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Body mass index and risk of autoimmune diseases: a study within the Danish National Birth Cohort

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Abstract

Background: A possible aetiological link between obesity and certain autoimmune diseases (ADs) has been suggested. We investigated the associations between body mass index (BMI, kg/m^2) and 43 ADs.

Methods: 75 008 women participating in the Danish National Birth Cohort were followed during a median time of 11 years. Diagnoses on ADs were retrieved from the Danish National Patient Register. Cox proportional hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated adjusting for potential confounders (smoking, alcohol, parity and socio-occupational status).

Results: During follow-up, 2430 women (3.2%) developed a total of 2607 new-onset ADs. Risk of any autoimmune disease was increased in obese women (HR, 1.27; 95% CI, 1.11 to 1.46) compared with normal weight women (18.5–$\leq$25 kg/m^2). Obese women (BMI $\geq$30 kg/m^2) were at increased risk of sarcoidosis (HR 3.59; 95% CI, 2.31 to 5.57) and type 1 diabetes mellitus (HR 2.67; 95% CI, 1.71 to 4.17). Risk of dermatitis herpetiformis increased by 14% (95% CI, 1% to 30%) per BMI unit. Conversely, risk of celiac disease and Raynaud's phenomenon decreased by 7% (95% CI, 1% to 13%) and 12% (95% CI, 4% to 19%) per BMI unit, respectively. Further associations between BMI and risk of psoriasis, rheumatoid arthritis and Crohn's disease were suggested.

Conclusions: BMI was found to be associated with several Ads. This was most pronounced between obesity and risk of sarcoidosis and and risk of type 1 diabetes mellitus. These novel findings need confirmation and the possible role of adipose tissue-derived immunological changes in the development of autoimmune reactions needs consideration.

Key words: Body mass index, obesity, inflammation, leptin, autoimmune disease

Key Messages

- In this large population-based cohort study of 75 008 younger Danish women, we examined the association between BMI and 43 autoimmune diseases (ADs). BMI was found to be associated with some, but not all ADs.
- Most pronouncedly, obesity (BMI ≥30) was associated with increased risk of sarcoidosis (>3-fold) and type 1 diabetes mellitus (>2-fold).
- A higher risk of psoriasis and rheumatoid arthritis was observed in obese women, and the association between BMI and Crohn's disease showed a U-shaped pattern [obese and underweight women (BMI<18.5) being at increased risk].
- Inverse associations between BMI and celiac disease and Raynaud's phenomenon were observed.
- BMI did not seem to influence risk of multiple sclerosis or thyroid autoimmunity.

Introduction

Obesity constitutes a serious health problem as reflected by the increased all-cause mortality among obese individuals.[1] Similarly, autoimmune diseases are among the leading causes of death among females in the UK[2] and the USA.[3] During the past decades Since 1980, a growing prevalence of obesity has been observed worldwide,[4–6] though perhaps reaching a plateau in the past years with more than one-third of adults being obese in the USA.[7]

Today, obesity is considered a low-grade systemic inflammatory condition with elevated levels of inflammatory markers such as leptin, C-reactive protein, tumour necrosis factor-α and interleukin-6.[8] The pro-inflammatory adipokine, leptin, which is secreted excessively in obesity by adipocytes, has been identified as a potent immune modulator possibly playing an important role in the development of autoimmune diseases (ADs).[9–11] The pro-inflammatory effect of leptin seems to sustain autoreactive cell proliferation, thereby increasing the risk of AD.[10,12]

An association between obesity and various ADs has been suggested but prospective cohort studies on the subject are sparse. High BMI (body mass index, kg/m^2) has been suggested to relate to development and progression of rheumatoid arthritis (RA),[12–14] but results are inconsistent.[15] Likewise, BMI may associate with thyroid autoimmunity[16]and psoriasis[17,18] but results are contradicting and many studies are based on BMI in patients with existing AD, hence containing risk of reverse causality. Children diagnosed with type 1 diabetes mellitus (T1DM) are increasingly overweight or obese[19,20] but whether obesity among adults is associated with T1DM is still unknown. The only prospective study of the impact of BMI on risk of inflammatory bowel disease (IBD) showed no associations[21] as opposed to a previous retrospective study linking high BMI to Crohn's disease (CD).[22] Further, obesity or obesity-related immunological changes have been suggested in a limited number of studies to associate with other ADs, such as multiple sclerosis (MS),[23,24] celiac disease[25,26] and systemic lupus erythematosus (SLE).[27]

The aim of this large-scale cohort study was to assess the relationship between pre-pregnancy BMI in Danish women of reproductive age and development of 43 different autoimmune diseases in the following decade, also considering the potential effect of weight changes in pregnancy and postpartum weight retention.

Methods

Ethical considerations

The study was purely register- and questionnaire-based without contact with participants and followed the regulations and instructions set up by the Danish Data Protection Agency (approval no. 2008-54-0472).

