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Multiple sclerosis and varicella zoster virus infection: A review

R. A. MARRIE[1] AND C. WOLFSON[2]*

[1] *Montreal Neurological Institute 3801 rue Universite, Montreal, Quebec H3A 2B4*
[2] *Department of Epidemiology and Biostatistics, McGill University and Centre for Clinical Epidemiology and Community Studies, Jewish General Hospital, 3755 Chemin de la Cote Ste Catherine, Montreal, Quebec, H3T 1E2*

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SUMMARY

We have evaluated the epidemiological evidence for an aetiological role of varicella zoster virus (VZV) infection in the development of multiple sclerosis (MS). A MEDLINE search of the English language literature for 1965–99 identified 40 studies. These studies were categorized as seroepidemiological (13), case-control (23), historical cohort (2) or ecological (2). One study used both case-control and historical cohort methodologies. Studies were then classified according to methodological rigour, using criteria derived from published guidelines for the epidemiological study of MS. There was a large variability in the quality of evidence. The five studies with the best methodology failed to show an increased risk of MS associated with varicella or zoster infections. At the present time there is insufficient evidence to support an important aetiological role of VZV infection in the development of MS.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) typically affecting young and middle-aged adults. A disorder of cell-mediated immunity is postulated, but the underlying aetiology remains unknown. Recently, a multifactorial aetiology was proposed, in which multiple environmental factors act together in a genetically susceptible individual to cause the disease [1]. Geographical and temporal variation in incidence and prevalence, and an apparent age-dependent change in disease risk with migration, support an aetiological role for environmental factors [2].

* Author for correspondence: Centre for Clinical Epidemiology and Community Studies, Sir Mortimer B. Davis-Jewish General Hospital, Rm A114, 3755 Chemin de la Cote Ste Catherine, Montreal, Quebec, H3T 1E2.

Infection is touted as a potential aetiological agent. Animal models of virally-mediated CNS demyelination exist, the mechanisms of which are unknown [3]. Viruses of the herpesvirus family are of interest because of their neurotropism, ubiquitous nature, and tendency to produce latent, recurrent infections [4]. Varicella zoster virus (VZV) is the herpesvirus that causes varicella (chickenpox) and zoster, representing primary infection and reactivation, respectively. By the age of 15 years, 95% of individuals in developed countries have acquired the infection [5].

Nasopharyngeal infection is followed by viraemia and then by the appearance of VZV-containing disseminated cutaneous vesicles [6]. Retrograde transport of the virus to trigeminal and dorsal root ganglion sensory neurons is followed by development of latent infection at these sites. Reactivation of the disease, as zoster, occurs in 1% of the general population per year [6]. Associated CNS complications of varicella

Table 1. *Criteria used for rating of studies*

Study rating	Seroepidemiological	Case-control	Historical cohort	Ecological
A	• Clearly described case definition including reference to established criteria. • Controls selected from an a priori defined study base. • Laboratory investigators blinded to subject status. • Statistical analysis specified and appropriate.	• Use of incident cases. • Clearly described case definition. • Controls selected from an a priori defined study base. • Exposure ascertainment methods with interviewers blinded to subject status/hypotheses. • Exposure ascertainment described, standardized for cases and controls. • Confirmatory source for recalled data. • Inclusion of an aetiologically relevant time period. • Statistical analysis specified and appropriate.	• Clearly defined cohort. • Exposure of interest defined. • Clearly described case definition. • Statistical analysis estimating relative risk.	• Use of completely assessed incidence or prevalence material with subclassification by childhood residence. • Disease rates across differing geographical regions determined by uniform methodology. • Adjustment for confounding variables such as age. • Selection of an appropriate time frame between exposure and disease. • Calculation of correlation coefficient with confidence interval.
B	• Clear definitions of cases and controls not reported. • Blinding not reported/absent. • Statistical analysis unspecified.	• Clear definitions of cases and controls but using prevalent cases. • Otherwise meeting criteria of A.	• Not meeting criteria of A.	• Disease occurrence measured by incidence rate only. • Non-uniform methods used to obtain disease rates. • Failure to consider confounding variables such as age. • Failure to calculate confidence interval for correlation coefficient. • Failure to select an appropriate time frame between exposure and disease.

