10.1007/s40279-015-0347-2>.
- J Antero-Jacquemin**, G Saulière, JF Toussaint. A medal in the Olympics: it runs in the family. *Am J Sports Med*, [Under Review].
- A Haïda, N Coulmy, F Dor, **J Antero-Jacquemin**, et al. Return-to-the-Performance after an Anterior Cruciate Ligament Rupture among French Alpine Skiers between 1980 and 2013. *Am J Sports Med*, 2015.
- A Haïda, Marquet LA, **J Antero-Jacquemin**, et al. Petit bilan de Sapiens au relevé de ses empreintes Londoniennes. Regards coirsés sur la performance sportive Olympique et Paralympique. p250-255, 2012.

HOSTING LABORATORY

IRMES - Institut de Recherche bioMédicale et d'Epidémiologie du Sport (EA7329) à l'INSEP - Institut National du Sport, de l'Expertise et de la Performance. Address: 11 avenue du Tremblay, 75012 Paris, France. Email: irmes@insep.fr, Phone: +33 1 4174 4129.

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INTRODUCTION

This chapter introduces the key concepts to apprehend the population studied: elite athletes, defined as sportsmen and women performing internationally at the highest level. Epidemiology, which studies health determinants in populations, is the academic approach of this work. The main indicator to assess elite health will be (i) mortality (measuring death rates in populations) and (ii) longevity (characterizing life duration). The required attributes for the athletes to reach elite level are presented, as well as the elements forging their performance: genetics, environment and training. Elite athletes stay at one extreme of the bell-shaped curve of performance, and encounter specific constraints distinguishing them from the general population. Such constraints, related to high training intensity, overexposure to injuries and, sometimes, to doping practices (through individual, collective or state organization), may have long-term consequences on the athletes' health, and ultimately on their longevity. The risks and benefits of such constraints are reviewed and discussed in light of the potential impact on elite athletes' mortality and longevity. This research questions about their mortality rates and the broadened use of elite athletes' data for apprehending human longevity. The state of the art reviews the research done in this field, while the analysis of the literature establishes the paucity of answers to our inquiries: there is a scarcity of studies on elite athletes' mortality, especially regarding sportswomen and French athletes, and there is a general lack of research relying on proper methods for quantifying longevity differences. The interests in answering the research questions are presented, for the sports movement' or in a public health' perspective, supporting the objectives of this thesis i.e.: to analyze elite athletes' mortality and to apprehend new aspects of human longevity trends.

1.1 EPIDEMIOLOGICAL APPROACH OF ELITE ATHLETES

1.1.1 STUDY POPULATION

The sports elite is a population formed by high level athletes reaching the top level of their discipline, enabling them to access the most important championships. Participation in the world's most competitive championships is reserved to a minority of exceptionally successful athletes, a common criterion worldwide, precisely defining the world's sports elite (Figure 1.1).

The pinnacle is participation in the Olympic Games (OG). For the disciplines featured in the Games, to become an Olympian is synonym of reaching the highest sport level and therefore entering the sports elite. For other sports such as professional ones, the major events, also reserved for the best athletes in the world, are determined by historical parameters, financial investments, media support and international competition [1,2]. Thus, the Tour de France (TDF) for a road cyclist or the World Cup for a football player are what the Olympics is to a gymnast.

Here, the elite sport population of interest is the group of Olympic athletes and the French professional cyclists participating in the TDF.

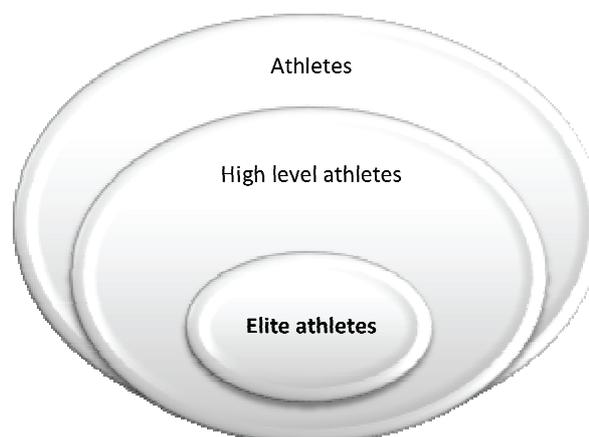


Figure 1.1: Hierarchy of athletes' level

1.1.1.1 AMATEUR AND PROFESSIONAL ATHLETES

The status of a high-level athlete varies between amateur, semi-professional and professional, according to the financial payment perceived by the athletes, which depends on the period, sport and performance.

Rewarding sports performance is an old practice. Professionalism was widespread in the Ancient OG, held from the eighth century B.C. to the fifth century A.C. in Ancient Greece. There were professional athletic guilds similar to today's Players' Associations. An athlete's prize money in Athens was around 500 drachma, corresponding to a sum important enough that he could live off of it for the rest of his life [3].

In 1527, the "lettres patentes" of Francis I, King of France, established the professional status of players in the *jeu de paume* (palm game) [4]. Over the centuries, other sports were created and evolved towards professionalism. For example, in the first TDF in 1903, cyclists were professional athletes sponsored by bicycle brands, and a financial award was presented to the winner [5].

In 1894, in opposition to Ancient practices, the committee that decided to restore the OG insisted on the valorization of amateur sport. It then fixed the rule of amateurism, establishing that only athletes not perceiving any financial or material advantage were allowed to participate to the Games, limiting sport access to the aristocracy [4]. Even if the International Olympic Committee was initially very strict about this rule, removing the titles of athletes who had received any kind of financial aid, amateurism became obsolete in the Olympic modern era.

Currently, only boxing and wrestling are still reserved for amateurs in the Olympics. Nevertheless, most of the current Olympic boxers and wrestlers benefit from contracts allowing them to dedicate themselves fully (or almost) to their practice and performance.

Thus, nowadays, a top athlete is not necessarily a professional, while participants in the Olympics are not necessarily pure amateurs. A sports governing body can decide to reserve certain competitions to their best athletes, who may happen to be professionals. This is usually the case for team sports like football, basketball, handball, volleyball, rugby and ice hockey [6]. In individual sports, such as tennis, track and field, swimming or table tennis, sports authorities do not set a professional framework and the athletes negotiate, on a collective or individual basis, contracts according their performance.

1.2 ELITE ATHLETES AND THE GENERAL POPULATION

1.2.1 PERFORMANCE, A PHENOTYPIC CRITERION

Athletic performance may be defined as the execution of physiological skills on sports, measured in time, distance or ranking, accomplished by trained athletes. It discerns the athlete's levels, and therefore is the criterion defining the elite athletes' population and distinguishing them from lower level athletes or from the general population.

This is an easily measurable criterion. Speed events, for example, have the exact same distance (measured in millimeters) around the world, while performance times are precisely measured in hundredths of a second. The height of a jump is historically recorded with the exactitude of a centimeter. This measurement accuracy, ranking different levels of performance, can draw the gradients of athletic performances and determine the place of an individual in a curve of phenotypic distribution. The phenotype is the constellation of observable characters of an individual dependent on the individuals' genotype, *i.e.* the expression of genes in interaction with the environment encountered.

Accordingly, athletic performance is the result of the dynamic interaction of various factors that will be grouped here didactically into three main components: genetics, environment and athletic training.

1.2.1.1 PERFORMANCE AND GENETIC INFLUENCE

The genetic influence on sports performance is related to the athletes' intrinsic aspects. For example, health, biometric and psychological factors, predisposition to sustain effort, response to training, recovery/resilience are all influenced by genetic traits.

Technological development of genetic studies has allowed for the identification of numerous individual variations contributing to athletic performance [7–10]. The identification of multiple genetic polymorphisms favoring sports abilities suggests a very strong interdependence of the genes associated with performance [8,11,12].

A polymorphism in the *ACTN3* gene, for instance, has been shown to be associated with muscular performance [11,13–15]. This gene encodes the muscle protein "alpha-actinin-3" [13]. The study of the polymorphism frequency shows different proportions of the RR variant (expressed in fast-twitch myofibers) among athletes with different muscular requirements. Power athletes (performing a very intense effort in a short period) have a significantly higher frequency of this variant than endurance

athletes (efforts of long duration) [13,16]. Individuals with this polymorphism have a better ability to perform powerful muscular contractions [17]. Conversely, endurance athletes have been shown to have genes favoring sustained effort, such as the *ACE* gene (Figure 1.2) or the *COL5A1* associated with the ultra-marathon performance [10].

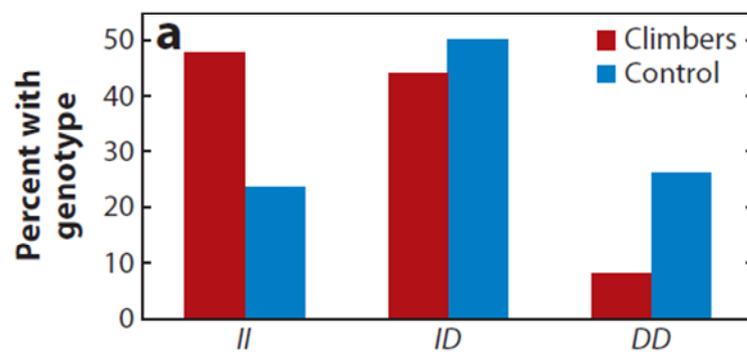


Figure 1.2: Distribution of *ACE* I/D genotypes in 25 elite British mountaineers and 1,906 healthy British men. It is noted an excess of II and a deficiency of DD genotype among the climbers. For the 15 climbers who had ascended to 8000m without oxygen, none were DD, and the best performers were all II homozygotes. (From Montgomery *et al*, 1998 [18]).

These inter-individual variations determine a predisposition to a particular type of effort as well as the level of the athletes, since the frequency of polymorphisms favoring specific performance increases with the sports level [15,19]. A study of the French rowing, cross country skiing and judo teams showed that the heterozygous mutation in the *HFE* gene, which improves oxygen transport, is doubled in these athletes compared to the general population and is 12 times more frequent among those reaching international podiums [20].

Beyond the genes and mutations promoting athletic performance, a selection of athletes is also carried out according to their phenotype, such as the athletes height [21,22], a trait highly dependent on genetic inheritance.

A study on Olympic medal "heritability" [23] has shown that the greater the genetic commonality between an Olympian and an Olympic medalist relative, the greater the likelihood of this athlete to also become an Olympic medalist (Figure 1.3).

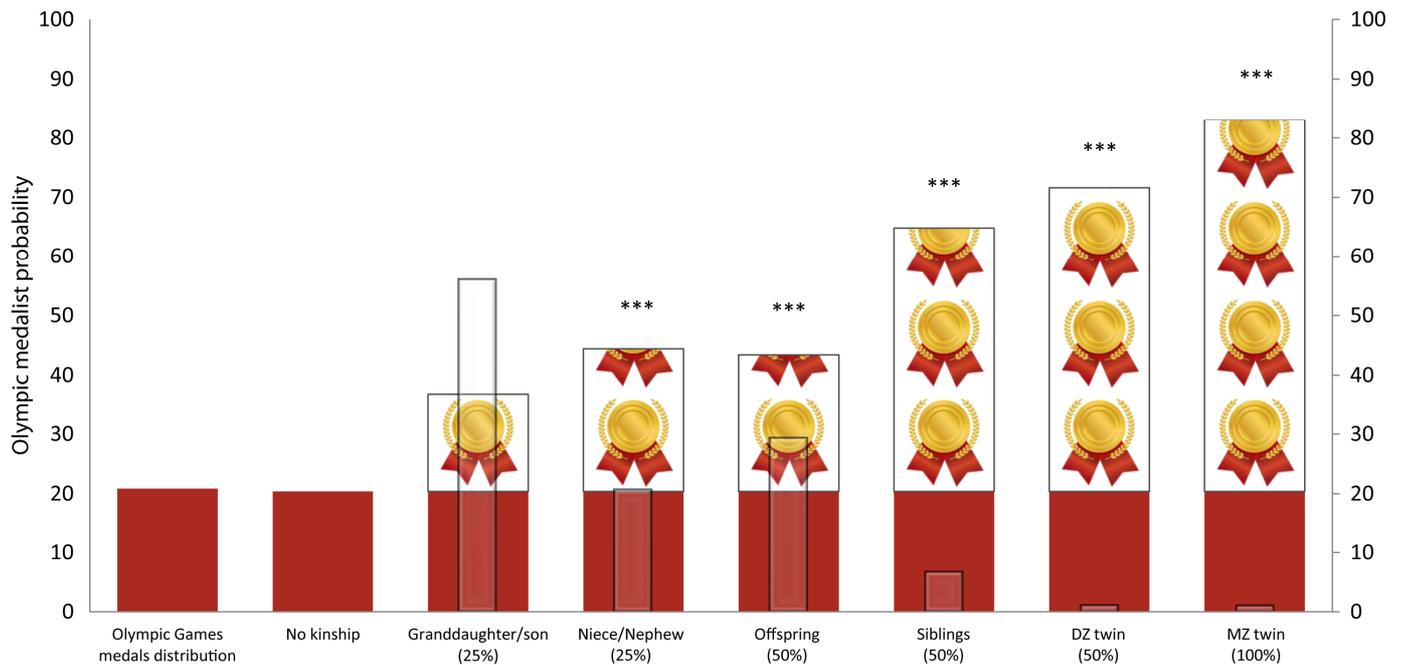


Figure 1.3: Frequencies of Olympic medals according to the family relationship. Bar plots from left to right: frequency of medals according to the number of Olympic participants. Frequency of medals among Olympians without kinship. Next six bar plots are represented in ascending order of percentage of common genes shared between an Olympian and her/his former kinship Olympic medalist (%) Dz = dizygotic (“fraternal”) twin; Mz = monozygotic (identical) twin. The red bars represent the expected frequency of medals according the medal distribution in the games. Drawn bars represent the additional proportion of medalists according to their degree of kinship. *** $p < .001$ for the test of the difference between frequency of medals within each group in relation to the medals distribution in the games. White bars illustrate the Olympic participation gap in years within each group of kinship (From Antero-Jacquemin *et al*, 2015 [23]).

Accordingly, an Olympian who has an aunt or uncle who was a medalist in the Games doubles his chances of becoming a medalist compared with an athlete having no kinship with any other Olympic medalist. This likelihood is greater if the medalist is a brother or a sister, exceeding 80% in the case of a homozygotous twin; and the shorter the time difference between the Olympic participation of the relatives, the higher the probability (Figure 1.3).

1.2.1.2 PERFORMANCE AND ENVIRONMENTAL INFLUENCE

The environment is defined as all the extrinsic aspects surrounding the athletes. For example, the climatic and physico-chemical parameters, the social, economical or technological conditions, the assistance (by the State, sports organization or sponsors) and all the factors that surround sports training, such as lifestyle.

Sports performance reveals a close entanglement between genetic and environmental factors. The everyday life of elite athletes is constantly dependent on environmental constraints, such as the nutrition habits adapted to the sports practice [24,25], the available technology [26], the coverage by the sports organizations, the medical staff and the psychosocial support. Human physiology is also subjected to extrinsic factors that interact with performance during training or competition: economy and geopolitics [27], weather [28,29], seasonality and sports calendar [30]. Subsequently, the environment promotes or limits the expression of the genotype and required traits; the optimal environment gathers a maximum of factors favorable to performance.

1.2.1.3 PERFORMANCE AND TRAINING INFLUENCE

Sports training is the regular practice of the physiological skills required to accomplish the best performance possible in a sporting event. It is therefore an extrinsic aspect, which also depends on the athletes' predisposition to engage and adapt to it. Training modulates the genetics-environment relation so as to promote and optimize performance and concerns all the factors related to the daily sports practice.

In addition to the genetic predispositions and environmental conditions necessary to meet the requirements of high level sports [31], a great amount of training is required for many years to achieve excellence in sports [32,33]. Excellence among elite athletes has a strong relation with the number of hours they accumulate in practice [34,35]. The widespread model of expertise suggests a minimum of 10,000 hours of exposure to training over a period of about 10 years to reach the elite [36,37].

Although this model is criticized for the rigidity of an established threshold for training hours in a given activity [38] (noting that the prior participation in other sports has a positive relation with sports excellence [39]), rare are the athletes reaching the expertise before 10 years of intense sports practice [40].

A study assessed the age at which athletes, who participated in the Olympics in 2000, started their sports activities. The authors found that on average athletes had begun during childhood, varying from the age of 7 in artistic sports to 10 years in team sports, and increased training load (*i.e.* both frequency and volume) with age [39].

As previously shown, the physiological peak of athletic performance is usually reached at the age of 25 years for a large number of sports [41,42]. Despite the

important variability from one sport to another and from one athlete to another, many years of training are essential to achieve an athlete's potential peak and climb the highest places of the world podiums.

Research describing elite athletes' load of training, for example, shows that, on average, soccer players practice 16 years before their first match in professional leagues [40]. Among hockey champions, 18 years on average were invested to obtain an international medal and 22 years before getting an Olympic gold [32].

Thus, the elite athletes' period of practice in relation to their whole life corresponds to an important part: for a person living up to 80 years it is approximately 20 to 30% of their life devoted to sport, taking into account all the years invested since childhood until their athletic maturity.

Hence, it is the favorable and additive interaction between innate and acquired factors, modulated by structured training that determines athletic excellence, and therefore, defines our population of interest.

1.2.2 ELITE ATHLETES: THE « SUPER-CONTROLS »

Athletic performance is consistent with a combination of distinctive characteristics allowing its classification as a quantitative (or multifactorial) trait: numerous factors concur to the trait's onset; greater concordance rates occur in identical twins than in dizygotic twins; trait frequency increases with the degree of relatedness; it runs in families without Mendelian inheritance patterns; it can occur in isolation and environmental influences increase or decrease the risk of the trait onset [43–46].

Most physiological traits follow a polygenic quantitative distribution [47,48]. Accordingly, the susceptibility to a given phenotype is distributed in the population following a bell-shaped curve [47,49]. Thus, performance traits exhibit a Galtonian pattern following a continuous variation: gradation in expression with no abrupt change from one phenotype (performance level) to another. Susceptibility being additive, most individuals have an intermediate phenotype [47]. The extremities of the curve represent individuals cumulating completely favorable or unfavorable conditions to a given phenotype; the farther from the mean, the rarer the phenotype [48]. Hence, elite athletes occupy the right extremity of a curve of sports' susceptibility.

Thinking quantitatively, the likelihood of individuals gathering all favorable conditions (innate and acquired) is very low, evidencing the exceptional character of high level performance. This also explains the rarity of athletes meeting the ideal phenotype required to perform at such a level.

Performance, which is a surrogate of the athletes' physiological capacities, may define their position in the capabilities' distributions among populations. Thus, from a

phenotypic point of view, elite athletes are the outliers of a population in terms of physiological capacities.

Therefore, their performance opens a privileged realm for analyzing human physiology. As formerly stated: "some of the most consistent physiological data are contained, not in books on physiology not even in books on medicine but in the world's records for running " [50]. This is because maximal performance gives the boundaries of biological capacities precisely measured through global standards.

Understanding high sports performance under this model broadens the perspectives regarding elite athletes. For instance, in such a curve, elite athletes are symmetrical to a population of subjects with rare disease conditions in a case-control study (Figure 1.4). The low and high ends in the bell-shaped curve define the super-control groups, which over-express a given quantitative trait [47].

Considering elite athletes as super-controls in quantitative traits of performance may have far-reaching implications in apprehending the extremes of these traits [47].

1.3 SPECIFIC CONSTRAINTS UPON ELITE ATHLETES

All the genetic and environment factors associated with athletic training imply very specific constraints that may contribute to specific risks or benefits to the athletes' health. Given the elite commitment - in both time and intensity - such constraints may lead to positive or negative effects on their morbi-mortality.

These main constraints will be addressed in the following four sections in view of the potential impact of these factors on the elite athletes' morbi-mortality: (i) intense physical training; (ii) over-exposure to injuries; (iii) access to doping and (iv) lifestyle.

1.3.1 INTENSE TRAINING (I)

1.3.1.1 HEALTH BENEFITS OF MODERATE PHYSICAL ACTIVITY

The health benefits of regular and moderate physical activity in the general population are well known [51,52]. The scientific literature provides major evidence of better physical and mental health for any age groups with regular physical activity. The benefits echo on the cardiovascular (CV), respiratory, immune, neuronal, metabolic, muscular and bone systems [53]. Physical activity also has a recognized facet of prevention, treatment and rehabilitation on several chronic diseases, with a major impact on populations' mortality [52].

CARDIOVASCULAR SYSTEM

The benefits of physical activity are well known for the prevention of CV problems [52]; moderate activity is recommended for primary and secondary prevention of CV diseases [54,55].

The regular practice of physical activity allows a better control of blood pressure, which is the main risk factor of mortality in the world, responsible for 13% of total deaths. The adaptation to daily physical activity leads to a blood pressure reduction of more than 2 mmHg and an even greater reduction in hypertensive subjects (-7 mmHg); this response is comparable to that of an anti-hypertensive monotherapy [56].

Epidemiological studies evidence the positive effect of sports activity on the incidence of CV diseases [57,58]. A meta-analysis including 33 studies with a total of 883 372 subjects demonstrated that moderate physical activity is associated with a marked reduction in CV women and men's mortality [59].

MUSCULOSKELETAL SYSTEM

Physical activity affects the volume of the total muscle mass, the metabolic and the contractile properties of muscles and their development in the different age groups [53]. Exercising preserves muscle function, essential to maintaining autonomy with ageing. Muscle activity affects the use of metabolic energy, the muscle system being the main compartment in uptake and utilization of glucose and fatty acids. Therefore the muscles are fundamental in the regulation of carbohydrate and lipid homeostasis and in the prevention of metabolic diseases [53].

Subsequently, physical activity is beneficial for the prevention of overweight and obesity, metabolic syndrome and type 2 diabetes, all the conditions that are related to the physiological role of the muscle system on the homeostasis of glucose and insulin sensitivity. This is a crucial role for public health, since hyperglycemia and obesity are among the main risks for global deaths [60]. Physical activity reduces the risk of developing type 2 diabetes in subjects intolerant to glucose [53]; this impact is superior to the effect of a drug treatment. Several longitudinal studies in adults demonstrate the positive effect of moderate physical activity on reducing biological disorders such as metabolic syndrome with hyperglycemia, high cholesterol or triglycerides, and obesity [61,62].

In addition, the mechanical stresses exerted on the skeleton during physical efforts induce the formation of bone tissue. This osteogenic effect is stronger when the mechanical stresses are varied. Exercise is thus also recommended for the prevention of osteoporosis [63].

NERVOUS SYSTEM

The literature shows that regular exercise can have many benefits for cognition [64–66]. Several neurophysiological mechanisms involving angiogenesis, neurotrophic factors released during exercise and greater brain plasticity, could contribute to explain the beneficial role of physical activity [64,65,67,68].

Recent prospective studies show the benefits of physical activity on degenerative brain diseases, which may affect more than half the subjects older than 85 years [53], a real issue of aging societies.

GLOBAL HEALTH

In view of all of its benefits, physical activity has a key role in the morbi-mortality and quality of life of the populations and a crucial impact in public health. In industrialized countries, 7 out of 10 deaths occur after 70 years because of chronic diseases (approximately one third for CV diseases and one third for cancers) [60]. In the

current context of aging populations, the importance of physical activity is even greater since it affects all major causes of death.

Besides the already mentioned benefits, physical activity also generates positive effects in the prevention and treatment of many cancers, leading to better rates of survival in particular after breast, colon and prostate cancer [69]. It acts at the beginning of the proliferative process and hampers the development of cancer cells [53]. Subjects practicing moderate to intense physical activity have an average reduction of 20 to 35% of colon cancer risk [70] as well as a reduction in the risk of developing a breast cancer of similar magnitude [71]. Several randomized controlled trials have reported that in tertiary prevention, physical activity improves physical function, quality of life and quality of sleep in patients with cancer [53,72] and decreases the risk of recurrence, improving overall and cancer-specific survivals [69].

Physical inactivity, by contrast, represents 6% of all deaths worldwide, the fourth overall death risk factor according to the World Health Organization (WHO) [60].

1.3.1.2 HEALTH CONSEQUENCES OF INTENSE TRAINING

DOSE-RESPONSE TO PHYSICAL ACTIVITY

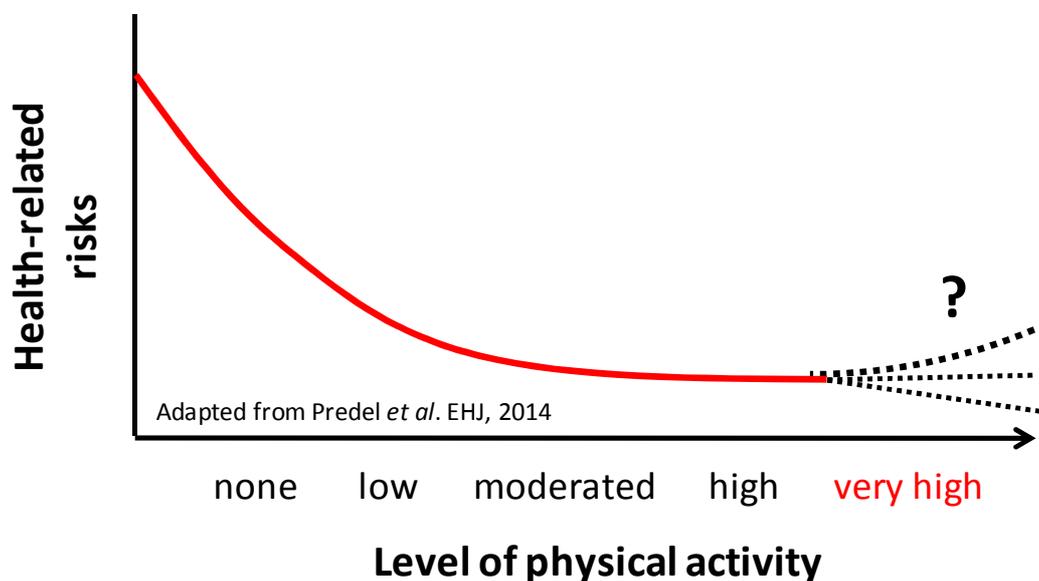


Figure 1.4 Dose-response between risks to health and intensity of physical activity (Adapted from Predel, 2014 [73]).

The minimum amount of physical activity impacting mortality has been studied by Wen and colleagues [52], in a prospective cohort of 416,175 subjects. This study shows that 15 minutes of physical activity per day reduces the mortality risk by 14%. Another

prospective cohort, the Copenhagen City Heart Study, based on 5048 healthy subjects has found that jogging between 1 and 4 hours per week was associated with a 71% reduction in mortality compared to a control group of sedentary subjects [74]. In agreement with these studies, several researches have shown that the benefits of physical activity begin in small doses in relation to a sedentary behavior [53]. The strength of this evidence has inspired the rationale that if exercise is beneficial for health, higher doses should then provide even more benefits.

During the 70s it was scientifically suggested that the preparation and success in long-distance races, such as a marathon, would be a lifelong factor of protection against coronary heart disease [75]. Contradictorily, the marathon race is named according to the legend of Philippidès, who would have run from Marathon to Athens to announce the victory against the Persians in 490 BC. and reportedly died on his arrival [76]. A similar and more recent case is the one of the American runner, Michael Hickman, who died at the age of 58 years during a 20 km race. The autopsy revealed idiopathic left ventricular hypertrophy [77]. In a bestseller, "Born to Run", his ultra endurance exploits were described: he used to run between 40 and 160 km per day [78].

However, the risk of sudden death during intense effort remains marginal [79,80]. Investigating more than 215,000 participants in popular USA marathons over 30 years of follow up, the authors showed that the sudden death risk associated with intense physical activity was extremely low: 1 in 50,000 subjects – which did not justify the systematic screening measures of CV disease in this type of population [80]. A more recent study, involving nearly 11 million subjects, bringing together runners of every level in an 11 year follow-up reached similar conclusions [79].

According to recent theoretical models the benefits of vigorous physical activity are justified by our evolution process [68]. Humans evolved from "tree-dwelling apes" to become capable of enduring long hours of bipedalism in order to pursue their prey, even during the hottest hours of the day [81]. The main factor of survival depending on the endurance capacity (long duration effort), humans may have developed several adaptations in this direction, such as skeletal and metabolic changes [81] or the capacity to dissipate heat through optimized thermoregulation [68].

Arguing against this theory, other researchers have suggested that running had not such an important role in our evolution because humans are poor runners compared to most quadrupeds [82,83]. For illustration purpose, the sprinter Usain Bolt, the current world's record holder with a mean speed of 10.44 m/s over 100 meters, is slower than a domestic cat (about 14m/s) and much slower than a cheetah (about 30m/s). Ethnographic research suggests that in this evolutionary context, our ancestors prioritized walking over running because it was a preferable means of locomotion in terms of mechanical and musculoskeletal efficiency [84] and that consequently, humans

would have adapted to moderate rather to intense effort. But developing both characteristics may further enhance the range of adaptation and therefore increase survival rates.

The current global recommendations of physical activity prescribed by the (WHO) are to practice a minimum of 30 minutes of physical activity per day for people aged 18 to 64 years. These incentive measures include activities of leisure, locomotion, professional, recreational, sports, household chores or structured exercise. To obtain additional benefits, the recommendation is to increase the duration of activity, maintaining a moderate intensity, up to 300 minutes per week [85].

Despite a limit introduced in the WHO recommendations regarding the duration of activity, the dose-response (the dose being defined as the volume of training), is not clearly defined (Figure 1.4).

A study by Wen and colleagues [52] has shown an additional reduction of 4% in overall mortality for every step of 15 minutes of exercise per day until a plateau is reached at 100 minutes per day, with no additional benefit beyond (Figure 1.5).

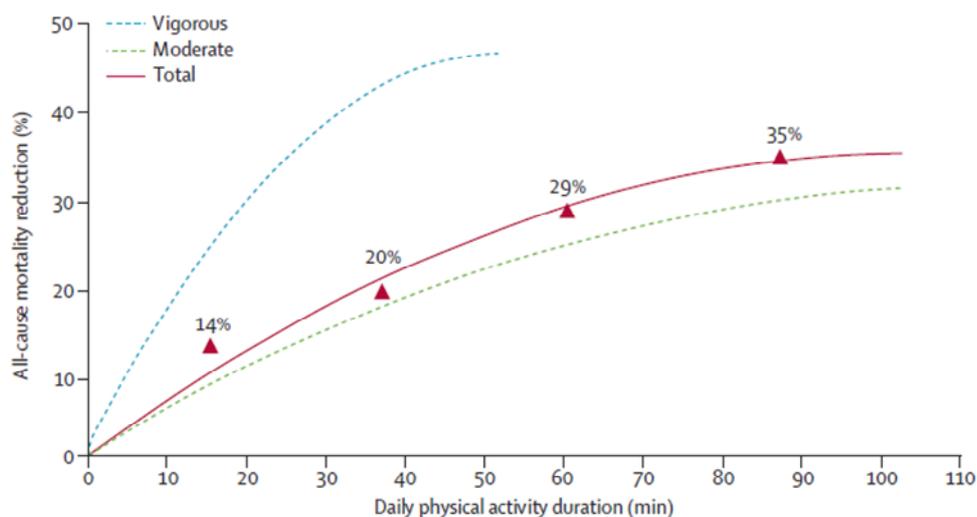


Figure 1.5: Physical daily activity duration and all-cause mortality reduction, according to intensity level (From Wen *et al*, 2011 [52]).

The Copenhagen City Heart Study [74] has shown greater mortality reduction for joggers belonging to the low-intensity group compared to joggers in the moderate and high intensity group.

Regarding higher intensities, the relation between training and health benefits is less well established, particularly for the CV system [73,86–88]. Some studies have

shown that exercise at very high intensity, especially those in endurance, could have a negative impact on the CV system [89] [90,91] such as troponin elevation [92], coronary remodeling [91] or calcifications [93], atrial fibrillation or flutter [90,94].

A threshold of 1500 lifetime hours at high level has been proposed above which exercise would trigger more frequent arrhythmias among endurance athletes [95]. Yet, since the reintroduction of the modern Games in 1896, the training and the level of physical intensity of elite athletes have been rising, distinguishing more clearly from that of the general population [96]. The growth of the world competition has generated a selection process pushing further increases in the doses of training. Cause or consequence, intensity of training among elite athletes is about 5 to 10 times higher than the recommendations [39,97]. The threshold of 1500 hours is easily exceeded by top athletes, possibly in less than 2 years. Epidemiological studies also suggest that vigorous exercise is associated with a higher incidence of infections in athletes' upper respiratory tracts, while low to moderate exercise is considered protective [98].

From this perspective, some researchers suggest that the level of training undertaken by elite athletes may be compared to drug overuse. The ideal dose is beneficial while the excess is harmful [97]. Thus, an adverse structural and electrical remodeling of the heart, induced by extreme and chronic exercise, could reverse part or even all of the benefits that moderate exercise provides to the CV system in terms of longevity. A "U-shaped" curve is then suggested for elite athletes, illustrating the association between training load and cardiovascular risk [73]. Elite athletes, especially in endurance, would be exposed to the same CV risk and mortality level as sedentary subjects [74,89]. However, most studies supporting the "U-shaped" curve (relation between training load and health risks) rely on data from intense training in the general population, which may have different profiles as compared to elite athletes.

A study on the CV health of 114 Olympic athletes, participating in intense endurance training for many years found no deterioration in the function or in the cardiac morphology, and no occurrence of symptoms or CV events [99]. Yet, it has been suggested that over 10% of elite cyclists who participated in the TDF may have a cardiac dysfunction (with a dilation of the left ventricular cavity) suggesting a possible dilated cardiomyopathy [100]. Others demonstrations have associated the cyclists' intense physical training to the electrophysiological abnormalities found among them [91].

The debate about intense training persists because most studies describing cardiac remodeling in elite athletes rely on transversal studies of low power to properly enable to elucidate the long-term effects of these clinical signs [99]. In conclusion, the long-term health consequences of the sport practice at elite level are still poorly understood (Figure 1.4).

1.3.2 OVEREXPOSURE TO INJURIES (II)

Another constraint over the elite athletes' population is their overexposure to injuries. The simple act of engaging in an sporting activity exposes the subjects to more immediate risks of injuries than staying at home watching TV, though, this latter activity may probably be more lethal on the long-term than anticipated.

Sports' injury can be defined as the occurrence of a lesion (of different grades) during sports activity, precluding the athlete from continuing, temporarily or permanently, her or his activities [101,102].

Injury incidence and prevalence vary widely according to sport, gender and level of practice. Despite the current paucity of well-designed epidemiological studies on the majority of Olympic sports [103], elite athletes have in common a high prevalence of injuries.

The probability of accidental harm increases with greater time under exposure. As elite athletes undertake great loads of intense training daily, they are greatly exposed to injuries.

In addition, the sports motto "faster, higher, stronger" which continuously encourages overcoming one's own limits, may be an additional risk factor for injuries. The incentive to break limits as well as the pressure (whether intrinsic or extrinsic) driving elite athletes toward better results, may place them at a threshold between performance and injury. As a consequence, the athletes may further push their body limits, training under pain, exposing themselves to injuries by overuse, or increasing the risk of accidents by training under fatigue. Frequently, athletes testify: "injury is part of the parameters of sports and pain is a trivial consequence" [104]. The resilience of training under pain or injury is a reality positively flaunted by athletes.

The training load and competition schedules are usually conflicting with post-injury recovery. What athletes fear the most is the activity interruption rather than the injury itself [104]. They may become deaf to their own body's demands and keep practicing despite sustained injury. This anxiety over the return to play constitutes additional risk factors to injury recurrence [105].

Finally, another factor exposing elite athletes to greater risk is the intensity and level of their activity. The risk undertaken by athletes during their career constitutes for many their main motivation. Athletes who have already suffered major sports injuries reported having preferences for stimulants and risky environments [106]. The faster the race, the higher the jumps, or the stronger the load/impact/power, the greater the risk of injuries, and the worst its severity.

Sports injuries can be lethal, as history reminds us [107,108]. Accidents under high inertia forces may increase the probability of fatal events due to accidental shocks or collisions. Such was the tragic fate of Nodar Kumaritashvili, a Georgian luger in the

winter Games of 2010, fatally injured in a crash during his final training run when he lost control at 143.6 km/h [109]. Permanent injuries also tarnish sports competitions. Taking into account only the last winter Games (2014), three athletes, one Canadian, one Russian and one Brazilian were permanently paralyzed after injuries while training or competing [110].

High impact repetitive injuries are especially common among contact sports, such as ice hockey, boxe or US football, and may engender chronic health consequences. Dementia pugilistica, a suite of neuropathological and cognitive dysfunction after chronic traumatic brain injury, is present in approximately 20% of retired boxers [111]. Similarly it has been shown that the onset of dementia-related syndromes may be initiated by repetitive cerebral concussions in professional football players [112], which are also associated with increased risk of clinical depression in retired athletes [113,114]. Recently, many countries and sports leagues organizations, have created policies, laws, or action plans enforcing a full recovery before returning to play after concussion [115].

Sports with lower inertia or without contact such as swimming, archery, or volleyball are not immune to injuries [105,116,117]. The repetition of similar movements' patterns, is a risk factor for overuse injuries [117], which accumulate, especially during youth, may have important long-term consequences on musculoskeletal system [118]. Overuse injury is also highly prevalent among elite athletes [119,120]. For instance, a slightly increased risk of osteoarthritis among athletes has been shown [121] following hip, knee, or ankle osteoarthritis over 21 years in former elite athletes [122].

In summary, elite athletes are overexposed to different types of injuries during their career, which are closely related with their practice, with a wide range of consequences, possibly impacting their morbi-mortality.

1.3.3 DOPING ACCESS (III)

Another aspect potentially impacting elite athletes' health is the practice of doping. Doping is defined as: 'the presence of a Prohibited Substance or its Metabolites or Markers in an Athlete's bodily Specimen and the Use or Attempted Use of a Prohibited Substance or a Prohibited Method to increase athletic performance' [123].

The use of substances designed to enhance athletic performance is as old as the human aspiration to break limits. Its use in sports dates back from the earlier Games [124]: in the 1904 Olympic Games, a marathon runner nearly died after mixing alcohol and strychnine [125]. Different types of drugs are used by athletes to enhance performance, reduce anxiety or heart rate, increase muscle mass, reduce weight or mask the use of other drugs [126]. Many sports, specially the professional ones, have been the object of controversies because of higher exposure to performance enhancing techniques

[127–130]. A list of prohibited substances was first published in the 60s and regularly updated, but none of them succeeded in restricting doping extensively [126].

However, the real prevalence of doping is unknown, and may considerably vary between sub-groups, sports, levels, nationalities or genders [131,132]. The statistics provided by the World Anti-Doping Agency (WADA) show that 2% of tested athletes are positive. Yet, in the words of the WADA director himself, David Howman, this estimation seems largely underestimated « we catch dopey dopers, not the sophisticated ones» [133]. A combination of recent approaches intending to estimate doping prevalence, suggests that 14–39% of elite athletes may be intentionally doped [132]. The real prevalence will probably remain unknown due to some obvious limitations in measuring it: i) chemical analyses cannot detect all doping substances; ii) the performance-enhancing effects often outlast the time window for detecting traces of a substance in an athlete's bodily specimen [134]; iii) despite positive controls, tests may not always be considered as such according to some procedural and judicial circumstances [135]; iv) there are huge barriers and costs in admitting to doping in public and even in private circumstances, which limits research based on personal input from athletes [132].

Doping practice has changed over the course of different periods [128]. After the alcohol-strychnine experiment [125], heroin and cocaine may have become more common since the 1920s, the latter still being frequently identified in solo or in cocktails [135,136]. Then, amphetamines were discovered and produced; they were widely used during the second world war, by soldiers as well as athletes [125,135]. Later and until the 1980s, synthetic hormones such as anabolic steroids took place [137]. Since 1990 the use of growth hormone and erythropoietin has spread widely [125,138]. Some types of substance abuse have clearly shown harmful effects; such is the case of hormonal doping practice in the 70s in East Germany [128]. These substances, especially administered to women have induced various anomalous medical conditions, including premature death [135].

The health side-effects of doping, however, depend on the class of the drug, the dose and duration of intake and the individual's sensitivity [126]. Drugs can be used sparsely or abusively, as a single drug or in a combination, leading to interactions and counteractions, and therefore to different acute and long-term consequences. Given the diversity of drugs, and the difficulty to identify users, the real hazards of doping drugs on health are only partially suspected and the long-term effects even less well understood [126,139]. So far, only the lethal or almost lethal acute effects have been documented in emblematic cases such as Tom Simpson's or Riccardo Ricco's [140,141]

Overuse of drugs may be associated with serious health complications, of which the most common and dangerous ones involve the CV system [126] (Figure 1.6). The effects of anabolic androgenic steroids (AAS) abuse, for instance, are well described and

includes altered serum lipoprotein profile, arteriosclerosis, cardiac hypertrophy and possible direct toxic effects on cardiac muscle and blood coagulation [142,143]. These adverse effects have been associated with increasing athletes' risk of CV disease and sudden cardiac death [144]. In addition, the mental side effects of this drug class has been demonstrated [145]: increased aggressiveness, psychosis, depression and suicide [139,142,146]. Among peptide hormones and analogues, human growth hormone (hGH) and erythropoietin (EPO) are both associated with adverse effects with greater CV risk [126].

	Hyper-tension	Arrhyth-mias	LVH	CAD	MI	HF	SCD
AAS	+	+	+	+	+	+	+
hGH		+	+			+	+
EPO	+					+	
Beta-2 agonists		+			+	+	+
Diuretics		+					
Amphetamines	+	+			+	+	+
Cocaine	+	+		+	+	+	+
Ephedrine	+	+		+	+		+
Narcotics							+
Cannabinoids		+			+		+
Glucocorticosteroids	+			+			
Alcohol	+	+			+	+	+

+ Indicates an effect on a parameter; LVH, left ventricular hypertrophy; CAD, coronary artery disease; MI, myocardial infarction; HF, heart failure; SCD, sudden cardiac death; AAS, androgenic-anabolic steroids; hGH, human growth hormone; EPO, erythropoietin.

Figure 1.6: Cardiac side-effects of doping substances. (From Deligiannis *et al*, 2006 [126]).

Yet, being aware of the side-effects does not restrain usage. Specific knowledge of doping has been shown to be better among users than non-users [147]. *Sports Illustrated* interviewed a cohort of elite Olympic athletes, asking, "If you were given a performance-enhancing substance, you would not be caught, and you would win, would you take it?" Ninety-eight percent of athletes answered yes. Even when the question included health concerns, the majority of answers were positive: "If you were given a performance-enhancing substance, and you would not be caught, win all competitions for 5 years, then die, would you take it?" More than 50% still said yes [148].

1.3.4 LIFESTYLE (IV)

Performing at high level requires health-related behaviors in order to optimize physical training. Elite athletes are constrained to normative lifestyle associated with health benefits [149], such as specific nutrition habits, adequate sleep and recovery time [150], restrained alcohol and tobacco consumption [151–153] and fitness.

Since former periods athletes have followed a routine of healthy behavioral patterns aimed at enhancing performance. In the Ancient Olympics, trainers paid close attention in balancing athlete's exercise and diet. The Greeks also related hygiene behavior with health. After exercising, they cleaned themselves by rubbing oil over their bodies and scraping the mix of oil, sweat, and dirt off with special instruments. According to ancient texts, athletes were supposed to take an oath mentioning that they had strictly followed the regulations for training for ten successive months before the Olympics [154].

During the Age of the Enlightenment, philosophers like John Locke argued for the need to enhance personal health in order to develop the body, particularly through good diet, adequate sleep and exercise [155].

Since the organization of sports' practice during the end of the 19th century and the early 20th century, sports have been understood in strong relation to health and lifestyle orientation [155].

Nowadays, researchers have tried to identify common lifestyle patterns among athletes. Healthy and risky behaviors are influenced by cultural contexts in multiple ways. Differences in national health care systems and policies, for instance, might influence norms and values related to healthy lifestyles. The way in which sport is organized and integrated in social life as well as different formal and informal organizational structures related to sports are also potential factors influencing health behaviors, during and post career [149].

Some common patterns, however, seem to stand out. A meta-analysis including different measurements of smoking showed that athletes were less likely to smoke than non-athlete referents [149,156]. Similarly, a majority of studies have reported a lower prevalence for illicit drug use [149] and delinquent behavior [157] among athletes. In addition, many studies have shown that the eating behavior of athletes was healthier [149], even though athletes engaged in aesthetic sports such as rhythmic gymnastics [158] or in sports with weight categories [159] were identified as being at relatively higher risk for eating disorders.

A risky behavior specifically present among athletes is the use of doping, discussed in the previous sections. Some researchers have also reported that athletes were more likely to engage in risky behaviors such as driving dangerously or having unsafe sexual intercourse [160]. Some studies have suggested that alcohol consumption

may be widespread among sport practitioners. A meta-analysis, flawed with considerable heterogeneity, suggested that they may present a higher proportion of alcohol consumers [149], but a recent national survey on more than 2000 high level athletes discarded this assumption showing a lower addictive behavior as compared to the general population rates [156].

Nonetheless, very little is known about athletes' lifestyle post career. Studies have showed that the transition out of elite sports is a dynamic and multifactorial process in which nationality and culture play an important role [161].

A group of researchers holds a valuable cohort of top level Finish athletes, and has followed their health status and behavior. This group has shown that elite athletes usually maintain healthier habits than the general population before, during and after their career [162], with lower smoking rates, good nutrition and more regular physical activity [163]. In addition, active physical exercise during youth (suggested by participation in competitions), is associated with a physically active lifestyle post-career [164]. Compared with controls, Finnish elite athletes remained more physically active at older ages [163].

Lifestyle patterns among elite athletes may differ according to period, athletic status, nationality and other factors but, in general, they seem to adopt a healthier behavior, during and post-career than the general population.

1.4 CONCLUSIONS REGARDING THE CONSTRAINTS UPON ELITE ATHLETES

IS THERE A LONG-TERM IMPACT OF BEING A TOP LEVEL ATHLETE?

In light of the major constraints upon elite athletes - high intensity of training, overexposure to injuries, lifestyle and doping access - all potentially affecting their health, whether with positive or negative long-term consequences, we inquired about their mortality status, especially in relation to the general population for whom they represent the end of the physiological capabilities spectrum.

The multidimensional character of health requires indicators that summarize its various components at the population level. Health indicators quantitatively describe health status among and between populations and its variations in time and space. Mortality and life expectancy are the main indicators of the populations' health [165–167].

1.4.1 HEALTH INDICATORS: MORTALITY, LIFE EXPECTANCY AND LONGEVITY

Mortality describes the frequency of deaths in a given population over a given period. As a *cross-sectional* indicator, mortality assesses the number of deaths in a population during a specific period. Mortality, as a *longitudinal* indicator, lists the events of deaths in each generation, enabling the calculation of another global health indicator: life expectancy. This indicator reflects the overall mortality level of a population, summarizing the mortality pattern that prevails across all age groups in a given year [168].

Lifespan and longevity are terms related with mortality and life expectancy indicators by their definition. Lifespan is operationally the age at death. The average longevity translates the average lifespan of individuals in a given population, while the potential longevity of a living being is the maximum life duration for which she/he/it is programmed; it is defined by the individual of her/his/its biological species reaching the most advanced age [169].

1.5 REVIEW OF THE LITERATURE

1.5.1 ELITE ATHLETES' MORTALITY

There is a current paucity of studies assessing elite athletes' longevity and mortality compared with their referents in the general population. Prior to this thesis, the single review on this subject included a total of 14 studies, of which 8 used standard epidemiologic indicators for longevity and mortality and included only elite athletes [170]. Studies comparing mortality based on misleading methods, *e.g.* comparing the average age of death of elite athletes and the country's life expectancy through a t-test, were disregarded. Also, studies including heterogeneous cohorts in terms of athletes' level were not taken into account, because elite athletes only represent a small minority.

By updating for new studies we searched for: i) reviewed English-language scientific articles available in Medline and Web of Science databases on mortality/longevity of athletic cohorts, ii) composed solely of professional athletes or elite athletes, iii) using a cohort study design providing survival functions, standard mortality ratio (SMR) or, alternatively, providing means to calculate the latter variable. We found 4 more cohort studies and one recent meta-analysis [171].

From the total of 12 studies, seven were related to professional sports: 5 in the USA [125,172–174] and 2 in Italy [175,176]. Two studies concerned different sports in Finland [96,177], two others assessed Danish [178] and Polish [179] athletes and one studied rugby players from New Zealand [180]. The results and methods vary according to the studied countries and sports, but they basically compared male athletes' mortality to their referents in the general population.

1.5.1.1 COHORT OF MULTIPLE SPORTS

DENMARK

The first study on elite athletes dates back to 1971 [178]. Prior to that study, university and collegiate athletes had been studied, reaching back to the study of Morgan in 1873, showing that university oarsmen in the Oxford/Cambridge boat races between 1829 and 1869 displayed better survival than the average Englishman [181,182].

