Comorbidities in alopecia areata: A systematic review and meta-analysis

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Background: Alopecia areata (AA) may be associated with various systemic diseases according to several studies.

Objective: To identify prevalent and incident diseases in patients with AA and quantify their prevalence and odds and hazard ratios compared with those in controls without AA.

Methods: A systematic review of the studies published before February 28, 2018, was performed by using the MEDLINE, Embase, Web of Science, and Cochrane Library databases. Observational studies on prevalent or incident diseases in patients with AA were included, whereas studies limited to pediatrics or providing only laboratory results or continuous data were excluded. The inverse variance method with a random-effects model was used for meta-analyses.

Results: A total of 87 studies were analyzed. Atopic diseases, metabolic syndrome, *Helicobacter pylori* infection, lupus erythematosus, iron deficiency anemia, thyroid diseases, psychiatric diseases, vitamin D deficiency, and audiologic and ophthalmic abnormalities were more prevalent in patients with AA. Patients with AA had a higher risk of developing autoimmune diseases.

Limitations: Some diseases were investigated by an insufficient number of studies to be meta-analyzed. Meta-analysis of incident diseases was not performed owing to the limited availability of cohort studies.

Conclusion: AA is associated with various systemic and psychiatric diseases. Physicians are encouraged to evaluate and manage potential comorbid conditions to achieve better outcomes. (J Am Acad Dermatol 2019;80:466-77.)

Key words: alopecia; areata; comorbid; comorbidities; comorbidity; prevalence; risk.

Alopecia areata (AA) is a chronic, relapsing disorder that results in nonscarring hair loss.[1] The primary targets are the scalp hair follicles, but extrascalp involvement, including body hair loss and nail dystrophies, is a common finding in AA. In addition, being a chronic autoimmune and inflammatory disorder, AA has

Abbreviations used:

AA:	alopecia areata
CI:	confidence interval
DM:	diabetes mellitus
HR:	hazard ratio
NMSC:	nonmelanoma skin cancer
OR:	odds ratio

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been suggested to be associated with diverse systemic diseases such as atopic, autoimmune, and rheumatoid diseases. AA causes morphologic disfigurement and thus, has a significant negative effect on patients' quality of life.[2] Several studies have reported a greater risk of psychiatric comorbidities in patients with AA. Therefore, mental and emotional support is claimed as another important axis of AA treatment.[3]

Recent studies using large-scale databases have provided new insights into the identification of comorbidities of AA. Nevertheless, they have caused confusion to patients and physicians, given their conflicting results.[4-7] Aside from providing patients with principal treatments for hair regrowth, evaluating potential comorbid conditions and providing the necessary care are crucial to improve outcome. However, despite several narrative reviews on comorbidities by the traditional vote-counting method,[8] the systematic approach and their quantification have rarely been studied. This systematic review and meta-analysis aimed to identify prevalent and incident diseases in patients with AA and quantify their prevalence, odds ratio (OR), and hazard ratio (HR) compared with those in controls without AA from observational studies.

CAPSULE SUMMARY

- Alopecia areata may be seen in association with systemic disease.
- This systematic review and meta-analysis showed a significant association with atopic, metabolic, rheumatoid, thyroid, and psychiatric diseases.
- Physicians' awareness of potential comorbid conditions is crucial for improved therapeutic management of patients with alopecia areata.

MATERIALS AND METHODS

Search strategy

We performed a comprehensive literature search to identify articles written in English or Korean because of the authors' language proficiency. The gray literature was also included regardless of publication status. Two main reviewers (S.L. and H.L.) searched the MEDLINE, Embase, Web of Science, and Cochrane Library databases for studies published before February 28, 2018.

Study selection

The 2 main reviewers independently evaluated the titles and abstracts of the retrieved studies. In cases of discrepancy between the 2 main reviewers, a final decision was reached by consensus with the other 2 reviewers (C.H.L. and W.S.L). Observational studies reporting binomial data of prevalent or incident diseases in patients with AA were included, whereas studies limited to pediatrics or providing only laboratory results or continuous data (eg, serum thyrotropin level, quality of life score) were excluded. However, analytic studies that did not fully meet the eligibility criteria but reported baseline characteristics of prevalent diseases in patients with AA were included as descriptive cross-sectional studies. If the abstract did not provide sufficient information to determine eligibility, a full-text evaluation was performed.

Data extraction and quality assessment

Data were compiled by the reviewers in predefined spreadsheets. Data on study year, design, population, mean age, proportion of female participants, and number of prevalent or incident diseases were extracted from each study. Quality assessment of the analytic studies was performed by using the Newcastle-Ottawa scale to ensure inclusion of only studies with adequate quality (score ≥4) in the meta-analysis.[9]

Data synthesis and outcomes

For case-control and cross-sectional studies, meta-analysis using an inverse variance method was performed to calculate meta-analyzed estimates for prevalent diseases. OR and prevalence were calculated from the case-control studies and all included studies, respectively. This quantification was implemented for diseases or conditions investigated by at least 1 case-control study. A random-effects model was used for data synthesis because a significant heterogeneity of the included studies was expected. In each subgroup analysis, heterogeneity and publication bias were evaluated with use of the I^2 statistic and the Egger linear regression test, respectively.[10] The trim and fill method was used to adjust OR when a significant publication bias was detected.[11] In contrast, for cohort studies, qualitative analysis was performed because of their limited availability.[12] Statistical analysis was performed with Comprehensive Meta-Analysis software (version 3.3.0, Biostat, Englewood, NJ). A P value less than .05 was considered statistically significant.

RESULTS

Study selection, identification, and data synthesis

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram is presented in Fig 1. Of the 87 included studies, 4 were cohort studies that investigated incident diseases; their

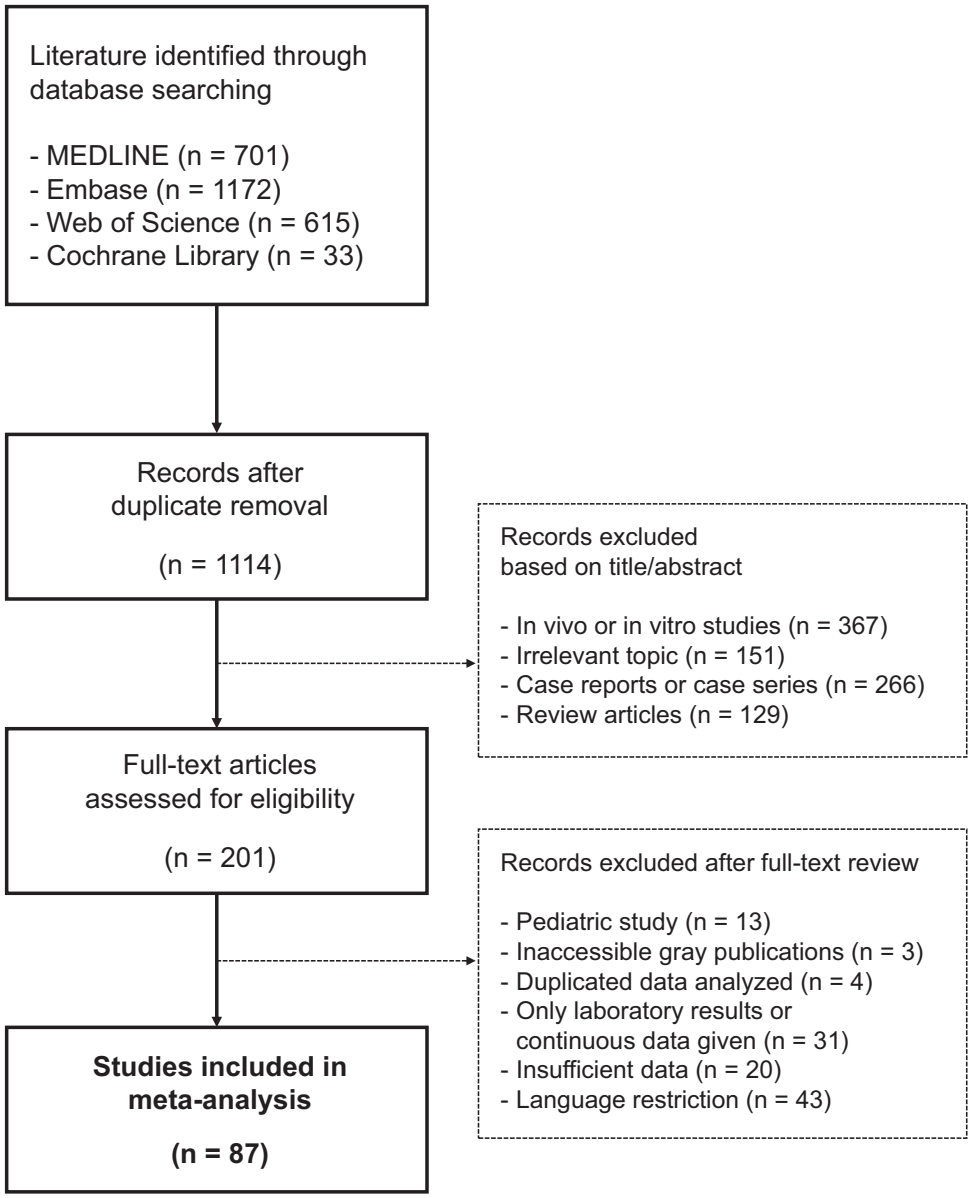

Fig 1. Literature search using the keywords including "alopecia areata", "comorb*", "prevalen*", "incident*", "associ*", "relation*" and "risk*". Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the literature search and study selection for systematic review of comorbidities in patients with alopecia areata.

characteristics and main findings are summarized in Table I.[4,5,13,14] Of the 83 studies that investigated prevalent diseases, 41 were case-control studies (Supplemental Table I[6,7,15-53]; available at http://www.jaad.org) and 42 were cross-sectional studies (Supplemental Table II[4,5,18,34,50,52-95]; available at http://www.jaad.org). No analytic study was excluded from the result of quality assessment (Supplemental Table III[4-7,13-53]; available at http://www.jaad.org). The meta-analyzed OR of prevalent diseases and their prevalence are shown in Figs 2 and 3, respectively.

