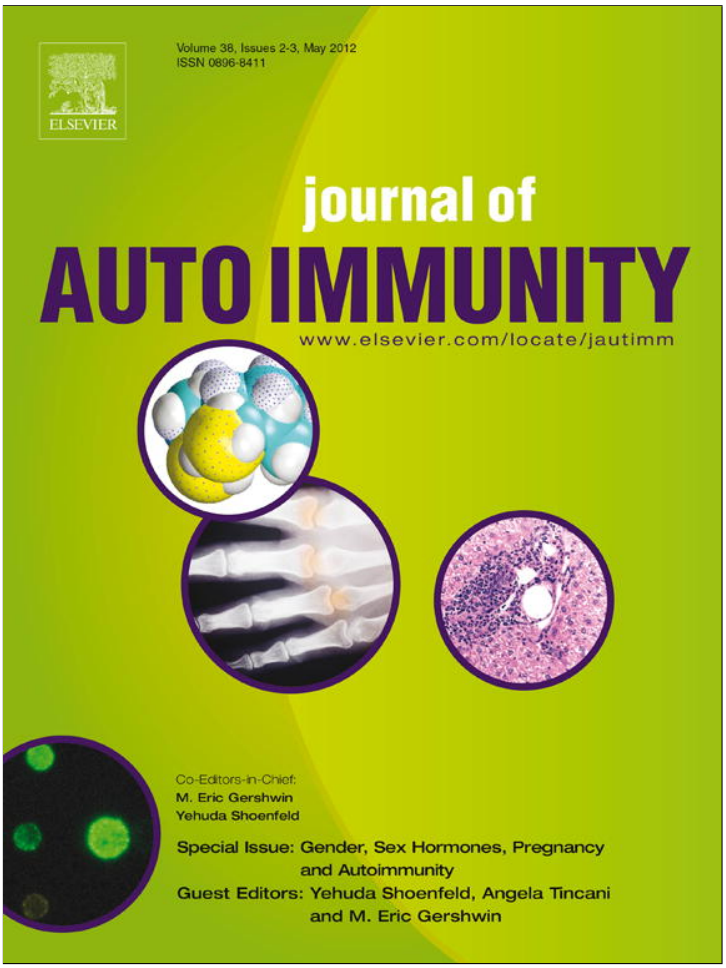

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Hyperemesis, gestational hypertensive disorders, pregnancy losses and risk of autoimmune diseases in a Danish population-based cohort

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ABSTRACT

The risk of some female predominant autoimmune diseases (ADs) has previously been shown to be higher in women who experience hyperemesis, gestational hypertensive disorders and idiopathic pregnancy losses. This study assessed the association between such pregnancy-related experiences and the subsequent risk of female predominant and other ADs.

Our study cohort comprised 1.6 million Danish women born since 1955 for whom we had information about hyperemesis, gestational hypertensive disorders and pregnancy losses and subsequent hospital contacts for 31 ADs between 1982 and 2008. Ratios of first hospitalization rates (RRs) with 95% confidence intervals (CIs) were calculated using Poisson regression, adjusting for age, birth cohort, calendar period, marital status and childbirths.

During 27.0 million person-years of follow-up 51,732 women were hospitalized with one or more ADs. Overall, compared with women without the specific pregnancy experiences, the risk of any AD was significantly increased for women with hyperemesis (RR = 1.41; 95% CI 1.30–1.51), gestational hypertensive disorders (1.21; 1.16–1.26), spontaneous abortions (1.10; 1.07–1.14), missed abortions (1.09; 1.04–1.13), stillbirths (1.25; 1.12–1.40), ectopic pregnancies (1.08; 1.02–1.14) and induced abortions (1.07; 1.04–1.09). Associations with female predominant ADs (i.e., ADs with a female:male ratio >2:1) were strongest in the first five years after the studied pregnancy experiences, but overall there was little difference between the RRs for groups of female predominant ADs and other ADs. Strong and potentially biological associations were observed for a number of specific ADs; including systemic lupus erythematosus, Graves' disease, type 1 diabetes mellitus and pernicious anemia, and for some specific ADs associations persisted even more than five years after the abnormal pregnancy experience.

Abnormal pregnancies are associated with increased risk of certain ADs, possibly because of underlying immunologic or hormonal factors that predispose to both adverse pregnancy experiences and AD development.

1. Introduction

Autoimmune diseases (ADs) are generally of unknown etiology. They may be complex multi-system diseases with manifestations involving diverse organ systems and tissue injury caused by abnormal immunological reactions directed against own tissues. A prominent feature shared by a large proportion of ADs is a clear, yet unexplained, female predominance [1–3].

In a recent study we showed that parous women were at 11% higher risk of developing ADs with a marked female predominance than women without children [4]. This rather modest risk difference between parous and nulliparous women suggests that normal pregnancy that results in a liveborn child explains little, if anything, of the characteristic female predominance in ADs. However, women with some ADs such as systemic lupus erythematosus (SLE), systemic sclerosis, type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, myasthenia gravis, and celiac disease, may be more likely to experience pregnancy complications or idiopathic pregnancy losses than other women [5–12]. Despite this relationship only little focus has been on the possible association between such pregnancy-related experiences and the subsequent risk of ADs.

The etiologies underlying hyperemesis, gestational hypertensive disorders and pregnancy losses are not well understood.

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Hyperemesis is characterised by persistent vomiting, weight loss and dehydration initiated within the first 9 weeks of gestation [13], while preeclampsia, a complication that usually occurs in the third trimester, is characterised by hypertension and proteinuria [14]. Chromosomal abnormalities have been reported to be responsible for about 50% of early pregnancy losses [15], but for later spontaneous abortions, missed abortions and stillbirths the underlying etiology is usually unknown. Hormonal and immunological imbalances have been suggested to be involved in all these different abnormal pregnancy outcomes [16–20]; conditions that might also contribute to the development of ADs. We have previously shown that spontaneous abortions, missed abortions and stillbirths are associated with increased risk of SLE and that hyperemesis, gestational hypertension and preeclampsia are associated with increased risk of rheumatoid arthritis [21,22]. In contrast, we observed no association between pregnancy complications or losses and subsequent risk of multiple sclerosis [23]. These findings for individual ADs are compatible with the idea that possible relationships between abnormal pregnancy experiences and ADs may be stronger for ADs with a clear female predominance.

