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Article

RISK OF ASTHMA AND AUTOIMMUNE DISEASES AND RELATED CONDITIONS IN PATIENTS HOSPITALIZED FOR OBESITY

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ABSTRACT

Background: Although there are putative mechanistic links between obesity and autoimmune disease and related conditions obesity is not considered as a risk factor for most autoimmune diseases.

Methods: Using the nationwide Hospital Discharge Register we define a cohort of 30,044 patients hospitalized for obesity since year 1964. The patients were followed for hospitalization for any of 34 autoimmune or related conditions through year 2007. Standardize incidence ratios (SIRs) were calculated for autoimmune diseases in obese individual compared to those who had not been hospitalized for obesity.

Results: Among 22 immune diseases diagnosed after obesity and including at least 5 patients, the overall SIR was 2.06. Among the individual diseases, 16 were significantly increased and none was decreased. The highest SIR was found for psoriasis (4.54), followed by Behcet disease (4.11), Hashimoto disease/hypothyroidism (4.11) and asthma (3.41). A small significant increase was also noted for the common autoimmune diseases Graves disease/hyperthyroidism (1.28) and rheumatoid arthritis (1.37).

Conclusions: The present population of obese individuals, at risk of many immune related conditions, was hospitalized at a relatively young age and further studies are needed to describe the morbidity in obese individuals at large.

KEY MESSAGES

Obesity and autoimmune disease share putative mechanistic links but obesity is not considered as a risk factor for most autoimmune diseases.

In the present study, 16 of the selected 34 autoimmune diseases were increased after hospitalization for obesity.

INTRODUCTION

Obesity is a risk factor for many common diseases, including asthma, autoimmune disease psoriasis, type 2 diabetes and cancer (1-7). Autoimmune processes are usually triggered by environmental or internal stimuli, the latter of which could be metabolic disturbances related to obesity (8). At the physiological level, obesity related chronic metabolic and hormonal disturbances affect the IGF pathway, adipokines and steroid hormone metabolism (6, 9, 10). Adipokines, leptin and adiponectin, are synthesized in the white adipose tissue at the site of energy storage and they act as links between nutritional status, metabolism and immunity (11, 12). Leptin is considered a safety factor regulating body weight by suppressing appetite and stimulating energy expenditure. It is also a pro-inflammatory may regulate of autoimmune responses (13-15). Adiponectin sensors insulin levels and is downregulated in obesity. Especially in visceral obesity, adiponectin reduction is associated with a parallel reduction in plasma concentration of interleukin-10, which is a major anti-inflammatory cytokine regulating the immune system (13). Inflammasome is a related sensor of metabolic disturbances, regulating the release of a potent pro-inflammatory cytokine interleukin-1 beta (16). This cytokine is believed to be an important driver of many diseases, including type 1 and type 2 diabetes and autoinflammatory diseases (16). Interleukin-1 beta receptor antagonist, anakinra is beneficial in rheumatoid arthritis and type 2 diabetes (16). Adiponectins and inflammatory cytokines appear as emerging mechanistic links between obesity and autoimmunity (13-16).

Immunologic mechanisms may thus be associated with both obesity and autoimmune conditions. In the present study we first define a cohort of 30,044 patients who have been hospitalized for obesity related conditions since year 1964. The patients were followed for hospitalization for

any of 34 autoimmune or related conditions through year 2007. Several autoimmune diseases were increased in the obese group compared to those who had never been hospitalized for obesity. The strengths of the present study were nation-wide recruitment of patients, prospective design and diagnostic accuracy of both obesity and autoimmune and related disease.

MATERIAL AND METHODS

The immune disease and obesity research database, used for this study, was obtained from the MigMed2 database, constructed by linking several national Swedish registers, as has been described earlier (17). Data on autoimmune diseases and related conditions and obesity were obtained from the Swedish Hospital Discharge Register that records complete data on all discharges with dates of hospitalization and diagnoses; the Register was started in some regions in 1964 and it became nation-wide in 1986. All linkages were performed by the use of an individual national identification number that is assigned to each person in Sweden for their lifetime. This number was replaced by a serial number for each person in order to provide anonymity. Over 11.8 million individuals were included in the database.

