Association of atopic dermatitis with thyroid diseases: a systematic review and meta-analysis

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- **Learning Objective:** To understand the association of atopic dermatitis (AD) and thyroid diseases
- **Takeaway Message:** AD is associated with thyroid diseases, particularly in paediatric patients, warranting endocrinological consultation and early intervention to mitigate potential impacts on growth and cognitive development.
- **Conflict of Interest:** None.
- **Contact:** Prof Ching-Chi Chi (e-mail: chingchi@cgmh.org.tw)

Immune dysregulation involved in AD

T helper (Th) 2 cells predominant

- Immunoglobulin (Ig) E production
- Associated atopic diseases: asthma, allergic rhinitis

Th1, Th17, Th22, regulatory T cells (Treg)

- Th1/17-mediated systemic autoimmune diseases:
  - Alopecia areata
  - Vitiligo
  - Inflammatory bowel diseases
  - Rheumatoid arthritis
  - Systemic lupus erythematosus

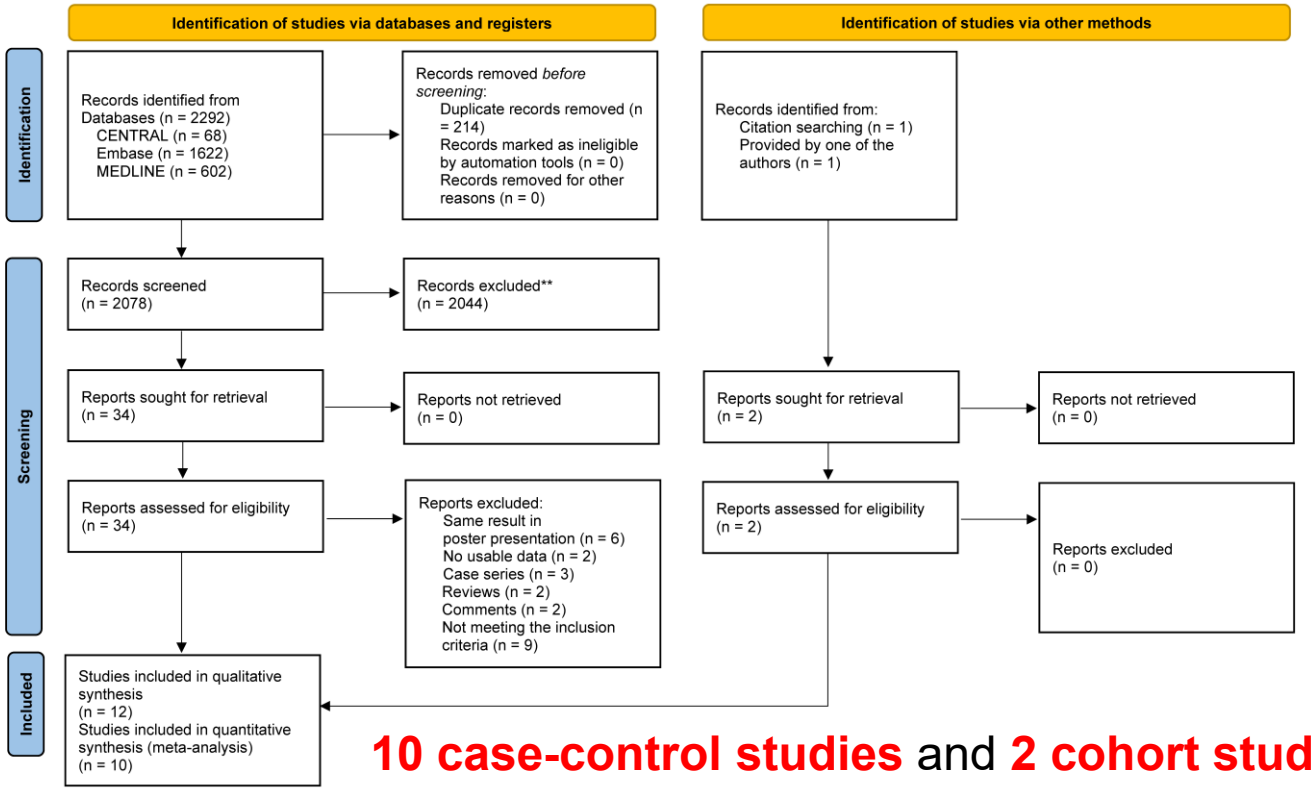
Thyroid diseases

- A range of chronic relapsing autoimmune disorders
- **Hashimoto disease**
  - 1st cause of hypothyroidism
  - Serum antibodies to thyroid peroxidase (TPO) and thyroglobulin (Tg) ↑
- **Graves disease**
  - 1st cause of hyperthyroidism
  - Serum autoantibodies to the thyrotropin receptor (TRAb)
- Clinical manifestations: palpitation, hand tremor,…..but **lack specificity**
- Diagnosis primarily depends on laboratory testing, imaging studies, cytology, and biopsy
- It is crucial to identify populations at high risk of developing thyroid diseases who may require heightened awareness for further diagnostic evaluation in case of suspicious symptoms