In this study we assessed the association between hyperemesis, gestational hypertensive disorders and pregnancy losses and the subsequent risk of a large number of ADs. We hypothesized that ADs with a clear female predominance would be more strongly associated with prior pregnancy complications and pregnancy losses than other ADs.

2. Materials and methods

The study cohort comprised Danish women born between 1955 and 1993. This cohort was linked to national health registers by the unique 10-digit identification number ascribed to all Danish inhabitants to get information about pregnancy complications, pregnancy losses, and subsequent hospital contacts for ADs.

2.1. Pregnancy complications and pregnancy losses

Information about hyperemesis, gestational hypertension, preeclampsia, spontaneous abortions, missed abortions and ectopic pregnancies was obtained from the Danish National Patient Registry [24] while information about induced abortions and stillbirths was obtained from the National Registry of Induced Abortions [25], and the Medical Birth Registry [26], respectively (Table 1).

Table 1
Pregnancy complications and pregnancy losses, corresponding ICD-8 and ICD-10 codes and the year from which data became available.

	ICD-8 codes	ICD-10 codes	Data available from
Pregnancy complications			
Hyperemesis	63809, 63899, 76249	O21	1977
Gestational hypertension	63700, 63702	O12, O13, O16	1977
Preeclampsia	63703, 63704, 63709, 63719, 63799, 63999, 76219, 76229, 76239, 76299	O14, O15	1977
Pregnancy losses			
Spontaneous abortions	643	O03	1977
Missed abortions	63461-63463, 63469, 6451	O021	1977
Stillbirths[a]	–	–	1973
Ectopic pregnancies	631	O00	1977
Induced abortions	640, 641, 642	O04-O06	1974

ICD, International Classification of Diseases.
[a] Information about stillbirths in the cohort was obtained from the Medical Birth Registry, which does not use ICD coding.

2.2. Autoimmune diseases

We obtained information about first hospital contacts for the 31 most prevalent ADs from the Danish National Patient Registry from January 1, 1982 to December 31, 2008 (including first outpatient hospital contacts for AD since January 1, 1995) (Table 2). For specific combinations of individual pregnancy experiences and ADs we only considered associations between those ADs where at least 500

Table 2
Autoimmune diseases, corresponding ICD-8 and ICD-10 codes, female:male ratios, and number of first hospitalizations between 1982 and 2008 in Danish women born between 1955 and 1993.

Autoimmune disease	ICD 8 codes	ICD 10 codes	Female:male ratio[a]	Cases
Hashimoto thyroiditis	24503	E063	8.3[b]	1953
Sjögren's syndrome	73490	M350	7.5[b]	793
Systemic lupus erythematosus	73419	M32	5.2[b]	1446
Graves' disease	2420	E050	5.1[b]	10,787
Primary biliary cirrhosis	57190	K743	3.9[b]	171
Systemic sclerosis	7340	M34	3.7[b]	417
Erythema nodosum	69529	L52	2.7[b]	1539
Rheumatoid arthritis	71219, 71229, 71239, 71259	M05, M06	2.4[b]	6404
Temporal arteritis	44630, 44631, 44639	M315, M316, M353	2.3[b]	294
Multiple sclerosis	340	G35	1.8	4925
Pernicious anemia	2810	D510	1.7	513
Vitiligo	70901	L80	1.6	477
Celiac disease	26900	K900	1.6	1175
Addison's disease	25510, 25511	E271, E272	1.6	360
Polymyositis/ dermatomyositis	716	M33	1.5	209
Hemolytic anemia	28390–28392	D590, D591	1.4	147
Crohn's disease	5630	K50	1.4	5855
Myasthenia gravis	73309	G700	1.4	270
Pemphigoid	69405	L12	1.3	46
Idiopathic thrombocytopenic purpura	28710	D693	1.3	771
Polyarteritis nodosa	44609	M300	1.3	107
Rheumatic fever	390391	I00, I01	1.2	234
Ulcerative colitis	56319, 56904	K51	1.2	9201
Psoriasis	69609–69619	L40	1.1	4455
Sarcoidosis	135	D86	1.0	2592
Type 1 diabetes mellitus[c]	249	E10	0.9	3968
Wegener's granulomatosus	44629	M313	0.9	156
Henoch-Schönlein purpura	28709	D690	0.8	417
Amyotrophic lateral sclerosis	34809	G122G	0.8	37
Guillain-Barré syndrome	35400	G610	0.8	401
Ankylosing spondylitis	71249	M45, M081	0.4	999
Women with female predominant autoimmune diseases[d]				22,876
Women with other autoimmune diseases[d]				30,738
Women with any autoimmune disease[d]				51,732

ICD, International Classification of Diseases.
[a] Reference [27].
[b] Female predominant autoimmune disease, defined as autoimmune diseases with a female:male ratio above 2.0 in the general Danish population.
[c] Type 1 diabetes mellitus was analyzed separately with a study period restricted to the years from 1987 to 2008. Type 1 diabetes mellitus was not included in the main disease groups.
[d] For autoimmune disease groups only the first group-specific autoimmune disease in a person has been included.

women in the cohort had a hospital contact for the particular disease between 1982 and 2008 and where at least 10 patients had experienced the particular pregnancy complication or pregnancy loss. Of the 31 ADs included in the main AD group, 16 diseases fulfilled this criterion. The Danish National Patient Registry also contains information about inpatient hospital contacts for the period from 1977 to 1981; patients with hospital contacts for ADs in that period were excluded from analyses pertaining to that particular AD. Patients with AD were identified using the International Classification of Diseases codes, eighth revision (ICD-8) from 1982 to 1993 or its tenth revision (ICD-10) from 1994 to 2008, and ADs were categorized as female predominant if the female to male lifetime risk ratio in the general Danish population was above 2:1 (Table 2), as described elsewhere [27]. The group of female predominant ADs included (in order of descending female:male ratio) Hashimoto thyroiditis, Sjögren's syndrome, SLE, Graves' disease, primary biliary cirrhosis, systemic sclerosis, erythema nodosum, rheumatoid arthritis, and temporal arteritis. The group of other ADs included multiple sclerosis, pernicious anemia, vitiligo, celiac disease, Addison's disease, polymyositis/dermatomyositis, hemolytic anemia, Crohn's disease, myasthenia gravis, pemphigoid, idiopathic thrombocytopenic purpura, polyarteritis nodosa, rheumatic fever, ulcerative colitis, psoriasis, sarcoidosis, type 1 diabetes mellitus, Wegener's granulomatosus, Henoch-Schönlein purpura, amyotrophic lateral sclerosis, Guillain-Barré syndrome and ankylosing spondylitis. For type 1 diabetes mellitus, the observation period began January 1, 1987, because ICD-8 codes did not permit a distinction between insulin-dependent and non-insulin-dependent diabetes mellitus before that date. We considered records of insulin-dependent diabetes mellitus as type 1 diabetes mellitus, but excluded patients recorded with insulin-dependent diabetes mellitus who had a preceding hospital contact for non-insulin-dependent diabetes mellitus from the analysis.

