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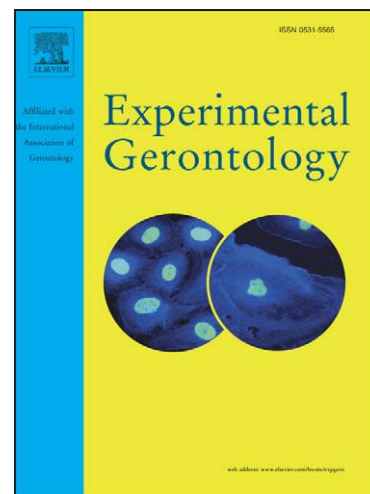
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THE EXTREME LONGEVITY: THE STATE OF THE ART IN ITALY

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ABSTRACT

The improvements of the social-environmental conditions, of the medical care, and the quality of life caused a general improvement of the health status of the population, and a consequent reduction of the overall morbidity and mortality, with a subsequent increase of life expectancy. Around the 1970s, in all industrialized countries, the progressive decline of mortality (1–2% per year) in individuals over 80 years old has increased, so that the number of centenarians has augmented about 20 times. Centenarians represent a cohort of select survivors who have, at least, markedly delayed diseases that often cause mortality in the general population at significantly younger ages. In this issue a number of contributions have been collected from Italian scholars of various aspects of human longevity and ageing to give to the readers a comprehensive and updated view on current contents on the research on human ageing and longevity in Italy. In particular, new findings together with some overviews related to different aspects of Italian centenarian study and human longevity are described. Ageing must be considered an unavoidable end point of the life history of each one, nevertheless our increasing knowledge about the mechanisms it is regulated by, allows us to envisage many different strategies to cope with, and delay it, in order to endow everybody with a long and good final part of the life.

1. INTRODUCTION

The improvements of the social-environmental conditions and medical cares and the quality of life caused a general improvement of the health status of the population, with a consequent reduction of the overall morbidity and mortality, resulting in an increase of life expectancy. The life expectancy at birth, also known as the average lifespan, represents the mean number of years lived and western world allows ever larger proportions of the population to reach an age that is far beyond that of the reproductive phase (Vasto and Caruso, 2004). After the demographic phenomena of the 19th century, characterized by an increase of the world population, we are now in the middle of a second demographic revolution, represented by the increase in the number of elderly people. Moreover, the improvement in public health has reduced the principal causes of mortality in the elderly, allowing an increasing number of individuals to reach the maximum lifespan age that represents the age of the longest lived member(s) of the population. Indeed, around the 1970s, in all industrialized countries, the progressive decline of mortality (1–2% per year) in individuals over 80 years old has increased, so that the number of centenarians has augmented about 20 times (Roush, 1996; Troen, 2003).

The life expectancy of *Homo sapiens* has been approximately 20–40 years for the most part of its evolutionary history, and very few subjects survived enough to be appreciably affected by ageing. Only in the last 200 years, and most dramatically during the last century, life expectancy is increased, especially in economically developed Western countries. In fact, at the beginning of the 19th century, the mean life expectancy was about 40 years (Abbott, 2004). Currently life expectancy in Italy is 76.8 years for men and 82.9 for women. In the more developed regions, the life expectancy at birth in 2000–2005 is 71.9 years for men and 79.3 years for women. The highest values are in Japan, i.e. 79.3 and 86.3 years for men and women, respectively (see Candore et al., 2006a). Thus, at the dawn of the 3rd millennium one of the most important demographic phenomena is the increasing ageing of the population, mainly due to a reduction in both birth rate and mortality rate, this latter being especially evident for the cohort of the over 80-years people.

The progressive increase of oldest old people has brought to a new condition, i.e. the increase of different age groups such as octogenarians, nonagenarians and centenarians. This situation leads to extremely complicated demographic phenomena and to new problems regarding the allocation of resources for old age pensions and care for the elderly.