Study population

The study was based on just above 92 000 women originally enrolled in the Danish National Birth Cohort (DNBC) during 1996–2002. Recruitment by general practitioners took place in early pregnancy throughout Denmark. Women were asked to participate in telephone interviews during pregnancy and early motherhood.[28] In the present study, we used information from the first (16 weeks of gestation), second (30 weeks of gestation), and third (6 months after delivery) interview. A few women gave birth to more than one child in the period 1996–2002, but in the present study only information on BMI related to the first

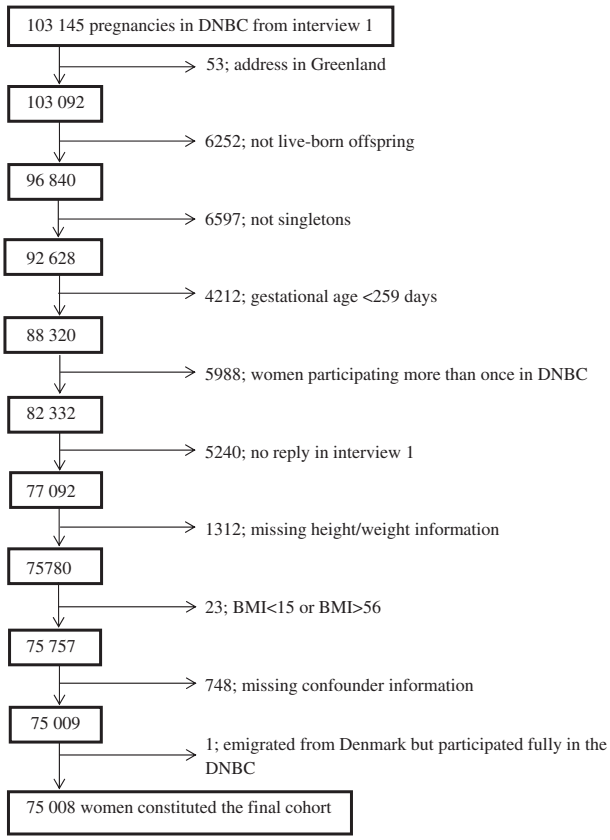

Figure 1. Flow chart describing the cohort consisting of women from the Danish National Birth Cohort.

pregnancy registered in the DNBC was used as an exposure variable. Less than 1% (n=748) of the cohort members were without complete information on confounders such as smoking and parity, and these women were excluded from the cohort. The final cohort consisted of 75 008 women; flow chart information can be viewed in Figure 1.

Exposure

The exposure variable pre-pregnancy body mass index (kg/m^2) was calculated from self-reported information on height ('How tall are you?') and pre-pregnancy weight ('What was your weight before the pregnancy?') in the first interview. Categories were based on the World Health Organization's BMI definitions where <18.5 kg/m^2 is considered underweight, 18.5–<25 kg/m^2 normal weight (reference), 25–<30 kg/m^2 overweight and ≥30 kg/m^2 obese.[29] Pre-pregnancy weight was used as an estimate of the woman's general weight in adult life prior to the pregnancy.

Outcomes

Study outcomes included first hospital contact (primary diagnoses on in- and outpatients, not including emergency room contacts) for the 43 most common autoimmune diseases obtained from the Danish National Patient Register (Table 1), using codes from the International Classification of Diseases, 8th (ICD-8) and 10th revision (ICD-10). ICD-8 codes were used to exclude prevalent AD patients before start of follow-up. The Danish National Patient Register has covered all inpatient hospital contacts since 1977 and all outpatient contacts since 1995. The 43 chosen autoimmune diseases are represented in a list from Harrison's Principles of Internal Medicine.[30,31] To be noted, women who were diagnosed with inflammatory bowel disease (IBD), but shifted diagnosis from Crohn's disease to ulcerative colitis or vice versa in the follow-up period, were given the latest recorded diagnosis but date of diagnosis was determined by the first IBD diagnosis.

Confounders

Confounders chosen a priori included: parity at pregnancy [0 children (reference), 1 child, ≥2 children]; ever smoking (during and/or after pregnancy reported in interview 1, 2, or 3; no smoking at any time as reference; smoking before pregnancy was not included in interviews); alcohol consumption per week [prior to pregnancy; 0 units (reference), 1–7 units, ≥8 units] and socio-occupational status at pregnancy based on the woman's current or most recent occupation within the past 6 months, or if in school, on type of education. Status 1, implied long duration of education or leaders in large companies (reference); status 2, middle-long education or leaders in small companies; status 3, short education, vocational or less; status 4, unskilled, other work or receiving unemployment benefits; status 5, on state welfare. Age was accounted for by using it as underlying timescale in all analyses.

Statistical analysis

Women were followed from time of delivery until development of AD (first hospital contact), emigration, death or end of follow-up on 31 December 2011. By starting follow-up after delivery, ADs directly related to pregnancy were avoided to some extent. Hazard ratios (HRs) with 95% confidence intervals (CIs) of first hospitalization for an autoimmune disease were calculated using Cox proportional hazards models with the woman's age as underlying timescale. The proportional hazards assumption was evaluated in two ways for the 'any AD' fully adjusted model. The effect of BMI at age ≤40 years was compared with the effect of BMI at age >40 years using an interaction test. Furthermore, the empirical score process[32] was used to evaluate the proportional hazards assumption in the complete age range. None of the tests showed any violation of the assumption.Women with any AD before start of