Regarding the elite, Schnohr and colleagues investigated the mortality of 297 male athletic champions from various sports in Denmark [178]. The studied cohort, comprising subjects born during 1880 and 1910, showed a significant lower mortality of 39% (no confidence intervals (CI) detailed) for the athletes under the age of 50 in comparison with the general population. No differences were observed among athletes

and the general population past 50 up to 80 years. Despite this lower overall mortality at younger ages, no differences regarding causes of deaths were found among the Danish athletes and the general population. This first study illustrates the importance of studying elite athletes' mortality as a function of their age.

FINLAND

The studies concerning Finnish athletes from eight sports have shown lower mortality among some groups of athletes compared with their referents [96,177]. In the first study in 1993, Sarna and colleagues compared the athletes with a control cohort of conscripts from the Finnish Defense Forces (conscripted is compulsory for all Finnish men). The referent subjects were classified as completely healthy at the age of 20 after medical examination.

Based on previous reports about the average maximal oxygen uptake (VO₂max), the authors divided the athletes into three categories: endurance (highest VO₂max), team sports (medium VO₂max), and power (lowest VO₂max). The results showed that only endurance athletes had a lower overall mortality 0.59 (95% CI 0.40, 0.85) as compared with controls, mainly associated to a lower mortality from cancers 0.36 (95% CI 0.12, 0.92) and CV diseases 0.49 (95% CI 0.26, 0.93). Athletes engaged in power or team sports, did not show any difference of all-cause mortality. Yet, the team sports group had lower CV mortality risk 0.61 (95% CI 0.41, 0.92). The power group had lower cancer mortality 0.55 (95% CI 0.33, 0.92) but a greater risk of death from external causes 2.0 (95% CI 1.04, 3.82).

Keeping track of nearly the same cohort, a later study analyzed the athletes' mortality this time in comparison with the general population in Finland [177]. Changing the reference population from healthy controls to the general population has proven to be a practical method with minimal implications: in comparison to the general population the athletes' mortality is slightly lower, and the confidence intervals shorter. For instance, the overall mortality ratio for endurance athletes has changed from 0.59 (95% CI 0.40, 0.85) when compared to healthy controls to 0.57 (95% CI 0.47, 0.68) in comparison to the general population [96,177].

Hence the new analyses showed similar results, displaying significantly lower overall mortality in endurance and mixed sports athletes and no difference of power sports with the general population. In relation to the causes of deaths the Finnish studies are not comparable due the different categories of diseases studied. But globally the results follow the same direction as the first study, with greater disease-specific reduction among endurance athletes, followed by mixed sports and power sports. These studies show the importance of taking further into account the characteristics prevailing in the sports analyzed, since this seems to supply some etiological cues for the findings.

POLAND

A study assessing elite athletes from various sports in Poland was the first and only one to include female athletes [179]. Men and women's overall mortality were compared to a healthy reference made up of actors/actresses and monks/nuns. The authors showed a significant 50% lower mortality (95% CI 0.44, 0.56) for Polish male athletes compared to controls. A similar, but not significant, trend was observed among women; probably a limitation came from a restrained size sample. Causes of deaths were not assessed, neither for female nor male athletes.

1.5.1.2 COHORT OF PROFESSIONAL SPORTS

USA

Baseball

A large study, performed by a life insurance company in 1975, showed a cohort-dependant mortality ratio: no significant difference was found among players debuting in the 1876-1900 period, but a 36% (no CIs detailed) lower mortality was seen among players debuting in 1901-1930, and a 45% lower one for players debuting in the 1931-1973 compared with the general US male cohort [173].

Targeting the same cohort, for players debuting their career during the 1911-1915 period only, another study found no mortality differences between athletes and their referents in the general population [174].

Finally, a more recent work on players debuting in the 1963 - 1996 period, also showed a 71% (95% CI 0.23,0.39) all-cause mortality reduction [172]. The authors have observed that education influenced mortality: the hazard rate of death for players who attended university was almost twice lower than for those who only attended high school. Another important determinant for longevity found was the players' race, a parameter that may include large socio-economical differences at distinct periods of life.

American Football

USA football league players debuting during 1959-1988 period have also been studied. Compared with the general population, they show a 47% (95% CI 0.48, 0.59) lower overall mortality [125]. The lower mortality is mainly associated with a lower risk of death from CV diseases and cancer.

However, analyzing the same cohort in a new study, the authors found that neurodegenerative mortality was 3 times higher than that of the general population. Among the major neurodegenerative subcategories, Alzheimer disease and amyotrophic lateral sclerosis (ALS), was 4 times higher among the retired players, especially among those in speed positions. This higher mortality may be related to recurrent traumatic brain injuries or concussions during their career [183]. However, it is important to consider that 7 deaths were added due to neurodegenerative causes whereas 296 were

avoided through a reduced risk of CV diseases or cancer. The two major causes of deaths (CV and cancer) together account for more than 40 times the deaths from neurological reasons, even in such a cohort which is still very exposed to the long range effects of concussions. These studies illustrate the importance of establishing the major risks of death operating in the target population.

ITALY

Soccer

In relation to Italian soccer players, one study included players active during the 1960-1996 period [175] ; the second one included players active in the 1975-2003 [176]. Even though the cohorts overlapped, the first study found that soccer players had the same death rates as the national average (with no difference regarding CV diseases), while the second one found a 32% (95% CI 0.52, 0.86) lower mortality with a reduced mortality risk from CV diseases 0.41 (95% CI 0.20, 0.73) and cancer 0.31 (95% CI 0.15, 0.55). This divergence may be due to a more recent cohort in the second study; the inclusion of league C (players of lower level) in the first study; and mostly to the different approaches used (the first study had used a proportionate mortality ratio, which is a relative measure of risk, while the second was based on a standardized mortality ratio (SMR) measurement¹.

Lower overall mortality may hide increased specific risks, related to the athletes' activity or way of life. Soccer players showed greater rates of car accidents 2.23 (95% CI 1.46, 3.27). Taioli also observed a significant greater mortality for ALS, 18.18 (95% CI 5.00, 46.55), due to four deaths while only 0.2 was expected according the rates in the Italian population. Such greater risk is currently debated, with publications from this same academic group that no longer confirm the initial results [185].

NEW ZEALAND

Rugby

No difference of survival was found when comparing 822 rugby players and the New Zealand general population [180], although an important survival advantage is highlighted for non-Maori players in relation to Maoris, following the trends of the New Zealand general population.

¹Standardization refers to methods of adjustment chosen to provide an "appropriate" basis for the comparison [184]. It is further detailed in the methods section.

1.6 ANALYSIS OF THE LITERATURE REVIEW

To summarize, most studies on top level athletes' mortality show that elite athletes live longer than their compatriots in the general population [171]. However, the main findings widely vary according to nationality, sport practiced or gender. In addition, the methods employed, the period of enrollment in sports or the follow-up time provide large variations in the results. Therefore the findings of these studies are not easily transposable to other elite populations.

The analysis of the literature highlights a need for further research, especially in relation to the five aspects discussed hereafter.

1.6.1 NATIONALITY (I)

Sports traditions vary from country to country. The practice, the technologies, the medical care, the facilities or culture in detecting and developing talents and retirement conditions post-career are different worldwide. Also, the level of the athletes is closely associated with their country's tradition and investment in sports: entering a national team in a given sport is more selective when the country's international ranking is higher. Thus, despite international rules in sports, nationality may play a distinct role in the sporting approach and have specific impact on athletes' longevity. In addition, the environment and culture of each country interacts with the athletes' performance and health. For instance, outdoor training in China, a country that exceeds the health limits on air pollution [186], may have different health consequences [187] than training in altitude in Kenya [188], or in the cold weather of Finland [189]. Finally, the behavior adopted by athletes after their career may also differ according to their nationality, as a result of cultural and social settings.

Therefore, findings observed in the aforementioned populations may not be extended straightforwardly for another one of different nationality.

FRENCH ELITE ATHLETES

The mortality of French elite athletes, whether professionals or amateurs, has never been studied before.

France has important traditions in sports, playing a major role in the historical context. Since the reintroduction of the modern OG in 1896 by the French Baron Pierre de Coubertin, France has participated in all summer and winter games. In addition, France has held the summer games in 1900 and 1924 and the winter games in 1968 and 1992. In the historical record, France is one of the top 5 countries according to the number of participants and the number of Olympic medals won. Besides the OG, other

major events, such as the TDF, also have had great enrollment and results for French athletes.

Therefore, French elite athletes mortality is of particular interest.

1.6.2 GENDER (II)

Currently there is a major gap in the scientific literature in relation to sportswomen's mortality in the world.

The sole study incorporating women in elite athletes' analysis of longevity was inconclusive, in reason of scarce data [179]. One other study, including female, but not elite athletes, also showed an insignificant trend for lower mortality, likewise due to insufficient data [190]. Women's participation in major events was restrained, particularly at the beginning of modern games when most sports were reserved to men. The first President of the International Olympic Committee was hostile to women's participation. Sports that had been historically popular among women were not included. Before 1924, the number of women per OG was inferior to 100, while more than 2000 men participated in the 1908 games.

Women integrated the whole Olympic program in 2012 only, even though the number of men enrolled remained greater. Outside the Games, most of professional sports are still reserved to men, like the American Football or the TDF, for instance.

In sports practiced by both sexes, studies report gender-related differences on health outcomes. For instance, it seems that women elite athletes, especially the younger ones, are at a particular risk in responding to stressors and staying healthy in training [191]. Gender differences have also been reported regarding injury risk and prevalence. An extensive epidemiological study during the 2010 winter Olympic Games reported a significantly higher incidence of injuries among female (131.1 injuries per 1000 athletes) than among male athletes (93.3) [107]. The following study in the 2012 summer OG showed similar injury rates in women (132.8) and men (121.0) [192]. A recent study surveying 14 top-level international track and field championships from 2007 to 2014 reported greater injury rates among male (110.3) than in female athletes (88.5) [193]. Despite wide variations in these findings, it seems that female and male athletes may be subjected to different risk regarding injury incidence, type, grade, mechanism or sports.

Concerning other health conditions, such as eating disorders, female elite athletes have shown to be at greater risk than male athletes [156,194]. Eating disorders generate health problems [195] and are common among women involved in weight-sensitive or aesthetic sports [195,196].

Sustained low energy availability may impair health, causing many medical complications such as the female athlete triad syndrome [195,197]. This syndrome, also linked with menstrual dysfunction, and decreased bone mineral density is relatively

common among female athletes [198]. The triad is associated with changes in the endocrine system affecting energy and bone metabolism. This may increase short and long term risks of premature osteoporosis, and affect the cardiovascular and reproductive systems [197,199].

These gender-related differences suggest particular consequences on female athletes health, and ultimately on their longevity, requiring a particular investigation. Hence it is relevant to specifically study female mortality, in order to examine whether gender has any influence on longevity among world class athletes.

1.6.3 SPECIFIC CAUSE OF DEATHS (III)

The analysis of the overall mortality of elite athletes is a first approach, which defines the framework of the athletes' population in relation to their compatriots. The demonstration of a higher overall mortality among athletes should target new preventive approaches, while lower mortality rates may induce new hypotheses on the origin of such an advantage. However, according to the study of Lehman and colleagues, a lower overall mortality may be associated with a higher specific cause of death mortality [183]. This last study shows an increased risk of neurodegenerative diseases among retired US football players despite a significantly lower overall mortality. Even similar overall mortality between elite athletes and their controls comprised reduced mortality from cancer and an increased mortality by external causes among power athletes in Finland [96]. Therefore it is essential to study the specific causes of death when describing the elite athletes' mortality status.

Eight studies have investigated one or more cause of deaths [96,174–178,183,200], but only five have included all causes of deaths found among the athletes [174–176,178,183].

As previously mentioned the results are specific to the studies' cohorts, varying from lower risk of CV and cancer mortality to higher risk of neurodegenerative and external causes of deaths. More studies are needed to better understand the long-term risks or benefits on longevity among elite athletes. No study has assessed French athletes' mortality; their causes of death are therefore unknown, both among men and women. As female athletes' causes of deaths have never been addressed before not even a trend can be put forward.

1.6.4 METHODS ON LONGEVITY ASSESMENT (IV)

Some published papers could not be included in the literature review as they relied on improper or wrong methodology to assess elite athletes' mortality and

longevity, particularly when attempting to quantify difference in life expectancy between the studied group and the general population.

For instance, the length of living of Czechoslovak Olympians who died during a certain period was compared with the mean length of life of their male compatriots [201]. Likewise, the longevity of cyclists in the Tour de France, was investigated through a polynomial regression curves and the average age of death between cyclists and the general population were compared [202]. It is a common pitfall to include only subjects who have experienced the event in the analysis, and to exclude the censored data [203,204].

Similarly inaccurate is to determine differences of life expectancies by analysis of variance and t-tests for comparing mean age at death [204], such the provided by the longevity analysis of major league baseball players in relation to the general population and among them [205]. Therefore the claim that baseball players live four years longer than the general population is highly susceptible to errors.

Investigating the effect of baseball players' career length on their longevity [206] without including it as a time-dependent variable induces an additional flaw [204]. There is a delay entry at baseline, because the group with longer career is older than the group with a shorter one. In addition, career length changes with time, provoking the classical statistical artifact seen in an investigation about the longevity of left-handed people [207]. Although death records show that left-handed players died younger, these findings are flawed by the fact that left-handedness increased through the 20th century because they were no longer forced to change of dominant hand, meaning that left-handers group, on average, were born later in that century.

To take in account whether or not a death event was observed during the trial, ignoring when the event occurred is also a problem seen in studies of athletes' survival. The frequency of observed deaths has been investigated according athletes caloric expenditure [208]. However, events will be observed more frequently in subjects with longer follow-up times, as was the case in the study. Therefore faulty interpretation may result from the underlying assumptions in those studies.

YEARS-LOST

Regarding the studies included in the literature review, most rely on the indirect standardization of elite athletes' mortality. This method highlights the difference in mortality between two previously adjusted populations. Accordingly, most studies have detected a difference between the athletes and the general population or controls, weather positive or negative.

While this is a standard and useful approach in mortality comparison, and also a valuable way to contextualize new research with past work, it may not be

straightforwardly interpreted. A 40% lower mortality is better than a 30% lower one, but what does a 10% difference mean in terms of life duration? To translate the results into a time dimension metric such as the number of life years lost or saved may have intuitive and meaningful interpretations [209]. The termed years lost method as proposed by Andersen and colleagues [209,210], quantifies the expected number of life years lost due to a given cause before a certain age. This method has been primarily conceived for cancer patients to measure the years lost from this specific disease.

In sports, the overall years lost - in case of shorter longevity than the reference population, or years saved otherwise - could be studied in relation to the specific constraints of the athletes' activities, and be partitioned according to their cause of deaths before a given age [210] and for each sport activity. Thus, applying this method for investigating elite athletes' cohort longevity could provide intuitive results relying on unbiased methods.

1.6.5 BROAD DATA ANALYSIS OF THE SPORTS' ELITE (IV)

The literature reveals that previous studies have used life tables to understand longevity and mortality among elite athletes, but have never attempted to use their data to understand longevity at the population level.

Data on elite athletes has been already used in other fields to apprehend biological traits. For instance, analyses of elite chess players have been supportive on understanding human cognition decline with age (Berthelot et al, *Age* 2012).

Large cohort studies have been set up to understand human cognition decline, or neuro-degenerative processes, such as Alzheimer's disease or dementia. The time of onset of cognitive decline remains the subject of large debate [211,212], but the implicit assumption made in previous studies is that there is little or no cognitive decline before 60 years old [212]. With growing knowledge on this area, it appears that the cohorts had been starting the subjects follow-up too late [213]. The Whitehall II cohort, including much younger subjects, starting from 45 years, showed that decline on cognition started much earlier [213] than usually investigated on longitudinal cohorts [214]. It is now argued that cognitive decline is a gradual process resulting from aging since adulthood for most of the cognition parameters (Figure 1.7a), followed by performance decrease with aging [215,216].

Interestingly, analysis of the performance of chess' grandmasters - a kind of cognition performance - has already suggested such aging process, starting much earlier in the third or fourth decade [41] even among individuals capable of such impressive cognitive performance (Figure 1.7b).

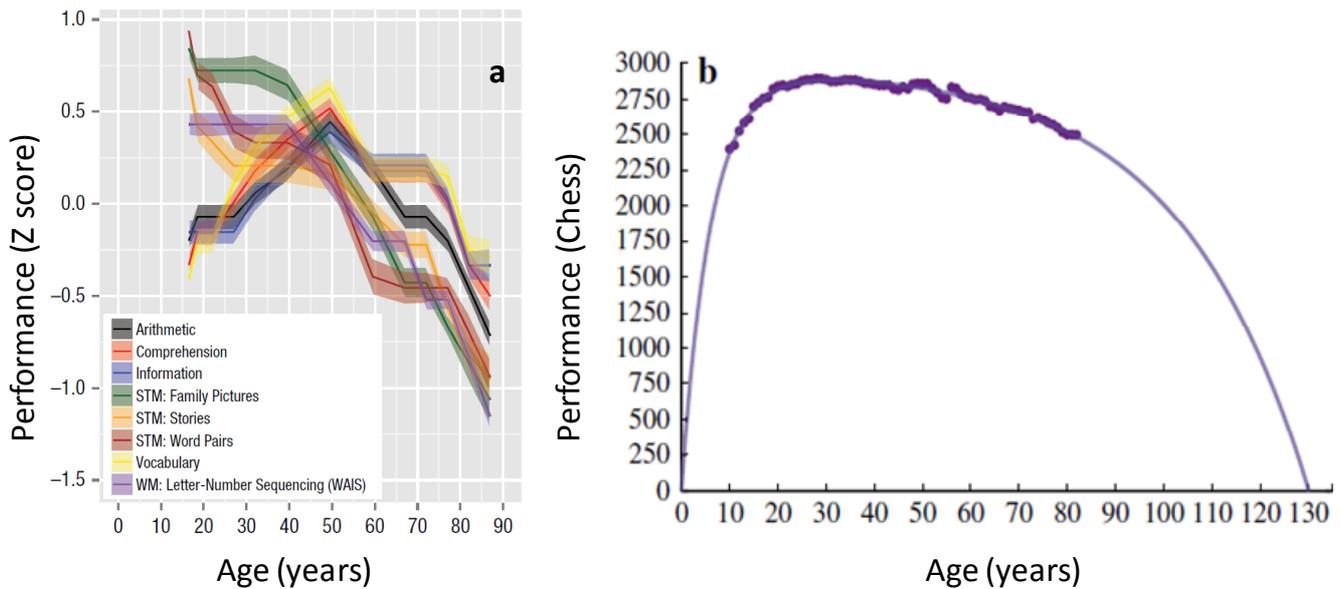


Figure 1.7: Similar exponential decline between cognitive performance and chess performance. a) Mean z-scored performance as a function of participants' age and cognitive task from the study of Hartshorne and Germini, 2015 [215]. Age-related cognitive performance according to different parameters: arithmetic, comprehension, information, short-term memory (STM), vocabulary and working memory (WM). b) The model to the best chess performance by age from the study of Berthelot and colleagues, 2012 [41].

Because sports performance is easily measurable, internationally calibrated and validated, from fully invested subjects providing exhaustive and publicly accessible performance measurements, sometimes dating back to the 19th century, elite athletes provide valuable data, which could be useful to interdisciplinary analyses, especially those assessing human maximal capabilities.

For instance, the analysis on sports' world records throughout the 20th century has shown that performance is a potentially limited biological trait, which has important implications on human physiology. Epidemiological analysis of quantified sport performances have demonstrated that performance progression follows a piecewise exponential decaying pattern, altered by historical events, such as world wars, or human technology innovations [26,217]. The rarefaction of world records would suggest, according to the authors, a limited human physiological progression.

Yet, to the best of our knowledge, epidemiological data on elite athletes' longevity and mortality have never attempted to include broader implications than sports medicine, in France or abroad. Particularly, tendencies among elite athletes and general population have never been part of an exploratory analysis aiming to better understand human

longevity. Lifespan is a multifactorial trait, as is sports performance, for which the elite represents one extremity in a distribution curve of physiological capability [47,48]. Bridging over data on elite athletes and the general population could have far reaching implications on human longevity.

1.7 CONCLUSION

The review of studies on elite athletes' mortality shows that French athletes' longevity or mortality has never been studied before, whether among professional or amateurs, male or female. Estimates from overseas may not accurately reflect the strength of the elite athletes' longevity in France. Their mortality status or specific causes of death are unknown.

The many subtle issues of survival analysis have caused papers reporting the differences on longevity to be flawed with misleading methods. No previous studies have properly assessed longevity losses or gains in elite athletes. This analysis is of main interest in relation to specific causes of death, since the literature reports particular concerns related with specific risks driven by each sports constraints.

Finally, exploratory analysis using elite athletes' data to better understand longevity trends at the population level has never been done before.

1.8 RESEARCH QUESTIONS

Given the identified gaps in the literature requiring further studies, and in light of all the specific constraints upon elite athletes distinguishing them from the general population, we investigate the following questions:

- Is female and male elite French athletes' mortality higher or lower than that of their compatriots?
- What are the causes of their deaths? Is there any excess death from a particular cause?
- Can their mortality status be translated into years lost/saved?
 - How many years do they lose or gain according to the type of physical activity they have performed in the Games?

In view of the place worldwide elite athletes occupy on the bell-shaped curve of quantitative traits, which is the far extremity of the curve, we inquire:

- Can we use data of elite athletes as a methodological approach to apprehend quantitative traits in the general population?
- Do elite athletes provide new insights into human longevity trends?

1.9 THE INTEREST IN ANSWERING THE RESEARCH QUESTIONS:

Studying elite athletes' mortality has potentially three main interests:

1.9.1 FOR THE ATHLETES AND THE SPORTS MOVEMENT (I)

Providing answers about the long-term consequences of a high-level practice is fundamental to the sport governing bodies and institutions willing to promote sports' practice.

The particular risks elite athletes are exposed to (injuries, accidents, intense training and doping) raise concerns about their post-career health, sometimes giving a negative image related to the practice of high level sports. Hence, for the athletes as well as for all the staff and structures involved with sports practice, it is necessary to understand the impacts on health including its later indicator: longevity.

Identifying benefits may soften the negative image, a relevant aspect in view of the model role the athletes have in the society. Identifying risks may justify certain protective measures in sports. For example, the association between repeated concussions in football and increased neuro-degenerative mortality, as well as other clinical implications, was used to implement measures of post-concussion management in the US.

Finally, giving a time dimension for the mortality status of elite athletes by measuring the number of years they lose or gain can be useful in clinical settings [209]. This may provide a quantification of the number of years lost, due to a specific cause of death, related to a specific type of sports activity.

1.12.2 FOR WOMEN IN SPORTS (II)

Female athletes' mortality is of particular interest. Studies have reported gender-related differences on athletes' health outcomes, but neither in France or abroad they have been investigated.

France has a long female tradition in sports: it is one of the six countries that have had women participate in the Olympics since 1900 [218]. Among these countries, France is the third with the largest female participation, fully supporting the interest for understanding the specificity of such a female cohort.

1.9.3 FOR PUBLIC HEALTH CONSEQUENCES (III)

Better understanding the risks and benefits of the elite practice may have large public health implications, notably through a wider view of the relation between physical activity and risk / benefit on one's health. On the one hand, the benefits allow reinforcing the preventive characteristic of sports and could be another approach to introduce the debate on physical activity recommendations by targeting a particular benefit. On the other hand, the risks justify protection measures to be adopted in the society. If subjects in the general population are not exposed to the same constraint level as the athletes, throughout a spectrum of distribution, there may be subjects more susceptible to diffuse risks justifying public measures. Finally, establishing the relation of such performance's outliers with longevity may provide a useful model as well as a new approach to understand human longevity trends.

1.10 OBJECTIVES

This thesis aims to describe and analyze the epidemiology of elite athletes' mortality and to apprehend new aspects of longevity in the general population. The main goals are:

- To measure and contextualize the longevity and causes of mortality of French elite athletes, comprising both Olympic athletes and cyclists in the TDF. In particular, to explore the relationship between survival and gender, as well as causes of mortality and type of sports' activity.
- To enlarge epidemiological methods for analyzing intra-class longevity among French Olympic athletes.
- To provide a rationale to use athletes' data to apprehend quantitative traits in the general population: the sports' elite as a methodological approach.
- To analyze data on worldwide elite athletes participating in the OG, to better understand longevity trends at the general population level.

1.11 MAIN HYPOTHESIS

The general hypotheses were formulated based on the findings highlighted in the previous review of the literature on elite athletes' mortality. The following hypotheses provide a guideline throughout the thesis. They refer to four levels:

- 1.** Hypothesis with regard to the French elite athletes' overall mortality:
 - a)** French elite athletes have lower overall mortality than their compatriots in the general population. Factors, such as the type of cohort (Olympic athletes or professional cyclists), and the sports assessed are involved with their mortality.

- 2.** Hypothesis with regard to gender and overall mortality among French elite athletes:
 - a)** Female Olympic athletes present similar lower mortality to that of male elite athletes.

- 3.** Hypotheses with regard to specific causes of death among French elite athletes:
 - a)** The main causes of deaths found among French elite athletes are the same as those found in the French general population, but at lower risk among the athletes.
 - b)** External causes of death (particularly by accidents) are higher among the athletes.
 - c)** The mortality risks related to specific causes of deaths are heterogeneous among the athletes, depending on their type of activity.

- 4.** Hypothesis on the use of data on elite athletes to apprehend human longevity:
 - a)** Supporting longevity analysis with elite athletes' data is a useful approach providing new insights into human maximal longevity trends.

1.12 THESIS STRUCTURE

The thesis structure is schematically illustrated in Figure 1.8, according to the approaches of each part, the studies conducted and the main academic field of investigation.

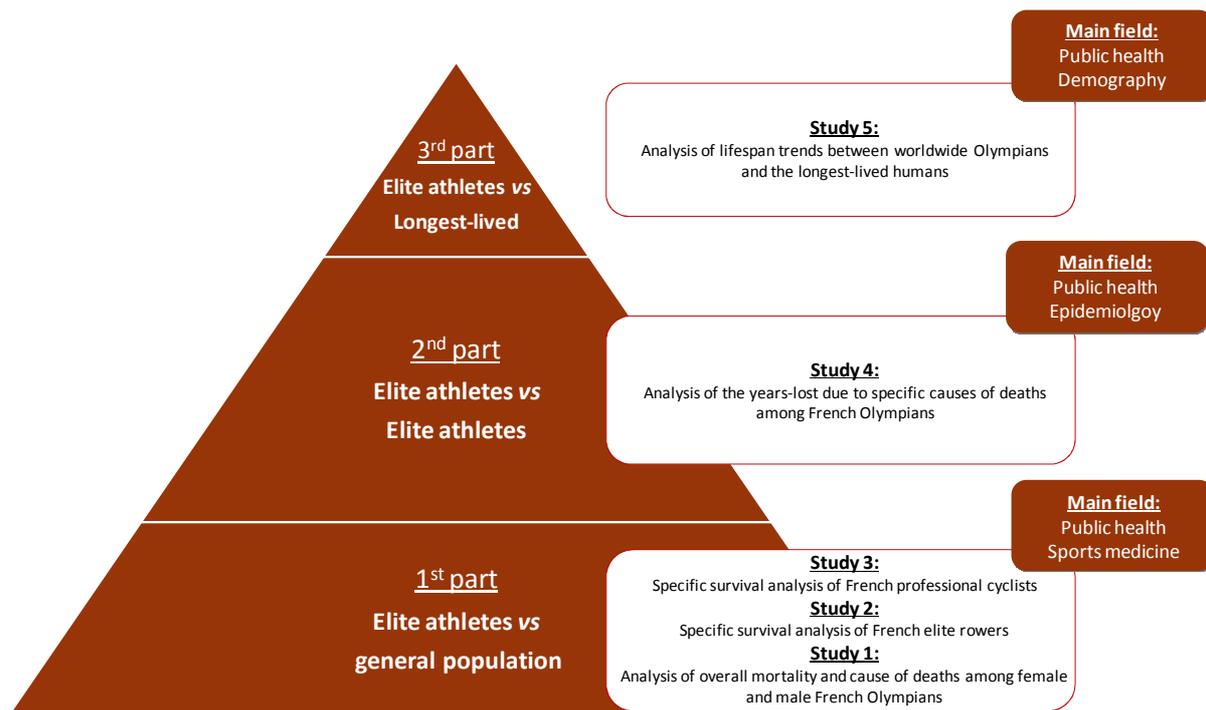


Figure 1.8: Schema of the thesis structure. The pyramid represents each part of the thesis organized according to the different approaches. In the middle are detailed the studies conducted within each part of the thesis. The boxes on the right display the leading academic fields of research associated with each study.

2

METHODS

This chapter specifies the research design, and describes the general methods employed to answer the main goals. We present in detail the target populations, which are Olympians and professional cyclists and justify their choice as elite athletes, establishing the context and historical background of the sports events we selected. The methods and sources of elite athletes' biographical and sportive data collection are provided for each cohort we studied. The procedures of vital status certification and causes of death identification for French athletes' cohorts are explained. The populations used as references, i.e. the French general population and worldwide supercentenarians, are established and the methods of their data collection described. At last the research ethics approval is presented.

2.1 RESEARCH DESIGN

All the studies performed are cohort studies, providing level of evidence 3 according to the hierarchical system of classifying evidence in evidence-based medicine.

2.2 GENERAL METHODS

In order to analyze elite athletes' mortality and causes of death, we collected historical data of French elite athletes creating a cohort of subjects participating either in the OG or in the TDF. These cohorts were then compared to the general population data, through French life tables, using mainly Standardized Mortality Ratio to describe differences on overall and specific mortality rates and Kaplan Meier curves to perform survival analyses.

To investigate the impact of different sports' physiological constraints on longevity and provide a time dimension measure for the athletes' longevity, inter-analyses were performed using the years-lost method, adapted to respond to the specificities of the French Olympian cohort.

Finally, to use elite athletes' data to apprehend new aspects of longevity in the general population we compared lifespan trends of Olympians worldwide with subjects living older than 110 years through density analysis, a specific methodological tool we developed for picturing longevity trends.

How each analysis was conducted, what were the eligibility criteria, the inclusion, exclusion and lost-to-follow-up within the studied cohorts, as well as the statistical methods employed, are detailed in the corresponding study.

2.2.1 THE STUDY POPULATION

The elite athletes composing the study population of this thesis are:

- **Olympians:** worldwide female and male athletes participating in the OG since its first edition of the modern era, 1896, in every sport, summer or winter games up to 2012.
- **Professional cyclists:** French male professional cyclists, participating at least once in the TDF between 1947 and 2012.

2.2.2 OLYMPICS AND TOUR DE FRANCE: TWO MAJOR SPORTS' EVENTS

2.2.2.1 HISTORICAL BACKGROUND, NOTORIETY, AND PARTICIPANTS IN THE OLYMPIC GAMES

OLYMPIANS

The OG, since their revival in 1896, are considered to be the world's foremost sports competition [219–221]. The modern OG are the leading international sporting event featuring summer and winter sports competitions in which, nowadays, more than 13,000 athletes from more than 200 nations worldwide participate in a large variety of sports (today there are 33 different sports and nearly 400 events) [222].

The OG are a very selective event, representing the apogee for most of the sports included in the program. Athletes participating in the Olympics underwent the most intense training and the most demanding selection process, both in terms of genetic and environmental predisposition. Olympians, as they are called, are the highest-level athletes of the countries they represent in the games.

The first modern Olympics were held in Greece (inspired by the ancient games) in 1896. The Games brought together 14 nations and 241 male athletes who competed in 43 events. Women took part in the Games in Paris in 1900, but their participation in the earlier editions was largely restrained [223] and solely in the last decades some countries equal the number of female and male athletes enrolled [222]. The games are held every four years, and the Winter Olympics, featuring sports practiced on ice or snow, were created in France in 1924 [224]. Until 1992, the Winter and Summer Games were held in the same years, and since each edition is alternated, occurring every four years but two years apart. World Wars led to the cancellation of the 1916, 1940 and 1944 Games, and a limited participation of the countries involved in the Cold War in the 1980 and 1984 Games [220,222].

The Olympic movement stood out as a major organization regarding its universal adherence along its historical existence and due to its selectivity: the ones entering the games constitute a high-standard sportive elite.

2.2.2.1 HISTORICAL BACKGROUND, NOTORIETY, AND PARTICIPANTS IN THE TOUR DE FRANCE

PROFESSIONAL CYCLISTS

The TDF is the world's most celebrated endurance cycling event, held annually since 1903 except during the two World Wars (1915-1919; 1940-1947) for male professional cyclists [225]. The Tour is held in France, as its name announces, but gained

extended popularity around the globe and among worldwide cyclists, being long considered as the most prestigious professional cycling event [226].

Characterized by particularly strenuous efforts, few individuals can achieve the level of performance necessary to accomplish the tour. This selective event is a multiple-stage bicycle race over 21 days of competition with 2 days of rest covering more than 3200 km, including passages through mountain chains [225]. The TDF is arguably one of the most physiologically demanding sports competitions [227].

The physical capacities required to perform such a race presuppose favorable genetic and environmental conditions, and strenuous training and preparation. Given the high physical demands and the solid French historical background, French professional cyclists constitute another interesting elite to look upon.

2.2.3 ELITE ATHLETES' DATA COLLECTION

Biographical and performance data on the target athletes were collected as follows:

2.2.3.1 INTERNATIONAL DATA – WORLDWIDE OLYMPIANS

Worldwide Olympians biographical and sportive information were obtained from reliable sources from an international consortium of Olympic historians and statisticians [228]. Since the 1980s, the group has been collecting and archiving data about every single Olympians' biographies and historical facts in the Games. Much of the early data came from previous publications of a former President and Co-Founder of the International Society of Olympic Historians [229,230].

The data gathered by the group place them as the most authoritative source of information on Olympians [228], providing support to the International Olympic Committee to complete its official archives. To build their database, the group draws on various sources: names and location information are obtained from official competitors' lists. Biographical information is complemented with data from national Olympic historians, as well as official sources such as birth registers. Information on events and locations comes from official reports and results for each Olympics, supplemented with magazines and newspapers for the early years. Information on Olympians' deaths is obtained from friends and relatives, Internet searches, international professional sporting clubs and bodies, and published obituaries [228].

The group checks and adds data almost daily. Sources have included virtually every well-known book on the OG, including all the Official Reports and Official Results [231].

2.2.3.1 FRENCH OLYMPIANS' DATA

The French Olympians biographical and sportive data, obtained as part of the data on aforementioned worldwide Olympians, were compared and confirmed with data from the official websites of each French federation, archiving athletes' biographies.

VITAL STATUS VERIFICATION

The identity information and vital status of French Olympians were verified by the National Registry of Identification of Physical Persons (RNIPP) up to January 1, 2013, the study endpoint, *via* the National Institute of Statistics and Economical Studies (INSEE), which inventories life status of French citizens living in or out of the French territory. Vital status was also followed up for Olympians who were born abroad but competed in the Olympic Games for France, as well as that of Olympians who emigrated.

CAUSE OF DEATH IDENTIFICATION

The cause of death of each deceased subject was obtained from the Centre for epidemiology on medical causes of death (CépiDc), which has been registering the causes of all deaths occurring on the French territory since 1968. Causes of death occurring abroad or before 1968 or in 2012 and later were not currently accessible due to a 2-year lag between the availability of death status and its corresponding cause. Therefore, the cohorts' causes of death were obtained from 1968 up to January 1, 2012. The vital status of Olympians who died abroad was identified even though the cause of their death could not be accessed.

2.2.3.2 PROFESSIONAL CYCLISTS' DATA

Due to their notoriety, data on professional cyclists are easily available on public websites, the sources of which are fans, amateur cyclists or sports journalists. Data on French TDF participants were collected from two official Websites (<http://www.memoire-ducyclisme.eu>, <http://www.letour.fr>) and complemented with two other sources (<http://www.wikipedia.org/>, <http://www.siteducyclisme.net/>).

Thereafter, we followed the same procedures of vital status verification and validation by the RNIPP and cause of death identification by the CépiDc as we did for the French Olympians.

2.2.4 THE REFERENCE POPULATION

The populations of reference used according to the specific objectives of each study are:

- **French general population:** civilian French death rates for individuals of the same sex, age at entry, birth year and followed for the same period of time as French Olympians' cohort.
- **Supercentenarians:** worldwide female and male subjects, born after 1800, and deceased after 110 years of age based on verified certificates of birth and death.

2.2.4.1 DATA COLLECTION OF THE REFERENCE POPULATION

FRENCH GENERAL POPULATION

General population data were derived from the French life tables. The source for the population death rates is available at the Human Mortality Database (<http://www.mortality.org/>) via CépiDc. Deaths reported by the military authority were not included. With the exception of 1914-20 and 1940-45 the data of the total population (including military) from 1912 to 2012 are identical to the civilian data.

SUPERCENTENARIANS

By definition, a validated supercentenarian is a properly documented subject who has lived to be at least the age of 110 years [232]. Their data were collected from the Gerontology Research Group [233], which collects, updates and publishes the list of certified living and deceased supercentenarians.

2.2.5 STATISTICAL ANALYSES

The statistical analyses, established according to the studies' specific goals, are detailed in each corresponding section.

2.2.6 RESEARCH ETHICS

This study was approved by the Advisory Committee on Information Processing in Research in the Field of Health (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL).

STUDY 1: French Olympians' overall and specific mortality

Intense physical activity has been associated with deleterious effect on elite athletes' health, in particular due to cardiovascular anomalies and an increased exposure to accidents. French Olympic athletes and women elite athletes' causes of death have not been studied. We aimed to measure overall and disease-specific mortality of French women and men Olympians compared with the French general population. The hypothesis is that Olympians, women and men, present lower mortality rates. We performed a cohort study of French elite athletes; 601 women and 1802 men participating in summer or winter Olympic Games from 1948 to 2010, had their vital status verified by national sources and were followed until 2013. Causes of death were obtained via the National Death registry from 1968 to 2012. Overall and disease-specific mortalities of Olympians were compared with the French general population through Standardized Mortality Ratios (SMR) and 95% CIs. Olympians' observed and expected survivals were illustrated by Kaplan-Meier curves. At the endpoint of the study, 13 women and 222 men had died. Overall mortality in Olympians compared with that of their compatriots was 51% lower (SMR = 0.49; 95% CI: 0.26–0.85) among women and 49% lower (SMR= 0.51; 95% CI: 0.45–0.59) among men. Olympians' survival is significantly superior to that of the French general population (women: $p=0.03$; men: $p<.001$). According to the total deaths occurring from 1968 to 2012 (12 among women, 202 among men), women Olympians died from neoplasm (50.0%), external causes (33.3%) and cardiovascular diseases (16.6%). The main causes of death among men are related to neoplasms (36.1%), cardiovascular diseases (24.3%) and external causes (14.4%). It was observed for main mortality causes among men Olympians: for neoplasms (SMR: 0.55, 95% CI: 0.43–0.69), for cardiovascular diseases (SMR: 0.55, 95% CI: 0.41–0.73) and for external causes (SMR: 0.66, 95% CI: 0.44–0.94). A lower overall mortality of similar magnitude is observed among sportswomen and men compared with the general population. The main causes of death in French Olympians are neoplasms, cardiovascular diseases and external causes.

3.1 STUDY 1

MORTALITY IN WOMEN AND MEN FRENCH OLYMPIANS: A 1948-2013 COHORT STUDY²

3.1.1 INTRODUCTION

Participants in the OG are a specific population owing to the selection process they undergo. The Games act as a filter allowing access only to the best competitors from each country, athletes who demonstrate rare physiological aptness and physical traits [234], suggesting predispositions (both genetic and environmental) [31] and high levels of training for long periods [39].

Sport-related risks expose Olympians to specific outcomes: with possible higher mortality due to cardiovascular anomalies [73,94,95], neurologic sequelae – due to recurrent concussions in some disciplines [112,183] or use of doping agents [126,129]. In addition, high forces in certain sports may increase the probability of fatal events due to accidents and collisions [107,108].

However, a recent meta-analysis on athletes' mortality evidenced that elite athletes live longer than their compatriots [171]. French Olympians were not part of the cohorts included in those studies. In addition there is a lack of studies considering sportswomen, and very few studies have analyzed athletes' causes of deaths or submitted vital status to National certification.

3.1.1.1 OBJECTIF

We aimed to assess the overall and cause-specific mortality of women and men French Olympians comparatively to their compatriots' in the French general population. We hypothesize that French Olympians, both women and men, present a lower mortality.

² Annex (i)

3.1.2 METHODS

STUDY DESIGN

Retrospective cohort study of French male and female Olympians.

PARTICIPANTS

The Olympians' cohort consisted of all women and men who represented France in the summer or winter Games after the Second World War - from 1948 up to 2010 - and had their vital status validated by the RNIPP.

DATA COLLECTION

All French athletes participating in at least one OG from 1948 up to 2010 were identified. Their biography information came from reliable historians' sources [228]. These data were compared and confirmed with data from the International Olympic Committee (Olympic.org) and data from each official website of International Federations archiving athletes' biographies.

Olympians' identity information and vital statuses were obtained from 1948 up to January 1st, 2013 (study endpoint) *via* the RNIPP from the INSEE, which inventories life status of French citizens living in or out of the French territory. Olympians who were born abroad but have competed in the OG for France, as well as Olympians who have emigrated also had their vital status followed up. Subjects who could not have their vital status properly certified by national sources were not included in the study (Figure 3.1). Such exclusions were homogeneous during the studied period for both sexes.

The cause of death of each deceased subject was obtained from the CépiDc, which has registered the causes of all deaths occurring on the French territory since 1968. Causes of death occurring abroad or prior to 1968 or in 2012 and later were not currently accessible due a 2-year lag between the availability of death status and its corresponding cause. Therefore the cohorts' causes of death were obtained from 1968 up to January 1st 2012 (Figure 3.1). Olympians who died abroad had their vital status identified even though the cause of their death could not be accessed.

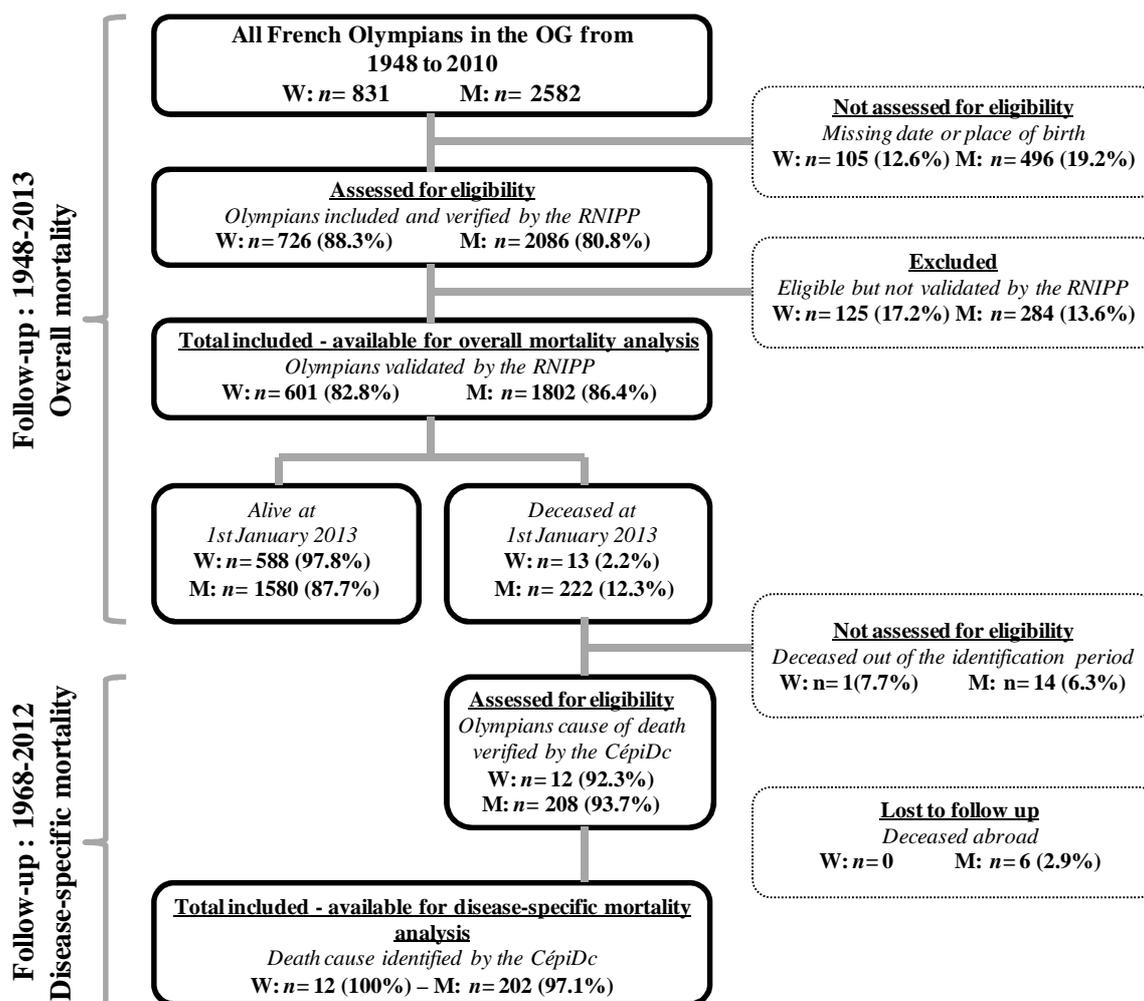


Figure 3.1: Flow diagram of Olympians' cohort. Inclusion and exclusion for overall and disease-specific mortality follow-up among French Olympians, women (W) and men (M). RNIPP = National Registry of Identification of Physical Persons. CépiDc= Centre for epidemiology on medical causes of death.

3.1.3 STATISTICAL ANALYSIS

Descriptive analyses of Olympians' cohort were expressed as means (\pm SD) and proportions (%) when suitable. We compared the mortality of French Olympians with that of the French general population using two methods: i) overall and disease-specific Standard Mortality Ratios (SMR) and its 95% confidence intervals (CI) [171]; ii) Kaplan-Meier curves to illustrate the observed and the expected survivals of Olympians [235].

SMR allow the mortality comparison of the studied cohort to the total population containing this cohort [236], with age and period adjustment. In practical terms, SMR is the ratio between the number of deaths observed in the Olympians cohort and the

number of expected deaths if Olympians had the same death rates as the French population. Death rates of the general population were assessed via CépiDc. Individuals in a cohort differ at time of risk exposure along their follow-up. Hence, Olympians' person-year was calculated, and is defined as the actual time-at-risk in years of Olympians follow-up. Therefore the SMR denominator was calculated by multiplying French death rates by the Olympians persons-years at the corresponding age group and period for each sex. Time was categorized in one-year intervals from 1948 to 2013. Age groups were calculated by 5-year intervals from 15-19 years up to the 100-104 years. The Olympians' follow-up starts with their date of first OG participation, and finishes with their date of death (if concerned) or with the study endpoint. A SMR equal to 1.0 means the number of observed deaths equals that of expected cases. If lower than 1.0 it indicates a lower mortality of Olympians compared to the general population. The 95% confidence intervals were calculated using the exact method [236].

The Kaplan-Meier expected survival was based on the French general population death rates and the difference with the Olympians' observed survival was assessed through the log-rank test [237]. P-values of <0.05 were considered to indicate statistical significance for all analyses.

SCENARIO

In order to address excluded subjects from the study due to absence of vital status official validation, we recalculated overall SMR analyses adding all the Olympians who had been excluded (Figure 3.1). We performed overall mortality analyses assuming as true the vital status from sources monitoring Olympians' deaths (every official International Federations website and Olympic historians' sources) [228].

DISEASE-SPECIFIC

For the disease-specific mortality we compared each cause of death found among Olympians with the specific rate of the general population by calculating SMRs for the available period, 1968 to 2012. Causes of deaths were classified according to the International Classification of Diseases - ICD (8th revision before 1978, 9th revision between 1979 and 1999, 10th revision after 2000).

AGE-EFFECT

To describe age-dependent differences in Olympians' mortality, SMR values were analyzed by 10-year age-classes from 25-34 up to 85-94 years. Age-classes inferior to 25 years or superior to 95 years were not studied because they account for only 2 deaths among women and men. R software v2.14.0 was used for the analysis.

3.1.4 RESULTS

OVERALL MORTALITY

The analyses were performed on 601 women and 1802 men French Olympians who had their vital status validated by national sources. Among those, 235 (n=13 women; n=222 men) died before the study endpoint. The cohort's description is presented in Table 3.1. The mean follow-up time for Olympians who were alive was 20.3 years (± 14.6) for women and 26.8 (± 16.7) for men. For those who died the follow-up time was 35.5 years (± 17.4) for women and 43.7 (± 13.5) for men. The overall SMR results were 0.49 (95% CI: 0.26–0.85, $p = .007$) for women and 0.51 (95% CI: 0.45–0.59, $p < .001$) for men Olympians.