2.THE CENTENARIANS

Study groups have been formed in all industrialized countries in order to define for the first time the characteristics of centenarians and thus to identify the factors responsible for their extreme longevity. These studies allowed us to appreciate the implications of the increased number of centenarians, as well as their peculiar needs. In July 1992, several Italian Institutes and Departments of Geriatrics, and Biomedicine formed a consortium called “The Italian Multicenter Study on Centenarians (IMUSCE)” aimed to study at integrated and interdisciplinary levels most of the complex aspects of the oldest old people, including epidemiological, clinical, immunological, genetic, biochemical and health care topics. The first activity was to screen the census data of a population of 16,541,802 inhabitants, which represented the 29.02 % of the Italian population at that time. Accordingly, 1,162 centenarians (234 males and 928 females) were identified, representing all the living centenarians of this population sample. By extrapolating this prevalence to the total Italian population at December 31, 1993, we obtained a total number of 4,004 centenarians in Italy, with a prevalence of 70.25 centenarians per 1 million of inhabitants. In Italy, in 1921 the number of centenarians was less than a hundred, while in 1981 it was increased up to 1304 (www.istat.it; IMUSCE, 1997).

In 1997, IMUSCE performed a second screen of the census data, regarding 14,274,591 inhabitants, and this study indicated that the previous prevalence of centenarians in Italy increased from 70.25 to 82.0 centenarians per 1 million inhabitants. The centenarians have been thoroughly investigated and their clinical conditions, health status (presence/absence of major pathologies), autonomy and self-sufficiency, cognitive status, analysed utilizing standardized tests in use, as well as a variety of biological parameters assessed. This comprehensive approach allowed the various

groups participating to IMUSCE to collect an unprecedented number of data on Italian centenarians (IMUSCE, 1997).

Nowadays it is reasonable to assume that the total number of centenarians is about two hundred thousand people worldwide, whereas in Italy at January 2005 they are 7102, being 200 of them 105 years old or even older. By 2050, the largest number of centenarians will be living in China, United States, Japan and India (Guralnik and Ferrucci, 2003; www.istat.it; www.unpopulation.org). These subjects are the best example of extreme longevity in our species, and they represent a selected population in which the appearance of major age-related diseases, such as cancer, and cardiovascular diseases among others, has been consistently delayed or escaped (Franceschi and Bonafè, 2003; Terry et al., 2003, 2004). The highest life span ever scored and properly validated is that reached by the French lady Jeanne Calment, who died in 1997 at the remarkable age of 122 years and 164 days (Abbott, 2004).

Life span is largely determined by genetics and environmental components as well as by their interaction, plus a stochastic component. Indeed, the increase of the human life span is not simply due to the improved economic and cultural conditions and social/health cares, but also to the interaction of these new conditions with the genetic variability present in human populations. These interactions are now the target of a variety of studies, aimed to identify the genes and their polymorphic variants, which likely could have a fundamental role in the attainment of extreme longevity in some individuals, in the various countries characterized by different genetic pool, cultural habit and survival probability. Thus, the scenario of human longevity is getting more and more complex, as demographic conditions change and scientific knowledge increases and let emerge new aspects of this puzzling topic, sometimes contradicting each other (Franceschi et al., 2005; Candore et al., 2006a; Salvioli et al., 2006; De Benedictis and Franceschi, 2006).

3.AGEING AND LONGEVITY: THE DEMOGRAPHIC REVOLUTION

Until some decades ago, it was believed that all the physiological functions of the organism underwent a simultaneous age-related decline (Maynard Smith, 1966). Other Authors tried to