Table 1. Autoimmune diseases with corresponding ICD-8 and ICD-10 codes

Autoimmune disease	ICD-8 codes	ICD-10 codes
Addison's disease	255.10, 255.11	E27.1, E27.2
Ankylosing spondylitis	712.49	M45, M08.1
Behcet's disease	136.02	M35.2
Buerger's syndrome	443.19	M31.1B, DI7.31
Celiac disease	269.00	K90.0
Crohn's disease	563.0	K50
Dermatitis herpetiformis	693.09	L13.0
Diabetes mellitus type 1	249	E10
Dupuytren's disease	733.90	M72.0
Erythema nodosum	695.29	L52
Goodpasture's syndrome	446.19	M31.0
Graves' disease	242.0	E05.0
Guillain-Barré syndrome	354.00	G61.0
Haemolytic anaemia	283.90–283.92	D59.0, D59.1
Hashimoto's thyroiditis	245.03	E06.3
Henoch-Schönlein purpura	287.09	D69.0
ITP[a]	287.10	D69.3
Kawasaki syndrome	446.92	M30.3
Localized lupus erythematosus	695.49	L93
Localized scleroderma	701.01, 701.08, 701.09	L94.0, L94.1, L94.3
Myasthenia gravis	733.09	G70.0
Multiple sclerosis	340	G35
Pemphigoid	694.05	L12
Pernicious anaemia	281.0	D51.0
Pemphigus foliacus	694.02	L10.2
Pemphigus vulgaris	694.00	L10.0
Polyarteritis nodosa	446.09	M30.0
Polymyositis/dermatomyositis	716	M33
Primary biliary cirrhosis	571.90	K74.3
Psoriasis	696.09–696.19	L40
Rheumatic fever	390, 391	I00, I01
Rheumatoid arthritis	712.19, 712.99, 712.39, 712.59	M05, M06
Raynaud's phenomenon	443.00-443.09	DI73.0
Reiter's disease	136.01	M02.3
Sarcoidosis	135	D86
Sjögren's syndrome	734.90	M35.0
Sympathetic ophthalmia	366.02	H44.1B
Systemic lupus erythematosus	734.19	M32
Systemic scleroderma	734.0	M34
Temporal arteritis	446.30, 446.31, 446.39	M31.5, M31.6, M35.3
Ulcerative colitis	563.19, 569.04	K51
Vitiligo	709.01	L80
Wegener's granulomatosis	446.29	M31.3

[a]Idiopathic thrombocytopenic purpura.

follow-up (self-reported in the DNBC or register-based diagnosis) were excluded from the analyses of 'any AD', but not in the examination of each specific disease where women were allowed to have other ADs before start of follow-up and to contribute with more than one type of AD. Before enrolment, 5.3% ($n = 4005$) of the women were registered as having at least one AD. Linear trend analyses using BMI as a continuous variable were performed for ADs with ≥ 5 cases and HRs per BMI unit were only estimated for diseases compatible with a linear trend. ADs with ≥ 50 cases in the cohort were categorized according to BMI (underweight, normal-weight, overweight, obese). HRs were estimated using normal weight as reference. All statistical tests were performed by Wald tests using SAS software version 9.3 (SAS Institute, Cary, NC, USA).

In sensitivity analyses for the 13 most prevalent ADs, referred to in the following as restricted diagnosis analysis, we restricted AD outcomes to include only women recorded at least twice with the same AD diagnosis in the Danish National Patient Register using the date of AD diagnosis on the date of the second diagnosis. This served to increase the validity and specificity of recorded diagnoses. To evaluate gestational weight gain (GWG; as a surrogate for sudden weight gain, in kg, continuous variable) and postpartum weight retention (PPWR; as a surrogate for persistent weight gain, $\leq$3, 3–8, $\geq$8 kg) at 6 months after delivery as potential mediators, separate adjustments for these variables were performed for ADs either showing compatibility with a linear trend with BMI or statistically different estimates across BMI categories. In testing whether the possible mediator effect was affected by women excluded due to missing information about GWG and PPWR, the same analyses were performed for the corresponding cohorts without the adjustment for the two potential mediators (Appendix Table 4, available as Supplementary data at *IJE* online).

Results

Overall, 75 008 women with a median age of 30.2 years (lower-upper quartile, 27.4–33.3 years) at start of follow-up were followed for a median of 11.4 years (lower-upper quartile; 10.2–12.5 years). The cohort consisted of women from all strata according to data on smoking, alcohol and socio-occupational status information, and 27.4% were overweight or obese (Table 2).

During follow-up, 3.2% ($n = 2430$) of the women developed at least one AD and 2607 new AD cases were recorded. The three most frequent ADs were Graves' disease (occurring in 0.8% of cohort members), ulcerative colitis (0.5%) and rheumatoid arthritis (0.4%). Co-occurrence of ADs was present in 303 women (0.4%); of these 270 had two, 31 had three and 2 women had five co-occurring ADs. In the relationship between BMI and later development of autoimmune disease, compatibility with a linear trend was found for all ADs except ankylosing spondylitis, ulcerative colitis and sarcoidosis. An increased risk of 14% (95% CI 1% to 30%) per BMI unit was found for dermatitis herpetiformis but was based on too few cases to be included in further analyses (Figure 2). Below, results of mediator analyses are only mentioned when relevant, but all results can be viewed in the Appendix (available as Supplementary data at *IJE* online).

Any autoimmune disease

Any autoimmune disease ($n = 2430$) occurred at a median of 5.7 (2.8–8.6) years after start of follow-up. The risk of any autoimmune disease was increased in obese women (HR, 1.27; 95% CI, 1.11 to 1.46) compared with

Table 2. Cohort characteristics at start of follow up ($n = 75\,008$)

Woman's age, median years (lower-upper quartiles)	30.2 (27.4–33.3)
Parity prior to pregnancy (%)	
0 children	37 173 (49.6)
1 child	26 045 (34.7)
2+ children	11 790 (15.7)
Alcohol consumption per week prior to pregnancy (%)	
0 units	9443 (12.6)
1–7 units	57 967 (77.3)
8+ units	7598 (10.1)
Smoking during or after pregnancy (%)	
Smoking reported in interview 1, 2 or 3	20 709 (27.6)
No smoking reported in interview 1, 2, or 3	54 299 (72.4)
Socio-occupational status in pregnancy (%)	
Long education / leaders in large companies	15 661 (20.9)
Middle-long education / leaders in small companies	23 901 (31.9)
Short education / vocational / less	28 372 (37.8)
Unskilled / other work / unemployment benefits	5467 (7.3)
On state welfare	1607 (2.1)
Body mass index prior to pregnancy (%)	
<18.5 kg/m^2	3319 (4.4)
18.5 –<25 kg/m^2	51 148 (68.2)
25 –<30 kg/m^2	14 470 (19.3)
≥ 30 kg/m^2	6071 (8.1)