Table 1. *Cont.*

Study rating	Seroepidemiological	Case-control	Historical cohort	Ecological
C	• Not meeting criteria of B.	• Use of prevalent cases. • Controls selected without regard to study base. • Incomplete/unreported blinding of exposure ascertainment. • Time period not aetiologically relevant or poorly presented. • No confirmatory source for recalled data. • Otherwise meeting criteria of A.	Not meeting criteria of A.	• Disease occurrence measured by incidence rate only. • Non-uniform methods used to obtain disease rates. • Failure to consider confounding variables such as age. • Failure to calculate confidence interval for correlation coefficient. • Failure to select an appropriate time frame between exposure and disease.
D		• Not meeting any criteria of A, B or C.		

are uncommon, with an observed incidence of less than 1% [5]. These include cerebellar ataxia, generalized meningoencephalitis, transverse myelitis, aseptic meningitis and Reye's syndrome [5]. Varicella zoster virus has been examined as a potential aetiologic agent in MS in numerous studies. In this article we evaluate the epidemiological evidence for an aetiologic role of VZV in MS.

METHODS

A MEDLINE search of the English language literature (1965–99) was conducted with subject headings 'multiple sclerosis' and 'varicella' or 'herpes zoster' or 'chickenpox' or 'shingles' or 'infection' or 'case-control' or 'cohort' or 'seroepidemiol*' or 'risk'. Bibliographies of all articles retrieved were searched for additional articles. Studies were categorized by design into four groups, seroepidemiological, case-control, historical cohort and ecological studies. Only case series, case reports and reviews were excluded as we wished to have a broad view of the evidence available. Ratings of methodological rigour were assigned by one of us (RAM) using criteria derived from published guidelines for the epidemiological study of MS [7–9] (Table 1). There were no previously published guidelines for the evaluation of sero-epidemiological studies in MS so these were created for this review using the basic principles of the other guidelines. In each category the criteria for a rating of 'A' were those considered to characterize an ideal study. The lowest rating assigned usually indicated a study lacking all of the ideal characteristics needed for an 'A' rating. Ratings between the highest and lowest ratings identified studies with some but not all of these ideal characteristics. Where necessary for complete evaluation of a study, any prior publications referenced were retrieved. We separately considered the evidence concerning frequency of infection, the age at which infection occurred, and antibody studies in serum and CSF.

RESULTS

Electronic and hand searches identified a total of 41 published papers. There were 13 seroepidemiological, 2 ecological, 2 historical cohort and 24 case-control studies. Out of these 41 papers, 2 were published twice and therefore each duplicate publication counted as one study, and a third included both a case-control

Table 2. *Case-control studies*

Author (year)	Number cases	Number controls	Results*: freq infection and seroprevalence	Results: age at infection	Design issues	Rating
Italian MS Study Group (1989) [13]	318 incident	1975	No difference in varicella OR = 0·85 (0·64–1·12), or zoster 1·19 (0·77–1·85) frequency			A
Casetta (1994) [14]	104 prevalent	150	No difference in frequency of varicella	No difference in varicella over age 5 yr OR = 0·9 (0·54–1·64)	Prevalent cases.	B
Gusev (1996) [15]	155 prevalent	169	No difference in varicella frequency OR = 1·00 (0·64–1·52)	No difference in varicella after age 15 yr OR = 0·33 (0·01–8·08)	Prevalent cases	B
Alter (1968) [16]	36 prevalent	72	No difference in frequency of varicella (OR = 1·36) or zoster (OR = 0·65)		Unblinded data collection. Prevalent cases. Lack of information on selection of subjects	C
Bansil (1997) [17]	156 prevalent	147	No difference in varicella frequency, OR = 0·8 ($P = 0·49$)	No difference in age at infection.	Prevalent cases. Lack of information on selection of cases and controls	C
Beebe (1969) [10]	379 prevalent	379	No zoster cases in either group		Prevalent cases. No diagnostic criteria. Lack of information on selection of subjects. Blinding not reported.	C
Berr (1989) [18]	63 prevalent	63	No difference in frequency of varicella **Zoster more frequent among cases, $P < 0·05$**	Tendency varicella at later ages	Prevalent cases. Unblinded data collection. Lack of information on selection of subjects.	C
Cendrowski (1969) [19]	300 prevalent	300	No difference in varicella frequency; Zoster less frequent, $P < 0·01$		Prevalent cases. Poor diagnostic criteria. More controls older and male. Blinding not reported.	C
Currier (1974) [20]	60 prevalent	60	No difference in frequency of varicella or zoster		Prevalent cases. Blinding not reported. Lack of information on selection of subjects.	C
Gronning (1993) [21]	155 prevalent	200	No difference in frequency of varicella OR = 1·1	No difference in age at varicella, $P = 0·47$ (7·2 yr *vs.* 7·1 yr).	Prevalent cases. Unblinded data collection.	C
Gudmundsdottir (1979) [38]	42 prevalent	42	No difference in seroprevalence of varicella antibodies; or in serum titers.		Prevalent cases. Blinding not reported.	C
Haile (1982) [22]	72 prevalent	72	No difference in varicella frequency OR = 1·13 (0·57–2·24)		Prevalent cases. Questionnaire use unblinded.	C
Hopkins (1991) [24]	18 prevalent	61	No difference in varicella frequency		Prevalent cases. Blinding not reported.	C
Kurtzke (1997) [25]	21 prevalent	187	No difference in varicella frequency.		Prevalent cases. Blinding not reported.	C
Panelius (1969) [11]	146 prevalent	146	No difference in varicella or zoster frequency, $P > 0·05$		Unblinded data collection. Prevalent cases.	C
Panelius (1970) [12]	229 prevalent	391	No difference in varicella or zoster frequency		Blinding not reported for interview. Prevalent cases.	C
Poskanzer (1980) [33]	77 prevalent	154		No difference in age at varicella	Blinding not reported. Prevalent cases	C