Atopic diseases

Patients with AA had higher odds of having atopic dermatitis (OR, 2.36; 95% confidence interval [95% CI], 1.80-3.09; prevalence, 9.6%) and allergic rhinitis (OR, 1.33; 95% CI, 1.19-1.47; prevalence, 17.7%) than did the controls without AA. Asthma tended to be more prevalent in patients with AA (OR, 1.24; 95% CI, 0.93-1.66; prevalence, 9.9%), albeit without statistical significance. However, this difference further diminished after adjustment for the detected publication bias (adjusted OR, 1.11; 95% CI, 0.84-1.46, trim and fill).

Table I. Characteristics and main findings of cohort studies

Study	Study design	Study population, N/mean age, y/female, n	Control setting, N/mean age, y/female, n	Main findings
Huang et al, 2016[4]	Retrospective cohort study, Research Patient Data Repository at Partners HealthCare	Patients with AA 1377/45.0/860	Propensity score–matched (age, sex, race, smoking status, and chronic disease [hypertension, diabetes, hyperlipidemia]) control 4131/44.4/2506	OR† for incident cardiovascular outcomes - Myocardial infarction: 0.91 (0.59-1.39) - Ischemic stroke: 0.39 (0.18-0.87)*
Kang et al, 2015[5]	Retrospective cohort study, Longitudinal Health Insurance Database 2000	Patients with AA age >18 y 3231/36.1/1643	Age group- and sex-matched control 16,155/36.2/8215	Adjusted HR‡ for developing stroke during the 3-year follow-up - Stroke (any): 1.61 (1.13-2.30)* - Hemorrhagic stroke: 2.18 (1.01-4.84)* - Ischemic stroke: 1.58 (1.00-2.45)* - Stroke (unspecified): 2.27 (1.19-4.31)*
Chen et al, 2016[13]	Retrospective cohort study, Longitudinal Health Insurance Database 2000	Patients with AA age >18 y 3448/NA/NA	Age group– and sex-matched control 17,240/NA/NA	Adjusted HR§ for developing autoimmune diseases during the 3-year follow-up - Autoimmune disease: 1.86 (1.32-2.63)* - Rheumatoid arthritis: 1.79 (1.07-3.00)* - Ankylosing spondylitis: 0.82 (0.53-1.29) - Systemic lupus erythematosus: 5.01 (2.08-12.05)* - Hashimoto thyroiditis: 2.47 (0.84-7.26) - Psoriasis: 2.02 (1.06-3.83)* - Diabetes mellitus type 1: 0.61 (0.14-2.67)
Mostaghimi et al, 2016[14]	Retrospective cohort study, Research Patient Data Repository at Partners HealthCare	Patients with AA 1414/46.4/900	Propensity score–matched (age, sex, race) control 4242/46.5/2777	OR† for incident skin cancer (unspecified follow-up period) - Nonmelanoma skin cancer: 0.63 (0.48-0.81)* - Malignant melanoma: 0.65 (0.39-1.09)

In column 5, HR and OR are expressed as a ratio (95% confidence interval).
AA, Alopecia areata; *HR*, hazard ratio; *NA*, not available; *OR*, odds ratio.
*$P < .05$ in the original source.
†No further adjustment performed because of prematched controls with propensity score.
‡Adjusted for monthly income, geographic region, hyperlipidemia, and coronary heart disease.
§Adjusted for geographic location, urbanization level, monthly income, and obesity.

Category	Disease	OR	95% CI	Study (n)	AA (n)	Control (n)	I^2 (%)	Egger's test
Atopic	Atopic disease *	1.05	0.52 – 2.12	2[38,45]	2136	634	75.1	-
	Atopic dermatitis	2.36	1.80 – 3.09	5[19,20,41,45,47]	7191	872218	53.3	.605
	Allergic rhinitis	1.33	1.19 – 1.47	5[20,32,41,45,47]	7081	785008	5.3	.932
	Asthma	1.24	0.93 – 1.66	5[20,32,41,45,47]	7081	785008	44.2	.048
Cardio Vascular	Hypertension	0.65	0.18 – 2.30	2[32,47]	108	120	0.0	-
	Dyslipidemia	0.43	0.02 – 10.89	1[32]	37	49	-	-
	Diabetes mellitus *	0.64	0.57 – 0.73	4[20,38,41,47]	5070	781777	0.0	.907
	Hyperinsulinemia	3.52	1.43 – 8.71	1[36]	51	36	-	-
	Metabolic syndrome	3.68	1.22 – 11.08	1[36]	51	36	-	-
Gastro Intestinal	Celiac disease	1.48	0.17 – 12.73	1[20]	584	172	-	-
	Helicobacter pylori infection	2.03	1.23 – 3.34	3[22,46,50]	142	135	0.0	.264
	Inflammatory bowel disease *	1.48	0.32 – 6.82	1[20]	584	172	-	-
	Ulcerative colitis	5.14	0.24 – 109.1	1[47]	71	71	-	-
	Irritable bowel syndrome	0.38	0.15 – 0.99	2[20,45]	2639	730	54.1	-
	Lactose intolerance	0.25	0.01 – 5.44	1[32]	37	49	-	-
	Hepatitis C virus infection	-	-	1[48]	40	50	-	-
Connective tissue / Dermatologic	Systemic lupus erythematosus	3.46	0.58 – 20.58	3[20,38,47]	736	319	0.0	.081
	Rheumatoid arthritis	1.18	0.49 – 2.85	3[20,38,41]	4999	784406	23.6	.716
	Lupus erythematosus	4.73	3.70 – 6.10	1[41]	4334	784158	-	-
	Psoriasis	1.79	0.82 – 3.92	4[20,38,41,45]	7054	784964	69.6	.396
	Vitiligo	1.72	0.35 – 8.59	3[38,41,47]	4486	784305	83.3	.092
Hematologic	Anemia *	2.53	1.45 – 4.40	2[20,47]	655	243	0.0	-
	Iron deficiency anemia	2.78	1.23 – 6.29	2[20,47]	655	243	0.0	-
	Pernicious anemia	0.50	0.03 – 9.66	2[38,47]	152	147	58.6	-
Malignancies	Bladder cancer	0.68	0.06 – 7.48	1[6]	636	215	-	-
	Breast cancer	0.76	0.55 – 1.06	2[6,7]	12835	61210	0.0	-
	Colorectal cancer	0.61	0.42 – 0.89	2[6,7]	12835	61210	0.0	-
	Endometrial cancer	0.17	0.02 – 1.86	1[6]	636	215	-	-
	Gastric cancer	0.56	0.40 – 0.78	1[7]	12199	60995	-	-
	Hepatocellular carcinoma	0.37	0.25 – 0.56	1[7]	12199	60995	-	-
	Lung cancer	0.71	0.33 – 1.50	2[6,7]	12835	61210	36.2	-
	Prostate cancer	0.34	0.02 – 5.41	1[6]	636	215	-	-
	Thyroid cancer	1.89	1.53 – 2.34	3[6,7,47]	12906	61281	0.0	.917
	Lymphoma	0.68	0.06 – 7.48	1[6]	636	215	-	-
	Leukemia	1.02	0.04 – 25.07	1[6]	636	215	-	-
Thyroid	Thyroid disease *	1.99	1.29 – 3.06	6[16,20,32,38,41,47]	5265	784684	67.0	.703
	Autoimmune thyroid disease *	1.66	0.82 – 3.38	1[16]	158	158	-	-
	Graves' disease	2.07	1.80 – 2.38	1[7]	12199	60995	-	-
	Hashimoto thyroiditis	2.15	1.71 – 2.70	1[7]	12199	60995	-	-
	Thyroid dysfunction *	4.36	1.19 – 15.99	3[26,30,43]	162	625	79.3	.388
	Hyperthyroidism	2.08	0.38 – 11.46	4[26,43,45,47]	2238	1223	74.9	.276
	Hypothyroidism	1.55	0.74 – 3.26	4[26,43,45,47]	2238	1223	14.9	.735
	Subclinical hyperthyroidism	5.55	1.73 – 17.85	2[26,43]	112	594	0.0	-
	Subclinical hypothyroidism	19.61	4.07 – 94.41	3[23,26,43]	212	644	11.4	.053
Psychiatric	Psychiatric disorder *	1.35	1.20 – 1.52	1[40]	5117	20468	-	-
	Anxiety *	2.00	1.51 – 2.65	7[20,27,29,34,39,40,42]	5945	20878	40.0	.014
	Obsessive–compulsive disorder	1.72	1.06 – 2.77	1[40]	5117	20468	-	-
	Phobia	1.46	0.75 – 2.82	1[40]	5117	20468	-	-
	Sleep disorder	1.20	0.67 – 2.14	1[20]	584	172	-	-
	Depression	2.27	1.52 – 3.37	8[20,27,29,34,39,40,42,51]	5976	20918	63.4	.006
	Bipolar disorder	1.13	0.75 – 1.70	1[40]	5117	20468	-	-
	Alexithymia	2.46	1.45 – 4.18	3[29,49,51]	102	192	0.0	.399
	Schizophrenia	0.61	0.43 – 0.88	1[40]	5117	20468	-	-
	Attention deficit disorder	1.03	0.62 – 1.70	1[40]	5117	20468	-	-
	Personality disorder	1.47	0.90 – 2.40	1[40]	5117	20468	-	-
Other	Audiologic abnormality	3.59	1.60 – 8.07	2[28,32]	88	100	0.0	-
	Retinal change	4.19	1.49 – 11.79	3[25,44,52]	190	170	36.8	.332
	Lens change	10.57	3.07 – 36.35	3[25,44,52]	190	170	56.8	.624
	Vitamin D deficiency	4.61	2.33 – 9.10	10[15,17,18,20,21,24,31,33,35,37]	1088	629	80.3	.481