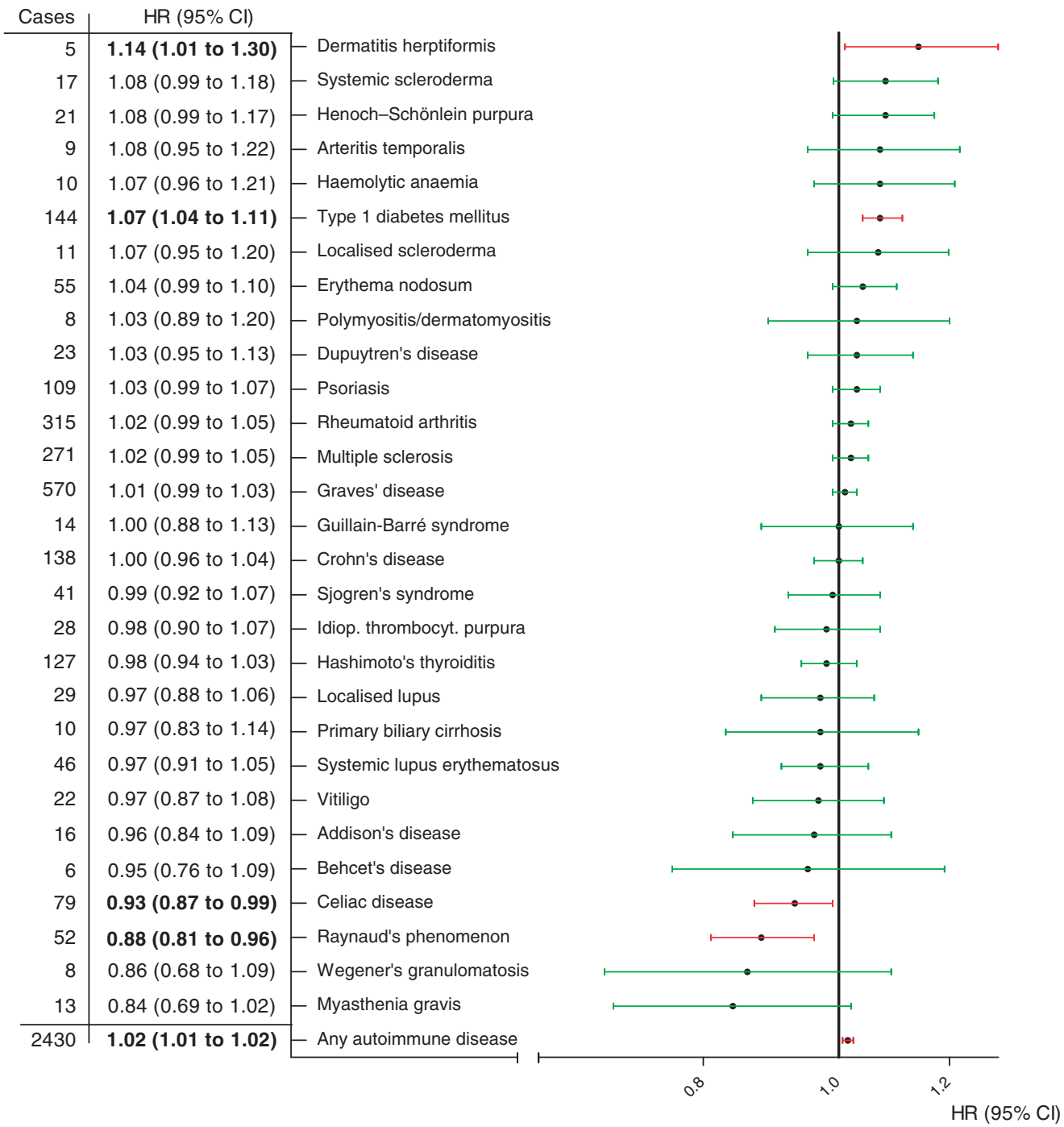

Figure 2. Hazard ratios (HRs) for autoimmune diseases per unit increase in body mass index in women ($n = 75008$). Emboldened HRs do not include 1.0. Diseases with ≥20 cases are adjusted for smoking, alcohol, parity, socio-occupational status. Diseases with ≤5 cases are not shown (Buerger's disease 1 case; Goodpasture's syndrome, 1, Kawasaki syndrome, 1; pernicious anaemia, 0; polyarteritis nodosa, 3; pemphigoid, 0; pemphigus foliaceus, 0; pemphigus vulgaris, 0; Reiter's disease, 1; rheumatic fever, 4; sympathetic ophthalmia, 0). Hazard ratios are only shown for diseases where the association between body mass index and the disease were compatible with a trend (not compatible with a trend: ankylosing spondylitis, ulcerative colitis and sarcoidosis).

normal-weight women (Table 3). Overall, a trend of linearity was observed for any autoimmune disease across BMI units ($P_{trend} < 0.01$) with an increasing risk of 2% (95% CI, 1% to 2%) per BMI unit (Figure 2).

