Diet and Multiple Sclerosis: a population-based study in the city of Biancavilla

Simona Toscano  
Department “GF Ingrassia”, Section of Neurosciences, Neurology Clinic, University of Catania

Clara Grazia Chisari  
Department “GF Ingrassia”, Section of Neurosciences, Neurology Clinic, University of Catania

Sebastiano Arena  
Department “GF Ingrassia”, Section of Neurosciences, Neurology Clinic, University of Catania

Salvatore Colandonio  
Department “GF Ingrassia”, Section of Neurosciences, Neurology Clinic, University of Catania

Maria Luisa Iudica  
ASP Catania, Adrano District, 95031 Catania

Maria Fiore  
Department “G.F. Ingrassia”, Environmental and Food Hygiene Laboratories, University of Catania, Catania

Margherita Ferrante  
Department “G.F. Ingrassia”, Environmental and Food Hygiene Laboratories, University of Catania, Catania

Alessandra Nicoletti  
Department “GF Ingrassia”, Section of Neurosciences, Neurology Clinic, University of Catania

Mario Zappia  
Department “GF Ingrassia”, Section of Neurosciences, Neurology Clinic, University of Catania

Francesco Patti (patti@unict.it)  
Department “GF Ingrassia”, Section of Neurosciences, Neurology Clinic, University of Catania

Research Article

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Abstract

Background

The influence of dietary habits on the pathogenesis of Multiple Sclerosis (MS) has been a topic of interest for years. The municipality of Biancavilla, in Southern Italy, is considered a high-risk area for MS, with a prevalence of 292.3/100,000 persons and an incidence of 16.8/100,000/year. We investigated the nutritional habits of this population to clarify the reasons of the increased incidence rate of MS recorded in this area in the last decades.

Methods

In this population-based case-control study conducted in the municipality of Biancavilla, we evaluated the intake frequency of different food products of 60 patients with MS and 174 sex-matched and age-matched controls. A semi-structured standardized questionnaire was administered to explore the weekly consumption of four categories of food (meat, fish, milk/dairy products, fat dressings of vegetable origin) during the periods of childhood-early adolescence (before the age of 15) and during late adolescence-adulthood (after 15 years).

Results

The intake of meat was not different between cases and controls, nor globally neither considering each type of meat (beef, pork, sheep meat, horse meat, cold meats, sausages, smoked meat, brain). Similarly, no differences were detected in the intake frequency of fish (bluefish, riverfish, smoked fish, crustaceans, mollusks), milk and dairy products of different animal origin, nor in the consumption of fat products of vegetable origin (margarine, olive and seed oils) between cases and controls.

Conclusion

The results of our study clearly indicate no association between the intake frequency of different food products and MS in the town of Biancavilla.

Background

In recent years, there has been much speculation about the influence of dietary habits on health. Since environmental factors are known to be implicated in both triggering and modulating the course of Multiple Sclerosis (MS) in genetically susceptible subjects, possible relations between nutritional habits and MS have been assumed (1, 2). Of note, the influence of dietary habits on MS could be sensitively different depending on the age of exposure, as for other environmental factors (3-7).
Particularly, the energy-dense, poor-fiber and animal-based diets of Western countries have been associated with changes in the composition of the gut microbiota, which are supposed to be responsible for the development of a chronic low-grade systemic inflammation (2), the translocation of bacteria from the gut into the circulation (8) and the disruption of the blood-brain barrier (2). This assertion is supported by reported findings of a distinct gut microbiota in MS patients compared with healthy controls (9), which proved to play a relevant role in the development of the experimental autoimmune encephalomyelitis (EAE) (10). Saturated fatty acids, trans fatty acids, red meat, sugar, refined carbohydrates and proteins of the milk fat globule membrane are considered as proinflammatory dietary factors (11) and some evidence of correlation between MS and a high consumption of red meat (12, 13) and milk and dairy products have been provided, though results are not univocally accepted (14–16). Conversely, omega-3 polyunsaturated fatty acids, vitamins, carotenoids, oligoelements, thiolic compounds and polyphenols exhibit anti-inflammatory properties, mostly acting as antioxidants (2). Particularly, some studies reported a beneficial effect of a low-fat diet with a preferred intake of polyunsaturated fatty acids on MS (2, 17). In this perspective, we investigated the nutritional habits of MS patients resident in the municipality of Biancavilla, in Southern Italy, as a part of a population-based project (18). With a prevalence of 292.3/100,000 persons, this town is considered a high-risk area for MS, whose mean annual incidence of MS has increased from 4.5/100,000 in the period 1992–1996 to 16.8/100,000 in 2012–2018. With this in mind, an investigation on the possible environmental risk factors for MS in this population could clarify the reasons of the increased incidence rate of MS recorded in this area in the last decades.