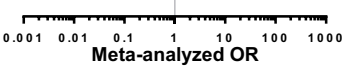

Fig 2. Meta-analyzed OR of prevalent diseases in patients with AA. Case-control studies were meta-analyzed to estimate the OR of each prevalent disease in patients with AA compared with that in controls without AA. AA was either positively or negatively associated with various systemic diseases and conditions. Red marks indicate an increased OR in patients with AA compared with that in controls without AA, whereas blue marks indicate a decreased OR with statistical significance. *Any or unspecified disease subtype. *AA*, Alopecia areata; *CI*, confidence interval; *OR*, odds ratio.

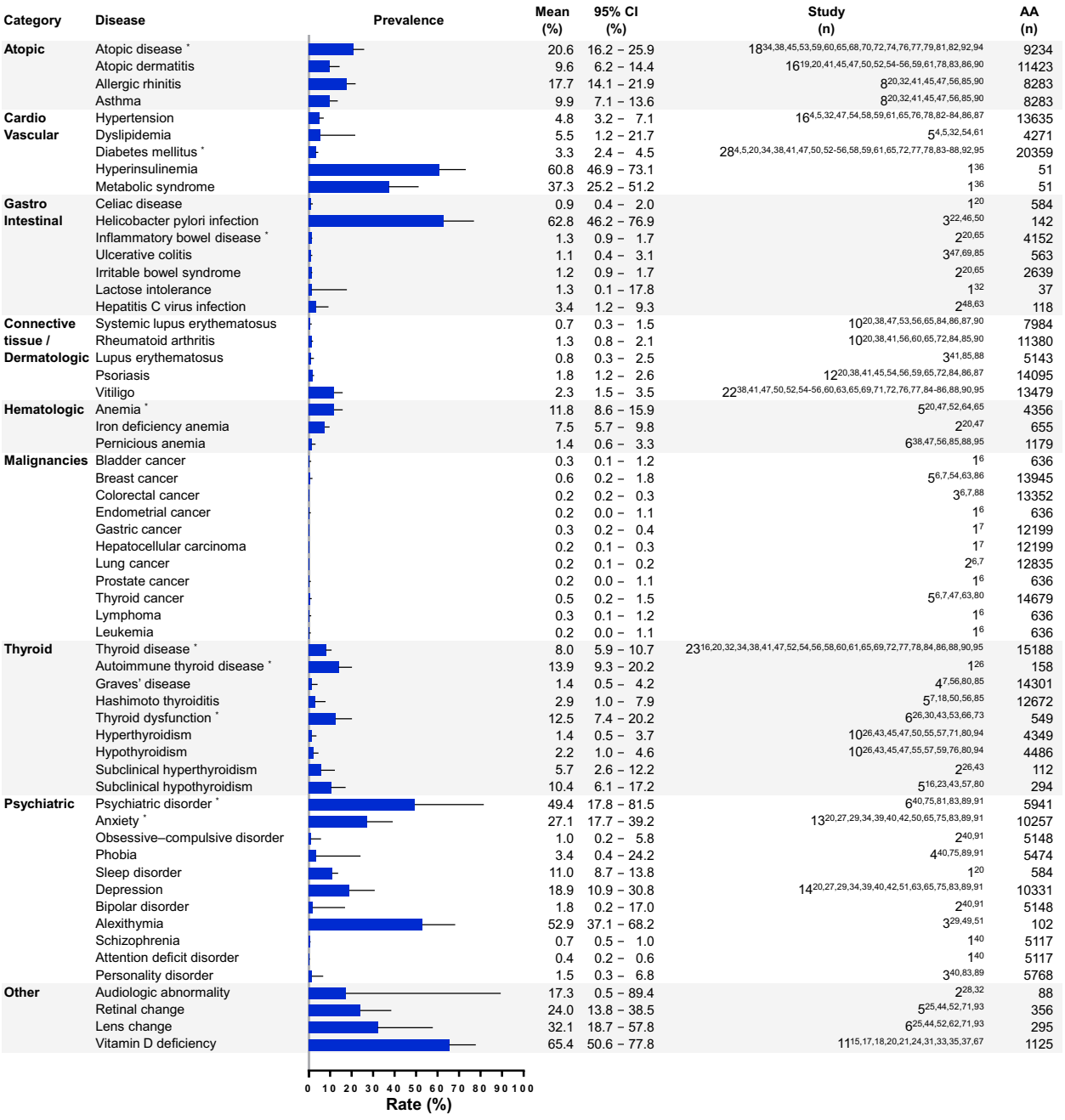

Fig 3. Meta-analyzed prevalence of comorbidities in patients with AA. Case-control and cross-sectional studies were meta-analyzed to estimate the mean prevalence of comorbidities, which were investigated by at least 1 case-control study. *Any or unspecified subtype of disease. *AA*, Alopecia areata; *CI*, confidence interval.

Cardiovascular diseases

Hyperinsulinemia (OR, 3.52; 95% CI, 1.43-8.71; prevalence, 60.8%) and metabolic syndrome (OR, 3.68; 95% CI, 1.22-11.08; prevalence, 37.3%) were more prevalent in patients with AA, but only 1 small study assessed these conditions.[36] In contrast, patients with AA had lower odds of having diabetes mellitus (DM) (OR, 0.64; 95% CI, 0.57-0.73; prevalence, 3.3%). However, ascertainment of either type 1 or 2 DM in patients with AA was not strictly controlled in all the included case-control studies. Moreover, the risk of incident type 1 DM was lower (HR, 0.61; 95% CI, 0.14-2.67) in patients with AA (Table I),[13] but the

results for the risk of incident stroke in patients with AA were conflicting in 2 large-scale cohort studies.[4,5]

Gastrointestinal diseases

Patients with AA had higher odds of having *Helicobacter pylori* infection (OR, 2.03; 95% CI, 1.23-3.34; prevalence, 62.8%) but lower odds of having irritable bowel syndrome (OR, 0.38; 95% CI, 0.15-0.99; prevalence, 1.2%). Inflammatory bowel diseases were not significantly associated with AA. In 1 study that investigated hepatitis C virus infection, no infection was observed in either patients with AA or controls without AA.[48]

Connective tissue and dermatologic diseases

Lupus erythematosus (OR, 4.73; 95% CI, 3.70-6.10; prevalence, 0.8%) was more prevalent in patients with AA. Systemic lupus erythematosus (OR, 3.46; 95% CI, 0.58-20.58; prevalence, 0.7%), rheumatoid arthritis (OR, 1.18; 95% CI, 0.49-2.85; prevalence, 1.3%), psoriasis (OR, 1.79; 95% CI, 0.82-3.92; prevalence, 1.8%), and vitiligo (OR, 1.72; 95% CI, 0.35-8.59; prevalence, 2.3%) tended to be more prevalent in patients with AA, albeit without statistical significance. However, patients with AA had a higher risk for developing incident diseases: autoimmune diseases (HR, 1.86; 95% CI, 1.32-2.63), rheumatoid arthritis (HR, 1.79; 95% CI, 1.07-3.00), systemic lupus erythematosus (HR, 5.01; 95% CI, 2.08-12.05) and psoriasis (HR, 2.02; 95% CI, 1.06-3.83) (Table I).[13]

Hematologic diseases

Patients with AA had higher odds of having anemia (OR, 2.53; 95% CI, 1.45-4.40; prevalence, 11.8%), especially iron deficiency anemia (OR, 2.78; 95% CI, 1.23-6.29; prevalence, 7.5%). However, no association was found between AA and pernicious anemia.

