

**Associations between specific autoimmune diseases and subsequent dementia: retrospective
record-linkage cohort study, UK**

Clare J Wotton, BSc (Hons), University of Oxford, clare.wotton@ceu.ox.ac.uk

Michael J Goldacre, FFPH, University of Oxford, michael.goldacre@dph.ox.ac.uk

Unit of Health-Care Epidemiology, Nuffield Department of Population Health, University of Oxford,
Old Road Campus, Old Road, Oxford, OX3 7LF, UK

Corresponding author: Professor Michael J Goldacre, Unit of Health-Care Epidemiology, Nuffield
Department of Population Health, University of Oxford, Old Road Campus, Oxford, OX3 7LF

Email: michael.goldacre@dph.ox.ac.uk

Tel: 01865 289378

Fax: 01865 289379

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What is already known on this subject?

Autoimmune and inflammatory mechanisms have been suggested as having a possible role in the development of dementia. There is little epidemiological data on whether autoimmune disease and dementia are associated. We recently reported on an association between type 1 diabetes and dementia.

What this study adds?

Autoimmune disease seems to be positively associated with dementia. Many individual autoimmune diseases were associated with an increase in dementia risk, although effect sizes were small. Further studies should confirm or refute this, and mechanisms should be sought.

ABSTRACT

Objective: To determine whether hospital admission for autoimmune disease is associated with an elevated risk of future admission for dementia.

Methods: Retrospective, record-linkage cohort study using national hospital care and mortality administrative data, 1999-2012. Cohorts of people admitted to hospital with a range of autoimmune diseases were constructed, along with a control cohort, and followed forward in time to see if they developed dementia. 1,833,827 people were admitted to hospital with an autoimmune disease; the number of people in cohorts for each autoimmune disease ranged from 1,019 people in the Goodpasture's syndrome cohort, to 316,043 people in the rheumatoid arthritis cohort.

Results: Rate ratio for dementia after admission for an autoimmune disease, compared with a control cohort, was 1.20 (95% confidence interval 1.19-1.21). Where dementia type was specified, the rate ratio was 1.06 (1.04-1.08) for Alzheimer's disease and 1.28 (1.26-1.31) for vascular dementia. Of 25 autoimmune diseases studied, 18 showed significant positive associations with dementia at $p < 0.05$ (with 14 significant at $p < 0.001$) including Addison's disease (1.48, 1.34-1.64), multiple sclerosis (1.97, 1.88-2.07), psoriasis (1.29, 1.25-1.34), and systemic lupus erythematosus (1.46, 1.32-1.61).

Conclusions: The associations with vascular dementia may be one component of a broader association between autoimmune diseases and vascular damage. Though findings were significant, effect sizes were small. Clinicians should be aware of the possible coexistence of autoimmune disease and dementia in individuals. Further studies are needed to confirm or refute our findings and to explore possible mechanisms mediating any elevation of risk.

INTRODUCTION

There are suggestions that Alzheimer's disease (AD) may have an autoimmune component, and that autoimmune and inflammatory mechanisms may play a role in the development of dementia.^{1,2} AD has been shown to have a similar female to male ratio as that in some autoimmune diseases such as multiple sclerosis and rheumatoid arthritis,³ and the risk of AD has been shown to be reduced in people who regularly take nonsteroidal anti-inflammatory drugs (NSAIDs)⁴⁻⁶ – drugs used to treat diseases such as rheumatoid arthritis – although findings from a recent systematic review were mixed.⁷ A relationship between levels of anti-thyroid antibodies and AD has been reported,⁸ and studies have found that in people with early-onset dementia, (those diagnosed when aged under 65) multiple sclerosis accounts for the dementia in 3-4% of cases.^{9,10} In a recent study, we report an association between admission to hospital with type 1 diabetes (i.e. diabetes with an autoimmune component) and subsequent admission for dementia.¹¹

We have used national Hospital Episode Statistics (HES) for England to construct retrospective cohorts of people admitted to hospital with a range of autoimmune diseases, in order to follow them forward in time for a hospital admission record of dementia. The objectives of the study were to determine whether hospital admission with an autoimmune diseases is associated with future admission with dementia more often than expected by chance.