Celiac disease

Celiac disease showed a decreased risk of 7% (1–13%) per BMI unit increase (Figure 2). Accordingly, the risk of celiac disease was increased in underweight women

Table 3. Hazard ratios (HRs) of autoimmune diseases appearing with ≥50 cases in the study cohort according to body mass index (BMI; kg/m^2) firstly including all women diagnosed at least once and, secondly, only including women with ≥2 diagnoses counted from second diagnosis of autoimmune diseases in the Danish National Patient Register

	N	BMI < 18.5	18.5 ≤ BMI < 25	25 ≤ BMI < 30	BMI ≥ 30	P_{trend}	$P_{homogeneity}$[a]
Ankylosing spondylitis	68	0.36 (0.05–2.60)	1 (ref)	1.55 (0.91–2.65)	0.73 (0.26–2.05)	–	0.20
≥2 diagnoses	35	–	1 (ref)	1.99 (0.97–4.10)	1.18 (0.36–4.00)	–	0.31
Celiac disease	79	2.59 (1.27–5.26)	1 (ref)	0.65 (0.33–1.28)	0.75 (0.30–1.89)	0.03	–
≥2 diagnoses	44	2.23 (0.79–6.33)	1 (ref)	0.70 (0.29–1.67)	0.55 (0.13–2.32)	0.07	–
Crohn's disease	138	1.99 (1.08–3.66)	1 (ref)	1.10 (0.71–1.70)	1.52 (0.89–2.62)	0.89	–
≥2 diagnoses	96	2.57 (1.30–5.06)	1 (ref)	1.11 (0.65–1.90)	1.88 (1.02–3.47)	0.89	–
Erythema nodosum	55	0.42 (0.06–3.05)	1 (ref)	0.99 (0.49–1.99)	1.68 (0.74–3.82)	0.13	–
≥2 diagnoses	24	1.05 (0.14–8.05)	1 (ref)	1.55 (0.59–4.07)	1.89 (0.53–6.73)	0.08	–
Graves' disease	570	0.75 (0.48–1.17)	1 (ref)	0.92 (0.74–1.15)	1.23 (0.93–1.62)	0.16	–
≥2 diagnoses	315	0.89 (0.51–1.55)	1 (ref)	0.90 (0.67–1.21)	1.13 (0.77–1.67)	0.72	–
Hashimoto's thyroiditis	127	1.75 (0.88–3.50)	1 (ref)	1.08 (0.69–1.70)	1.06 (0.55–2.06)	0.40	–
≥2 diagnoses	39	2.23 (0.78–6.38)	1 (ref)	0.76 (0.31–1.85)	0.31 (0.04–2.30)	0.08	–
Multiple sclerosis	271	1.31 (0.78–2.19)	1 (ref)	1.28 (0.96–1.72)	1.00 (0.63–1.58)	0.21	–
≥2 diagnoses	201	1.43 (0.79–2.60)	1 (ref)	1.32 (0.94–1.85)	1.15 (0.69–1.92)	0.28	–
Psoriasis[b]	109	0.91 (0.33–2.51)	1 (ref)	1.38 (0.87–2.20)	2.16 (1.25–3.72)	0.14	–
≥2 diagnoses	30	–	1 (ref)	1.16 (0.46–2.95)	3.03 (1.24–7.42)	0.02	–
Raynaud's phenomenon	52	1.01 (0.31–3.27)	1 (ref)	0.23 (0.07–0.73)	0.50 (0.15–1.62)	<0.01	–
≥2 diagnoses[c]	12	1.35 (0.17–10.53)	1 (ref)	–	–	<0.01	–
Rheumatoid arthritis	315	0.82 (0.45–1.50)	1 (ref)	1.12 (0.85–1.49)	1.53 (1.07–2.18)	0.08	–
≥2 diagnoses	176	1.05 (0.51–2.14)	1 (ref)	1.00 (0.68–1.48)	1.09 (0.63–1.88)	0.72	–
Sarcoidosis	140	1.06 (0.43–2.65)	1 (ref)	1.90 (1.27–2.84)	3.59 (2.31–5.57)	–	<0.01
≥2 diagnoses	84	1.16 (0.36–3.78)	1 (ref)	2.26 (1.35–3.79)	4.30 (2.47–7.50)	–	<0.01
Type 1 diabetes mellitus	144	0.83 (0.34–2.06)	1 (ref)	1.42 (0.95–2.14)	2.67 (1.71–4.17)	<0.01	–
≥2 diagnoses	108	1.10 (0.44–2.75)	1 (ref)	1.32 (0.83–2.13)	2.01 (1.15–3.51)	<0.01	–
Ulcerative colitis[d]	394	1.10 (0.70–1.74)	1 (ref)	0.99 (0.77–1.28)	0.92 (0.63–1.34)	–	0.94
≥2 diagnoses	280	1.20 (0.71–2.04)	1 (ref)	0.93 (0.68–1.27)	0.77 (0.48–1.25)	–	0.60
Any autoimmune disease	2430	1.08 (0.89–1.30)	1 (ref)	1.09 (0.98–1.20)	1.27 (1.11–1.46)	<0.01	–
≥2 diagnoses	1439	1.24 (0.98–1.56)	1 (ref)	1.05 (0.92–1.21)	1.23 (1.02–1.47)	0.11	–

All HRs are adjusted for smoking, alcohol, parity, socio-occupational status.

[a]Test of homogeneity was used when associations were not compatible with a linear trend.

[b]In a subanalysis dividing BMI into five categories instead of four, women with 30 < BMI ≤ 35 ($n = 16$) had an increased risk of psoriasis (HR 2.78; 95% CI, 1.59 to 4.85) and BMI > 35 ($n = 1$) had a decreased risk of psoriasis (HR 0.47; 95% CI, 0.06 to 3.37).