Malignancies

Associations between solid organ malignancies and AA were minimal, with the only exceptions being thyroid cancer (OR, 1.89; 95% CI, 1.53-2.34; prevalence, 0.5%) being more prevalent in patients with AA. Colorectal cancer (OR, 0.61; 95% CI, 0.42-0.89; prevalence, 0.2%), gastric cancer (OR, 0.56; 95% CI, 0.40-0.78; prevalence, 0.3%), and hepatocellular carcinoma (OR, 0.37; 95% CI, 0.25-0.56; prevalence, 0.2%) were less prevalent in patients with AA. Further, hematologic malignancies, including lymphoma and leukemia, were not prevalent in patients with AA. With respect to cutaneous malignancies, patients with AA had a reduced risk of developing nonmelanoma skin cancer (NMSC) (HR, 0.63; 95% CI, 0.48-0.81) (Table I).[14] The risk of malignant melanoma (HR, 0.65; 95% CI, 0.39-1.09) tended to be decreased, albeit without statistical significance.

Thyroid diseases

AA was significantly associated with various thyroid diseases. Autoimmune thyroid diseases (OR, 1.66; 95% CI, 0.82-3.38; prevalence, 13.9%), including Graves disease (OR, 2.07; 95% CI, 1.80-2.38; prevalence, 1.4%) and Hashimoto thyroiditis (OR, 2.15; 95% CI, 1.71-2.70; prevalence, 2.9%), were more prevalent in patients with AA. Moreover, patients with AA had higher odds of having thyroid dysfunction (OR, 4.36; 95% CI, 1.19-15.99; prevalence, 12.5%), especially subclinical hyperthyroidism (OR, 5.55; 95% CI, 1.73-17.85; prevalence, 5.7%) and subclinical hypothyroidism (OR, 19.61; 95% CI, 4.07-94.41; prevalence, 10.4%).

Psychiatric diseases

Psychiatric diseases were remarkably prevalent in patients with AA (OR, 1.35; 95% CI, 1.20-1.52; prevalence, 49.4%), including anxiety (OR, 2.00; 95% CI, 1.51-2.65; prevalence, 27.1%), obsessive-compulsive disorder (OR, 1.72; 95% CI, 1.06-2.77; prevalence, 1.0%), depression (OR, 2.27; 95% CI, 1.52-3.37; prevalence, 18.9%), and alexithymia (OR, 2.46; 95% CI, 1.45-4.18; prevalence, 52.9%). In contrast, schizophrenia was less prevalent (OR, 0.61; 95% CI, 0.43-0.88; prevalence, 0.7%). Despite a significant publication bias detected for anxiety (adjusted OR, 1.72; 95% CI, 1.33-2.24, trim and fill) and depression (adjusted OR, 1.49; 95% CI, 1.01-2.21, trim and fill), they were still more prevalent in patients with AA after adjustment.

Other diseases or conditions

Audiologic (OR, 3.59; 95% CI, 1.60-8.07; prevalence, 17.3%) and ophthalmic abnormalities, including retinal (OR, 4.19; 95% CI, 1.49-11.79; prevalence, 24.0%) and lens (OR, 10.57; 95% CI, 3.07-36.35; prevalence, 32.1%) changes, were also prevalent in patients with AA. Moreover, patients with AA had higher odds of having vitamin D deficiency (OR, 4.61; 95% CI, 2.33-9.10; prevalence, 65.4%).

DISCUSSION

Atopic diseases

AA was closely associated with atopic diseases, particularly atopic dermatitis and allergic rhinitis. A history of atopic disease was traditionally considered an independent factor of poor prognosis in AA.

Moreover, filaggrin gene mutation was associated with severe AA and poor prognosis.[96] Also, high levels of serum total IgE or *Dermatophagoides farinae*– and *Dermatophagoides pteronyssinus*–specific IgE were associated with early-onset severe AA independent of atopic history.[97] Evaluating these factors might be helpful to more precisely provide prognostic information.

Cardiovascular diseases

There have been several debates about the relevance of AA to cardiovascular or metabolic disease, but with inconsistent conclusions. Interestingly, all the studies included in our meta-analysis showed a rather negative association between DM and AA. However, we could not confirm whether this relationship was specifically related to type 1 or 2 DM. Despite a decreased risk of incident type 1 DM in patients with AA, whether AA is a protective factor or a risk factor for type 1 DM remains controversial.[38,88,98] Moreover, hyperinsulinemia and metabolic syndrome were more common in patients with AA than in controls without AA; however, this finding was reported by only 1 available small study,[36] which suggests a potential association between AA and metabolic diseases (possibly including type 2 DM). Therefore, larger studies controlling for type 1 and 2 DM will be required to arrive at a definitive conclusion as to their associations with AA. The results for the risk of incident stroke from 2 recent large-scale cohort studies were contradictory: Huang et al[4] reported a decreased risk of ischemic stroke in patients with AA, whereas Kang et al[5] reported an increased risk of all stroke types, including ischemic stroke. These conflicting results may have resulted from ethnic differences among study populations, but divergence in their sampling and statistical methods used to correct for confounding factors might be one of the important contributors. Thus, additional studies are required to definitely determine their association.

Gastrointestinal diseases

Gastrointestinal diseases were less likely to be significantly associated with AA. *Helicobacter pylori* infection has been associated with AA and various dermatoses.[22,46,50] The mechanisms are poorly understood, but the upregulation of local and systemic proinflammatory cytokines may contribute. Interestingly, there was no significant association between AA and inflammatory bowel diseases, which was consistent with the results of a nationwide population-based study reporting that the prevalence of AA in patients with inflammatory bowel disease did not differ from that in normal populations.[99]

Connective tissue and dermatologic diseases

AA is an autoimmune disease that is thought to be associated with various rheumatoid or connective tissue diseases. Despite the fact that except for lupus erythematosus, such diseases were not prevalent in patients with AA, there was an increased risk of incident autoimmune diseases in patients with AA.[13] With respect to dermatologic diseases, there had been compelling evidence on the association between AA and vitiligo or psoriasis. In our analysis, dermatologic diseases tended to be more prevalent in patients with AA, albeit without statistical significance. However, there was an increased risk of incident psoriasis in patients with AA,[13] which may be related to upregulation of type 1 helper T-cell pathway cytokines (which constitute one of the main pathogenetic mechanisms involved in both psoriasis and AA).[100,101]

Hematologic diseases

Anemia was one of the prevalent conditions in patients with AA. Traditionally, AA had been thought to be associated with pernicious anemia as an autoimmune disease. However, in our analysis, AA was associated with iron deficiency anemia. Previous studies have reported reduced ferritin levels in patients with AA, and there appears to be a common pathogenesis for AA and androgenetic alopecia.[102] Nevertheless, no study has investigated the therapeutic benefits of correction of anemia on hair regrowth in patients with AA.[103]

Malignancies

Only thyroid cancer was a highly prevalent malignancy in patients with AA. However, the detection bias could be its important contributor because of increased interest in screening for thyroid diseases in patients with AA. Conversely, a minimal or rather negative association between AA and other malignancies was found. The decrease in their prevalence seems to be associated with the negative effect of autoimmune diseases on carcinogenesis. Moreover, patients with AA had a lower risk of developing skin cancer.[14] Although several reports described an increased risk of developing NMSC with other types of inflammatory alopecia,[104-107] our results indicated that patients with AA had a lower risk of developing NMSC. Moreover, despite an increase in the scalp's sun exposure because of hair loss, there was no difference in the distribution of NMSC in patients with AA and the non-AA population. This may have resulted from the photoprotective effect induced by increased p53 expression, as observed in vitiligo.[108]

Thyroid diseases

According to several studies, abnormal findings from thyroid function tests were highly prevalent in patients with AA, especially with subclinical diseases. In addition, there have been several reports of a higher rate of thyroid autoantibody positivity in patients with AA.[38] However, the need for routine screening for thyroid diseases in asymptomatic patients remains controversial. Nevertheless, considering the substantial evidence indicating their high prevalence in patients with AA, such screening should not be neglected.

