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MS has been described in various populations and geographical regions with different frequencies.

Generally, the most commonly used frequencies in epidemiological studies of diseases are prevalence and incidence.

As described in the next subsection (etiopathogenesis), regional differences in MS prevalence and incidence have contributed to formulating a hypothesis on its pathogenesis.

Prevalence is traditionally defined as a measurement of the proportion of “events” in a population at a given point of time. “Event” is defined as the occurrence of any phenomenon that can be discretely characterized, for example: infection, presence of antibodies, pregnancy. In epidemiology, diseases or infections are the most commonly used events, and therefore prevalence can be defined as the proportion of people in a population (of a state, region, province) that, at any given time, are affected by the disease. Incidence, on the other hand, measures the number of new cases of a disease occurring during a given period (for example, in a month or a year) and identifies the risk (i.e. probability) of developing the disease in the considered population. Since incidence indicates a change in a quantity (new people affected) compared with the change in another quantity (time), it is considered to be a dynamic measure.

Epidemiological studies, as well as other studies, are made difficult by the particular nature of MS. In fact, epidemiological researches aimed at formulating and testing etiopathogenetic hypotheses demand levels of diagnostic accuracy

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which overlap in different geographical regions so that diagnostic criteria shared by the scientific community and applicable in different clinical settings are required.

In the case of MS, in the past but in the present too, the accuracy and application of well- defined and uniform criteria (such as the use of MRI criteria for MS diagnosis) cannot be taken for granted. In considering the accuracy of MS epidemiological studies, there is also the difficulty of identifying a control group of suitable size and characteristics. While presenting a higher incidence in a specific age range, MS may occur from childhood until the seventh decade; in particular, the onset of the disease often remains unrecognized for many years.

Another aspect to be considered is the role that genetic and racial factors play in susceptibility to the disease; these factors, although not yet clearly identified, are undoubtedly relevant variables.

Despite the above-mentioned difficulties, several epidemiological studies have been published [see 1–3] since the first prevalence surveys conducted from 1926 to 1929 [4–6].

The worldwide prevalence is estimated to be about 2.5 million people, 400,000 of whom live in the USA and 350,000 in Europe. Some studies have measured the death rate due to MS in a particular nation or geographic area, or in different geographic areas within the same nation, analyzing this event at the same time or different times. Other studies have aimed to identify prevalence or incidence rates as discussed above, in this case too taking account of the geographical and temporal parameters already mentioned. All these studies obviously consider the differences related to sex and race, but also other aspects related to social, economic and cultural factors. The most important information emerging from these studies is: mortality rates due to MS appear to be higher in temperate regions than in the tropics and subtropics, higher in Europe and North America than in Africa, South America, Asia and Mediterranean regions, higher in women than in men, in Caucasians than in non-Caucasians while, at least in the United States, the different rates between urban and rural areas do not seem to be significant.

Prevalence studies have shown a geographic distribution characterized by three distinct areas of disease frequency related to latitude. It is generally accepted that the prevalence of MS tends to increase with increasing distance from the equator. High-risk areas including Northern Europe, Southern Canada and Northern USA; medium-risk areas including southern Europe, the southern United States and Australia; and finally, low-risk areas including Asia, Alaska and Africa have been described. The current prevalence rates (50–80 cases/100,000 population) put Italy among the countries with the highest risk of the disease. In Italy MS incidence is approximately 3–8 cases/100,000 population per year, with significant regional variations and peaks in Sicily and Sardinia, reaching 45 cases/100,000 population. However, this hypothesis, based on latitude gradient, is not applicable in the most methodologically adequate studies designed to make reliable comparisons between

incidence rates and prevalence rates [2]. A meta-analysis of epidemiological studies published between 1980 and 1998, which standardized rates by sex and age applied to the European and the world population, found no correlation between MS frequency and latitude [7]. Small clusters with high prevalence were identified in northwestern Sardinia [8, 9], Sicily [10, 11] and in the north of Croatia [12].

In the United Kingdom and North America, the risk of MS developing in immigrants from the Far East remains low, while the risk increases in the second generation of immigrants from India [13]. These differences between immigrants and their descendants could reflect very early exposure to a possible environmental factor. Migration studies have led the way for research on possible environmental factors, suggesting a role of sun exposure in MS pathogenesis [14].

Studies carried out on populations from South Africa, Israel, Hawaii and immigrants in Britain correlate the risk of developing the disease with the place of residence during childhood [15–18].

People who migrate before age 15 to an area with a different risk from that of their original homeland, acquire the risk of their new homeland [16]. However, in Australia, an analysis performed on an extremely homogeneous population showed no effect related to migration age (cut-off age of 15 years), suggesting that the exposure risk covers a wider age range than initially hypothesized [18].

These data support the fundamental role of environmental factors in the pathogenesis of the disease, suggesting the hypothesis that MS is acquired long before its clinical onset. However, migration studies also have limitations due to estimates made on rates originating from samples which are numerically not representative and are not able to identify the exact moment when the exposure to environmental factor or factors occurred (cumulative effect).

MS usually begins at an age between 25.3 and 31.8 years, with an incidence peak at around 29.2 years [19]. However, cases of pediatric MS (2.7 %) and cases with onset after 60 years are also described [20, 21].

The average age of onset tends to be lower in the eastern Mediterranean (26.9) and to increase in Europe (29.2), Africa (29.3), America (29.4), and South-East Asia (29.5) as far as the Western Pacific areas, where the highest values are reported (33.3). It is generally accepted that low-income countries have an average age of onset of 28.9 years, while the average age of onset in high-income countries is 29.5 [19].

MS mostly affects the female sex, with a male/female ratio of 0.5 (range 0.40–0.67); the ratio is lower in Europe (0.6) and higher in Africa (0.33) and in areas of the Western Pacific (0.31). There are no differences between the social classes [19]. The ratio is higher for onset around or after puberty (0.2–0.4), but it is inverted if only very early onset MS cases are considered [22]. The female/male ratio seems to increase over time: a Canadian longitudinal study found that MS in women has approximately tripled over the past 60 years and that the female to male sex ratio now exceeds three women with MS for every one man (3.2:1) [23]

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