Table 3.1: French Olympians' cohort from 1948 to 2013.

Cohort	Women (n=601)	Men (n=1802)
Nb. of person-years	12075.6	51170.3
Mean age at cohort's entry (SD)	23.3 (± 4.6)	25.2 (± 4.6)
Birth year range	1920 to 1992	1905 to 1991
Death year range	1986 to 2012	1973 to 2012
Age range at study's endpoint (alive)	21 to 92	22 to 94
Age range at study's endpoint (deceased)	23 to 92	26 to 95

SCENARIO

The analyses were performed adding 125 women and 284 men who had their vital status identified by non-official sources, totalizing 726 women and 2086 men French Olympians. Among those, 280 (n=16 women; n=264 men) had a date of death known before the study endpoint. This scenario shows a significantly lower mortality in women (SMR: 0.38, 95% CI: 0.22–0.62, $p < 0.001$) and men (SMR: 0.51, 95% CI: 0.45–0.57, $p < 0.001$) Olympians than in the general population.

SURVIVAL ESTIMATIONS

The observed and expected survival curves for women and men Olympians are illustrated in Figure 3.2. Olympians' observed curve is significantly different from the

expected curve derived from the matched general French population for women ($p=0.03$) and men ($p<.001$). Men's observed curve diverges and shifts to the right early in the follow-up period and narrows the gap at the end of the follow-up. Women's observed curve separates later from the expected curve and is clearly superior only at the end of the follow-up.

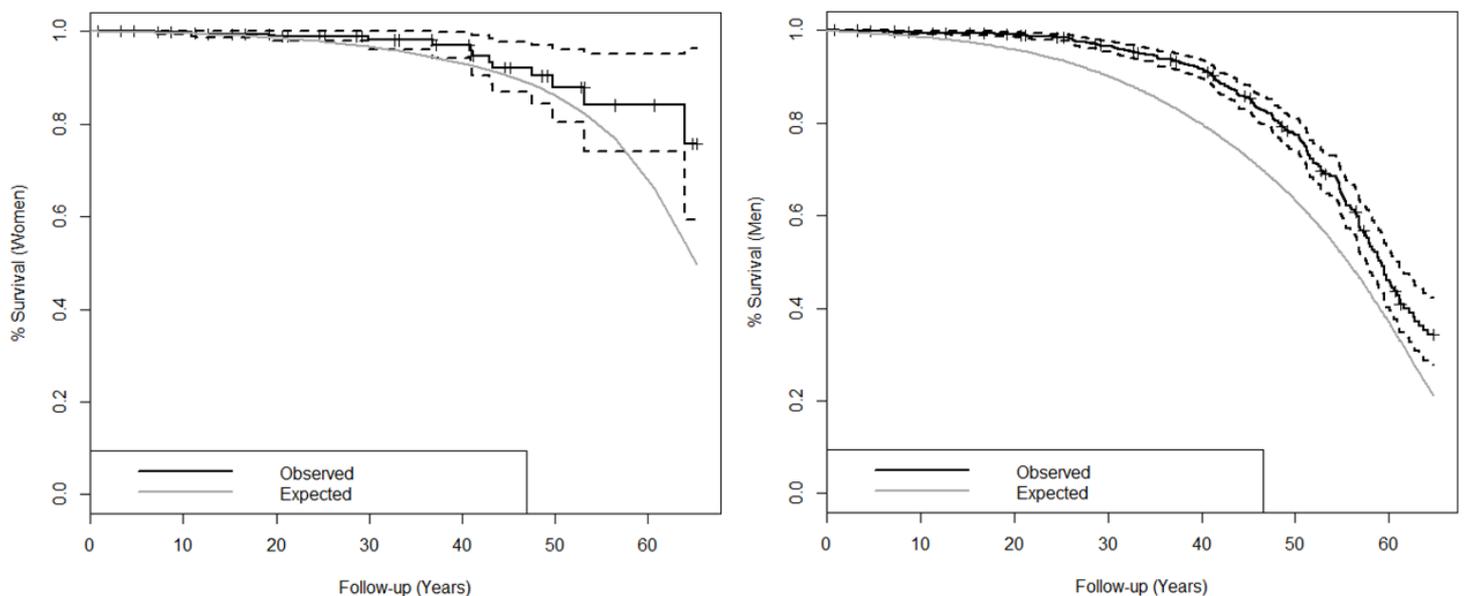


Figure 3.2: French Olympians' observed and expected survival curves. Right: Women. Left: Men. Olympians' observed survival is represented by the solid black curve and its dashed confidence interval. The gray curve refers to the expected survival derived from the matched general French population.

CAUSES OF DEATH

Among all deaths observed ($n = 235$), one woman and 14 men died after 2012. Nobody died before 1968. Among women, the causes of all deaths that occurred during the available identification period were identified. Concerning men, 202 had the underlying cause of their deaths identified; six died abroad and their causes of deaths could not be established.

SMR results are represented for each cause of death identified among women and men Olympians (Figure 3.3). The three causes of death observed among women were neoplasm (50.0%), external causes (33.3%) and cardiovascular diseases (16.6%), without significant differences with the general population.

The main causes of death among men were neoplasms (36.1%), cardiovascular diseases (24.3%) and external causes (14.4%). The mortality rates for these causes and

due to mental disorders, respiratory system diseases, endocrine or nutritional diseases and digestive system diseases were significantly lower compared with the mortality rates of their compatriots (Figure 3.3).

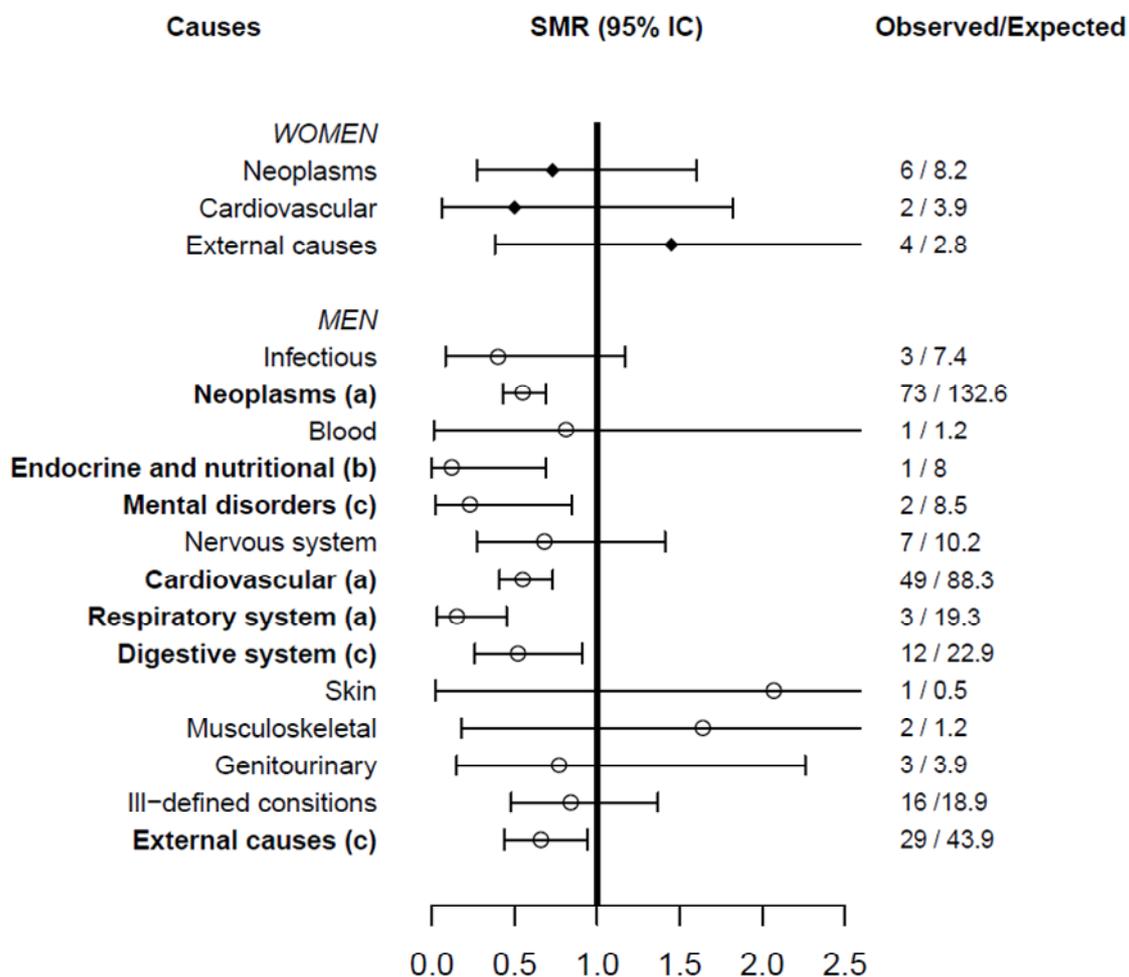


Figure 3.3: Olympians' disease-specific mortality from 1968 to 2012. Causes of deaths were classified according to the International Classification of Diseases (8th revision before 1978, 9th revision between 1979 and 1999, 10th revision after 2000). The vertical bold line represents the general population reference value (SMR=1). The causes of death that are significantly different from those of the general population are in bold. (a) $p < .001$; (b) $p < .01$; (c) $p < .05$.

AGE-CLASS MORTALITY

A significantly lower mortality was observed among men Olympians from the 25-34 to the 75-84 age-classes compared with that of the general population (Figure 3.4).

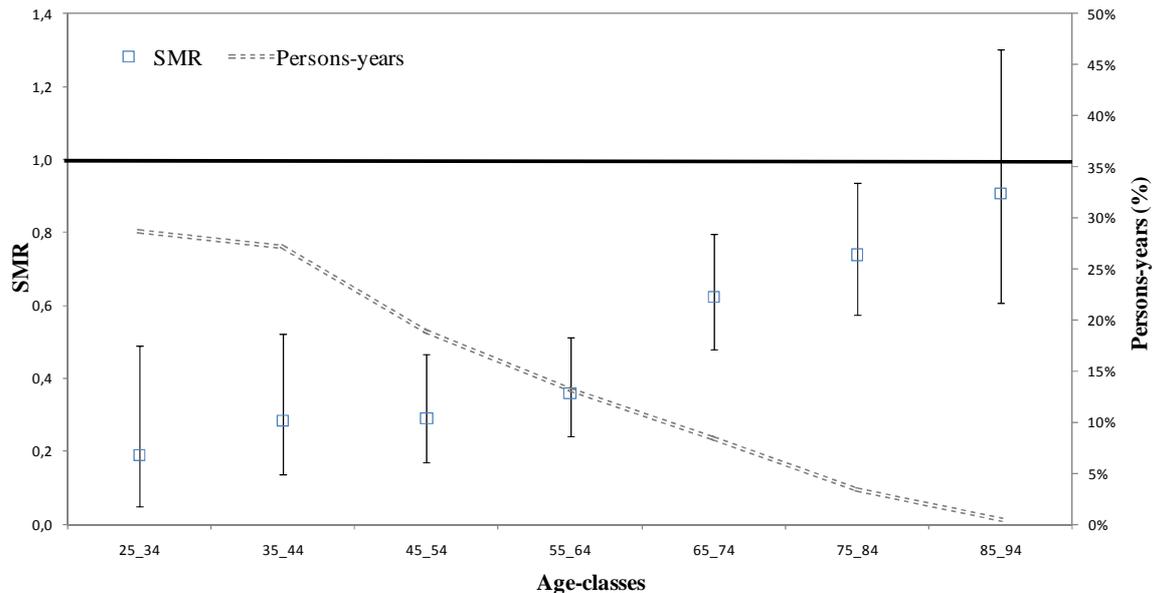


Figure 3.4: Overall standardized mortality ratios of men Olympians by age-classes. SMR and its 95% confidence interval by 10-year age-class for French athletes participating in the Olympic Games from 1948 to 2010. The horizontal line represents the general population reference value (SMR=1). The dashed line represents the percentage of person-years who were followed up.

The lowest mortality was seen among the youngest (SMR: 0.19, 95% CI: 0.05–0.48). Olympians older than 85 years did not show significant mortality difference (SMR: 0.90, 95% CI: 0.60–1.30). The lower mortality in Olympians at younger ages is based on a larger sub-cohort's size than for older ages, as represented by the decreased percentage of persons-years with age (Figure 3.4). No significant differences with the general population were observed per age-classes among women Olympians.

3.1.5 DISCUSSION

MORTALITY IN WOMEN OLYMPIANS

Our study shows a 51% lower mortality among women Olympians compared with their referents in the French population. To the best of our knowledge, this is the first study that evidences sportswomen's lower mortality compared with the general population based on national certified vital status.

The lower risk of all-cause mortality found among women is similar to that of men: both demonstrate a large survival advantage over their compatriots. Such findings highlight that men and women elite athletes share common determinants to a greater longevity, from joining the sports elite and possibly from all that requires and follows

their Olympic participation. French Olympians' survival advantage reinforces previous studies showing higher longevity among elite athletes [171,206,238].

However, the Kaplan-Meier curves among women show a different dynamic from that of men Olympians, as women's advantage over the general population occurs later on. Their survival deviates further from that of the general population at the end of the follow-up. That means that the most part of the small sample of women who could be followed up further than 60 years are still alive. Probably the advantage elite sportswomen already show will widen in case of a longer follow-up.

Also singular is the narrowing between survival curves at the beginning of women's follow-up. We expected to find a survival dynamic similar to that displayed among men Olympians, for whom the survival advantage starts with their Olympic participation - due to the cohort selection effect [239]. The few deaths occurring among young women could explain such narrowing, even though the mortality analysis by age-classes does not show any significant difference by age.

Women's disease-specific mortality also presents a particularity, regarding the external causes of deaths (which comprise deaths from accidents, falls, homicides and suicides). Whereas the main causes of deaths observed in men Olympians have analogous proportions to the main causes in the general population, the external causes among women Olympians are in larger proportions than in the general population. Nevertheless, no mortality difference by specific cause of death was shown among women.

Our results based on very few deaths certainly give rise to limited interpretation and analysis. Hence, the findings regarding women's survival dynamics, age-dependence and disease-specific mortality reveal a path requiring further investigation. Yet this is the largest cohort of elite sportswomen ever followed up, corresponding to 85% of all cohorts of sportswomen altogether taken in account in a recent meta-analysis [171], and it provides evidence of higher longevity among French women Olympians.

MORTALITY IN MEN OLYMPIANS

In relation to men Olympians we show consistent lower mortality across men's age-classes until advanced ages. The risk of all-cause mortality among men age-class varies from 81% lower at younger ages down to 27% in the 75-84 year age-class, and no difference with the general population at 85 years of age or older. Such age-mortality behavior could be due to a survival selection process. At younger ages Olympians are at the maximum of their capacity [234]. With ageing a selection also operates in the general population and at very advanced ages, both groups include highly selected individuals.

The overall mortality found among men Olympians is mainly associated with lower risk of three major causes of deaths seen among them: neoplasms, cardiovascular diseases and external causes (which are 34% to 45% lower than those found in the general population). In addition, French men Olympians display a significantly lower mortality from mental disorders, endocrine or nutritional diseases, digestive system diseases and an 85% lower risk of mortality due to respiratory system diseases. The mortality from other causes is not statistically different from that of the general population. Rare causes of death, however, are based on few deaths only, resulting in large confidence intervals hardly interpretable.

The benefits of moderate physical activity are well-known for preventing cardiovascular problems [52]. Intense training however has been associated with cardiovascular events: coronary remodeling [91], artery calcification [93], atrial fibrillation and flutter [94], though an association has not been clearly established [240,241]. A triggered arrhythmia threshold has been proposed [95], but the 1500 lifetime hours of intense exercise are largely exceeded by Olympic athletes [39]. Hence, a "U" shape curve has been proposed for elite athletes, relating training load and cardiovascular risk [73].

Here we show a 45% lower mortality from cardiovascular diseases among men Olympians. Previous findings are consistent with French Olympians' long-term outcome [96]. Indeed the 4- to 17-year follow-up of Italian Olympians did not show any deterioration in left ventricular function or increased rate of cardiovascular events [99]. There is growing evidence that the cardiovascular benefits of practicing sports at an elite level would outweigh potential negative effects [171,240,241]. These elements may suggest another association between health impact and exercise load: an "L" shape for risk/exercise relation, without risk resurgence at the highest exercising levels for previously healthy subjects.

These results, however, should be interpreted in light of the heterogeneity of sports within the cohort, sampling a wide range of athletes from pure anaerobic to fully aerobic sports.

A two-way relation is possibly operating among Olympians: rare traits enable high-level sport practice and high-level sport conditions maintain capacities that reduce cardiac and overall mortality.

COHORT SELECTION EFFECT

Performance selection processes result in selecting healthy subjects in a favorable environment and with genetic predisposition [242]. Olympians constitute the fittest athletes with a highly unusual set of physical and psychological traits [47,156]. Genotypes related to lower disease risk among elite athletes have been debated

[243,244]. The Olympians' survival advantage concerns individuals who have undergone an inevitable selection process. It therefore needs to be cautiously interpreted, because this advantage may not be extendable to the general population. Other highly selected men cohorts showed comparable low overall mortality, including in comparison with healthy references [96,179]. The comparison of Olympians with their compatriots reveals the effect of a phenotypic selection on death rates. The relatively lower mortality found is certainly enhanced by the existence of chronically ill subjects in the reference population. The problem is however symmetrical to the definition of a control group in clinical studies of rare polygenic diseases [47].

INTENSE PHYSICAL ACTIVITY

Dose-response relations between training intensity and health benefits are not well established [73,89,245], but the overexposure to high-level training does not seem to be deleterious to French Olympians. This suggests that elite athletes are probably capable of adapting to intense activity [68] and still get benefits from it, at least in terms of longevity. Intense sports participation has nonetheless been associated with increased risk of musculoskeletal/connective tissue diseases [121]. Even if such risk does not seem to affect survival rates - here only two deaths were related to musculoskeletal diseases - it remains unclear whether Olympians' higher longevity is associated with higher morbidities and to which extent the presence of morbidities may impact their quality of life.

No significant excess death was observed for any specific cause, in contrast with previous demonstrations: higher mortality due to amyotrophic lateral sclerosis among Italian soccer players [176], or due to neurodegenerative diseases among American football players [183] or greater suicide rate among Swedish power sport athletes [139]. Hence, it seems that if sports are not directly unsafe, high-intensity training does not provide further deleterious effects throughout life on previously healthy people.

MAINTAINING A HEALTHY LIFESTYLE AFTER SPORTS CAREER

We have not assessed French elite athletes' lifestyle post-career. Previous studies, however, have reported that athletes usually maintain healthier habits than the general population before, during and after their career [162] such as low smoking rates, good nutrition and exercising [163]. In addition, the Olympians' level of fitness may constitute a "health bank"; this advantage may last over years, as shown by the lower mortality across men Olympians' age-classes. Human capacities decay with ageing [234] but elite athletes start from a higher level. Hence, for a formerly well-trained person, physical activity may be effortlessly performed, allowing her/him to keep practicing throughout life [163].

USE OF PERFORMANCE-ENHANCING SUBSTANCES

The use of substances designed to enhance athletic performance dates back to the earlier Games [124]. The first listing of prohibited substances came in the 60s, but has restricted doping only partially, although the adverse effects on users' health have been shown [126]. We do not know which athletes in our cohort have made use of doping agents, and therefore it is difficult to assess to what extent the use of such substances has contributed to minimize the large survival benefit experienced by French Olympic athletes.

METHODOLOGICAL CONSIDERATIONS

No causal inference can be made between Olympic participation and the observed lower mortality of Olympians, particularly because only age and period could be adjusted for potential confounding factors. We simulated a scenario to address the possible changes in our results that the excluded athletes could cause. The lower mortality found adding excluded Olympians is similar to the outcomes presented here, with similar results among men and even lower mortality among women. Therefore, it is unlikely that the athletes excluded from the study may overturn the overall mortality results presented here. Yet, we acknowledge a limit related with the deaths occurring abroad or too recently to have their causes identified. Our method's advantages rely on an extensive follow-up of highest-level athletes and for both sexes based on national vital status certification.

PERSPECTIVES

Disease-specific studies assessing larger samples of elite sportswomen are necessary to understand better the causes of death that are associated with their lower overall mortality. Analytical studies controlling the possible interference factors on elite athletes' mortality are now required to decipher this phenomenon: sport type, country, training methods, performance level, biometrics, career period, doping practice and post-career lifestyle, including athletes' quality of life.

CONCLUSION

Lower overall mortality of similar magnitude is observed among sportswomen and men compared with their compatriots.

The main causes of death observed among Olympians are neoplasms, cardiovascular diseases and external causes. These three major causes of death are significantly lower among men Olympians than in the general population. Studies based on larger cohorts of women elite athletes are required for better comprehension of their survival advantage over their compatriots.

3.2 PANEL: RESEARCH IN CONTEXT

3.2.1 OLYMPIANS' MORTALITY

WHAT WERE THE ISSUES AROUND THIS SUBJECT?

The long-term health consequences of being an elite athlete are poorly known. Mortality studies on this population have been relatively sparse and the results are somewhat conflicting. French Olympic athletes and women elite athletes' causes of death have not been studied before.

WHAT DOES THIS STUDY ADD TO EXISTING KNOWLEDGE?

Lower overall mortality, of around 50%, is observed among French Olympians. Both women and men Olympians display a survival advantage over their compatriots. Neoplasms, cardiovascular diseases and external causes of deaths are the main causes of death among French Olympians and they are significantly lower among men Olympians than in the general population.

3.3 TRANSLATIONAL OUTLOOK

This is the first study on French elite athletes' mortality, Olympic athletes composing this elite. It provides a complete mortality overview of athletes of the highest level from the full spectrum of sports disciplines in the Olympics.

However, with more than 30 sports in the Olympic program, the cohort we studied is highly heterogeneous in terms of type of physical training requirements, ranging from sports demanding power strength, such as weightlifting, to sports like 12-hour cycling events (past event), for which important aerobic conditioning is needed. The effort may be continuous during a 20-km walking race event, or intermittent during a handball match. The intensity may vary from static events, such as shooting, to highly demanding sports such as rowing. These parameters, in addition to many other factors, may have different impacts on the athletes' health. Searching for consistency of the general findings within single-sport sub-cohorts, we aimed to perform a mortality analysis focusing on a single sport.

The priority sport to be studied was defined according to the following criteria:

- 1) It is a sport previously related to long-term health concerns, but that has not been studied before, justifying specific interest;
- 2) There is no difference in the type of physical effort performed according to the position the athletes occupy in the event for a better homogeneity of the effort exertion;
- 3) It has been continuously present in the Olympic program;
- 4) It involves a cohort of athletes large enough to be studied separately.

The cohort of French Olympic rowers is the largest cohort fulfilling the aforementioned criteria. Hence, we studied the overall and cause-specific mortality of Olympic French rowers as detailed in the next section.

STUDY 2: French rowers' overall and specific mortality

High intensity training has been associated with deleterious effects on elite rowers' health, especially due to cardiac abnormalities, but mortality rates in this population have never been investigated before. We aimed to describe overall mortality and main causes of deaths of male French rowers participating in at least one Olympic Game (OG) from 1912 to 2012 in comparison with the French general population. Identity information and vital status of French Olympic rowers were validated by National sources from 1912 to 2013 (study's endpoint) among 203 rowers; 52 out of 255 (20.3%) were excluded because their vital statuses could not be confirmed. Main causes of deaths were obtained from the National registry from 1968 up to 2012. Overall and disease-specific mortalities were calculated through standardised mortality ratios (SMRs) with its 95% confidence intervals (CIs). The overall mortality was calculated for the whole rowers' cohort (PT) and for two periods apart: (P1) including rowers from 1912 to 1936 OG, a cohort in which all rowers have deceased and (P2) considering rowers from 1948 to 2012 OG. Among the 203 rowers analysed, 46 died before the study's endpoint, mainly from neoplasms (33%), cardiovascular diseases (21%) and external causes (18%). PT demonstrates a significant 42% lower overall mortality (SMR: 0.58, 95% CI: 0.43–0.78, $p < 0.001$), P1 a 37% reduction (SMR: 0.63, 95% CI: 0.43–0.89, $p = 0.009$) and P2 a 60% reduction (SMR: 0.40, 95% CI: 0.23 - 0.65, $p < 0.001$) compared with their compatriots. Mortality due to cardiovascular diseases is significantly reduced (SMR: 0.41, 95% CI: 0.16–0.84, $p = 0.01$) among rowers. French Olympic rowers benefit of lower overall mortality compared with the French general population. Among rowers' main causes of death, cardiovascular diseases are reduced in relation to their compatriots. Analytical studies with larger samples are needed to understand the reasons for such reductions.

4.1 STUDY 2

Row for Your Life: A Century of Mortality Follow-Up of French Olympic Rowers³

4.1.1 INTRODUCTION

Rowing has been reported as a safe contactless sport with low injury rate, providing health benefits to its practitioners [246,247]. Although high occurrence of cardiac diseases, and alterations on cardiovascular morphology has been previously reported in university rowers [248,249], epidemiological studies have described higher life expectancy in Harvard and Yale university rowers as in Oxford-Cambridge boat racers compared with their non-athletic referents [250,251].

If regular physical activity has been demonstrated to provide large health benefits [51,252,253] studies have reported that strenuous exercises and training of elite athletes could be associated with deleterious effects [73]: cardiac abnormalities [90,91] more likely triggering a sudden death during high demanding effort [254,255], with higher incidence rate among men varying according sports practice [256] and deregulated inflammatory responses [257]. In addition, training cessation after international career has showed to be deleterious in retired athletes [258–261]. Conversely, a recent meta-analysis of epidemiological studies has concluded that top-level athletes live longer than the general population [171].

The Olympics is the highest competition level for rowing athletes; thus Olympians are exposed to the most extraneous training program and performance exigencies.

4.1.1.1 OBJECTIVE

This study aims to assess the overall mortality and main causes of deaths of male French Olympic rowers competing from 1912 up to 2012 compared with their referents in the French population.

³ Annex (ii)

4.1.2 METHODS

STUDY DESIGN

Retrospective cohort study of French Olympic rowers.

PARTICIPANTS

The cohort was composed of all male rowers who represented France in at least one OG, from 1912 up to 2012, and had their vital status validated by the RNIPP. Coxswains were not accounted as rowers.

Three periods were taken into account to analyse rowers' overall mortality. The first (P1) included only rowers that participated in the OG from 1912 up to 1936. This period was chosen for a separated analysis because all rowers, who participated in those games, had already deceased, allowing for a complete follow-up until the entire cohort's extinction. The second period (P2) is an uninterrupted period of OG after World War II, from 1948 to 2012. Finally, we considered the total period (PT), analysing the totality of rowers participating in the OG from 1912 up to 2012 (Figure 4.1). The discontinuity at the rowers' entry in the cohort between 1912-1920 and 1936-1948 is related to the Games interruption due both World Wars.

DATA COLLECTION

Data concerning rowers' biography came from historians' sources as previously reported [262]. These records were confirmed by data of the International Olympic Committee (olympic.org) and the French Federation of Rowing (<http://www.avironfrance.asso.fr/>). Rowers' identity information and vital statuses were collected since their first Olympic participation up to January 1st 2013 (study's endpoint) from the RNIPP.

The causes of death of each deceased subject were obtained from the CépiDc for the available period, from 1968 up to January 1st, 2012.

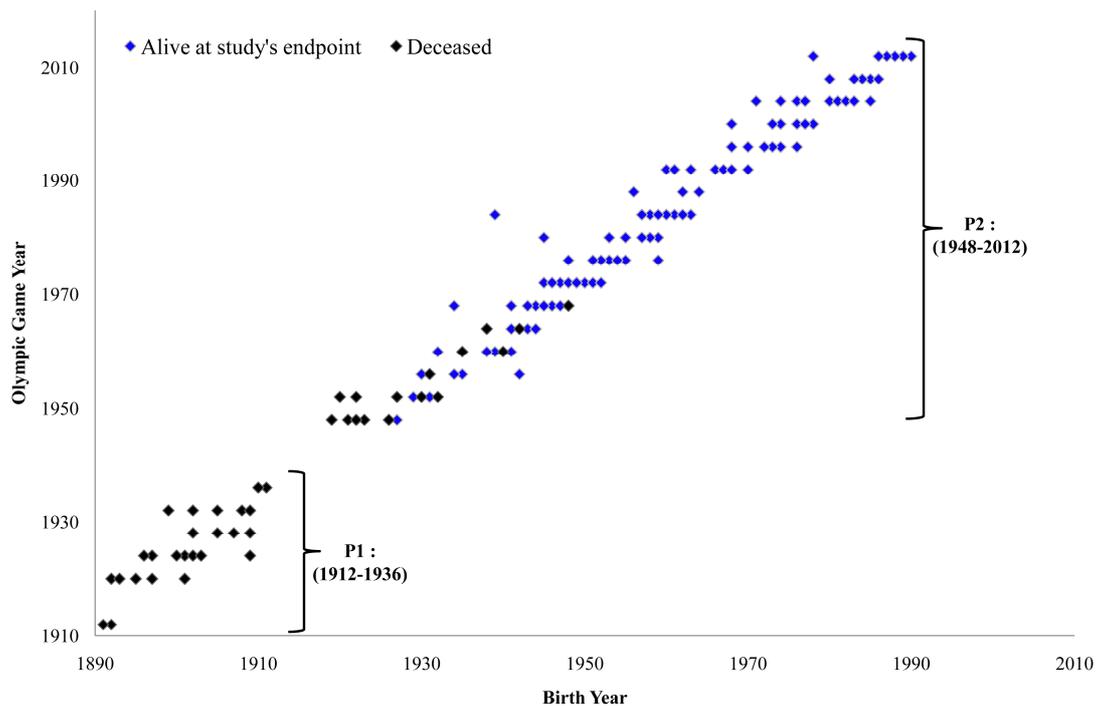


Figure 4.1: French Olympic rowers by Olympic Games and birth year. Black diamond represents deceased subjects and blue diamond represents the subjects alive at the study's endpoint. The two periods studied apart are schematically indicated.

4.1.3 STATISTICAL ANALYSIS

We compared the mortality of French rowers with the French general population by calculating overall and disease-specific Standard Mortality Ratio (SMR) with age and period adjustment [263], and its 95% confidence intervals (CI).

The rowers' follow-up starts with their date of first OG participation and finishes with their date of death (if concerned) or with the study's endpoint. The rowers' entries in the cohort are represented in Figure 4.1.

The observed and expected survival estimations were illustrated by Kaplan-Meier curves [235] and were compared with use of the log-rank test.

For the disease-specific mortality we compared each cause of death found among rowers with the specific rate in the general population by calculating SMR's for the available identification period, 1968 to 2012. Causes of death were classified according to the International Classification of Diseases - ICD (8th revision before 1978, 9th revision between 1979 and 1999, 10th Revision after 2000).

The 95% confidence intervals were calculated using the exact method [236]. R software v2.14.0 was used for the analysis.

4.1.4 RESULTS

OVERALL MORTALITY

A total of 255 male rowers represented France in the Olympics from 1912 up to 2012. All rowers verified by the RNIPP had their vital status validated, except for fifty-two (20.3%) who were not included in the study since they were born prior to 1891 (n=10) or their date or place of birth were not properly validated (n=42). Therefore, the analyses were performed on 203 French rowers.

Among rowers' cohort, 46 deaths occurred before the study's endpoint; 30 within P1 (Table 4.1). The age of death ranged from 35 to 100 years old. The mean age of death was 72.5 (\pm 15.6) in P1 and 74.0 (\pm 9.1) in P2. The PT overall mortality is significantly reduced by 42% compared with the French general population. Significant overall mortality reduction is also observed among rowers for both cohort periods considered apart (Table 4.1).

Table 4.1: French Olympic rowers' cohort description and their overall mortality compared with the French general population.

Cohort	PT (n=203)	P1 (n=30)	P2 (n=173)
Cohort's entry period	1912-2012	1912-1936	1948-2012
Nb. of person-years	6724.2	1528.4	5195.8
Mean age at cohort's entry in years (SD)	24.1 (\pm 3.6)	24.1 (\pm 3.7)	24.1 (\pm 3.6)
Mean follow-up time in years (SD)	33.8 (\pm 18.5)	48.4 (\pm 15.7)	31.0 (\pm 17.7)
SMR (95% CI)*	0.58 (0.43 - 0.78)	0.63 (0.43 - 0.89)	0.40 (0.23 - 0.65)
p-value	<0.001	0.009	<0.001

*SMR lower than 1.0, indicates a reduced mortality of rowers compared with the reference population.

The rowers observed and expected survival curves are illustrated in Figure 4.2. The rowers observed curve is significantly different from the expected curve derived from the matched general French population (p=0.008). The observed rowers' curve diverges and shifts to the right early in the follow-up period. The gap widens until 45 years of follow-up, and narrows afterwards until the end of follow-up. With increasing time, progressively fewer rowers contribute to the survival estimate.

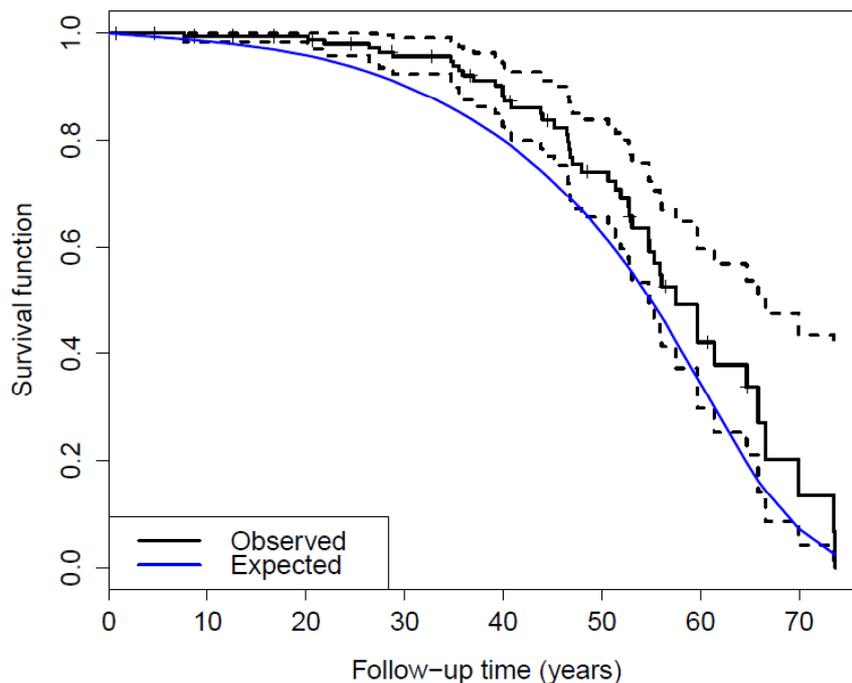


Figure 4.2: French Olympic rowers' observed and expected survival curves. Rowers' observed survival is represented by the solid black curve and its dashed confidence interval. The blue curve refers to the expected survival derived from the matched general French population.

MAIN CAUSES OF DEATH

Among the 46 deaths observed, 36 occurred during the available period of death's cause identification (1968-2012). From those, 3 died abroad and their cause of death were not available. Therefore, 33 rowers had their underlying cause of death identified. The main causes of death (Table 4.2) observed were neoplasms, $n=11$ (33%), followed by cardiovascular diseases $n=7$ (21%) and external causes $n=6$ (18%). The ICD chapter of external cause comprises deaths related to accidents, homicides, suicides and falls. The remaining causes observed (nervous system diseases, genitourinary diseases, respiratory diseases, skin diseases and ill-defined conditions) together account for 27% of all causes of death identified. Concerning the three main causes observed among French Olympic rowers, cardiovascular diseases are 59% significantly lower than found in the general population. Neoplasms and external causes are not significantly different from the general population (Table 4.2).

Table 4.2: French Olympic rowers' main disease-specific mortality compared with the French general population.

Main causes of death (n)	Observed/ Expected deaths	SMR (95% CI)	p-value
Neoplasms (11)	11/18.4	0.59 (0.29 – 1.07)	0.09
Cardiovascular diseases (7)	7/17.0	0.41 (0.16 - 0.84)	0.01
External causes (6)	6/5.7	1.0 (0.38 - 2.29)	0.99

4.1.5 DISCUSSION

To our knowledge the present study is the first to describe a survival advantage of elite rowers compared with their referents in the general population. The follow-up over the last century shows a 42% reduction of the overall mortality of French Olympic rowers. The early cohort of rowers (P1) followed until its complete extinction as well rowers competing post Wars up to 2012 (P2) showed a consistent mortality reduction.

The difference between observed and expected survival curves since the beginning of the follow-up illustrates the rowers' survival advantage over the general population. This advantage, visible since the beginning of the follow-up, increases with time and rowers deviate most from the expected when they are 50 to 70 years old. At older ages the rowers' survival approaches the curve of their compatriots.

The increased selectivity of the Olympics in the modern era may require increased training intensity and may further develop the use of enhancing performance techniques, with potential adverse effects on athletes' health [126]. The consequence of such period changes on elite rowers' mortality will only be fully acknowledged after the entire extinction of the current young rowers, as it will allow a complete retrospective analysis. Up to now, our results suggest that recent rowers' longevity (P2) follows the survival advantage trend observed among P1 rowers; the mortality difference with the general population even seems to widen. However our results should be cautiously interpreted as we compare healthy individuals at cohort's entry with the general population, including ill and handicapped individuals. This "healthy worker effect" [264] probably overestimates the mortality reduction found among rowers.

French rowers' survival advantage appears associated with a reduced mortality from cardiovascular diseases. The benefits of leisure endurance sports on the cardiovascular health are well known in the general population [265,266] but some studies have underlined possible risks to the cardiovascular system due to excess training [93,94,254]. The preparation to OG includes important training volumes with

rowers reaching more than 1000h of training per year [267]. Such training loads undertaken during years of practicing produces major adaptations of the athletes' cardiovascular system [99,249] a phenomenon probably enhanced by a previously selection process [31,163]. Among French Olympic rowers, rather than a risk, the cardiovascular adaptation to training requirements to access the OG seems to be protective in light of the 59% mortality reduction found among them. Previous studies assessing cardiovascular diseases of endurance elite athletes as defined by the ICD show: a 51% reduction among Finish long distance running and cross country skiing [96]. Finally, our findings among Olympic rowers are also in line with longevity studies assessing rowers from lower competitive level [250,251].

Similar reduced overall mortality have been reported among other elite athletes cohorts [96,171,179,268], including recent findings considering endurance athletes [269]. The lower injury incidence among rowers might be behind the contrast with American football players' mortality [183]. Despite an overall mortality reduction of 47% the players presented an increased mortality due to neurodegenerative diseases claimed to be related with concussive blows to the head.

We limited our cohort to Olympic athletes in order to focus on the highest sports level for which health consequences of intense training remains debatable [73]. Nevertheless, our results are based on a small absolute number of subjects, especially those concerning causes of death; hence they should be interpreted with caution. In addition, we are not able to determine how the excluded athletes might alter the magnitude of our findings. Finally, except for age and period, we could not adjust for potential confounding factors. Our methods advantage, however, relies on an extensive follow-up of French Olympic rowers followed during a century of OG, allowing for a complete follow-up of the rowers competing in the first Games. In addition, the vital status and causes of deaths assessed and validated by National sources reduces uncertainty.

Further investigations based on larger cohorts and in a large variety of countries are now needed to better apprehend elite athletes' reduced mortality. As it is out of an observational study's scope to determine causality, analytical studies are necessary to explain elite athletes' survival advantage. The assessment of lifestyle or physical activity post-career of elite athletes may provide better understanding of their mortality determinants.

CONCLUSION

French elite rowers followed-up during a century of Olympic Games benefit of lower overall mortality compared with the French general population. The cohort composed only of deceased rowers from the early Olympic Games analyzed apart and

followed until its complete extinction shows also an important mortality reduction. Among elite rowers' main causes of death, cardiovascular diseases are reduced in relation to their compatriots. Analytical studies with larger samples controlling for confounders such as elite athletes' training-load and lifestyle after career are needed to understand the reasons behind elite athletes' survival advantage.

4.2 PANEL: RESEARCH IN CONTEXT

4.2.1 ROWERS' MORTALITY

WHAT WERE THE ISSUES AROUND THIS SUBJECT?

The scientific literature describes elite rowers' type of training as a possible source of long-term cardiac alterations, but no investigation has focused on such a cohort. We previously showed that French Olympians had lower cardiovascular mortality compared to their compatriots, but the cohort is heterogeneous regarding the type of sports and the cardiovascular demands. We do not know if, inside the Olympic cohort, rowers display different trends.

WHAT DOES THIS STUDY ADD TO EXISTING KNOWLEDGE?

French Olympic rowers have a lower mortality than their referents in the French general population. Findings focusing on a sub-cohort of rowers participating in the Olympics from 1912 to 1936 and followed until its complete extinction also reveal an important mortality reduction. Such a reduction is mainly due to the 60% lower cardiovascular mortality found.

4.3 TRANSLATIONAL OUTLOOK

The findings based on the entire cohort of Olympians or focused on a single sport like rowing consistently reveal lower overall mortality rates among French elite athletes. Even though Olympians represent one of the highest levels of performance achievement for a large diversity of sports, they are not the sole elite athletes in France.

It is difficult to know whether the findings based on Olympians' cohorts may be transposed to other elite cohorts exposed to particular issues and constraints, such as professional athletes, for instance.

Previous studies on professional athletes mostly investigated American football or baseball players and found inconsistent results [172,174,183,200].

One French cohort of professional athletes, with relevant historical background and resembling important particularities, is the cyclists on the TDF. Their activity is one of the most physiologically grueling events in the world [202,227]. Another aspect distinguishing feature of this sportive event is the controversies related with widespread doping use [130,270] in view of the many participants' confessions, including from prominent cyclists declaring that it consists in a widespread behavior [130,271] that is sometimes labeled as the epo-epidemic [272].

Studying the long-term outcomes in elite professional cyclists is therefore of particular interest.

We therefore undertook a study aiming to evaluate and compare overall mortality and specific causes of death among French participants in the TDF with those of the French general population, study detailed in the next section. The cyclists' cohort was studied through similar methods as those employed to study the Olympians' cohort, and over a comparable period of time, that is, since the first sports event occurring after the Second World War interruption, *i.e.* 1947, to 2012.

5

STUDY 3: French professional cyclists' overall and specific mortality

In the context of recent concerns regarding performance enhancing techniques and potential negative health effects of high-level physical activity, data on the long-term outcomes and causes of death in elite endurance cyclists are of particular interest. Characteristics and vital status of all French participants in the Tour de France were collected for the 1947–2012 period. Causes of death were obtained from 1968. Overall and disease-specific mortalities were compared with the French male population using overall and specific standardized mortality ratios (SMRs) with their 95% confidence intervals (CIs). Among the 786 French cyclists who participated at least once between 1947 and 2012, 208 (26%) died by 1 September 2012. Neoplasms and cardiovascular diseases accounted for 61% of deaths. We observed a 41% lower mortality in French cyclists (SMR: 0.59, 95% CI: 0.51–0.68, $P < 0.0001$), which did not change over time ($P = 0.70$). It was observed for main mortality causes: for neoplasms (SMR: 0.56; 95% CI: 0.42–0.72, $P < 0.0001$) and for cardiovascular death (SMR: 0.67; 95% CI: 0.50–0.88, $P = 0.004$), except mortality related to external causes (SMR: 1.06, 95% CI: 0.71–1.53, $P = 0.80$). We observed a substantially and significantly lower mortality in participants in the Tour de France, compared with the general male population. However, our results do not allow us to assess in detail the balance between positive effects of high-level sports activity and selection of healthy elite athletes, vs. any potential deleterious effects of excessive physical exercise or alleged doping.

5.1 STUDY 3

Mortality of French participants in the Tour de France (1947–2012)⁴

5.1.1 INTRODUCTION

The Tour de France is the world's most celebrated endurance cycling event and celebrates its 100th race in 2013 [273]. As the Tour gained prominence and popularity, the race was lengthened and its popularity extended around the globe. This is a 21 days competition with 2 days of rest during July covering more than 3200 km.

The benefit of regular physical activity is well known and has been recommended for both primary and secondary prevention of cardiovascular diseases [54,55,274]. While the benefit of moderate regular physical activity has been clearly demonstrated, recent controversy exists regarding the potential adverse effects of regular strenuous physical exercise [52,265,275]. In this context, the long-term outcome of elite athletes is of particular interest, although data are scarce on this issue [170,178]. To the best of our knowledge, there are, very few data on cycling [202,276] and none addressed the issue of specific causes of death. The TDF is arguably one of the most physiologically demanding sports competition [227]. The effort involved has been compared with 'running a marathon several days a week for nearly three weeks', while the total elevation of the climbs was compared with 'climbing three Everests' [127,277]. In addition, as recently emphasized, the TDF has been the subject of many controversies because of exposure to performance enhancing techniques, in the past and still recently [130,276], described as potentially promoting an increase in mortality [129].

5.1.1.1 OBJECTIF

We therefore undertook a study aiming to evaluate and compare overall mortality and specific causes of death among French participants in the TDF from 1947 to 2012, vs. the community average.

⁴ Annex (iii)

5.1.2 METHODS

STUDY DESIGN

Retrospective cohort study of French professional cyclists.

DATA COLLECTION

Data on TDF French participants, for the 1947–2012 period, were collected via website sources.

Identity information and vital status was confirmed via RNIPP from the INSEE. Causes of death were obtained from the CépiDc. In the current study, the mortality status of all the French cyclists who had participated at least once in TDF from 1947 to 2012 was available by September 2012, while the specific causes of deaths could be retrieved until 2010. Causes of deaths were classified according to the International Classification of Diseases (8th revision before 1978, 9th revision between 1979 and 1999, 10th Revision after 2000).

5.1.3 STATISTICAL ANALYSIS

Characteristics of subjects were described as means \pm SD, proportions (%), median, and inter-quartile ranges (IQR) when appropriate. The overall mortality (from 1947 to 2012) and specific causes of death (from 1968 to 2010) of the French cyclists who had participated at least once in TDF from 1947 to 2012 were compared with that of the French male population of comparable age during the same period. The follow-up for each cyclist was defined by the difference between the date of endpoint (1 September 2012 if alive or date of death) and the date of its first participation to the Tour de France. Person years and standardized mortality ratio (SMR) were computed [278]. Standardized mortality ratios were calculated by 5-year-age class and 1-year interval, and their 95% confidence intervals were calculated using the exact method [236].

The period effect was explored using two complementary approaches. First, to address (indirectly) the possible effect of doping on long-term mortality, cyclists were grouped according to three 20-year-time periods of participation to the TDF (1947–70, 1971–90, and 1991–2010), corresponding schematically with the reported or suspected use of amphetamines, steroid, and erythropoietin, respectively [126]. Thereafter, SMRs according to the period of participation were calculated accordingly.

Since only the youngest are considered for the last period, no death was observed in this group by 1 September 2012. Secondly, to account for mortality trends over time, deaths that occurred within each 20-year-time period were considered and the corresponding SMRs estimated. To further take into account a possible age period interaction, we performed a binomial model (SAS PROC GENMOD). Overall mortality rate

from the community was calculated using the Human Mortality Database (<http://www.mortality.org/>). P-values of, 0.05 were considered to indicate statistical significance.

5.1.4 RESULTS

GENERAL POPULATION AND CYCLISTS OVERALL MORTALITY

A total of 786 French elite cyclists participated at least once in the TDF between 1947 and 2012 (Figure 5.1). With a mean participation of 2.5 TDF by cyclist, they represented 29.7% of the total participants. The median age at the first participation was 25.1 (23.7–26.6) years, and year of birth of the participants ranged from 1910 to 1989. The median duration (IQR) of follow-up was 37.4 (23.5–49.8) years.