Psychiatric diseases

AA was extensively associated with psychiatric comorbidities, given their chronic, relapsing nature and negative effect on the cosmetic aspect. Our analysis indicated that alexithymia, anxiety, and depression were the most prevalent psychiatric conditions in patients with AA. Therefore, physicians should provide emotional support and refer these patients for proper management as needed. Of note, some studies also reported that antidepressants, aromatherapy, or hypnotherapy for mental relaxation have beneficial effects on hair regrowth in patients with AA.[109]

Other diseases or conditions

Audiologic abnormalities were prevalent in patients with AA, which could be attributed to changes in melanocytes of the membranous labyrinth in the inner ear.[28] Ophthalmic abnormalities were also prevalent in patients with AA, and these changes were more frequent in patients with AA with atopic disease than in those without.[44] Therefore, the higher prevalence of such changes may also be associated with higher prevalence of atopic diseases in patients with AA. However, evidence of the benefit of routine screening for audiologic or ophthalmic abnormalities in patients with AA remains scant to date. There have been several pieces of evidence regarding higher prevalence of vitamin D deficiency in patients with AA.[110] Impairment of the immunomodulatory effect of vitamin D may contribute to their association. However, their causal interaction is still poorly understood. Moreover, there is no evidence regarding whether oral vitamin D supplementation confers a therapeutic benefit in patients with AA with vitamin D deficiency.

Limitations

This study has several limitations. First, some diseases were investigated by an insufficient number of studies to be quantitatively meta-analyzed. Second, owing to the limited availability of cohort studies, meta-analysis of incident diseases could not be performed. Third, meta-analyzed estimates might have been affected by data heterogeneity and inconsistent matching for controls without AA across the included studies.

CONCLUSIONS

This systemic review and meta-analysis summarized the prevalent and incident diseases in patients with AA. To provide optimal evaluation and management, physicians should be aware of different comorbid conditions that may likely affect their patients. Further controlled and prospective studies with longitudinal observations are necessary to elucidate the interaction and causality between AA and its comorbidities.

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Supplemental Table I. Characteristics and main findings of case-control studies

Study	Study source and design	Study population, N	Mean age, y/ female patients with AA, n	Control, N	Mean age, y/female controls, n	Finding (prevalent disease [in patients with AA/total patients with AA, in controls/total controls])
Seo et al, 2018[7]	Retrospective chart review, Korean National Health Insurance Service —National Sample Cohort	Patients with AA (12,199)	NA/5959	Age- and sex-matched (60,995)	NA/29,795	Graves disease (279, 682) Hashimoto thyroiditis (106, 248) Thyroid cancer (117, 311) Breast cancer (38, 258) Colorectal cancer (29, 235) Gastric cancer (39, 349) Hepatocellular carcinoma (25, 334) Lung cancer (19, 198)
Daroach et al, 2018[15]	Case-control, single-center	Patients with AA (30)	29.0/19	Age- and sex-matched (30)	31.2/14	Vitamin D deficiency (29, 22)
Wang et al, 2017[16]	Case-control, single-center	Patients with AA age >18 y (158)	40/74	Age- and sex-matched (158)	82/76	Any thyroid abnormality (54, 25) Thyroid antibody (44, 22)
Marahatta, 2017[17]	Case-control, single-center	Patients with AA (30)	28.4/NA	Unspecified (30)	NA/NA	Vitamin D deficiency (25, 16)
Erpolat et al, 2017[18]	Case-control, single-center	Patients with AA (41)	32.8/15	Unspecified (32)	32.7/14	Vitamin D deficiency (35, 30)
Drucker et al, 2017[19]	Questionnaire, Nurses' Health Study II	Patients with newly diagnosed AA (147)	NA/147	Unspecified (87,259)	NA/87,259	Atopic dermatitis (26, 9208)
Conic et al, 2017[6]	Case-control, Cleveland Clinic Alopecia Registry	Patients with AA (636)	39.7/456	Age-matched (215)	39.9/159	Breast cancer (11, 3) Bladder cancer (2, 1) Lymphoma (2, 1) Endometrial cancer (1, 2) Prostate cancer (1, 1) Colon cancer (1, 1) Thyroid cancer (1, 0) Leukemia (1, 0) Lung cancer (0, 2)

Continued

Supplemental Table I. Cont'd

Study	Study source and design	Study population, N	Mean age, y/ female patients with AA, n	Control, N	Mean age, y/female controls, n	Finding (prevalent disease [in patients with AA/total patients with AA, in controls/total controls])
Conic et al, 2017[20]	Retrospective chart review, Cleveland Clinic Alopecia Registry	Patients with AA (584)	35.54/400	Age-matched (172)	35.8/126	Allergic rhinitis (100, 20) Atopic dermatitis (83, 7) Asthma (79, 14) Thyroid disease (110, 13) Diabetes mellitus (21, 14) Psoriasis (15, 2) Rheumatoid arthritis (8, 1) Systemic lupus erythematosus (7, 0) Anxiety (80, 17) Depression (86, 19) Sleep problems (64, 16) Vitamin D deficiency (228, 22) Anemia (98, 13) Iron deficiency anemia (43, 5) Irritable bowel syndrome (5, 7) Inflammatory bowel disease (10, 2) Coeliac disease (5, 1)
Bhat et al, 2017[21]	Case-control, single-center	Patients with AA (50)	22.4/NA	Age- and sex-matched (35)	29.2/NA	Vitamin D deficiency (21, 10)
Behrangi et al, 2017[22]	Case-control, single-center	Patients with AA (81)	34.9/33	Age- and sex-matched (81)	38.2/36	*Helicobacter pylori* infection (43, 27)
Bin Saif GA, 2016[23]	Case-control, single-center	Patients with AA (100)	22.7/52	Age- and sex-matched (50)	22.4/26	Subclinical hypothyroidism (11, 1)
Bakry et al, 2016[24]	Case-control, unspecified	Patients with AA (60)	20.7/24	Age, sex, body mass index, skin phenotype-matched (60)	23.7/32	Vitamin D deficiency (50, 14)
Ergin et al, 2015[25]	Case-control, single-center	Patients with AA (32)	NA/16	Age- and sex-matched (20)	NA/10	Cataract (9, 1) Papillary hypertrophy (29, 0) Retinopathy (6, 0)

Continued

Supplemental Table I. Cont'd

Study	Study source and design	Study population, N	Mean age, y/ female patients with AA, n	Control, N	Mean age, y/female controls, n	Finding (prevalent disease [in patients with AA/total patients with AA, in controls/total controls])
Diaz-Angulo et al, 2015[26]	Case-control, single-center	Patients with AA (54)	44.2/28	Age- and sex-matched (282)	NA/NA	Thyroid dysfunction (12, 7) Hypothyroidism (0, 2) Hyperthyroidism (3, 2) Subclinical hypothyroidism (5, 0) Subclinical hyperthyroidism (4, 3)
Baghestani et al, 2015[27]	Case-control, single-center	Patients with AA >18 y (68)	35.4, 19	Age, sex, education level-matched (68)	33.8/19	Anxiety (32, 16) Depression (38, 15)
Ucak et al, 2014[28]	Case-control, single-center	Patients with AA age >18 and <55 y (51)	27.5/NA	Unspecified (51)	28.1/NA	Sensorineural hypoacusis (28, 13) Bilateral hearing loss (22, 9)
Sellami et al, 2014[29]	Case-control, single-center	Patients with AA (50)	32.92/26	Age- and sex-matched (50)	NA/NA	Alexithymia (31, 19) Anxiety (31, 17) Depression (19, 10)
Nguyen and Goh, 2014[30]	Case-control, single-center	Patients with AA (50)	NA/NA	Unspecified	NA/49.5	Thyroid dysfunction (8, 5)
Mahamid et al, 2014[31]	Case-control, single-center	Patients with AA (23)	24.2/9	Age- and sex-matched (20)	27/7	Vitamin D deficiency (16, 5)
de Hollanda et al, 2014[32]	Case-control, single-center	Patients with AA age >18 y (37)	35.9/23	Age- and sex-matched (49)	34.6/23	Arthrosis (1, 0) Asthma (4, 1) Dyslipidemia (0, 1) Thyroid disease (3, 1) Hypertension (2, 4) Allergic rhinitis (4, 1) Chronic urticaria (1, 0) Abnormal auditory acuity (1, 0) Lactose intolerance (0, 2)
Aksu Cerman et al, 2014[33]	Case-control, single-center	Patients with AA (86)	32.2/30	Age- and sex-matched (58)	32.6/24	Vitamin D deficiency (78, 19)
Aghaei et al, 2014[34]	Case-control, single-center	Patients with AA (40)	NA/25	Age- and sex-matched (40)	NA/NA	Depression (20, 10) Anxiety (18, 10) Extraversion (12, 13) Neurosis (17, 13) Psychosis (5, 6) Lying (10, 11)