Methods

We administered a face-to-face semi-structured standardized questionnaire (19) to 60 patients, diagnosed with MS according to 2017 revision of McDonald’s criteria, whose onset of disease occurred before December 2017. As controls, we enrolled 174 sex-matched and age-matched (± 5 years old) healthy subjects. All subjects provided informed consent to participate the study and for publication of any identifying information included in the manuscript. The study was conducted according to the guidelines of the Declaration of Helsinki of 1964 and later amendments, and approved by the Ethics Committee of the A.O.U. Policlinico-San Marco of Catania.

Speculating a different impact of nutritional habits in triggering MS depending on the age of exposure, we investigated the intake of different food products during childhood-early adolescence, identified as the period “before 15 years”, and during late adolescence-adulthood, identified as the period “after 15 years”. The questionnaire explored the weekly consumption of different food products, belonging to four categories: meat, fish, milk/dairy products, fat dressings of vegetable origin. Particularly, the first subsection investigated the intake frequency of beef, pork, sheep meat, horsemeat, cured meats, sausages, smoked meat, brain. The second item included questions about the frequency of fish consumption, distinguishing between bluefish, river fish, crustaceans, molluscs and smoked fish. The third item explored the dietary intake of milk and dairy products, including cow’s milk, sheep’s milk, cow’s cheese, sheep’s cheese, smoked varieties and butter. The last category investigated the intake of fat dressings of vegetable origin, including margarine, olive oil and seed oil.
For each question, one of the following five answers was provided: never/very rarely, less than once a month, less than once a week, from one to six times a week, daily. Likert-type answers obtained from the survey for each food product were considered as ordinal data, ranging from 0 to 4. Median and interquartile range were used to synthetize the consumption of each category of food (meat, fish, milk/dairy products, fat vegetable dressings), then Wilcoxon rank-sum test were used to compare the intake between cases and controls (Table 2). For further analysis, dichotomous values were used, considering the intake frequency as “less than 1/week” when answers 0, 1 or 2 were provided, while “more than 1/week” when answers 3 or 4 were given, reporting the respective frequencies and percentages of consumption. We estimated the risk of MS by calculating the odds ratio (OR) and 95% confidence intervals (CI) in binary logistic regression models, including sex, age and educational attainment as covariates and the rare or frequent consumption of each food product as an independent variable, considering a p value of <0.05 as significant for all tests. The power analysis was reported as 1-β, considering α = 0.05.

Results

The demographic and clinical characteristics of the study population are reported in Table 1. We recruited 60 cases and 174 sex-matched and age-matched (± 5 years old) healthy controls. Of them, 55 cases (92%) and 166 controls (95%) completed the survey. Some differences were detected in the educational attainment between cases (22.1% graduated high school, 7.1% got a university degree) and the age- and sex-matched controls (14.3% graduated high school, 12.5% got a degree), though not reaching statistical significance ($\chi^2(5) = 10.5; p = 0.06; V = 0.22$).
Table 1
Demographic and clinical characteristics, by case and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>20 (33.3)</td>
<td>51 (29.3)</td>
</tr>
<tr>
<td>N; %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study entry age, y</td>
<td>42.1 ± 11.4 (22–71)</td>
<td>40.9 ± 13.0 (16–69)</td>
</tr>
<tr>
<td>Mean ± SD; range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational attainment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N; %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No education</td>
<td>12 (7.1)</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td>Primary school</td>
<td>47 (28.0)</td>
<td>26 (46.4)</td>
</tr>
<tr>
<td>Middle school</td>
<td>60 (35.7)</td>
<td>11 (19.6)</td>
</tr>
<tr>
<td>High school</td>
<td>10 (6.0)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Professional training course</td>
<td>27 (16.1)</td>
<td>6 (10.7)</td>
</tr>
<tr>
<td>Degree</td>
<td>12 (7.1)</td>
<td>7 (12.5)</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>28.4 ± 10.6</td>
<td>-</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>31.52 ± 10.80</td>
<td>-</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, m</td>
<td>164.7 ± 106.6</td>
<td>-</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS at diagnosis</td>
<td>1.75 (1.0-3.5)</td>
<td>-</td>
</tr>
<tr>
<td>Median (25th -75th )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS phenotype</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>N; %</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>RRMS</td>
<td>50 (83.3)</td>
<td>-</td>
</tr>
<tr>
<td>PPMS</td>
<td>4 (6.7)</td>
<td>-</td>
</tr>
<tr>
<td>SPMS</td>
<td>6 (10.0)</td>
<td>-</td>
</tr>
</tbody>
</table>