quantify such a decline on the basis of cross-sectional comparison of data obtained from groups of subjects of different age belonging to different cohorts, who showed a decrease of about 1% per year for most of the physiological functions, and these data were considered valid for the great majority of the organs of the body. Such a decrease would be detectable from thirty years of age onwards according to some authors (Andres and Tobin, 1977), whilst for some others, it would become evident even earlier, since the age of sexual maturation (Bafitis and Sargent, 1977). Longitudinal studies suggested that the most striking age-related changes occur after the age of seventy (Svanborg et al., 1982). An updated vision of the phenomenon proposes that human ageing should be considered as a dynamic process leading to a continuous adaptation of the body to the life-long exposure to harmful stresses. This vision has been conceptualised in the so-called "remodelling theory of ageing" (Franceschi and Cossarizza, 1995; Franceschi et al., 1995), which is mostly based on evidences obtained from studies on immunosenescence. In particular, these results show that immune functions are differently affected by ageing, being some parameter strongly affected whereas some other remain unchanged or even increased (Wack et al., 1998; Fagnoni et al., 2000; Franceschi et al., 2000a). The same can be observed in centenarians in good health conditions, who have some types of immune response which are well preserved (Mariotti et al., 1992; Sansoni et al., 1993; Cossarizza et al., 1996; Candore et al., 1997; Bagnara et al., 2000; Listì et al., 2006).

Centenarians are by definition old people who show all the signs of a prolonged ageing process and consequently it is not surprising that centenarians are very frail individuals. Nevertheless, extreme longevity should be considered as a new phase of life, different from the previous one, for which standardized laboratory parameters and normality ranges are mostly lacking. Just to give an example, the tests and the questionnaires used to assess important parameters such as cognitive status and physical performances are validated only for subjects below the age of 80.

Waiting for an international Consensus Conference on such a critical topic, a classification of centenarians has been proposed, which subdivides them into three categories, named A, B and C (Franceschi et al., 2000b). In the "A" category are included centenarians who live autonomously, that are able to walk, to read newspapers and to live their social lives without major physical handicaps; in the "C" category are included centenarians in bad shape, with a poor cognitive status and very limited physical conditions; subjects included in the "B" category are in an intermediate status between A and C categories. This classification differs from another one proposed recently by other authors in which the categorisation has been made based on the presence or absence of major age-related pathologies (Evert et al., 2003). According to this second classification, centenarians are divided in "survivors" (who were diagnosed for one or more pathologies before the age of 80); "delayers" (who were diagnosed between the age of 80-99); and "escapers" (who reached the age of 100 in absence of diseases). A more recent classification of Gondo et al. (2006) divided centenarians into 4 categories according to their functional status, i.e. "Exceptional," with all of their functions graded as excellent, "Normal," exhibiting maintenance of fine cognitive and physical functions, "Frail," exhibiting impairment of either cognitive or physical functions, and "Fragile," exhibiting deterioration of both physical and cognitive functions. On the whole, these classifications allow to appreciate the extreme heterogeneity of centenarians as a group and the differences present between men and women, who likely follow different strategies to reach extreme longevity (Franceschi et al., 2000b; Candore et al., 2006a).

Indeed, it must be noted that, all around the world, the number of centenarian women is constantly higher than that of centenarian men. Italy is quite peculiar from this point of view, as a geographic North-to-South gradient is present: women-men ratio is about 7:1 in the Northern regions and it decreases progressively to 2:1 in the Southern regions. In very isolated surroundings like Sardinia island, this ratio is 1:1. The reason for such a gradient is at present unknown, even if it is likely that an important role can be played by the different rates of mortality between men and women, as well as social, genetics and anthropological differences. However, it has been reported

that this ratio is higher in population where life expectancy increases for economic and social reasons and tends to decrease in geographically isolated areas. Hence, a complex interaction of environmental, historical, and genetic factors, differently characterizing the various parts of Italy, likely plays an important role in determining the gender-specific probability of achieving longevity (Franceschi et al., 2000b; Passarino et al., 2002; Poulain et al., 2004; Caselli and Lipsi, 2006; Candore et al., 2006a; Robine et al., 2006; Rigby and Dorling, 2007).

Besides, in Italy men appear to be more selected with respect to women, and indeed, as reported in this issue by Franceschi et al., an association between polymorphisms of candidate genes and longevity is often more present in men than in women. These data on the demography of centenarians in Italy can represent a reference point for similar studies in other countries. The importance of these studies lies in the fact that half of the population (males) lives approximately 10% shorter lives than the other half (females) (Candore et al., 2006a). Understanding the different strategies that men and women seem to follow to achieve longevity may help us to comprehend better the basic phenomenon of aging and allow us to search for safe ways to increase male lifespan.