The International Classification of Diseases codes for obesity as the main diagnosis were ICD7 = 287.00, 287.09; ICD8 = 277.99; ICD9 = 278A; ICD-10= E65-E68. The codes for autoimmune and related diseases were described earlier (18, 19). Risk of autoimmune disease was determined for persons who had been previously hospitalized for obesity any time between 1964 and 2007 compared to persons who had not been hospitalized for obesity. The 34 diseases were autoimmune, inflammatory and related conditions, selected because of etiological hypothesis,

case numbers or previous positive studies (asthma, tested as a proof of principle). Person-years were calculated for autoimmune disease from hospitalization for obesity until hospitalization for autoimmune disease, death, emigration, or closing date, on December 31, 2007. Standardized incidence ratios (SIRs) were used to measure the relative risk for obese persons to be hospitalized for an immune related condition compared with others never hospitalized for obesity. The SIR was calculated as the ratio of observed (O) to expected (E) number of autoimmune cases using the indirect standardization method, as specified:

$$SIR = \frac{\sum_{j=1}^{J} o_j}{\sum_{j=1}^{J} n_j \lambda_j^*} = \frac{O}{E^*},$$

Where $O = \sum o_j$ denotes the total observed number of autoimmune cases in the study group (hospitalized for obesity) ; E^* is calculated by applying stratum-specific standard incidence rates (λ_j^*) obtained from the reference group (no hospitalization for obesity) to the stratum-specific person-year (n_j) experience of the study group. o_j represents the observed cases that the cohort subjects contribute to the jth stratum and J represents the strata defined by the cross-classification of various adjustment variables including age (5-year groups), sex, socioeconomic status, period (5-year group), and region (6 groups) (20, 21). Confidence intervals at a 5% levels (95%CI) were calculated assuming Poisson distribution (22). All of the analyses were performed using the SAS statistical package v 9.2. (SAS Institute Inc., Cary. NC. USA).

The study was approved by the regional ethical review board at Lund.

RESULTS

The number of patients hospitalized for obesity as main diagnosis was 30,044, constituting of 23.4% men and 76.6% women (Table 1). The age groups with most common first hospitalizations were 40-49 years for men and 30-39 years for women. Only about 10% of the hospitalizations were in age groups older than 59 years. Table 1 also shows the numbers (450,224) of autoimmune and related conditions in the control group, those never hospitalized for obesity.

Among autoimmune and related diseases diagnosed after obesity, only those 22 diseases with at least 5 cases are shown in Table 2; none of the others were significant. The SIR for all autoimmune and related diseases was 2.06. Asthma accounted for more than 1/3 of all cases; the SIR without asthma was lower, 1.69. Among the individual diseases, 16 were significantly increased and none was decreased. The highest SIR was found for psoriasis (4.54), followed by Behcet disease (4.11), Hashimoto disease/hypothyroidism (4.11) and asthma (3.41). A small significant increase was also noted for the common autoimmune diseases Graves disease/hyperthyroidism (1.28) and rheumatoid arthritis (1.37). The highest risks for many diseases, including the latter four, were found within the year of hospitalization for obesity. However for almost all diseases with a significant overall excess, increased SIRs were observed at some follow-up time other than the first year of hospitalization for obesity. The exceptions were immune thrombocytopenic purpura and multiple sclerosis but even for these the SIRs were above unity at all follow-up times.

Table 3 shows autoimmune disease risks according to age at hospitalization for obesity when follow-up was started one year after hospitalization. For the diseases with high risk, including psoriasis, Hashimoto disease/hypothyroidism and asthma, the age at hospitalization appeared not to be critical. For ankylosing spondylitis, Crohn disese, type 1 diabetes, multiple sclerosis and sarcoidosis, young age (<30 years) at hospitalization for obesity associated with the risk. For Graves disease/hyperthyroidism, Sjögren syndrome and ulcerative colitis, age over 49 at hospitalization for obesity associated with the highest risks.