Methods

- Systematic review (SR) & meta-analysis (MA) of observational studies (case-control, cross-sectional, & cohort studies) on the association of AD with thyroid diseases.
- MOOSE reporting guideline was followed.
- Protocol registered with PROSPERO (CRD42024504157)
- We searched MEDLINE, Embase, and CENTRAL for relevant studies until 12th April, 2024.
- No restrictions on language, geographic regions, or publication status.
- References of eligible studies: manually scrutinized for additional studies (i.e., snowballing).
- Relevant published conference abstracts: tracked for subsequent full publications.
- Newcastle-Ottawa Scale was used for risk of bias assessment.
- We performed a random-effects model meta-analysis when there were $\geq$ three included studies providing usable data for one outcome.
- We also performed a subgroup analysis based on age, distinguishing between adult (≥ 18 years) and children (< 18 years) subgroups.

PRISMA study flowchart



10 case-control studies and **2 cohort studies** with a total of 93,547,813 subjects were included.

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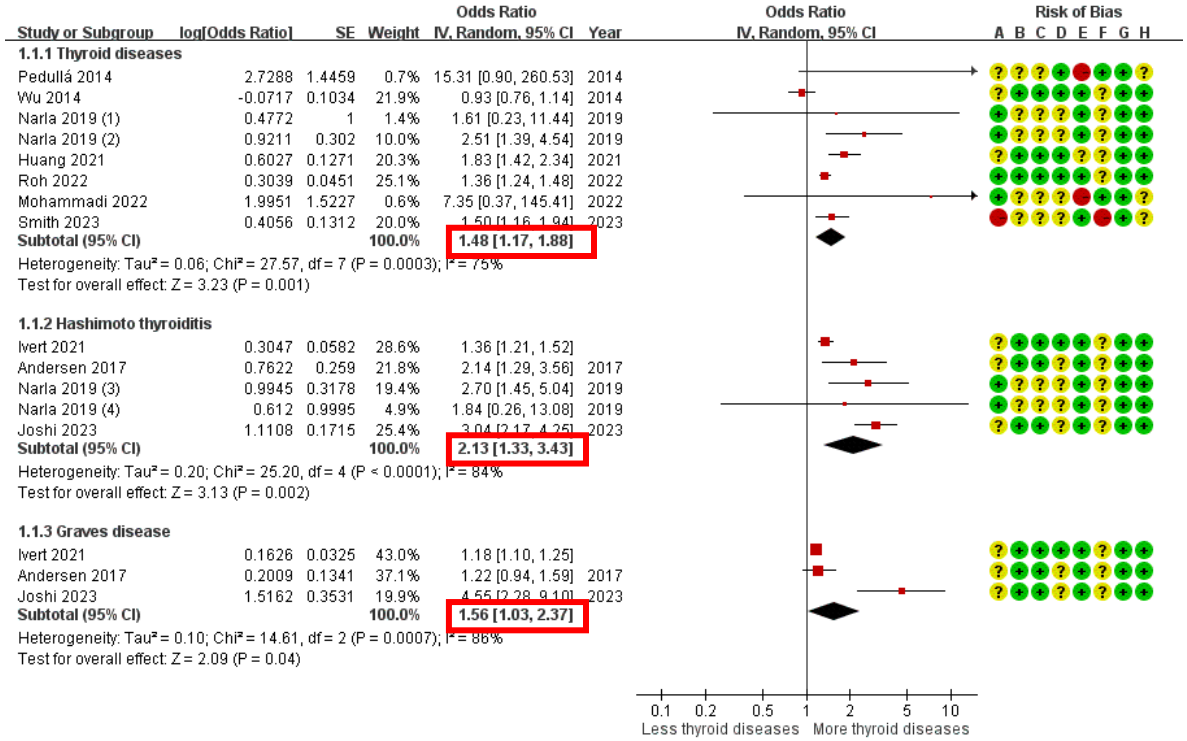
First author, year, country	Study design	Case group	Control group	Risk (95% CI) for thyroid diseases	Risk (95% CI) for Hashimoto disease	Risk (95% CI) for Graves disease
Andersen, 2017, Denmark	Case-control	8,112 AD patients aged ≥18 years	40,560 Age- and sex-matched controls	NA	OR: 2.14 (1.29–3.56)	OR: 1.22 (0.94–1.59)
