

Relative risk of schizophrenia for people with autoimmune intestinal diseases

Autoimmune diseases in cases or parents	Prevalence per 1000		Relative risk	
	Cases (7997)	Controls (199 915)	Univariate	Adjusted* (95% CI)
Coeliac disease	1.5	0.5	3.2	3.2 (1.8-5.9)
Crohn's disease	4.5	3.4	1.3	1.4 (1.0-1.9)
Ulcerative colitis	6.2	4.7	1.3	1.4 (1.0-1.8)

*Adjusted for wealth quarter of parents, urban residence, and family history of schizophrenia.

invited chose not to undertake self management and may therefore not consider this a desirable option. To our knowledge this is the first UK trial that invited unselected patients to self manage warfarin and as such may give a real indication of expected uptake. For patients keen to undertake self management three quarters were able to complete training. These patients considered it a convenient and valuable method of controlling their own health and most were enthusiastic to continue after the trial. If self management by patients is to become established standardisation and dissemination of training are needed, accompanied by practical guidelines to encourage back up from clinicians.

Contributors: EM managed the study, drafted the paper, and is a lead investigator. DF is principal investigator and critically revised the paper. DMCC and CF were research associates involved in field work, training, and assessing patients' data collection and management, and both reviewed the paper. HS produced the databases supported data cleaning and analysis and reviewed the paper. EM and DF are the guarantors.

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Ethical approval: Midland Research Ethics Committee.

- 1 Fitzmaurice DA, Murray ET, Gee KM, Allan TF, Hobbs FDR. A randomised controlled trial of patient self-management of oral anticoagulation treatment compared with primary care management. *J Clin Pathol* 2002;55:845-9.
- 2 Fitzmaurice DA, Machin SJ. Recommendations for patients undertaking self management of oral anticoagulation. *BMJ* 2001;323:985-9.
- 3 Sawicki PT. A structured teaching and self-management program for patients receiving oral anticoagulation. A randomized controlled trial. *JAMA* 1999;281:145-50.
- 4 Morsdorf S, Erdlenbruch W, Taborski U, Schenk JF, Erdlenbruch K, Novotny-Reichert G, et al. Training of patients for self management of oral anticoagulant therapy: standards, patient suitability and clinical aspects. *Semin Thromb Hemost* 1999;25:109-15. (Accepted 10 October 2003)

Coeliac disease and schizophrenia: population based case control study with linkage of Danish national registers

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Dohan proposed that an inherited defect interacting with an environmental trigger of gluten precipitated schizophrenia in some individuals, and provided supportive epidemiological evidence.¹ Some clinical trials and case studies showed that a cereal free diet improved remission of symptoms of schizophrenia.² The most important genetic marker found in the study of coeliac disease (6p23-p22.3)³ is very close to the dysbindin locus, which has been implicated in schizophrenia.⁴

Participants, methods, and results

The case sample comprised 7997 people older than 15 who were admitted to a Danish psychiatric facility for the first time between 1981 and 1998 with a diagnosis of schizophrenia and known maternal identity. For each case we randomly selected 25 controls from a subsample of all available controls, matched by year of birth and sex.

We searched records of the national patients' register for a history of autoimmune diseases in cases, controls, and their parents, in a manner that protected the anonymity of the participants. Denmark has few private health facilities, and treatment is free of charge, so that coverage of visits is nearly 100% complete. Diagnoses were according to the International Classification of Diseases (8th revision, 1981-94; 10th revision, 1995-8). We included coeliac disease (and closely related dermatitis herpetiformis), on the basis of prior scientific literature, and two autoimmune gastrointestinal conditions (ulcerative colitis and Crohn's dis-

ease), for which little or no scientific literature exists that implies an association with schizophrenia. We included major risk factors for schizophrenia because these might be confounders of an association with coeliac disease: socioeconomic position, urban residence, and family history of schizophrenia.⁵ Four patients, five mothers of patients, and three fathers of patients were being treated for coeliac disease before the patient entered a psychiatric facility (1.5 per 1000 population, table). In a conditional logistic regression model the relation of risk factors for schizophrenia replicated that found in the literature.⁵ The univariate relative risk for schizophrenia, given coeliac disease, was 3.2 ($P < 0.0001$), unchanged by addition of the covariates (table). The adjusted relative risks for Crohn's disease and ulcerative colitis, when using the covariates discussed above, were both 1.4 ($P < 0.08$ for Crohn's disease, and $P < 0.03$ for ulcerative colitis). When coeliac disease and four additional cases of dermatitis herpetiformis were combined in an adjusted model as described above, the relative incidence for either of the two disorders compared with neither disorder was 3.1 (95% confidence interval 1.8 to 5.2).