4. IMMUNOSENESCENCE AND INFLAMM-AGEING

A decreased ability to maintain homeostasis in response to external stressful stimuli, e.g. physical stress, starvation, can be demonstrated in the elderly. This deficit decreases the ability to maintain homeostasis, with an increased occurrence of diseases and death (Franceschi et al., 2000c). In Western countries, the mortality of individuals over 60 years old is up to 25 times that of people 25 to 44 years old; whereas the mortality rate increases in people over 65 years, if compared with individuals 25 to 44 years old by the following factors: 92-fold for heart disease, 43-fold for cancer, 100-fold for stroke, 100-fold for chronic lung disease, and 89-fold for pneumonia and influenza (Troen, 2003). These data suggest a key role for clonotypic and innate immunity in the control of the survival of the elderly, because resistance to these diseases depends, in part, on a well-functioning immune system (Licastro et al., 2005).

The ageing of the immune system, immunosenescence, is the consequence of the continuous attrition caused by chronic antigenic overload. Some of the most important characteristics of clonotypic immunity in ageing are compatible with this assumption since it is characterized by a decrease of virgin T cells and by the filling up of the immunological space by "megaclones" of memory T cells, resistant to apoptosis and capable of exerting negative regulatory functions (Franceschi et al., 2000a; De Martinis et al., 2005; Pawelec et al., 2004, 2005). Concomitantly, the antigenic load results in the progressive generation of inflammatory responses involved in age-related diseases, for which the name "inflamm-aging" has been proposed (Franceschi et al., 2000c). Most of the parameters influencing immunosenescence appear to be under genetic control, and research is trying to address this point (Licastro et al., 2005; Candore et al., 2006b). Therefore, immunosenescence fits the basic assumptions of evolutionary theories of ageing, such as antagonistic pleiotropy. In fact, the immune system, by neutralizing infectious agents, plays a beneficial role until the time of reproduction and parenting. Subsequently, determining a chronic inflammation can play a detrimental role late in life, a period largely unforeseen by evolution (Wick et al., 2003).

Thus, immunological features such as a powerful innate immunity and a high capacity to mount a strong inflammatory response, useful to survive infections at younger age in the past centuries and millennia, can become detrimental later in life in economically developed countries which allow people to survive for several decades after the age of reproduction. Inflamm-aging can thus be considered the main driving force for major age-related diseases and the evolutionary price to pay for an immune system fully capable of defending against infectious diseases at younger, reproductive age (Caruso et al., 2005; Candore et al., 2006b; Franceschi et al., 2007; Vasto et al., 2007). These major features of immunosenescence fit the data collected in the framework of the Italian centenarians, as discussed in the present issue by Sansoni et al..

Besides the pro-inflammatory status, these subjects are characterized by a state of hypercoagulability. This last point suggest that high plasma levels of the coagulation activation markers

in older population do not necessarily mirror a higher risk of arterial or venous thrombosis and it is compatible with the attainment of extreme ages, as described in this issue by Mari et al..

5.METABOLIC FEATURES

Data collected within the Italian centenarians also suggest that age-related changes in metabolic pathways and endocrine functions may occur. The findings on the higher frequency of the apolipoprotein-E (APOE) $\epsilon 4$ allele in middle-aged subjects than in centenarians were substantially confirmed. On the contrary, Italian findings did not confirm previous data on increased prevalence of the high-risk angiotensin I converting enzyme 1 (ACE1) D allele in French centenarians. The variability in the strength of association between ACE1 polymorphism and longevity could be related to regional differences in ACE1*D frequency in Europe, as recently reported for apoE $\epsilon 2$ and $\epsilon 4$ allele in centenarians (Panza et al., 2004).