METHODS

Population and data

We undertook a retrospective cohort analysis using a dataset of English national Hospital Episode Statistics (HES) in which successive episodes of care for each person were linked to each other, and linked to a dataset of all deaths in England, during the period 1st April 1998 to 31st March 2012.¹² The HES data includes clinical, demographic, and administrative information on all hospital admissions, including day cases (people admitted who do not stay overnight), in all National Health

Service (NHS) hospitals in England. The great majority of medical admissions in England are in NHS rather than private hospitals. The HES data were supplied by the English national Health and Social Care Information Centre; and the linked dataset (filename da_cips_14yr_v01b_alluhcert) was built by the Oxford record linkage group using, as identifiers, the encrypted values of the NHS number and of their HES number (both unique to each individual). Mortality data derives from death registration records, and were supplied by the Office for National Statistics, with identifiers encrypted in the same way. The methods used were similar to those described in previous studies^{11,13,14}. Methods here are described for the example of admission for multiple sclerosis (MS) followed by admission for dementia, but the same methods were used for each of the autoimmune diseases studied. Analyses by dementia subtype, age at dementia onset and by sex were carried out in the same way.

Exposure disease definition

A cohort of people with MS was constructed by identifying each person's first recorded episode of day case care or inpatient admission for MS coded in any diagnostic field on the hospital discharge abstract. The International Classification of Disease (ICD) code, tenth revision, used for MS was G35; codes used for each of the autoimmune diseases are in given in Table footnotes.

Control condition definition

A control cohort was constructed by identifying the first admission for each individual with various other medical and surgical conditions and injuries as the main diagnoses (listed in Table 2 footnotes). This is based on a 'control group' of conditions that has been used in other studies of associations between diseases^{11,14}. Standard epidemiological practice was followed, in using hospital controls, of selecting a very diverse range of clinical conditions rather than relying on a narrow range (in case any of the latter are themselves atypical in their risk of dementia).

Outcome disease definition

We searched the dataset for any subsequent NHS hospital care for, or death from, dementia in the MS and the control cohorts. The ICD codes used for dementia in the 9th and 10th revisions were 290

and 331.0 in ICD9, and F00-F01, F03 and G30 in ICD10 (ICD9 was used for deaths in 1999 and 2000, and ICD10 from 2001; ICD10 was used for hospital discharge data throughout the period covered by this study). We considered dementia cases as those coded in any diagnostic field on the discharge abstract. We subdivided people with an admission for dementia into those who were specifically recorded as having an admission for AD (331.0 in ICD9 and F00 and G30 in ICD10) and those recorded as having an admission for vascular dementia (290.4 in ICD 9 and F01 in ICD10). People were included in the MS cohort, or in the control cohort, if they did not have an admission for dementia either before or at the same time as the admission for MS or control condition. Additionally, we analysed the data separately for men and women and according to time interval between the first known record of autoimmune disease admission and the first known dementia admission to obtain information on temporality.

Statistical analysis

In comparing the MS cohort with the control cohort, we stratified and then standardised by age (in five-year age groups), sex, calendar year of first recorded admission, region of residence, and quintile of patients' Index of Deprivation score (a standard measure of socio-economic status used in England). Statistical methods are given in detail elsewhere¹³. All calculations were done, comparing the cohorts, within the individual strata (e.g. within 5-year age groups, single year of hospital admission, etc.). The direct method of standardisation was used with the combined MS and control cohort as the standard population; and the stratum-specific rates were then applied to the number of people in each stratum within, first, the MS cohort, and then, separately, the control cohort. This calculation gave the expected number of cases of dementia in each stratum in, respectively, the MS and control cohorts. The observed and expected numbers within each stratum were then summed to give totals in the broader age groups shown in the tables and then at all ages. Results were expressed as stratum-standardised rate ratios (RRs) comparing the multiple sclerosis cohort with the control cohort, using the formula O^{ms}/E^{ms} divided by O^{con}/E^{con} , where O and E are the observed and

expected numbers of dementia in the MS and control cohorts, respectively. The calculation of expected values, the rate ratios, their confidence intervals and p values used standard, published statistical methods.¹⁵

Ethical approval for our multi-purpose programme of work linking and analysing routine medical datasets was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176).

RESULTS

1 833 827 people were admitted to hospital with an autoimmune disease. The number of people in the cohorts for each specific autoimmune disease ranged from 1 019 people in the Goodpasture's syndrome cohort, to 316 043 people in the rheumatoid arthritis cohort. Around 7 million people were included in the control cohort; numbers varied slightly depending on each specific autoimmune disease being studied (see exclusion criteria when dementia was recorded on the exposure or control record prior to, or at the same time as, the autoimmune disease or control condition, Method). Table 1 shows the mean age at entry, the mean period of follow-up and the percentage of men in the cohort for each of the autoimmune diseases.

Table 1. Mean age at entry into cohort, period of follow-up and percentage males for each autoimmune disease.