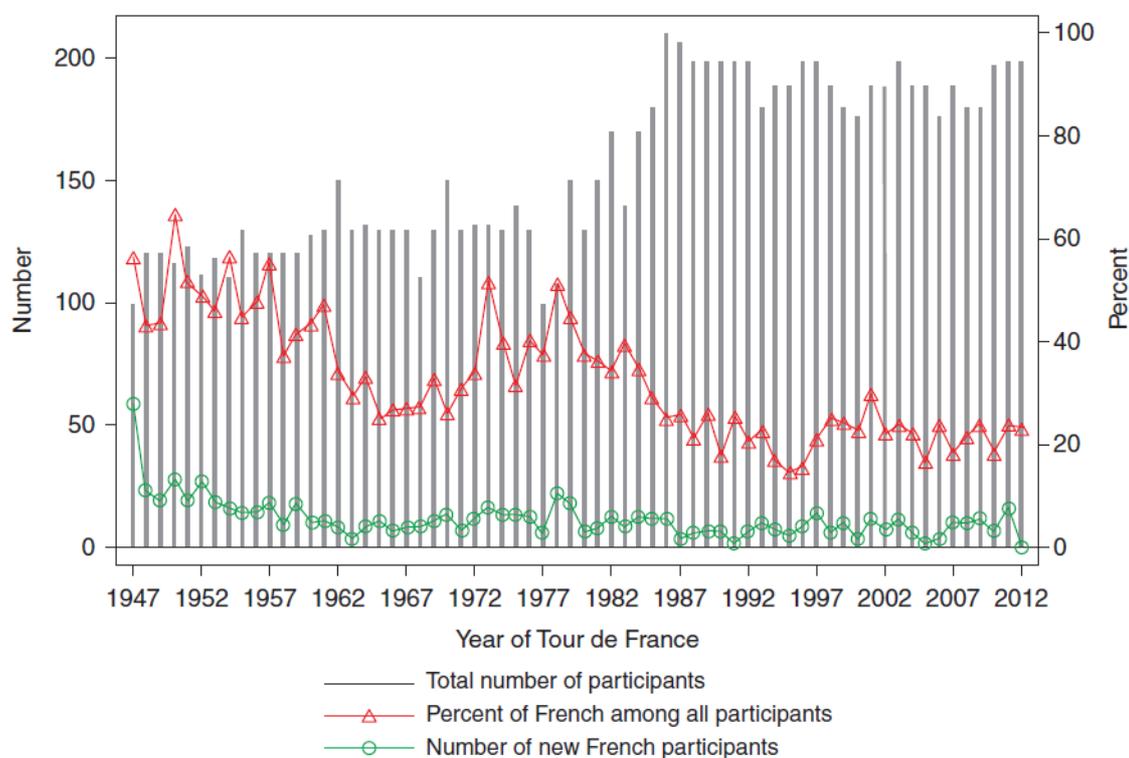


Figure 5.1: Proportion of French participants to the tour from 1947 to 2012.

Among this cohort of 786 French cyclists, 208 (26%) were known to have died by 1 September 2012. Compared with the general population, we observed a 41% lower mortality in French cyclists (SMR:0.59; 95% CI: 0.51–0.68, $P < 0.0001$). Standardized mortality ratios were consistent across age, except for ages < 30 years in whom a non-significant SMR of 1.65 (0.75–3.25) was observed (Figure 5.2).

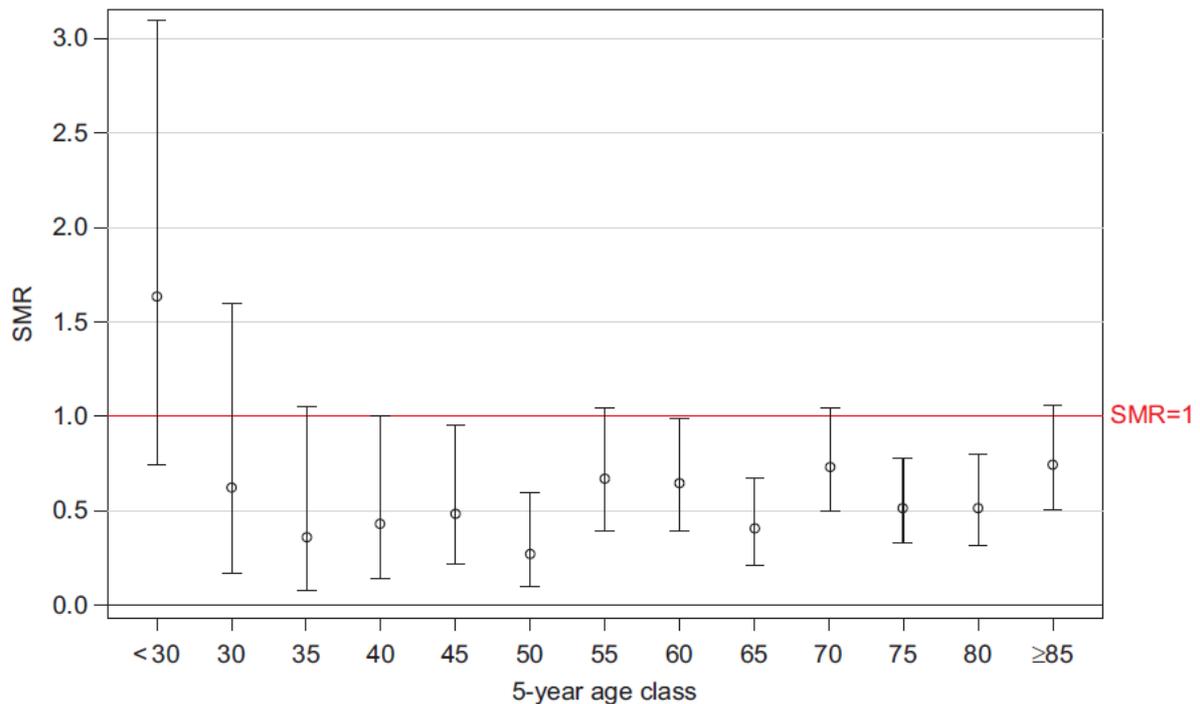


Figure 5.2: Standardized mortality ratio by 5-year-age class. Standardized mortality ratios were consistent across age, except for ages <30 years among whom only nine cyclists died. For this latter, an excess of mortality was suggested although the standardized mortality ratio was not statistically significant.

Standardized mortality ratios were also consistent after grouping cyclists by their period of participation to the TDF. Of the 391, 220, and 175 cyclists who participated to the TDF in the 1947–70, 1971–90, and 1991–2012 periods, respectively, 188, 20, and 0 had died by September 2012. This yielded SMRs of 0.59 (0.51–0.69) and 0.68 (0.39–1.11) for those who participated in the 1947–70 and 1971–90 periods, respectively. Furthermore, Figure 5.3 illustrates the lower mortality in the cyclists when compared with the male general population across the three time periods (1947–70, 1971–90, and 1991–2010): 0.56 (95% CI: 0.28–1.01), 0.54 (95% CI: 0.39–0.72), and 0.62 (95% CI: 0.52–0.73), respectively (P for difference = 0.70, P for age period interaction = 0.49).

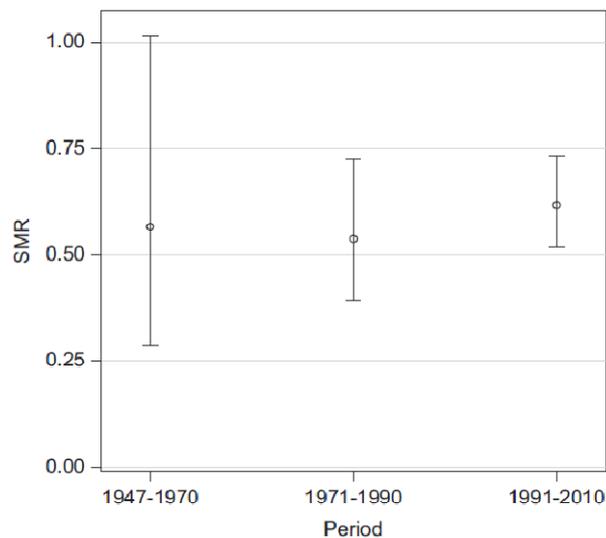


Figure 5.3: Standardized mortality ratio over time. We observed a lower mortality in the cyclists as compared to the male general population across the three time periods (1947–70, 1971–90, and 1991–2010), without any significant difference over time.

CAUSES OF DEATH

Although there was no loss to follow-up for total mortality, specific causes of deaths were missing in seven cyclists (three were due to death which occurred outside France and four were of undetermined cause). The three principal causes of death were neoplasms (32.2%), cardiovascular diseases (29.0%), and external (mainly trauma-related) causes (15.8%). The three main cancers were digestive (35%), lung (22%), and prostate (7%). Among the 53 deaths related to cardiovascular diseases, we denoted 39 cardiac deaths (74%). Other causes of death included infectious diseases (2.2%), endocrine and nutritional diseases (2.2%), neurological (2.2%), digestive system diseases (2.2%), and genitourinary disease (1.1%).

There was no death due to blood disease. Among the nine deceased cyclists aged, 30 years, six (66%) were related to accidents (races and traffic accident), two to cardiac causes, and one to an unknown cause. Of note, no death occurred during the TDF among these 786 French participants.

Table 5.1 shows the SMRs for specific cause of death. Overall, the direction and the magnitude of the SMRs by cause of death were comparable to the overall SMR: neoplasms (SMR: 0.56, 95% CI: 0.42–0.72, $P < 0.0001$), cardiovascular diseases (SMR: 0.67, 95% CI: 0.50–0.88, $P = 0.004$), and respiratory system diseases (SMR: 0.28, 95% CI: 0.09–0.65, $P = 0.003$), digestive system diseases (SMR: 0.22, 95% CI: 0.06–0.56, $P = 0.001$). However, no clear difference was observed between cyclists and the general population regarding mortality related to external causes (SMR: 1.06, 95% CI: 0.71–1.53, $P = 0.80$).

Table 5.1: Standardized mortality ratio by causes of death

	Expected	Observed	SMR	95%CI
Infectious diseases	5.44	4	0.74	(0.20–1.88)
Neoplasms	106.01	59	0.56	(0.42–0.72)
Endocrine and nutritional diseases	6.90	4	0.58	(0.16–1.48)
Mental disorders	6.61	3	0.45	(0.09–1.33)
Nervous system diseases	9.05	4	0.44	(0.12–1.13)
Cardiovascular diseases	78.87	53	0.67	(0.50–0.88)
Respiratory system diseases	17.87	5	0.28	(0.09–0.65)
Digestive system diseases	18.21	4	0.22	(0.06–0.56)
Musculoskeletal diseases	1.11	1	0.90	(0.02–5.02)
Genitourinary system diseases	3.66	2	0.55	(0.07–1.98)
Ill defined conditions	14.03	8	0.57	(0.25–1.12)
External causes	27.29	29	1.06	(0.71–1.53)

5.1.5 DISCUSSION

We observed a significant 41% lower mortality among French elite cyclists from the Tour de France, compared with the general male population. This reduction in overall mortality was relatively homogeneous across ages (except for ages <30), time periods, and major causes of death (except for external causes of death).

It has been traditionally suggested that a higher dose of physical activity has an additional benefit on reducing all-cause mortality (that is, a dose-response relationship) [279,280]. The recent results of two large cohort studies have proposed the concept of a U curve, with a strong benefit of moderate physical activity, but possibly a deleterious effect in case of particularly strenuous and sustained physical activity [52,265]. These new findings have been illustrated by recent basic and clinical published data on the effects of 'excessive' sport exposure and cardiac remodeling [90,91,100,275,281,282]. Training induces volume- and time dependent morphological and functional changes in the heart. Heart rhythm disorders, such as atrial arrhythmia (including atrial fibrillation and atrial flutter), are a well-established association with such long-term endurance practice [283,284]. Veteran athletes have a higher prevalence of atrial fibrillation and sinus node disease [283–285]. It has been also recently suggested that long-term excessive exercise may accelerate ageing in the heart, as evidenced by increased coronary artery calcification, diastolic ventricular dysfunction and large-artery wall

stiffening [93]. Finally, although shorter exercise duration has been associated with favourable antioxidant and vascular effects, longer exercise seems to blunt these beneficial effects and to yield adverse effects on vascular function [286].

The observed significant reduction in overall mortality in our cohort of French participants in the TDF, compared with the community average, should be interpreted with caution for the following reasons. First, there is a significant selection bias, as only the healthiest and fittest individuals are likely to be able to compete at such elite levels [287]. Such excellence in sport may be due in part to genetic predisposing factors [170,288,289]. On the other hand, the reference population includes males from the community with potentially prevalent chronic disease and illness putting them at a higher risk of death, exaggerating, therefore, the difference in mortality between the cyclists of the TDF and the community average. Secondly, participation in the TDF and the preceding years of training represent only a part of each athlete's lifespan, and thus it is hard to attribute the observed lower mortality solely to participation in the TDF. Thirdly, and as a corollary, confounding factors may have played a role in this observed lower mortality. In particular, data on the lifestyle habits after their athletic career would have been informative but were unfortunately unavailable in the present study. Interestingly, former elite athletes, especially endurance athletes, tend to maintain active and healthy lifestyles later in life, by engaging in more physical activity and smoking less than those in the general population [156,162,163].

As recently emphasized, the TDF seems to have been the matter of controversies because of exposure to performance enhancing techniques [127]. Doping is associated with serious health complications, of which the most common and especially dangerous involve the cardiovascular system [126]. Doping may have attenuated the association between participation to the TDF and lower long-term mortality in our cohort. Three main periods of prohibited substances use have been described: amphetamines and cocaine use in the 1950–60s; androgens and anabolic steroids use between the 1970s and 80s, and since 1990, the use of growth hormone and erythropoietin. Although we could not directly estimate the effect of doping, analysis by time period is rather reassuring.

These are exploratory analysis and we lacked time of follow-up for the last period, *i.e.* the possible effect of erythropoietin on long-term mortality. To the best of our knowledge, comparable data on overall mortality among elite cyclists are only available from the study of Sanchis-Gomar et al [202]. Although their data have added substantial information to the field, their findings remained limited to cyclists who participated to the TDF before 1964, without specific cause of death analysis. Specific cause of death analysis has been addressed in athletes in general or in specific sports such as soccer or American football [175–178,183,290]. Our findings confirm the significant reduction in overall mortality, as well as the relatively homogeneous risk reduction distributed across

different causes of death. Notably, we found particularly low-specific mortality rates regarding cancer and cardiovascular diseases compared with the general population of the same age. In contrast, we did not observe any excess mortality in any specific mode of death, contrasting, for example, with the experience among soccer players (who had more amyotrophic lateral sclerosis) reported so far. However, these studies are limited by the relatively few absolute numbers of deaths, as well as large differences in the accuracy of death certificates in different areas of the same country [175–177,183,290,291]. Furthermore, we found consistent lower mortality across age group. Notably, a non-significant excess mortality was observed in the youngest. Although speculative, these young cyclists may harbour cardiomyopathy or ion channel disease that is more likely to trigger a sudden death during such demanding effort [254,292–294]. In our study however, a particularly high frequency of death related to traffic or race accident was observed in that young age group.

METHODS CONSIDERATIONS

Although we report here the first cause of death analysis among elite cyclists compared with the general French population and had no loss of follow-up regarding their mortality status, we acknowledge some limitations. First, as an observational study, no causal inference can be made between participation in the Tour and the observed lower mortality. In particular, except age, and time periods, we were not able to adjust for potential confounding factors. Secondly, French cyclists represent only 30% of all Tour participants, and the extent to which these results apply to other nationalities is uncertain [276]. Third, analysis was restricted to mortality while morbidity and quality of life data were not available. Finally, the reliability of death certificates for the diagnosis of the causes of death and of sudden death in particular is questionable [295].

CONCLUSION

We observed a substantially and significantly lower mortality in participants in the TDF, compared to the general male population. However, our results do not allow us to assess in detail the balance between positive effects of high level sports activity and selection of healthy elite athletes, vs. any potential deleterious effects of excessive physical exercise or alleged doping.

5.2 PANEL: RESEARCH IN CONTEXT

5.2.1 PROFESSIONAL CYCLISTS' MORTALITY

WHAT WERE THE ISSUES AROUND THIS SUBJECT?

The TDF is extremely demanding to its athletes, and this kind of vigorous activity has been linked with adverse long-term health effects, such as cardiac troubles and increased risk of sudden death, especially in view of the practice of doping, known to be widespread among professional cyclists. However, causes of death of professional cyclists have never been studied.

WHAT DOES THIS STUDY ADD TO EXISTING KNOWLEDGE?

Lower mortality is observed among French cyclists participating in the TDF. Major causes of deaths are cancer, cardiovascular diseases and external causes of death. Mortality due to cardiovascular diseases is 37% lower among cyclists than in the general population, similarly to cancer that is 44% lower.

5.3 TRANSLATIONAL OUTLOOK

Like Olympians, professional cyclists display a survival advantage over their compatriots. Summarizing the last three studies, we demonstrated that French elite athletes, whether professional cyclists, rowers or Olympians altogether, consistently have a lower overall mortality, mainly related with reduced mortality due to the major causes of deaths, notably cardiovascular mortality.

These studies provided a global appreciation of the mortality status of French elite athletes answering the first main objective of this thesis. Such descriptive analyses were necessary to build the basis for future studies, and define more precisely subsequent hypotheses, given that French elite athletes' mortality was unknown.

At present, in light of the survival advantage found among elite athletes, new questions emerge: how much longer do they live? How many more years of life does the 50% mortality reduction found mean for Olympians? Is this gain related with the physiological constraint of the type of sports performed?

From the studies on Olympians and cyclists some differences came into light regarding external causes of death, or the age-effect on mortality, raising hypotheses of different risk exposure during the sportive career. The lowest age-class mortality found among Olympians corresponds to the years when most of them are still active, contrasting with the higher mortality found among the youngest cyclists. The higher mortality was related with the accidental deaths found in cyclists under 30 years old. Such findings may also explain the equivalent mortality due to external causes between cyclists and the general population, contrary to Olympians who benefit of a 34% lower mortality than their compatriots. Most Olympians carry out much of their training indoor (*i.e.* in pools or gymnasiums) or in a controlled outdoor environment (*i.e.* in stadiums), safer conditions than road cycling, which may explain such divergence.

These differences suggest specific risks related to the physiological constraints of each sportive practice, which may impact in a particular way the causes of death. But this difference may not be clearly distinguished on overall mortality analyses, relying on indirect standardization of mortality. Analytical approaches are now required to investigate the impact of different types of physiological demands on the risk-specific of mortality. Therefore in the next study we implement a method to apply to the Olympians cohort, quantifying gains in life duration due to specific causes of death among elite athletes according to their sports' main physiological characteristics.

6

STUDY 4: Years-saved from cardiovascular death in elite athletes

Studies have shown lower mortality among elite athletes compared with the general population, but none has assessed the impact of the type of elite effort on the athletes' specific CV longevity. At this lack of studies is added an absence of appropriate methods to quantify the longevity gains according to a particular cause of death in a population that outlives their referents. There were two goals for this study, methodological and analytical: i) to implement the un-biased years lost methodology in a context of a cohort that outlives the general population; ii) to quantify elite athletes' years lost/saved to CV and cancer diseases according to their main type of physiological effort. All French athletes participating from 1912 up to 2012 Olympic Games, with vital status validated and cause of death (if concerned) identified by the national registries were included ($n = 2814$, 455 died) and classified according 6 categories of effort: 1. POWER ($n = 440$, continuous effort $<45s$); 2. INTERMEDIATE ($n = 813$, $45s <$ continuous effort $<600s$); 3. ENDURANCE ($n = 272$, continuous effort $> 600s$); 4. POLYVALENT ($n = 278$, participating in different events from different classifications, i.e. decathlon), 5. INTERMITTENT ($n = 915$, discontinuous effort, i.e. team sports); 6. PRECISION ($n = 96$, more static events, i.e. shooting). The years lost method was applied to calculate the longevity gains in years using the competing risk model. We found that all categories save on average of 6.9 [95% CI 6.3, 7.6] years of life ($p <.001$) compared to the general population, with no significant differences between the categories. Concerning CV diseases, INTERMEDIATE (2.2; 95% CI [1.6, 2.8] $p <.001$), POLYVALENT (2.7; 95% CI [1.9, 3.6] $p <.001$) and INTERMITTENT (2.2; 95% CI [1.7, 2.8] $p <.001$) categories save more years of life than POWER (1.3; 95% CI [0.4, 2.2] $p <.01$) category. ENDURANCE (0.8; 95% CI [-0.7, 2.2] $p >.05$) and PRECISION (1.4; 95% CI [-0.6, 3.4] $p >.05$) categories do not save years of life in comparison with the general population. All categories significantly saved on average 2.2 years of life (95% CI [1.8, 2.6]; $p <.001$) from cancer death.

6.1 STUDY 4

Years-saved from cardiovascular death in elite athletes: efforts too short or too long are not too good

6.1.1 INTRODUCTION

Elite athletes' cohorts evidence lower all-cause mortality in comparison to their compatriots in the general population [171,296–298]. Studies including disease-specific mortality description show that elite athletes' major causes of deaths - CV and cancer diseases - tend also to be lower in relation to the general population [171,177,296,298]. However, these cohorts are highly heterogeneous in term of sports and the impact of different type of physiological demand on athletes' risk specific of mortality is unclear. Particularly, the long-term effect on the CV system of vigorous endurance disciplines (*i.e.*, efforts of long duration requiring sustained cardiac work) is highly debated, whether among veterans athletes [89,97,99,299–304] or in the general population [52,54,74,305].

The CV adaptations to elite training vary according to the main effort performed, which is a proxy of the type of discipline practiced [102,306–308]. Regarding different types of effort, sustained endurance among elite athletes has been suggested to induce adverse alterations in cardiac function, harmful at long-term [90,97,299,300], potentially outstripping the proved benefits that moderate physical activity confers to the CV system [73,89,97,302,303,308]. However, no study has assessed the CV longevity benefits over elite athletes' life-span according to their type of physiological effort.

There is an equivalent lack of studies considering cancer mortality among elite athletes. It has been previously described different cancer rates accordingly the type of sports practiced [96,177,309], yet, little is known about the relation between type of physiological effort and cancer mortality over the athletes' lifespan.

Therefore, the impact of different type of physiological demand on the risk-specific of mortality due to the major causes of deaths in elite athletes requires analytical approaches, so far, only assessed by descriptive tools, consisting mainly of indirect standardization of mortality [171].

The years lost method, is an easily interpretable metric quantifying the difference in years of the studied cohorts' longevity. This method is of particular interest: i) in cohorts that outlive the general population (like elite athletes) and therefore cannot be analyzed with the usual methodology of the relative survival field which relies on the

assumption that cohort survives worse than the referents and ii) when studying survival due to a specific cause of death.

The many subtle issues of survival analysis have caused many papers reporting the differences on longevity to be importantly flawed with results entirely misleading (e.g:[207,310,311]). Assessing the effect of a specific cause on life years lost brings additional complications and is usually done by comparing life expectancy with and without that cause operating. This “cause-delete” approach relies on the unverifiable assumption that disease-specific risks are independents. An additional drawback of such method is that it is not additive over cause of death: the years lost to all-causes is not partitioned over the years lost for each cause, resulting in life years lost due to a specific disease greater than the number of years lost to all-causes of death (e.g. [312]).

A milestone method for quantifying the years lost by specific cause of death was recently proposed in a joint effort of biostatisticians and demographers through the competing risk model [209,210,313]. This approach, primary conceived for clinical epidemiology aiming to measure the patients’ years lost due to her/his specific disease, has the desirable properties of additivity of death causes and does not rely on the independence assumptions.

6.1.1.1 OBJECTIVE

Therefore this study has two purposes, methodological and analytical: i) to implement the un-biased years lost methodology [209] in a context of a cohort that outlives the general population; ii) to quantify elite athletes’ years lost/saved to CV and cancer diseases according to their main type of physiological effort.

6.1.2 METHODS

STUDY POPULATION

The studied population consists in all male and female French athletes participating at least once in the summer or winter OG between 1912 and 2012 that had their vital status validated by the RNIPP.

The biographic and sportive data of each athlete was collected as previously described (study 1). From the 4708 athletes representing France in the studied period, 1390 were not assessed for eligibility because place and/or date of births, required to certify their vital status was not available (n=1171), or they were born before 1891, out of the available period of identification (n= 219).

Of the 3318 whose vital statuses were verified – starting from their last Olympic participation up to January 1st, 2013 (study’s endpoint) - 2814 were certified: 2359 alive, 455 deceased. Among the subjects deceased, 448 died during the available period of cause of death identification (1968-2012) by the national sources. Their underlying

causes were obtained via the CépiDc and were classified according to the International Classification of Diseases (8th revision before 1978, 9th revision between 1979 and 1999, 10th revision after 2000).

Thereafter, the cohort of 2814 French Olympians (2118 male and 696 female) was classified according the main type of effort they have accumulated over the years of training required to be optimal in the event(s) they have participated in the games.

CLASSIFICATION OF THE TYPE OF EFFORT

In order to classify a century of a wide diversity of sports' events within the OG a constant criterion was required. Along the modern games, French athletes have participated in 448 events: some had its rules changed; some sports have been excluded while others have integrated later the Olympic program. In addition, there is an heterogeneity of events within a single sport (*e.g.*, 200m K-2 and 10 000m C-1 in canoeing, or throwing events and marathon race in athletics) as well as an heterogeneity related to the participation of the athletes (some have participated in multiple events and some in different sports). Thus, the previous sports classification reported in the literature (Kujala et al. 2001; Mitchell et al. 2005) could not be applied in this study because they classify few sports currently existent only.

The criterion chosen to classify the main effort of each Olympian was the time of effort duration to accomplish her/his performance. We first determined the average time of effort to accomplish each event French Olympians have participated during the Games from 1912 to 2012. Thereafter we identified the events every Olympian has participated. The time of effort was collected accordingly the event structure, initially regarding events of continuous effort.

For the race sports, we collected the average time of the finalists for each period. For instance, if in 1976, the finalists in the 1000m speed skating men category accomplished this event in 70 seconds on average, this was the time of effort attributed to the athletes engaged on this event, for this period. For relay events, the individual time of the athletes on average was taken in account, not the event time.

For the events of continuous effort that were not a race, we measured the time of effort following the event rules, a video analysis and the specific literature of the events physiological principles. For instance, in sports such as synchronized swimming or in figure skating, the athletes have a minimum and maximal time to perform their routines. The average time was attributed to each athlete following the rules of the period they were engaged in the games. For sports not timed, we collected the time of effort through video analyses: for instance, we measured the time between the beginning of impulsion in the standing long jump (not in the Olympic program anymore) until the end of the task, or the beginning of the race in vault event in gymnastics until the land. For some

events with a specific literature of the physiological basis clearly differentiating two types of effort during the event, the time taken in account was the time of the main effort that is determinant to the final performance. For instance, in the ski jump (large or normal hill), the time of main effort started with the phase of impulsion followed of the flying and finishing with the landing, ignoring the phase on descending before impulsion [314]. For bobsleigh, power is required for the push off start and is critical for a great run, and this was the time taken in account [315].

The particularity of each of the 448 events was considered. For instance, in the individual sprint in cycling, the early part of each race is tactical with riders pedalling slowly, as they jockey for position. For this event, the average time between the beginning of the real sprint up to the end of the race was considered. For the combined events, such the decathlon in athletics, or omnium event on cycling, or the all-around in gymnastics, the time of effort for each discipline was measured.

All these events of continuous effort were classified according the main energy system required, that is time dependent [155,316,317]. Although efforts cannot be strictly categorized, some threshold points, based on the principles of physiology can be schematically defined [316–318]: the main energy pathway for exercises at nearly maximal intensity, shorter than 45 seconds is anaerobic. Efforts longer than 45 second up to 600 seconds, combine anaerobic lactic and aerobic. Longer efforts are mainly aerobic [318,319].

Therefore, the athletes whose events demanded an effort shorter than 45 seconds were grouped into the category **Power**. Those engaged in events lasting longer than 600 seconds, were grouped into category **Endurance**. Those whose efforts were comprised between 45 and 600 seconds were grouped into the category **Intermediate**. For those competing in different events, or in combined events, that would enter different classifications, they were grouped into category **Polyvalent**.

The athletes participating in events of discontinuous effort, such is the case of team sports, were grouped into the category **Intermittent**.

Finally, the sports of precision, such archery or shooting, formed the category of **Precision**.

Therefore, the 2814 French Olympians were divided into 6 categories of effort: Power (15.6%), Intermediate (28.9%), Endurance (9.7%), Polyvalent (9.9%), Intermittent (32.5%) and Precision (3.4%) (Table 4.1).

Table 4.1: Description of the Olympians' cohort according to their main category of effort.

Categories	Power N =440	Intermediate N =813	Endurance N =272	Polyvalent N =278	Intermittent N =915	Precision N =96
Median time of effort duration ^a (seconds)	10.0	174.4	3015.0	240 ^b 120	-	-
Mean Age at entry Years (\pm SD)	24.1 (3.7)	24.2 (5.1)	25.6 (4.4)	22.3 (4.0)	25.6 (4.1)	28.5 (7.2)
Nb deaths (%)	74 (17.0)	130 (16.0)	44 (16.2)	46 (17.0)	148 (16.2)	13 (14.0)
Mean Follow-up time Years (\pm SD)	29.6 (20.4)	27.0 (19.3)	27.2 (18.3)	29.0 (20.4)	26.5 (19.3)	21.9 (17.2)
Female Olympians (%)	26.8	27.7	21.5	33.4	19.8	25.0

^a Continuous effort only. ^b Olympians Polyvalent participate in events classified in different groups. The gap between their shorter and longer effort was measured; the median of this measure is presented for this category.

6.1.3 STATISTICAL ANALYSIS

Cohort description was expressed as mean, median (\pm SD) when necessary.

The athletes were included into the study at the time of their first Olympics participation and followed up until death, January 1st 2013 or the age of 90, whichever came first.

The average number of life years lost from the time of Olympics participation until the age of 90 in our observed cohort was estimated by calculating the area below the estimated probability of dying (at each age) as described by Andersen [209]. The remaining life expectancy of the counterparts of our athletes in the general population was calculated using the French population mortality tables. The difference between the two areas estimates the average number of years saved. The same methodology was used when estimating years saved from a certain cause, by replacing the overall probabilities of dying with the cumulative incidence functions for a specific cause.

Standard errors of the athletes' life expectancy were calculated as described in Andersen [209]. By regarding the population life expectancy as given (not random), the same standard errors were used to construct the confidence intervals for the difference.

The analyses were also performed focusing on Olympians engaged in athletics events in order to assess a more homogeneous cohort: athletics is the sport with greater number of French Olympians ($n = 537$), present since the begging of the games, and

covering all categories of continuous effort, that is Power (n= 243), Intermediate (n=139), Endurance (n=78) and Polyvalent (n=77).

A 2-tailed p-value < 0.05 was considered evidence of statistical significance. Statistical analyses were carried out using R software v3.2.0.

6.1.4 RESULTS

The analyses were performed on 2814 French Olympians, whose vital statuses were validated by national sources. Their mean (\pm SD) age at first Olympic participation is 24.7 (\pm 4.7), and their median follow-up time was 52.7 for the 455 subjects that died before January 1st, 2013, and 20.7 for the subjects alive. The oldest Olympian died at age of 100 years.

OLYMPIANS AND THE GENERAL POPULATION

French Olympians demonstrate significantly lower risk for all-causes of deaths ($p < .001$) in relation to the general population (figure 4.1a). Their major causes of deaths are CV diseases, representing 28.8% of all deaths at total, followed by cancer (26.6%) and external causes of death (10.0%). The other causes altogether account for 34.5% of the total of deaths (figure 4.1b). Olympians present significant lower risk of death due to CV diseases ($p < .001$) (figure 4.1c) and cancer ($p < .001$) (figure 4.1d).

YEARS-MAILED ACCORDING THE TYPE OF EFFORT

All-causes of death

The lower risk of death over the Olympians lifespan could be translated into years saved, and its CIs calculated, as represented in the figure 4.2, according each category of effort.

Regarding overall causes of death, all categories saved on average 6.9 years of life [95% CI: 6.3, 7.6; $p < .001$] in relation to the general population until the final age-point of 90 years, without significant differences between the categories (Figure 4.2a). The categories with smaller number of subjects have larger CIs, which is especially the case of the Precision group.

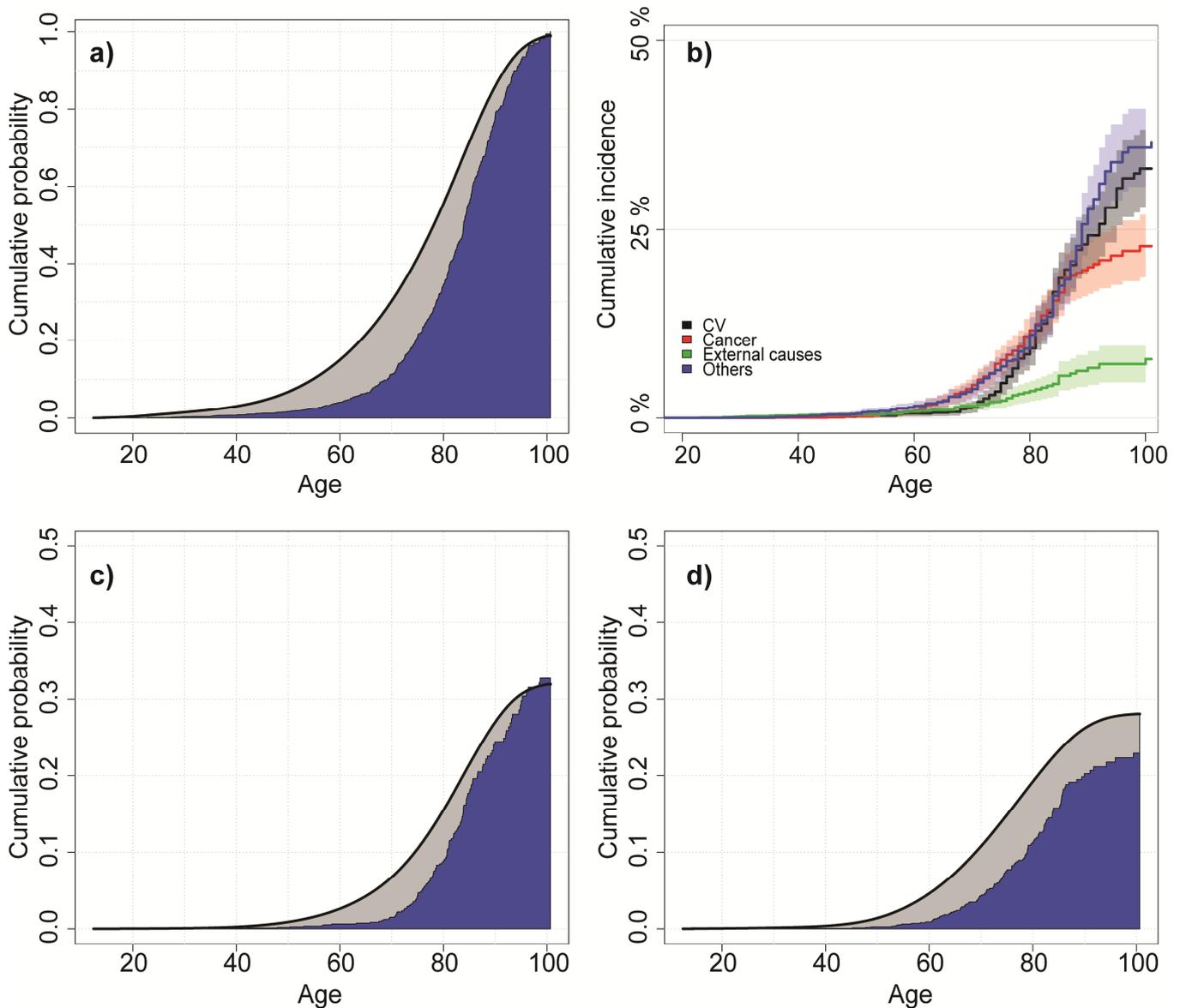


Figure 4.1: a) Cumulative probability of death for the Olympians (blue) by age in relation to their referents in the general population (black). The grey area between the curves represents the lower risk of death among Olympians. b) Cumulative incidence of CV (black), cancer (red), external causes (green) and all others causes of deaths (blue) among Olympians by age. c) Cumulative probability of death from CV diseases and from d) cancer, among Olympians (blue) by age in relation to their referents in the general population (black).

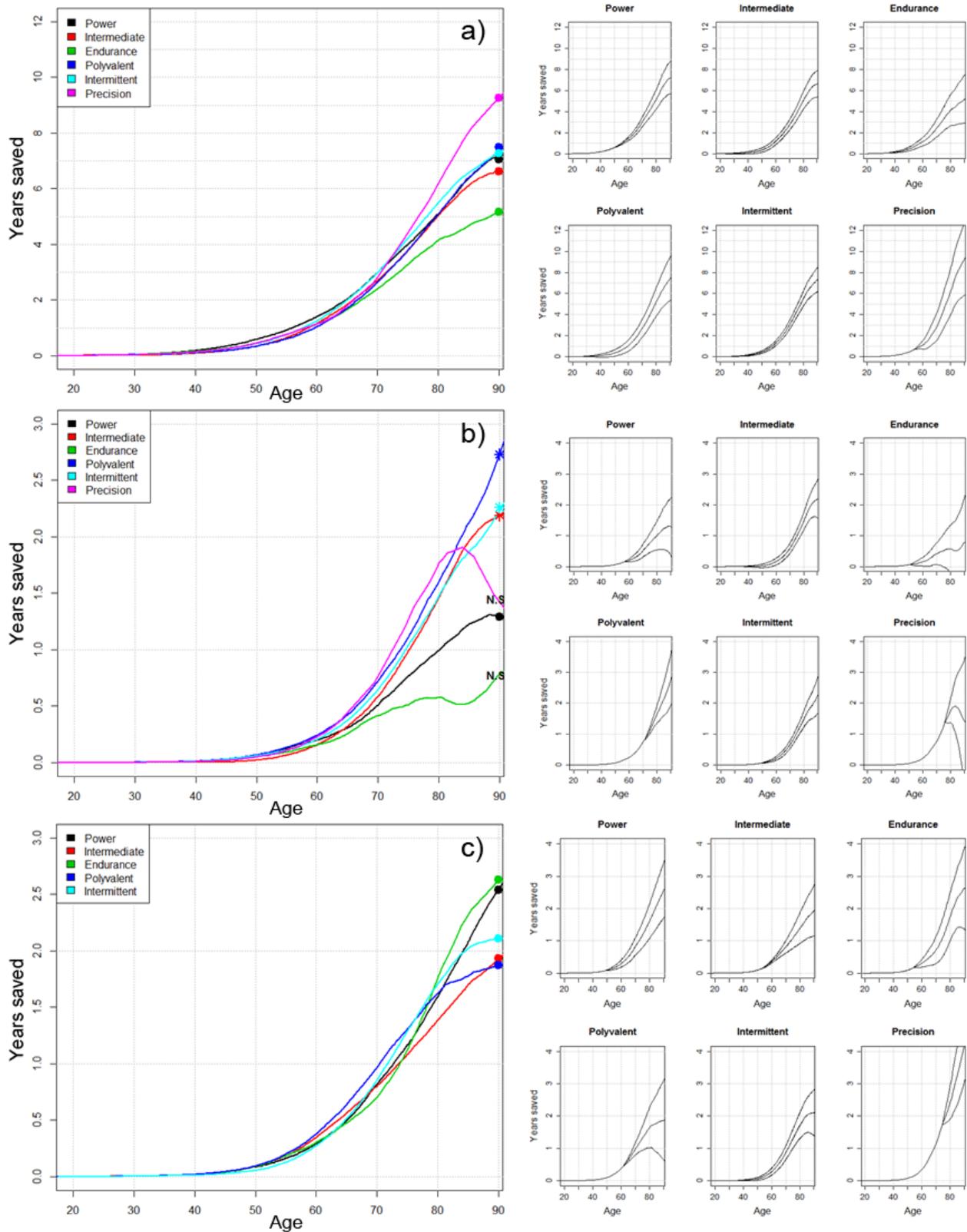


Figure 4.2: Years-saved from all-causes and from the major causes of deaths according to the Olympians' category of effort by age. a) Years-saved from all-causes of death. b) Years-saved from CV death. c) Years-saved from cancer death. Precision curve was not illustrated because only one death was registered due to cancer. **N.S** = non-significant

($p > .05$) number of years-saved in relation to the general population; ● significant ($p < .05$) years-saved compared with the general population ($p < .05$); *significant ($p < .05$) years-saved compared with the general population and with the other categories. At right every curve of years-saved is represented with its confidence interval for each graph.

Cardiovascular death

Following the competing risk model, the years saved by the Olympians could be studied according their major causes of deaths.

In relation to CV diseases, only Power (1.3; 95% CI [0.4, 2.2]; $p < .01$), Intermediate (2.2; 95% CI [1.6, 2.8]; $p < .001$), Polyvalent (2.7; 95% CI [1.9, 3.6]; $p < .001$) and Intermittent (2.2; 95% CI [1.7, 2.8]; $p < .001$) categories significantly saved years of life at the final age-point (figure 4.2b). Among these four categories, Polyvalent, Intermittent and Intermediate Olympians saved on average 1.0 year more (95% CI [0.5, 2.0]; $p < .05$) from CV death, than Power category. Even though the Precision group curve is superior to Power, the few subjects account for greater CI, and no significant gains was demonstrated (1.4; 95% CI [-0.6, 3.4]; $p > .05$). The endurance category did not save years from CV death regarding the general population (0.8; 95% CI [-0.7, 2.2]; $p > .05$).

Cancer

All categories significantly saved on average 2.2 years of life (95% CI [1.8, 2.6]; $p < .001$) from cancer death regarding the general population (figure 4.2c), without significant differences between the categories.

YEARS-MAILED IN ATHLETICS EVENTS

Olympians engaged in athletics events demonstrate similar trends of the whole Olympians cohort regarding continuous effort categories. Power (7.2; 95% CI [5.4, 9.0]; $p < .001$), Intermediate (8.7; 95% CI [6.8, 10.8]; $p < .001$), Endurance (6.3; 95% CI [2.6, 9.9]; $p < .001$) and Polyvalent (10.9; 95% CI [8.4, 13.3]; $p < .001$) track and field athletes significantly saved years of life from all-causes of deaths (Figure 4.3a). Without significant differences inter-categories ($p > .05$), they totalized on average 8.1 (95% CI [6.9, 9.2]; $p < .001$) more years than their compatriots, placing these athletes in the highest quartile of years-saved regarding the whole cohort of Olympians.

In relation to CV mortality, Endurance athletes do not show significant difference with the general population (-1.8; 95% CI: -4.8, 1.3; $p > .05$). Polyvalent (2.6; 95% CI: 1.5, 3.8; $p < .001$) and Intermediate (2.8; 95% CI: 2.0, 3.6; $p < .001$) category significantly saved 1.8 more years (95% CI: 0.5-3.1; $p < .001$) than Power athletes (1.0; 95% CI: 0.1, 2.1; $p < .05$) (figure 4.3b).

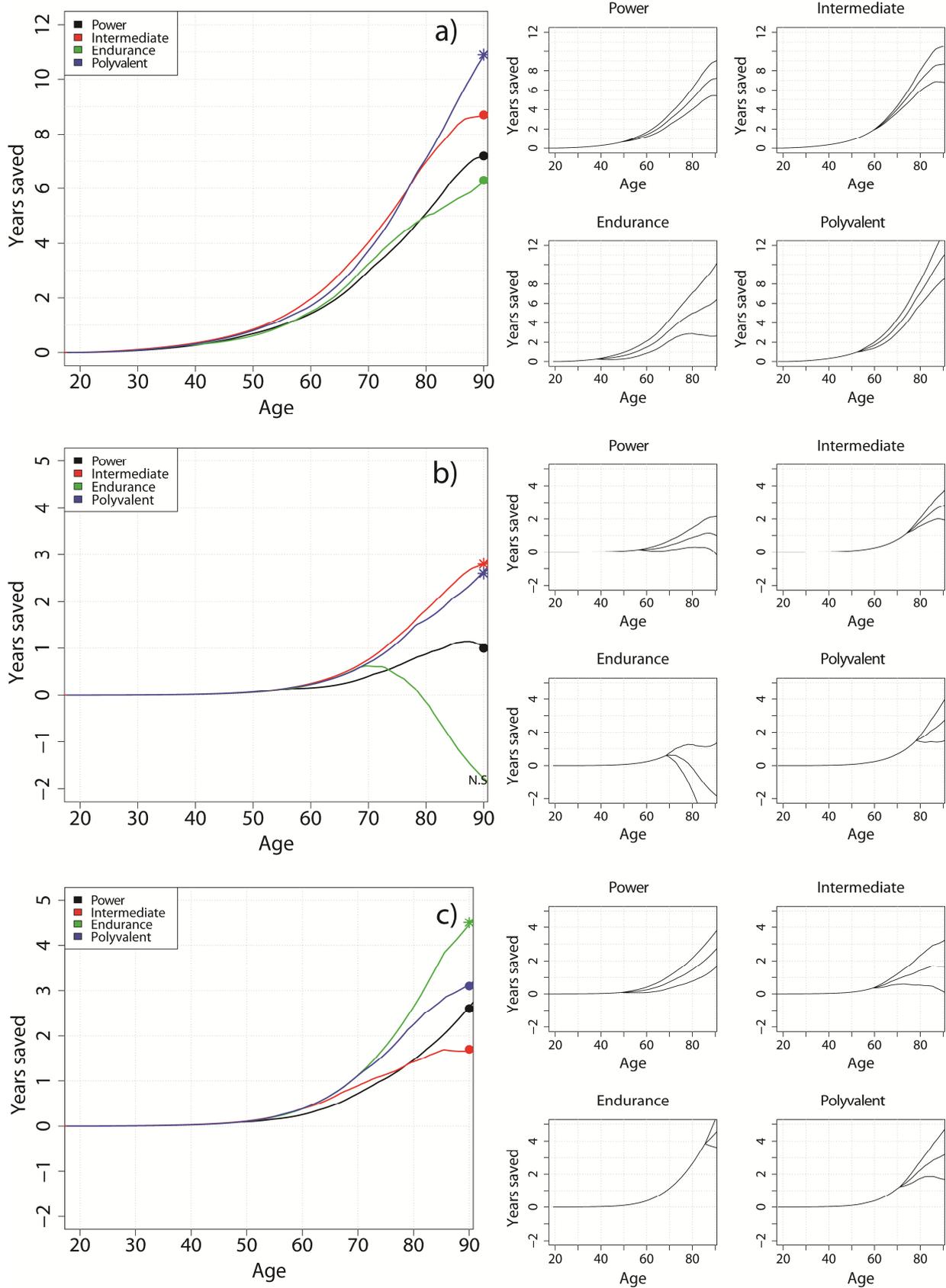


Figure 4.3: Years-saved from all-causes and from the major causes of deaths according to the category of effort by age among track and field athletes. a) Years-saved from all-causes of death. b) Years-saved from CV death. c) Years-saved from cancer death. N.S =

non-significant ($p > .05$) number of years-saved in relation to the general population; ●significant ($p < .05$) years-saved compared with the general population ($p < .05$); *significant ($p < .05$) years-saved compared with the general population and with the other categories. At right every curve of years-saved is represented with its confidence interval for each graph.

Regarding cancer mortality (Figure 4.3c), all categories significantly saved years of life: Power (2.6; 95% CI [1.6, 3.7]; $p < .001$), Intermediate (1.7; 95% CI [0.2, 3.2]; $p < .05$), Endurance (4.5; 95% CI [3.6, 5.3]; $p < .001$), Polyvalent (3.1; 95% CI [1.7, 4.6]; $p < .001$), without significant differences among the categories, totalizing on average 2.6 more years of life (95% CI [1.9, 3.3]; $p < .001$) due to lower cancer risk in relation to the general population.

SENSITIVITY ANALYSIS

The relation between years-saved from all-causes and specific-causes of deaths with the categories of effort, whether among the whole Olympians cohort or the track and field athletes are essentially the same after a sensitivity analysis including the 7 causes of deaths non-identified.

Similarly, excluding the Olympians engaged in the games after 2000 (once there are only few deaths among them, does not alter the relation of the results according to a sensitivity analysis performed.

6.1.5 DISCUSSION

YEAR-MADE METHOD

We extended the decomposition of year lost by cause of death to the context of years-saved providing confidence intervals, which facilitate its application. The years-saved method under competing risks provides an easier interpretation of longevity findings.

Aiming such readability, some studies assessing the benefits of exercising on longevity rather calculate the life expectancy decrease in non-active people which usually is the main result highlighted in the abstract section (*e.g.* [312]). Such method usually requires unverifiable assumptions, large cohort size [52], and are not endorsed by confidence intervals (*e.g.* [52,265,312]).

Our proposal overcame these issues and can be especially useful when performing inter-class analysis associated with specific diseases: for assessing longevity benefits of physical activity, or like aimed here, for assessing type of effort and related cause of mortality, fields rather relying on more standard methods on previous studies [96,177].

YEARS-MAILED AMONG OLYMPIANS

Applying the years-saved method in a cohort of elite athletes provided three major findings: first, all types of effort categorized consistently saved on average a total of 7 years of life from overall mortality and 2 years from cancer mortality. Second, French Olympians engaged on endurance events do not save years from CV mortality in relation to the general population. Third, the greater CV longevity is found among Olympians engaged in events of combined type of effort.

Physiological adaptations to intense training, induces structural, functional, and electrical remodeling of the heart, depending on the main physiological demand on the CV system according to the type of activity performed [102,306–308]. The categories divided accordingly the time of effort of each event on the Olympics, categorize types of successful and intense training, accumulated over years which has led to the highest level of a specific performance. Different types of effort, reveals similar overall and cancer mortality benefits, but different CV longevity.