Comment

A history of coeliac disease is a risk factor for schizophrenia, as shown in this epidemiological study. The risk relation is strong but reflects a small proportion of cases of either disorder, since both disorders are rare.

Coeliac disease is presumably underascertained in this study. Only coeliac disease occurring before onset of schizophrenia in the case was considered, and only cases in hospitals or specialty clinics are included. Clinical symptoms of coeliac disease occur in only a fraction (about one in seven) of people with the pathognomic antibody.

Ascertainment bias does not explain the results because it would exist with equal strength for Crohn's disease and ulcerative colitis, and the relative risk for them is weak. Ascertainment bias would not affect the relation of schizophrenia and coeliac disease in parents, which had similar strength to that in cases.

Removal of gluten from the diet is not dangerous or expensive and is an effective treatment for coeliac disease. Failure of replication in earlier clinical trials of gluten withdrawal may have been the result of sampling fluctuation since coeliac disease is rare. New screening tests for coeliac disease are inexpensive and carry minimal risk and discomfort. An important question is the degree to which removal of gluten from the diet will alleviate symptoms in the small proportion of people with schizophrenia who screen positively for coeliac disease but do not show its classical symptoms.

Contributors: WWE and PBM designed the study. WWE, EA, and MB conducted the analyses of data. WWE drafted the manuscript. All authors contributed to the design of the analysis, interpretation of data and reporting of results. Noel Rose, Peter Zandi, and Alessio Fasano provided helpful advice. WWE had full access to (anonymous) data and assumes responsibility for the decision to submit the paper for publication.

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- 1 Dohan F. Cereals and Schizophrenia Data and Hypothesis. *Acta Psychiatrica Scand* 1966;42:125-52.
- 2 Singh MM, Kay S. Wheat gluten as a pathogenic factor in schizophrenia. *Science* 1976;191:191-2.
- 3 Zhong F, McCombs CC, Olson JM, Elston RC, Stevens FM, McCarthy CF, et al. An autosomal screen for genes that predispose to celiac disease in the western counties of Ireland. *Nature Genetics* 1996;14:329-33.
- 4 Straub RE, MacLean CJ, O'Neill FA, Burke J, Murphy B, Duke F, et al. A potential vulnerability locus for schizophrenia on chromosome 6p24-22: evidence for genetic heterogeneity. *Nature Genetics* 1995;11:287-93.
- 5 Mortensen PB, Pedersen CB, Westergaard T, Wohlfahrt J, Ewald H, Mors O, et al. Familial and non-familial risk factors for schizophrenia: a population-based study. *N Engl J Med* 1999;340:603-8. (Accepted 15 October 2003)

Case-control study of the effect of mechanical trauma on the risk of herpes zoster

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Herpes zoster results from reactivation of latent varicella zoster virus infection. Risk of zoster increases with age and with depressed cell mediated immunity, but relatively little is known about other factors.¹⁻³ Case reports and case series have indicated that mechanical trauma may be a risk factor.⁴ But these studies had no control group, and physical mishaps and surgical trauma are common in older people. We investigated whether trauma is associated with increased risk of zoster using a case-control design.

Methods and results

This investigation was part of a study based in general practice in London of the determinants of zoster in adults without underlying immunosuppression. Elsewhere, we describe recruitment and definitions of cases (patients with incident zoster) and controls (patients with no previous zoster, individually matched to cases by age, sex, and general practice) elsewhere.⁵ Participants gave informed consent.

We hypothesised that trauma increases the risk of zoster at the trauma site within one month of the trauma, as indicated by a previous case series.⁴ We asked participants about all physical trauma severe enough to cause bruising (without prompting as to the site of trauma) and about surgical procedures in the six months before interview. We compared occurrence of trauma among cases and their matched controls in the month before the case developed zoster, evaluating

both trauma at the site of the case's rash and trauma occurring elsewhere. We used matched comparisons of the timing and site of trauma because the risk of trauma varies seasonally, and trauma occurs at certain body sites more often. We used multivariable conditional logistic regression to determine the independent effects of trauma on risk of zoster.

We got information on trauma for 243/244 cases (median age 57.2 years; range 16.5-91.2 years) and 483 matched controls. In the six months before interview, cases and controls had a similar frequency of trauma at body sites other than the site of the cases' zoster. But cases more often reported prior trauma at the site of their rash—this was associated with an eightfold increased risk of zoster as determined by multivariable analysis (table). Fourteen of the 22 participants who experienced trauma to the same site as subsequent zoster (mostly the trunk or head) did so in the month before the rash started (see table A on bmj.com). This recent trauma was associated with an adjusted 12-fold increased risk of zoster (table). Again, cases and controls had similar frequency of trauma to other body sites.

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Table A on bmj.com gives details of 14 people who had recent trauma at the site of subsequent rash in the case



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