Autoimmune disease	Mean age at entry into autoimmune disease cohort (years)	Mean period of follow-up (years)	% males
Addison's disease (E27.1)	57.6	5.5	43.3
Ankylosing spondylitis (M45)	57.3	5.7	71.8
Autoimmune haemolytic anaemia (D59.1)	67.1	3.8	47.3
Chronic active hepatitis (K73.2)	58.2	6.0	31.4
Crohn's disease (K50)	48.9	6.2	49.2
Celiac disease (K90.0)	51.8	5.5	36.9
Dermatomyositis/polymyositis (M33)	59.0	5.0	37.9
Goodpasture's syndrome (M13)	59.8	4.0	53.3
Hashimoto's thyroiditis (E06)	54.6	5.8	14.7
Idiopathic thrombocytopenia purpura (D69.3)	55.8	5.3	48.4
Myasthenia gravis (G70.0)	65.1	5.4	52.8
Multiple sclerosis (G35)	53.4	6.4	33.0
Myxoedema (E03.8-E03.9)	68.7	4.4	20.5
Pemphigus (L10)	66.0	4.3	46.1
Pemphigoid (L12)	77.9	3.3	45.6
Pernicious anaemia (D51.0)	74.3	3.9	32.6
Polyarteritis nodosa (M30.0)	62.2	5.0	56.7
Primary biliary cirrhosis (K74.3)	65.4	4.4	15.8
Psoriasis (L40)	56.5	5.4	55.3
Rheumatoid arthritis (M05-M06)	67.2	5.3	30.0
Scleroderma (M34)	61.7	4.9	18.9
Sjogren's syndrome (M35.0)	64.0	5.0	12.0
Systemic lupus erythematosus (M32.1-M32.9)	52.3	5.9	15.3
Thyrotoxicosis (E05)	64.2	4.7	23.6
Ulcerative colitis (K51)	53.1	6.2	55.6
All autoimmune diseases ¹	63.4	5.1	31.4

¹ People admitted to hospital with any of the reported autoimmune diseases

Dementia risk in people with an autoimmune disease (Table 2)

Overall, people admitted to hospital with an autoimmune disease were 20% more likely to have a subsequent admission for dementia than those without an admission for an autoimmune disease (rate ratio 1.20; 95% confidence interval 1.19-1.21). Of the 25 autoimmune diseases studied, 18 showed significant positive associations with dementia at $p < 0.05$ (with 14 significant at $p < 0.001$) including conditions as diverse as Addison's disease (RR 1.48, 95% CI 1.34-1.64), MS (1.97, 1.88-2.07), polyarteritis nodosa (1.43, 1.12-1.82), psoriasis (1.29, 1.25-1.34), systemic lupus erythematosus (1.46, 1.32-1.61), and thyrotoxicosis (1.31, 1.27-1.34). Though significant, effect sizes were small. To ensure that the diagnosis of dementia was not the result of an admission soon after the autoimmune disease admission, as a result of its incidental diagnosis in the latter (i.e. to guard against surveillance bias), we additionally examined the data after the exclusion of cases of dementia that were first recorded within a year of the first specific autoimmune disease admission. There were no notable differences in the RRs for dementia whether or not the first year cases were included. Accordingly, the main results shown are for all cases.

The type of dementia was often not recorded: of a total of 81 502 people with an autoimmune disease and dementia, 20 032 had a record of AD and 22 536 of vascular dementia. The rate ratio for AD in people admitted with an autoimmune disease was 1.06 (1.04-1.08) and that for vascular dementia was 1.28 (1.26-1.31). RRs for vascular dementia after individual autoimmune disease were, on the whole, slightly higher than those for AD. The risk of vascular dementia, but not AD, was elevated in association with hospital admission for idiopathic thrombocytopenia purpura, pemphigus, polyarteritis nodosa, scleroderma, Sjogren's syndrome, and systemic lupus erythematosus. The risk of AD was elevated in association with hospital admission for Addison's disease, myxoedema, pemphigoid, pernicious anaemia, psoriasis, and thyrotoxicosis (Table 2). Although there was an elevated risk of vascular dementia after an admission for rheumatoid

arthritis, the RR for AD was actually significantly low in people following an admission for rheumatoid arthritis (0.89, 0.86-0.93).

Table 2. Occurrence of dementia in people admitted to hospital after an admission for an autoimmune disease.

