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# A Possible Role of an Interaction of the Age at Common Childhood Infections and Selected Dietary Factors at Young Age, for the Risk of Multiple Sclerosis

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## Abstract

An increased risk of multiple sclerosis (MS) had been found when individuals had consumed large amounts of processed meat and sausages at young age (Lauer, 2014). Furthermore it was found in many studies that MS patients had acquired a number of common childhood infections at higher ages than controls. Therefore, MS patients from an epidemiological long-term investigation in Germany and different hospital controls, were evaluated for a statistical interaction of these two factors. 324 MS patients and 242 hospital controls were inquired. The study focussed on age 0 - 16. Subjects were tested for additive interaction by multiple linear regression analysis (Knol et al., 2007). There was an additive interaction of the age at any common childhood infection with the consumption of scalded sausages (regression estimate = 0.1370; standard error = 0.0603; p = 0.0239). In contrast, no such interaction could be shown for: animal fats; smoked meat (e.g. ham and bacon); and cold - smoked German salami. Thus there was a synergy of the intake of scalded sausages (e.g. frankfurters, bolognas, etc.) and age at common childhood infections, for the later risk of MS.

Key-words: multiple sclerosis; epidemiology; diet; childhood infections; interaction.

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## Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the human central nervous system (CNS) with many autoimmune characteristics. The disease typically starts at age 15 - 50, and the clinical course is quite variable. In many patients it leads to permanent neurologic disability [1]. The multifactorial aetiology of the disease includes a variety of genetic factors, in particular those involved in immune functions [2-4], but the majority of the overall risk (ca. 70%) is caused by the environment [5,6]. Epidemiological research of the past 20 years has revealed a number of factors which bear an increased risk of MS, i.e. late infection with Epstein-Barr virus (EBV) [7], vitamin D deficiency [8-10], tobacco smoking [10], and consumption of processed meat and sausages in the diet [11,12]. However, conclusions on the definite role of all these factors and their causal pathway cannot yet be drawn. In particular, the inconsistency of the wide distribution of all these factors in the normal population of industrialized countries on one hand and the rather exceptional occurrence of MS on the other, make them unlikely to play an isolated role. An interaction, however, with other genetic and / or environmental factors might be quite possible.

The type of interaction in epidemiological studies is still a matter of debate [13-20]. Recent papers argued much in favour of additive models when public health issues are concerned [16-20]. In case - control investigations, we [21,22] and many others [e.g. 23-25] have reported a higher risk of MS if one or another type of infection typically occurring in early life (e.g. measles; rubella; pertussis; chickenpox; and infectious mononucleosis), were acquired later in childhood, in adolescence, or even in adulthood. Another risk factor in the causality of MS was the intake of processed meat, in particular of scalded sausages (frankfurters; bolognas; etc) [11,12], which are cured with nitrites and subsequently smoked at higher temperatures (> 50°C). In the present study, the data pool of the epidemiological long - term investigation of MS in Southern Hesse, Germany [21,22], and two subsequent case - control investigations [26,27] were analysed, which used the same pool of MS patients but different types of hospital controls. The age when childhood infections occurred and several food variables were tested for additive interaction at age 0 -16 for the later risk of MS [16,19,20].

## Methods

Data of 324 patients with definite or probable MS (230 females, 94 males) according to Bauer's criteria (29) from Southern Hesse, Germany [21,22,28] were included in the present study. All patients had two or more attacks, or a primary progressive course of MS. The mean year of birth (YOB) of the MS patients was 1948 (SD: 13.1 years; range 1913 - 1974). The epidemiological study, including the questioning of all MS patients on their diet in childhoor and early adolencence, lastet from 1985 - 1998. 242 hospital controls (139 females; 103 males) were collected in three phases: (a) 41 patients with lumbar disc herniation, or other types of orthopaedic low - back pain, were interrogated by K.L. from 1986 - 1987, with the same questionnaire as the MS patients [21]; (b) a second group (n = 99) with the same diagnoses was interrogated by A.W. in 1994 - 1996 as part of a doctoral thesis [26]; and (c) a third group (n =

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102) which had been treated by varying minor surgeries (e.g. appendectomy; herniotomy; cholecystectomy; etc.), were interrogated in 1997 - 1998 by M.G. at the Department of Surgery of the Elisabethenstift Hospital in Darmstadt, Germany as part of another doctoral thesis; patients with a severe overall status and all cancer cases were excluded from the latter group [27]. The mean YOB of all hospital controls (n = 242) was 1949 (SD: 13.8 years; range 1912 - 1978).