Continued

Supplemental Table I. Cont'd

Study	Study source and design	Study population, N	Mean age, y/ female patients with AA, n	Control, N	Mean age, y/female controls, n	Finding (prevalent disease [in patients with AA/total patients with AA, in controls/total controls])
Nassiri et al, 2013[35]	Case-control, single-center	Patients with AA age >10 y (28)	27.8/9	Unspecified (44)	33.2/28	Vitamin D deficiency (9, 23)
Karadag et al, 2013[36]	Case-control, single-center	Patients with AA (51)	31.5/26	Unspecified (36)	32.6/18	Hyperinsulinemia (31, 11) Metabolic syndrome (19, 5)
d'Ovidio et al, 2013[37]	Case-control, National Mediterranean Alopecia Areata Association	Patients with AA (124)	37.8/111	Unspecified (148)	34.5/130	Vitamin D deficiency (66, 44)
Serarslan et al, 2012[38]	Case-control, single-center	Patients with AA (81) (43 children excluded)	33.27/31	Age- and sex-matched (76) (38 children excluded)	33.5/NA	Vitiligo (6, 4) Psoriasis (4, 2) Diabetes mellitus (35, 36) Thyroid disease (19, 25) Atopic disease (22, 27) Systemic lupus erythematosus (1, 0) Rheumatoid arthritis (0, 3) Pernicious anemia (0, 4)
Sellami et al, 2012[39]	Case-control study, survey	Patients with AA (50)	32.92/26	Age- and sex-matched (50)	NA/NA	Depression (19, 6) Anxiety (31, 18)
Chu et al, 2012[40]	Case-control study, National Health Insurance Database	Patients with AA (5117)	NA/2600	Age- and sex-matched (20,468)	NA/10400	Any psychiatric disorder (412, 1246) Anxiety (257, 672) Attention deficit disorder (19, 74) Bipolar disorder (29, 103) Depression (146, 444) Manic disorder (11, 32) Obsessive-compulsive disorder (24, 56) Phobia (12, 33) Personality disorder (22, 60) Schizophrenia (35, 227)

Continued

Supplemental Table I. Cont'd

Study	Study source and design	Study population, N	Mean age, y/ female patients with AA, n	Control, N	Mean age, y/female controls, n	Finding (prevalent disease [in patients with AA/total patients with AA, in controls/total controls])
Chu et al, 2011[41]	Retrospective cohort study, National Health Insurance Database	Patients with AA (4334)	32.2/2211	Unspecified (784,158)	NA/372820	Atopic dermatitis (218, 14654) Asthma (245, 43983) Allergic rhinitis (618, 87064) Psoriasis (81, 5184) Thyroid disease (311, 31738) Vitiligo (14, 430) Lupus erythematosus (64, 2468) Rheumatoid arthritis (45, 6329) Diabetes mellitus (240, 65324)
Ataseven et al, 2011[42]	Case-control, single-center	Patients with AA (43)	23.42/12	Age- and sex-matched (30)	26.73/11	Depression (18, 9) Anxiety (17, 7)
Angulo et al, 2010[43]	Case-control, single-center	Patients with AA (58)	29/50.0	Unspecified (312)	235/44.8	Thyroid dysfunction (11, 11) Overt hypothyroidism (1, 6) Subclinical hypothyroidism (4, 0) Overt hyperthyroidism (3, 2) Subclinical hyperthyroidism (2, 3)
Pandhi et al, 2009[44]	Case-control, single-center	Patients with AA (83)	20.1/36	Age- and sex-matched (80)	NA/NA	Pigmentary clumping (6, 1) Choroidal sclerosis (7, 1) Lattice (4, 0) Macular degeneration (5, 0) Abnormal vascular change (5, 0)

Continued

Supplemental Table I. Cont'd

Study	Study source and design	Study population, N	Mean age, y/ female patients with AA, n	Control, N	Mean age, y/female controls, n	Finding (prevalent disease [in patients with AA/total patients with AA, in controls/total controls])
Barahmani et al, 2009[45]	Case-control, National Alopecia Areata Registry	Patients with AA (2055)	38.5/1476	Unspecified (558)	40.8/361	Atopic disease (554, 116) Asthma (202, 43) Atopic dermatitis (275, 43) Hay fever (353, 79) Autoimmune disease (103, 36) Irritable bowel syndrome (27, 13) Psoriasis (27, 9) Hyperthyroidism (5, 4) Hypothyroidism (48, 11) Atopic or autoimmune disease (600, 138)
Abdel Hafez et al, 2009[46]	Case-control, single-center	Patients with AA (31)	24.5/10	Age- and sex-matched (24)	27.5/10	*H pylori* infection (18, 10)
Thomas and Kadyan, 2008[47]	Case-control, single-center	Patients with AA (71)	NA/20	Age- and sex-matched (71)	NA/NA	Atopic dermatitis (10, 4) Neurodermatitis (5, 3) Seborrheic dermatitis (4, 8) Verruca (4, 6) Vitiligo (2, 5) Lichen planus (1, 4) Lichen sclerosus et atrophicus (1, 1) Furunculosis (2, 7) Thyroid disease (13, 4) Hypothyroidism (10, 2) Hyperthyroidism (2, 2) Papillary thyroid carcinoma (1, 0) Anemia (8, 3) Iron deficiency anemia (6, 2) Pernicious anemia (2, 1) Allergic rhinitis (3, 6) Asthma (3, 2) Diabetes mellitus (5, 7) Hypertension (2, 3) Ulcerative colitis (2, 0) Systemic lupus erythematosus (1, 0)

Continued

Supplemental Table I. Cont'd

Study	Study source and design	Study population, N	Mean age, y/ female patients with AA, n	Control, N	Mean age, y/female controls, n	Finding (prevalent disease [in patients with AA/total patients with AA, in controls/total controls])
Jadali et al, 2006[48]	Case-control, single-center	Patients with AA (45)	26.4/15	Unspecified (50)	27.3/18	Hepatitis C virus infection (0, 0)
Picardi et al, 2003[49]	Case-control, single-center	Patients with AA age >18 and <60 y (21)	34.3/7	Unspecified (102)	35.1/65	Alexithymia (7, 20)
Rigopoulos et al, 2002[50]	Case-control, unspecified	Patients with AA (30)	31.5/15	Age-, sex-matched (30)	32/15	*H pylori* infection (24, 22)
Sayar et al, 2001[51]	Case-control, single-center (military hospital)	Patients with AA (31)	23.8/0	Unspecified (40)	22.7/0	Alexithymia (18, 14) Depression (17, 13) Hopelessness (10, 3)
Recupero et al, 1999[52]	Case-control, single-center	Patients with AA (75)	30.4/50	Age-matched (70)	36.2/45	Lens abnormalities (38, 2) Fundus abnormalities (31, 16)
Puavilai et al, 1994[53]	Case-control, single-center	Patients with AA (152)	29.3/71	Age- and sex-matched (152)	NA/NA	Thyroid dysfunction (0, 0)

AA, Alopecia areata; *NA*, not available.

Supplemental Table II. Characteristics and main findings of cross-sectional studies

Study	Study source/study population, N	Mean age, y/female patients with AA, N	Finding (prevalent disease [in patients with AA])
Vaño-Galván et al, 2017[54]	Multicenter/patients with AT and AU (132)	26.0/92	Autoimmune disease (31) Thyroid disease (26) Vitiligo (4) Diabetes mellitus (3) Atopic dermatitis (27) Dyslipidemia (12) Hypertension (7) Psoriasis (4) Solid cancer (2) Breast cancer (1) Ovarian cancer (1)
Erpolat et al, 2017[18]*	Single-center/patients with AA (41)	32.8/15	Hashimoto thyroiditis (4)
Shahzadi et al, 2016[55]	Single-center/patients with AA (120)	22.8/57	Atopic dermatitis (35) Vitiligo (5) Hypothyroidism (5) Diabetes mellitus (5) Hyperthyroidism (1)
Huang et al, 2016[4]*	Research Patient Data Registry at Partners HealthCare/patients with AA (1377)	45.0/860	Hypertension (366) Diabetes mellitus (140) Hyperlipidemia (402)
Noso et al, 2015[56]*	Single-center/patients with AA (110)	37.5/76	Thyroid disease (11) Graves disease (7) Hashimoto thyroiditis (4) Vitiligo (3) Rheumatoid arthritis (1) Type 1 diabetes mellitus (0) Systemic lupus erythematosus (0) Addison disease (0) Pernicious anemia (0) Psoriasis (0) Atopic dermatitis (34) Asthma (14) Allergic rhinitis (38) Allergic conjunctivitis (16)
Lyakhovitsky et al, 2015[57]	Single-center/patients with AA (78)	32.7/32	Overt hypothyroidism (1) Overt hyperthyroidism (1) Subclinical hypothyroidism (12)
Kang et al, 2015[5]	Longitudinal Health Insurance Database 2000/patients with AA age >18 y (3231)	36.1/1643	Hyperlipidemia (642) Hypertension (560) Diabetes mellitus (317) Coronary heart disease (285) Atrial fibrillation (23) Heart failure (41)
Jang et al, 2015[58]	Single-center/patients with AA age >60 y (35)	NA/34	Hypertension (10) Diabetes mellitus (4) Liver disease (3) Thyroid disease (1) Pruritus (3) Urticaria (1) Seborrheic dermatitis (1)