2.3. Stratification of person-years and autoimmune disease outcomes

An incident case of AD was defined as the first occurrence of the particular AD in an individual, as determined by the date of first recorded inpatient or outpatient hospital admission. When studying AD groups, i.e., all ADs, female predominant ADs and other ADs, the first occurrence of any of the group-specific ADs was counted as incident.

Each cohort member contributed person-years at risk from her 15th birthday or January 1, 1982, whichever came later, to the date of first hospital contact for the AD in question, death, emigration, disappearance, or December 31, 2008, whichever came first. By the end of study on December 31, 2008, women in the cohort born 1955 or later were 15–53 years old. Person-years and AD outcomes were stratified according to values of a series of explanatory variables and potential confounders including age, birth cohort, calendar period (all in 1-year age groups), marital status (unmarried, married, separated/divorced, or widowed), each of the following livebirth-related variables: number of children (0, 1, 2, 3, 4+), and age at birth of first child (<20, 20–24, 25–29, 30+ years), according to the number of pregnancies complicated by hyperemesis (0, 1+), gestational hypertension or preeclampsia/eclampsia (0, 1+), each of the following pregnancy losses: number of spontaneous abortions (0, 1+), missed abortions (0, 1+), stillbirths (0, 1+), induced abortions (0, 1+), and ectopic pregnancies (0, 1+) and time since most recent pregnancy complication or pregnancy loss (0–4, 5+ years). The time-dependent handling of exposures, potential confounders and outcomes ensured that only pregnancy complications and pregnancy losses that occurred before the first recorded AD hospital contact were considered.

Table 3
Rate ratios of autoimmune diseases overall and in the interval 0–4 years and 5+ years after pregnancy complications among women born between 1955 and 1993 in the study period from 1982 to 2008.

	Pregnancies with hyperemesis							Pregnancies with pregnancy-associated hypertension or preeclampsia						
	Cases	Overall		0–4 years		5+ years		Cases	Overall		0–4 years		5+ years	
		RR[a]	95% CI	RR[a]	95% CI	RR[a]	95% CI		RR[a]	95% CI	RR[a]	95% CI	RR[a]	95% CI
Autoimmune diseases, overall	699	1.41	1.30–1.51	1.51	1.34–1.70	1.34	1.22–1.48	2520	1.21	1.16–1.26	1.32	1.23–1.42	1.17	1.11–1.23
Female-predominant autoimmune diseases	348	1.40	1.26–1.55	1.78	1.50–2.08	1.21	1.05–1.39	1319	1.26	1.19–1.33	1.57	1.41–1.73	1.16	1.08–1.24
Hashimoto thyroiditis	32	1.38	0.95–1.92	1.84	1.05–2.95	1.13	0.67–1.76	129	1.41	1.17–1.68	1.46	1.02–2.01	1.39	1.12–1.71
Sjögren's syndrome	17	1.79	1.06–2.81	1.83	0.57–4.29	1.78	0.97–2.96	61	1.43	1.09–1.85	0.88	0.35–1.81	1.53	1.15–2.01
Systemic lupus erythematosus	14	1.12	0.63–1.82	1.10	0.39–2.37	1.13	0.54–2.05	94	1.82	1.46–2.24	1.99	1.34–2.84	1.75	1.34–2.24
Graves' disease	184	1.49	1.28–1.72	2.24	1.82–2.72	1.09	0.87–1.33	615	1.20	1.10–1.30	1.57	1.37–1.80	1.06	0.96–1.18
Erythema nodosum	14	1.10	0.64–1.85	1.29	0.64–2.60	0.91	0.41–2.04	72	1.57	1.22–1.99	1.84	1.29–2.62	1.40	1.01–1.93
Rheumatoid arthritis	93	1.35	1.09–1.64	1.22	0.79–1.78	1.40	1.09–1.76	360	1.18	1.05–1.31	1.38	1.11–1.70	1.12	0.99–1.27
Other autoimmune diseases	384	1.42	1.28–1.57	1.32	1.11–1.56	1.48	1.30–1.67	1331	1.18	1.12–1.25	1.19	1.07–1.31	1.18	1.11–1.26
Multiple sclerosis	53	1.10	0.83–1.43	0.85	0.48–1.39	1.23	0.88–1.66	233	1.12	0.98–1.27	1.08	0.82–1.39	1.13	0.97–1.31
Pernicious anemia	14	2.46	1.37–4.05	1.67	0.41–4.39	2.82	1.45–4.91	33	1.41	0.96–1.99	1.96	0.97–3.52	1.25	0.79–1.87
Celiac disease	23	1.98	1.27–2.94	2.06	0.98–3.74	1.94	1.09–3.17	54	1.19	0.89–1.56	1.18	0.67–1.90	1.19	0.85–1.63
Crohn's disease	65	1.61	1.25–2.04	1.81	1.26–2.51	1.45	1.00–2.01	167	1.05	0.89–1.22	1.01	0.77–1.30	1.07	0.88–1.29
Idiopathic thrombocytopenic purpura	6	–	–	–	–	–	–	42	1.53	1.09–2.07	1.69	1.02–2.80	1.44	0.96–2.15
Ulcerative colitis	104	1.34	1.09–1.62	1.33	0.97–1.78	1.34	1.03–1.71	320	0.99	0.88–1.10	1.02	0.83–1.23	0.97	0.84–1.11
Psoriasis	56	1.33	1.01–1.71	0.78	0.40–1.33	1.60	1.18–2.13	220	1.22	1.06–1.40	1.21	0.92–1.57	1.23	1.04–1.44
Sarcoidosis	38	1.37	0.97–1.86	1.17	0.66–1.90	1.52	0.99–2.23	178	1.68	1.43–1.96	1.76	1.35–2.25	1.64	1.34–1.98
Type 1 diabetes mellitus[b]	34	1.05	0.74–1.45	0.99	0.51–1.70	1.09	0.70–1.60	292	2.37	2.09–2.68	2.57	2.04–3.20	2.30	1.99–2.66
Ankylosing spondylitis	17	1.63	0.96–2.55	2.12	0.96–3.99	1.35	0.64–2.45	58	1.40	1.06–1.82	1.14	0.62–1.90	1.50	1.09–2.01

RR, rate ratio; CI, confidence interval.