The number of hospitalizations for obesity may be an indication of the severity of the disease, which was analyzed in Table 4. For all autoimmune diseases, the number of hospitalizations correlated with an increased SIR, and among individual diseases the increasing trend was evident for asthma (increase from 2.88 to 4.79) and psoriasis (increase from 3.96 to 6.22). However, most obesity patients were only hospitalized once which resulted in a small number of cases for many rarer autoimmune diseases.

DISCUSSION

As a proof of principle we could show that psoriasis showed the highest risk of 4.54 and asthma the fourth highest risk of 3.41. For both of these, obesity is a known risk factor and/or co-morbidity (3, 7). However, for most of the 14 other significantly increased autoimmune diseases limited or no data are available. Some of the diseases are rare and not easily amenable to epidemiological study with designs other than the present approach, based on nation-wide hospitalizations. Thus, for example Behcet disease, primary biliary cirrhosis and Sjögren

syndrome, all with SIRs over 2.0, but 10 or less cases among the population treated for obesity, would be difficult to study by other approaches.

The use of hospital discharge data to define obesity has the advantage that the diagnoses are most likely correct. Wolk et al validated the obesity data in the Swedish Hospital Discharge Register (23). In a sample of 221 reviewed records, all patients were overweight and 85% of men and 95% of women were obese. The median BMI values were 33.7 kg/m^2 for men and 35.3 kg/m^2 for women. These groups included some morbidly obese individuals but the median BMI values were not extreme. As most hospitalizations took place in early adulthood and mid-life it is likely that the condition was chronic and the patients wanted to seek medical help to their condition. Obviously, obesity was the reason for seeking medical advice as very few of the concomitant diagnoses appeared to be related to autoimmunity; these included type 2 diabetes, sleep disorders, heart diseases, hypertension and diseases of liver and gallbladder and hernia ((23) and unpublished observations). Importantly, the increase in many autoimmune diseases remained even after 10 years of hospitalization for obesity, implying that lead time or observation biases were unlikely explanations for the findings. The reference population included all persons not hospitalized for obesity, thus including many obese individuals and causing an underestimation of the true effects.

The use of Hospital Discharge Register to identify patients with autoimmune diseases offers the access to a nation-wide patient pool with a reasonably high diagnostic accuracy; the discharge diagnoses are often delivered by specialists during extended examinations in the clinic. The degree of hospitalization for the covered 34 diseases probably vary extensively depending on the

seriousness of the condition and alternative forms of treatment, as we have discussed for some of the covered diseases elsewhere (17, 24-26). Another issue relating to the interpretation of the results is the change of SIRs depending on the definition of the follow-up time, as seen in Table 2. For most diseases, the highest SIRs were observed in the year following hospitalization for obesity, which is likely to be due to lead time bias. However, in as far as the diagnoses are correct, the lead time bias only shifts the diagnoses earlier. For conservative risk estimation in Tables 3 and 4, we eliminated the patients diagnosed during the first year, however noting that this may lead underestimation of risk.

A concern with the present design is that hospitalization may involve selections, whereby persons once hospitalized may be more likely to be hospitalized again for the same or other causes. Some 25% of obese patients were hospitalized more than once for obesity and it is possible that some would have been hospitalized for side effects of treatment for obesity or for related causes. 'Brittle' asthma, type 1 diabetes and Addison disease have been described in the literature among patients whose disease is unstable or unpredictable, thereby leading to frequent hospitalizations (27, 28). One could try and guard against this type of bias by selecting as a control group persons hospitalized for a non-obesity related cause. However, it may be difficult, a priori, to nominate a disease with large numbers of hospitalizations that is not related to obesity. Instead we believe that internal comparisons among the presents diseases should be reassuring that 'brittle' disease is probably not an important contributor to the findings with high SIRs. For example, a common disease ulcerative colitis showed no overall risk in Table 2, and the SIRs for rheumatoid arthritis and Graves disease/hyperthyroidism, the most common diseases after asthma, were only increased to about 1.3.