Continued

Supplemental Table II. Cont'd

Study	Study source/study population, N	Mean age, y/female patients with AA, N	Finding (prevalent disease [in patients with AA])
Guruprasad et al, 2015[59]	Single-center/patients with AA (100)	NA/49	Atopic disease (20) Hypertension (2) Diabetes mellitus (5) Hypothyroidism (5) Polymorphic light eruption (4) Atopic dermatitis (1) Seborrheic dermatitis (1) Lichen planus (2) Psoriasis (1)
Ranawaka, 2014[60]	Single-center/patients with AA age >18 y (290)	31.8/112	Atopic disease (60) Thyroid disease (5) Vitiligo (6) Rheumatoid arthritis (1)
Lee et al, 2014[61]	Single-center/patients with AA (871)	NA/426	Hypertension (45) Diabetes mellitus (30) Dyslipidemia (14) Thyroid disease (94) Atopic dermatitis (29)
De Andrade et al, 2014[62]	Single-center/patients with AA (22)	38.9/15	Madarosis (12) Lens change (4) Cataract (3) Pseudophakia (1)
Aghaei et al, 2014[34]*	Single-center/patients with AA (40)	NA/25	Atopic disease (8) Diabetes mellitus (1) Thyroid disease (1)
Wu et al, 2013[63]	2-center/patients with AA age >50 y (73)	NA/49	Thyroid abnormalities (4) Hepatitis C virus infection (3) Hepatitis B virus infection (2) Vitiligo (2) Interstitial pneumonitis (1) Essential thrombocytopenia (1) Chronic urticaria (1) Sjögren syndrome (1) Chronic actinic dermatitis (1) Depression (1) Breast cancer (1) Cervical cancer (1) Thyroid cancer (1) Thymoma (1) Laryngeal squamous cell carcinoma (1) Transitional cell carcinoma (1)
Qadim et al, 2013[64]	Single-center/patients with AA (58)	30.1/25	Anemia (5)
Huang et al, 2013[65]*	Research Patient Data Registry at Partners HealthCare/patients with AA (3568)	42.0/1304	Atopic disease (808) Contact dermatitis (759) Depression or anxiety (539) Hyperlipidemia (518) Hypertension (463) Anemia (415) Gastroesophageal reflux disease (365) Thyroid disease (309) Diabetes mellitus (234) Inflammatory bowel disease (42) Systemic lupus erythematosus (92) Rheumatoid arthritis (83) Vitiligo (59) Psoriasis and Psoriatic arthritis (133)
Ahmed et al, 2012[66]	Single-center/patients with AA (112)	18.3/67	Thyroid dysfunction (10)
Levin et al, 2011[67]	Single-center/patients with AA (37)	NA/33	Vitamin D deficiency (16)

Continued

Supplemental Table II. Cont'd

Study	Study source/study population, N	Mean age, y/female patients with AA, N	Finding (prevalent disease [in patients with AA])
Yang et al, 2010[68]	Single-center/patients with AA (464)	NA/232	Atopic disease (44) Autoimmune disease (28)
Tang et al, 2010[69]	Single-center/patients with AA (497)	25/200	Thyroid disease (4) Ulcerative colitis (1) Vitiligo (1)
Qi et al, 2010[70]	Single-center/patients with AA (655)	NA/335	Atopic disease (65)
Ejaz et al, 2009[71]	Single-center/patients with AA (83)	21.4/23	Endemic goiter (1) Thyrotoxicosis (1) Vitiligo (1) Hypertension (14)
Goh et al, 2006[72]	Multiple-source/patients with AA (513)	36.3/381	Atopic disease (233) Thyroid disease (98) Psoriasis (20) Vitiligo (12) Diabetes mellitus (7) Rheumatoid arthritis (6)
Seyrafi et al, 2005[73]	Single-center/patients with AA (123)	24.1/66	Thyroid dysfunction (11)
Park et al, 2004[74]	Single-center/patients with AA (189)	27/93	Atopic disease (23)
Ruiz-Doblado et al, 2003[75]	Single-center/patients with AA (32)	NA/61	Adjustment disorder (8) Generalized anxiety disorder (7) Depressive episode (2) Social phobia (2) Somatoform disorder (1)
Jain and Marfatia, 2003[76]	Single-center/patients with AA (150)	NA/56	Atopic manifestations (17) Tuberculosis (4) Vitiligo (3) Hypothyroidism (2) Hypertension (2) Eczema (1)
Tan et al, 2002[77]	Single-center/patients with AA (219)	25.2/124	Atopic disease (133) Thyroid disease (5) Vitiligo (9) Diabetes mellitus (7) Down syndrome (3)
Tak et al, 2002[78]	Single-center/patients with AA (732)	26.8/342	Seborrheic dermatitis (97) Allergic contact dermatitis (25) Liver disease (22) Hypertension (18) Diabetes mellitus (16) Urticaria (16) Atopic dermatitis (14) Thyroid disease (8)
Rigopoulos et al, 2002[50]*	Unspecified/patients with AA (30)	31.5/15	Vitiligo (2) Hashimoto thyroiditis (1) Atopic dermatitis (1) Hyperthyroidism (2) Diabetes mellitus (1) Anxiety (13)
Kaur et al, 2002[79]	Single-center/patients with AA age >12 y (100)	NA/24	Atopic disease (34)
Sharma et al, 1999[80]	Single-center/patients with AA (1700)	NA/NA	Goiter (5) Hypothyroidism (5) Hyperthyroidism (3) Toxic multinodular goiter (1) Graves disease (1) Thyroid cancer (1)

Continued

Supplemental Table II. Cont'd

Study	Study source/study population, N	Mean age, y/female patients with AA, N	Finding (prevalent disease [in patients with AA])
Recupero et al, 1999[52]*	Single-center/patients with AA (75)	30.4/50	Thyroid disease (24) Atopic dermatitis (17) Vitiligo (2) Diabetes mellitus (3) Neuropsychiatric disorder (15) Anemia (3) Down syndrome (1)
García-Hernández and Rodríguez-Pichardo, 1999[81]	Single-center/patients with AA (110)	NA/52	Psychiatric comorbidity (84) Atopic disease (25)
Sharma et al, 1998[82]	Single-center/patients with AA (356)	NA/122	Atopic disease (60) Hypertension (48) Autoimmune disease (9)
Byung et al, 1998[83]	Single-center/patients with AA (357)	27.6/152	Seborrheic dermatitis (44) Atopic dermatitis (13) Liver disease (9) Diabetes mellitus (8) Urticaria (8) Allergic contact dermatitis (6) Hypertension (3) Congenital heart disease (3) Psychiatric comorbidity (238) Psychosomatic disorder (203) Anxiety disorders (17) Personality disorder (6) Depression (4) Adjustment disorder (2) Hypochondriasis (2)
Sharma et al, 1996[84]	Single-center/patients with AA (808)	NA/276	Thyroid disease (8) Vitiligo (15) Systemic lupus erythematosus (1) Discoid lupus erythematosus (1) Rheumatoid arthritis (2) Morphea (1) Lichen planus (6) Pemphigus foliaceus (1) Diabetes mellitus (4) Psoriasis (5) Hypertension (8) Down syndrome (1) Turner syndrome (1) Neuropsychiatric disorder (14)

Continued

Supplemental Table II. Cont'd

Study	Study source/study population, N	Mean age, y/female patients with AA, N	Finding (prevalent disease [in patients with AA])
Safavi et al, 1995[85]	Single-center/patients with AA (292)	NA/149	Hay fever (41) Asthma (27) Eczema (26) Malignant disease (11) Hashimoto thyroiditis (8) Vitiligo (6) Type 1 diabetes mellitus (3) Type 2 diabetes mellitus (3) Graves disease (3) Rheumatoid arthritis (3) Down syndrome (2) Lichen planus (2) Lupus erythematosus (2) Ulcerative colitis (2) Pernicious anemia (1)
Ro BI, 1995[86]	Single-center/patients with AA (905)	28.9/393	Seborrheic dermatitis (40) Atopic dermatitis (17) Hepatitis (14) Hypertension (9) Heart disease (7) Thyroid disease (6) Pulmonary disease (5) Vitiligo (4) Brain disease (4) Psoriasis (4) Systemic lupus erythematosus (3) Diabetes mellitus (3) Disc herniation (3) Breast cancer (2) Arthritis (1) Urinary stone (1) Duodenal ulcer (1) Benign prostate hyperplasia (1) Cystitis (1) Hemorrhoid (1) Paronychia (1) Ovarian tumor (1) Carbon monoxide intoxication (1) Rheumatic carditis (1) Nephritis (1)
Kumar et al, 1995[87]*	Single-center/patients with AA (106)	NA/42	Hypertension (2) Spondyloarthritis (1) Systemic lupus erythematosus (1) Lichen planus (2) Melanonychia (1) Psoriasis (1) Urticaria (1) Diabetes mellitus (0)