MS patients and hospital controls were personally interviewed with a questionnaire which had identical questions on the study variables. Childhood infectious diseases were interrogated, with the possible answers "yes" or "no", and if "yes" the age was questioned when the respective disease (measles; chickenpox; rubella; whooping cough; infectious mononucleosis in part of the interviewees) had occurred (0 – 5 years; 6-9 years; 10+ years). "Any childhood infection with manifestation at age 0 - 5 (score 0) vs. 6+ years (score 1)" was finally taken as the first exposure. The questions on food were dichotomized, and the following food variables were interrogated: "intake of animal fat"; and ingestion of: "smoked meat (ham; bacon)"; "cold - smoked German salami"; and "scalded sausages (e.g. frankfurters; bolgnas; etc.)". These were the second of exposure variables, respectively. All subjects gave their informed consent for inclusion. The study was conducted in accordance with the Declaration of Helsinki.

Additive interaction was tested by the standard procedure of multiple linear regression [16,19], where the model included altogether the intake of: "animal fat"; "smoked meat"; "cold - smoked German salami"; and a product term of "scalded sausages plus age 6+ at any childhood disease" ("yes" = score 1; "no" = score 0). The statistical software Statistica for the Windows$^{R}$ [30] was used for all calculations.

## Results

There was no significant difference of the YOB between MS cases and hospital controls (Student's t = 0.0691; not significant), but the sex distribution of MS cases showed a higher number of females than among the hospital controls (fourfold - table test: $chi^2 = 11.21$; p = 0.0008).

To test for collinearity of the independent variables, a correlation analysis by Spearman's rho was made, after stratification for MS patients and hospital controls. Among controls, there was a borderline correlation between the intake of "scalded sausages" and "cold - smoked German salami"; and a significant correlation between the latter factor and "smoked meat". No association was found between the intake of "scalded sausages" and "animal fat" (Table 1).

**Table 1**

Among MS patients, there was a highly significant correlation between "cold - smoked German salami" and "scalded sausages", and between "animal fat" and "smoked meat". No correlation of "smoked meat" with "cold - smoked German salami" was found, and even a reversed borderline association of "scalded sausages" with the intake of "animal fat" was apparent (Table 2).

**Table 2**

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In order to test for a role of single dietary variables on the risk of MS, these factors were individually included into logistic models, with adjustment for sex (or unadjusted for "sex", and "smoked meat" because of high collinearity) (Table 3). The analysis revealed significant results for "female sex", "animal fats", "cold - smoked German salami", "smoked meat" (borderline), and "scalded sausages" (borderline)(Table 3).

**Table 3**

In order to test for a possible interaction, both age at childhood infections (age 0-5 vs.6+ years) and all the dietary variables were simultaneously included into one single linear regression model. The interaction variable of "scalded sausages plus late childhood infection at age 6+" was significant, whereas the interaction of all other dietary variables with age at childhood infections were not (Table 4). Age at childhood infection showed a borderline reversed association with MS in the multivariate model, and female sex was independently associated with MS, as was YOB later than 1950.

**Table 4**

## Discussion

In the present study, an additive interaction of "age at any childhood infection" and "consumption of scalded sausages at age 0-16 years" was found to be a risk factor for later MS. Both factors were insignificant if they were studied individually. The findings were all the more remarkable, as there was considerable confounding between most of the dietary exposures tested which, however, should diminish, and not exaggerate, the Odds Ratios (31).

The term "any childhood infections", as used in the present investigation, only partly included infectious mononucleosis, which became apparent as a risk factor for MS first in the course of the epidemiologic long - term study. Meanwhile infectious mononucleosis has been shown by many authors, including ourselves [e.g. 26,32,33], to be related to the risk of MS, and a role of the infection with EBV was demonstrated in a meta - analysis [34]. Since infectious mononucleosis was not recorded in all the patients of the present study, it was not feasible to analyse it in a proper way. A major contribution of EBV to the overall association seems possible, but a higher age at infection with EBV or other neurotropic agents during childhood might also be an explanation. Our data are in agreement with ecological studies in 16 regions so far [11,12,35,36] which have shown a risk of processed meat or sausage intake for the later acquisition of MS. Furthermore, there was a considerable limitation in the time frame when this risk factor truly occurred, and it is prudent to advise all young patients with any infectious disease to abstain from all processed meats and sausages during symptomatic infection (e.g. with cough; fever, malaise; etc.) and a rather short period of recovery (ca. one week).