The differences on CV longevity found seem to illustrate an optimal relation regarding the type of intense training and CV advantages: the best advantages are found among trainings combining different types of effort, while very short or very long duration effort confers none or small gains. Static events like in precision sports reveal no significant CV gains. Short CV effort, such in power events reveals small gains compared to other types of training. In the other end of the spectrum, efforts of long duration, such in endurance sports also reveals no gains. The categories in between, related with combined type of efforts, are those saving more years from CV death, on average 2 years, such is the case of sports of intermediated duration, like middle distance runners, or intermittent sports, like collective events, or such is the case of polyvalent Olympians, who are engaged on different events, requiring different types of effort.

The Physical Activity Guidelines and previous researches support combined type of training for optimal health benefits in the general population [320–322]. In terms of CV health, this seems to be extendable even for highly trained individuals, even though their aim with training is to optimize their performances rather than to obtain health benefits.

The findings regarding a more homogeneous cohort composed of track and field athletes are consistent with the findings on the whole cohort of Olympians: the four categories of continuous effort represented saved around 8 years of life at total, placing athletics on the higher end of years-saved distribution in relation to the whole cohort of Olympians. Still, the total years of life saved among endurance runners cannot be attributed to a CV advantage.

Intense endurance effort, is the specific type of exercise raising concerns about cardiac overuse injury [73,89,97,301,307,308]. For the adaptations provoked, intense

endurance training has been suggested to induce adverse alterations in cardiac function, potentially dangerous at long-term: chronic structural changes and reduced RV function [90]; possibility persistent residual LV hypertrophy after long-term detraining [299], sinus node disease [300], coronary remodeling [91], artery calcification [93], and atrial fibrillation and flutter [94,281,302,323].

The few studies assessing CV mortality in endurance elite athletes [96,177,298,309] have shown lower CV mortality among them than in the general population or healthy controls, through indirect standardization of mortality. Although this is a classical and reliable method [324], it is a global measure that does not capture the time or age dependence, which could explain such divergence.

The mechanism which physical activity contributes to lower cancer risk is barely known and the categories could not be established accordingly. Being an Olympian, independently of the type of activity, has shown benefits regarding cancer mortality. While this advantage may be interpreted in light of a health cohort effect, cohort selection bias and genetic forces [244], the differences relating type of effort and CV benefits show that Olympians' career may play a role on their longevity.

METHODOLOGICAL CONSIDERATIONS

The primary limit to this study is that the Olympians post-career lifestyle is unknown as well as how they have changed their physical activity habits and the extent it may impact the athletes' health over their lifespan. The training type the athletes endured before the Olympics could only be indirectly stipulated accordingly their time of effort in the Olympics. However, we do know that their training was intense and successful enough to allow the athletes reach the best performances of the world for their period, and probably higher the level, higher the degree of specificity. It is likely then, that current Olympians, displaying better performances, are more training-specific and the differences found among the categories may accentuate with time.

We also acknowledge a limit regarding the Olympians' entry in the cohort. As the vital status identification process starts on 1891, Olympians engaged in the earlier games, are the youngest and much fewer, since the number of participants increases with time. In addition, there are two entry period interruptions related with the two world wars. However, a sensitivity analysis shows similar results when excluding more recent Olympians and when adding the deaths without identification of the cause (once they occurred out of the period identification). Finally, the analysis concerning French Olympians may limit the generalizability of the findings to other countries.

The strengths of this study include the solid method adapted and applied to investigate mortality of physical active cohort, allowing distinguishing specific gains inside overall benefits and providing results easily comparable to future studies. In

addition, the findings rely on an extensive mortality follow-up, with death certification, and focus on athletes of the highest level where the impact of intense training is potentially over expressed.

PERSPECTIVES

The year-saved method may benefit future studies investigating healthy behaviors procuring life advantage, communicating longevity gains rather than losses. The relation between the type of physical activity and specific health benefits needs to be better understood to precise exercise prescription [325]. These novel findings require replication in other elite populations, especially regarding endurance athletes and CV longevity.

6.2 PANEL: RESEARCH IN CONTEXT

6.2.1 YEAR-MAILED IN ELITE ATHLETES

WHAT WERE THE ISSUES AROUND THIS SUBJECT?

Intense endurance training has been accused of inducing long-term cardiac alterations. Studies have demonstrated lower mortality among elite athletes compared with the general population, but none has assessed the impact of the type of effort on their CV longevity. To this lack of studies is added an absence of appropriate methods to quantify the longevity changes due to a particular cause of death in a population that outlives their referents.

WHAT DOES THIS STUDY ADD TO EXISTING KNOWLEDGE?

All types of effort among French Olympians saved years of life considering overall causes of death and specifically cancer mortality. However, the results suggest an optimal relationship between the type of effort performed and CV longevity, for which the most significant gains are associated with events combining different types of effort. The types of effort highly specialized in power or endurance, as well as static activities, confer little or no CV gains on longevity.

6.3 TRANSLATIONAL OUTLOOK

In the first part, the cohorts of French elite athletes, formed by Olympians, rowers and cyclists were compared to the general population. This means that we compared the high-end of a performance distribution curve to its entire curve, as is usually done in case-control studies [47], acknowledging all limits that such a comparison engenders. Doing so, we have demonstrated a survival advantage of elite athletes over their compatriots.

For the second part, we compared the elite athletes among themselves. We show heterogeneous CV longevity according to the groups studied, yet a consistently greater overall longevity for all groups of elite athletes compared with the general population.

Knowing the Olympians' propensity to live longer, for the following part we compared elite athletes with another highly selected population in terms of survival, that is, the longest-lived humans. One of our general hypotheses stated that elite athletes provide valuable data, which could be useful to interdisciplinary analyses, especially the ones assessing human maximal capabilities.

Physical performance is a leading indicator of human physiological capabilities. For instance, the walking speed, or even the grip strength are powerful predictors of future disability, morbidity and mortality [326–328]. Lifespan is another expression of human performance, for which the longest-lived humans occupy the high ends of a lifespan curve in the same way as Olympians do in a curve of physiological capabilities.

While athletic performance has shown proofs of limited progression [217], the existence of a limit for life duration progression is an issue that sharply divides the scientific community. The so-called *prolongevists* suggest a steady increase in life expectancy and therefore human lifespan, while *biogerontologists* strongly deny it, suggesting instead a limit to lifespan progression.

Hence, the comparison of both outliers' populations, having in common a propensity to live longer, may be informative for the debate over the existence of a limit to lifespan progression.

The next study therefore aims at a broaden application of elite athletes' data: to advance the use of their data in multifactorial traits analysis like aging, and provide new arguments for the intriguing debate around human lifespan trends.

STUDY 5: Life-span trends in Olympians and Supercentenarians

Life-span trends progression has worldwide practical implications as it may affect the sustainability of modern societies. We aimed to describe the secular life-span trends of populations with a propensity to live longer—Olympians and supercentenarians—under two hypotheses: an ongoing life-span extension versus a biologic “probabilistic barrier” limiting further progression. In a study of life-span densities (total number of life durations per birth date), we analyzed 19,012 Olympians and 1,205 supercentenarians deceased between 1900 and 2013. Among most Olympians, we observed a trend toward increased life duration. This trend, however, decelerates at advanced ages leveling off with the upper values with a perennial gap between Olympians and supercentenarians during the whole observation period. Similar tendencies are observed among supercentenarians, and over the last years, a plateau attests to a stable longevity pattern among the longest-lived humans. The common trends between Olympians and supercentenarians indicate similar mortality pressures over both populations that increase with age, scenario better explained by a biologic “barrier” forecast.

7.1 STUDY 5

LEARNING FROM LEADERS: LIFE-SPAN TRENDS IN OLYMPIANS AND SUPERCENTENARIANS⁵

7.1.1 INTRODUCTION

Is the continuous rise in world's lifespan still a plausible forecast? This topic is of great concern for public health and policymakers and has worldwide implications as it may affect the sustainability of modern societies and health-care systems [329–331]. Yet, the issue of longevity trends has divided researchers and remains a matter of controversy [332]. The origin of this divergence is not only a philosophical matter, but it is also supported by differing methods of investigation. Based on past life table trends, the prolongevist side claims that life expectancy will continue to increase linearly [333,334]. Best practices research has proposed dramatic increases in longevity outcomes, affirming that most children born in developed countries since 2000 will reach 100 years [335]. Supported by biological constraints and evolution-based, the other side argues that such a forecast is fundamentally unreachable [336,337] because human lifespan is biologically determined and we are already approaching a “barrier” to life expectancy increase [169,329]. Each side's conclusions point to opposite directions.

We propose an intermediate approach to investigate lifespan trends with novel tools. The approach consists in analyzing lifespan density trends of two highly selected populations with a propensity to live longer. Their current maximum lifespan trends may figure the general population in the near future.

The analysis of longer-lived cohorts' lifespan trends may guide the debate towards the prolongevist or biologist direction based on one of the different hypotheses: accepting the scenario whereby the historic rise in life expectancy will continue, it is necessary to assume that people will more often live longer than 100, 110 and 120 years [330]; precursor populations would then present signs of provable life extension. Conversely, a deceleration among longer-lived cohorts could be seen as a sign of a close lifespan limit [330].

The first population selected was made up of all worldwide Olympic athletes that had participated in the OG and were already deceased. Olympians have demonstrated an important survival advantage in comparison with their compatriots in developed nations [96,179,263]. To the best of our knowledge, Olympians constitute the sole worldwide

⁵ Annex (iv)

well defined population that has a proven survival advantage, including all ethnicities and dating back to the 19th century.

The registered longest-lived member of any species defines its maximum lifespan [169]. Hence, the second population selected was made up of elite survivors [338]: all deceased supercentenarians (individuals over 110 years old) worldwide [233].

We analyzed both populations' lifespan through density analysis. The density analysis (total number of life durations per birth date) reveals distinct lifespan trends according to the number of subjects with time. Hence, it allows for a highly informative description of lifespan upper limits and its relative relevance within the wide range of lifetime values.

7.1.1.1 OBJECTIVE

We aimed to describe lifespan density trends of worldwide deceased Olympians and supercentenarians.

7.1.2 METHODS

STUDY POPULATION – OLYMPIANS

Day, month and year of birth and death were collected for 19012 ($n=17815$ men, $n=1197$ women) who had participated in at least one summer or winter OG competition since the first modern edition in 1896, up to 2012 and deceased up to 2013 (study's date point). Data came from the most authoritative source of Olympians biography [262]. The Olympians' complete cohort (the cohort in which all subjects have entirely died out) ranges from 1828 to 1906. The Olympians population is mostly composed of adults from high income countries in Western Europe and North America (Table 7.1).

STUDY POPULATION – SUPERCENTENARIANS

A verified and validated complete cohort of deceased supercentenarians born after 1800 was collected from the Gerontology Research Group [233]. Overall, 1205 supercentenarians ($n=125$ men, $n=1080$ women) born up until 1897 - the last year without any registered proof of a supercentenarian alive - were included. The majority of supercentenarians also come from high income countries (Table 7.1).

Table 7.1: Olympians and supercentenarians cohort description

	Olympians (N=19012)	Supercentenarians (N=1205)
Range of birth year	1828-1991	1807-1897
Range of death year	1900-2013	1917-2013
World distribution by region* (%)	Af 1.7, Am 19.8, As 2.6, Eu 73.7, Oc 2.1	Af 0.4, Am 50.8, As 11.8, Eu 35.4, Oc 1.4
Age at cohort's entry, Mean (SD)	26.5 (6.6)	110
Range of lifespan in years (y) and days (d)	15y 120d – 105y 305d	110y 0d – 122y 164d

*Af= Africa, Am = America, As = Asia, Eu = Europe, Oc = Oceania

LIFESPAN DENSITY FUNCTION

The lifespan density of Olympians and supercentenarians was estimated over a two-dimensional mesh. Let X, Y be the date of birth and lifespan respectively, such that the data of an individual is expressed as X_i, Y_i with $i = 1, \dots, N$. The density of lifespan is estimated over the nodes of a mesh M . The boundaries of the two-dimensional mesh M were designed to encapsulate all the X_i and Y_i : lower boundaries of M [L_X ; L_Y] were defined as the largest integers that does not exceed [$\min(X_i)$; $\min(Y_i)$]. Upper boundaries [U_X ; U_Y] were defined as the smallest integers that is not less than [$\max(X_i)$; $\max(Y_i)$].

Note that the boundaries difference of the birth date dimension X : $\Delta_X = U_X - L_X$ was always greater than the one of the lifespan dimension Y : $\Delta_Y = U_Y - L_Y$, such that $\Delta_X > \Delta_Y$. The numbers of nodes in the X, Y dimensions were respectively denoted n_x and n_y , with respect to: $n_x, n_y \in N^*$ and $n_x, n_y \geq 2$. M was set as a homogeneous mesh, such that each node was separated by the value a in both dimensions, with:

$$a \in]0, \Delta_Y] \quad (1)$$

Such that the maximum possible distance between two nodes did not exceed U_y . The resolution r of M was given by:

$$r = n_x \times n_y = \left[\frac{U_X - L_X}{a} + 1 \right] \times \left[\frac{U_Y - L_Y}{a} + 1 \right] \quad (2)$$

ESTIMATION OF THE DENSITY

The number of lifespan d_j falling into the area of a j ($j=1, \dots, n$) node was summed, such that:

$$d_j = \text{Card}\left(X_i \subseteq \left[X_j - \frac{a}{2}; X_j + \frac{a}{2}\right], Y_i \subseteq \left[Y_j - \frac{a}{2}; Y_j + \frac{a}{2}\right]\right) \quad (3)$$

is an estimate of the local continuous density. $\text{Card}()$ denotes the cardinal number.

CHOOSING A REPRESENTATION OF THE DENSITY

To avoid information loss due to an inadequate resolution of the mesh, we set the value of a in view of the quantity of information provided by M at a given resolution r . Shannon entropy was previously demonstrated as a good proxy for maximizing the information quantity in a viewpoint [339]. In our approach, we used the relative frequency of d_j in M of a given resolution providing the value of a (1). In other word, we searched for the values of a that maximized entropy:

$$H(M) = -\sum_{j=1}^n p(d_j) \log_2 p(d_j) \quad (4)$$

where $H(M)$ is the entropy of M , measured in bits and:

$$p(d_j) = \frac{\text{Card}(d_j)}{\text{Card}(d)} \quad (5)$$

with $d_j \neq 0$. We browsed the values of $H(M)$ for the values of a in the interval defined in [1] using a step size of 0.1. We looked for the maximum of $H(M)$. As a consequence, we set $a=2$ (leading to $r=4067$ nodes) as a good representation of d given the data set (Figure 7.1).

ANALYSIS OF THE INSTANTANEOUS DYNAMICS IN A SPECIFIC TIME FRAME

In order to assess the development of lifespan among Olympians, we analyzed the dynamics of the density in a specific time window, focusing on a frame defined by the coordinates of birth date in [1880;1907] and lifespan in [85;106] years old, without time constraint (no Olympians born during this period are still alive).

For each birth date in the selected frame, we collected the differences between adjacent elements of the densities in the Y (lifespan) direction: $a_j = [d_2-d_1, d_3-d_2, \dots, d_n-d_{n-1}]$. The total velocity per birth dates $\bar{\alpha}$ is then estimated, for a given birth date.

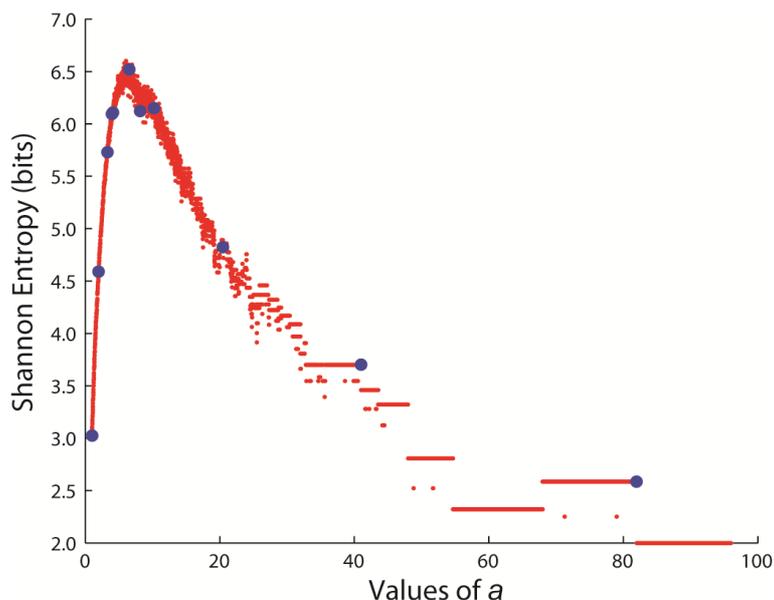


Figure 7.1: Shannon entropy (quantity of information) represented by different meshes of different resolutions, given different values of a . 'Exotic' values of a that lead to a mesh with $n_x, n_y \in R^*$, in contradiction to eq. (2) are plotted in red (red dots). Correct values are shown in blue.

ANALYSIS OF THE DYNAMICS OF LIFESPAN TRENDS IN A SPECIFIC TIME FRAME

To assess the trends among the lifespan upper values, the superior contour of each density layers was smoothed through a 2D convolution kernel. The frame was defined within the intervals: $X_{(\text{Olympians})}$ in [1865;1906]; $Y_{(\text{Olympians})}$ in [80;123] and $X_{(\text{Supercentenarians})}$ in [1865;1897]; $Y_{(\text{Supercentenarians})}$ in [110;123]. The frame selected in X corresponded to the first year forming a density layer up to the last year of a complete cohort. The selected frame in Y corresponded to a lifespan superior to 80 years up to its maximum values.

The lifespan trends dynamics, for each birth date in the selected frame was calculated by the sum of differences between adjacent densities in the Y (lifespan) direction (see Supplementary material). All analyses were performed using Matlab 7.13 (Math works Inc) software.

7.1.3 RESULTS

OLYMPIANS AND SUPERCENTENARIANS LIFESPAN DENSITY

The lifespan density of worldwide Olympians and supercentenarians is presented in figure 7.2

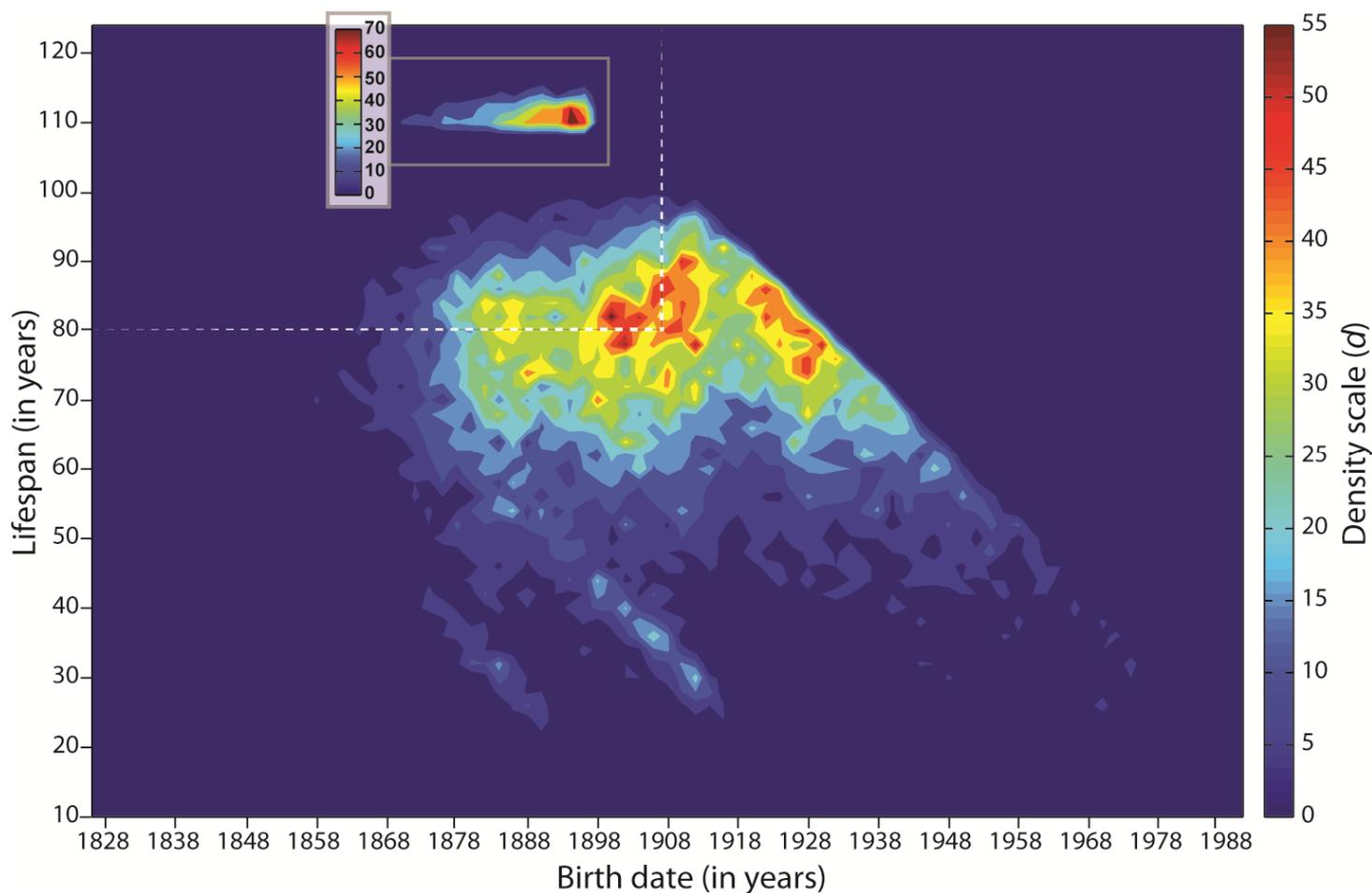


Figure 7.2: Lifespan (collected in days and represented in years) density of all deceased Olympians ($N= 19012$) and all validated supercentenarians ($N = 1205$) born since 1800 in function of their birth date (represented in years). Window: $X_{(\text{Olympians})}$ in $[1828;1991]$; $Y_{(\text{Olympians})}$ in $[10;123]$ and $X_{(\text{Supercentenarians})}$ in $[1828;1897]$; $Y_{(\text{Supercentenarians})}$ in $[110;123]$. The resolution was defined as $a=2$ years. The density scale ranges from dark blue illustrating the lowest density values with fewer subjects' lifespan to dark red corresponding to the highest density values. The vertical dashed line delimitates the complete cohort, when the population has entirely died out. The horizontal dashed line delimits lifespan values superior to 80 years within the complete cohort. Isolated lifespans are not represented in the figure because of their small densities values.

The first modern Games occurred in 1896. Thus, Olympians born before 1870 participated in the early editions at a more advanced age (42.5 ± 8.1 years old) relative to the mean age at first participation (26.5 ± 6.6 years old) of the full cohort.

Olympians' deaths were observed in every age group, ranging from 15 years and 120 days up to 105 years and 305 days. Deaths under 40 years mainly correspond to two birth periods: 1874-1890 and 1896-1915 and include men only.

The denser areas, corresponding to the lifespan that concentrates the highest number of subjects, is formed by Olympians born between 1900 and 1904 that died around 80 years old.

None of the Olympians reached the status of supercentenarian; therefore a gap separates the two populations throughout the entire period.

The denser area among the supercentenarians is formed by subjects born between 1893 and 1895 that died around 111 years old. The world's record lifespan is 122 years and 164 days for Jeanne Calment a French woman born in 1875.

LIFESPAN UPPER LIMITS

The top-left corner in figure 7.2 is the focus of the lifespan upper limit analysis for both populations as they constitute the lifespan upper values of both complete cohorts. The development of different levels of densities, forming lifespan layers may be visualized in this corner.

The superior layer, formed by the greatest lifespan values of Olympians creates a survival convex envelope at approximately 98 years. The convex envelope points out the Olympians lifespan upper limit observed. The density layers, below this convex envelope, move upward with birth date levelling off with the upper limit envelope.

A similar pattern is present among supercentenarians. Their lifespan creates a survival convex envelope at approximately 115 years. The densities layers above this envelope evolve with time but the upper limit remains steady and a plateau may be visualized up to now.

LIFESPAN DENSITY LINE TRENDS

The superior contour of each density layers at the top-left corner on figure 7.2 are illustrated in figure 7.3A for both populations. We observe a different slope progression of the density lines according to the lifespan. The density slope of Olympians decelerates with time as their lifespan increases.

Regarding supercentenarians, the density slope increases slightly with time at the beginning of the observation period, at a similar pace among the densities layers. Then, the densities slopes remains stable for the upper values. This results in a plateau attesting a stable phenomenon among supercentenarians in recent years.

DENSIFICATION PHENOMENON

Lifespan increase levelling off with the upper values entails an accumulation of individuals close to the survival convex envelope, and reveals a densification phenomenon. This phenomenon was assessed in the ancillary graphs (Figure 7.3B and 7.3C). The graphs describe an increased densification trend more continuous and more intense among supercentenarians than among Olympians.

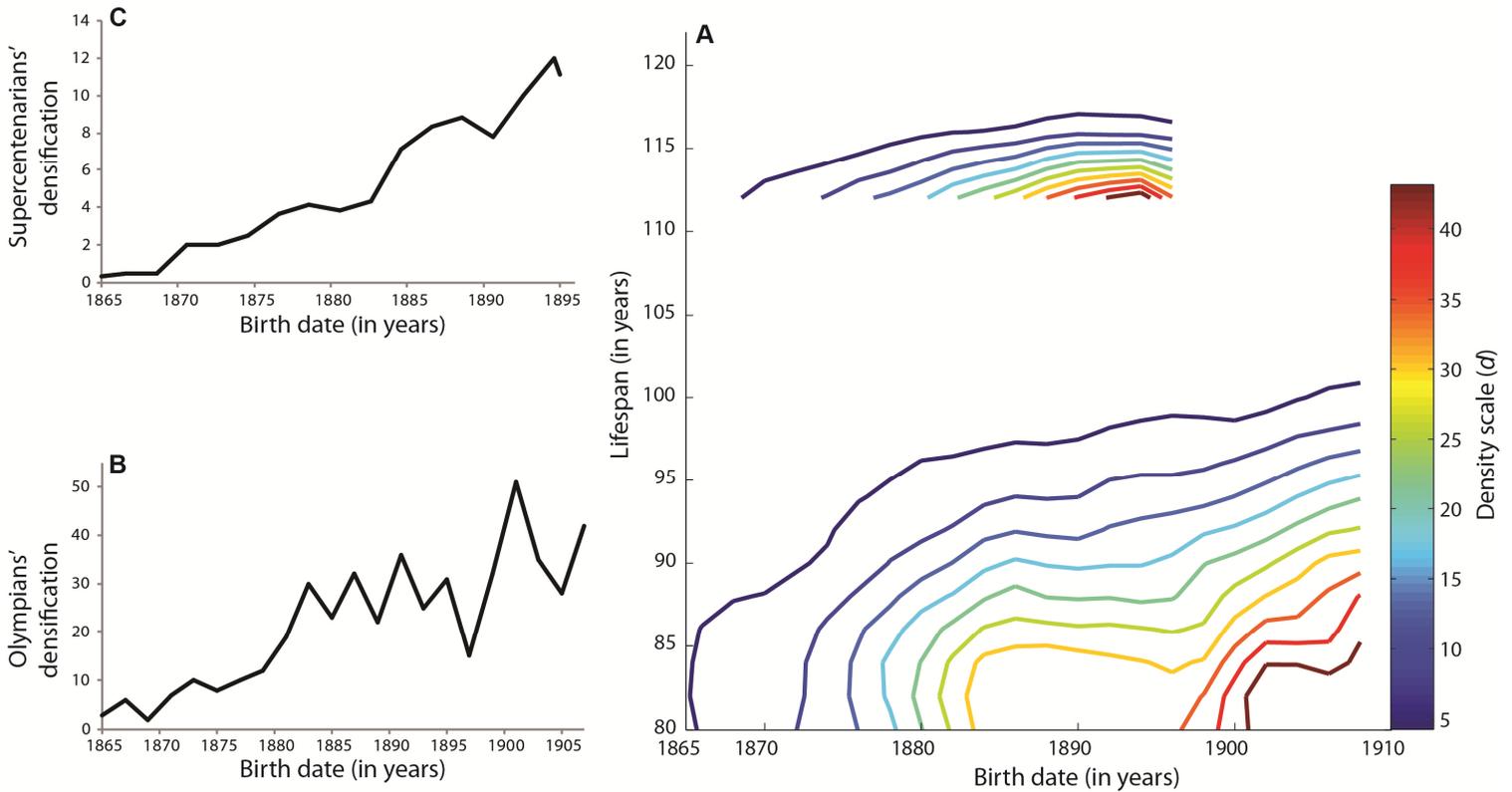


Figure 7.3: (A) Contour of the lifespan density layers of Olympians and Supercentenarians. Selected window: $X_{(Olympians)}$ in $[1865;1906]$ (First year forming a density layer up to the last year of a complete cohort) ; $Y_{(Olympians)}$ in $[80;123]$ and $X_{(Supercentenarians)}$ in $[1865;1897]$; $Y_{(Supercentenarians)}$ in $[110;123]$. (B) Olympians' densification phenomenon. (C) Supercentenarians' densification phenomenon. The Y-axis in B and C represents the sum of the differences in the Y (lifespan) direction ($\sum \alpha_j$) between the density layers by birth date. Graphs (B) and (C) represent the increase of the density layers with time in the direction of the upper lifespan values measuring the densification phenomenon.

7.1.4 DISCUSSION

LEARNING FROM LEADERS

This study demonstrates the lifespan trends in populations with a propensity to live longer, Olympians and supercentenarians. Among Olympians we observe a trend of increasing life duration, which slows down at advanced ages. The dynamics observed leads to a densification phenomenon, as a result of a lifespan compression between the denser areas and the maximum ages.

Olympic participants undergo a highly selective phenotypic process based on rare physiological aptness [41]. At the age of cohort entry they were healthy subjects under favourable conditions (genetic and environmental) [177] reaching high standards of physical performances. Studies have shown that Olympians have healthier lifestyles after their career and maintain a good physical condition [163]. All these factors contribute to greater longevity [163,266,340]. The selection criteria for Olympians' may explain their survival advantage over the general population, but it is not enough to allow them to reach the supercentenarians status: Olympians and supercentenarians have different performance-advantage sets. A gap clearly discriminates both populations attesting that the factors contributing to enhance general populations' longevity may not be sufficient to highlight the path required to become a supercentenarian. Accordingly, a longitudinal analysis of centenarians and supercentenarians has demonstrated a significant association between better physical function with survival advantage until 110 years. Beyond that age physical function or biomedical parameters may less accurately predict mortality [340].

Despite the gap, Olympians and supercentenarians present similar lifespan trends and densification phenomenon, intensified among supercentenarians. This common pattern may indicate that both populations are under similar mortality pressures, despite the different phenotypic selection criteria of each population. Such forces increase with age, and both populations respond similarly by a densification phenomenon.

Concerning supercentenarians, the increasing densities slope at the beginning of the observation period may be related to the greater number of recruited subjects and to a more reliable registry. Thereafter the stable trends observed attest for a lifespan plateau over the recent years. Mathematically speaking, Jeanne Calment's lifespan record may have been beaten by people born until 1891. After this record, only a single person (born in 1880) has lived for 119 years, and since then, no one has lived to more than 116. Accordingly, the lifespan density trends provide no signs of a recent increased longevity pattern among the longest-lived, despite of an intense densification phenomenon.

We find better support to explain our results in arguments such an "invisible barrier", as previously suggested [329,341]. This scenario seems to be represented here,

through the densification phenomenon, alluding to a rectangularization of the survival curves [342,343]. The slower pace in the trend of lifespan maximum observed among Olympians is even more stable among supercentenarians illustrating a “barrier” represented by the survival convex envelope. To support lifespan extension forecasts, we would expect to find signs of expansion trends, people living each time longer at advanced ages [330]. This scenario is hardly supported by the description of supercentenarians’ and Olympians’ current trends.

LIFESPAN RECORD HOLDERS

The fittest subjects of each country compose the worldwide Olympians cohort [262]. This population is mostly formed by athletes from regions that have historically dominated sport performances and the world record for life expectancy as well. Olympians are not the only longer-lived cohort, although they are the largest one, comprising various ethnicities and originating from a wide range of social conditions. Even though in the absolute sense Olympians constitute a small subset of gifted athletes, validated supercentenarians compose an even smaller subset of outliers. Women usually live longer than men but the Olympian cohort is mainly supported by male data because women’s entry in the first Games was restricted. Yet, Olympian women present the same pattern of density layers as men, and their superior lifespan density synchronises with the men’s.

OLYMPIANS FOLLOW GENERAL POPULATION TRENDS

The analysis of Olympians’ deaths - observed in every age group - highlights a pronounced heterogeneity even in a highly selected population. The two periods concentrating most deaths under 40 years can be attributed to both world wars, which reveal that Olympian men were neither excluded from the war effort nor spared its consequences.

The trend among most Olympians toward an increased lifetime throughout the century is similar to what has been described in terms of life-expectancy [333,344] and lifespan modal analyses [331] in record-holding countries. Modal age at death, estimated in USA, Canada and France, show similar increasing trends. Japan, however, has recently levelled off [331] comparably to Olympians lifespan trend at advanced ages.

THE GAP

The gap between Olympians and supercentenarians may indicate a potential for further life expectancy increase. But even among a highly selected population of Olympians, surpassing the general population in terms of average age of death [262], none reached the status of a supercentenarian attesting the exceptional character of reaching 110 years [345]. The similar densification among Olympians and

supercentenarians and their unclosing gap both strengthen the arguments defending that human biology may not allow most of us to become a centenarian [346]. Indeed, becoming one of them takes a complex sequence of rare and specific circumstances, involving constant favourable interactions between genetics [347] and environment [348]. Hence it seems appropriate to distinguish the interpretation of actuarial trends on all-cause mortality from biological ageing possibilities.

METHODS CONSIDERATIONS

Our study reinforces biological forecasts [169,345,349] contrasting with extension claims [350–352]. However our period of observation is restricted, and the size of the population studied is relatively small. In addition, life expectancy increase has been discontinuous due to historical changes; our cohorts could reveal a transitional trend only. But it is unlikely this may occur synchronically for both studied populations, in view of the different cohorts' selection criteria. Nevertheless, analyses of the most recent centenarians' birth cohort are time limited to 1914. After this period, all demographic forecasts are based on period life tables (death rates from a calendar year applied to people still alive) and remain speculative [337]. The underlying assumptions are deterministic – based on the premise that the future will repeat past trends. In addition, death rates at extremely older ages are uncertain [353]. Hence, analyzing a concrete cohort presenting a survival advantage may be an alternative method for understanding the present dynamics of maximal age trends.

In light of the continuous reductions in mortality rates at advanced ages in high income countries [334] possibly the densification phenomenon will intensify in most developed countries. For instance, compression of deaths above the mode - a comparable measure for densification - has been observed in high income countries [331]. Then, the probability of surviving people, pushing the limits forward and leading to a lifespan extension may be bigger. However, this scenario defended by prolongeivists, seems to be possible only if nutritional, climatic, social or economic conditions continuously improve. Important medical and technological advances may also lead to life extension [352], but major health determinants already contribute to reduce life expectancy progression in developed countries [354,355]. In addition, the current tendency in world climate change and environmental resources degradation may result in adverse health consequences especially affecting the eldest individuals [356].

CONCLUSION

Most Olympians follow the general population tendency of a lifespan increase with time, a trend which decelerates as lifespan increases. At advanced ages the slow pace on life duration progression leads to a densification of subjects dying simultaneously after

reaching the highest ages. Similar but intensified tendencies are observed among supercentenarians resulting in the stagnation of mankind's oldest women and men - despite a sharp increase in the number of new supercentenarians.

The common trends between Olympians and supercentenarians indicate similar mortality pressures over both populations. These forces increase with age, scenario better explained by a biological barrier limiting further lifespan progression. Although this forecast may be felt to be less optimistic, to consider the line of reasoning underlying it may contribute to a better understanding of lifespan trends and better prevent what may decelerate further progression.

7.2 PANEL: RESEARCH IN CONTEXT

7.2.1 OLYMPIANS AND SUPERCENTENARIANS' LIFESPAN TRENDS

WHAT WERE THE ISSUES AROUND THIS SUBJECT?

Is the continuous rise in world's lifespan still a plausible prediction? This topic of great concern for public health and policymakers has strongly divided the scientific community.

WHAT DOES THIS STUDY ADD TO EXISTING KNOWLEDGE?

The common lifespan trends between Olympians and supercentenarians indicate similar mortality pressures bearing over both populations and increasing with age, a scenario that is better explained by a biological "barrier" limiting further progression. The supercentenarians' density trends show a current stagnation of the human longevity progress.

8

DISCUSSION

We summarize here the main contributions of this work for the questions regarding elite athletes' mortality and human longevity trends. The considerations arising from such contributions are discussed. Initially, our findings are reviewed in light of previous studies in the field. The aspects related to health enhancing physical activity are discussed based on what we have demonstrated, taking into consideration its public health relevance. The contributions of our findings to the dose-response relationship between the dose of physical activity and health benefits are presented. The CV aspects of chronic, intense training are reviewed, especially for endurance athletes and its implication for the general population. We extrapolate the findings and the public health concerns provided by the snapshot of the lifespan trends of Olympians and supercentenarians. We addressed the issue of how the data analysis of sports may highlight physiological limits. The methodological considerations are presented, summarizing the limits and the strengths of this work, as well as the possibilities for future research in this field. At last the final conclusions are presented.

8.1 MAIN CONTRIBUTIONS

The main contributions of this thesis are: 1) the overall and cause-specific mortality description of elite French athletes involved in a wide range of sports, including female athletes; 2) the analysis of Olympians' longevity according to their type of effort, classified by duration of effort, a method which allows inter-studies comparisons; 3) the translation of differences in mortality rates among elite athletes into years of life gained due to specific causes of death; 4) new insights into human longevity trends.

Accordingly, we found that elite French athletes, whether female or male athletes, from all Olympic sports or from the professional cycling circuit, whatever the type of effort performed during their career, consistently show lower mortality rates when compared to their compatriots. These findings are mostly related to the lower mortality due to the athletes' major causes of deaths: CV and cancer diseases. No excess mortality was observed in any of the cohorts studied.

The elite athletes' lower mortality rates were translated into life years-saved revealing that French Olympians gain, on average, 7 years of life in relation to the general population for all types of effort performed at the Games. This gain was partitioned according to specific causes of deaths revealing that CV longevity benefits are associated with the type of sports practiced during an Olympic career. Most CV advantages were found among Olympians performing combined types of effort rather than efforts of very short or very long duration. In relation to cancer mortality, all types of effort studied were associated with greater longevity.

The usual explicative hypothesis advanced to account for elite athletes' greater longevity is the cohort selection effect, *ie* the comparison of a group of healthy subjects to a population including ill people at baseline. The findings evidencing differences on athletes' CV longevity according to the duration of effort performed show that the type of physical activity during an Olympian's career may actually play an important role on their longevity.

Despite having a longevity advantage, the lifespan of worldwide Olympians reveals that, up until now, none ever reached extremely great longevity, over the age of 110 years. Their lifespan trends progression has slowed in the past century; resulting in a densification phenomenon close to the upper limit. Similar trends among the longest living humans may be implicated in the current stagnation of the maximal human longevity. From the findings of elite athletes' lifespan trends, compared to supercentenarians, we support arguments of a biological barrier now limiting the continuous rise of human longevity.

8.2 HEATH ENHANCING PHYSICAL ACTIVITY

Overall, past studies almost exclusively assessed male elite athletes abroad and found similar results when comparing their mortality to the general population or to healthy references (Table 8.1).

Among all the factors distinguishing elite athletes from the general population, the intense physical activity they all endured may probably be the predominant factor. It may also be the common denominator between elite athletes from foreign countries and French athletes.

These findings gain greater importance in the context of a growing debate over the health effects of vigorous physical activity, particularly in light of the current society's paradox of an increasing number of sedentary people [357] concomitant to the increasing number of people engaged in vigorous training [358].

About one third of the world's population is now very inactive [359] increasing its risk of chronic diseases and mortality [52,360]. The current society favours a sedentary lifestyle that may prevent the latest life expectancy progression in high income countries [357]. Physical activity is a public health solution; it is cost-effective, with extended health benefits.

A holistic approach contemplating the whole population, from sedentary people up to elite athletes, is essential to fully cover all levels of exercise engagement and better understand its health benefits. Low doses, such as 15 minutes of physical activity per day, have been proven to reduce chronic diseases and mortality [52,325] compared to sedentary subjects. As for any medicine, an excessive dose can cause harm and even death in extreme overdoses [303,361]. Vigorous training, such as what elite athletes undertake, has been considered much superior to the so-called "too much" of exercise [74,362], being, therefore, highly controversial in regard to its overall benefits [358], so that its practice has been discouraged [301,361,363].

Table 8.1: Reviewed English-language scientific articles available in Medline and Web of Science databases on mortality/longevity of athletic cohorts composed solely of professional athletes or elite athletes using a cohort study design providing standard mortality ratio (SMR) with 95% CI.

Reference year	Cohorts	All-cause SMR (95% CI)	SMR due to CVD (95% CI)	SMR due to cancers (95% CI)	SMR due to external causes (95% CI)
Baron et al, 2012	N=3439 National Football League players with >5 pension-credited playing seasons from 1959 to 1988	0.53 (0.48,0.59)	0.68 (0.56,0.81)	0.58 (0.46,0.72)	0.37 § (0.28,0.46)
Gajewski et al, 2008	N=2113 (424 women) Female (F) and male (M) Polish participants in the Olympic Games from 1924 to 2000	F=0.73 (0.48,1.10) M=0.50 (0.44,0.56)	NI	NI	NI
Kalist and Peng, 2007	N=2641 Major US league baseball players who were born between 1945 and 1964	0.31 (0.23,0.39)	NI	NI	NI
Taioli, 2007	N=5389 Soccer players from the Italian professional leagues A and B between 1975 and 2003	0.68 (0.52,0.86)	0.41 (0.20,0.73)	0.31 (0.15,0.55)	DC
Belli et al, 2005	N=24,000 Italian professional soccer players active during 1960-1996 in the 3 top leagues (A, B, or C)	1.00 # (0.90,1.10)	0.83 # (0.69,1.00)	NI	1.01 # (0.90,1.30)
Kujala et al, 2001	N=2009 International Finnish competitors during 1920-1965 who were alive in January 1971	0.74 (0.69,0.79)	0.72 (0.64,0.82)	0.36 (0.24,0.52)	NI
Sarna 1993	N = 2613 International Finnish competitors 1920-1965, divided into endurance (E)*, Team Sports (T) and Power Sports (P)* The reference cohort, 1712 men from the Finnish Defence forces	E =0.59 (0.40,0.85) T=0.90 (0.69,1.16) P= 1.02 (0.82,1.27)	E=0.49 (0.26,0.93) T= 0.61 (0.41,0.92) P=1.04 (0.77,1.42)	E=0.36 (0.12,0.92) T=0.80 (0.47,1.35) P= 0.55 (0.33,0.92)	E=1.23 (0.31,4.89) T =1.86 (0.86,4.04) P =2.0 (1.04,3.82)
Waterbor et al, 1988	Professional baseball players in the United States between 1911 and 1915 who survived until 1925	0.94 (0.88,1.00)	NI	1.05 (0.89,1.22)	DC
Schnohr, 1971	N=297 Danish Elite athletes born between 1880 and 1910	1.00 (0.80,1.20)	0.95 (0.63,1.26)	0.94 (0.56,1.32)	DC
Studies 1 to 3					
Antero-Jacquemin et al, 2015	N = 2403 (601 women) Female (F) and male (M) French Olympic athletes from 1948 to 2010	F= 0.49 (0.26,0.85) M= 0.51 (0.45,0.59)	F=0.51 (0.08,1.69) M=0.55 (0.41,0.73)	F= 0.73 (0.30,1.52) M= 0.55 (0.43,0.69)	F= 1.42 (0.45,3.44) M= 0.66 (0.44,0.94)
Antero-Jacquemin et al, 2014	N = 203 French elite rowers, from 1912 to 2012	0.58 (0.43,0.780)	0.41 (0.16,0.84)	0.59 (0.29,1.07)	1.0 (0.38,2.29)
Marijon et al, 2013	N=786 French cyclists who competed in 1 or more editions of the Tour de France, from 1947 to 2012	0.59 (0.51,0.68)	0.67 (0.50,0.88)	0.56 (0.42,0.72)	1.06 (0.71,1.53)

§ causes of deaths may have been presented in the references using other classifications, but they were detailed enough in order to allow for a re-classification similar to the one we have used in our studies. NI = non investigated. # standardized proportionate mortality ratio. DC = Different classification. *Endurance = long distance runners and cross country skiing. *Power Sports = boxing, wrestling, weight lifting, throwers.

8.2.1 IS THE ELITE TRAINING REALLY “TOO MUCH”?

Epidemiological studies reporting a U-curve pattern between dose of physical activity and healthy benefits [301,312,361,364] in the general population established “too much” at the level when greater doses of exercise jeopardize the benefits. This will vary depending on the risks taken in account as well as the populations studied (and therefore the predispositions to physical activity).

“TOO MUCH” FOR WHICH RISKS?

Based on our findings, it appears that different types of intense training provide particular benefits and risks, and the “too much” dose depends, therefore, on the specific risk considered. Among elite French athletes, no risk was prominent enough to jeopardize the overall benefits of longevity.

Because their dose of physical activity is among the highest in the world, elite athletes are representative of the end of the physical activity dose “spectrum”. Thus, the findings of their longevity outcomes contribute to determine that even the least end of the dose-response relationship still remains positively associated with overall health, among subjects selected on the basis of their performance and sports predisposition.

“TOO MUCH” FOR WHICH POPULATIONS?

Such a finding needs to be understood in light of the elite athletes’ selection processes, as well their development to high level training. All passed through a filter designed to select the fittest ones. The healthier subjects with genetic predispositions to certain sports may also possibly come from favourable environments and social settings. They endure training from a very young age, allowing for a gradual acclimatization to greater loads of exercise before reaching the upper level [32,39]. In addition, most of them are closely accompanied by medico-technical staff along their careers. The overall health benefits demonstrated specially concerns a population that passed such filters. It is unknown the health outcomes of the athletes excluded during the multilevel selection process leading up to the elite.

Genetic predispositions have been proposed to favour parameters of physical fitness that could be related to disease prevention, partially explaining the lower mortality verified among elite athletes [244]. However, there is no evidence yet that elite athletes’ genetics is further associated with favourable disease-risk mutations or polymorphisms compared with controls [243], probably due to the complexity of such multi-level genetic associations.

In the previous studies displaying the U-shape curve [361,364] between dose of physical activity and overall mortality, the ends of the curves are represented by very small groups of subjects displaying much lower exercise doses (*i.e.*; \approx 1.5h/day) with

greater heterogeneity than in our cohorts of elite athletes. Furthermore, the process undertaken by the subjects to reach intense training is unknown. The gradual process to reach top level training with specialized assistance, in addition to a predisposition to sports among elite athletes, may explain part of the divergences in the dose-response relationship regarding intense training.

Therefore, we highlight a potential difference between an empirical “too much”, and the “too much for whom”. Better understanding of this difference may enhance the inclusion of people wanting to engage in intense sports while remaining outside the category of “high level”. In addition, a better understanding of the consequences of intense training may avoid claims which would discourage an already sedentary society to exercise, as recently seen in the press after a U-curve publication [364] under the headings: “Too much jogging can seriously damage the health” [365] or, “Training very hard 'as bad as no exercise at all' ” [366], even though the restricted number of subjects and low statistical power in the high-doses group did not provide such clear cut evidence [362].

Establishing the relationship between vigorous training and health benefits is also relevant for the sport movement and institutions willing to promote sports practice. The overall benefits demonstrated here support a positive impact associated with the capacity to train hard. This type of physical activity has a meaning for those who practice it, usually searching for a higher performance level that cannot be acquired with less intense circumstances.

The capacity of elite athletes to adapt to intense activity and obtain survival benefits may find rationale from an evolutionary perspective: humans are designed to move [68,367], and not to remain sedentary. The weighted evidence indicates that humans evolved in environments that required higher levels of mobility than those required today [367]. Energy balance has been a central selective force throughout evolution [368], and humans evolved with the highest levels of energy expenditure and yields [369] to reach their daily nutrients from the environment [367]. In that perspective, the recent inactivity levels measured in all continents and societies may have much larger consequences than what has been estimated so far [370].

Further research should prioritize the identification of specific risks related to a particular activity in order to minimize those and maximize the benefits obtained from physical activity.