Moreover, centenarians appear to have a remarkably low level of insulin resistance and favourable marker of glucose metabolism as discussed in the present issue by Barbieri et al.. Accordingly, the phenomenon of insulin resistance shows an age-related increase, and it reaches the highest peak in the cohort of 80-90-years old people, but there is a significant reduction of insulin resistance in subjects of 90 and 100 years. The major finding of such studies was that age-related insulin resistance is not an obligatory finding in the elderly. Why oldest old subjects have a lower degree of insulin resistance compared to aged (age >65 years) subjects, is unknown. The lack of insulin resistance in healthy centenarians should be considered the living evidence that a successful metabolic age-dependent remodelling might provide a consistent contribution for the extreme life span in this special group of subjects.

On the other hand, it results that a severe D hypovitaminosis plays an important role in the oldest old as a factor inducing a vicious circle involving hypocalcaemia, secondary hyperparathyroidism, even in the presence of sufficient renal functions, accompanied by a biochemical situation indicating a consistent loss of bone mass as discussed by Passeri et al., in the present issue.

Furthermore, to better understand the effect of some neuroendocrine changes in aging process, the adrenocortical, pineal and thyroid secretion in old and very old healthy subjects was studied by Ferrari et al. (present issue). Their findings suggest the maintenance of a certain circadian organization of melatonin secretion in centenarians and this could be considered as a marker of successful ageing.

6. PRESENCE OF DISEASES

From a clinical point of view, centenarians appear to be characterized by a large heterogeneity. Indeed their clinical status may vary from people in quite good shape from a physical and a cognitive point of view to subjects in bad shape affected by physical disability and dementia. Two pathologies appear to have a higher frequency in centenarians than in the elderly, *i.e.* cognitive impairment and respiratory pathologies. The former is about the 82.6% in all the centenarians; the latter strike a percentage of centenarians double with respect to the elderly, basing on autoptic data on broncopneumonias and chronic obstructive pulmonary disease; moreover clinical data indicate that, apart cough and catarrh, respiratory pathologies are present in 26.2 % of centenarians (IMUSCE unpublished observations).

Among centenarians, smoking is extremely rare, and even when it occurs among them, it is correlated almost exclusively to bad health conditions and non-autosufficiency, indicating that it compromises health status and the quality of life even in extremely long living subjects (Nicita-Mauro, this issue).

Moreover, it appears that diseases as Parkinson disease, diabetes, thyreopathies are less frequent in centenarians than in elderly people. This conclusion clearly emerges from a comparison between the 602 centenarians of the IMUSCE study with 5632 elderly people (age-range 65-84 years of age) from the Italian Longitudinal Study on Ageing (ILSA, 1997; IMUSCE unpublished observations). In particular, it is interesting to note that, as reported in the present issue by Motta et al., diabetes occurs in the oldest old population with a lower frequency than in the normal elderly, and becomes clinically apparent usually only after 90 years of age. Diabetes in the oldest old

persons is paucisymptomatic, and neodiagnosed diabetes is most frequently found in centenarians. The long-lasting diabetes, which starts at an age of about 60 years or earlier, usually does not allow attaining 100 years of age.

Another major killer in old age is represented by cardiovascular diseases. It would be expected that centenarians are protected from this type of pathologies (Terry et al., 2003; 2004; Galioto et al., this issue) and indeed the data on 140 autopsies in centenarians compared with the same number of autopsies in elderly subjects suggest that, while ischemic cardiopathies and cerebrovascular pathologies are similar in the two groups, acute myocardial infarction and cardiac amyloidosis are much less and much more frequent in centenarians than in elderly people, respectively. As far as the presence of tumors is concerned, data from autopsies reveal a higher prevalence of tumors and metastases in the elderly compared with centenarians (55.0% vs. 26.0%) (IMUSCE unpublished observations).

As far as the survival of centenarians (A-B-C groups), those belonging to Group A displayed 2.3 years survival in average (32.5% of them up to 3.0 years) while those belonging to Group C had only 1.6 years of mean survival (31.0% of them died within 1 year) (IMUSCE, unpublished observations).