As epidemiological support to the emerging mechanistic links between obesity and immune related diseases, we show here that 16 of the selected 34 diseases were increased after hospitalization for obesity. In addition to the known associations with psoriasis and asthma, high risks were observed for Behcet disease and Hashimoto disease/hypothyroidism. Small but significant increases were also noted for the common autoimmune diseases Graves disease/hyperthyroidism and rheumatoid arthritis. Such kind of small effects could however be related to the higher likelihood of further hospitalizations among those once hospitalized. The present study was based on a population of obese individuals hospitalized at a relatively young age and other studies are needed to describe to what extent autoimmune and related inflammatory conditions are related to obesity at large.

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CONFLICT OF INTEREST

None

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Table 1. Number of cases first hospitalized for obesity in men and women and number of controls hospitalized for asthma and autoimmune diseases without prior hospitalization for obesity

	First hospitalizations for obesity						First hospitalizations for autoimmune and related diseases without obesity	
Age at diagnosis	Men		Women		All		All	
(years)	N	%	N	%	N	%	N	%
0-9	166	2.4	213	0.9	379	1.3	82765	18.4
10-19	816	11.6	1064	4.6	1880	6.3	37443	8.3
20-29	746	10.6	3009	13.1	3755	12.5	36241	8.0
30-39	1378	19.6	6372	27.7	7750	25.8	42321	9.4
40-49	1729	24.6	5926	25.7	7655	25.5	47021	10.4
50-59	1450	20.7	4236	18.4	5686	18.9	58111	12.9
60-69	562	8.0	1595	6.9	2157	7.2	63701	14.1
70-79	136	1.9	491	2.1	627	2.1	57307	12.7
>=80	38	0.5	117	0.5	155	0.5	25314	5.6
All	7021	100.0	23023	100.0	30044	100.0	450224	100.0

Table 2. SIR for subsequent autoimmune and related disorders of patients with obesity