y: years; m: months; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; RRMS: relapsing-remitting MS; PPMS: primary progressive MS; SPMS: secondary progressive MS
The consumption of different food products was not significantly different between cases and controls, neither before nor after the age of 15 years (Table 2).

More specifically, the intake of meat did not differ between cases and controls, also considering the type of meat (beef, pork, sheep meat, horse meat, cold meats, sausages, smoked meat, brain; see Additional file 1 for details). Similarly, the intake frequency of fish was comparable between cases and controls and there were also no differences for specific kind of products (bluefish, riverfish, smoked fish, crustaceans, mollusks; see Additional file 2 for details). Intakes of milk from different animals (cows and sheep), as well as of dairy products (cheese from cow’s and sheep’s milk, smoked cheese, butter), were not different between cases and controls (see Additional file 3 for details). Fat products of vegetable origin (margarine, olive and seed oils) were consumed similarly by cases and controls (see Additional file 4 for details).

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumption of different food products before and after the age of 15 in case and control groups.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meat</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15 years</td>
<td>1.5 (1.0–2.0)</td>
<td>1.5 (0.5-2.0)</td>
<td>0.64</td>
</tr>
<tr>
<td>&gt; 15 years</td>
<td>1.5 (1.0–2.0)</td>
<td>1.5 (0.5-2.0)</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Fish</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15 years</td>
<td>0.0 (0.0–1.0)</td>
<td>0.0 (0.0–1.0)</td>
<td>0.90</td>
</tr>
<tr>
<td>&gt; 15 years</td>
<td>1.0 (0.0–1.0)</td>
<td>1.0 (0.0–1.0)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Milk/dairy products</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15 years</td>
<td>1.0 (0.0–2.0)</td>
<td>1.0; 0.0–2.0</td>
<td>0.98</td>
</tr>
<tr>
<td>&gt; 15 years</td>
<td>0.5 (0.0-1.5)</td>
<td>1.0; 0.0–2.0</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Fat products of vegetable origin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 15 years</td>
<td>2.0 (1.0–3.0)</td>
<td>1.0 (0.0–2.0)</td>
<td>0.35</td>
</tr>
<tr>
<td>&gt; 15 years</td>
<td>2.0 (1.0–3.0)</td>
<td>1.0 (0.0–2.0)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Values refer to a Likert-type scale ranging from 0 (never/very rarely) to 4 (daily). *Wilcoxon test was used for this comparison

Discussion
The results of our study clearly indicate no association between the intake frequency of different food products and MS in the population of Biancavilla. At present there is no clear advice to follow a specific diet for people with MS, as confirmed by data coming from the NARCOMS registry, which investigated the prevalence of 19 different diets among 6990 MS patients without recognizing a specific alimentary regimen among patients (20).

Furthermore, despite some evidence of a proinflammatory role of the Western-type diet has been reported (2, 21), results are not univocal. Evidence from the literature reported a moderate correlation between prevalence of MS and total meat intake ($r = 0.61, p < 0.01$), particularly pork consumption ($r = 0.97, p < 0.001$) (12), while an OR = 2.07 (1.18–3.63) and an OR = 1.38 (1.13–1.68) were reported for processed and unprocessed meat (13). However, other studies reported no association between meat and MS (22, 23). In order to solve the ongoing debate, the association between the intake of different red and processed meat intake and the development of chronic inflammatory diseases, including MS, during a follow-up period of 25 years, will be evaluated in an ongoing study developed out of a Danish open register-based cohort study involving 57'053 persons (24).