8. THE GENETICS OF LONGEVITY.

An impressive and coherent series of epidemiological data in different populations indicate the presence of a strong familial component of longevity. These studies demonstrate that parents, siblings and offspring of long-lived subjects (but not the spouses of the long-lived subjects who shared with them most part of their adult life) have a significant survival advantage, a higher probability to have been or to become long-living persons and to have a lower risk to undergo the most important age-related diseases, such as cardio- and cerebro-vascular diseases, diabetes and cancer, when compared to the appropriate control (Perls et al., 2002; Terry et al., 2003, 2004; Ikeda et al., 2006; Shoenmaker et al., 2006; Franceschi and De Benedictis, 2006).

The genetics of longevity appears to be quite peculiar, owing to the fact that it regards the post-reproductive period of life, a period largely non predicted by evolution and characterized by a progressive decrease of the force of selection. This can explain some paradox of the genetics of longevity, such as the increase of homozygosity in several polymorphisms regarding a variety of candidate genes in centenarians with respect to younger subjects and the possibility that today centenarians may have originated from an initial frail part of the cohort which was able to survive at younger (reproductive) age and it was later allowed to exploit genes useful in the post reproductive period of life. Again, it emerges that the remodelling process is crucial for longevity and that genetic traits which are useful in coping with stressors and are important for survival at younger age may become detrimental later in life. Vice versa it can be hypothesized that genes neutral or dangerous at younger age can become useful at old or extremely old age. Actually, it is clear that centenarians are part of a special biology in which different tissues and organs could not have reached the same level of senescence, a kind of mosaicism, and their genetics is post-reproductive (Franceschi and De Benedictis, 2006; Franceschi et al., 2005; Salvioli et al., 2006).

In this issue, the data collected on the genetics of human longevity, resulting from studies on Italian centenarians, are extensively commented by Franceschi et al. Data indicate that the model of centenarians is not simply an additional model with respect to well-studied organisms, and the study of humans has revealed characteristics of ageing and longevity (geographical and sex differences, role of antigenic load and inflammation, role of mtDNA variants) which did not emerge from studies in laboratory model systems and organisms. Moreover, many associations between gene variants and longevity have been found only in Italian population. This should not be unexpected, since ageing and longevity are complex traits resulting not only and not exclusively from genetics, but rather from the interactions between genetics, environment and chance (Candore et al., 2006a). In this perspective, it is conceivable that longevity can be achieved by different combinations of these three components, and thus, when gene pool and environment change, the combinations leading to longevity change as well (Franceschi et al., present issue)..

In particular, the data coming from the long-living male Italian population under study shows that the genetic polymorphisms responsible for a low inflammatory response might result in an increased chance of long life-span in an environment with a reduced pathogen burden. Such modern and healthy environment also permits to obtain a lower grade of survivable atherogenic inflammatory response (Candore et al., 2006b,c; Vasto et al., 2007).

Finally, some genetic determinants of longevity have been claimed to reside in those polymorphisms for the immune system genes that regulate immune responses. Many longevity association studies focused their attention on HLA (the human major histocompatibility complex) polymorphisms, but discordant results have been obtained as discussed by Caruso et al., 2000, 2001. In the present issue, Scola et al. report the results of a study performed on Sardinian centenarians. Their findings, although not significant, suggest that some HLA haplotypes might have a role in determining life span expectancy and longevity in Sardinians.

9. CONCLUSIONS.

A true successful ageing is apparently not possible despite the presence of almost normal haemato-biochemical parameters, as described in this issue (Ferlito et al.). Indeed, in a more realistic way “successful ageing”, can be defined as absence of overt or severe diseases and disabilities, maintenance of high levels of physical and cognitive abilities and preservation of the social and productive activities. In this perspective, the study of 602 centenarians performed within the framework of IMUSCE, allowed us to identify a consistent subgroup of centenarians devoid of clinically overt major diseases, maintaining good physical and cognitive abilities and rather autonomous in their daily life. However, none of them fitted the criteria of “maintaining the social and productive ability” and in this sense they cannot strictly be considered as “successfully aged”. Nonetheless, assuming less strict criteria, and avoiding any reference to any working activity, according to the IMUSCE results, we are confident that about 20% of the Italian centenarians we have studied were in “*good health status for their age*”. This is the best definition we can propose for the top subgroup of centenarians which emerges from the IMUSCE study. It combines the