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The present data suggest the following hypothetical scenario for the generation of MS: a young individual (e.g. at age 5 - 15 [37,38]) has acquired one or another infectious disease caused by some neurotropic agent (including, but not restricted to infectious mononucleosis) which is a very common event. In a limited time period of the infectious disease process, the individual has a disturbance of both the mucosal barrier in the gut [39] and the blood - brain barrier [40,41] due to the infection. In the great majority of cases, central nervous system (CNS) inflammation is clinically not apparent, although a disruption of the BBB is present in a surprisingly high number of cases [40]. Only when this individual is exposed, within this critical period, to nitro

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- phenylated carrier conjugates in form of smoked and nitrite - cured meat products [42] (e.g. scalded sausages), an autoimmune process is started which involves the CNS because also the BBB is disturbed at that particular time. Alternatively. a compound specific to animal myelin (e.g. myelin basic protein; proteolipid protein; myelin oligodendrocyte glycoprotein; etc.) might be acting as a carrier for nitro - phenylated haptens [43]. In that case, the situation may be similar to experimental animals which develop an autoimmune disease of the thyroid, if they are treated with nitro - phenolic thyroglobulin [44]. The nitro - phenol conjugates in the meat, [42] may be considered an “amplifier” towards an autoimmune status of the consumer. In fact, animal proteolipid protein, a specific marker of CNS tissue used in the diagnosis of bovine spongiform encephalitis (BSE), was shown to occur in a surprisingly high number of sausage types sold on the market in Bavaria, Germany; animal brain material had been added silently by the manufacturers due to its excellent emulsifying property and low costs [43]. It seems likely that the formation of clinical autoimmunity takes a longer time of months, or even years; the time, however, until the start of symptomatic autoimmune disease might be considerably shortened and clinical disease possibly aggravated, if the same scenario occurs repeatedly in time in one individual, with either the same or some other infectious agent(s).

In conclusion, there was a significant interaction between the age at any childhood infection and the consumption of scalded sausages early in life, for the later risk of MS. Further studies elsewhere to corroborate the findings are needed.

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**Conflict of Interest:**
The authors declare no conflict of interest.

**Authors contribution:**
K.L. interrogated all MS patients and part of the hospital controls. He made all statistical calculations, and wrote the paper. A.W. and M.G. interrogated two other, different parts of hospital controls, respectively.

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**Table 1**

| variables | no. | Spearman's rho | p - level |
|---|---|---|---|
| animal fat * German salami | 139 | -0.0321 | n.s. |
| animal fat * smoked meat | 140 | 0.1372 | n.s. |
| animal fat * scalded sausage | 138 | 0.0341 | n.s. |
| smoked meat * German salami | 202 | 0.1465 | 0.0375 |
| smoked meat * scalded sausage | 202 | 0.1015 | n.s. |
| German salami * scalded sausage | 202 | 0.1345 | 0.0563 |

Table 1: Rank correlation of independent variables in hospital controls. n.s. = not significant ($p > 0.10$).* = correlated with.

**Table 2**

| variables | no. | Spearman's rho | p - level |
|---|---|---|---|
| animal fat * German salami | 268 | -0.0836 | n.s. |
| animal fat * smoked meat | 270 | 0.2035 | 0.0008 |
| animal fat * scalded sausage | 271 | -0.1012 | 0.0963 |
| smoked meat * German salami | 272 | 0.0423 | n.s. |
| smoked meat * scalded sausage | 275 | 0.1152 | 0.0563. |
| German salami * scalded sausage | 273 | 0.1679 | 0.0054 |

Table 2: Rank correlation of independent variables in MS cases. Further legend cf. Table 1.

**Table 3**

| variable | estimate | SE | p – level |
|---|---|---|---|
| female sex* | 0.5950 | 0.1784 | 0.0009 |
| animal fats | 1.0248 | 0.2133 | < 0.0001 |
| smoked meat* | 0.3594 | 0.1919 | 0.0617 |
| German salami | 0.4484 | 0.2067 | 0.0306 |
| scalded sausage | 0.3568 | 0.1896 | 0.0605 |

Table 3: Logistic regression of food variables with MS when only sex, or no variable*, were adjusted.

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**Table 4**

| variable | B | SE | p - level |
|---|---|---|---|
| intercept | 0.6095 | 0.1195 | <0.0001 |
| female sex | 0.1599 | 0.0561 | 0.0046 |
| YOB 1951+ | 0.1407 | 0.0562 | 0.0129 |
| animal fat | 0.0465 | 0.1115 | n.s. |
| smoked meat | -0.1138 | 0.1213 | n.s. |
| German salami | 0.1062 | 0.1076 | n.s. |
| scalded sausage | 0.0031 | 0.0045 | n.s. |
| any CI at age 6+ | -0.2302 | 0.1266 | 0.0699 |
| “animal fat” plus “any CI at age 6+” | 0.1317 | 0.1233 | n.s. |
| “smoked meat” plus “any CI at age 6+” | 0.1045 | 0.1356 | n.s. |
| “German salami” plus “any CI at age 6+” | 0.0771 | 0.1251 | n.s. |
| “scalded sausage” plus “any CI at age 6+” | 0.1370 | 0.0603 | 0.0239 |

Table 4: Multiple linear regression model for testing additive interaction [16, 19]. B = linear regression estimate. SE = standard error. CI = childhood infection. n.s. = not significant.