8.3 CARDIOVASCULAR ASPECTS OF INTENSE TRAINING

Our findings suggest either that intense training at early ages have positive long-lasting effects on health or that the selective methods of detection and training (including resilience to this intense process) select athletes with predisposition associated with survival advantage. Both however contribute to the health benefits that may vary according to the types of activity performed. It is expected that different training types provide different benefits due to specific physiological demands and body responses. This may explain the heterogeneity demonstrated among Olympians' CV longevity: the greater benefits were found among combined types of efforts, saving on average 2 years of life from CV diseases while no differences with the general population were demonstrated among athletes performing efforts of very short- (power and precision) or very long- (endurance) duration.

However, what is intriguing is that the endurance training that is the type of effort which produces the largest CV benefits with low-to-moderate doses of training, such as jogging [52,54,325], did not show any long-term CV benefits among endurance Olympians (such as long distance runners). This may be an example of "too much" dose from a type of physical activity (endurance) according to a specific risk (CV diseases) for this population (elite athletes). The absence of CV benefits for this highly selective cohort of endurance athletes may draw attention to a possible risk of intense endurance training to the CV system.

This is an important advancement of the topic since, to the best of our knowledge, it is the first demonstration of CV longevity in elite athletes associated with the type of effort performed.

Clinical findings - and animal models - suggested that chronic endurance effort may foster abnormal changes in a previously normal heart [97,266,275,281,303,307,308,361,371]. In a recent long-distance, cross-country ski study, the investigators found a higher risk of developing arrhythmias in those who had completed more races; myocardial damage for marathon runners were also demonstrated [93,362,372]. However no long-term relation was made with longevity until now.

Even though the absence of CV advantage in highly-selected endurance athletes compared to the general population may be considered as an adverse effect of intense endurance training, care must be taken in order to avoid alarming messages. We may advocate that even with no CV benefits, elite endurance athletes still display greater overall longevity.

Without scaremongering, concerns may also be raised about concrete risks for the general population. Though physical activity in the general population is less intense than among Olympic athletes, some people may also be more vulnerable, less predisposed to sports, and with lower medical surveillance. Nowadays, over 2 million people in the United States alone are enrolled in long distance races [79]. Most of the researches on the CV impact of intense endurance training in the general population focus on immediate or short-term risks, such as sudden death or clinical effects post-effort. In this matter, the incidence of sudden death in marathons are extremely low, which may not justify the systematic screening measures in this population [79,80]. The alterations commonly observed in the hearts of marathon and ultra-marathon runners, sometimes result in myocardial damage, but most seem to be transitory [373,374]. Yet, it is not clear if consecutive bouts of post-exercise dysfunction impact the runners' hearts on the long-term and reduce longevity in the general population [374].

Recent researches started to use mortality evaluation to determine the long-term CV consequences of chronic participation in long races in the general population. However, some of the methodological problems in survival analysis for elite athletes have also been present in these researches investigating the general population. Among the few studies conducted on this topic, the methods used to specifically discriminate CV risk from other risks have been shown to be misleading by using flawed tools when describing the differences in longevity (resulting in life years lost due to specific diseases being greater than the total number of years lost to all causes of death, *e.g.* [312]). In an attempt to translate mortality changes to longevity gains, the comparison of life expectancy among groups with different age-classes provide potentially faulty values, even though the findings relying on mortality rates are not compromised (*e.g.* [52]). An additional statistical artefact comes from the exclusion of deaths from causes that are not the cause of interest, instead of censoring them (*e.g.* [312]).

Based on the absence of CV benefits in endurance athletes (for whom we would have expected it to be among the greatest ones), further studies relying on proper methods of survival analyses are necessary to understand the CV risk in the general population – as well as replicated studies on elite athletes - related to chronic participation in long distance races.

According to the current evidences, to adhere to The Physical Activity Guidelines recommendations, a mix of efforts (aerobic and strength training) seems optimal for those aiming for CV benefits (« 2008 Physical Activity Guidelines for Americans » 2008; Church et al. 2010; Sigal et al. 2007).

8.4 HUMAN LONGEVITY TRENDS

The cardinal results from the study of lifespan trends of Olympians and supercentenarians demonstrate the current stagnation of human maximum longevity, strengthening arguments of a biological barrier limiting further progression. It is a difficult message to agree with as it means accepting the possibility of a physiological limit constraining the hope of a durable increase of our longevity. Yet, these boundaries delimit the scope of action for important public concerns.

Resistances to this message have appeared after the media disclosure of the study, expressing this kind of denial: "nothing opposes much longer longevity, because our own antibodies, taken directly from our birth and kept preserved in banks of immune cells will restore our organs into our twenty years [375]".

We are among the generations that have experienced a dramatic increase in life expectancy - from about 40 years for our great-grandparents to more than 80 years now. Why should we expect a limit?

To address this issue, we voluntarily extrapolate the discussion of our findings. For that purpose, we confront the two aspects that could potentially interact with human lifespan : i) our biology is physiologically limited, or ii) our biology is malleable (in a relatively short evolutionary period) [336].

In the first case, the medical, social, technological, and environmental efforts invested for progresses in longevity would just bring more people towards the upper limit, resulting in a general trend of densification of the human phenotypic expression [341]. By being biologically limited, despite all efforts invested, this inherently determined limit would be exceeded only by rare exceptional subjects taking advantage of a maximum of highly favourable conditions, but it would not constitute a demographic movement of public implications, that would be much larger than the current one [376].

In the second case, some considerations are presented here, which assume the possibility of limit modulation. First, among all possibilities of a reaction norm [377] a phenomenon of phenotypic expansion occurs when environmental constraints are favourable [234]. In the early twentieth century, vaccines and hygiene recommendations appeared, reducing infant mortality, registering an unforeseen increase in life expectancy. It has been followed by economic growth, wealth, and better living conditions, allowing greater investments in research and technology, producing better health care and continuous increases in life expectancy [378]. But this development comes with an intense environmental degradation, resource depletion, pollution, and, more recently, the resurgence of infections and economic decline allowing us to believe it will be more difficult now to have gains in life expectancy than it was at the beginning of

the twentieth century [356,379]. Also, gains in life expectancy are much larger when decreasing infant mortality rather than reducing senile mortality [378].

Despite the remarkable increase of life expectancy of the world's population [380], one or two centuries of progress is a very short period in terms of human evolution, not allowing, at least not yet, for the adaptation and selection of a different genetic constitution [381].

A pioneer work on a healthy supercentenarian [382] demonstrated that, at 115 years old, only two stem cells were left in her blood from the approximate 11,000 present at birth. This stresses the dependence of our biological constitution: once stem cells reach a state of exhaustion, this also may impose a limit on lifespan. Stem cells gradually die out and steadily diminish the body capacity to regenerate vital tissues and cells.

Therefore, at the crossroad of a stable genetic constitution and a degrading environment, the slowing down of the current progress sounds to be a reasonable forecast due to increasing constraints.

8.4.1 SPORT AND PHYSIOLOGICAL LIMITS

Parallel to the longevity stagnation displayed by the longest lived humans, Olympians show similar trends. This is not the first biological limit inspired by the analysis of historical data from elite athletes.

The trends of sport records have already been subject to similar inquiries. In 2004, Tatem and colleagues [383] in one of the best two science journals, claimed a linear trend progression of racing speed records (Figure 8.1), suggesting an unlimited progress of human performance, similar to linear progresses of life expectancy [333] supported by prolongivists (Figure 8.2).

In relation to the trends in sports' records, the proposed linearity has been strongly rejected, based on the demonstrations that human performances follow an exponentially decaying function instead and the current world records are approaching an asymptote [217,384–388]. The incoherence of both forecasts is probably to analyze the data ignoring the underlying biological functions.

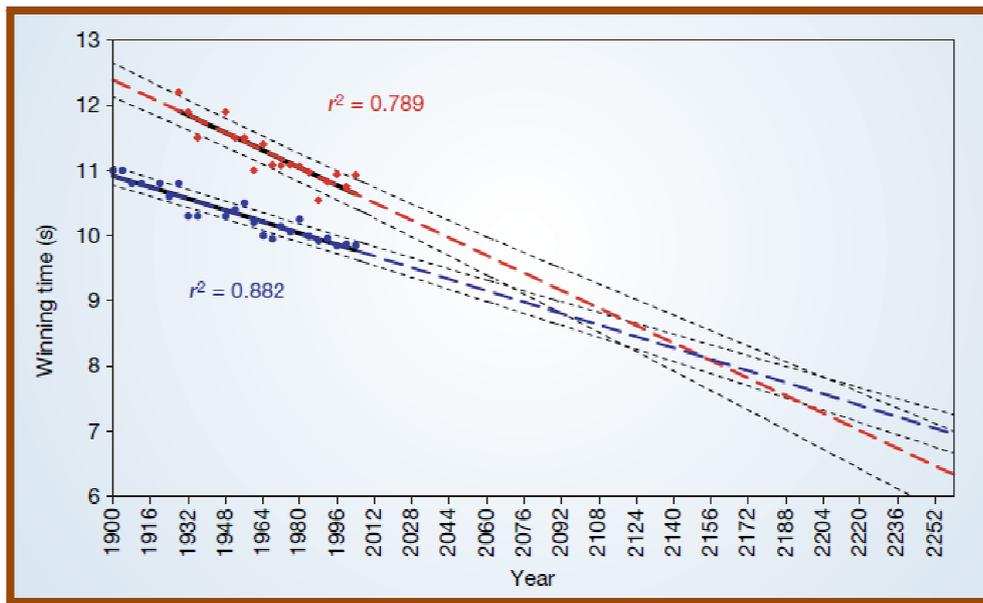


Figure 8.1: The winning Olympic 100-metre sprint times for men (blue points) and women (red points), with superimposed best-fit linear regression lines (solid black lines) and coefficients of determination. The regression lines are extrapolated (broken blue and red lines for men and women, respectively) and 95% confidence intervals (dotted black lines) based on the available points are superimposed. The projections intersect just before the 2156 Olympics, when the winning women’s 100-metre sprint time of 8.079 s will be faster than the men’s at 8.098 s. From Tatem et al, Nature, 2004 [383].

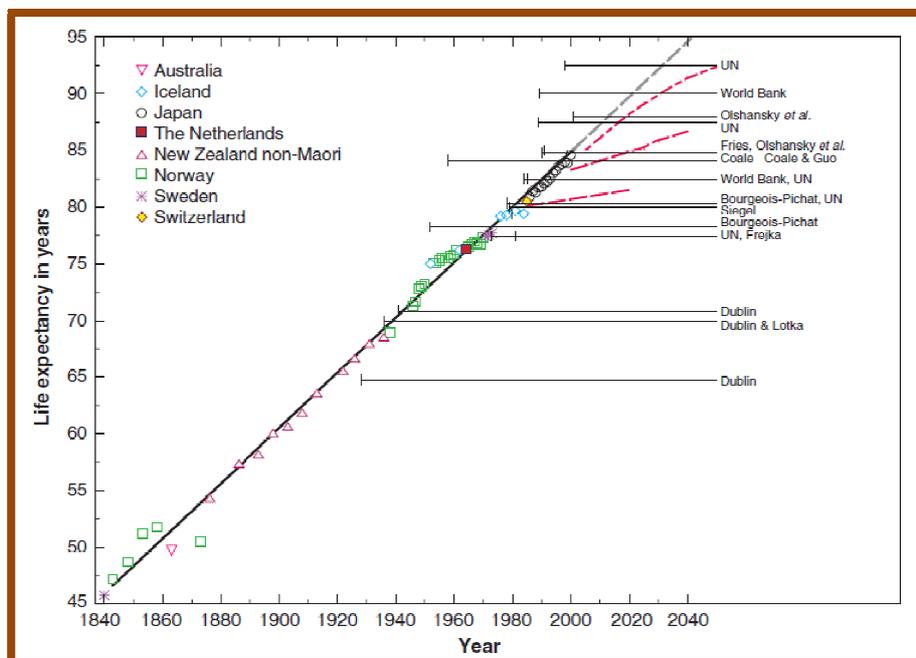


Figure 8.2: Record female life expectancy from 1840 to the present. The linear-regression trend is depicted by a bold black line and the extrapolated trend by a dashed

gray line. The horizontal black lines show asserted ceilings on life expectancy, with a short vertical line indicating the year of publication. The dashed red lines denote projections of female life expectancy in Japan published by the United Nations in 1986, 1999, and 2001. From Oeppen and Vaupel, *Science*, 2002 [333].

The twentieth century was full of record-breaking, distance running performances, which are similar to longevity records among exceptional survivors. For instance, the world record for running one mile has improved from 4'28" in 1852 to the actual world record established in 1999 of 3'43"13. Following an exponential decaying function [217], we should not expect it to fall by 3.5 seconds or more [389]. That would mean that when Hicham El Guerrouj established the world record 16 years ago, he was running to within 1.5% of maximum human capacity [389]. Because this is so close to a possible maximum, it is becoming almost impossible to beat: that's the longest time the world record mile has ever been unchanged, despite the fact that the world has more runners with better technical and technological support than ever before [389]. The closer we approach a limit, the more the pressure increases, limiting progress and resulting in a phenomenon of densification such as the one we demonstrated among Olympians and supercentenarians.

Accordingly, human world records, whether represented as speed races or maximum lifespan, may no longer be broken except for technological outburst. If there were no limit to life expectancy, longevity would be the first biological trait with no upper limit [390]. Leonard Hayflick, owner of the eponymous *Hayflick Limit*, which refers to the finite number of times that normal human cells can divide (about 50) before they succumb to senescence, illustrated the relation of performance in sports and lifespan: "to imagine that the current rate of life expectancy increase will continue indefinitely is as absurd as extrapolating the diminishing time taken to run a mile and concluding that it will sooner or later be done in one second" [391].

Even among a cohort of Olympians with a survival advantage, showing intense densification after 80 years old, none reached the status of a supercentenarian, showing how exceptional is to become one of them. The accessibility to exceptional performance is another aspect for which sports performance provides a good illustration: "It is tempting to hold up the cohort of supercentenarians as an example of what is theoretically achievable for all, but this would be equivalent to declaring that because few exceptional athletes can run one mile in four minutes, everyone should therefore be able to do so" [376].

In biology most variables show an asymptotic limit [390], as it is observed for world records in sports as rare individuals approach the limit boundaries. Another

example is adult height. The rate of increase between successive birth cohorts is decreasing in younger cohorts of Western European countries known to have the tallest people (*e.g.* Denmark, Netherlands or Germany) as mean human height may start to show some early signs of a plateau [390,392].

In the light of our results and the considerations presented, it is noteworthy to consider an increasing part of the population becoming older. This gathers greater proportions of elderly people becoming closer to the potential lifespan upper limit. The interest to anticipate it is to regulate and demystify forecasts, which is of important societal implications. The difficulty in managing the care of the great number of elderly people is already a reality and the economic costs may become extremely high. Especially in the presence of health constraints, for instance, France has shown an expansion of certain disabilities with early onset [393], whereas large gaps has been observed among European countries for the life expectancy in good health [394]. In the scenario of limited longevity, the interest on strategies for increasing the quality of life reaches even greater importance.

8.5 METHODOLOGICAL CONSIDERATIONS

8.5.1 LIMITS

The main limits were systematically discussed within each study according to its specificities. The limits of the present work are globally related to the following aspects: no causal inference can be made at this point between elite career parameters and their greater longevity, particularly because only age and period could be adjusted for potential confounding factors. In addition, the constraints upon elite athletes during their careers were not assessed and their lifestyles post-career is unknown. Comparing selected subjects with a reference population that include subjects with many health status from all backgrounds is another classical limit, though it can be discussed in a very different way when studying the exhaustive range of human capabilities. We also acknowledge that the eligibility restrictions of subjects to enter the studies and important exclusion criteria limited more subgroup analyses.

8.5.2 STRENGTHS

The strength of this work relies on an extensive follow-up of the highest-level athletes from different sports and for both sexes based on national vital status and death certifications.

The methods applied fulfil the Strobe recommendations [395], but three specific methods stand out as possibly providing the main original contributions: time of performance to categorize main types of physical effort, the years-saved method, and the analysis of lifespan densification trends.

TIME OF PERFORMANCE TO CLASSIFY TYPES OF PHYSICAL EFFORT

The estimation of the type of effort through performance time provided an easy and universal measure which allowed to classify a century of a wide diversity of sports' events under a constant criterion. It showed to be fairly discriminative of different types of effort and may be easily applied in future studies.

THE YEARS-MAILED METHOD

The years-saved method under competing risks is a solid method adapted to the specificity of our study, which provides an easier interpretation of longevity findings with the additional attractiveness of its positive output. This method may be useful when assessing specific longevity benefits of exercising, which is a growing research field.

ANALYSIS OF LIFESPAN DENSIFICATION TRENDS

The human longevity trend has strongly divided researchers with no compromise between claims of unlimited longevity extension or of limited biology. Each side supports its conclusion by completely different approaches investigating longevity trends. We proposed here an intermediate approach through novel tools. A densification analysis (total number of life durations per birth date) reveals distinct lifespan trends according to the number of subjects and time. Hence, it allows for a highly informative description of lifespan upper limits and its relative relevance within the wide range of lifetime values. By adding elite athletes' data analysis, we provided real data (not an estimation) of a worldwide, well-defined population including all ethnicities, with proven survival advantages that most optimistic forecasts would not expect to be reached within a near future.

8.6 PERSPECTIVES

Because of the richness of this subject and lack of studies, the realm for new research questions on elite athletes' mortality and human longevity is vast.

Further research should now focus on elite athletes' morbidities and quality of life, especially in light of their overexposure to injuries. Even if such constraints do not seem to affect survival rates, it remains unclear whether elite athletes' greater longevity is accompanied by higher morbidity and to what extent it may affect their quality of life.

In addition, disease-specific studies assessing larger samples of elite sportswomen are necessary to better understand the causes of death that are associated with their lower overall mortality.

From a public health point of view, the relationship between the type and dose of exercise and the specific health benefits produced needs to be better understood in order to precise the prescription of physical activity. Identifying the risks related to types of training is equally relevant. The findings regarding elite athletes' endurance and long-term CV outcomes require replication in other elite populations as well as in subjects from the general population subjected to equivalent type of training.

8.6.1 PERSPECTIVES ACCORDING TO PILOT STUDIES

Some exploratory studies performed during this work have also provided insights into new hypotheses that could be investigated.

ENVIRONMENTAL CONDITIONS AND ELITE ATHLETES' MORTALITY

We have exploited the differences on survival of Olympians training outdoor in the cold weather. The interest relies on previous studies reporting that chronic intense training may be deleterious to the respiratory tract of elite athletes due to the high ventilation in such environment [98,396,397].

We, therefore, categorized the Olympians' cohort (described in the study 4) into outdoor and indoor athletes and performed a Kaplan-Meyer analysis, adjusted by sex and year of entry in the cohort, according to summer or winter games. A log-rank test was used to test differences on survival curves.

We found no significant differences (Figure 8.3) on overall survival of indoor or outdoor Olympians whether in summer ($p = 0.051$) or winter ($p > 0.05$).

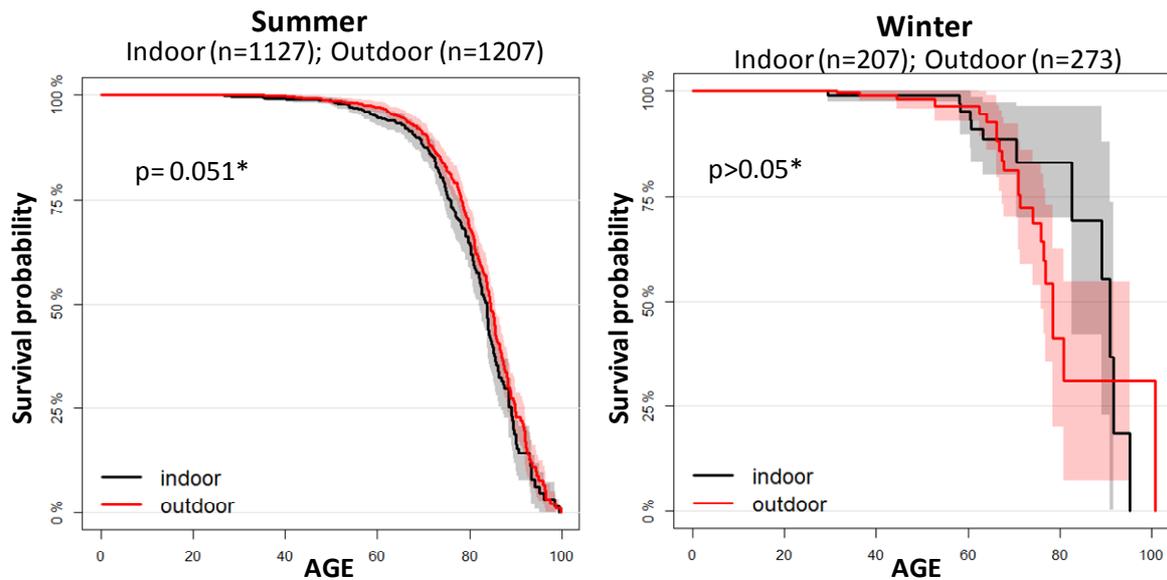


Figure 8.3: Survival probability of Olympic athletes participating in events indoor and outdoor, in summer and winter Games.

However, different trends seemed to appear. In summer games, outdoor athletes display trends of better survival functions than indoor athletes, while the opposite seemed to occur in winter games. Researchers have reported that winter athletes have high prevalence of respiratory symptoms with potentially long-term consequences [397]. Therefore, a study could be proposed using the years-saved method to investigate differences due to respiratory diseases. This pilot analysis highlighted the interest to pursue such a hypothesis relying on greater samples.

SPORTS UNDER PARTICULAR CONSTRAINTS

We observed that some high level practices may expose the athletes to more immediate risk of death, related to the sports constraints, such as downhill at high speed on a bike during the TDF. Then, another important goal might be to study high inertia sports, such as motor race pilots, or extreme sports like skydiving, surfing, and mountaineering. To access the causes of deaths in these cohorts may allow exploiting the hypothesis of greater mortality by accidental deaths in this population.

Finally, sports with specific constraints may contribute to a better understanding of the respective roles of physical activity and cohort selection in elite athletes' longevity. This may also be the case for chess players (high cognitive demand associated with a sedentary behaviour); the sumo fighters (high level of activity associated with overweight constraints); and Paralympic athletes (high level of performance associated with various types and degrees of handicap).

8.7 CONCLUSION

This research addresses the longevity and causes of mortality in elite athletes. Based on cohort studies, we found that French elite athletes show consistently lower mortality ($\approx 40\text{-}50\%$ lower) than their compatriots, whether female Olympians, male Olympians, or professional cyclists, mostly related with a lower cardiovascular ($\approx 40\text{-}60\%$ lower) and cancer mortality ($\approx 45\%$ lower). No excess mortality was observed in elite athletes for any of the specific causes of death we studied.

Our work evidenced heterogeneous CV longevity among the groups of athletes classified according to the type of effort they performed in the Games. Combined types of effort display the greatest CV longevity. Endurance effort, which usually procures most benefits to the cardiovascular system at moderate doses of training, shows among Olympians no CV advantage in relation to the general population. The same can be observed for short-duration efforts, like in power or precision sports. Yet, all types of effort saved seven years of life on average in relation to the general population, from which two years on average are saved from cancer diseases.

Despite their survival advantage, no Olympian in the world, to this date, has ever reached the status of a supercentenarian; the longest-lived was 106 years old. Their lifespan trend progression has slowed in the past century, resulting in a densification phenomenon close to the upper limit. Similar but intensified trends among the longest-living humans imply a current stagnation of the maximal human longevity strengthening arguments of a "biological ceiling" limiting further progression.

9

SYNTHESE

En accord avec

l'article 11 de la loi du 4 août 1994 relative à l'emploi de la langue française: « La langue de l'enseignement, des examens et concours, ainsi que des thèses et mémoires dans les établissements publics et privés d'enseignement est le français [...] » Art. 8 de l'arrêté du 18 janvier 1994 : « Lorsque cette langue n'est pas le français, la rédaction est complétée par un résumé substantiel en langue française »,

une synthèse substantielle de la thèse est présentée en langue française.

9.1 LONGEVITE ET CAUSES DE MORTALITE DE L'ELITE SPORTIVE

ACTIVITE PHYSIQUE ET BENEFICES POUR LA SANTE

Les bénéfices sanitaires de la pratique d'une activité physique régulière et modérée sont bien connus en population générale [51,52]. La littérature scientifique fournit des preuves majeures d'une meilleure santé physique et mentale pour ces pratiquants de toutes classes d'âge. Des bénéfices au niveau du système cardiovasculaire, respiratoire, immunitaire, nerveux, métabolique, musculaire, osseux ont été largement rapportés [53]. L'exercice a un caractère reconnu de prévention, de traitement et de réhabilitation de plusieurs maladies chroniques, ayant un impact majeur sur la mortalité [54,55,274].

Toutefois, la relation entre dose d'activité physique et bénéfices sanitaires n'est pas bien établie : l'impact de la pratique intense sur la santé est actuellement débattu, notamment sur le plan cardiovasculaire.

La quantité minimale d'activité physique impactant positivement la mortalité a été étudiée sur une cohorte prospective de 416 175 sujets [52]. Cette étude a montré que 15 minutes d'activité physique par jour génère déjà des bénéfices, entraînant une réduction de 14% de la mortalité globale.

Les recommandations mondiales actuelles, préconisées par l'OMS, sont de pratiquer un minimum de 30 minutes d'activité physique par jour pour des personnes âgées entre 18 et 64 ans. L'ensemble de ces mesures englobent les activités de loisirs, les déplacements, les activités professionnelles, les tâches ménagères, les activités ludiques, les sports ou l'exercice planifié. Pour tirer des bénéfices supplémentaires, la recommandation est d'augmenter la durée d'activité, en maintenant une intensité modérée, allant jusqu'à 300 minutes par semaine.

POPULATION D'ETUDE

La population des sportifs d'élite est soumise à des charges d'entraînement de 5 à 10 fois supérieures aux recommandations [39], avec de potentielles répercussions négatives sur leur état de santé [73,89,97].

L'élite sportive est composée d'athlètes de haut-niveau, ayant atteint le niveau le plus élevé de leur discipline, leur permettant d'accéder aux championnats les plus relevés au monde. Pour la plupart des sports dits amateurs, l'apogée sont les Jeux Olympiques (JO). Pour les sports professionnels, les manifestations majeures se déterminent par l'investissement financier, médiatique et par la concurrence [1,2], les compétitions les

plus prestigieuses étant également réservées aux meilleurs athlètes au monde. Ainsi, le Tour de France (TDF) est à un cycliste sur route, ou la Coupe du Monde à un joueur de football, ce que les Jeux Olympiques sont à un gymnaste. La participation aux championnats internationaux les plus prestigieux reste ainsi réservée à une minorité de sportifs exceptionnellement performants.

CRITERE DE SELECTION

La performance sportive peut être définie comme l'exécution d'habilités physiques et cognitives en pratique sportive par des athlètes entraînés, mesurée par le temps, par la distance ou par le classement. La performance des athlètes élites est ainsi un marqueur de leurs capacités physiologiques et c'est donc le critère qui délimite précisément l'élite sportive mondiale, les distinguant des athlètes de niveau inférieur ou de la population générale.

La performance sportive est le résultat d'une combinaison de caractéristiques permettant sa classification en tant que trait multifactoriel [23,31]. Les performances suivent ainsi une distribution quantitative polygénique [47,48,289]. En conséquence, la prédisposition à un phénotype⁶ donné est distribué dans la population selon une courbe en forme de cloche [43,47]. Les athlètes d'élite occupent l'une des extrémités de cette courbe. Ils sont alors les « outliers » d'une population en termes de capacités physiologiques maximales et leurs performances ouvrent un champ privilégié pour l'analyse de la physiologie humaine [50].

Pour atteindre un tel niveau de performance, des prédispositions génétiques et environnementales sont un pré-requis [31], couplées à de très fortes charges d'entraînement pendant de longues années [32,33]. L'entraînement module l'interaction génome-environnement afin de maximiser la performance.

L'excellence sportive parmi les athlètes élite est corrélée aux heures cumulées de pratique [34,35]. Le modèle d'expertise largement répandu suggère un minimum de 10000 heures d'entraînement cumulées sur une période d'environ 10 années de pratique structurée afin d'atteindre l'élite [36,37]. Bien que ce modèle soit critiqué [38], rares sont les athlètes atteignant le niveau élite avant 10 ans de pratique sportive intense [40]. Le temps total de pratique des athlètes élite représente donc une part importante de leur vie : pour une personne vivant 80 ans, c'est environ 20 à 30% du temps total qui a été consacré au sport, en prenant en compte l'ensemble des années investies depuis l'enfance [39] et les années de maturité athlétique [41,42].

⁶ Correspond à l'ensemble des caractères observables d'un individu, résultat de l'expression du génotype, c'est-à-dire, l'expression des gènes en interaction avec l'environnement.

CONTRAINTES SUR L'ÉLITE SPORTIVE

Un certain nombre d'études démontre que l'exercice à très haute intensité, et spécialement celui en endurance, pourrait avoir un impact néfaste sur le système cardiovasculaire [89–91] tel qu'une élévation des troponines [92], un remodelage [91] ou des calcifications coronaires [93], une fibrillation ou un flutter auriculaire [90,94].

Un seuil de 1500 heures à haut niveau a été proposé, au-dessus duquel l'exercice déclencherait de plus fréquentes arythmies parmi les athlètes d'endurance [95]. Or, depuis la réintroduction des Jeux modernes en 1896, l'entraînement et le niveau d'intensité physique des athlètes olympiques n'ont cessé de croître, se distinguant de plus en plus clairement de celui de la population générale [96]. La progression de la concurrence mondiale a généré un processus de sélection qui a entraîné une importante augmentation du volume d'entraînement. Cause ou conséquence, les intensités d'entraînement des athlètes élités sont devenues très élevées et le seuil de 1500 heures est largement dépassé, parfois en moins de 2 ans [39].

Dans cette optique, des chercheurs défendent l'idée que le volume d'entraînement subi par les athlètes élités puisse être comparé à une « overdose » de médicament. La dose idéale est bénéfique mais l'excès serait délétère [74,89,97]. Ainsi, un remodelage structurel et électrique du cœur induit par l'exercice extrême et chronique, pourrait annuler une partie ou la totalité des avantages que l'exercice modéré confère au système cardiovasculaire sur le plan de la longévité [97,301,358,363]. En accord avec ces arguments, des auteurs proposent que l'exercice extrême chronique annihilerait les bénéfices de l'activité physique, rendant l'athlète élite comparable aux sujets de la population générale ne pratiquant pas d'activité physique [89]. Une courbe en «U» était ainsi proposée pour ces athlètes, illustrant l'association entre charge d'entraînement et risque pour la santé [73]. Les athlètes élités, notamment d'endurance, seraient alors exposés au même risque de mortalité que les sujets sédentaires [74,89].

Les contraintes sur l'élite sportive augmentent par l'intensité et la durée d'exposition lors de l'entraînement et des compétitions, soumettant les sportifs à des blessures récurrentes et aux accidents. Ceux-ci sont étroitement liés à leur pratique, avec un large éventail de conséquences, impactant possiblement leur santé à long-terme [103,107,192].

A ces contraintes s'ajoute un mode de vie particulier visant à optimiser leur performance [162–164]. Il est rapporté que les athlètes élite ont en général une bonne hygiène de vie, pendant et après leur carrière, favorisant une meilleure santé [163,164]. Mais d'autres pratiques comme l'utilisation de produits dopants, pourrait en avoir des conséquences néfastes [125,126,130,132,133].

L'ensemble de ces contraintes, (charge d'entraînement totale, surexposition aux blessures et accidents, hygiène de vie et, dans certains cas, l'utilisation de produits

dopants) entraîne des bénéfices et des risques possiblement impactant la mortalité des sportifs d'élite.

ETAT DE L'ART

Cette thèse s'interroge donc sur la mortalité et la longévité des meilleurs sportifs, en particulier par rapport à la population générale, pour laquelle l'élite représente l'une des extrémités d'une courbe de distribution des capacités physiologiques.

L'état de l'art sur le sujet révèle que la longévité ou la mortalité des athlètes français n'ont jamais été rigoureusement étudiée auparavant, que ce soit parmi les professionnels ou les amateurs, hommes ou femmes. Le peu d'études réalisées sur des cohortes d'athlètes étrangers [96,125,171-175,177-179] ne sont pas facilement transposables aux athlètes français. Leur mortalité ou leurs causes spécifiques de décès demeurent inconnues.

De plus, l'appui sur des méthodes erronées pour l'analyse de survie, identifiées sur des études antérieures, ont rapporté des différences de longévité entre cohortes potentiellement biaisées (*e.g.* [201,205,206]). En outre, la révision de la littérature montre qu'il n'y a pas d'études ayant estimé des différences de longévité (soit en gain, soit en perte) entre l'élite sportive et la population générale en fonction des causes spécifiques de décès.

Enfin, une analyse exploratoire des tendances de durée de vie des athlètes élités afin d'aborder les tendances actuelles de la longévité humaine n'a jamais été faite auparavant. La durée de vie est un trait multifactoriel, comme l'est la performance sportive [47,48]. Rapprocher l'analyse des données de l'élite et de la population générale pourrait permettre une compréhension de la longévité humaine sous un autre angle, original et instructif.

9.1.1 L'OBJECTIF PRINCIPAL

L'objectif principal de cette thèse est ainsi d'investiguer la longévité et les causes de mortalité des athlètes élités Français. L'intérêt de porter l'investigation sur cette population réside aussi dans leurs particularités physiques, biologiques, psychologiques ou sociologiques d'*outliers*, occupant l'extrémité de la courbe de distribution des capacités humaines. Ces caractéristiques permettent de développer de nouvelles approches pour apprécier les tendances de la longévité humaine.

9.1.2 METHODES

Nous avons fait un recueil exhaustif des données biographiques et de performance sportive de l'ensemble des athlètes Français ayant participé aux JO de 1912 à 2012 (n = 4708) et de l'ensemble des athlètes français ayant participé au TDF depuis 1947 jusqu'à 2012 (n=786). Ensuite, nous avons vérifié, auprès du Répertoire National d'Identification des Personnes Physiques (RNIPP), les statuts vitaux de l'ensemble de ces athlètes. Pour les sujets concernés, nous avons examiné leurs causes de décès auprès du Centre d'épidémiologie sur les causes médicales de décès (CépiDc).

Pour une approche descriptive de la mortalité des sportifs en comparaison à la population générale, nous nous sommes appuyés sur des méthodes d'analyse différentielle des taux de mortalité, la « *Standardized Mortality Ratio* » (SMR) et la méthode de *Kaplan-Meier*. Nous avons ainsi comparé la mortalité globale et par cause spécifique de décès de l'élite sportive avec les tables de mortalité civile de la France (selon chaque chapitre de la classification internationale des maladies). Nous avons utilisé le teste de log-rank [237] pour vérifier les différences entre les courbes de survie des cohortes d'athlètes et celle qui serait attendu s'ils apercevaient les mêmes taux de mortalité que la population générale.

9.1.3 MORTALITE DES ATHLETES ELITES FRANÇAIS

ETUDE 1

Nos résultats révèlent que les Olympiens français, tous sports confondus, présentent une mortalité globale réduite de 50% environ. La mortalité globale chez les hommes par rapport à leurs compatriotes est réduite de 49% (SMR = 0,51; IC 95% : 0,45 ; 0,59). De même, les femmes, qui n'avaient pas fait l'objet d'étude comparable auparavant, présentent un avantage en termes de survie tout aussi important : une mortalité réduite de 51% (SMR = 0,49; IC 95% : 0,26 ; 0,85). La survie des athlètes olympiques est significativement supérieure à celle de la population générale française (femmes: p = 0,03; hommes: p <0,001). Par rapport au nombre total de décès survenus entre 1968 et 2012, les Olympiennes sont décédées majoritairement de cancer (50,0%), suivi des causes externes de décès (i.e. accidents, homicides, 33,3%) et des maladies cardiovasculaires (16,6%). Les principales causes de décès chez les hommes sont liées aux cancers (36,1%), aux maladies cardiovasculaires (24,3%) et aux causes externes (14,4%). Les principales causes de décès chez les Olympiens sont toutes significativement réduites : les cancers (SMR=0,55 ; IC 95% : de 0,43 ; 0,69), les maladies cardio-vasculaires (SMR = 0,55 ; IC 95% : 0,41 ; 0,73) et les causes externes (SMR= 0,66 ; IC 95% : 0,44 ; 0,94). Les Olympiens ont également un risque très inférieur de maladies du système digestif (SMR = 0,52 ; IC 95% : 0,26 ; 0,91), de

troubles mentaux (SMR = 0,23 ; IC 95% : 0,02 ; 0,85), de maladies du système respiratoire (SMR = 0,15 ; IC 95% : 0,03 ; 0,45) et de maladies endocriniennes ou métaboliques (SMR = 0,12 ; IC 95% : 0,01 ; 0,69). Les classes d'âge de 25-34 ans à 75-84 ans montrent toutes une réduction significative de la mortalité générale. La réduction la plus importante a été observée parmi le plus jeunes (SMR = 0,19 ; IC 95% : 0,05 ; 0,48).

Des analyses similaires ont été élargies à deux autres cohortes plus homogènes d'un point de vue physiologique et sportif.

ETUDE 2

La première s'est concentrée sur l'élite de l'aviron français. La littérature scientifique décrit leur type d'entraînement comme une source possible d'altérations cardiaques. Nos analyses portant sur un siècle de suivi (1912-2012) révèlent au contraire une importante réduction de la mortalité générale des rameurs (SMR = 0.58 ; IC 95% 0,43 ; 0,78) et aussi cardiovasculaire (SMR = 0.41 ; IC 95% : 0,16 ; 0,84) par rapport à la population générale. Leur courbe de survie est significativement différente de la courbe attendue provenant de la population générale française ($p = 0,008$).

ETUDE 3

La deuxième étude, composée d'une cohorte de cyclistes professionnels du TDF, a fait objet d'un intérêt particulier en raison de la haute demande physiologique de cette épreuve associée à de nombreux aveux de dopage [130,271,272]. De façon similaire aux cohortes précédentes, les cyclistes présentent une réduction de la mortalité générale de 41% (SMR = 0,59 ; IC 95% : 0,51 ; 0,68) sans variation significative tout au long de la période de suivi ($p = 0,70$). Cette mortalité diminuée est principalement liée à un risque diminué de décès par cancers (SMR: 0,56; IC 95% : 0,42 ; 0,72) et de maladies cardiovasculaires (SMR = 0,67 ; IC 95% : 0,50 ; 0,88). Une mortalité légèrement augmentée a été observée parmi les plus jeunes liée aux accidents pendant la carrière. Contrairement aux Olympiens, les causes externes de décès chez les cyclistes ne sont pas significativement réduites par rapport la population générale (SMR = 1,06 ; IC 95% : 0,71 ; 1.53).

9.1.4 LONGEVITE PAR TYPE D'EFFORT

Ces études ont fourni une appréciation globale de l'état de la mortalité des athlètes élités français, répondant au premier objectif de cette thèse. Ces analyses descriptives ont été nécessaires pour construire l'embase de futures études, étant donné que la mortalité des athlètes élités français était inconnue, et a fait émerger de nouvelles hypothèses plus précises. Les études sur la mortalité par cause spécifique de

décès chez les Olympiens et les cyclistes ont fait ressortir des différences liées par exemple aux causes externes de décès.

Ces différences suggèrent des risques spécifiques liés aux contraintes physiologiques de chaque pratique sportive, pouvant impacter d'une manière particulière les causes de décès. Mais cette différence ne peut pas être clairement distinguée à travers les analyses globales de mortalité, comme celle fondée sur la standardisation indirecte de la mortalité.

L'entraînement intense d'endurance, c'est-à-dire la répétition prolongée d'une action sportive soutenue dans la durée, est le type d'entraînement qui a été le plus sujet à controverses. Les conséquences cardiovasculaires à long-terme en réponse à ce type d'entraînement sont d'intérêt particulier [97].

Des études antérieures ont montré une mortalité réduite chez les athlètes élités par rapport à la population générale, mais aucune n'a investigué l'impact du type d'effort sur la longévité cardiovasculaire des athlètes. A ce manque d'études s'ajoute une absence de méthodes appropriées pour évaluer les gains de longévité en fonction d'une cause spécifique de décès dans une population qui présente une mortalité globale diminuée.

Pour investiguer l'impact des contraintes physiologiques de chaque pratique sportive sur des causes spécifiques de décès, nous avons dû innover sur le plan méthodologique. Car, à l'inverse de la majorité des populations pour lesquelles les méthodes d'analyse de survie ont été conçues [209], les sportifs vivent plus longtemps que la population de référence.

L'estimation de l'impact d'une cause spécifique de décès sur le total d'années de vie perdues apporte des complications supplémentaires à l'étude de survie. Cette analyse est habituellement faite en comparant l'espérance de vie avec et sans l'effet de cette cause. Cette approche d'« exclusion des causes de décès sauf celle étudiée » repose sur l'hypothèse d'indépendance des délais d'événements [209]. Un inconvénient additionnel d'une telle méthode est qu'elle n'est pas additive sur les causes de décès: les années perdues pour toutes causes de décès ne sont pas partitionnées en fonction du nombre d'années perdues pour chaque cause spécifique. Ainsi, la somme des années de vie perdues pour chacune des causes de décès est supérieure au nombre total d'années de vie perdues (ex : [312]).

Une méthode de référence pour quantifier le nombre d'années de vie perdues suivant les causes spécifiques de décès a été récemment proposée à travers le modèle de risques concurrents [209,210,313]. Cette approche prend en compte le phénomène d'additivité des causes de décès et ne repose pas sur l'hypothèse d'indépendance des risques.

ETUDE 4

Nous avons repris alors le modèle des risques concurrents en survie pour une approche cohérente avec la spécificité de notre cohorte.

Le double objectif, d'un point de vue méthodologique et analytique, est de : i) fournir une méthode non biaisée pour calculer les années de vie gagnées en raison du risque diminué pour une maladie spécifique, dans les populations ayant une mortalité diminuée par rapport à leurs référents; ii) quantifier les années de vie gagnées chez les athlètes élités pour toute cause de décès et en raison des causes principales (maladies cardiovasculaires et cancers), selon le type d'effort réalisé aux JO.

Afin de classer l'effort principal de chaque athlète, un critère commun à la grande diversité d'épreuves sportives devrait être créé. Le critère choisi a été la durée de l'effort, en prenant en compte la particularité de chacune des 448 disciplines pratiquées par les athlètes français tout au long de l'ère Olympique moderne.

La filière énergétique prédominante pour réaliser un effort dépend de la durée de l'épreuve [155,316–319]. Ainsi, tous les événements sportifs ont été classés en six catégories d'effort selon leur demande énergétique principale, de la façon suivante : 1. PUISSANCE (n=440, durée d'effort continu en compétition < 45s); 2. INTERMEDIAIRE (n=813, 45s < durée d'effort continu < 600s); 3. ENDURANCE (n=272, durée d'effort continu > 600s); 4. POLYVALENTS (n=278, engagement dans des compétitions avec plus d'un des 3 types d'effort continu, ex : Décathlon) ; 5. INTERMITTENT (n=915, effort non continu, ex : sports d'équipe); 6. PRECISION (n = 96, épreuves avec dépense énergétique plus faible, ex : tirs).

La méthode développée ici pour mesurer les années de vie gagnées fournit une analyse quantitative et facilement interprétable des gains de longévité dus à des maladies spécifiques. Précisément, toutes les catégories d'effort gagnent en moyenne 6,9 années de vie [IC 95% : 6,0 ; 7,1 ; p < 0,001] lors d'un suivi allant jusqu'à l'âge de 90 ans, par rapport à la population générale, sans différence significative entre les catégories. De façon similaire, toutes les catégories d'effort ont significativement gagné en moyenne 2,2 années de vie (95% IC : 1,8 ; 2,6; p < 0,001) en raison d'une mortalité par cancer diminuée.

Néanmoins, la longévité cardiovasculaire est hétérogène entre les sportifs. Nous montrons une association entre la durée de l'effort et le nombre d'années de vie gagnées par réduction du risque cardiovasculaire, révélant une possible relation optimale entre le type d'effort physique et les bénéfices cardiovasculaires, dont les plus grands bénéfices enregistrés concernent les épreuves combinant différents types d'activité physique. Les catégories INTERMEDIAIRE (2,2 [IC 95% : 1,6 ; 2,8] p < 0,001), POLYVALENT (2,7 [IC 95% : 1,9 ; 3,6] p < 0,001) et INTERMITTENT (2,2 [IC 95% : 1,7 ; 2,8] p < 0,001) gagnent plus d'années de vie que la catégorie PUISSANCE (1,3 [IC 95% : 0,4 ; 2,2] p <

0,01). Mais les catégories ENDURANCE (1,0 [IC 95% : -0,7 ; 2,2] $p > 0,05$) et PRECISION (1,4 [IC 95% : -0,6 ; 3,4] $p > 0,05$) ne gagnent pas d'années de vie en comparaison avec la population générale. Ainsi, les types d'effort très spécialisés en puissance et en endurance de même que les activités statiques ne confèrent que peu ou pas de gain cardiovasculaire.

L'effort d'endurance produit les plus grands avantages cardiovasculaires lorsqu'il est réalisé à des doses faibles à modérées d'entraînement, comme le jogging par exemple [52,54,325]. Notre étude ne montre pas de bénéfices cardiovasculaires à long terme pour les Olympiens réalisant une performance classifiée d'endurance (comme les coureurs de longue distance), révélant alors un possible sur-risque cardiovasculaire de ce type d'activité dans cette population. L'absence d'avantages cardiovasculaires à long-terme pour cette cohorte hautement sélectionnée, peut révéler une possible surcharge du système cardiovasculaire qu'il conviendra investiguer au cours de futures recherches. Il s'agit de la première démonstration d'une variabilité de la longévité cardiovasculaire des athlètes élités selon le type d'effort performé.

9.1.5 L'ELITE SPORTIVE VIT PLUS LONGTEMPS

Ainsi, nos recherches montrent que la longévité des athlètes élités est globalement plus grande que celle de la population générale. Elle est cependant dépendante des caractéristiques de chaque sport, affectant alors différemment les causes spécifiques de décès, notamment les causes cardiovasculaires et les causes externes.

Malgré l'absence de bénéfices cardiovasculaires pour les athlètes pratiquant des sports d'endurance ou de précision, ou un risque d'accidents pendant la carrière plus important pour les cyclistes sur route, tous les types d'effort étudiés permettent de gagner en moyenne 7 années de vie, en considérant la globalité des causes de décès.

Sachant leur dose d'activité parmi les plus élevées au monde, l'élite représente la fin de la relation dose-réponse entre activité physique et bénéfices sanitaires. Ainsi, les démonstrations portant sur ces athlètes contribuent à déterminer que même la fin de cette relation reste associée à un impact positif, parmi les sujets sélectionnés par leur prédisposition et leur performance sportive.

L'intérêt d'identifier les risques et bénéfices de la pratique sportive parmi l'élite peut avoir des répercussions en santé publique : les bénéfices permettent de renforcer les caractères préventifs du sport autant que les risques justifient des mesures spécifiques à mettre en place.

9.1.6 TENDANCES CONCERNANT LA LONGEVITE HUMAINE

ETUDE 5

Afin d'extrapoler l'analyse de l'élite sportive pour mieux comprendre les tendances de la longévité humaine, nous avons développé un dernière axe de recherche. Sachant que les sportifs vivent plus longtemps que la population générale, nous avons comparé les tendances évolutives de leur durée de vie à celle de l'ensemble des doyens de l'humanité au cours du XX^{ème} siècle. Le rapprochement des deux populations se justifie du fait que les doyens, comme les sportifs, sont des sujets hautement sélectionnés par leur rare phénotype, détenteurs d'une performance exceptionnelle.

L'une de nos hypothèses préconisait l'analyse interdisciplinaire des données physiologiques fournis par les athlètes d'élite, en particulier sur les capacités humaines maximales.

Ainsi, nous avons recueilli des données sur l'ensemble des Olympiens décédés, toutes nationalités confondues, ayant participé aux JO entre 1896 et 2012 (n = 19 012) et tous les supercentenaires (> 110 ans) décédés entre 1900 et 2013 (n = 1205) afin d'analyser leurs tendances en termes de durée de vie.