Table 2 (*cont.*)

Author (year)	Number cases	Number controls	Results*: freq infection and seroprevalence	Results: age at infection	Design issues	Rating
Riikonen (1989) [35]	28 prevalent	184		No difference in age at varicella	Included cases with optic neuritis. Blinding not reported. Prevalent cases.	C
Souberbielle (1990) [26]	153 incident (most)	153	No difference in varicella frequency, 60·1 % *vs.* 62 %		Unblinded data collection. Prevalent cases.	C
Bachmann (1998) [36]	606 prevalent	Entire pop'n		**81·9 % MS patients had varicella at age 5–19 years vs. 39·0 % controls**	Data collection not standardized and unblinded. Prevalent cases.	C
Compston (1986) [27]	177 incident, prevalent	164	No difference in zoster frequency		Unblinded data collection. Only acutely relapsing patients, and those with isolated demyelinating lesions included.	C
Lenman (1969) [28]	50 prevalent	50	No difference in varicella frequency. Zoster more frequent in cases, $P < 0{\cdot}05$		No diagnostic criteria. Data collection not standardized and unblinded. Prevalent cases.	D
Ross (1965) [29]	76 prevalent	76	No difference in varicella or zoster frequency		No diagnostic criteria. Blinding not reported. Lack of information on selection of cases.	D
Sullivan (1984) [37]	88 prevalent	88		No difference in age at varicella	Subjects from previous cohort for genetic study and sporadic; selection poorly described. Prevalent cases.	D

* Statistically significant results in **bold**.

design as well as a cohort design and therefore counted as two study designs [10].

Frequency of infection

Case-control studies

Panelius et al. published two articles with results derived from a single study; thus all results were considered together. This study was rated as 'C' [11, 12]. The remaining 18 studies included 1 'A', 2 'B', 12 'C', and 3 'D' studies [10, 13–29] (Table 2).

The only 'A' study was conducted by the Italian MS Study Group, enrolled incident cases, and assessed past exposure using a questionnaire administered by trained interviewers. No statistically significant difference in the reported frequency of varicella or herpes zoster among cases and controls was detected [13]. The 'B' studies of Casetta et al., and Gusev et al. enrolled prevalent cases, used trained interviewers, and had results consistent with those of the Italian MS Study Group for both varicella and herpes zoster infection [14, 15].

The 'C' studies used prevalent cases, generally provided less information about the selection process for cases and controls, and either lacked or did not report blinding of exposure ascertainment [10, 11, 16–26]. None of these studies detected a difference in the reported frequency of varicella. Five of those studies also assessed zoster but again, none detected a difference in the reported frequency of herpes zoster [11, 16, 20, 23, 26].