Autoimmune disease (ICD code) ¹	Any dementia (F00-F01,F03,G30)			Alzheimer's disease (F00,G30)			Vascular dementia (F01)		
	Number of people with dementia in each autoimmune disease cohort	Adjusted rate ratio ² (95% CI)	p-value	Number of people with Alzheimer's disease in each autoimmune disease cohort	Adjusted rate ratio ² (95% CI)	p-value	Number of people with the vascular dementia in each autoimmune disease cohort	Adjusted rate ratio ² (95% CI)	p-value
Addison's disease (E27.1)	370	1.48 (1.34-1.64)	<0.001	89	1.30 (1.04-1.60)	0.02	101	1.53 (1.25-1.86)	<0.001
Ankylosing spondylitis (M45)	519	1.07 (0.98-1.17)	0.12	150	1.12 (0.95-1.31)	0.18	146	1.05 (0.88-1.23)	0.60
Autoimmune haemolytic anaemia (D59.1)	287	1.02 (0.90-1.14)	0.77	60	0.80 (0.61-1.03)	0.09	82	1.11 (0.89-1.38)	0.36
Chronic active hepatitis (K73.2)	110	1.18 (0.97-1.42)	0.09	33	1.21 (0.84-1.71)	0.31	33	1.41 (0.97-1.97)	0.06
Crohn's disease (K50)	2014	1.10 (1.05-1.15)	<0.001	537	1.5 (0.96-1.15)	0.25	517	1.07 (0.98-1.16)	0.15
Coeliac disease (K90.0)	1196	1.08 (1.02-1.14)	0.009	284	0.91 (0.81-1.02)	0.13	337	1.13 (1.02-1.26)	0.02
Dermatomyositis/polymyositis (M33)	137	1.11 (0.93-1.31)	0.24	32	0.92 (0.63-1.30)	0.72	38	1.13 (0.80-1.55)	0.52
Goodpasture's syndrome (M13)	19	1.16 (0.70-1.81)	0.60	-	-	-	-	-	-
Hashimoto's thyroiditis (E06)	182	0.96 (0.83-1.12)	0.66	41	0.74 (0.53-1.01)	0.06	54	1.09 (0.81-1.42)	0.60
Idiopathic thrombocytopenia purpura (D69.3)	853	1.15 (1.07-1.23)	<0.001	184	0.91 (0.79-1.06)	0.23	264	1.32 (1.16-1.49)	<0.001
Myasthenia gravis (G70.0)	390	0.91 (0.82-1.01)	0.08	101	0.87 (0.71-1.06)	0.18	111	0.95 (0.78-1.15)	0.65
Multiple sclerosis (G35)	1800	1.97 (1.88-2.07)	<0.001	250	0.95 (0.83-1.07)	0.40	275	1.17 (1.04-1.32)	0.01
Myxoedema (E03.8-E03.9)	48146	1.20 (1.18-1.21)	<0.001	12311	1.12 (1.10-1.15)	<0.001	13605	1.30 (1.27-1.32)	<0.001
Pemphigus (L10)	103	1.33 (1.09-1.61)	0.004	23	1.12 (0.71-1.68)	0.68	38	1.77 (1.25-2.43)	<0.001
Pemphigoid (L12)	1137	1.53 (1.44-1.62)	<0.001	241	1.21 (1.06-1.38)	0.003	331	1.65 (1.48-1.84)	<0.001
Pernicious anaemia (D51.0)	5093	1.31 (1.27-1.34)	<0.001	1262	1.20 (1.14-1.27)	<0.001	1442	1.41 (1.34-1.49)	<0.001
Polyarteritis nodosa (M30.0)	69	1.43 (1.12-1.82)	0.003	11	0.80 (0.40-1.43)	0.54	29	2.12 (1.42-3.05)	<0.001
Primary biliary cirrhosis (K74.3)	322	1.29 (1.15-1.44)	<0.001	76	1.05 (0.83-1.32)	0.71	91	1.40 (1.13-1.72)	0.002
Psoriasis (L40)	3039	1.29 (1.25-1.34)	<0.001	715	1.08 (1.01-1.17)	0.03	930	1.43 (1.34-1.53)	<0.001
Rheumatoid arthritis (M05- M06)	14264	1.13 (1.11-1.15)	<0.001	3075	0.89 (0.86-0.93)	<0.001	3765	1.16 (1.12-1.20)	<0.001
Scleroderma (M34)	261	1.16 (1.03-1.31)	0.02	65	1.03 (0.80-1.31)	0.85	83	1.48 (1.17-1.83)	<0.001
Sjogren's syndrome (M35.0)	528	1.14 (1.04-1.24)	0.004	122	0.90 (0.75-1.08)	0.29	160	1.29 (1.10-1.51)	0.001
Systemic lupus erythematosus (M32.1-M32.9)	394	1.46 (1.32-1.61)	<0.001	77	0.97 (0.76-1.21)	0.83	120	1.69 (1.40-2.02)	<0.001
Thyrotoxicosis (E05)	5813	1.31 (1.27-1.34)	<0.001	1416	1.17 (1.11-1.23)	<0.001	1699	1.45 (1.38-1.52)	<0.001
Ulcerative colitis (K51)	3617	1.06 (1.03-1.10)	<0.001	968	1.02 (0.95-1.08)	0.65	987	1.08 (1.02-1.15)	0.01