[a] RRs are compared to the reference group which is women with no pregnancies complicated by hyperemesis, and gestational hypertension or preeclampsia, respectively. RRs were adjusted for age, calendar period, birth cohort, marital status, number of childbirths and age at first childbirth.

[b] Type 1 diabetes mellitus was analyzed separately with a study period restricted to the years from 1987 to 2008. Type 1 diabetes mellitus was not included in the main disease groups.

Table 4
Rate ratios of autoimmune diseases overall and in the interval from 0 to 4 years and 5+ years after idiopathic pregnancy losses among women born between 1955 and 1993 in the study period from 1982 to 2008.

	Spontaneous abortions							Missed abortions							Stillbirths						
	Cases	Overall		0–4 years		5+ years		Cases	Overall		0–4 years		5+ years		Cases	Overall		0–4 years		5+ years	
		RR[a]	95% CI	RR[a]	95% CI	RR[a]	95% CI		RR[a]	95% CI	RR[a]	95% CI	RR[a]	95% CI		RR[a]	95% CI	RR[a]	95% CI	RR[a]	95% CI
Autoimmune diseases, overall	4437	1.10	1.07–1.14	1.15	1.09–1.22	1.08	1.04–1.12	2137	1.09	1.04–1.13	1.13	1.06–1.21	1.06	1.00–1.12	316	1.25	1.12–1.40	1.60	1.32–1.92	1.12	0.98–1.28
Female-predominant autoimmune diseases	2318	1.15	1.10–1.20	1.28	1.19–1.39	1.10	1.05–1.16	1085	1.10	1.03–1.17	1.29	1.17–1.41	0.99	0.91–1.07	166	1.30	1.11–1.50	2.20	1.72–2.77	1.01	0.82–1.22
Hashimoto thyroiditis	175	0.95	0.81–1.11	1.16	0.87–1.51	0.88	0.73–1.06	126	1.29	1.07–1.55	1.37	1.02–1.81	1.25	0.98–1.56	15	1.30	0.74–2.08	2.14	0.85–4.35	1.03	0.49–1.86
Sjögren's syndrome	107	1.33	1.08–1.63	1.15	0.68–1.81	1.38	1.09–1.71	42	1.12	0.80–1.51	1.44	0.84–2.28	0.98	0.65–1.43	5	–	–	–	–	–	–
Systemic lupus erythematosus	137	1.33	1.10–1.59	1.58	1.17–2.08	1.21	0.96–1.51	80	1.71	1.34–2.13	2.10	1.51–2.83	1.41	1.00–1.93	20	3.03	1.88–4.58	6.33	3.38–10.68	1.69	0.77–3.17
Graves' disease	1163	1.20	1.13–1.28	1.42	1.28–1.58	1.11	1.03–1.20	552	1.14	1.04–1.24	1.34	1.17–1.51	1.01	0.89–1.13	90	1.45	1.17–1.77	2.24	1.58–3.05	1.17	0.89–1.52
Erythema nodosum	110	1.25	1.02–1.53	1.32	0.98–1.79	1.20	0.93–1.56	46	1.03	0.76–1.38	1.10	0.73–1.65	0.95	0.62–1.46	8	–	–	–	–	–	–
Rheumatoid arthritis	628	1.06	0.97–1.15	0.95	0.79–1.13	1.09	1.00–1.20	253	0.91	0.80–1.03	0.94	0.75–1.15	0.89	0.76–1.04	33	0.88	0.61–1.22	1.33	0.66–2.33	0.77	0.50–1.13
Other autoimmune diseases	2324	1.06	1.02–1.11	1.05	0.98–1.13	1.07	1.02–1.13	1141	1.07	1.01–1.14	1.00	0.91–1.09	1.13	1.05–1.22	161	1.18	1.01–1.38	1.11	0.81–1.47	1.22	1.01–1.45
Multiple sclerosis	414	1.00	0.90–1.11	0.96	0.79–1.15	1.02	0.90–1.15	198	0.99	0.85–1.13	0.73	0.56–0.93	1.16	0.98–1.37	30	1.17	0.80–1.64	1.17	0.53–2.18	1.17	0.74–1.73
Pernicious anemia	70	1.64	1.26–2.12	2.23	1.42–3.34	1.44	1.04–1.95	24	1.10	0.71–1.63	0.74	0.29–1.52	1.32	0.79–2.06	8	–	–	–	–	–	–
Celiac disease	94	1.04	0.83–1.29	1.09	0.72–1.56	1.03	0.79–1.31	48	0.99	0.73–1.31	0.69	0.38–1.14	1.18	0.82–1.64	10	1.79	0.90–3.16	0.67	0.04–2.95	2.21	1.06–4.01
Crohn's disease	329	1.07	0.95–1.20	1.00	0.83–1.20	1.11	0.96–1.28	159	1.07	0.91–1.25	0.99	0.77–1.25	1.14	0.91–1.40	27	1.44	0.96–2.05	0.60	0.19–1.41	1.89	1.22–2.78
Idiopathic thrombocytopenic purpura	59	1.11	0.83–1.45	1.40	0.94–2.10	0.95	0.67–1.36	42	1.63	1.17–2.21	1.82	1.17–2.82	1.47	0.94–2.30	4	–	–	–	–	–	–
Ulcerative colitis	655	1.06	0.97–1.15	1.19	1.04–1.35	0.99	0.89–1.10	327	1.08	0.96–1.20	1.16	0.98–1.35	1.01	0.86–1.17	35	0.91	0.64–1.24	1.25	0.72–2.00	0.75	0.47–1.13
Psoriasis	399	1.16	1.04–1.29	1.00	0.80–1.22	1.22	1.08–1.38	176	1.07	0.92–1.24	1.06	0.82–1.34	1.08	0.88–1.30	30	1.38	0.94–1.94	1.68	0.81–3.04	1.28	0.81–1.92
Sarcoidosis	229	1.10	0.96–1.27	0.95	0.74–1.21	1.19	1.00–1.39	104	1.00	0.82–1.22	0.89	0.64–1.20	1.09	0.84–1.40	11	0.85	0.44–1.45	0.72	0.18–1.88	0.90	0.41–1.68
Type 1 diabetes mellitus[b]	300	1.13	1.00–1.27	1.31	1.07–1.60	1.05	0.90–1.21	129	1.05	0.87–1.25	1.20	0.92–1.54	0.94	0.73–1.19	32	1.95	1.35–2.72	3.43	1.97–5.48	1.41	0.84–2.20
Ankylosing spondylitis	72	0.85	0.66–1.08	0.67	0.39–1.06	0.93	0.70–1.21	53	1.29	0.96–1.70	0.71	0.38–1.20	1.71	1.22–2.32	4	–	–	–	–	–	–