Continued

Supplemental Table II. Cont'd

Study	Study source/study population, N	Mean age, y/female patients with AA, N	Finding (prevalent disease [in patients with AA])
Wang et al, 1994[88]	Questionnaire by Help Alopecia International Research/patients with AA (517)	NA/362	Thyroid disease (76) Type 1 diabetes mellitus (1) Type 2 diabetes mellitus (6) Vitiligo (46) Pernicious anemia (15) Addison disease (5) Lupus erythematosus (0) Peptic ulcer disease (20) Colon cancer (2)
Puavilai et al, 1994[53]*	Single-center/patients with AA (152)	29.3/71	Atopic disease (13) Type 1 diabetes mellitus (1) Systemic lupus erythematosus (1) Goiter (4)
Koo et al, 1994[89]	Help Alopecia International Research, Questionnaire/patients with AA (294)	NA/NA	Major depressive episode (26) Generalized anxiety disorder (54) Social phobia (10) Paranoid disorder (13)
Shellow et al, 1992[90]	Help Alopecia International Research, Questionnaire/patients with AA (800)	NA/NA	Atopic dermatitis (187) Asthma (116) Allergic rhinitis (199) Rheumatic arthritis (34) Thyroid disease (94) Dermatomyositis (14) Scleroderma (2) Systemic lupus erythematosus (6) Addison disease (3) Vitiligo (24) Crohn disease (2)
Colon et al, 1991[91]	Single-center, psychiatric interview/ patients with AA (31)	35/22	Major depression (12) Generalized anxiety disorder (12) Tobacco use disorder (11) Psychosexual dysfunction (8) Phobia (7) Alcohol or drug abuse (7) Dysthymic disorder (5) Antisocial personality disorder (4) Panic disorder (4) Bipolar disorder (2) Posttraumatic stress disorder (1) Obsessive-compulsive disorder (1) Bulimia (1) Pathologic gambling (1)
Al-Khawajah, 1991[92]	Single-center/patients with AA (92)	18.9/47	Atopic disease (12) Diabetes mellitus (2)
Tosti et al, 1985[93]	Single-center/patients with AA (83)	NA/37	Lens change (65) Tobacco dust opacity (36) Coronary opacity (20) Light scattering (36) Retinal epithelial change (28) Drusen (11) Pigmentary abnormality (19)

Continued

Supplemental Table II. Cont'd

Study	Study source/study population, N	Mean age, y/female patients with AA, N	Finding (prevalent disease [in patients with AA])
De Weert et al, 1984[94]	Single-center/patients with AA (100)	NA/64	Atopic disease (22) Hyperthyroidism (1) Hypothyroidism (1) Turner syndrome (1) Neurotic personality (8) Behavioral disorder (7) Educational problem (1) Epilepsy (1)
Friedmann, 1981[95]	Single-center/patients with AA (108)	NA/NA	Thyroid disease (4) Diabetes mellitus (1) Pernicious anemia (0) Vitiligo (3)

AA, Alopecia areata; *AT*, alopecia totalis; *AU*, alopecia universalis; *NA*, not available.
*Data on underlying diseases at baseline in patients with AA were extracted from case-control or cohort studies in which their prevalence was compared with that in controls without AA.

Supplemental Table III. Quality assessment of analytic studies using the Newcastle-Ottawa scale

Study name	Case definition	Case representability	Control selection	Control definition	Matching for age/sex	Additional matching	Exposure ascertainment	Same method for ascertainment	Nonresponse rate	Overall quality score
Seo et al, 2018[7]	a,*	a,*	b	a,*	a,*	—	a,*	a,*	a,*	7
Daroach et al, 2018[15]	a,*	b	a,*	a,*	a,*	—	a,*	a,*	a,*	7
Wang et al, 2017[16]	a,*	b	c	a,*	a,*	—	a,*	a,*	a,*	6
Marahatta et al, 2017[17]	a,*	b	b	a,*	a,*	—	a,*	a,*	a,*	6
Erpolat et al, 2017[18]	a,*	b	b	a,*	—	—	a,*	a,*	a,*	5
Drucker et al, 2017[19]	a,*	b	a,*	a,*	—	—	d	a,*	a,*	5
Conic et al, 2017[6]	a,*	b	b	a,*	—	—	d	a,*	a,*	4
Conic et al, 2017[20]	a,*	b	b	a,*	—	—	d	a,*	a,*	4
Bhat et al, 2017[21]	a,*	b	b	a,*	a,*	—	a,*	a,*	a,*	6
Behrangi et al, 2017[22]	a,*	b	b	a,*	a,*	—	a,*	a,*	a,*	6
Mostaghimi et al, 2016[14]	a,*	b	b	a,*	a,*	—	d	a,*	a,*	5
Huang et al, 2016[4]	a,*	b	b	a,*	a,*	—	d	a,*	a,*	5
Chen et al, 2016[13]	a,*	b	b	a,*	a,*	—	d	a,*	a,*	5
Bin Saif GA, 2016[23]	a,*	b	c	a,*	a,*	—	a,*	a,*	a,*	6
Bakry et al, 2016[24]	a,*	b	c	a,*	a,*	b,*	a,*	a,*	a,*	7
Kang et al, 2015[5]	a,*	b	b	a,*	a,*	—	d	a,*	a,*	5
Ergin et al, 2015[25]	a,*	b	b	a,*	a,*	—	a,*	a,*	a,*	6
Diaz-Angulo et al, 2015[26]	a,*	b	b	a,*	a,*	—	a,*	a,*	a,*	6
Baghestani et al, 2015[27]	a,*	b	a,*	a,*	a,*	—	c	a,*	a,*	6
Ucak et al, 2014[28]	a,*	b	c	a,*	—	—	a,*	a,*	a,*	5
Sellami et al, 2014[29]	a,*	b	a,*	a,*	a,*	—	c	a,*	a,*	6
Nguyen and Goh, 2014[30]	a,*	b	c	a,*	—	—	a,*	a,*	a,*	5
Mahamid et al, 2014[31]	a,*	b	b	a,*	a,*	—	a,*	a,*	a,*	6
de Hollanda et al, 2014[32]	a,*	b	b	a,*	a,*	—	d	a,*	a,*	5
Aksu Cerman et al, 2014[33]	a,*	b	a,*	a,*	a,*	—	a,*	a,*	a,*	7
Aghaei et al, 2014[34]	a,*	b	c	a,*	a,*	—	d	a,*	a,*	5
Nassiri et al, 2013[35]	a,*	b	b	a,*	a,*	—	a,*	a,*	a,*	6
Karadag et al, 2013[36]	a,*	b	b	a,*	—	—	a,*	a,*	a,*	5
d'Ovidio et al, 2013[37]	a,*	b	b	a,*	a,*	—	a,*	a,*	a,*	6
Serarslan et al, 2012[38]	a,*	b	b	a,*	a,*	—	c	a,*	a,*	5
Sellami et al, 2012[39]	a,*	b	a,*	a,*	a,*	—	d	a,*	a,*	6
Chu et al, 2012[40]	a,*	b	b	a,*	a,*	—	d	a,*	a,*	5
Chu et al, 2011[41]	a,*	b	b	a,*	—	—	d	a,*	a,*	4
Ataseven et al, 2011[42]	a,*	b	c	a,*	a,*	—	a,*	a,*	a,*	6
Angulo et al, 2010[43]	a,*	b	c	a,*	—	—	a,*	a,*	a,*	5
Pandhi et al, 2009[44]	a,*	b	b	a,*	a,*	—	a,*	a,*	a,*	6
Barahmani et al, 2009[45]	a,*	b	b	a,*	—	—	d	a,*	a,*	4

Continued

Supplemental Table III. Cont'd

Study name	Case definition	Case representability	Control selection	Control definition	Matching for age/sex	Additional matching	Exposure ascertainment	Same method for ascertainment	Nonresponse rate	Overall quality score
Abdel Hafez et al, 2009[46]	a,*	b	b	a,*	a,*	—	a,*	a,*	a,*	6
Thomas and Kadyan, 2008[47]	a,*	b	c	a,*	—	—	a,*	a,*	a,*	5
Jadali et al, 2006[48]	a,*	b	c	a,*	—	—	a,*	a,*	a,*	5
Picardi et al, 2003[49]	a,*	b	b	a,*	—	—	c	a,*	a,*	4
Rigopoulos et al, 2002[50]	a,*	b	c	a,*	a,*	—	a,*	a,*	a,*	6
Sayar et al, 2001[51]	a,*	b	b	a,*	—	—	c	a,*	a,*	4
Recupero et al, 1999[52]	a,*	b	c	a,*	—	—	a,*	a,*	a,*	5
Puavilai et al, 1994[53]	a,*	b	c	a,*	a,*	—	a,*	a,*	a,*	6

Please see http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf for a definition of the Newcastle-Ottawa scale (a, b, and c).
*Score provided.