La durée de vie est un critère très intégrateur de la performance humaine. Les doyens de l'humanité occupent l'une des extrémités d'une courbe de distribution de la longévité (à l'instar des Olympiens sur la courbe représentant les capacités physiologiques maximales). La performance sportive a déjà montré les preuves d'une progression limitée [217,384–388], mais l'existence d'une limite à la progression de la durée de vie est une question qui divise profondément la communauté scientifique [332]. D'un côté, les « *prolongevists* » suggèrent une augmentation illimitée de l'espérance de vie. Selon ces études, les tendances observées dans le passé devraient se poursuivre, de telle façon que l'augmentation linéaire de l'espérance de vie observée au XX^{ème} siècle devrait continuer [333–335]. D'un autre côté se placent une majorité de biogérontologistes. Selon eux, une telle prévision est fondamentalement inaccessible, car nos contraintes évolutives et biologiques limitent notre longévité, et nous serions actuellement proches de cette «barrière biologique» [329,336,346,381].

La comparaison des Olympiens et des supercentenaires, ces deux populations « *d'outliers* », ayant en commun une propension à vivre plus longtemps, peut être instructive pour le débat sur l'existence d'une limite à la progression de l'espérance de vie. L'intérêt d'une telle approche est que les tendances actuelles de durée de vie maximales dans ces populations peuvent représenter l'avenir des populations générales.

Cette dernière étude vise aussi à suggérer une plus ample application des données de l'élite sportive : faire progresser l'analyse de leurs données pour appréhender les traits multifactoriels, comme le vieillissement, et de fournir de nouveaux arguments pour ce débat autour des tendances de la durée de vie humaine.

Pour cette analyse nous avons développé un outil méthodologique spécifique permettant la comparaison des tendances séculaires de la longévité de sportifs olympiques et supercentenaires. Ces deux populations ont été comparées par un outil d'analyse de densité (nombre total des durées de vie en fonction des dates de naissances). L'analyse de la densité différencie les tendances de durée de vie selon le nombre de personnes concernées et ceci en fonction du temps. Par conséquent, cet outil permet une description des tendances des limites supérieures de la longévité en vue de sa pertinence par rapport à l'ensemble de la distribution des durées de vie.

Nos résultats révèlent des tendances communes entre les deux cohortes, suggérant des forces de mortalité similaires augmentant avec l'âge. Nous avons observé une tendance croissante de la durée de vie des athlètes olympiques. Toutefois, cette progression ralentit dans les dernières décennies, comme si un plafond naturel empêchait désormais leur progression. La dynamique observée conduit ainsi à un phénomène de densification dans la tranche d'âge 80 – 105 ans. Les doyens de l'humanité révèlent des tendances similaires aux Olympiens, mais encore plus marquées : la progression de leur longévité plafonne depuis 1997. Le ralentissement de la croissance de la longévité maximale humaine renforce ainsi les arguments d'une barrière biologique à l'origine de ces limites, autant qu'une réduction de nos marges de progression [377].

9.1.7 LES CONTRIBUTIONS PRINCIPALES ET CONCLUSIONS

Les principales contributions de cette thèse sont les suivantes: 1) la description de la mortalité globale et l'analyse des causes spécifiques de décès au sein de l'élite sportive française, y compris les athlètes féminines; 2) l'analyse de la longévité des olympiens selon le type d'effort, classés par la durée de performance, une méthode qui devrait permettre des comparaisons inter-études; 3) l'estimation des années de vie gagnées chez les athlètes élites en fonction des risques spécifiques de décès ; 4) de nouveaux éclairages sur les tendances de la longévité humaine.

Les limites principales sont liées aux aspects suivants: des relations de causalité entre la carrière des athlètes et leur plus grande longévité ne peuvent pas être établies à ce jour, en particulier parce que seuls l'âge et la période ont été ajustés parmi l'ensemble des facteurs de confusion possibles. En outre, les contraintes qui pèsent sur les athlètes d'élite, avant, pendant ou après leur carrière (comme la charge et le type d'entraînement, leur historique de blessures, leur mode de vie et l'utilisation de produits dopants) n'ont pas été évaluées. La comparaison de sujets hautement sélectionnés avec une population de référence comprenant des sujets avec tous types d'état de santé est une autre limite. Cependant, l'exhaustivité du recueil et la compréhension des comportements aux limites permettent justement de s'en affranchir [398].

La force de ce travail repose sur un vaste suivi des athlètes hommes et femmes, du niveau sportif le plus haut, sur une large gamme de sports, reposant sur la vérification et la certification de leurs statuts vitaux et leurs causes de décès. Parmi les méthodes employées, trois ressortent comme étant innovantes par rapport aux études antérieures sur le sujet : i) le classement du type d'effort par la durée de performance, qui s'est montrée discriminante pour classifier les différents types d'épreuves olympiques ; ii) la mise en place de la méthode des années-gagnées, qui fournit une interprétation facilitée des analyses de la longévité et pourrait être utile lors de l'évaluation des bénéfices spécifiques en longévité suivant les différents types d'activité physique ; iii) l'analyse de la densité des tendances de deux populations hautement sélectionnées en termes de durée de vie.

En perspective, de nouvelles recherches devraient maintenant investiguer la morbidité et la qualité de vie des athlètes élite. Il paraît aussi important de conduire de nouvelles études sur les causes spécifiques de décès chez les femmes sportives pour mieux comprendre les causes de décès associées à leur mortalité réduite. Du point de vue de la santé publique, la relation entre le type et la dose d'exercice et les bénéfices et risques sanitaires associés doit être mieux comprise afin de bien préciser la prescription de l'activité physique.

L'ensemble de ces recherches s'inscrit dans différents domaines scientifiques : en médecine du sport et physiologie, par une meilleure compréhension des effets du sport et de ses bénéfices sanitaires; en santé publique et en épidémiologie, par les méthodes spécifiques d'analyse développées et la transposition de leurs résultats en population générale.

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11

ANNEX

Published papers: **i)** *Mortality in Female and Male French Olympians: A 1948-2013 Cohort Study*; **ii)** *Row for Your Life: A Century of Mortality Follow-Up of French Olympic Rowers*; **iii)** *Mortality of French participants in the Tour de France (1947-2012)*; **iv)** *Learning from Leaders: Life-span trends in Olympians and Supercentenarians*.

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Mortality in Female and Male French Olympians

A 1948-2013 Cohort Study

Juliana Antero-Jacquemin,^{*†‡} MSc, Grégoire Rey,[§] PhD, Andy Marc,[†] MSc, Frédéric Dor,[†] PhD, Amal Haïda,^{†||} MSc, Adrien Marck,[†] MSc, Geoffroy Berthelot,^{†‡} PhD, Alain Calmat,[¶] MD, Aurélien Latouche,[#] PhD, and Jean-François Toussaint,^{†‡**} MD, PhD
Investigation performed at Institut de Recherche bioMédicale et d'Epidémiologie du Sport, Paris, France

Background: Whereas intense physical activity has been associated with deleterious effects on elite athletes' health, in particular due to cardiovascular anomalies, long-term follow-ups have suggested lower mortality rates among elite athletes. Causes of death for French Olympic athletes and female elite athletes have not been studied.

Hypothesis/Purpose: We aimed to measure overall and disease-specific mortality of French female and male Olympians compared with the French general population. We hypothesize that Olympians, both women and men, have lower mortality rates.

Study Design: Cohort study; Level of evidence, 3.

Methods: French elite athletes (601 women and 1802 men) participating in summer or winter Olympic Games from 1948 to 2010 had their vital status verified by national sources and were followed until 2013. Causes of death were obtained via the National Death registry from 1968 to 2012. Overall and disease-specific mortalities of Olympians were compared with those of the French general population through standardized mortality ratios (SMRs) and 95% CIs. Olympians' observed and expected survivals were illustrated by Kaplan-Meier curves.

Results: At the endpoint of the study, 13 women and 222 men had died. Overall mortality in Olympians compared with that of their compatriots was 51% lower (SMR, 0.49; 95% CI, 0.26-0.85) among women and 49% lower (SMR, 0.51; 95% CI, 0.45-0.59) among men. Olympic athletes' survival is significantly superior to that of the French general population (women, $P = .03$; men, $P < .001$). According to the total deaths occurring from 1968 to 2012 (12 among women, 202 among men), female Olympians died from neoplasm (50.0%), external causes (33.3%), and cardiovascular diseases (16.6%). The main causes of death among men were related to neoplasms (36.1%), cardiovascular diseases (24.3%), and external causes (14.4%). Regarding the main causes of mortality among male Olympic athletes, the SMRs were as follows: 0.55 for neoplasms (95% CI, 0.43-0.69), 0.55 for cardiovascular diseases (95% CI, 0.41-0.73), and 0.66 for external causes (95% CI, 0.44-0.94).

Conclusion: French Olympians live longer than their compatriots: A lower overall mortality of similar magnitude is observed among male and female athletes compared with the general population. The main causes of death in French Olympians are neoplasms, cardiovascular diseases, and external causes.

Keywords: overall mortality; disease-specific mortality; elite athletes; epidemiology

Participants in the Olympic Games are a specific population owing to the selection process they undergo. Olympic athletes are the best competitors from each country, athletes who demonstrate rare physiological aptness and physical traits,⁴ suggesting athletic predispositions (both genetic and environmental)³⁶ and high levels of training for long periods.¹⁶

Sport-related risks expose Olympians to specific outcomes: These athletes possibly have higher mortality due

to cardiovascular anomalies,^{8,26,35} neurologic sequelae resulting from recurrent concussions in some disciplines,^{17,21} or use of doping agents.^{6,29} In addition, high forces in certain sports may increase the probability of fatal events due to accidents and collisions.^{9,11}

However, a recent meta-analysis on athletes' mortality evidenced that elite athletes live longer than their compatriots.¹⁴ French Olympians were not part of the cohorts included in those studies. In addition, there is a lack of studies considering female athletes, and very few studies have analyzed athletes' causes of deaths or submitted vital status to national certification.

We aimed to assess the overall and cause-specific mortality of female and male French Olympic athletes

compared with their compatriots in the French general population. We hypothesized that French Olympians, both women and men, will have a lower mortality.

METHODS

Study Design

Retrospective cohort study of French male and female Olympians.

Participants

The study cohort consisted of all women and men who represented France in the summer or winter Olympic Games after World War II—from 1948 up to 2010—and whose vital status was validated by the National Registry of Identification of Physical Persons (RNIPP).

Data Collection

All French athletes participating in at least 1 Olympic Games from 1948 up to 2010 were identified. Their biographical information came from reliable historians' sources.⁵ These data were compared and confirmed with data from the International Olympic Committee (Olympic.org) and data from each official website of international federations that archive athletes' biographies.

The identity information and vital status of the study athletes were obtained from 1948 up to January 1, 2013 (study endpoint) via the RNIPP from the National Institute of Statistics and Econometric Studies (INSEE), which inventories life status of French citizens living in or out of the French territory. Vital status was also followed up for Olympians who were born abroad but competed in the Olympic Games for France, as well as Olympians who emigrated. Subjects who could not have their vital status properly certified by national sources were not included in the study (Figure 1). Such exclusions were homogeneous during the studied period for both sexes.

The cause of death of each deceased subject was obtained from the Centre for epidemiology on medical causes of death (CépiDc), which has registered the causes of all deaths occurring in French territory since 1968. Causes of death occurring abroad or before 1968 or in 2012 and later were not currently accessible due a 2-year lag between the availability of death status and its corresponding cause. Therefore, the cohorts' causes of death

were obtained from 1968 up to January 1, 2012 (Figure 1). The vital status of Olympians who died abroad was identified even though the cause of their death could not be accessed.

This study was approved by the Advisory Committee on Information Processing in Research in the Field of Health (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL).

Statistical Analysis

Descriptive analyses of the study cohort were expressed as means (\pm SD) and proportions (%) when suitable. We compared the mortality of French Olympic athletes with that of the French general population using two methods: (1) overall and disease-specific standard mortality ratio (SMR) and its 95% confidence interval¹⁴ and (2) Kaplan-Meier curves to illustrate the observed and the expected survival rate of Olympians.³³

The SMR allows comparison of the mortality of the studied cohort with that of the total population containing this cohort,²² with age and period adjustment. In practical terms, SMR is the ratio between the number of deaths observed in the Olympic cohort and the number of expected deaths if the Olympians had the same death rates as the French population. Death rates of the general population were assessed via CépiDc. Individuals in a cohort differ in the time of risk exposure along their follow-up. Hence, Olympian person-year was calculated, which was defined as the actual time at risk, in years, of Olympians' follow-up. Therefore, the SMR denominator was calculated by multiplying French death rates by the Olympian person-years for the corresponding age group and period for each sex. Time was categorized in 1-year intervals from 1948 to 2013. Age groups were calculated by 5-year intervals from 15-19 years up to 100-104 years. The study athletes' follow-up started with the date of their first participation in the Olympic Games and finished with their date of death (if concerned) or with the study endpoint. An SMR equal to 1.0 means that the number of observed deaths equals that of expected cases. If lower than 1.0, the SMR indicates a lower mortality of Olympians compared with the general population. The 95% confidence intervals were calculated using the exact method.²²

The Kaplan-Meier expected survival was based on the French general population death rates, and the difference with the Olympic athletes' observed survival was assessed through the log-rank test.³¹ *P* values of $<.05$ were considered to indicate statistical significance for all analyses.

*Address correspondence to Juliana da Silva Antero-Jacquemin, MSc, IRMES, Institut de Recherche bioMédicale et d'Epidémiologie du Sport, INSEP, Institut National du Sport, de l'Expertise et de la Performance, 11 avenue du Tremblay, 75012 Paris, France (e-mail: juliana.antero@insep.fr).

¹Institut de Recherche bioMédicale et d'Epidémiologie du Sport (IRMES), Institut National du Sport de l'Expertise et de la Performance (INSEP), Paris, France.

²Université Paris Descartes, Paris, France.

³INSERM, Centre for Epidemiology on Medical Causes of Death (CépiDc), Le Kremlin-Bicêtre, France.

⁴Université de Rouen, Rouen, France.

⁵Comité National Olympique Sportif Français (CNOSF), Paris, France.

⁶Conservatoire National des Arts et Métiers (cnam), Paris, France.

⁷Centre d'investigations en médecine du sport (CIMS), Paris, France.

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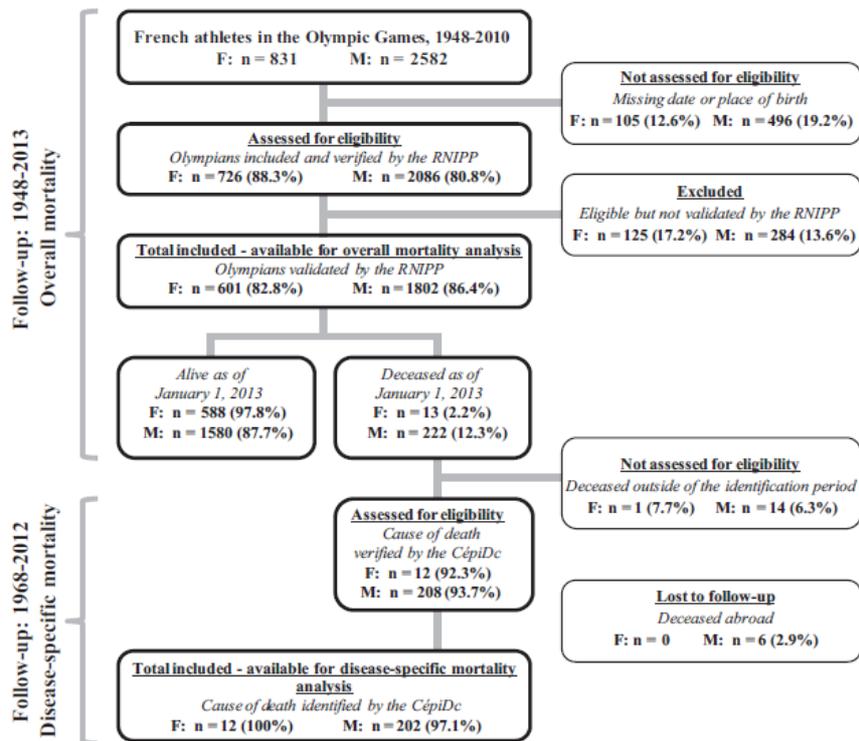


Figure 1. Flow diagram for overall and disease-specific mortality follow-up among the study cohort of female (F) and male (M) French Olympic athletes. CépiDc, Centre for epidemiology on medical causes of death; RNIPP, National Registry of Identification of Physical Persons.

Scenario

To address subjects who were excluded from the study due to absence of vital status official validation, we recalculated overall SMR analyses, adding all the Olympians who had been excluded (Figure 1). We performed overall mortality analyses assuming as true the vital status from sources monitoring Olympians' deaths (every official international federation's website and Olympic historian sources).⁵

Disease-Specific Mortality

To determine the disease-specific mortality, we compared each cause of death found among Olympians with the specific mortality rate of the general population by calculating SMRs for the available period, 1968 to 2012. Causes of deaths were classified according to the International Classification of Diseases (ICD) (8th revision before 1978, 9th revision between 1979 and 1999, 10th revision after 2000).

Age Effect

To analyze age-dependent differences in Olympians' mortality, SMR values were grouped according to 10-year age intervals from 25-34 up to 85-94 years. Age groups younger than 25 years or older than 95 years were not studied

because they accounted for only 2 deaths among women and men. R software v2.14.0 was used for the analysis.

RESULTS

Overall Mortality

The analyses were performed on 601 female and 1802 male French Olympians whose vital status was validated by national sources. Among those, 235 (n = 13 women; n = 222 men) died before the study endpoint. The characteristics of the study cohort are presented in Table 1. The mean (SD) follow-up time for Olympians who were alive was 20.3 years (± 14.6) for women and 26.8 (± 16.7) for men. For those who died, the follow-up time was 35.5 years (± 17.4) for women and 43.7 (± 13.5) for men. The overall SMR results were 0.49 (95% CI, 0.26-0.85, $P = .007$) for female Olympians and 0.51 (95% CI, 0.45-0.59, $P < .001$) for male Olympians.

Scenario

The analyses were performed adding 125 women and 284 men whose vital status was identified by nonofficial sources, totaling 726 female and 2086 male French Olympians. Among those, 280 (n = 16 women; n = 264 men) had a date of death known before the study endpoint. This scenario

TABLE 1
Cohort of French Olympic Athletes, 1948-2013

Characteristic	Women (n = 601)	Men (n = 1802)
No. of person-years	12,075.6	51,170.3
Age at study entry, y, mean \pm SD	23.3 (\pm 4.6)	25.2 (\pm 4.6)
Birth year range	1920-1992	1905-1991
Death year range	1986-2012	1973-2012
Age range at study endpoint, y		
Alive	21-92	22-94
Deceased	23-92	26-95

shows a significantly lower mortality in female (SMR, 0.38; 95% CI, 0.22-0.62, $P < .001$) and male (SMR, 0.51; 95% CI, 0.45-0.57, $P < .001$) Olympians than in the general population.

Survival Estimations

The observed and expected survival curves for female and male Olympians are illustrated in Figure 2. Olympians' observed curve is significantly different from the expected curve derived from the matched general French population for women ($P = .03$) and men ($P < .001$). The men's observed curve diverges and shifts to the right early in the follow-up period and narrows the gap at the end of the follow-up. The women's observed curve separates later from the expected curve and is clearly superior only at the end of the follow-up.

Causes of Death

Among all deaths observed ($n = 235$), 1 woman and 14 men died after 2012. Nobody died before 1968. Among women, the causes of all deaths that occurred during the available identification period were identified. Concerning men, the cause of death was identified for 202 men; 6 men died abroad and their causes of deaths could not be established.

The SMR results are represented for each cause of death identified among female and male Olympians (Figure 3). The 3 causes of death observed among women were neoplasm (50.0%), external causes (33.3%), and cardiovascular diseases (16.6%), without significant differences with the general population.

The main causes of death among men were neoplasms (36.1%; SMR, 0.55 [95% CI, 0.43-0.69]), cardiovascular diseases (24.3%; SMR, 0.55 [95% CI, 0.41-0.73]), and external causes (14.4%; SMR, 0.66 [95% CI, 0.44-0.94]). The mortality rates for these causes and for those due to mental disorders, respiratory system diseases, endocrine or nutritional diseases, and digestive system diseases were significantly lower for Olympians compared with their compatriots (Figure 3).

Mortality by Age Group

A significantly lower mortality rate was observed among male Olympians from the 25-34 to the 75-84 age groups compared with the general population (Figure 4). The

lowest mortality was seen among the youngest group (SMR, 0.19; 95% CI, 0.05-0.48). Olympians older than 85 years did not show a significant mortality difference (SMR, 0.90; 95% CI, 0.60-1.30). The lower mortality rate in younger Olympians is based on a larger subcohort size for younger athletes than for older ones, as represented by the decreased percentage of persons-years with age (Figure 4). No significant differences with the general population were observed for age groups among female Olympians.

DISCUSSION

Mortality in Female Olympians

Our study shows a 51% lower mortality among female Olympians compared with their referents in the French population. To the best of our knowledge, this is the first study that evidences female athletes' lower mortality compared with the general population based on national certified vital status.

The lower risk of all-cause mortality found among female Olympians is similar to that of male Olympians: Both demonstrate a large survival advantage over their compatriots. Such findings highlight that male and female elite athletes share common determinants to a greater longevity, such as a predisposition to achieve elite athletic status and possibly the training and lifestyle required by Olympic participation. The survival advantage experienced by French Olympians reinforces findings of previous studies showing higher longevity among elite athletes.^{1,3,10,14}

However, the Kaplan-Meier curves among women show a different dynamic from that of male Olympians, as women's advantage over the general population occurs later in life. Their survival deviates further from that of the general population at the end of the follow-up. That means that of the small sample of women who could be followed up beyond 60 years of age, most are still alive. Probably the advantage elite female athletes already show will widen in case of a longer follow-up.

Also singular is the narrowing between survival curves at the beginning of the women's follow-up. We expected to find a survival dynamic similar to that displayed among male Olympians, for whom the survival advantage starts with their Olympic participation—due to the cohort selection effect.¹⁵ The few deaths occurring among young women could explain such narrowing, even though the mortality analysis by age groups does not show any significant difference by age.

Women's disease-specific mortality also presents a particularity regarding the external causes of deaths (which comprise deaths from accidents, falls, homicides, and suicides). Whereas the main causes of deaths observed in male Olympians have analogous proportions to the main causes in the general population, the external causes among female Olympians are in larger proportions than in the general population. Nevertheless, no mortality difference by specific cause of death was shown among women.

Our results, based on very few deaths, certainly give rise to limited interpretation and analysis. Hence, the

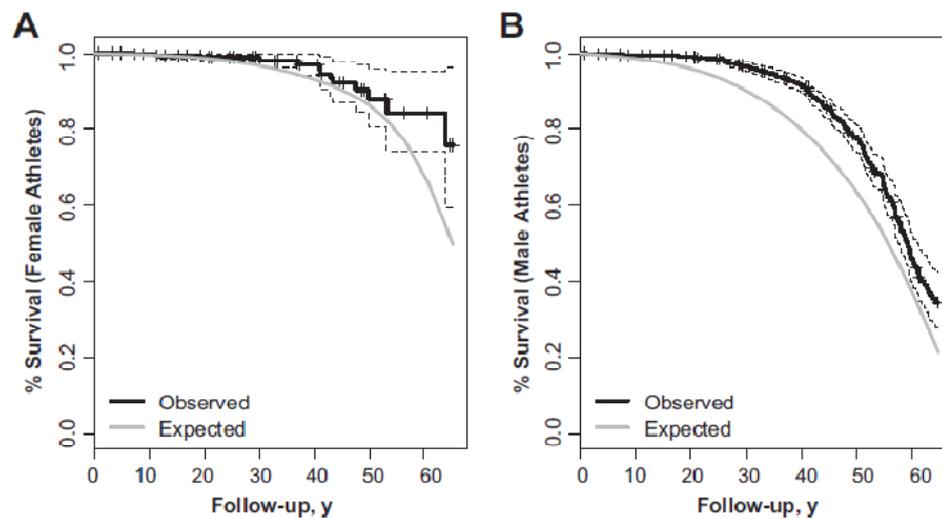


Figure 2. Observed and expected survival curves for French (A) female and (B) male Olympic athletes. The observed survival rate is represented by the solid black curve and its dashed confidence interval. The gray curve refers to the expected survival rate derived from the matched general French population.

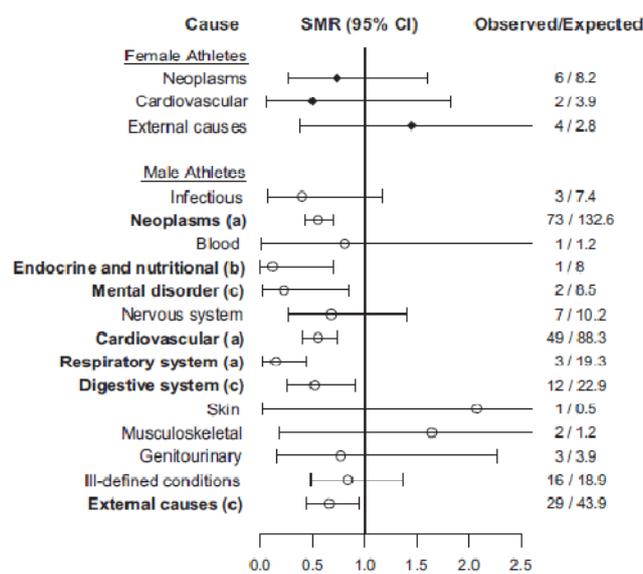


Figure 3. Disease-specific mortality of French Olympic athletes from 1968 to 2012. Cause of death was classified according to the International Classification of Diseases (8th revision before 1978, 9th revision between 1979 and 1999, 10th revision after 2000). The vertical bold line represents the general population reference value (standard mortality ratio [SMR] = 1). The causes of death that were significantly different from those of the general population are in bold. (a) $P < .001$; (b) $P < .01$; (c) $P < .05$.

findings regarding women's survival dynamics, age dependence, and disease-specific mortality reveal a path requiring further investigation. Yet this is the largest cohort of elite sportswomen ever followed up, corresponding to 85%

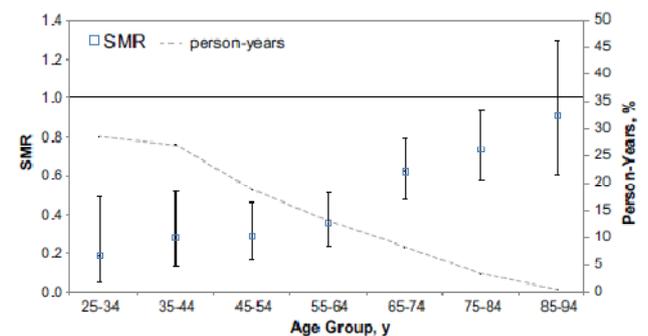


Figure 4. Overall standardized mortality ratios (SMRs) and 95% confidence intervals by 10-year age intervals for French athletes participating in the Olympic Games from 1948 to 2010. The horizontal line represents the general population reference value (SMR = 1). The dashed line represents the percentage of person-years followed.

of all cohorts of sportswomen accounted for in a recent meta-analysis,¹⁴ and it provides evidence of higher longevity among French female Olympians.

Mortality in Male Olympians

We found consistently lower mortality rates for male Olympians versus their male compatriots until advanced ages. The risk of all-cause mortality among men by age group varies from 81% lower at younger ages to 27% lower in the 75- to 84-year age group, and there is no difference with the general population at 85 years of age or older. Such age-related mortality patterns could be due to a survival selection process. At younger ages, Olympians are at the maximum of their capacity.⁴ With aging a selection

also operates in the general population, and at very advanced ages both groups include highly selected individuals. A study comparing Olympians to supercentenarians shows that among worldwide participants in the Olympic Games since 1896, none has lived to 110 years.² Olympians live longer but are not the longest-lived.

The overall mortality found among male Olympians is mainly associated with lower risk of 3 major causes of deaths seen among them: neoplasms, cardiovascular diseases, and external causes (which are 34%-45% lower than those found in the general population). In addition, French male Olympians display a significantly lower mortality from mental disorders, endocrine or nutritional diseases, and digestive system diseases and an 85% lower risk of mortality due to respiratory system diseases. The mortality from other causes is not statistically different from that of the general population. Rare causes of death, however, are based on a few deaths only, resulting in large confidence intervals that are hardly interpretable.

The benefits of moderate physical activity are well known for preventing cardiovascular problems.⁴⁵ Intense training, however, has been associated with cardiovascular events: coronary remodeling,⁷ artery calcification,²⁵ and atrial fibrillation and flutter,²⁶ although an association has not been clearly established.^{20,38} A triggered arrhythmia threshold has been proposed,⁸ but the 1500 lifetime hours of intense exercise are largely exceeded by Olympic athletes.¹⁶ Hence, a U-shape curve has been proposed for elite athletes, relating training load and cardiovascular risk.³⁵

Here we show a 45% lower mortality from cardiovascular diseases among male Olympians compared with the general male population. This long-term outcome for French Olympians is consistent with previous findings.^{3,24,39} Indeed, a 4- to 17-year follow-up of Italian Olympians did not show any deterioration in left ventricular function or an increased rate of cardiovascular events.³⁰ There is growing evidence that the cardiovascular benefits of practicing sports at an elite level outweigh potential negative effects.^{14,20,37} These elements may suggest another association between health effect and exercise load: an L-shape for the relation between risk and exercise, where there is no risk resurgence at the highest exercising levels for previously healthy subjects.

These results, however, should be interpreted in light of the heterogeneity of sports within the cohort, given that we sampled a wide range of athletes participating in activities from pure anaerobic to fully aerobic sports.

A two-way relation is possibly operating among Olympians: Rare traits enable high-level sport practice, and high-level sport conditions maintain capacities that reduce cardiac and overall mortality.

Cohort Selection Effect

Performance selection processes result in selecting healthy subjects who are in a favorable environment and have genetic predispositions.⁴⁴ Olympians constitute the fittest athletes who have a highly unusual set of physical and psychological traits.^{32,40} The presence of genotypes related to lower disease risk among elite athletes has been debated.^{15,46} The Olympians' survival advantage affects

individuals who have undergone an inevitable selection process. It therefore needs to be cautiously interpreted, because this advantage may not be extendable to the general population. In other studies, highly selected male cohorts showed comparably low overall mortality, including in comparison with healthy references.^{13,39} The comparison of Olympians with their compatriots reveals the effect of a phenotypic selection on death rates. The relatively lower mortality found is certainly enhanced by the existence of chronically ill subjects in the reference population. This situation is symmetrical to the selection of a control group in clinical studies of rare polygenic diseases.³²

Health-Enhancing Physical Activity

Dose-response relations between training intensity and health benefits are not well established,^{28,34,35} but the overexposure to high-level training does not seem to be deleterious to French Olympians. This suggests that elite athletes are probably capable of adapting to intense activity²⁷ and still derive benefits from it, at least in terms of longevity. Intense sports participation has nonetheless been associated with increased risk of musculoskeletal and connective tissue diseases.⁴² Even if such risk does not seem to affect survival rates—here only 2 deaths were related to musculoskeletal diseases—it remains unclear whether Olympians' higher longevity is associated with higher morbidities and to what extent the presence of morbidities may affect their quality of life.

No significant excess death was observed for any specific cause, in contrast with previous findings of higher mortality due to amyotrophic lateral sclerosis among Italian soccer players,⁴¹ neurodegenerative diseases among American football players,²¹ and suicide among Swedish power sport athletes.²³

The lowest mortality age group corresponds to the years when most Olympians are still active, contrasting with the higher mortality found during cyclists' careers.²⁴ Most Olympians spend much of their training indoors or in controlled outdoor environments, a safer condition than road cycling, which may explain such divergence. Hence, it seems that if sports are not directly unsafe, high-intensity training does not provide further deleterious effects throughout life on previously healthy people.

Maintaining a Healthy Lifestyle After a Sports Career

We have not assessed French elite athletes' lifestyles after their career. Previous studies, however, have reported that athletes usually maintain healthier habits than the general population before, during, and after their career,¹² such as low smoking rates, good nutrition, and exercising.¹⁹ In addition, the Olympians' level of fitness may constitute a "health bank"; this advantage may last over years, as shown by the lower mortality across male Olympians' age groups. Human capacities decay with aging⁴ but elite athletes start from a higher level. Hence, for a formerly well-trained person, physical activity may be effortlessly performed, allowing him or her to keep practicing throughout life.¹⁹

Use of Performance-Enhancing Substances

The use of substances designed to enhance athletic performance is as old as the human aspiration to break limits, and its use during the Olympics dates back to the first Games.^{4,5} The first listing of prohibited substances was made in the 1960s, but it has restricted doping only partially; however, the adverse health-related effects of substances have been shown.⁶ We do not know which athletes in our cohort used doping agents, and therefore it is difficult to assess to what extent the use of such substances might have minimized the large survival benefit experienced by French Olympic athletes.

Methodological Considerations

No causal inference can be made between Olympic participation and the observed lower mortality of Olympians, particularly because only age and period could be adjusted for potential confounding factors. We simulated a scenario to address the possible changes in our results that the excluded athletes could cause. The lower mortality found by adding excluded Olympians is similar to the outcomes presented here, with similar results among men and even lower mortality among women. Therefore, it is unlikely that the athletes excluded from the study may overturn the overall mortality results presented here. Yet, we acknowledge a limitation with regard to the deaths that occurred abroad or too recently for causes to be identified. Our method's advantages rely on an extensive follow-up of athletes of both sexes and of the highest performance levels based on national vital status certification.

Perspectives

Disease-specific studies assessing larger samples of elite sportswomen are necessary to understand better the causes of death that are associated with their lower overall mortality. Analytical studies controlling the factors that might influence elite athletes' mortality are now required to decipher this phenomenon: sport type, country, training methods, performance level, biometrics, career period, doping practice, and postcareer lifestyle, including athletes' quality of life.

CONCLUSION

French Olympians live longer than their compatriots: A lower overall mortality of similar magnitude is observed among sportswomen and sportsmen compared with their compatriots. The main causes of death observed among Olympians are neoplasms, cardiovascular diseases, and external causes. These 3 major causes of death are significantly lower among male Olympians than in the general population. Studies based on larger cohorts of women elite athletes are required for better comprehension of their survival advantage over their compatriots.

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Row for Your Life: A Century of Mortality Follow-Up of French Olympic Rowers

Juliana Antero-Jacquemin^{1,2*}, François Deni Desgorces^{1,2}, Frédéric Dor¹, Adrien Sedeaud¹, Amal Haïda¹, Philippe LeVan^{3,4}, Jean-François Toussaint^{1,2,5}

1 Institut de Recherche bioMédicale et d'Epidémiologie du Sport (IRMES), Institut National du Sport de l'Expertise et de la Performance (INSEP), Paris, France, **2** Université Paris Descartes, EA 7329, Sorbonne Paris Cité, Paris, France, **3** Comité National Olympique et Sportif Français (CNOSF), Medical Commission, Paris, France, **4** Institut National du Sport de l'Expertise et de la Performance (INSEP), Medical Department, Paris, France, **5** Centre d'Investigations en Médecine du Sport, Hôpital Hôtel-Dieu, Assistance Publique-Hôpitaux de Paris, Paris, France

Abstract

Background/Aim: Strenuous endurance training required to participate in the highest sports level has been associated with deleterious effects on elite athletes' health and cardiac abnormalities. We aimed to describe overall mortality and main causes of deaths of male French rowers participating in at least one Olympic Game (OG) from 1912 to 2012 in comparison with the French general population.

Methods: Identity information and vital status of French Olympic rowers were validated by National sources from 1912 to 2013 (study's endpoint) among 203 rowers; 52 out of 255 (20.3%) were excluded because their vital statuses could not be confirmed. Main causes of deaths were obtained from the National registry from 1968 up to 2012. Overall and disease-specific mortalities were calculated through standardised mortality ratios (SMRs) with its 95% confidence intervals (CIs). The overall mortality was calculated for the whole rowers' cohort (PT) and for two periods apart: (P1) including rowers from 1912 to 1936 OG, a cohort in which all rowers have deceased and (P2) considering rowers from 1948 to 2012 OG.

Results: Among the 203 rowers analysed, 46 died before the study's endpoint, mainly from neoplasms (33%), cardiovascular diseases (21%) and external causes (18%). PT demonstrates a significant 42% lower overall mortality (SMR: 0.58, 95% CI: 0.43–0.78, $p < 0.001$), P1 a 37% reduction (SMR: 0.63, 95% CI: 0.43–0.89, $p = 0.009$) and P2 a 60% reduction (SMR: 0.40, 95% CI: 0.23–0.65, $p < 0.001$) compared with their compatriots. Mortality due to cardiovascular diseases is significantly reduced (SMR: 0.41, 95% CI: 0.16–0.84, $p = 0.01$) among rowers.

Conclusions: French Olympic rowers benefit of lower overall mortality compared with the French general population. Among rowers' main causes of death, cardiovascular diseases are reduced in relation to their compatriots. Analytical studies with larger samples are needed to understand the reasons for such reductions.

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Data Availability: The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. Data concerning vital statuses and death causes are available from RNIPP via INSEE for researchers who meet the criteria for access to confidential data. The requests to access need to be addressed to French National Commission for Data Protection and Liberties (CNIL) which regulates the access to secured data: <http://www.cnil.fr/english/>. Data are from the study of French athletes whose authors may be contacted at IRMES (11 av du Tremblay, Paris, 75012, France).

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* Email: juliana.antero@insep.fr

Introduction

Rowing has been reported as a safe contactless sport with low injury rate, providing health benefits to its practitioners [1,2]. Although high occurrence of cardiac diseases, and alterations on cardiovascular morphology has been previously reported in university rowers [3,4], epidemiological studies have described higher life expectancy in Harvard and Yale university rowers as in Oxford-Cambridge boat racers compared with their non-athletic referents [5,6].

If regular physical activity has been demonstrated to provide large health benefits [7–9] studies have reported that strenuous

exercises and training of elite athletes could be associated with deleterious effects [10]: cardiac abnormalities [11,12] more likely triggering a sudden death during high demanding effort [13,14], with higher incidence rate among men varying according sports practice [15] and deregulated inflammatory responses [16]. In addition, training cessation after international career has showed to be deleterious in retired athletes [17–20]. Conversely, a recent meta-analysis of epidemiological studies has concluded that top-level athletes live longer than the general population [21].

Olympic Games (OG) are the highest competition level for rowing athletes; thus Olympians are exposed to the most extreme training program and performance exigencies. This

study aims to assess the overall mortality and main causes of deaths of male French Olympic rowers competing from 1912 up to 2012 compared with their referents in the French population.

Methods

Design and participants

Retrospective cohort study of French Olympic rowers. The cohort was composed of all male rowers who represented France in at least one OG, from 1912 up to 2012, and had their vital status validated by the National registry of Identification of Physical Persons (RNIPP). Coxswains were not accounted as rowers.

Three periods were taken into account to analyse rowers' overall mortality. The first (P1) included only rowers that participated in the OG from 1912 up to 1936. This period was chosen for a separated analysis because all rowers, who participated in those games, had already deceased, allowing for a complete follow-up until the entire cohort's extinction. The second period (P2) is an uninterrupted period of OG after World War II, from 1948 to 2012. Finally, we considered the total period (PI), analysing the totality of rowers participating in the OG from 1912 up to 2012 (Figure 1). The discontinuity at the rowers' entry in the cohort between 1912–1920 and 1936–1948 is related to the Games interruption due both World Wars.

Data collection

Data concerning rowers' biography came from historians' sources as previously reported [22]. These records were confirmed by data of the International Olympic Committee (olympic.org) and the French Federation of Rowing (<http://www.avironfrance.asso.fr/>). Rowers' identity information and vital statuses were collected since their first Olympic participation up to January 1st

2013 (study's endpoint) from the RNIPP via INSEE (National Institute of Statistics and Economical Studies), which registers vital status of all French people since 1891. Hence, rowers born before 1891 were not included in the study.

The causes of death of each deceased subject were obtained from the C epiDc (Epidemiologic Centre on Medical Causes of Death). Currently, causes of deaths occurring on French territory are available via National registry from 1968 up to January 1st, 2012. Thus, only deaths occurring during this period were submitted to investigation of its causes.

This study was approved by the Advisory Committee on Information Processing in Research in the Field of Health (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL).

Statistical Analysis

We compared the mortality of French rowers with the French general population by calculating overall and disease-specific Standard Mortality Ratio (SMR) and its 95% confidence intervals (CI). SMR is the ratio between the number of deaths observed in the rowers' cohort and the number of expected deaths if the athletes had the same death rates of the French population with age and period adjustment [23]. The source for general population death rates was the French life tables available at the Human Mortality Database (<http://www.mortality.org/>) via C epiDc.

The number of expected deaths was therefore calculated by multiplying male French death rates by the rowers' person-years at the corresponding age and period. Person-years were computed so that each rower contributes for one record of each year during his follow-up.

The rowers' follow-up starts with their date of first OG participation and finishes with their date of death (if concerned) or

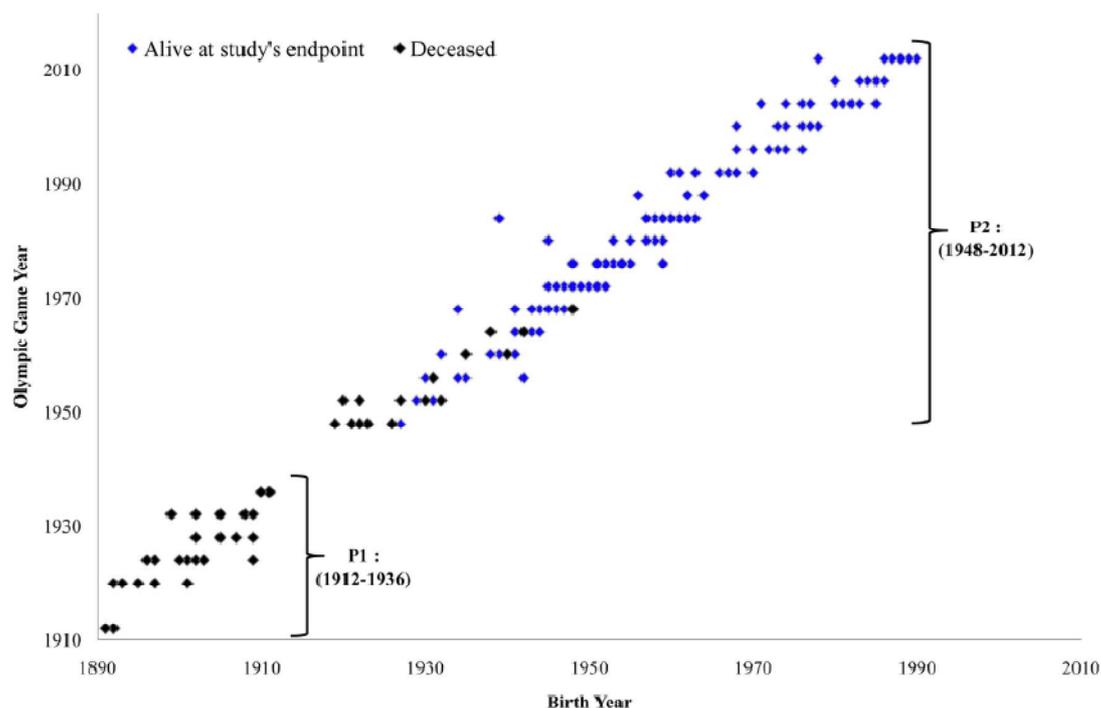


Figure 1. French Olympic rowers by Olympic Games and birth year. Black diamond represents deceased subjects and blue diamond represents the subjects alive at the study's endpoint. The two periods studied apart are schematically indicated. doi:10.1371/journal.pone.0113362.g001

Mortality Follow-Up of French Olympic Rowers

with the study's endpoint. The rowers' entries in the cohort are represented in Figure 1.

The observed and expected survival estimations were illustrated by Kaplan-Meier curves [24] and were compared with use of the log-rank test.

For the disease-specific mortality we compared each cause of death found among rowers with the specific rate in the general population by calculating SMR's for the available identification period, 1968 to 2012. Causes of death were classified according to the International Classification of Diseases - ICD (8th revision before 1978, 9th revision between 1979 and 1999, 10th Revision after 2000).

The 95% confidence intervals were calculated using the exact method [25]. R software v2.14.0 was used for the analysis.

Results

Overall mortality

A total of 255 male rowers represented France in the Olympics from 1912 up to 2012. All rowers verified by the RNIPP had their vital status validated, except for fifty-two (20.3%) who were not included in the study since they were born prior to 1891 ($n = 10$) or their date or place of birth were not properly validated ($n = 42$). Therefore, the analyses were performed on 203 French rowers.

Among rowers' cohort, 46 deaths occurred before the study's endpoint; 30 within P1 (Table 1). The age of death ranged from 35 to 100 years old. The mean age of death was $72.5 (\pm 15.6)$ in P1 and $74.0 (\pm 9.1)$ in P2. The PT overall mortality is significantly reduced by 42% compared with the French general population. Significant overall mortality reduction is also observed among rowers for both cohort periods considered apart (Table 1).

The rowers observed and expected survival curves are illustrated in Figure 2. The rowers observed curve is significantly different from the expected curve derived from the matched general French population ($p = 0.008$). The observed rowers' curve diverges and shifts to the right early in the follow-up period. The gap widens until 45 years of follow-up, and narrows afterwards until the end of follow-up. With increasing time, progressively fewer rowers contribute to the survival estimate.

Main causes of death

Among the 46 deaths observed, 36 occurred during the available period of death's cause identification (1968–2012). From those, 3 died abroad and their cause of death were not available. Therefore, 33 rowers had their underlying cause of death identified. The main causes of death (Table 2) observed were neoplasms, $n = 11$ (33%), followed by cardiovascular diseases $n = 7$ (21%) and external causes $n = 6$ (18%). The ICD chapter of external cause comprises deaths related to accidents, homicides,

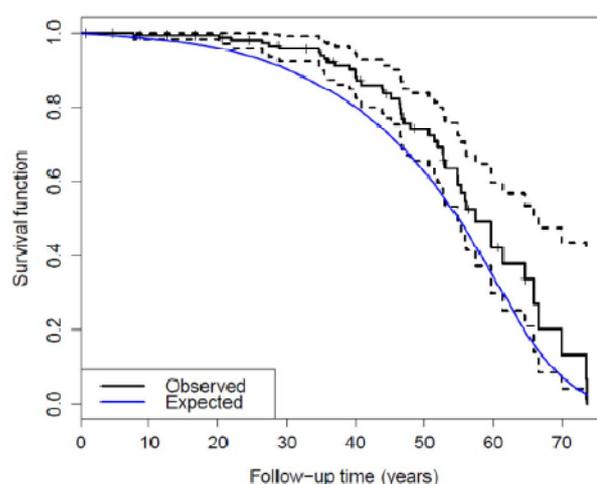


Figure 2. French Olympic rowers' observed and expected survival curves. Rowers' observed survival is represented by the solid black curve and its dashed confidence interval. The blue curve refers to the expected survival derived from the matched general French population.

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suicides and falls. The remaining causes observed (nervous system diseases, genitourinary diseases, respiratory diseases, skin diseases and ill-defined conditions) together account for 27% of all causes of death identified. Concerning the three main causes observed among French Olympic rowers, cardiovascular diseases are 59% significantly lower than found in the general population. Neoplasms and external causes are not significantly different from the general population (Table 2).

Discussion

To our knowledge the present study is the first to describe a survival advantage of elite rowers compared with their referents in the general population. The follow-up over the last century shows a 42% reduction of the overall mortality of French Olympic rowers. The early cohort of rowers (P1) followed until its complete extinction as well rowers competing post Wars up to 2012 (P2) showed a consistent mortality reduction.

The difference between observed and expected survival curves since the beginning of the follow-up illustrates the rowers' survival advantage over the general population. This advantage, visible since the beginning of the follow-up, increases with time and rowers deviate most from the expected when they are 50 to 70

Table 1. French Olympic rowers' cohort description and their overall mortality compared with the French general population.

Cohort	PT (n = 203)	P1 (n = 30)	P2 (n = 173)
Cohort's entry period	1912–2012	1912–1936	1948–2012
Nb. of person-years	6724.2	1528.4	5195.8
Mean age at cohort's entry in years (SD)	24.1 (± 3.6)	24.1 (± 3.7)	24.1 (± 3.6)
Mean follow-up time in years (SD)	33.8 (± 18.5)	48.4 (± 15.7)	31.0 (± 17.7)
SMR (95% CI)*	0.58 (0.43–0.78)	0.63 (0.43–0.89)	0.40 (0.23–0.65)
p-value	<0.001	0.009	<0.001

*SMR lower than 1.0, indicates a reduced mortality of rowers compared with the reference population.

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Table 2. French Olympic rowers' main disease-specific mortality compared with the French general population.

Main causes of death (n)	Observed/Expected deaths	SMR (95% CI)	p-value
Neoplasms (11)	11/18.4	0.59 (0.29–1.07)	0.09
Cardiovascular diseases (7)	7/17.0	0.41 (0.16–0.84)	0.01
External causes (6)	6/5.7	1.0 (0.38–2.29)	0.99

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years old. At older ages the rowers' survival approaches the curve of their compatriots.