RR, rate ratio; CI, confidence interval.

[a] RRs are compared to the reference group which is women with no pregnancy losses (i.e., spontaneous abortions, missed abortions, and stillbirths, respectively). RRs were adjusted for age, calendar period, birth cohort, marital status, number of childbirths and age at first childbirth.

[b] Type 1 diabetes mellitus was analyzed separately with a study period restricted to the years from 1987 to 2008. Type 1 diabetes mellitus was not included in the main disease groups.

2.4. Poisson regression analysis

The statistical analysis of the resulting table of stratum-specific counts of person-years, ADs and confounders was carried out as a log-linear Poisson regression analysis, yielding rate ratios (RRs) of first hospitalization rates for ADs with 95% confidence intervals (CIs). All analyses were adjusted for age, birth cohort, and calendar period using cubic splines restricted to be linear in the tails [28], as well as for marital status, number of liveborn children and age at birth of first child. Two-sided statistical tests were applied, and *P*-values <0.05 and 95% CIs excluding unity were considered statistically significant.

In a supplementary analysis for the AD groups (i.e., all ADs, female predominant ADs and other ADs) we also adjusted for potential socio-economic confounders obtained in the Integrated Database for Labor Market Research [29]. Specifically, we adjusted for the highest obtained educational level among adults in the household (basic school, high school, vocational education, short higher, medium higher, and long higher education), and relative household income for the calendar year two years before the year of observation calculated as a percentage of the average household income per adult according to birth year ($<$50%, 50–$<$75%, 75–$<$125%, 125–$<$150%, $\geq$150%).

2.5. Ethics

The study was approved by the Danish Data Protection Agency (Approval no. 2008-41-2374).

3. Results

In the cohort of 1,564,567 women born in 1955–1993 a total of 51,732 women had 57,151 first AD diagnoses recorded during 27.0 million person-years of follow-up between 1982 and 2008 (not including 3968 cases of type 1 diabetes mellitus that was analyzed separately). Numbers of AD patients, corresponding ICD codes and the female to male ratios are shown in Table 2.

3.1. Pregnancy complications

Among women who had been hospitalized with hyperemesis, a total of 699 women had at least one subsequent AD diagnosis during the study period. This corresponded to an overall RR of 1.41 (95% CI 1.30–1.51) compared to women without hyperemesis (Table 3). Similar overall associations with hyperemesis were found for female predominant ADs and the group of other ADs. However, while the RR of female predominant ADs was higher in the first 5 years after hyperemesis (0–4 years: RR 1.78; 1.50–2.08, 5+ years: RR 1.21; 1.05–1.39) the RR of other ADs was fairly similar in these two time intervals (0–4 years: RR 1.32; 1.11–1.56, 5+ years: RR 1.48; 1.30–1.67). RRs for associations between hyperemesis and specific ADs are shown in Table 3. For female predominant ADs statistically significant associations were seen for Sjögren's syndrome (1.79; 1.06–2.81), Graves' disease (1.49; 1.28–1.72) and rheumatoid arthritis (1.35; 1.09–1.64), whereas for other ADs statistically significant associations were observed for pernicious anemia (2.46; 1.37–4.05), celiac disease (1.98; 1.27–2.94), Crohn's disease (1.61; 1.25–2.04), ulcerative colitis (1.34; 1.09–1.62) and psoriasis (1.33; 1.01–1.71). A particularly strong association was seen for Graves' disease, a female predominant AD, in the first five years after hyperemesis (2.24; 1.82–2.72) while no increased risk was seen five or more years after hyperemesis. For rheumatoid arthritis, pernicious anemia, celiac disease, Crohn's disease, ulcerative colitis and psoriasis RRs remained significantly elevated also more than five years after hyperemesis (Table 3).

A total of 2520 women with a hospital contact for pregnancy-associated hypertension or preeclampsia had at least one subsequent AD diagnosis, which corresponded to an overall RR of 1.21 (1.16–1.26), ranging from 1.32 (1.23–1.42) in the first five years to 1.17 (1.11–1.23) more than 5 years after the pregnancy complication (Table 3). For female predominant ADs the RR was 1.57 (1.41–1.73) in the first five years but only 1.16 (1.08–1.24) in the 5+ period. In contrast, for the group of other ADs RRs were similar in the two time periods (0–4 years: RR 1.19; 1.07–1.31, 5+ years: RR 1.18; 1.11–1.26). RRs for associations between gestational hypertensive disorders and specific ADs are shown in Table 3. Pregnancy-associated hypertensive disorders were associated with significantly elevated risks for each of the specific female predominant ADs studied, being most pronounced for SLE with an RR of 1.82 (1.46–2.24). Again the risk of Graves' disease, but also of rheumatoid arthritis, was only increased in the first five years after the pregnancy complication, in contrast to the longer lasting risk elevations seen for Hashimoto thyroiditis, Sjögren's syndrome, SLE, and erythema nodosum. For other ADs a strong association was seen for type 1 diabetes mellitus (2.37; 2.09–2.68). Other statistically significant RRs, ranging from 1.22 to 1.68 were observed for ITP, psoriasis, sarcoidosis and ankylosing spondylitis.

