

# A possible role of an interaction of the age at common childhood infections and selected dietary factors at young age, for the later 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 scalded sausages in childhood and adolescence. Furthermore, it was found in many studies that MS patients had acquired one or another common childhood infection at higher ages than controls. As a consequence, MS patients from an epidemiological long-term investigation in Germany, and two different hospital control groups, were analysed for a statistical interaction of these two factors. 324 MS patients and 242 hospital controls from an epidemiological long-term investigation was inquired. The study focussed on age up to 16 years. Individuals were tested for additive interaction by multiple linear regression analysis. There was an additive interaction of a higher age at one or another common childhood infection and the consumption of sausages cured with nitrate or nitrite, and were additionally hot-smoked at >50°C (regression estimate = 0.1370; standard error = 0.0603;  $p = 0.0239$ ). In contrast, no such an interaction could be demonstrated for: animal fats; smoked meat (e.g. ham and bacon); and cold-smoked (German) salami. In conclusion, there was a synergy of the intake of scalded sausages (e.g. frankfurters, bolognas, etc.) and the age at common childhood infections, for the risk of MS later in life.

## 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 years, and the clinical course is quite variable. In many patients, it leads to a permanent neurologic disability [1]. The multifactorial aetiology of the disease includes a variety of genetic factors, particularly those involved in immune functions [2-4], but the bulk of the overall risk (ca. 70%) is caused by environmental factors [5,6]. Epidemiological research of the past 30 years has revealed some items which bear an increased risk of MS, e.g. late infection with Epstein-Barr virus (EBV) [7], deficiency of vitamin D [8-10], tobacco smoking [10], and dietary factors as insufficient amounts of vegetables and fruit [11-13], rareness of fish and seafood [12,14], and high intake of processed meat [15,16]. However, conclusions on the definite role of all these factors and their causal pathway cannot yet be drawn. In particular, an inconsistency of the wide distribution of these factors in the normal population of Western 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 other environmental factors is possible.

The type of interaction, i.e. multiplicative or additive, in epidemiological studies is a matter of debate [17 - 24]. Recent reports argued much in favour of additive models when public health issues are concerned [20-24]. In case-control investigations, we [25,26] and many others [e.g. 27 - 29] 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, particularly of scalded sausages (e.g. frankfurters and bolognas) [15,16]. For preservation, these sausages are processed by curing 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 [25,26], and of two subsequent case-control investigations [30,31] were analysed. These two studies used the same pool of MS patients, but two different kinds of hospital controls. The age when childhood infections occurred, and several food variables were tested for an additive interaction at age 0-16 for the risk of MS later in life [20,23,24]. Childhood was focused, because important risk factors occur at this early age [32 - 34].

## Methods

Data of 324 patients with definite or probable MS (230 females, 94 males) according to Bauer's criteria [35] from Southern Hesse, Germany [25,26,36] 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, was done during 1985 – 1998,

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including questioning of all MS patients on their diet in childhood and early adolescence. 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. with an identical questionnaire as the MS patients from 1986 - 1987 [25]; (b) a second group (n = 99) with the same orthopaedic diagnoses were interrogated by A.W., as part of her doctoral thesis, in 1994 - 1996 [30]; and (c) a third group (n = 102) which had been treated with varying minor surgeries (e.g. appendectomy; herniotomy; cholecystectomy; etc.), were interrogated by M.G. at the Department of Surgery of the *Elisabethenstift* Hospital in Darmstadt, Germany, as part of another doctoral thesis in 1997 - 1998; patients with a severe general condition and all cancer cases were excluded from the latter group [31]. The mean YOB of all the hospital controls (n = 242) was 1949 (SD: 13.8 years; range 1912 - 1978).

MS patients and hospital controls were personally interviewed by one of the authors, with a questionnaire that 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 taken as the first exposure. The following food variables were interrogated: “intake of animal fat”; and ingestion of: “smoked meat (ham; bacon)”; “cold - smoked (German) salami”; and “scalded sausages”. All food items were originally asked by means of a food - frequency questionnaire (FFQ) with four ordered categories, which were finally dichotomized to “at least once per week” vs. “more rarely”. 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 [20,23]. The model included, altogether, the intake of: “animal fat”, “smoked meat”, “cold - smoked salami”, and a product term of “scalded sausages and age 6+ at any childhood disease” (“yes” = score 1; “no” = score 0). The statistical software (German) Statistica for the Windows™ [37] was used for all calculations.

## Results

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

For testing for collinearity of the independent variables, a correlation analysis by Spearman’s rho was made, after stratification in MS patients and hospital controls. In controls, there was a borderline correlation between “scalded sausages” and “cold - smoked (German) salami”. A correlation was also found between “cold - smoked (German) salami” and “smoked meat”. No association occurred between “scalded sausages” and “animal fat” (Table 1).

In 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 shown (Table 2).

For testing a role of single dietary variables on the risk of MS, these factors were individually included into logistic models, with adjustment

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

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 2.** Rank correlation of independent variables in MS cases. n.s. = not significant ( $p > 0.1$ ). \* = correlated with.