	Follow-up interval (years)																			
	<1				1-4				5-9				>=10				All			
Autoimmune disorders	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Amyotrophic lateral sclerosis	0				2	1.39	0.13	5.11	1	0.53	0.00	3.02	3	0.62	0.12	1.83	6	0.72	0.26	1.57
Ankylosing spondylitis	0				4	2.37	0.62	6.12	7	**4.38**	**1.73**	**9.07**	4	1.59	0.41	4.12	15	**2.47**	**1.38**	**4.09**
Asthma	46	**11.22**	**8.21**	**14.97**	75	**2.72**	**2.14**	**3.41**	101	**3.68**	**3.00**	**4.48**	142	**2.98**	**2.51**	**3.51**	364	**3.41**	**3.07**	**3.78**
Behcet disease	2	**22.22**	**2.09**	**81.72**	2	3.39	0.32	12.47	3	**5.45**	**1.03**	**16.15**	1	1.82	0.00	10.42	8	**4.49**	**1.92**	**8.90**
Chronic rheumatic heart disease	0				4	1.12	0.29	2.90	5	1.39	0.44	3.28	2	0.33	0.03	1.20	11	0.80	0.40	1.43
Crohn disease	2	1.59	0.15	5.84	9	1.16	0.53	2.21	14	**1.86**	**1.01**	**3.13**	17	1.36	0.79	2.18	42	**1.44**	**1.04**	**1.95**
Diabetes mellitus type I	1	3.13	0.00	17.91	8	**3.96**	**1.69**	**7.84**	1	0.82	0.00	4.70	1	2.63	0.00	15.08	11	**2.79**	**1.39**	**5.01**
Graves, hyperthyroidism	6	2.22	0.80	4.87	15	0.86	0.48	1.42	21	1.25	0.77	1.91	41	**1.46**	**1.05**	**1.99**	83	**1.28**	**1.02**	**1.58**
Hashimoto/hypothroidism	11	**23.40**	**11.62**	**42.02**	22	**7.07**	**4.43**	**10.73**	5	1.57	0.50	3.70	16	**2.51**	**1.43**	**4.08**	54	**4.11**	**3.09**	**5.37**
Immune thrombocytopenic purpura	1	6.67	0.00	38.22	2	2.13	0.20	7.82	3	2.94	0.55	8.71	4	1.67	0.44	4.33	10	**2.22**	**1.06**	**4.10**
Multiple sclerosis	3	2.80	0.53	8.30	10	1.51	0.72	2.78	9	1.43	0.65	2.73	16	1.64	0.94	2.67	38	**1.60**	**1.13**	**2.20**
Pernicious anemia	1	6.25	0.00	35.83	1	0.84	0.00	4.82	2	1.59	0.15	5.84	7	**3.30**	**1.31**	**6.84**	11	**2.33**	**1.15**	**4.18**
Polymyalgia rheumatica	2	2.99	0.28	10.98	10	1.97	0.94	3.64	13	**2.08**	**1.10**	**3.56**	23	1.35	0.85	2.02	48	**1.65**	**1.22**	**2.19**
Primary biliary cirrhosis	0				1	2.27	0.00	13.03	1	1.82	0.00	10.42	5	**3.57**	**1.13**	**8.40**	7	**2.85**	**1.13**	**5.90**
Psoriasis	8	**10.26**	**4.38**	**20.31**	28	**5.47**	**3.63**	**7.91**	25	**4.96**	**3.21**	**7.33**	28	**3.23**	**2.14**	**4.67**	89	**4.54**	**3.64**	**5.58**
Rheumatoid arthritis	5	1.79	0.57	4.22	25	1.28	0.83	1.90	29	1.41	0.94	2.03	55	**1.36**	**1.02**	**1.77**	114	**1.37**	**1.13**	**1.65**
Sarcoidosis	1	1.75	0.00	10.06	6	1.63	0.59	3.58	8	2.33	0.99	4.60	16	**2.82**	**1.61**	**4.59**	31	**2.32**	**1.58**	**3.30**
Sjören syndrome	0				3	3.85	0.73	11.39	4	**4.44**	**1.16**	**11.49**	3	1.45	0.27	4.29	10	**2.59**	**1.23**	**4.78**
Systemic lupus erythematosus	0				2	0.75	0.07	2.75	0				6	1.45	0.52	3.18	8	0.82	0.35	1.62
Systemic sclerosis	0				4	2.47	0.64	6.38	3	1.79	0.34	5.29	4	1.40	0.36	3.62	11	1.72	0.85	3.09
Ulcerative colitis	3	1.89	0.36	5.59	9	0.91	0.41	1.73	13	1.35	0.72	2.32	18	1.08	0.64	1.71	43	1.14	0.82	1.53
Wegener granulomatosis	0				2	0.83	0.08	3.05	2	0.77	0.07	2.82	2	0.51	0.05	1.88	6	0.65	0.23	1.42
All of above	92	**4.88**	**3.93**	**5.99**	244	**1.95**	**1.71**	**2.21**	270	**2.15**	**1.90**	**2.42**	414	**1.83**	**1.66**	**2.02**	1020	**2.06**	**1.93**	**2.19**
All of above minus asthma	46	**3.12**	**2.28**	**4.16**	169	**1.73**	**1.48**	**2.01**	169	**1.72**	**1.47**	**2.00**	272	**1.52**	**1.35**	**1.72**	656	**1.69**	**1.56**	**1.82**

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval.
Bold type: 95% CI does not include 1.00.

Table 3. SIR for subsequent autoimmune and related disorders in obese patients by age at hospitalization; follow-up was started 1 year after last hospitalization for obesity