3.2. Idiopathic pregnancy losses

Among women with idiopathic pregnancy losses a total of 4437, 2137, and 316 women with spontaneous abortions, missed abortions and stillbirths, respectively, had at least one subsequent hospital contact for AD (Table 4). For spontaneous abortions and missed abortions this corresponded to overall RRs of 1.10 (1.07–1.14) and 1.09 (1.04–1.13), respectively. As for hyperemesis and gestational hypertensive disorders the risk of female predominant ADs was higher in the first five years after a pregnancy loss (spontaneous abortions 0–4 years: RR 1.28; 1.19–1.39, 5+ years: RR 1.10; 1.05–1.16, missed abortions 0–4 years: RR 1.29; 1.17–1.41, 5+ years: RR 0.99; 0.91–1.07) while the risk of other ADs was generally similar or higher five or more years after a pregnancy loss than in the period 0–4 years after (spontaneous abortions 0–4 years: RR 1.05; 0.98–1.13, 5+ years: RR 1.07; 1.02–1.13, missed abortions 0–4 years: RR 1.00; 0.91–1.09, 5+ years: RR 1.13; 1.05–1.22). RRs for associations between idiopathic pregnancy losses and specific ADs are shown in Table 4. Particularly noteworthy associations were seen for SLE where women with spontaneous and missed abortions were at increased risk especially during the first five years after a pregnancy loss (spontaneous abortions 0–4 years: RR 1.58; 1.17–2.08, missed abortions 0–4 years: RR 2.10; 1.51–2.83). Also a higher risk was seen for pernicious anemia among women with spontaneous abortions (overall: 1.64; 1.26–2.12) and for idiopathic thrombocytopenic purpura among women with missed abortions (overall: 1.63; 1.17–2.21).

Stillbirths were associated with increased risk of ADs (overall: 1.25; 1.12–1.40), notably in the first five years (0–4 years: 1.60; 1.32–1.92). Women who had experienced a stillbirth had a 1.30-fold (1.11–1.50) increased risk of female predominant ADs, however, the risk appeared to be increased only in the first five years (0–4 years: 2.20; 1.72–2.77). In contrast, the RR of other ADs 5 or more years after a stillbirth was significantly increased (5+ years: 1.22; 1.01–1.45) while the short-term risk was not. The association with stillbirths was particularly pronounced for SLE (overall: 3.03; 1.88–4.58) and mostly so in the first five years (0–4 years: 6.33; 3.38–10.68), but also for Graves' disease (0–4 years: 2.24; 1.58–3.05) a higher risk was seen in the first five years after a stillbirth. For other ADs, women who had experienced stillbirth were at a 1.95-fold (1.35–2.72) increased risk of developing type 1

diabetes mellitus, however the RR was only statistically significant within the first 0–4 years following stillbirth (3.43; 1.97–5.48) (Table 4).

3.3. Ectopic pregnancies and induced abortions

Among women with ectopic pregnancies and induced abortions 1215 and 11,764 women, respectively, had one or more subsequent AD diagnoses. Overall, RRs of ADs were only weakly associated with ectopic pregnancies and induced abortions (ectopic pregnancies: RR 1.08; 1.02–1.14, induced abortions: RR 1.07; 1.04–1.09) and for most specific ADs only weak associations were seen (Table 5). However, women experiencing ectopic pregnancies (1.28; 1.07–1.53) or induced abortions (1.33; 1.24–1.42) were at significantly increased risk of psoriasis.

3.4. Socio-economic factors

In a supplementary analysis of the association between each of the studied pregnancy complications and pregnancy losses on one side and groups of ADs (i.e., all ADs, female predominant ADs, and other ADs) on the other further adjustment for household income and highest educational level had only minor effects on the overall risk estimates. For instance, after adjusting for household income and educational level RRs of ADs in women with hyperemesis (1.36; 1.26–1.47), pregnancy-associated hypertension or preeclampsia (1.18; 1.14–1.23), spontaneous abortions (1.07; 1.04–1.10), missed abortions (1.07; 1.02–1.12), stillbirths (1.22; 1.09–1.36), ectopic pregnancies (1.05; 0.99–1.11) and induced abortions (1.02; 0.99–1.04) were similar to RRs obtained in the main analysis where no adjustment was made for socio-economic factors.

4. Discussion

This is the first study that has systematically addressed the relationship between pregnancy complications and pregnancy losses and subsequent risk of ADs. The division of ADs into a “female predominant” and an “other” group enabled us to assess whether these pregnancy experiences might provide clues to the unexplained female predominance in ADs. The salient observations were that women with a history of pregnancies complicated by hyperemesis, gestational hypertensive disorders or idiopathic pregnancy losses were at higher risk of ADs than women without such pregnancy experiences.

We have previously shown that women who experience pregnancy complications such as hyperemesis, gestational hypertension and preeclampsia are at increased risk of rheumatoid arthritis [21] while women experiencing idiopathic pregnancy losses are at increased risk of SLE [22]. These findings were confirmed and expanded in the current study that included substantially more cases. In the present study we included both inpatient and outpatient hospital contacts for rheumatoid arthritis, SLE and 29 other ADs and our results might thus to a greater extent represent associations existing in the general patient populations.

Overall we found 41% and 21% elevated risks of ADs among women who had experienced pregnancies complicated by hyperemesis or gestational hypertensive disorders, respectively, and 10%, 9% and 25% elevated risks in women with previous spontaneous abortions, missed abortions and stillbirths, respectively. Elevated risks of female predominant ADs were found especially during the first five years after hyperemesis, gestational hypertensive disorders and idiopathic pregnancy losses, but for hyperemesis this relationship could be ascribed to a 2.2-fold increased risk of the most prevalent AD, Graves’ disease, in that time period. Transient hyperthyroidism is common in women with hyperemesis [13] and

Table 5
Rate ratios of autoimmune diseases overall and in the interval from 0 to 4 years and 5+ years after ectopic pregnancies and induced abortions among women born between 1955 and 1993 in the study period from 1982 to 2008.