[c]Not adjusted for socio-occupational status due to few cases.

[d]Ulcerative colitis did not show compatibility with a linear trend which was visualized through adding an extra BMI category (30 ≤ BMI < 35; HR 0.67; 95% CI, 0.41 to 1.12 and BMI ≥ 35; HR 1.57; 95% CI, 0.92 to 2.70).

($P_{trend} = 0.03$) (HR 2.59; 95% CI, 1.27 to 5.26) (Table 3). In the restricted diagnosis analysis, no association between underweight and development of celiac disease was seen ($P_{trend} = 0.07$), however underweight women tended to have a 2-fold increased risk of celiac disease (HR 2.23; 95% CI, 0.79 to 6.33) although statistically insignificant (Table 3).

Crohn's disease

Overall, no association was observed between BMI and Crohn's disease (HR 1.00; 95% CI, 0.96 to 1.04, $P_{trend} = 0.89$) (Figure 2). However, performing restricted diagnosis analysis resulted in an increased risk in both underweight (HR 2.57; 95% CI, 1.30 to 5.06) and obese women (HR 1.88; 95% CI, 1.02 to 3.47) compared with normal-weight women, pointing to a U-shaped association (Table 3).

Psoriasis

No linear associations between BMI and psoriasis were observed (HR 1.03; 95% CI, 0.99 to 1.07, $P_{trend} = 0.14$)

(Figure 2), but when comparing BMI categories, an increased risk of psoriasis was seen in obese women (HR 2.16; 95% CI, 1.25 to 3.72) compared with normal-weight women (Table 3). Further, trend of linearity in restricted diagnosis analysis (Table 3) was found ($P_{trend} = 0.02$) with a more than 3-fold risk of psoriasis in obese women (HR 3.03; 95% CI, 1.24 to 7.42).

Rheumatoid arthritis

Rheumatoid arthritis showed no overall linear association with BMI (HR 1.02; 95% CI, 0.99 to 1.05, $P_{trend} = 0.08$) (Figure 2) but an increased risk of rheumatoid arthritis was observed in obese women (HR 1.53; 95% CI, 1.07 to 2.18) compared with normal-weight women (Table 3). The increased risk in obese women did, however, not persist in restricted diagnosis analysis (HR 1.09; 95% CI, 0.63 to 1.88) (Table 3).

Raynaud's phenomenon

An inverse association between BMI and Raynaud's phenomenon was observed with a decreasing risk of 12% (4–19%) per BMI unit increase ($P_{trend} < 0.01$) (Figure 2). Underweight women were at no increased risk of Raynaud's phenomenon, whereas overweight women appeared to be at a reduced risk (HR 0.23; 95% CI, 0.07 to 0.73) compared with normal-weight women (Table 3). The inverse association with overweight persisted when adjusting for GWG (HR 0.19; 95% CI, 0.05 to 0.80) and PPWR (HR 0.21; 95% CI, 0.05 to 0.86) (Appendix Table 4, available as Supplementary data at *IJE* online). There were too few cases to estimate HRs in the restricted diagnosis analysis for overweight and obese women.

Sarcoidosis

Sarcoidosis showed the highest risk in obese women among all studied ADs but the association was not compatible with a linear trend. Heterogeneity between BMI and risk of sarcoidosis was observed across BMI categories ($P_{homogeneity} < 0.01$) with an increased risk in overweight (HR 1.90; 95% CI, 1.27 to 2.84) and obese (HR 3.59; 95% CI, 2.31 to 5.57) women. Restricted diagnosis analysis (Table 3) showed a more than 2-fold increased risk of sarcoidosis in overweight (HR 2.26; 95% CI, 1.35 to 3.79) women and a more than 4-fold increased risk in obese women (HR 4.30; 95% CI, 2.47 to 7.50)($P_{homogeneity} < 0.01$).

Type 1 diabetes mellitus

The risk of T1DM increased by 7% (4–11%) per BMI unit increase ($P_{trend} < 0.01$). Accordingly, a 2.7-fold increased risk was found in obese women (HR 2.67; 95% CI, 1.71 to 4.17) (Table 3). In restricted diagnosis analyses, the association between BMI and T1DM remained with a 2-fold increased risk of T1DM among obese women (HR 2.01; 95% CI, 1.15 to 3.51). Adjusting for GWG showed no association in obese women (HR 1.66, 95% CI 0.96–2.85) and no linear trend was observed ($P_{trend} = 0.12$). Adjusting for PPWR did not change estimates (Appendix Table 4, available as Supplementary data at *IJE* online).

Other frequent ADs

Risks of other frequent ADs, including ankylosing spondylitis, Graves' disease, Hashimoto's thyroiditis, ulcerative colitis, erythema nodosum, and multiple sclerosis were not associated with BMI.

Discussion

This large population-based cohort study of 75 008 Danish women suggests an association between BMI and development of several autoimmune diseases. Associations were found between increasing BMI and ADs in overall analyses for 'any AD', dermatitis herpetiformis and especially T1DM and sarcoidosis. Despite no overall trends, we also found a higher risk of psoriasis and rheumatoid arthritis in obese women. In restricted analyses, a U-shaped pattern between BMI and Crohn's disease was observed. Inverse associations between BMI and celiac disease and Raynaud's phenomenon were seen.

The primary strength of this study was the assessment of a well-characterized large cohort of women followed prospectively for more than a decade after collection of height and weight data and with detailed information on potentially important confounders and mediators such as smoking, alcohol, gestational weight gain and postpartum weight retention. Another advantage was the ability to exclude prevalent AD cases at baseline with high completeness due to access to both self-reported and register-based information. Additionally, we had access to information on BMI prior to diagnosis of ADs, hence avoiding recall bias. The use of interview data from DNBC combined with register information made it possible to investigate an exposure such as BMI, usually not accessible in registers, and outcomes covering 43 different ADs.