Huang, 2021, US	Case-control	86,969 AD patients aged <18 years	116,564 Age- and sex-matched controls	OR: 1.83 (1.42-2.34)	NA	NA
Ivert, 2021, Sweden	Case-control	104,832 AD patients aged ≥15 years	1,022,435 Age- and sex-matched controls	NA	OR: 1.36 (1.21-1.52)	OR: 1.18 (1.10-1.25)
Joshi, 2023, US	Case-control	13,756 AD patients of all ages	55,024 Age-, race/ethnicity-, and sex-matched controls	NA	OR: 3.04 (2.17-4.25)	OR: 4.55 (2.28-9.10)
Mohammadi, 2022, Iran	Case-control	62 AD patients aged <18 years	62 Controls	OR: 4.32 (2.15-10.81)	NA	NA
Narla, 2019, US	Case-control	9,290 AD patients aged ≥18 years	72,098,787 Controls	OR: 2.51 (1.39-4.54)	OR: 2.70 (1.45-5.04)	NA
		10,196 AD patients aged <18 years	14,934,882 Controls	OR: 1.61 (0.23-11.44)	OR: 1.84 (0.26-13.08)	NA
Pedullá, 2014, Italy	Case-control	147 AD patients aged <18 years	70 Age-matched controls	OR: 15.31 (0.90-260.53)	NA	NA
Roh, 2022, US	Case-control	39,779 AD patients aged 18–64 years	353,743 Age- and sex-matched controls	OR: 1.36 (1.24-1.48)	NA	NA
Smith, 2023, US	Case-control	1,056 AD patients aged 20–59 years	9,004 Controls	OR: 1.50 (1.16-1.94)	NA	NA
Wu, 2014, Taiwan	Case-control	41,950 AD patients of all ages	167,800 Age- and sex-matched controls	OR: 0.93 (0.76-1.14)	NA	NA
de Lusignan, 2022, UK	Cohort	173,709 AD patients of all ages	694,836 Age-, sex-, and general practitioner practice-matched controls	NA	HR: 1.17 (1.09- 1.25)	HR: 1.03 (0.78- 1.36)
Krishna, 2019, UK	Cohort	1,393,570 patients of all ages	2,170,618 Age- and sex-matched controls	IRR: 1.13 (1.05–1.22)	NA	NA