Three of the 'C' studies assessed only zoster [10, 18, 19]. Beebe et al. used US Army records to conduct a study of 379 cases and (matched) controls [10]. They neither provided diagnostic criteria for cases, nor described the method of selection for the cases and controls. Assuming that there was no association between zoster and MS, only one-third of a case of zoster would have been expected in each of the case and the control group. Indeed, no zoster was observed in either group. Berr et al. identified an increased frequency of zoster among MS patients (17·5%) as compared to controls (5·3%), $P < 0{\cdot}05$, but data collection was conducted by one of the investigators who was presumably aware of both the study hypothesis and the disease status of the study subjects [18]. No difference was found in the frequency of varicella infection. Cendrowski et al. found a decreased frequency of zoster, $P < 0{\cdot}01$, but not varicella among cases [19]. In this study the control group was more frequently male and was older. As zoster occurs with increasing frequency with increasing age this discrepancy in the age distribution in the comparison groups may have been responsible, at least in part, for the observed difference in zoster frequency.

Compston et al. ('D') did not detect a difference in zoster frequency [27]. Exposure ascertainment by Compston et al. was not blinded and the case definition included MS cases only if the patients were acutely relapsing, and also included subjects with isolated demyelinating lesions [27]. Ross et al. did not report the diagnostic criteria used, describe the source of the cases, or discuss blinding of exposure ascertainment [29]. They found no difference in the reported frequency of zoster. Lenman et al. found an increased frequency of zoster among MS cases, but this was one of the earliest studies, suffering from the same limitations as Ross et al. [28, 29]. The definition of multiple sclerosis was not clearly described, data collection was not standardized, and the interviewer was not blinded [28].

Historical cohort studies

There were two historical cohort studies, both 'B' rated [10, 30] (Table 3). Ragazzino and Kurland identified a cohort of 590 patients with zoster by chart review and accumulated 9389 person-years of follow-up, yet were unable to detect an increased incidence of MS among this group as compared to an expected number calculated from age and sex-specific incidence rates in Rochester, USA [30]. However, this study was underpowered as the authors themselves estimated that 190000 person-years of follow-up would be required in order to detect a threefold increase in MS incidence with a power of 85%. Beebe et al. used the US Veterans' database to assemble a cohort of 636 US veterans hospitalized for zoster [10]. They estimated that in a cohort of this size less than one case of MS would be expected. No cases were observed. Based on these results Beebe et al. concluded that there was no association between zoster and multiple sclerosis, but the sample size was probably too small. Furthermore the diagnostic criteria were not discussed.

Ecological studies

Ross et al. conducted two ecological studies concerning varicella, one rated 'A' and the other 'B' [31, 32]. The 'A' study examined the association between varicella incidence rates in the 5–14 year age-group,

Table 3. *Historical cohort studies*

Author (year)	Cohort size	Design issues	Results	Rating
Ragazzino (1983) [30]	590	Underpowered to detect a difference	No cases of MS	B
Beebe (1969) [10]	636	Lacking diagnostic criteria; possibly underpowered	Expected 1/7th of a case; none observed	B

and MS case-to-control ratios in the United States [31]. There were positive correlations between mean ($r = 0{\cdot}344$, $P = 0{\cdot}037$), median ($r = 0{\cdot}384$, $P = 0{\cdot}019$) and maximum ($r = 0{\cdot}301$, $P = 0{\cdot}07$) varicella incidence rates and MS ratios, but there were clear outliers in both Arizona and Nebraska. Arizona has a low case-control ratio of MS but a high incidence of varicella, while Nebraska has a high case-control ratio of MS but a low incidence of varicella. The other study compared the incidence rates of MS, zoster and varicella among the Hutterite population of Manitoba, Canada, to those of non-Hutterites matched for age, sex and area of residence [32]. MS, varicella and zoster all occurred significantly less frequently among the Hutterites than would be expected for the Manitoban population as a whole ($P < 0{\cdot}02$, $P < 0{\cdot}001$, $P < 0{\cdot}0001$, respectively).

Age at acquisition of infection

In addition to the reported occurrence of infection several studies also examined the age of infection.