	Ectopic pregnancies							Induced abortions						
	Cases	Overall		0–4 years		5+ years		Cases	Overall		0–4 years		5+ years	
		RR[a]	95% CI	RR[a]	95% CI	RR[a]	95% CI		RR[a]	95% CI	RR[a]	95% CI	RR[a]	95% CI
Autoimmune diseases, overall	1215	1.08	1.02–1.14	1.05	0.94–1.16	1.09	1.02–1.17	11764	1.07	1.04–1.09	1.06	1.02–1.10	1.07	1.04–1.10
Female-predominant autoimmune diseases	593	1.04	0.96–1.13	0.99	0.83–1.15	1.06	0.96–1.16	5726	1.08	1.05–1.11	1.07	1.01–1.13	1.08	1.05–1.12
Hashimoto thyroiditis	47	0.92	0.68–1.21	0.80	0.40–1.40	0.96	0.68–1.31	455	0.97	0.87–1.08	0.90	0.73–1.09	0.99	0.88–1.12
Sjögren's syndrome	28	1.18	0.79–1.68	0.21	0.01–0.94	1.42	0.94–2.04	245	1.18	1.01–1.38	1.04	0.74–1.40	1.22	1.03–1.44
Systemic lupus erythematosus	39	1.27	0.91–1.73	1.20	0.64–2.02	1.31	0.87–1.88	324	1.10	0.96–1.25	1.08	0.87–1.32	1.11	0.95–1.29
Graves' disease	288	1.04	0.93–1.17	0.95	0.75–1.19	1.08	0.94–1.23	2827	1.12	1.07–1.17	1.20	1.11–1.29	1.09	1.04–1.15
Erythema nodosum	23	1.01	0.66–1.52	0.88	0.44–1.76	1.10	0.66–1.83	270	1.05	0.91–1.21	1.10	0.90–1.34	1.02	0.85–1.21
Rheumatoid arthritis	174	1.05	0.90–1.21	1.25	0.93–1.65	0.98	0.82–1.17	1612	1.03	0.97–1.10	0.90	0.80–1.00	1.08	1.01–1.15
Other autoimmune diseases	670	1.11	1.03–1.20	1.07	0.93–1.23	1.13	1.02–1.23	6498	1.05	1.02–1.08	1.04	1.00–1.09	1.05	1.02–1.09
Multiple sclerosis	117	0.98	0.81–1.17	0.78	0.53–1.11	1.06	0.85–1.30	1168	1.03	0.96–1.10	0.96	0.85–1.08	1.06	0.98–1.14
Pernicious anemia	12	0.92	0.49–1.55	0.60	0.10–1.87	1.02	0.51–1.82	116	0.94	0.75–1.16	0.84	0.55–1.23	0.97	0.76–1.23
Celiac disease	27	1.12	0.75–1.61	1.01	0.43–1.97	1.17	0.72–1.77	225	0.91	0.78–1.06	1.03	0.80–1.30	0.85	0.71–1.02
Crohn's disease	96	1.14	0.92–1.39	1.07	0.75–1.47	1.18	0.91–1.51	1025	1.05	0.97–1.12	0.99	0.89–1.10	1.09	0.99–1.19
Idiopathic thrombocytopenic purpura	9	–	–	–	–	–	–	119	0.75	0.61–0.91	0.93	0.70–1.25	0.65	0.50–0.84
Ulcerative colitis	195	1.15	0.99–1.32	1.09	0.84–1.39	1.17	0.98–1.39	1783	0.98	0.93–1.03	0.95	0.87–1.03	1.00	0.93–1.06
Psoriasis	126	1.28	1.07–1.53	1.11	0.76–1.56	1.35	1.09–1.65	1206	1.33	1.24–1.42	1.35	1.20–1.50	1.32	1.22–1.43
Sarcoidosis	50	0.92	0.69–1.20	1.11	0.70–1.66	0.82	0.55–1.16	539	0.94	0.85–1.03	1.00	0.85–1.16	0.91	0.81–1.02
Type 1 diabetes mellitus[b]	86	1.09	0.88–1.35	0.97	0.62–1.42	1.15	0.89–1.47	766	0.96	0.88–1.04	1.00	0.88–1.14	0.94	0.85–1.04
Ankylosing spondylitis	24	1.02	0.66–1.50	0.99	0.43–1.93	1.04	0.61–1.62	237	1.03	0.88–1.20	1.06	0.82–1.36	1.02	0.85–1.21

RR, rate ratio; CI, confidence interval.

[a] RRs are compared to the reference group which is women with no ectopic pregnancies and induced abortions, respectively. RRs were adjusted for age, calendar period, birth cohort, marital status, number of childbirths and age at first childbirth.

[b] Type 1 diabetes mellitus was analyzed separately with a study period restricted to the years from 1987 to 2008. Type 1 diabetes mellitus was not included in the main disease groups.

fetal losses are more likely to occur in untreated thyrotoxic women than in women receiving adequate treatment [30]. However, the increased risk of Graves' disease shortly after hyperemesis, gestational hypertensive disorders and idiopathic pregnancy losses indicates that, somehow, the development of Graves' disease may be initiated in such abnormal pregnancies.

While the long-term maternal health consequences after hyperemesis are largely unknown [13], preeclampsia predisposes to cardiovascular disease [31]. The higher risks of ADs more than 5 years after hyperemesis, as seen for rheumatoid arthritis, pernicious anemia, celiac disease, Crohn's disease, ulcerative colitis and psoriasis might indicate that hyperemesis and these specific ADs to some degree share common underlying pathological pathways. Shared etiological factors might also explain long-term associations between gestational hypertensive disorders and Hashimoto thyroiditis, Sjögren's syndrome, SLE, erythema nodosum, psoriasis, sarcoidosis, type 1 diabetes mellitus and ankylosing spondylitis.

Considering the large proportion of early pregnancy losses that are related to chromosomal rather than immunological abnormalities [15], the rather modest overall risk associations seen for spontaneous and missed abortions may reflect considerably stronger associations for pregnancy losses with a non-chromosomal cause. For the association between idiopathic pregnancy losses and SLE it is well established that women who already have SLE at the time of pregnancy have an increased risk of pregnancy loss [32,33]. This relationship is believed to result from factors pertaining to the course of the disease itself, including the presence of SLE flares, lupus nephritis, hypertension, antiphospholipid syndrome and thrombocytopenia [34]. We also noted a strong association between spontaneous abortions and the subsequent risk of pernicious anemia, findings which have not been reported previously. Even though pernicious anemia may be associated with other ADs like Hashimoto thyroiditis, Graves' disease and type 1 diabetes mellitus [35], none of these diseases were as strongly associated with spontaneous abortions as pernicious anemia. Pernicious anemia, a common cause of vitamin B12 deficiency, is normally preceded by years of autoimmune gastritis [35,36], and as such autoimmune gastritis may well have been present before the studied pregnancies. Our findings thus suggest that the immunological disturbances that precede the diagnosis of pernicious anemia might possibly affect the pregnancy outcome. Women with type 1 diabetes mellitus are at a higher risk of pregnancy complications and pregnancy losses than other women [12]. Therefore the 1.95-fold increased risk of type 1 diabetes mellitus following stillbirths and the 2.4-fold increased risk after gestational hypertensive disorders might reflect this relationship.