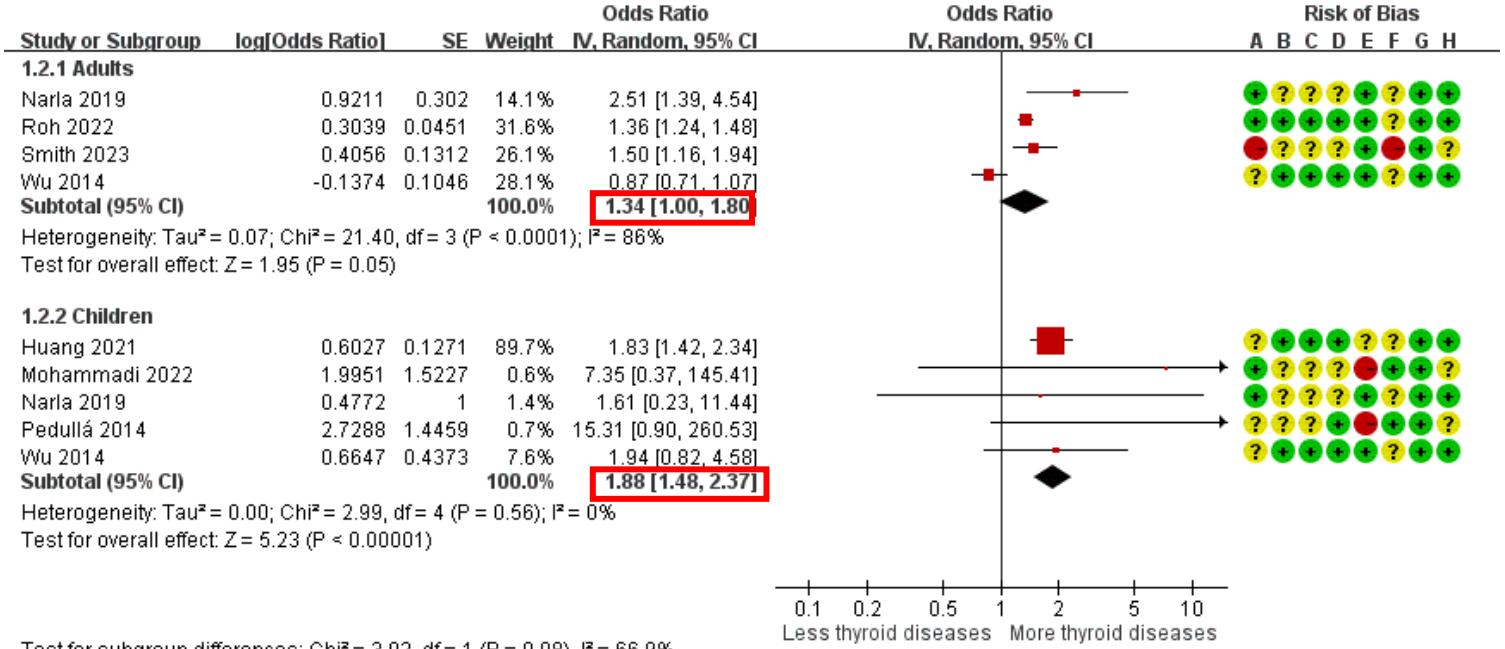
AD & thyroid diseases: Case-control studies



Footnotes
(1) Children
(2) Adults
(3) Adults
(4) Children

Risk of bias legend
(**A**) Adequacy of case definition
(**B**) Representativeness of cases
(**C**) Selection of controls
(**D**) Definition of controls
(**E**) Comparability of cases & controls
(**F**) Ascertainment of exposure
(**G**) Same method of ascertainment for cases and controls
(**H**) Non-response rate

Subgroup analysis by age



Test for subgroup differences: Chi² = 3.02, df = 1 (P = 0.08), I² = 66.9%

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Potential mechanisms linking AD and thyroid diseases (1)

Shared immune dysfunction: T cells imbalance & IgE autoimmunity

- **Acute AD**: filaggrin↓ → damaged keratinocytes produce epidermal alarmins → activate **Th2** + interleukin (IL)-4, IL-5, IL-13, IL-31 & chemokine ligand (CCL) 18↑; **Th22** + of IL-22 and S100A proteins↑
- **Chronic AD**: **Th2** & **Th22** expression ↑ + **Th1** & **Th17** activation → **Treg**↓ by Th17
- Development of **autoimmune thyroid diseases**, including Hashimoto disease and Graves disease, also involves complex interactions of **Th1**, **Th2**, **Th17**, and **Th22** cytokines.
- **IgE autoimmunity**:
  - Correlated with disease development & severity of both **AD** & **thyroid diseases**
  - **Prevalence of thyroid autoimmunity**: IgE-mediated > non-IgE-mediated AD children

Potential mechanisms linking AD and thyroid diseases (2)

Shared genetic susceptibility

- **Genome-wide association studies**: overlapped major susceptibility loci for AD and thyroid diseases
  - Chromosome 3q21: anti-TPO antibodies
  - Chromosome 1p22: defects in the beta subunit of thyroid stimulating hormone
  - Chromosome 19p13: Hashimoto disease
  - Chromosome 4q27: Graves disease
- **HLA-DRB1** variations in both AD and thyroid diseases
- **Single nucleotide polymorphisms:** Protein tyrosine phosphatase nonreceptor type 22, a regulator of T-cell & B-cell activity, linked to both AD and autoimmune thyroid diseases

Limitations

- No studies have investigated the association between **varying severities** of AD and thyroid diseases
- Most included studies originated from Western countries, with only two studies from **Asia** and none from **Africa**
- Most included studies were case-control design, with **only two cohort studies** meeting our inclusion criteria

Conclusions & take home message

- AD is associated with thyroid diseases, including Hashimoto and Graves diseases, particularly in **paediatric patients**.
- We should be aware and keep alert of this association.
- Early diagnosis and treatment of thyroid diseases in children and adolescents with AD may be important to prevent lifelong disabilities in growth and cognitive development.