With regard to fish intake, there is some evidence in literature about a protective role towards MS. An OR = 0.69 (0.55–0.87) (23) and a OR = 0.77 (0.64–0.92) (25) were reported in literature for the consumption of 0.5–2.99 fresh fish servings per week between cases and controls. These results have been confirmed in a more recent study by Hedström and coworkers, which assessed an association between an increased risk of MS and a low intake of fish (OR 1.2, 95% CI 1.1–1.4) (26). As regards the association between the intake of milk and dairy products and the development of MS, such hypothesis had been speculated several years ago, also relying on the evidence of molecular mimicry between butyrophilin and myelin oligodendrocyte glycoprotein (MOG) (15, 27). However, such a molecular mechanism was found to have possibly a non-pathogenic role and rather to prevent the development of the experimental autoimmune encephalomyelitis (EAE) through an upregulation in IL-10 secretion and a reduction in Th1 proliferation (28). A worldwide study, conducted in 1992, reported a correlation between cow milk consumption and MS prevalence with $r = 0.84 (p < 0.001)$ and between butter intake and MS with $r = 0.62 (p = 0.01)$. However, results have been inconclusive and conflicting here too, with some studies reporting a significant lower intake of dairy products in cases compared with controls (29). Finally, despite many patients frequently use alternative therapies and dietary supplements, the role of dietary intervention as a complementary treatment on MS outcomes is unclear and the strength of the evidence existing in literature is limited by the small number of the cohort and the retrospective nature of the studies (30). At the current stage, the best option is probably still represented by the Mediterranean diet, which is recommended by the American Heart Association (31), particularly for its beneficial effect in decreasing cardiovascular risk and improving glycemic control (32).

According to our results, the high incidence of MS in the town of Biancavilla (18) is likely to be not related to dietary habits. However, our study has several limitations. First of all, its retrospective case-control design makes it prone to selection and recall bias, and possibly to reverse causality, which should all be taken into account in interpreting analysis (33). Nevertheless, case-control studies are the most suitable
in order to investigate environmental factors, since cohort studies are expensive and rarely available for low-incidence diseases as MS, requiring a very large study population and a long follow-up time to collect enough cases. Secondly, some possible confounders may not have been considered nor obtained from the collected data, as BMI during childhood and adolescence, smoking status, alcohol intake and the consumption of some foods excluded from the questionnaire, as fruits, vegetables, poultry and sugar. Finally, the small simple size does not allow us to generalize our results, but is due to the population-based nature of the study (18).

**Conclusion**

The results of this study cannot clarify the role of nutrition in the development of the disease, as only large, well-designed and prospective studies would be able to do. However, they can lead to shift the focus on the investigation of other environmental factors, possibly justifying the increased incidence rate of MS observed in Biancavilla. For this purpose, results from the other sections of the questionnaire used in this study will be evaluated, particularly data about exposure to toxicants and pesticides, contact with animals, agricultural or industrial work, comorbidities, infectious diseases during childhood and vaccinations, in order to comprehensively investigate most of the currently known risk factors for the development of MS (34, 35) (Fig. 1).

**Declarations**

*Ethics approval and consent to participate.* The study was conducted according to the guidelines of the Declaration of Helsinki of 1964 and later amendments, and approved by the Ethics Committee of the A.O.U. Policlinico-San Marco of Catania.

*Consent for publication.* All subjects involved in the study provided informed consent to participate the study and for publication of any identifying information included in the manuscript.

*Availability of data and materials.* The datasets analyzed during the current study are available from the corresponding author on reasonable request.

*Competing interests.* The authors declare no competing interests.

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*Authors’ contributions.* Conceptualization: Simona Toscano, Clara Grazia Chisari, Francesco Patti, Alessandra Nicoletti; Data curation: Simona Toscano; Clara Grazia Chisari, Sebastiano Arena, Salvatore Colandonio; Formal analysis: Simona Toscano, Clara Grazia Chisari, Maria Fiore; Funding acquisition: Francesco Patti; Investigation: Francesco Patti, Salvatore Colandonio; Methodology: Francesco Patti, Simona Toscano, Clara Grazia Chisari, Maria Fiore, Margherita Ferrante, Alessandra Nicoletti; Project Administration: Francesco Patti, Clara Grazia Chisari, Simona Toscano; Resources/participants
References


Figures
Prevalence and Incidence of Multiple Sclerosis in the City of Biancavilla

Figure 1

Schematic of the population-based case-control study conducted in the town of Biancavilla.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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- Additionalfile3.pdf
- Additionalfile4.pdf