Nevertheless, the study also has limitations to consider. Diagnoses of ADs were extracted from a hospital register containing information on diagnoses from all Danish inpatient and outpatient settings. However, milder cases of some of the ADs are likely to be diagnosed and treated by general practitioners or specialists, which is why our findings may apply mainly to the more severe cases of AD. Onset of disease might have occurred sometime before hospital contact, but this is not likely to have influenced results markedly, as women were followed for more than

11 years and the median (lower-upper quartile) time from start of follow-up to diagnosis of an AD was 5.8 (2.9–8.6) years. Incidence of some autoimmune diseases such as thyroiditis, Sjögren's disease and rheumatoid arthritis peak after age 50 years and a long follow-up period would be preferable, but most autoimmune diseases can be diagnosed at any age and many in the reproductive years.[3] Concerning validity of the Danish National Patient Register, the register includes information on all somatic hospital admissions sin 1977, with inclusion of outpatients and emergency patients in 1995.[33] For several of the ADs in question, e.g. T1DM, ulcerative colitis (UC), CD, MS and RA, the register has been validated.[34–37] To further evaluate validity of the studied ADs, we performed sensitivity analyses with cases recorded at least twice with the same diagnosis. This had little impact on results, adding robustness to the results. Women of low socio-occupational status could be a source of selection bias as this group has previously been found underrepresented in the DNBC.[38] Also, cohort members of the DNBC have in a previous study been found somewhat healthier in terms of weight and smoking than the general population. However, odds ratios of three different associations, including BMI and risk of stillbirth, were not biased by non-participation in the DNBC.[39] This in combination with an assumed low rate of women dropping out from the DNBC due to symptoms of a yet undiagnosed AD, indicates that selection bias is unlikely to have influenced findings markedly. Another consideration in relation to selection bias worth mentioning is infertility. Studies suggest that clinical (and thereby possibly also subclinical) AD[40] and to a greater extent high/low BMI[41] are associated with infertility (i.e. less likely to be included in the DNBC). Potentially, this may create selection bias; however, as the association between subclinical AD (which is the focus variable in this context since women with diagnosed AD before start of follow-up were excluded from analyses of that specific AD) and infertility is still considered inconsistent, we consider a possible selection bias due to the exclusion of infertile women negligible and if anything only likely to underestimate our results. BMI was only measured at start of follow-up, but a recent study found that weight increased equally for all BMI categories in women from early adulthood throughout the following 18 years of life.[42] Further, adjustments for weight changes linked to pregnancy, as represented by GWG and PPWR, were performed and the only noticeable observed effect was for GWG in the association between BMI and T1DM. Correction for multiple testing was not applied in this study since we assessed hypotheses for specific autoimmune diseases, not only an overall association between BMI and 'any' autoimmune disease.

Sarcoidosis

Of all the ADs, the highest risk (more than 3-fold) in obese women was observed for sarcoidosis, a disease that, to our knowledge, has not previously been related to obesity besides increased BMI in patients with existing sarcoidosis.[43] The aetiology of sarcoidosis remains unknown but the disease involves immunological changes similar to those seen in obesity, including TNF-α production.[44,45] Infectious agents, such as mycobacteria, have been suspected as cause of sarcoidosis but, more possibly, disease development may depend on a combination of genetic polymorphisms, the triggering antigen itself and immune system status[46] in which the changed immunology caused by obesity could play a role. Besides, hypothalamic-pituitary locations of sarcoidosis are rare,[47] which is why it seems unlikely that the association is explained by an effect on the satiety centre in the hypothalamus that could lead to overnutrition and thereby obesity.

Type 1 diabetes mellitus

To our knowledge, the >2-fold increased risk of T1DM in obese adults (women) represents a novel finding, though misclassification between type 1 and type 2 diabetes mellitus should be considered. Most studies of obesity and T1DM development have been performed in children and adolescents already diagnosed with T1DM, in whom the prevalence of overweight and obesity at time of diagnosis is increasing despite the fact that weight loss often precedes T1DM diagnosis.[19,20] The earliest disease mechanisms in T1DM are suggested to take place early in life,[48] perhaps even *in utero* because of maternal obesity-related immunological changes. Obesity is often passed on between generations and therefore it could be hypothesized that obesity in adult life and T1DM are linked, even though the disease was triggered already *in utero* due to maternal obesity. This theory is compatible with the observation that GWG seemed to be a mediator in the observed association.

Psoriasis

Although no overall linear increase per BMI unit was observed, we found a >2-fold increased risk of psoriasis in obese women when compared with normal-weight women. The lack of significance could be due to lack of power in the very obese group. Further, the trend was significant in the restricted diagnosis analysis with a >3-fold increased risk of psoriasis in obese women. Contrary to T1DM, a possible relationship between obesity and psoriasis has been more thoroughly investigated, e.g. high BMI in adolescent girls has been connected to later psoriasis hospitalization,[49] but often studied in patients with existing disease.[50] A previous prospective study within the Nurses' Health Study II including 78 626 women followed for a

14-year period also found an association of similar strength between BMI and psoriasis.[51] The Nurses' Health Study was, however, based solely on self-reported psoriasis, whereas in the present study diagnoses were based on hospital diagnoses with exclusion of self-reported and register-based cases before start of follow-up, thereby strengthening the validity. Nevertheless, the two similar findings point to an association between obesity and development of psoriasis as has been observed in obese adolescents as well. At the molecular level, leptin and other adipokines have been suggested to be involved in the pathogenesis of psoriasis in overweight individuals[52] and further, leptin might serve as a marker of severity and chronicity in psoriasis.[53]

Rheumatoid arthritis

In our study, we found only a weak association between BMI and RA though obese women had a 1.5 increased risk of RA development compared with normal-weight women. A recent review emphasized that the association between leptin/high BMI and RA is still questionable,[11] and the increased risk found in some case-control studies[13,14] may reflect an increased risk of RA following obesity but possibly only valid in a subgroup of RA patients without auto-antibodies against cyclic citrullinated peptides;[54,55] subgroups not possible to identify in our study.