	Age at hospitalization for obesity (years)																			
	<30				30-39				40-49				50-59				>=60			
Autoimmune disorders	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Amyotrophic lateral sclerosis	1	2.22	0.00	12.74	1	1.09	0.00	6.23	2	0.97	0.09	3.55	2	0.67	0.06	2.46	0			
Ankylosing spondylitis	7	**3.70**	**1.47**	**7.67**	2	1.27	0.12	4.66	4	3.01	0.78	7.78	1	1.30	0.00	7.44	1	4.55	0.00	26.06
Asthma	52	**2.84**	**2.12**	**3.72**	70	**4.10**	**3.20**	**5.18**	73	**3.07**	**2.41**	**3.87**	90	**3.44**	**2.76**	**4.23**	33	**1.90**	**1.31**	**2.67**
Behcet disease	1	1.72	0.00	9.88	1	3.13	0.00	17.91	1	3.33	0.00	19.11	2	7.41	0.70	27.24	1	4.76	0.00	27.30
Chronic rheumatic heart disease	0				2	1.49	0.14	5.49	1	0.34	0.00	1.97	5	1.05	0.33	2.46	3	0.87	0.16	2.59
Crohn disease	20	**1.92**	**1.17**	**2.96**	10	1.55	0.74	2.87	6	1.04	0.37	2.28	4	1.04	0.27	2.70	0			
Diabetes mellitus type I	10	**2.76**	**1.32**	**5.10**	0				0				0				0			
Graves, hyperthyroidism	17	1.10	0.64	1.77	16	1.06	0.60	1.73	21	1.52	0.94	2.32	19	**1.71**	**1.03**	**2.68**	4	0.58	0.15	1.50
Hashimoto/hypothroidism	4	2.58	0.67	6.67	6	**2.84**	**1.02**	**6.23**	12	**4.05**	**2.08**	**7.10**	9	**2.77**	**1.26**	**5.28**	12	**4.27**	**2.20**	**7.48**
Immune thrombocytopenic purpura	3	3.03	0.57	8.97	1	1.19	0.00	6.82	2	2.04	0.19	7.51	3	3.06	0.58	9.06	0			
Multiple sclerosis	14	**2.29**	**1.25**	**3.85**	11	1.61	0.80	2.89	7	1.20	0.47	2.48	2	0.65	0.06	2.40	1	1.27	0.00	7.26
Pernicious anemia	1	4.76	0.00	27.30	2	6.45	0.61	23.73	0				6	**4.35**	**1.56**	**9.53**	1	0.51	0.00	2.91
Polymyalgia rheumatica	1	0.62	0.00	3.56	5	1.87	0.59	4.41	7	1.19	0.47	2.47	18	**1.91**	**1.13**	**3.02**	15	1.70	0.95	2.81
Primary biliary cirrhosis	1	4.35	0.00	24.92	3	**6.67**	**1.26**	**19.73**	2	2.82	0.27	10.36	0				1	3.57	0.00	20.47
Psoriasis	14	**3.66**	**2.00**	**6.17**	18	**4.75**	**2.81**	**7.52**	26	**5.20**	**3.39**	**7.63**	13	**3.04**	**1.61**	**5.22**	10	**5.05**	**2.41**	**9.32**
Rheumatoid arthritis	11	1.39	0.69	2.50	14	1.07	0.58	1.80	35	**1.59**	**1.11**	**2.21**	29	1.20	0.80	1.72	20	1.50	0.92	2.33
Sarcoidosis	12	**3.73**	**1.92**	**6.53**	6	2.17	0.78	4.76	8	**2.61**	**1.11**	**5.16**	4	1.50	0.39	3.87	0			
Sjören syndrome	1	2.17	0.00	12.46	0				1	0.89	0.00	5.12	4	**4.08**	**1.06**	**10.55**	4	**9.52**	**2.48**	**24.63**
Systemic lupus erythematosus	3	1.31	0.25	3.88	0				1	0.44	0.00	2.55	2	1.14	0.11	4.18	2	2.56	0.24	9.43
Systemic sclerosis	3	2.73	0.51	8.07	3	2.48	0.47	7.34	1	0.63	0.00	3.61	2	1.35	0.13	4.97	2	2.63	0.25	9.68
Ulcerative colitis	11	0.86	0.43	1.54	10	1.18	0.56	2.18	6	0.84	0.30	1.84	11	**2.08**	**1.03**	**3.74**	2	0.82	0.08	3.00
Wegener granulomatosis	0				0				1	0.66	0.00	3.77	2	0.66	0.06	2.41	3	0.92	0.17	2.73
All of above	187	**1.98**	**1.71**	**2.29**	181	**2.03**	**1.75**	**2.35**	217	**1.96**	**1.71**	**2.24**	228	**2.03**	**1.77**	**2.31**	115	**1.63**	**1.35**	**1.96**
All of above minus asthma	135	**1.78**	**1.49**	**2.10**	111	**1.54**	**1.27**	**1.86**	144	**1.66**	**1.40**	**1.95**	138	**1.60**	**1.34**	**1.89**	82	**1.54**	**1.23**	**1.91**

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval. Bold type: 95% CI does not include 1.00.