Case-control studies

Poskanzer et al. published two articles with results derived from a single study; thus all results were considered together and the study rated as 'C' [33, 34]. Therefore, 2 'B', 5 'C', and 3 'D' studies examined the association between MS and the age at which varicella infection occurred [14, 15, 18, 21, 22, 25, 33, 35–37]. The 'B' studies did not find a difference in the reported ages of varicella infection [14, 15]. Casetta et al. [14] and Gusev et al. [15] enrolled prevalent cases and assessed past exposure using questionnaires administered by trained interviewers.

Haile et al. and Berr et al. found non-significant increases in the reported age at which varicella infection occurred among MS patients relative to controls [18, 22]. Prevalent cases were used and questionnaires were administered by one of the investigators. None of the other studies detected a difference [21, 25, 33, 35].

Bachmann ('D') found a shift in the age-at-acquisition curve among cases to later age ($P = 0{\cdot}01$) [36]. Bachmann compared retrospectively collected data from cases with prospectively collected population data, likely representing a different cohort. Compston et al. and Sullivan et al. did not detect a difference in the age at varicella infection [27, 37].

Seroprevalence studies

Case-control studies

Seroprevalence data were presented in three case-control studies all rated as 'C' [23, 33, 38]. This group of studies used prevalent cases and generally did not discuss blinding of laboratory procedures. Panelius et al. found an increased prevalence of VZV antibodies and increased titres among MS patients [23]. The other two studies did not find significant differences in either prevalence or titres of VZV antibodies [33, 38]. Two studies, both rated as 'D', measured titres but not the prevalence of varicella antibodies in serum [27, 29]. Ross et al. found that varicella titres were increased in MS patients ($P < 0{\cdot}05$) [29]. Compston et al. did not detect a difference [27].

Seroepidemiological studies

Two 'B' studies and one 'C' study measuring seroprevalence were identified [39–41] (Table 4). These three studies found no difference in the prevalence of VZV antibodies. Seven other studies (3 'B', 4 'C') measured VZV antibody titres in MS patients and comparison groups [42–48]. As a group the seroepidemiological studies provided poorer descriptions of case definitions and of the sources of cases and controls. Several studies also failed to discuss blinding of laboratory investigations. None of the studies rated as 'B' detected a difference in VZV antibody titres [42, 47, 48]. Sample sizes were 19–134.

Table 4. *Seroepidemiological studies*

Author (year)	Number cases	Number controls	Design issues	Results*	Rating
Leinikki (1982) [49]	18 incident	120		MS cases: no difference in seroprevalence; **higher prevalence of CSF antibodies**	A
Salmi (1974) [51]	87 prevalent	101		No difference in CSF prevalence	A
Bray (1983) [39]	313 prevalent	406	Poor description source of subjects	No difference in seroprevalence	B
Chiodi (1987) [47]	28 prevalent	7	Blinding not reported	No difference in proportion with VZV antibodies in serum or CSF	B
Cremer (1980) [48]	134 prevalent	165	Blinding not reported	No difference in serum VZV titres or CSF prevalence	B
Forghani (1980) [50]	128 prevalent	151	Blinding not reported	**Higher prevalence CSF antibodies to varicella in cases, $P < 0{\cdot}01$**	B
Kinnunen (1990) [42]	19 prevalent	19	Blinding not reported	No difference in mean serum antibody titres of VZV	B
Myhr (1998) [40]	144 prevalent	170	Blinding not reported	No difference in seroprevalence of VZV antibodies, OR = 0·84 ($P = 0{\cdot}84$)	B
Brody (1971) [45]	97 prevalent	100			C
Ito (1975) [46]	59 prevalent	267	Blinding and diagnostic criteria not reported	**MS cases: mean serum VZV titres higher vs. all non-MS except rheumatoid arthritis; CSF antibody titres to VZV higher**	C
Nikoskelainen (1972) [43]	52 prevalent	91	Blinding, source of subjects and diagnotic criteria not reported	**No difference in serum VZV titres**	C
Sever (1971) [44]	106 prevalent	202	Diagnostic criteria not reported	**MS cases: Vermont- higher serum VZV titres, $P = 0{\cdot}025$**	C
Vartdal (1980) [41]	12 prevalent	12	Blinding not reported. Source of subjects not reported	MS cases: higher proportion with evidence intrathecal antibody synthesis	C

* Statistically significant results in **bold**.

