
LETTER TO THE EDITOR:

The food pattern in geographical relation to the risk of multiple sclerosis in the Mediterranean and Near East region

Since numerous investigations point to a cooperation of genetic and environmental factors in the aetiology of multiple sclerosis, epidemiological research is permanently challenged to identify putative risk factors and to generate new hypotheses. A prominent part of the human environment, when both frequency and intensity of contact are considered, is nutrition, which comprises numerous microbial (including viral) agents and immunologically and metabolically active compounds. Since multiple sclerosis has many characteristics of an autoimmune disorder, the fact that the gut associated immune system (GALT) is the most extended compartmentalised immunological organ¹ also justifies further attempts to identify putative risk factors in that special field by epidemiological means.

In ecological studies, a number of nutritional factors, mostly of animal origin and related to both meat²⁻⁷ and milk⁸ in particular, were suggested as multiple sclerosis related, whereas case-control investigations did not confirm these hypotheses;⁹⁻¹³ however, the low validity of that approach and the special value of ecological studies in the search for dietary risk factors have been emphasised.¹⁴

The remarkable geographic pattern of multiple sclerosis in the Mediterranean and Near East region offers special opportunities both to test these earlier views and to generate new hypotheses. Whereas more recent studies had revealed high to medium range prevalence rates (> 20 per 100 000) in southern Europe,^{15 16} in Israel,¹⁷ and in both population groups of Cyprus,¹⁸ low rates (\leq 10 per 100 000) were found in Libya,¹⁹ Tunisia,²⁰ Saudi Arabia,²¹ and among native Kuwaitis,²² although the methods of assessment varied in these developing countries. A particularly impressive finding was the steep gradient of the multiple sclerosis prevalence between Sicily (30-60 per 100 000) and Malta (4 per 100 000).²³

In a comprehensive list edited by the Food and Agriculture Organisation (FAO) of the United Nations,²⁴ the annual per caput intake of a variety of nutrients between 1962 and 1977 and of numerous individual food commodities between 1975 and 1977 is presented for many countries. These data were used for comparative evaluation of six countries at high/medium risk for multiple sclerosis (Italy, Spain, Yugoslavia, Greece, Cyprus, Israel) and four at low risk (Malta,

Tunisia, Libya, Saudi Arabia). Sixteen nutrients and 76 commodities from the FAO list were compared between both groups of countries by means of the Mann-Whitney U test. In addition, information on the habit of smoking for food preservation^{5 6} was sought in numerous works on ethnology, agriculture, and culinary arts, and in encyclopaedias from the countries or regions, respectively, under study; the practice of smoking was tested as a categorical variable by the Fisher test and by χ^2 analysis between high/medium risk and low risk countries. Those items that reached the admitted level of statistical significance ($p=0.1$) were further tested for compatibility with the multiple sclerosis distribution both worldwide and within Europe. The list of high/medium risk countries was then extended by the addition of the United Kingdom, France, Switzerland, Norway, Denmark, West Germany, Poland, and Hungary, and that of the low risk countries by Japan, Korea, and Malaysia (total 21 countries), using published multiple sclerosis data. All food items that showed a significant association with multiple sclerosis (U test; $p=0.05$) at this step were further tested between six northern/central European high risk countries (the United Kingdom, Norway, Sweden, Denmark, Finland, West Germany) and five Mediterranean medium risk countries (Italy, Spain, Greece, Yugoslavia, Portugal) making allowance for remaining differences in multiple sclerosis prevalence between northern and southern Europe¹⁶ (U test; $p=0.1$).

In the table, those food items are listed that met the criteria of a significant association with multiple sclerosis in all three tests along with the exact consumption data from Italy and Malta. As the result of this stepwise exclusion procedure, comparatively few factors remained compatible with the multiple sclerosis epidemiology in more general terms, although a great number of nutrients and commodities were originally associated in the Mediterranean/Near East region (eg, different nuts, many fruits, some vegetables such as potatoes and beans) (data not shown). It must be mentioned, however, that any type of dairy food, animal fat as such or specific animal fat products (lard, butter), wheat and oat products, and offals (as a surrogate marker for animal brain) were not significantly associated with multiple sclerosis in the region of main interest, and that distilled alcohol consumption was not in agreement with the worldwide pattern of multiple

sclerosis. From the nine items that were associated with multiple sclerosis in all three tests (table), only "coffee", "margarine", and "smoke preservation" were in agreement with the multiple sclerosis gradient between Italy and Malta. The latter factor was strongly associated with multiple sclerosis in the Mediterranean/Near East region and worldwide, but showed per se no clear variation between northern and southern Europe. When, however, quantitative data are taken into account, and a combined factor "smoked meat" or "smoked pork" is formed, the association is very high throughout. This factor is also compatible with the high risk of multiple sclerosis in Scotland and particularly in the Orkney and Shetland Islands and with the only transiently high incidence in the Faroe Islands,⁵ whereas coffee can hardly explain both epidemiological features.

Arguments for the biological plausibility of some agents occurring in smoked and cured meat (in particular nitrophenol haptens and their protein conjugates) have been put forward.²⁵ There appears at present to be no plausibility for the factor "margarine", which was also not compatible with the temporal pattern of multiple sclerosis in the Faroe Islands.⁵ Nevertheless, it seems justified to test all these variables (table) in case-control investigations, which should be restricted to younger multiple sclerosis patients having a relapsing-remitting course and include the parents in each case.

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Levels of significance (p, Mann-Whitney U test) reached by the food items associated with the multiple sclerosis (MS) prevalence in the Mediterranean/Near East region (Test A; p ≤ 0.1), in a worldwide comparison covering 21 countries (Test B), and in a third comparison covering six northern/central and five southern European countries (Test C). Data on per caput consumption in Italy and Malta are also given, along with final compatibility with MS considering all comparisons.

Commodity/nutrient	Test A (p)	Test B (p)	Test C (p)	Italy	Malta	Final compatibility with MS
Animal protein (g/d)	0.05	0.002	0.01	40.5	39.9	-
Total fat (g/d)	0.05	0.002	0.01	117	97	-
Calcium (mg/d)	0.1	0.05	0.02	747	735	-
Riboflavin (mg/d)	0.1	0.002	0.01	1.47	1.50	-
Pork (kg/year)	0.05	0.002	0.1	15.9	12.1	-
Total meat* (kg/year)	0.1	0.002	0.01	40.6	30.0	-
Margarine (kg/year)	0.1	0.01	0.01	1.2	0.6	+
Coffee (kg/year)	0.01	0.002	0.05	2.8	0.9	+
Beer (kg/year)	0.1	0.02	0.01	13.6	31.6	-
Smoke preservation (yes/no)	0.01	0.001	NS	yes	no	+

*Mammalian meat only

This work was supported by the Hertie Foundation, Frankfurt (Germany)

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