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

for sex, or unadjusted for “sex” and “smoked meat” because of high collinearity (Table 3). There was a significant association with “female sex”; “animal fats”; “cold - smoked (German) salami”; “smoked meat” (borderline); and “scalded sausages” (borderline) (Table 3).

To test for an interaction, age at childhood infections (age 0 - 5 vs. 6+ years) and all of the dietary variables were included in a linear regression model. The interaction variable of “scalded sausages and late childhood infection at age 6+” was significant, whereas the interaction of all the other dietary variables with age at childhood infections were not (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 MS later in life. Both factors were not related to, or only borderline associated with MS, respectively, when studied individually. The findings are, all the more, remarkable as there was a considerable confounding between most dietary exposures that were tested (Tables 1 and 2). Confounding, however, should rather more diminish instead of exaggerate the Odds Ratios (38).

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 during our epidemiologic long - term studies. Meanwhile, infectious mononucleosis has been shown by many authors, including ourselves, to be associated with the risk of MS [30,39,40], and a role of the infection with EBV was demonstrated in a meta - analysis [41]. Since infectious mononucleosis was not recorded in all 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 is possible, but a higher age at infection with other, including several, neurotropic agents during childhood

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

variables	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 4.** Multiple linear regression model for testing additive interaction [16, 19]. B = linear regression estimate. SE = standard error. YOB = year of birth. CI = childhood infection. n.s. = not significant.

Variables	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” + “any CI at age 6+”	0.1317	0.1233	n.s.
“smoked meat” + “any CI at age 6+”	0.1045	0.1356	n.s.
“German salami” + “any CI at age 6+”	0.0771	0.1251	n.s.
“scalded sausage” + “any CI at age 6+”	0.1370	0.0603	0.0239

and adolescence might be another explanation. Our data agree with ecological studies in 16 regions which showed a risk of processed meat for MS later in life [15,16,42,43]. Furthermore, there was a considerable limitation in the time frame when both risk factors occur together in one individual. Thus, it is prudent to advise young patients with any infectious disease, including those with only minor symptoms such as cough, fever and malaise, to abstain from all scalded sausages during symptomatic infection and a rather short period of recovery.

In accordance with the literature, the present data suggest the following hypothetical scenario: a young individual (e.g. at age 5 - 15 [33,34]) has acquired one or another infectious disease caused by some neurotropic agent. This is a very common event. In a very limited period of the infection, the individual has a leakage of both the mucosal barrier in the gut [44] and of the blood - brain barrier [45,46] due to that infection. In the great majority of cases, central nervous system (CNS) inflammation, though common, is clinically not apparent although a disruption of the blood - brain barrier is present in a high number of cases [45]. Only when, in this critical period of both leaky barriers, scalded sausages are presented to the individual, an autoimmune process is started which involves the CNS, because also the BBB is damaged at that time. Nitro - phenylated carrier conjugates which are formed in smoked and nitrite - cured meat products [47], may play a critical role. It is even possible that a compound of animal myelin (e.g. myelin basic protein; proteolipid protein; myelin oligodendrocyte glycoprotein) present in the meat [48], might act as a carrier for the nitro - phenylated haptens. In that way, the situation may be comparable to experimental animals which develop an autoimmune disease of the thyroid, when they are treated with nitro - phenolic thyroglobulin [49]. The nitro - phenol conjugates in the meat [47] may be considered “amplifiers” towards an autoimmune status of the individual. In fact, animal proteolipid protein, a specific marker of CNS tissue which is commonly used in the diagnosis of bovine spongiform encephalitis (BSE), was present in a high number of sausage types

sold on the market in southern Germany, where this brain material of animal origin had been added by manufacturers due to its good emulsifying property at low cost [48].

The long exposure time in the present study may argue for additional factors than nitrophenol haptens, which are present in the meat product. For example, in many countries, sausages contain whole milk or milk powder [50,51]. In Germany, however, milk is not permitted in sausage fabrication (with very few exceptions) [52]. Furthermore, there was no evidence for milk consumption as a risk factor for MS in our case - control studies [30,31]. Thus, e.g. the hypothesis of a role of milk butyrophilin that was shown to cross - react with epitopes of myelin oligodendrocyte glycoprotein (MOG) [53], is not supported by the present data.

It seems very likely that the formation of clinical autoimmunity takes months, or even years. The time, however, until the start of a symptomatic autoimmune disease might be considerably shortened, and the clinical disease aggravated, when the same scenario occurs repeatedly in time in one individual, with either the same or different infectious agent(s).

It should be clearly stated that a reduction of the severity of MS by other dietary measures (e.g. increased intake of: n6 - polyunsaturated fatty acids as vegetable oils [54]; polyphenols from vegetables and fruits [12,55]; and n3 - polyunsaturated fatty acids from fish and seafood [56-59]), are not referred to by the present data. They should be studied also more in detail.

In conclusion, there was a significant interaction between the age at any childhood infection and the consumption of scalded sausages at the age up to 16 years, for the risk of MS later in life. Further investigations to corroborate the findings in other populations, and studies of population controls, are warranted.

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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 the other hospital controls.

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