All autoimmune diseases ³	81502	1.20 (1.19-1.21)	<0.001	20032	1.06 (1.04-1.08)	<0.001	22536	1.28 (1.26-1.31)	<0.001
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Table contains observed number of people with dementia in each of the autoimmune disease cohorts, ratio of rate in the autoimmune disease cohorts to that in the control cohort⁴, and 95% confidence intervals for the rate ratio.

Data suppressed where there were less than 5 observed cases.

¹ ICD10 codes for each disease

² Adjusted for sex, age in 5-year bands, time-period in single calendar years, region of residence and deprivation score associated with patients' area of residence, in quintiles. Rate ratios were calculated as the ratio of the observed/expected numbers in the cohort for autoimmune disease/dementia, to the observed/expected numbers in the reference cohort

³ People admitted to hospital with any of the reported autoimmune diseases

⁴ Conditions used in control cohort, with Office of Population, Censuses and Surveys code edition 4 for operations and ICD10 code for diagnosis (with equivalent codes used for other coding editions): appendicectomy (H01-H03), hip arthroplasty (W37-W39), knee arthroplasty (W40-W42), tonsillectomy (E20,F24,F36), squint (H49-H51), otitis externa, otitis media (H60-H67), varicose veins (I83), haemorrhoids (I84), upper respiratory tract infections (J00-J06), deflected septum, nasal polyp (J33,J34.2), impacted tooth and other disorders of teeth (K00-K03), inguinal hernia (K40), ingrowing toenail and other diseases of nail (L60), sebaceous cyst (L72.1), bunion (M20.1), internal derangement of knee (M23), selected fractures (S42,S52,S62,S82,S92), dislocations, sprains and strains (S03,S13,S23,S33,S43,S53,S63,S73,S83,S93) and superficial injury and contusion (S00,S10,S20,S30,S40,S50,S60,S70,S80,S90).

Men and women (Table 3)

Autoimmune diseases are generally more common in women than men (Table 1). We analysed data for men and women separately, as well as together. For all autoimmune diseases combined, the rate ratio was slightly but significantly higher in men as evidenced by the non-overlapping confidence intervals (1.32; 1.30-1.35, $p<0.001$) than women (1.17; 1.16-1.18, $p<0.001$). The excess risk of dementia was significantly higher in men with multiple sclerosis than in women (RR 2.52; 2.32-2.74 in men versus 1.79; 1.69-1.89 in women). For most of the individual autoimmune diseases, rate ratios for dementia were broadly similar for men and women.

Table 3. Occurrence of dementia in males and females admitted to hospital after an admission for an autoimmune disease.