Apart from a modestly increased risk of psoriasis, we found no strong influence from ectopic pregnancies or induced abortions. Tobacco smoking has been shown to be a risk factor for both ectopic pregnancy and psoriasis [37,38], and as such, a possible confounding influence of tobacco consumption cannot be excluded for this particular relationship. However, we have no reason to suspect that primary immunologic or hormonal imbalances are involved in ectopic pregnancies or induced abortions, and thus, there would be little reason to expect any strong association with ADs. Moreover, these findings suggest that it is not the pregnancy termination per se or the possible subsequent increased surveillance after an abnormal pregnancy that would explain the higher risk of ADs seen after the other pregnancy complications and idiopathic pregnancy losses.

For the groups of female predominant ADs and other ADs similarly increased overall risks were seen after the various pregnancy experiences. However, the risk of female predominant ADs was higher in the first five years after the occurrence of any of the various pregnancy experiences, whereas the risk of other ADs was higher more than five years after hyperemesis, missed abortions and stillbirths. This difference suggests that the observed risk associations with female predominant ADs and other ADs have different explanations. When considering possible biological mechanisms for the increased risk of ADs following hyperemesis, hypertensive pregnancies and idiopathic pregnancy losses it should be recalled that disease-specific immunological changes, as seen for rheumatoid arthritis and SLE, may occur even decades before the clinical diagnosis [39–42]. For instance the short-term associations, mostly found for the female predominant ADs, might reflect that AD disease development might be induced by an abnormal pregnancy event, or that a subclinical predisease state might complicate pregnancy before the disease itself becomes clinically apparent. However, the persistent long-term relationships seen for some ADs might reflect a shared predisposition to both adverse pregnancy experiences and ADs. Such predisposition might possibly work through an underlying immunologic or hormonal mechanism. Still the magnitude of these differences between female predominant ADs and other ADs is small and cannot explain much of the general female predominance in ADs. Another mechanism to be considered is fetal microchimerism. Fetal microchimerism is the persistence of immunocompetent fetal cells in the mother's circulation after pregnancy [43]. This phenomenon has been hypothesized to play a role in the female predominance of certain ADs, notably systemic sclerosis, but its role in maternal health is still largely unknown [43–45]. Women with preeclampsia have been shown to have higher concentrations of fetal cells in circulation than women in normotensive pregnancies, while fetal cells have been shown to be undetectable in the maternal circulation 30 days after induced abortions or spontaneous abortions [43,46,47]. Thus, the observed increased risk of ADs following pregnancy-associated hypertensive disorders is compatible with a microchimeric mechanism. Theoretically, the impact of fetal microchimeric cells on AD risk might depend on the mother's ability to clear the fetal cells, a feature which might differ between women with various pregnancy complications and women with normal pregnancies.

As in other large-scale epidemiologic studies, we relied on routinely collected register data, so the information about abnormal pregnancy events and AD outcomes in our study needs consideration. To identify AD outcomes in our study, we used hospital diagnoses among our cohort members. A hospital contact may occur rather late after the onset of the disease. For the cohort members who developed an AD in our study, we do not know when the initial immunologic changes took place that eventually led to the diagnosis of AD. Thus, we cannot exclude the possibility that in some women the disease process leading to AD hospitalization might have preceded the abnormal pregnancy event.

Furthermore, an unknown proportion of Danish patients with AD could not be identified for the present study because they had milder disease that did not require hospitalization, and the cohort only comprised women in the age span 15–53 years. Therefore, our findings may not necessarily apply to patients with mild AD or women with onset at older age. We relied on hospital diagnoses of ADs recorded in the Danish National Patient Registry. For a number of ADs, e.g., rheumatoid arthritis, ulcerative colitis, Crohn's disease and type 1 diabetes mellitus, this register has been evaluated systematically and found to be of sufficiently good quality for epidemiologic studies [48–50]. However, for the remaining ADs no systematic validation effort has been undertaken. While records of stillbirths, and induced abortions in Danish registers are believed to be close to 100% valid and complete, formal validation of the other pregnancy variables has been undertaken only for preeclampsia and spontaneous abortions, reporting that these records are of sufficiently good quality for epidemiologic research [51,52]. The decision to treat and to hospitalize a patient with a complicated pregnancy may be influenced by a number of individual factors in

addition to those related to the severity of symptoms and clinical signs, such as a person's threshold for reporting pregnancy problems and the patient's health seeking behavior. Thus, we can not exclude the possibility that patients who actually become hospitalized with a pregnancy complication such as hyperemesis may be those who are most severely affected with nausea and vomiting, and our findings may therefore not necessarily apply to women with milder cases of pregnancy-associated nausea and vomiting. Some early spontaneous abortions are not recognized by women, and only 70% of those spontaneous abortions that women actually know of will also be recorded in the Danish registers [53]. However, any possible influence of misclassification in hospital diagnoses of ADs and underascertainment of certain pregnancy experiences would most likely be non-differential and would either not affect RR estimates or tend to favor null findings. Nonetheless, the associations between pregnancy experiences and ADs shown in the present study may not necessarily apply to the whole AD patient population; especially reservations have to be made to patients with mild ADs or patients with onset at older age.

This study shows that women who experience pregnancy complications or pregnancy losses, especially hyperemesis, gestational hypertensive disorders and stillbirths, are at increased risk of ADs. Theoretically, immunologic or hormonal imbalances operating in hyperemesis, gestational hypertensive disorders and idiopathic pregnancy losses might predispose to subsequent AD development. Alternatively, considering the well established excess of adverse pregnancy events in women with established SLE and type 1 diabetes mellitus, our findings could reflect an effect on pregnancies of subclinical disease in women destined to develop ADs. Although risk patterns differed between female predominant ADs and other ADs, the studied pregnancy complications and pregnancy losses do not seem to provide major clues to a better understanding of the enigmatic female predominance in several ADs.

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