The 'C' studies had variable results [43–47]. Sever et al. found that VZV titres were increased in the MS patients at only one of the three study sites (Vermont) [44]. Ito et al. also found that MS patients had higher titres, but Nikoskelainen et al. and Brody et al. did not [43, 45, 46]. Only Brody et al. discussed blinding of laboratory procedures [43–47].

CSF antibody studies

Seroepidemiological studies

Four studies examined the prevalence of VZV antibody in CSF [48–51]. Cremer et al. had also measured serum antibodies as noted above. The two studies rated as 'A' produced inconsistent results. Leinikki et al. found that a higher proportion of MS patients had VZV antibodies, but Salmi et al. did not [49, 51]. Similarly, the 'B' studies had conflicting results [48, 50]. Neither study discussed blinding of laboratory procedures.

One 'B' and one 'C' study compared VZV titres in CSF [46, 47]. No difference was detected by Chiodi et al. [47]. Twenty-eight prevalent cases with clinically definite MS were enrolled along with seven controls. However, the diagnostic criteria used were not indicated, nor were the source(s) of the cases and controls. Ito et al. found that titres were significantly increased among MS patients in their study [46]. This study also did not report the diagnostic criteria used for MS and blinding was not discussed.

DISCUSSION

Our search strategy evaluated only the English language medical literature. Important studies published in other languages could have been missed. The failure to contact experts in the field for studies may have missed unpublished studies. Due to publication bias these may have been more likely to be negative studies. The use of both electronic and hand searching should have minimized the number of studies written in the English language which were missed. All the studies identified, except case series, case reports and reviews were included in the study as we wanted a broad view of the literature available. The data available in most studies, however, were insufficient to allow a pooling of the results for a formal meta-analysis.

There is geographical and temporal variation in MS incidence rates, and there is an apparent change in disease risk associated with migration between areas with differing risks of MS, depending upon the age at migration [2]. Migration studies have been interpreted to indicate the importance of exposure to an environmental factor in early life between the ages of 10 and 15 years [2]. This has led to hypotheses that infections are aetiological factors in MS and that timing of these exposures is important.

The aetiological role of VZV infection in the development of MS has been examined in seroepidemiological, historical cohort, case-control and ecological studies. Cohort studies provide a strong level of observational evidence. These studies have the advantage of establishing exposure without the bias of already knowing the disease outcome. Case-control studies can also provide a strong level of evidence. These studies are strongest if incident cases are used, thus avoiding the risk of selective survivor biases and reducing the impact of recall bias. Ecological studies provide very weak epidemiological evidence. In these latter studies the average exposure of the population to a risk factor in the environment is examined. An individual classified in the exposed group may not actually share the exposure of the group, and there may be unidentified counfounding factors. These studies are best regarded as hypothesis generating. Seroepidemiological studies document evidence of prior infection but cannot establish when an infection occurred, its severity or even whether it was clinically symptomatic or asymptomatic. These studies are more appropriate for generating than testing hypotheses of risk. Ideally well-designed studies of each type would provide a consistent association. These weaker studies were included in order to see if there was such a consistent association throughout the literature.

In our evaluation of the epidemiological evidence, two historical cohort studies failed to detect a difference in the frequency of varicella infection between subjects with and without MS, however both were probably underpowered to detect a difference. The case-control studies reviewed consistently failed to show an association. The case-control studies with the strongest methodologies also failed to show an increased frequency of zoster among MS patients. Among the nine studies assessing age at infection, only the study with the weakest methodology found a significant difference. The seroepidemiological studies produced inconsistent and unconvincing results. Ecological studies provided the only evidence to support an aetiological role for varicella in multiple sclerosis but these studies are of minimal importance. At the

present time the epidemiological evidence is insufficient to support an aetiologic role of VZV infection in the development of MS.

Varicella zoster virus infection may be one of many factors causing MS in a genetically susceptible individual and may be neither a necessary nor a sufficient cause [52]. Exposure is likely to be highly prevalent among persons with and without MS, requiring large sample sizes to identify an effect. MS is relatively rare, probably with a long latency between exposure and symptom onset, making it difficult to verify the temporal relationship between exposure and disease onset. Future analytical studies should use large numbers of incident cases with blinded, trained interviewers using confirmatory sources for recalled data.

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