Autoimmune disease (ICD code) ²	Males			Females		
	Number of males with dementia in each autoimmune disease cohort	Adjusted rate ratio ² (95% CI)	p-value	Number of females with the dementia in each autoimmune disease cohort	Adjusted rate ratio ² (95% CI)	p-value
Addison's disease (E27.1)	120	1.45 (1.20-1.73)	<0.001	250	1.50 (1.32-1.70)	<0.001
Ankylosing spondylitis (M45)	300	1.12 (1.00-1.25)	0.06	219	1.02 (0.89-1.16)	0.85
Autoimmune haemolytic anaemia (D59.1)	95	0.98 (0.79-1.20)	0.86	192	1.04 (0.90-1.20)	0.60
Chronic active hepatitis (K73.2)	18	1.20 (0.71-1.89)	0.52	92	1.18 (0.95-1.44)	0.13
Crohn's disease (K50)	665	1.12 (1.04-1.21)	0.004	1349	1.09 (1.03-1.15)	0.003
Celiac disease (K90.0)	391	1.12 (1.02-1.24)	0.02	805	1.06 (0.99-1.13)	0.12
Dermatomyositis/polymyositis (M33)	45	1.23 (0.90-1.65)	0.18	92	1.06 (0.85-1.30)	0.64
Goodpasture's syndrome (M13)	9	1.09 (0.50-2.06)	0.94	10	1.23 (0.59-2.27)	0.62
Hashimoto's thyroiditis (E06)	27	1.22 (0.80-1.77)	0.36	155	0.93 (0.79-1.09)	0.40
Idiopathic thrombocytopenia purpura (D69.3)	347	1.25 (1.12-1.39)	<0.001	506	1.09 (0.99-1.19)	0.06
Myasthenia gravis (G70.0)	190	0.87 (0.75-1.00)	0.06	200	0.96 (0.83-1.11)	0.61
Multiple sclerosis (G35)	580	2.52 (2.32-2.74)	<0.001	1219	1.79 (1.69-1.89)	<0.001
Myxoedema (E03.8-E03.9)	8003	1.38 (1.35-1.41)	<0.001	40131	1.17 (1.16-1.18)	<0.001
Pemphigus (L10)	31	1.22 (0.83-1.74)	0.30	72	1.38 (1.08-1.74)	0.007
Pemphigoid (L12)	432	1.70 (1.55-1.87)	<0.001	704	1.44 (1.33-1.55)	<0.001
Pernicious anaemia (D51.0)	1506	1.55 (1.47-1.63)	<0.001	3584	1.22 (1.18-1.27)	<0.001
Polyarteritis nodosa (M30.0)	32	1.36 (0.93-1.92)	0.10	37	1.51 (1.06-2.08)	0.02
Primary biliary cirrhosis (K74.3)	38	1.53 (1.08-2.10)	0.01	283	1.26 (1.12-1.42)	<0.001
Psoriasis (L40)	1234	1.36 (1.29-1.44)	<0.001	1805	1.25 (1.19-1.31)	<0.001
Rheumatoid arthritis (M05-M06)	3048	1.21 (1.16-1.25)	<0.001	11211	1.11 (1.08-1.13)	<0.001
Scleroderma (M34)	46	1.69 (1.23-2.25)	<0.001	215	1.09 (0.95-1.25)	0.22
Sjogren's syndrome (M35.0)	57	1.34 (1.02-1.74)	0.03	471	1.11 (1.02-1.22)	0.02
Systemic lupus erythematosus (M32.1-M32.9)	62	1.36 (1.04-1.75)	0.02	331	1.47 (1.32-1.64)	<0.001
Thyrotoxicosis (E05)	915	1.42 (1.33-1.51)	<0.001	4897	1.29 (1.26-1.33)	<0.001
Ulcerative colitis (K51)	1541	1.12 (1.30-1.35)	<0.001	2076	1.03 (0.98-1.07)	0.24
All autoimmune diseases ⁴	17934	1.32 (1.30-1.35)	<0.001	63545	1.17 (1.16-1.18)	<0.001

Table contains observed number of males or females with dementia in each of the autoimmune disease cohorts, ratio of rate in the autoimmune disease cohorts to that in the control cohort⁴, and 95% confidence intervals for the rate ratio

Data suppressed where there were less than 5 observed cases.

See Table 2 for footnotes

Time intervals (Table 4)

It is difficult to be sure of the temporal sequence of autoimmune disease and dementia in this type of study. To try to address this, we studied the time intervals between the first recorded admission for the autoimmune disease and the first recorded admission for dementia. Most of the associations remained significant 5 or more years after admission for the autoimmune disease, although associations were generally stronger with shorter time intervals.

Table 4. Time intervals between autoimmune disease admission and subsequent admission for any type of dementia, for selected associations.