awareness that centenarians are *de facto* extremely old, and show the sign of ageing, but at the same time clearly indicate that they are in good shape notwithstanding their very advanced age, on the basis of standardized criteria regarding the cognitive and physical abilities. With all these methodological limitations in mind, these data suggest that “healthy ageing” is a real possibility for human beings and cast some doubt on the pessimistic view that extreme age must always be accompanied with severe diseases and/or disabilities.

To conclude, ageing must be considered an unavoidable end point of the life history of each one, nevertheless our increasing knowledge about the mechanisms it is regulated by, allows us to envisage many different strategies to cope with, and delay it, in order to endow everybody with a long and good final part of the life.

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**Appendix 1.

The Italian Multicenter Study on Centenarians (IMUSCE)

Coordinators: M. Motta, C. Franceschi, L. Motta

List of participants of IMUSCE:

University of Bari: A. Capurso, F. Panza, V. Solfrizzi, A. D'Introno, A.M. Colacicco, S. Capurso
 University of Bologna: M. Capri, S. Salvioli, S. Valensin.
 University of Catania: M. Malaguarnera, E. Bennati, L. Ferlito, A. Franzone, R. Rapisarda
 University of Cosenza: G. De Benedictis, M. Berardelli
 University of Firenze : G. Masotti, E. Petruzzi, I. Petruzzi, P. Pinzani, F. Mantelacchi, M. Pazzagli, F.M. Antonini
 University of Foggia: C. Capurso University of Messina: V. Nicita-Mauro, C. Lo Balbo, A. Mento, C. Nicita-Mauro, G. Maltese, G. Basile
 University of Milano: D. Mari, R. Coppola, R. Provengano
 University of Modena: G. Salvioli, M.V. Baldelli, C. Mussi
 University of Napoli : M. Varricchio, M. Barbieri, A. Gambardella, G. Paolisso
 University of Palermo: G. Candore, C. Caruso, G. Colonna-Romano, D. Lio, L. Scola
 University of Parma: P. Sansoni, R. Vescovini, C. Biasini, F. Zanni, L. Zanlari, A. Telera, G. Lucchini, G. Passeri, M. Passeri
 University of Pavia: E. Ferrari, L. Cravello, L. Barili., S.B. Solerte, M. Fioravanti, F. Magri, F. Fagnoni
 University of Perugia: U. Senin, P. Mecocci, A. Cherubini
 University of Roma "La Sapienza": V. Marigliano, L. Tafaro, P. Cicconetti, F. Tombesi, M.T. Tombolillo, E. Ettore
 University of Siena : S. Forconi, S. Boschi, G.A. Righi, M. Guerrini
 University of Trieste: L. Giarelli†, G. Stanta
 National Institute on Aging, National Institutes of Health, Baltimore, Bethesda, MD (USA): L. Ferrucci, A. Ble, E.J. Metter, J M. Guralnik
 Istituto Superiore di Sanità, Department of Pharmaca, Roma: R. Pacifici, P. Zuccaro, I. Palmi
 Local Sanitary Unit No.3, Operative Unit of Geriatrics, Acireale (CT): S. Branca, M. Passamonte, M. P. Gargante, C. Risino
 Local Sanitary Unit No.6, Azienda Ospedaliera dei Bianchi, Corleone (PA): G. Fradà.

Physiotherapist: F. Motta

Laboratory technician: G. Crimi

All the listed participants of this study have contributed to the identification of cases, elaboration and compilation of the clinical records, to collection and evaluation of the data, therefore, the present work is the result of an intense collegial activity. We declare that all participants of IMUSCE have equal merits in all parts of this work.