Table 4. SIR for subsequent autoimmune and related disorders in obese patients by number of hospitalizations; follow-up was started 1 year after last hospitalization for obesity

	Number of hospitalizations for obesity											
	1				2				>=3			
Autoimmune disorders	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Amyotrophic lateral sclerosis	3	0.51	0.10	1.51	2	1.46	0.14	5.37	1	1.06	0.00	6.10
Ankylosing spondylitis	12	**2.84**	**1.46**	**4.97**	2	2.08	0.20	7.66	1	1.59	0.00	9.10
Asthma	216	**2.88**	**2.51**	**3.29**	50	**2.99**	**2.22**	**3.94**	52	**4.79**	**3.58**	**6.28**
Behcet disease	5	**3.94**	**1.24**	**9.26**	0				1	6.25	0.00	35.83
Chronic rheumatic heart disease	5	0.51	0.16	1.20	3	1.41	0.27	4.17	3	2.17	0.41	6.44
Crohn disease	27	1.32	0.87	1.93	9	2.01	0.91	3.84	4	1.37	0.36	3.54
Diabetes mellitus type I	6	1.96	0.71	4.30	4	**10.00**	**2.60**	**25.86**	0			
Graves, hyperthyroidism	53	1.17	0.88	1.53	16	1.53	0.87	2.49	8	1.23	0.52	2.43
Hashimoto/hypothroidism	26	**2.82**	**1.84**	**4.13**	11	**5.16**	**2.56**	**9.27**	6	**4.72**	**1.70**	**10.35**
Immune thrombocytopenic purpura	4	1.27	0.33	3.27	5	**6.85**	**2.16**	**16.11**	0			
Multiple sclerosis	30	**1.82**	**1.23**	**2.61**	3	0.79	0.15	2.35	2	0.81	0.08	2.99
Pernicious anemia	9	**2.66**	**1.21**	**5.08**	1	1.30	0.00	7.44	0			
Polymyalgia rheumatica	31	**1.51**	**1.02**	**2.14**	13	**2.71**	**1.44**	**4.65**	2	0.65	0.06	2.39
Primary biliary cirrhosis	4	2.35	0.61	6.08	1	2.38	0.00	13.65	2	7.41	0.70	27.24
Psoriasis	54	**3.96**	**2.97**	**5.17**	14	**4.50**	**2.45**	**7.57**	13	**6.22**	**3.30**	**10.67**
Rheumatoid arthritis	79	**1.36**	**1.08**	**1.70**	18	1.33	0.79	2.11	12	1.33	0.68	2.32
Sarcoidosis	23	**2.46**	**1.56**	**3.70**	4	1.89	0.49	4.88	3	2.27	0.43	6.73
Sjören syndrome	6	2.25	0.81	4.92	3	4.69	0.88	13.88	1	2.22	0.00	12.74
Systemic lupus erythematosus	4	0.59	0.15	1.52	3	1.95	0.37	5.77	1	0.99	0.00	5.68
Systemic sclerosis	7	1.57	0.62	3.26	2	1.96	0.18	7.21	2	2.90	0.27	10.66
Ulcerative colitis	32	1.20	0.82	1.70	3	0.52	0.10	1.53	5	1.32	0.42	3.11
Wegener granulomatosis	5	0.75	0.24	1.77	1	0.68	0.00	3.90	0			
All of above	641	**1.84**	**1.70**	**1.99**	168	**2.14**	**1.83**	**2.49**	119	**2.34**	**1.94**	**2.80**
All of above minus asthma	425	**1.56**	**1.41**	**1.72**	118	**1.91**	**1.58**	**2.29**	67	**1.68**	**1.30**	**2.13**

O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval. Bold type: 95% CI does not include 1.00.