Autoimmune disease	Time interval	Number of people with dementia in each autoimmune disease cohort	Any dementia	
			Adjusted rate ratio ³ (95% CI)	p-value
Addison's disease	<1yr	83	1.71 (1.36-2.13)	<0.001
	1-4yrs	167	1.54 (1.32-1.79)	<0.001
	5+yrs	120	1.30 (1.08-1.55)	0.005
Crohn's disease	<1yr	396	1.30 (1.18-1.44)	<0.001
	1-4yrs	803	1.02 (0.95-1.10)	0.55
	5+yrs	815	1.09 (1.02-1.17)	0.01
Coeliac disease	<1yr	235	1.13 (0.99-1.29)	0.06
	1-4yrs	560	1.13 (1.04-1.23)	0.004
	5+yrs	401	0.99 (0.89-1.09)	0.85
Idiopathic thrombocytopenia purpura	<1yr	225	1.27 (1.11-1.45)	<0.001
	1-4yrs	383	1.11 (1.00-1.23)	0.04
	5+yrs	245	1.11 (0.97-1.26)	0.12
Multiple sclerosis	<1yr	312	2.35 (2.09-2.63)	<0.001
	1-4yrs	704	1.89 (1.75-2.03)	<0.001
	5+yrs	784	1.93 (1.80-2.07)	<0.001
Myxoedema	<1yr	12174	1.30 (1.27-1.33)	<0.001
	1-4yrs	23738	1.21 (1.19-1.23)	<0.001
	5+yrs	12234	1.12 (1.10-1.15)	<0.001
Pemphigus	<1yr	32	1.62 (1.10-2.28)	0.009
	1-4yrs	49	1.45 (1.07-1.92)	0.01
	5+yrs	22	0.92 (0.58-1.40)	0.78
Pemphigoid	<1yr	423	2.04 (1.85-2.24)	<0.001
	1-4yrs	532	1.50 (1.37-1.63)	<0.001
	5+yrs	182	1.02 (0.88-1.18)	0.83
Pernicious anaemia	<1yr	1417	1.46 (1.38-1.54)	<0.001
	1-4yrs	2425	1.27 (1.22-1.32)	<0.001
	5+yrs	1251	1.24 (1.17-1.31)	<0.001
Polyarteritis nodosa	<1yr	17	1.85 (1.08-2.96)	0.02
	1-4yrs	28	1.26 (0.84-1.82)	0.27
	5+yrs	24	1.44 (0.92-2.15)	0.09
Primary biliary cirrhosis	<1yr	68	1.25 (0.97-1.58)	0.08
	1-4yrs	153	1.35 (1.15-1.58)	<0.001
	5+yrs	101	1.23 (1.00-1.50)	0.04
Psoriasis	<1yr	676	1.42 (1.31-1.53)	<0.001
	1-4yrs	1396	1.32 (1.25-1.39)	<0.001
	5+yrs	967	1.19 (1.12-1.27)	<0.001
Rheumatoid arthritis	<1yr	2773	1.04 (1.00-1.08)	0.05
	1-4yrs	6691	1.16 (1.13-1.19)	<0.001
	5+yrs	4800	1.14 (1.10-1.17)	<0.001
Scleroderma	<1yr	59	1.29 (0.98-1.66)	0.06
	1-4yrs	118	1.20 (1.00-1.44)	0.05
	5+yrs	84	1.04 (0.83-1.29)	0.73
Sjogren's syndrome	<1yr	84	0.89 (0.71-1.10)	0.30
	1-4yrs	230	1.08 (0.94-1.23)	0.26
	5+yrs	214	1.36 (1.18-1.55)	<0.001
Systemic lupus erythematosus	<1yr	71	1.43 (1.12-1.81)	0.003
	1-4yrs	182	1.52 (1.31-1.76)	<0.001
	5+yrs	141	1.39 (1.17-1.64)	<0.001
Thyrotoxicosis	<1yr	1536	1.46 (1.38-1.54)	<0.001
	1-4yrs	2804	1.33 (1.28-1.38)	<0.001
	5+yrs	1473	1.16 (1.10-1.22)	<0.001
Ulcerative colitis	<1yr	607	1.14 (1.05-1.24)	0.001
	1-4yrs	1495	1.05 (1.00-1.11)	0.06
	5+yrs	1515	1.05 (0.99-1.10)	0.09
All autoimmune diseases	<1yr	18962	1.29 (1.26-1.31)	<0.001
	1-4yrs	38595	1.20 (1.19-1.22)	<0.001
	5+yrs	23945	1.16 (1.15-1.18)	<0.001

DISCUSSION

Main findings and comparisons with other studies

There have been suggestions that autoimmune and inflammatory mechanisms may play a role in the development of dementia,² and there is evidence that people with AD may have higher levels of anti-thyroid autoantibodies when compared to people without dementia.⁸ However, there is little epidemiological data on whether autoimmune disease and dementia are associated. We recently reported that hospitalisation with type 1 diabetes was associated with subsequent hospitalisation with dementia,¹¹ but further evidence of a link between autoimmune disease and dementia is lacking. Here we report that people admitted to hospital with autoimmune disease were more likely to be admitted to hospital with dementia, at a later date, than a control group. Our findings for thyroid autoimmune disease and rheumatoid arthritis are consistent with previous data^{4,8} and there is little else published with which to compare our findings.

The risk of vascular dementia after an admission with an autoimmune disease was slightly higher than the risk of AD, and some individual autoimmune diseases were significantly associated with an elevated risk of future vascular dementia, but not AD. The associations with vascular dementia might reflect associations between autoimmune disease and risk factors for cardiovascular and cerebrovascular diseases more generally. We have undertaken similar analyses to those reported here for coronary heart disease (CHD) and ischaemic stroke (which we will report in detail elsewhere). The rate ratios for CHD and ischaemic stroke in people with autoimmune disease (all those in Table 1 combined) were, respectively, 1.53 (1.52-1.54) and 1.46 (1.44-1.47).