The increased selectivity of the Olympics in the modern era may require increased training intensity and may further develop the use of enhancing performance techniques, with potential adverse effects on athletes' health [26]. The consequence of such period changes on elite rowers' mortality will only be fully acknowledged after the entire extinction of the current young rowers, as it will allow a complete retrospective analysis. Up to now, our results suggest that recent rowers' longevity (P2) follows the survival advantage trend observed among P1 rowers; the mortality difference with the general population even seems to widen. However our results should be cautiously interpreted as we compare healthy individuals at cohort's entry with the general population, including ill and handicapped individuals. This "healthy worker effect" [27] probably overestimates the mortality reduction found among rowers.

French rowers' survival advantage appears associated with a reduced mortality from cardiovascular diseases. The benefits of leisure endurance sports on the cardiovascular health are well known in the general population [28,29] but some studies have underlined possible risks to the cardiovascular system due to excess training [13,30,31]. The preparation to OG includes important training volumes with rowers reaching more than 1000 h of training per year [32]. Such training loads undertaken during years of practicing produces major adaptations of the athletes' cardiovascular system [4,33] a phenomenon probably enhanced by a previously selection process [34,35]. Among French Olympic rowers, rather than a risk, the cardiovascular adaptation to training requirements to access the OG seems to be protective in light of the 59% mortality reduction found among them. Previous studies assessing cardiovascular diseases of endurance elite athletes as defined by the ICD show: a 51% reduction among Finnish long distance running and cross country skiing [36] and a 37% reduction among French cyclists [37]. Finally, our findings among Olympic rowers are also in line with longevity studies assessing rowers from lower competitive level [5,6].

Similar reduced overall mortality have been reported among other elite athletes cohorts [21,36,38,39], including recent findings considering endurance athletes [40]. A study of French cyclists in the *Tour de France* with comparable methods - although the number of subjects and follow-up period are different - has shown a 41% reduction of cyclists overall mortality [37]. Although road cycling risks are greater than rowing [2], French rowers and cyclists presents similar mortality advantage over their compatriots. Yet, the lower injury incidence among rowers might be behind the contrast with American football players' mortality [41]. Despite an overall mortality reduction of 47% the players presented an increased mortality due to neurodegenerative diseases claimed to be related with concussive blows to the head.

We limited our cohort to Olympic athletes in order to focus on the highest sports level for which health consequences of intense training remains debatable [10]. Nevertheless, our results are based on a small absolute number of subjects, especially those concerning causes of death; hence they should be interpreted with caution. In addition, we are not able to determine how the excluded athletes might alter the magnitude of our findings. Finally, except for age and period, we could not adjust for potential confounding factors. Our methods advantage, however, relies on an extensive follow-up of French Olympic rowers followed during a century of OG, allowing for a complete follow-up of the rowers competing in the first Games. In addition, the vital status and causes of deaths assessed and validated by National sources reduces uncertainty.

Further investigations based on larger cohorts and in a large variety of countries are now needed to better apprehend elite athletes' reduced mortality. As it is out of an observational study's scope to determine causality, analytical studies are necessary to explain elite athletes' survival advantage. The assessment of lifestyle or physical activity post-career of elite athletes may provide better understanding of their mortality determinants.

Conclusions

French elite rowers followed-up during a century of Olympic Games benefit of lower overall mortality compared with the French general population. The cohort composed only of deceased rowers from the early Olympic Games analyzed apart and followed until its complete extinction shows also an important mortality reduction. Among elite rowers' main causes of death, cardiovascular diseases are reduced in relation to their compatriots. Analytical studies with larger samples controlling for confounders such as elite athletes' training-load and lifestyle after career are needed to understand the reasons behind elite athletes' survival advantage.

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All authors had full access to the data and were fully involved in the data analysis.

Author Contributions

Conceived and designed the experiments: JAJ FDD FD PLV JFT. Performed the experiments: JAJ AS AH. Analyzed the data: JAJ FDD FD JFT. Contributed reagents/materials/analysis tools: JAJ AS AH. Wrote the paper: JAJ FDD FD.

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Mortality of French participants in the Tour de France (1947–2012)

Eloi Marijon^{1,2,3,4*}, Muriel Tafflet^{1,2,5}, Juliana Antero-Jacquemin^{1,5}, Nour El Helou^{1,5,6}, Geoffroy Berthelot^{1,5}, David S. Celermajer⁷, Wulfran Bougouin^{1,2,4}, Nicolas Combes⁸, Olivier Hermine^{1,9,12,13}, Jean-Philippe Empana^{1,2}, Grégoire Rey¹⁰, Jean-François Toussaint^{1,5,11†}, and Xavier Jouven^{1,2,3,4†}

¹Paris Descartes University, Paris, France; ²Paris Cardiovascular Research Center (PARCC), INSERM UMR5-970, Paris, France; ³Cardiology Department, Georges Pompidou European Hospital and Assistance Publique–Hôpitaux de Paris (AP-HP), Paris, France; ⁴Sudden Death Expertise Center, Paris, France; ⁵Institut de Recherche BioMédicale et d'Épidémiologie du Sport (IRMES), Paris, France; ⁶St Joseph University, Beirut, Lebanon; ⁷University of Sydney, Sydney, Australia; ⁸Clinique Pasteur, Toulouse, France; ⁹Service d'hématologie Adultes, CNRS-UMR8147, Hôpital Necker-Enfants-Malades, Paris, France; ¹⁰CépiDc/INSERM, Paris, France; ¹¹CIMS, Hôtel-Dieu, AP-HP, Paris, France; ¹²Imagine, Institut des Maladies Génétiques, Paris, France; and ¹³Laboratory of Excellence GR-EX, Paris, France

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Aims

In the context of recent concerns regarding performance enhancing techniques and potential negative health effects of high-level physical activity, data on the long-term outcomes and causes of death in elite endurance cyclists are of particular interest.

Methods and results

Characteristics and vital status of all French participants in the Tour de France were collected for the 1947–2012 period. Causes of death were obtained from 1968. Overall and disease-specific mortalities were compared with the French male population using overall and specific standardized mortality ratios (SMRs) with their 95% confidence intervals (CIs). Among the 786 French cyclists who participated at least once between 1947 and 2012, 208 (26%) died by 1 September 2012. Neoplasms and cardiovascular diseases accounted for 61% of deaths. We observed a 41% lower mortality in French cyclists (SMR: 0.59, 95% CI: 0.51–0.68, $P < 0.0001$), which did not change over time ($P = 0.70$). It was observed for main mortality causes: for neoplasms (SMR: 0.56; 95% CI: 0.42–0.72, $P < 0.0001$) and for cardiovascular death (SMR: 0.67; 95% CI: 0.50–0.88, $P = 0.004$), except mortality related to external causes (SMR: 1.06, 95% CI: 0.71–1.53, $P = 0.80$).

Conclusion

We observed a substantially and significantly lower mortality in participants in the Tour de France, compared with the general male population. However, our results do not allow us to assess in detail the balance between positive effects of high-level sports activity and selection of healthy elite athletes, vs. any potential deleterious effects of excessive physical exercise or alleged doping.

Keywords

Cycling • Doping • Cardiovascular • Mortality • Athletes

Introduction

The Tour de France is the world's most celebrated endurance cycling event and celebrates its 100th race in 2013.¹ The race has been held annually since 1903 except during the two World Wars. As the Tour gained prominence and popularity, the race was lengthened and its popularity extended around the globe. This is a 21 days competition with 2 days of rest during July covering more than 3200 km.

The benefit of regular physical activity is well known and has been recommended for both primary and secondary prevention of cardiovascular diseases.^{2–4} While the benefit of moderate regular physical activity has been clearly demonstrated, recent controversy exists regarding the potential adverse effects of regular strenuous physical exercise.^{5–7} In this context, the long-term outcome of elite athletes is of particular interest, although data are scarce on this issue.^{8,9} To the best of our knowledge, there are, very few data on cycling,^{10,11} and none addressed the issue of specific causes of death. The Tour de

* Corresponding author. Tel: +33 662833848 (FRA); +1 310 912 4998 (USA); Fax: +33 153987954, Email: eloi_marijon@yahoo.fr

† The two last authors contributed equally.

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France is arguably one of the most physiologically demanding sports competition.¹² The effort involved has been compared with 'running a marathon several days a week for nearly three weeks', while the total elevation of the climbs was compared with 'climbing three Everests'.^{13,14} In addition, as recently emphasized, the Tour de France has been the subject of many controversies because of exposure to performance enhancing techniques, in the past and still recently.^{11,15} described as potentially promoting an increase in mortality.¹⁶

We therefore undertook a study aiming to evaluate and compare overall mortality and specific causes of death among French participants in the Tour de France from 1947 to 2012, vs. the community average.

Methods

Data collection

Data on Tour de France French participants, for the 1947–2012 period, were collected from the two official Websites (<http://www.memoire-du-cyclisme.eu>, <http://www.letour.fr>) and complemented with two other sources (<http://www.wikipedia.org/>, <http://www.siteducyclisme.net/>). Identity information was confirmed via the National Registry for Identification of Physical Persons (RNIPP) from the National Institute of Statistics Economical Studies (INSEE). The study was approved by the ethical committee Advisory Committee on Information Processing in Research in the Field of Health (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL) in 2012.

Vital status was confirmed via the National Registry for Identification of Physical Persons (RNIPP) from the National Institute of Statistics Economical Studies (INSEE). Causes of death were obtained from the French Center on Medical Causes of Death (CépiDc–INSERM), which is able to provide the causes of death occurring in France since 1968. A 2-year lag exists between the availability of mortality status and the corresponding cause of death. Therefore, in the current study, the mortality status of all the French cyclists who had participated at least once in Tour de France from 1947 to 2012 was available by September 2012, while the specific causes of deaths could be retrieved until 2010. Causes of deaths were classified according to the International Classification of Diseases (8th revision before 1978, 9th revision between 1979 and 1999, 10th Revision after 2000).

Statistical analysis

Characteristics of subjects were described as means \pm SD, proportions (%), median, and inter-quartile ranges (IQR) when appropriate. The overall mortality (from 1947 to 2012) and specific causes of death (from 1968 to 2010) of the French cyclists who had participated at least once in Tour de France from 1947 to 2012 were compared with that of the French male population of comparable age during the same period. The follow-up for each cyclist was defined by the difference between the date of endpoint (1 September 2012 if alive or date of death) and the date of its first participation to the Tour de France. Person-years and standardized mortality ratio (SMR) were computed.¹⁷ Standardized mortality ratios were calculated by 5-year-age class and 1-year interval, and their 95% confidence intervals were calculated using the exact method.¹⁸ Standardized mortality ratio is the ratio of the number of observed deaths in our cyclists over the expected number of deaths in the cyclists if they had had the mortality rate of a referent population of similar age, here the male French population. An SMR < 1 indicates lower mortality, whereas an SMR > 1 indicates higher mortality in the cyclists when compared with the referent population. The period effect was explored using two complementary approaches. First, to address (indirectly) the possible effect of doping on long-term mortality,

cyclists were grouped according to three 20-year-time periods of participation to the Tour de France (1947–70, 1971–90, and 1991–2010), corresponding schematically with the reported or suspected use of amphetamines, steroid, and erythropoietin, respectively.¹⁹ Thereafter, SMRs according to the period of participation were calculated accordingly. Since only the youngest are considered for the last period, no death was observed in this group by 1 September 2012. Secondly, to account for mortality trends over time, deaths that occurred within each 20-year-time period were considered and the corresponding SMRs estimated. To further take into account a possible age period interaction, we performed a binomial model (SAS PROC GENMOD).

In addition, as an exploratory analysis, we estimated the number of additional years gained among the cyclists when compared to the general male population. For that purpose, we assessed the life span in the deceased cyclists and compared it to the life expectancy of the male general population of same age and period. This was done only in years where the deceased cyclists accounted for more than 60% of the cohort (i.e. 1947 to 1951).

Overall mortality rate from the community was calculated using the Human Mortality Database (<http://www.mortality.org/>). *P*-values of < 0.05 were considered to indicate statistical significance. All data were analysed using SAS software v9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

General population and cyclists overall mortality

A total of 786 French elite cyclists participated at least once in the Tour de France between 1947 and 2012 (*Figure 1*). With a mean participation of 2.5 Tour de France by cyclist, they represented 29.7% of the total participants. The median age at the first participation was 25.1 (23.7–26.6) years, and year of birth of the participants ranged from 1910 to 1989. The median duration (IQR) of follow-up was 37.4 (23.5–49.8) years.

Among this cohort of 786 French cyclists, 208 (26%) were known to have died by 1 September 2012. Compared with the general population, we observed a 41% lower mortality in French cyclists (SMR: 0.59; 95% CI: 0.51–0.68, $P < 0.0001$). Standardized mortality ratios were consistent across age, except for ages < 30 years in whom a non-significant SMR of 1.65 (0.75–3.25) was observed (*Figure 2*). Standardized mortality ratios were also consistent after grouping cyclists by their period of participation to the Tour de France. Of the 391, 220, and 175 cyclists who participated to the Tour de France in the 1947–70, 1971–90, and 1991–2012 periods, respectively, 188, 20, and 0 had died by September 2012. This yielded SMRs of 0.59 (0.51–0.69) and 0.68 (0.39–1.11) for those who participated in the 1947–70 and 1971–90 periods, respectively. Furthermore, *Figure 3* illustrates the lower mortality in the cyclists when compared with the male general population across the three time periods (1947–70, 1971–90, and 1991–2010): 0.56 (95% CI: 0.28–1.01), 0.54 (95% CI: 0.39–0.72), and 0.62 (95% CI: 0.52–0.73), respectively (P for difference = 0.70, P for age period interaction = 0.49).

Causes of death

Although there was no loss to follow-up for total mortality, specific causes of deaths were missing in seven cyclists (three were due to death which occurred outside France and four were of

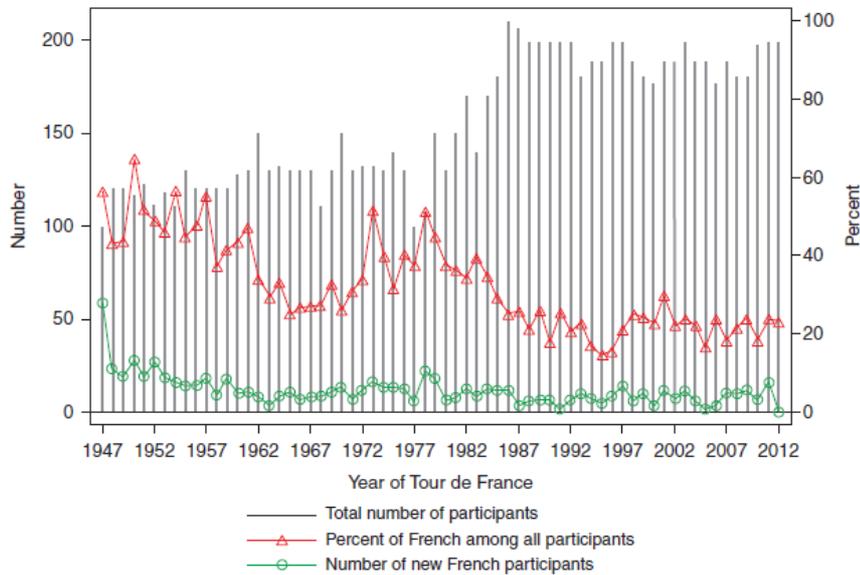


Figure 1 Proportion of French participants to the tour from 1947 to 2012.

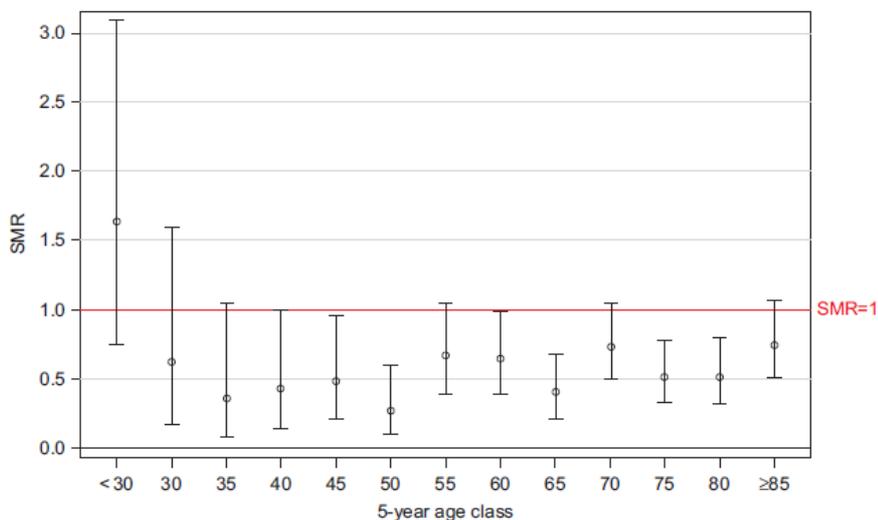


Figure 2 Standardized mortality ratio by 5-year-age class. Standardized mortality ratios were consistent across age, except for ages <30 years among whom only nine cyclists died. For this latter, an excess of mortality was suggested although the standardized mortality ratio was not statistically significant.

undetermined cause). The three principal causes of death were neoplasms (32.2%), cardiovascular diseases (29.0%), and external (mainly trauma-related) causes (15.8%). The three main cancers were digestive (35%), lung (22%), and prostate (7%). Among the 53 deaths related to cardiovascular diseases, we denoted 39 cardiac deaths (74%). Other causes of death included infectious diseases (2.2%), endocrine and nutritional diseases (2.2%), neurological (2.2%), digestive system diseases (2.2%), and genitourinary disease (1.1%).

There was no death due to blood disease. Among the nine deceased cyclists aged <30 years, six (66%) were related to accidents (races and traffic accident), two to cardiac causes, and one to an unknown cause. Of note, no death occurred during the Tour de France among these 786 French participants.

Table 1 shows the SMRs for specific cause of death. Overall, the direction and the magnitude of the SMRs by cause of death were comparable to the overall SMR: neoplasms (SMR: 0.56, 95% CI:

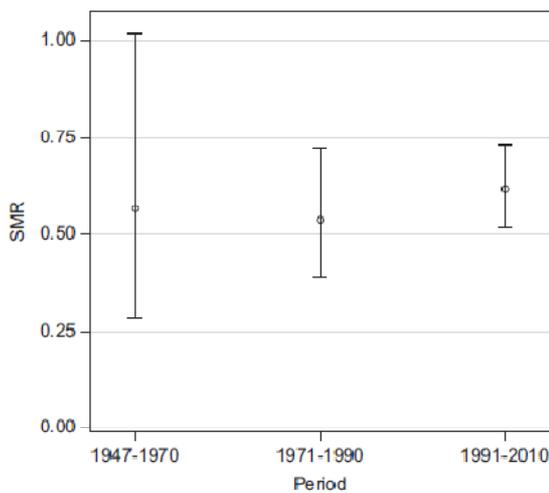


Figure 3 Standardized mortality ratio over time. We observed a lower mortality in the cyclists as compared to the male general population across the three time periods (1947–70, 1971–90, and 1991–2010), without any significant difference over time.

0.42–0.72, $P < 0.0001$), cardiovascular diseases (SMR: 0.67, 95% CI: 0.50–0.88, $P = 0.004$), and respiratory system diseases (SMR: 0.28, 95% CI: 0.09–0.65, $P = 0.003$), digestive system diseases (SMR: 0.22, 95% CI: 0.06–0.56, $P = 0.001$). However, no clear difference was observed between cyclists and the general population regarding mortality related to external causes (SMR: 1.06, 95% CI: 0.71–1.53, $P = 0.80$).

To put into perspective the potential benefit in terms of life-years gained, we estimated the additional life span of cyclists who participated to the Tour. Among the 109 cyclists who participated in the Tour between 1947 and 1951, mean additional life span was 6.3 years compared to the general population.

Discussion

We observed a significant 41% lower mortality among French elite cyclists from the Tour de France, compared with the general male population. This reduction in overall mortality was relatively homogeneous across ages (except for ages < 30), time periods, and major causes of death (except for external causes of death).

It has been traditionally suggested that a higher dose of physical activity has an additional benefit on reducing all-cause mortality (that is, a dose–response relationship).^{20,21} The recent results of two large cohort studies have proposed the concept of a U curve, with a strong benefit of moderate physical activity, but possibly a deleterious effect in case of particularly strenuous and sustained physical activity.^{5,6} These new findings have been illustrated by recent basic and clinical published data on the effects of ‘excessive’ sport exposure and cardiac remodelling.^{7,22–27} Training induces volume- and time-dependent morphological and functional changes in the heart. Heart rhythm disorders, such as atrial arrhythmia (including atrial fibrillation and atrial flutter), are a well-established association with such long-term endurance practice.^{28,29} Veteran athletes have a higher

Table 1 Standardized mortality ratio by causes of death

	Expected Death	Observed Death	SMR	95% CI
Infectious diseases	5.44	4	0.74	(0.20–1.88)
Neoplasms	106.01	59	0.56	(0.42–0.72)
Endocrine and nutritional diseases	6.90	4	0.58	(0.16–1.48)
Mental disorders	6.61	3	0.45	(0.09–1.33)
Nervous system diseases	9.05	4	0.44	(0.12–1.13)
Cardiovascular diseases	78.87	53	0.67	(0.50–0.88)
Respiratory system diseases	17.87	5	0.28	(0.09–0.65)
Digestive system diseases	18.21	4	0.22	(0.06–0.56)
Musculoskeletal diseases	1.11	1	0.90	(0.02–5.02)
Genitourinary system diseases	3.66	2	0.55	(0.07–1.98)
Ill-defined conditions	14.03	8	0.57	(0.25–1.12)
External causes	27.29	29	1.06	(0.71–1.53)

Causes of deaths were classified according to the International Classification of Diseases (8th revision before 1978, 9th revision between 1979 and 1999, 10th Revision after 2000).

prevalence of atrial fibrillation and sinus node disease.^{28–30} It has been also recently suggested that long-term excessive exercise may accelerate ageing in the heart, as evidenced by increased coronary artery calcification, diastolic ventricular dysfunction and large-artery wall stiffening.³¹ Finally, although shorter exercise duration has been associated with favourable antioxidant and vascular effects, longer exercise seems to blunt these beneficial effects and to yield adverse effects on vascular function.³²

The observed significant reduction in overall mortality in our cohort of French participants in the Tour de France, compared with the community average, should be interpreted with caution for the following reasons. First, there is a significant selection bias, as only the healthiest and fittest individuals are likely to be able to compete at such elite levels.³³ Such excellence in sport may be due in part to genetic predisposing factors.^{9,34,35} On the other hand, the reference population includes males from the community with potentially prevalent chronic disease and illness putting them at a higher risk of death, exaggerating, therefore, the difference in mortality between the cyclists of the Tour de France and the community average. Secondly, participation in the Tour de France and the preceding years of training represent a relatively small part of each athlete’s lifespan, and thus it is hard to attribute the observed lower mortality solely to participation in the Tour de France. Thirdly, and as a corollary, confounding factors may have played a role in this observed lower mortality. In particular, data on the lifestyle habits after their athletic career would have been informative but were unfortunately unavailable in the present study. Interestingly, former elite

athletes, especially endurance athletes, tend to maintain active and healthy lifestyles later in life, by engaging in more physical activity and smoking less than those in the general population.^{36–38}

As recently emphasized, the Tour de France seems to have been the matter of controversies because of exposure to performance enhancing techniques.¹⁴ Doping is associated with serious health complications, of which the most common and especially dangerous involve the cardiovascular system.¹⁸ Doping may have attenuated the association between participation to the tour de France and lower long-term mortality in our cohort. Three main periods of prohibited substances use have been described: amphetamines and cocaine use in the 1950–60s; androgens and anabolic steroids use between the 1970s and 80s, and since 1990, the use of growth hormone and erythropoietin. Although we could not directly estimate the effect of doping, analysis by time period is rather reassuring. These are exploratory analysis and we lacked time of follow-up for the last period, i.e. the possible effect of erythropoietin on long-term mortality.

To the best of our knowledge, comparable data on overall mortality among elite cyclists are only available from the study of Sanchis-Gomar *et al.*¹⁰ Although their data have added substantial information to the field, their findings remained limited to cyclists who participated to the Tour de France before 1964, without specific cause of death analysis. Specific cause of death analysis has been addressed in athletes in general or in specific sports such as soccer, American football, and cross-country skiing.^{8,39–43} Our findings confirm the significant reduction in overall mortality, as well as the relatively homogeneous risk reduction distributed across different causes of death. Notably, we found particularly low-specific mortality rates regarding cancer and cardiovascular diseases compared with the general population of the same age. In contrast, we did not observe any excess mortality in any specific mode of death, contrasting, for example, with the experience among American Football league players (with neurodegenerative mortality estimated to be three times higher than that of the general US population, possibly related to the higher chronic traumatic encephalopathy), or among soccer players (who had more amyotrophic lateral sclerosis) reported so far. However, these studies are limited by the relatively few absolute numbers of deaths, as well as large differences in the accuracy of death certificates in different areas of the same country.^{39,40,44} Furthermore, we found consistent lower mortality across age group. Notably, a non-significant excess mortality was observed in the youngest. Although speculative, these young cyclists may harbour cardiomyopathy or ion channel disease that is more likely to trigger a sudden death during such demanding effort.^{45–48} In our study however, a particularly high frequency of death related to traffic or race accident was observed in that young age group.

Although we report here the first cause of death analysis among elite cyclists compared with the general French population and had no loss of follow-up regarding their mortality status, we acknowledge some limitations. First, as an observational study, no causal inference can be made between participation in the Tour and the observed lower mortality. In particular, except age, and time periods, we were not able to adjust for potential confounding factors. Secondly, French cyclists represent only 30% of all Tour participants, and the extent to which these results apply to other nationalities is uncertain.¹¹ Although genetic background and some environmental

factors may differ between countries, it seems likely that the characteristics of such highly selected athletes are broadly comparable across countries. Third, analysis was restricted to mortality while morbidity and quality of life data were not available. Finally, the reliability of death certificates for the diagnosis of the causes of death and of sudden death in particular is questionable.⁴⁹

Conclusion

We observed a substantially and significantly lower mortality in participants in the Tour de France, compared to the general male population. However, our results do not allow us to assess in detail the balance between positive effects of high level sports activity and selection of healthy elite athletes, vs. any potential deleterious effects of excessive physical exercise or alleged doping.

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Learning From Leaders: Life-span Trends in Olympians and Supercentenarians

Juliana da Silva Antero-Jacquemin,^{1,2} Geoffroy Berthelot,^{1,2} Adrien Marck,^{1,2}
 Philippe Noirez,^{1,2} Aurélien Latouche,³ and Jean-François Toussaint^{1,2,4}

¹Institut de Recherche bioMédicale et d'Epidémiologie du Sport, Institut National du Sport de l'Expertise et de la Performance, Paris, France.

²Université Paris Descartes, EA 7329, Sorbonne Paris Cité, France.

³Conservatoire National des Arts et Métiers, Paris, France.

⁴Centre d'Investigations en Médecine du Sport, Hôtel-Dieu, AP-HP, Paris, France.

Address correspondence to Juliana da Silva Antero-Jacquemin, MSc, Institut de Recherche bioMédicale et d'Epidémiologie du Sport, Institut National du Sport, de l'Expertise et de la Performance, 11 Avenue du Tremblay, 75012 Paris, France. Email: juliana.antero@insep.fr

Life-span trends progression has worldwide practical implications as it may affect the sustainability of modern societies. We aimed to describe the secular life-span trends of populations with a propensity to live longer—Olympians and supercentenarians—under two hypotheses: an ongoing life-span extension versus a biologic “probabilistic barrier” limiting further progression. In a study of life-span densities (total number of life durations per birth date), we analyzed 19,012 Olympians and 1,205 supercentenarians deceased between 1900 and 2013. Among most Olympians, we observed a trend toward increased life duration. This trend, however, decelerates at advanced ages leveling off with the upper values with a perennial gap between Olympians and supercentenarians during the whole observation period. Similar tendencies are observed among supercentenarians, and over the last years, a plateau attests to a stable longevity pattern among the longest-lived humans. The common trends between Olympians and supercentenarians indicate similar mortality pressures over both populations that increase with age, scenario better explained by a biologic “barrier” forecast.

Key Words: Demography—Longevity—Life span—Limit.

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IS the continuous rise in world's life span still a plausible forecast? This topic is of great concern for public health and policymakers and has worldwide implications as it may affect the sustainability of modern societies and health care systems (1–3). Yet, the issue of longevity trends has divided researchers and remains a matter of controversy (4). The origin of this divergence is not only a philosophical matter, but it is also supported by differing methods of investigation. Based on past life table trends, the prolongevist side claims that life expectancy will continue to increase linearly (5,6). Best practices research has proposed dramatic increases in longevity outcomes, affirming that most children born in developed countries since 2000 will reach 100 years (7). Supported by biologic constraints and evolution based, the other side argues that such a forecast is fundamentally unreachable (8,9) because human life span is biologically determined and we are already approaching a “barrier” to life expectancy increase (1,10). Each side's conclusions point to opposite directions.

We propose an intermediate approach to investigate life-span trends with novel tools. The approach consists in analyzing life-span density trends of two highly selected populations with a propensity to live longer. Their current

maximum life-span trends may figure the general population in the near future.

The analysis of longer lived cohorts' life-span trends may guide the debate towards the prolongevist or biologist direction based on one of the different hypotheses: accepting the scenario whereby the historic rise in life expectancy will continue, it is necessary to assume that people will more often live longer than 100, 110, and 120 years (2); precursor populations would then present signs of provable life extension. Conversely, a deceleration among longer lived cohorts could be seen as a sign of a close life-span limit (2).

The first population selected was made up of all worldwide Olympic athletes that had participated in the Olympic Games and were already deceased. Olympian medallists have demonstrated a 3-years' survival advantage in comparison with their compatriots in 13 developed nations (11). Other sources analyzing Olympians longevity, whether medallists or not, have demonstrated a similar advantage (12,13). To the best of our knowledge, Olympians constitute the sole worldwide well-defined population that has a proven survival advantage, including all ethnicities and dating back to the 19th century.

The registered longest-lived member of any species defines its maximum life span (10). Hence, the second

population selected was made up of elite survivors (14): all deceased supercentenarians (individuals >110-years-old) worldwide (15).

We analyzed both populations' life span through density analysis. The density analysis (total number of life durations per birth date) reveals distinct life-span trends according to the number of subjects with time. Hence, it allows for a highly informative description of life-span upper limits and its relative relevance within the wide range of lifetime values.

Therefore, we aimed to describe life-span density trends of worldwide deceased Olympians and supercentenarians.

METHODS

Study Population—Olympians

Day, month, and year of birth and death were collected for 19,012 ($n = 17,815$ men and $n = 1,197$ women) who had participated in at least one summer or winter Olympic Games competition since the first modern edition in 1896, up to 2012 and deceased up to 2013 (study's date point). Data came from the most authoritative source of Olympians biography (11). The Olympians' complete cohort (the cohort in which all subjects have entirely died out) ranges from 1828 to 1906. The Olympians population is mostly composed of adults from high-income countries in Western Europe and North America (Table 1).

Study Population—Supercentenarians

A verified and validated complete cohort of deceased supercentenarians born after 1800 was collected from the Gerontology Research Group (15). Overall, 1,205 supercentenarians ($n = 125$ men and $n = 1,080$ women) born up until 1897—the last year without any registered proof of a supercentenarian alive—were included. The majority of supercentenarians also come from high-income countries (Table 1).

Table 1. Olympians and Supercentenarians Cohort Description

	Olympians ($N = 19,012$)	Supercentenarians ($N = 1,205$)
Range in years		
Birth	1828–1991	1807–1897
Death	1900–2013	1917–2013
World distribution by region (%)		
Africa	1.7	0.4
The Americas	19.8	50.8
Asia	2.6	11.8
Europe	73.7	35.4
Oceania	2.1	1.4
Age at cohort's entry, mean (SD)	26.5 (6.6)	110
Range of life span in years (y) and days (d)	15 y and 120 d–105 y and 305 d	110 y and 0 d–122 y and 164 d

Life-span Density Function

The life-span density of Olympians and supercentenarians was estimated over a two-dimensional mesh. X and Y were the date of birth and life span, respectively, such that the data of an individual are expressed as X_i and Y_i with $i = 1, \dots, N$ (see Supplementary Material).

Analysis of the Dynamics of Life-span Trends in a Specific Time Frame

To assess the trends among the life-span upper values, the superior contour of each density layers was smoothed through a two-dimensional convolution kernel. The frame was defined within the intervals: $X_{(\text{Olympians})}$ in [1865; 1906]; $Y_{(\text{Olympians})}$ in [80; 123]; and $X_{(\text{supercentenarians})}$ in [1865; 1897]; $Y_{(\text{supercentenarians})}$ in [110; 123]. The frame selected in X corresponded to the first year forming a density layer up to the last year of a complete cohort. The selected frame in Y corresponded to a life span superior to 80 years up to its maximum values.

The life-span trends dynamics, for each birth date in the selected frame, was calculated by the sum of differences between adjacent densities in the Y (life span) direction (see Supplementary Material). All analyses were performed using Matlab 7.13 (MathWorks Inc.) software.

RESULTS

Olympians and Supercentenarians Life-span Density

The life-span density of worldwide Olympians and supercentenarians is presented in Figure 1.

The first Modern Games occurred in 1896. Thus, Olympians born before 1870 participated in the early editions at a more advanced age (42.5 ± 8.1 -years-old) relative to the mean age at first participation (26.5 ± 6.6 -years-old) of the full cohort.

Olympians' deaths were observed in every age group, ranging from 15 years and 120 days up to 105 years and 305 days. Deaths under 40 years mainly correspond to two birth periods: 1874–1890 and 1896–1915 and include men only.

The denser areas, corresponding to the life span that concentrates the highest number of subjects, is formed by Olympians born between 1900 and 1904 that died around 80-years-old.

None of the Olympians reached the status of supercentenarian; therefore, a gap separates the two populations throughout the entire period.

The denser area among the supercentenarians is formed by subjects born between 1893 and 1895 that died around 111-years-old. The world's record life span is 122 years and 164 days for Jeanne Calment, a French woman born in 1875.

Life-span Upper Limits

The top-left corner in Figure 1 is the focus of the life-span upper limit analysis for both populations as they constitute the life-span upper values of both complete cohorts.

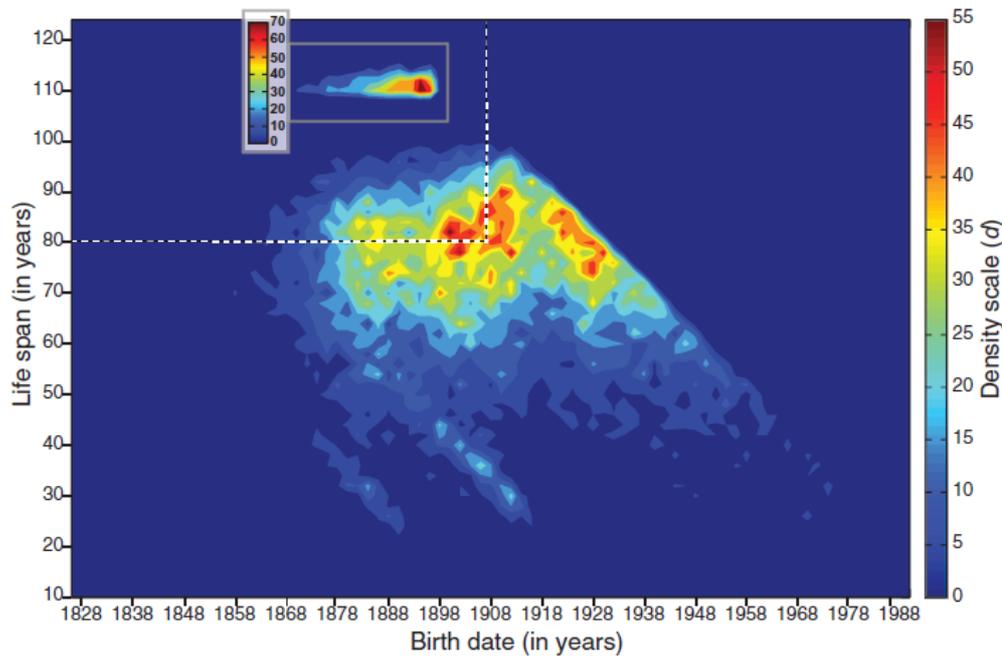


Figure 1. Life-span (collected in days and represented in years) density of all deceased Olympians ($N = 19,012$) and all validated supercentenarians ($N = 1,205$) born since 1800 in function of their birth date (represented in years). Window: $X_{(\text{Olympians})}$ in [1828;1991]; $Y_{(\text{Olympians})}$ in [10;123]; $X_{(\text{supercentenarians})}$ in [1828;1897]; and $Y_{(\text{supercentenarians})}$ in [110;123]. The resolution was defined as $a = 2$ years (see [Supplementary Material](#)). The density scale ranges from dark blue illustrating the lowest density values with fewer subjects' life span to dark red corresponding to the highest density values. The vertical dashed line delimitates the complete cohort, when the population has entirely died out. The horizontal dashed line delimits life span values superior to 80 years within the complete cohort. Isolated life spans are not represented in the figure because of their small density values.

The development of different levels of densities, forming life-span layers may be visualized in this corner.

The superior layer, formed by the greatest life-span values of Olympians, creates a survival convex envelope at approximately 98 years. The convex envelope points out the Olympians life-span upper limit observed. The density layers, below this convex envelope, move upward with birth date leveling off with the upper limit envelope.

A similar pattern is present among supercentenarians. Their life span creates a survival convex envelope at approximately 115 years. The densities layers above this envelope evolve with time, but the upper limit remains steady and a plateau may be visualized up to now.

Life-span Density Line Trends

The superior contour of each density layers at the top-left corner on [Figure 1](#) are illustrated in [Figure 2A](#) for both populations. We observe a different slope progression of the density lines according to the life span. The density slope of Olympians decelerates with time as their life span increases.

Regarding supercentenarians, the density slope increases slightly with time at the beginning of the observation period, at a similar pace among the densities layers. Then, the density slopes remains stable for the upper values. This results in a plateau attesting a stable phenomenon among supercentenarians in recent years.

Densification Phenomenon

Life span increase leveling off with the upper values entails an accumulation of individuals close to the survival convex envelope and reveals a densification phenomenon. This phenomenon was assessed in the ancillary graphs ([Figure 2B](#) and [C](#)).

The graphs describe an increased densification trend more continuous and more intense among supercentenarians than among Olympians.

DISCUSSION

Learning From Leaders

This study demonstrates the life-span trends in populations with a propensity to live longer, Olympians and supercentenarians. Among Olympians, we observe a trend of increasing life duration, which slows down at advanced ages. The dynamics observed leads to a densification phenomenon, as a result of a life span compression between the denser areas and the maximum ages.

Olympic participants undergo a highly selective phenotypic process based on rare physiological aptness (16). At the age of cohort entry, they were healthy subjects under favorable conditions (genetic and environmental) (17) reaching high standards of physical performances. Studies have shown that Olympians have healthier lifestyles after their career and maintain a good physical condition (18). All these factors contribute to greater longevity (18–20).

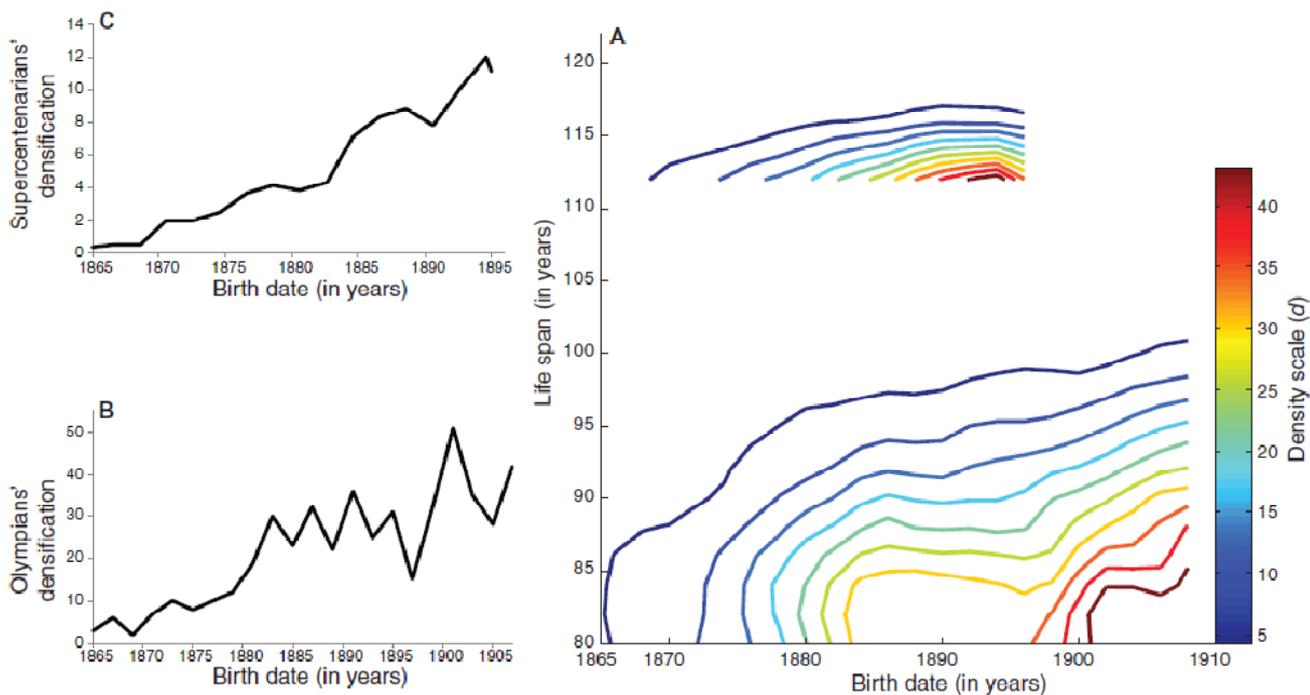


Figure 2. (A) Contour of the life-span density layers of Olympians and supercentenarians. Selected window: $X_{(\text{Olympians})}$ in [1865;1906] (first year forming a density layer up to the last year of a complete cohort); $Y_{(\text{Olympians})}$ in [80;123]; and $X_{(\text{supercentenarians})}$ in [1865;1897]; $Y_{(\text{supercentenarians})}$ in [110;123]. (B) Olympians' densification phenomenon. (C) Supercentenarians' densification phenomenon. The y-axis in B and C represents the sum of the differences in the Y (life span) direction ($\Sigma\alpha_j$) between the density layers by birth date (see Supplementary Material). Graphs (B) and (C) represent the increase of the density layers with time in the direction of the upper life span values measuring the densification phenomenon.

The selection criteria for Olympians' may explain their survival advantage over the general population, but it is not enough to allow them to reach the supercentenarians status: Olympians and supercentenarians have different performance-advantage sets. A gap clearly discriminates both populations attesting that the factors contributing to enhance general populations' longevity may not be sufficient to highlight the path required to become a supercentenarian. Accordingly, a longitudinal analysis of centenarians and supercentenarians has demonstrated a significant association between better physical function with survival advantage until 110 years. Beyond that age physical function or biomedical parameters may less accurately predict mortality (20).

Despite the gap, Olympians and supercentenarians present similar life-span trends and densification phenomenon, intensified among supercentenarians. This common pattern may indicate that both populations are under similar mortality pressures, despite the different phenotypic selection criteria of each population. Such forces increase with age, and both populations respond similarly by a densification phenomenon.

Concerning supercentenarians, the increasing density slope at the beginning of the observation period may be related to the greater number of recruited subjects and to a more reliable registry. Thereafter, the stable trends observed attest for a life-span plateau over the recent years. Mathematically speaking, Jeanne Calment's life-span

record may have been beaten by people born until 1891. After this record, only a single person (born in 1880) has lived for 119 years, and since then, no one has lived to more than 116 years. Accordingly, the life-span density trends provide no signs of a recent increased longevity pattern among the longest-lived, despite of an intense densification phenomenon.

We find better support to explain our results in arguments such an "invisible barrier," as previously suggested (1,21). This scenario seems to be represented here, through the densification phenomenon, alluding to a rectangularization of the survival curves (22,23). The slower pace in the trend of life span maximum observed among Olympians is even more stable among supercentenarians illustrating a "barrier" represented by the survival convex envelope. To support life-span extension forecasts, we would expect to find signs of expansion trends, people living each time longer at advanced ages (2). This scenario is hardly supported by the description of supercentenarians' and Olympians' current trends.

Life-span Record Holders

The fittest subjects of each country compose the worldwide Olympians cohort (11). This population is mostly formed by athletes from regions that have historically dominated sport performances and the world record for life expectancy as well. Olympians are not the only longer lived

cohort, although they are the largest one, comprising various ethnicities and originating from a wide range of social conditions. Even though in the absolute sense Olympians constitute a small subset of gifted athletes, validated supercentenarians compose an even smaller subset of outliers. Women usually live longer than men, but the Olympian cohort is mainly supported by male data because women's entry in the first Games was restricted. Yet, Olympian women present the same pattern of density layers as men, and their superior life-span density synchronizes with the men's.

Olympians Follow General Population Trends

The analysis of Olympians' deaths—observed in every age group—highlights a pronounced heterogeneity even in a highly selected population.

The two periods concentrating most deaths under 40 years can be attributed to both world wars, which reveal that Olympian men were neither excluded from the war effort nor spared its consequences.

The trend among most Olympians toward an increased lifetime throughout the century is similar to what has been described in terms of life expectancy (5,24) and life-span modal analyses (3) in record-holding countries. Modal age at death, estimated in United States, Canada, and France, show similar increasing trends. Japan, however, has recently leveled off (3) comparably to Olympians life-span trend at advanced ages.

The Gap

The gap between Olympians and supercentenarians may indicate a potential for further life expectancy increase. But even among a highly selected population of Olympians, surpassing the general population in terms of average age of death (11), none reached the status of a supercentenarian attesting the exceptional character of reaching 110 years (25). The similar densification among Olympians and supercentenarians and their unclosing gap both strengthen the arguments defending that human biology may not allow most of us to become a centenarian (26). Indeed, becoming one of them takes a complex sequence of rare and specific circumstances, involving constant favorable interactions between genetics (27) and environment (28). Hence, it seems appropriate to distinguish the interpretation of actuarial trends on all-cause mortality from biologic aging possibilities.

Method Considerations

Our study reinforces biologic forecasts (10,25,29) contrasting with extension claims (7,30,31). However, our period of observation is restricted, and the size of the population studied is relatively small. In addition, life expectancy increase has been discontinuous due to historical

changes; our cohorts could reveal a transitional trend only. But it is unlikely this may occur synchronically for both studied populations, in view of the different cohorts' selection criteria. Nevertheless, analyses of the most recent centenarians' birth cohort are time limited to 1914. After this period, all demographic forecasts are based on period life tables (death rates from a calendar year applied to people still alive) and remain speculative (9). The underlying assumptions are deterministic—based on the premise that the future will repeat past trends. In addition, death rates at extremely older ages are uncertain (32). Hence, analyzing a concrete cohort presenting a survival advantage may be an alternative method for understanding the present dynamics of maximal age trends.

In light of the continuous reductions in mortality rates at advanced ages in high-income countries (6) possibly the densification phenomenon will intensify in most developed countries. For instance, compression of deaths above the mode—a comparable measure for densification—has been observed in high-income countries (3). Then, the probability of surviving people, pushing the limits forward and leading to a life-span extension may be bigger. However, this scenario defended by prolongeists, seems to be possible only if nutritional, climatic, social, or economic conditions continuously improve. Important medical and technological advances may also lead to life extension (31), but major health determinants already contribute to reduce life expectancy progression in developed countries (33,34). In addition, the current tendency in world climate change and environmental resources degradation may result in adverse health consequences especially affecting the eldest individuals (35).

CONCLUSION

Most Olympians follow the general population tendency of a life span increase with time, a trend which decelerates as life span increases. At advanced ages, the slow pace on life duration progression leads to a densification of subjects dying simultaneously after reaching the highest ages. Similar but intensified tendencies are observed among supercentenarians resulting in the stagnation of mankind's oldest women and men—despite a sharp increase in the number of new supercentenarians.

The common trends between Olympians and supercentenarians indicate similar mortality pressures over both populations. These forces increase with age, scenario better explained by a biologic barrier limiting further life-span progression. Although this forecast may be felt to be less optimistic, to consider the line of reasoning underlying it may contribute to a better understanding of life-span trends and better prevent what may decelerate further progression.

SUPPLEMENTARY MATERIAL

Supplementary material can be found at: <http://biomedgerontology.oxfordjournals.org/>

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CONFLICTS OF INTEREST

The authors confirm that there are no conflicts of interest. All authors read and approved the final version of the manuscript.

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