Celiac disease and dermatitis herpetiformis

Interestingly, we found an increased risk of celiac disease in underweight women. This observation points towards reverse causation; however, evidence of overweight/obesity in patients at time of diagnosis of celiac disease is evolving.[25,26,56,57] Against this, undiagnosed celiac disease or celiac disease diagnosed outside hospital settings might have caused underweight before registration of the celiac disease diagnosis in the Danish National Patient Register. Furthermore, dermatitis herpetiformis, which is closely associated with gluten sensitivity as in celiac disease,[58] showed the highest risk with increasing BMI (14% per BMI unit) among all investigated ADs. To our knowledge, the only previous study on BMI and dermatitis herpetiformis showed a linearly higher prevalence of this disease with increasing BMI among patients with untreated celiac disease, thereby supporting our results.[59]

Crohn's disease

We found an increased risk of CD in underweight women compared with normal weight, and an increased risk among obese women. In a recently published study by Chan and colleagues on BMI and development of IBD, the underweight category was not investigated.[21] Whether our results reflect an actual increased risk in underweight women and not reverse causation due to early disease-induced weight loss is unclear. In support of our findings, a U-shaped relationship of BMI and risk of CD was previously found in a retrospective study by Mendall and colleagues[22] who suggested that this might be caused by underweight women having a more severe subtype and obese a less severe subtype of CD. Further, Chan and colleagues found no associations between high BMI and later development of UC or CD.[21] This is in line with our results for UC but, in restricted diagnosis analysis of CD, we found a 1.9 increased risk of CD in obese women. Chan and colleagues mainly investigated late-onset IBD with a median age at recruitment between 50 and 53 years, which may represent IBD of a different pathogenesis compared with IBD diagnosed earlier in life as in our study. Moreover, the study did not adjust for gender or age, even though BMI has been found both gender- and age-dependent when used as an indicator of body composition.[60] Alternatively, a possible role of the gut microbiome underlying the risk between BMI and CD should be considered, as the intestinal bacterial flora has been associated with obesity[61] and IBD in individuals with a genetic predisposition.[62] Our data do not permit a more detailed evaluation of this possibility.

Raynaud's phenomenon

Our finding of a decreased risk of Raynaud's phenomenon with increasing BMI remains unexplained and has, to our knowledge, not previously been reported.

Multiple sclerosis and thyroid autoimmunity

Lastly, and against expectations, MS was not found to be associated with BMI. Two former studies have shown an increased risk of MS in individuals who were obese in childhood[63] and adolescence,[23,24] whereas no association with BMI at time of disease occurrence has been observed,[23] hence suggesting adolescence to be critical in determining risk of MS. Likewise, thyroid autoimmunity was not found to be associated with BMI though a connection with leptin and obesity has been suggested.[16]

Shared mechanisms?

Overall, the suggested association between BMI and development of ADs in this study could be linked to the finding that several ADs such as psoriasis, IBD, RA, T1DM and MS have been related to changes in adipokine and cytokine levels which are seen in obesity as well.[10,11,53] Except for MS and UC, this corresponds to our findings. Co-occurrence of several ADs has been suggested, including RA, autoimmune thyroiditis and T1DM,[64] hence supporting a common aetiology or shared risk factors. On the other hand, the study

found an inverse association between RA and MS. Genetically this is supported by a study suggesting a shared risk allele between T1DM, RA and thyroiditis, but not MS.[65] To our knowledge, a shared genetic link between obesity and autoimmune diseases has not been investigated. Further, the modest effect of BMI on risk of 'any AD' may reflect that ADs comprise a too heterogeneous group of diseases to share BMI as a common aetiological factor. At the cellular level, the proliferation of regulatory T cells, which are known to dampen autoreactive responses under normal conditions, is suggested to be inversely correlated with leptin in early stages of autoimmune disease, and obesity has even been proposed to be an autoimmune disorder in itself.[11,66] Additionally, recent research suggests Th17 cell expansion to be a prominent element of pro-inflammatory diseases in obesity[67] and has been found to be connected to autoimmune diseases such as RA, ankylosing spondylitis, SLE, MS, psoriasis and IBD.[68] Possibly, the unstable Th17 cells are converted into either Th1 or Th2 phenotype, causing Th1- or Th2-mediated autoimmune diseases.[68] Another hypothesis could be the fact that leptin levels have been found 2- to 3-fold higher in women compared with men due to a higher percentage of body fat in females at a given weight or BMI.[69] Along with a predominance of ADs in women,[70] this adds to the possible relationship between obesity and AD development.

In conclusion, this cohort study of young Danish women showed an increased risk of some but not all ADs in obese women, most notably for sarcoidosis and T1DM. These novel results are interesting in light of the rising prevalence of obesity and some ADs and may reflect obesity-related complex immunological changes leading to autoimmune reactions. Underlying mechanisms and observed associations need further investigation.

Supplementary Data

Supplementary data are available at *IJE* online.

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