A previous admission with rheumatoid arthritis seemed to protect against AD, but elevated the risk of vascular dementia. Although evidence that non-steroidal anti-inflammatory drugs (NSAIDs) reduce the risk of AD is not conclusive,⁴⁻⁷ our findings might add circumstantial evidence to the data

supporting the hypothesis that NSAIDs protect against AD. People with rheumatoid arthritis generally take NSAIDs to manage their condition, so if rheumatoid arthritis is at least partially a proxy for NSAID use, the real association may be between NSAID use and a reduced risk of AD. Although one could argue that the association may actually be between rheumatoid arthritis and AD, one study did find that the association between NSAID use and AD did not appear to be confounded by arthritis.⁶ We do not have data on potential confounders (other than basic demographics like age, socio-economic status and region of residence), so cannot explore the association further. A recent case-control study found that NSAID use was positively associated with vascular dementia (OR 1.33, 1.29-1.38).¹⁶ Thus it seems possible that NSAID use may reduce the risk of AD but increase the risk of vascular dementia.

Strengths and Limitations

The main strengths of the study are that it is very large in size, and allowed us to study the risk of dementia, both overall, and for AD and vascular dementia separately, following a wide range of autoimmune diseases, in a single, geographically defined population.

Limitations include that the study is restricted to people who were admitted to hospital or who received day case care, and the lack of data on confounders. The autoimmune disease cohorts are based on prevalent cases, the first recorded hospital admission or episode of day case care, rather than being cohorts with follow-up from the date of diagnosis. The diagnoses of the conditions studied are confined to those recorded on the hospital discharge summary for each person, and due to privacy regulations, we are unable to examine the records to ascertain their accuracy. Confining data collection to hospital admissions and episodes of day case care will mean that we miss cases of autoimmune disease and dementia that did not require hospital day case care or admission.

Dementia sub-groups are not well coded on hospital records, indeed are often not coded at all. The separate analyses of AD and vascular dementia, therefore, should be viewed with some caution; but we suggest that the results with dementia as a whole have fewer limitations. The likelihood is that

cases that really are AD are under-estimated as AD, coded as such in HES; and that, accordingly, unspecified dementia in HES actually contains a higher percentage of AD than of vascular dementia. Because of the nature of the data, some misdiagnosis and miscoding are inevitable. However, it is worth noting that any lack of diagnostic specificity of dementia type will affect both cases and controls alike and should not distort the RRs themselves.

We studied a large number of associations between autoimmune diseases and subsequent dementia. The effect of making multiple comparisons needs to be considered. For this reason, we give exact p-values in the tables, as well as confidence intervals, so that the reader can see the degree of significance of each association. It is possible that some of the associations that are significant at a level of $p < 0.05$ or even $p < 0.01$ may result from making multiple comparisons and the play of chance. On the other hand, even with the number of comparisons that we have made, findings with a significance level < 0.001 are unlikely to be attributable to chance alone. Further, 18 of the 25 disease-dementia associations were significant: by chance alone, only one or two would be significant at $p = 0.05$.

Possible mechanisms

Our study design cannot be used to investigate mechanisms of association. Diseases may occur in combination more often than expected by chance because one (the 'exposure' disease) predisposes to another (the 'outcome' disease); or because they share environmental and/or genetic mechanisms in common; because a specific treatment used in the exposure disease alters the risk of the outcome disease; or because the exposure disease causes changes in risk factors for pathology of which the outcome disease is just a part. Considering the latter, a speculative example is that autoimmune diseases (or their treatment) may increase the risk of circulatory disease, generally, of which vascular dementia is one component in some people.

Conclusions

For reasons given above, our findings should be considered as indicative rather than definitive. However, the negative association between rheumatoid arthritis and AD reflects the literature on NSAID use and AD risk, and gives some face-validity to our findings. People admitted to hospital with an autoimmune disease, likely to be those at the severe end of the disease spectrum, do appear to have an elevated risk of dementia. This finding is consistent with the theory that Alzheimer's disease may have an autoimmune component. If our findings are confirmed in other studies, clinicians and epidemiologists will wish to know that some people with some autoimmune diseases have an elevated risk of dementia. The effect size, at least in our study, is small. The findings may be relevant to furthering understanding of the pathogenesis of AD and of vascular dementia. Studies should be considered to confirm or refute our findings; and, if confirmed, to explore possible mechanisms mediating the associations.

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Competing interests

The authors have no competing interests.

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Ethical approval

Ethical approval for analysis of the record linkage study data was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176).

CJW proposed the study, analysed the data and wrote the first draft. MJG is the guarantor of, and designed, the study. All authors contributed to the interpretation of the data and revision of the manuscript for important intellectual content.

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