DRAFT

Online Supplement

Guidelines of Care for the Management of Atopic Dermatitis with Awareness and Attention to Comorbidities

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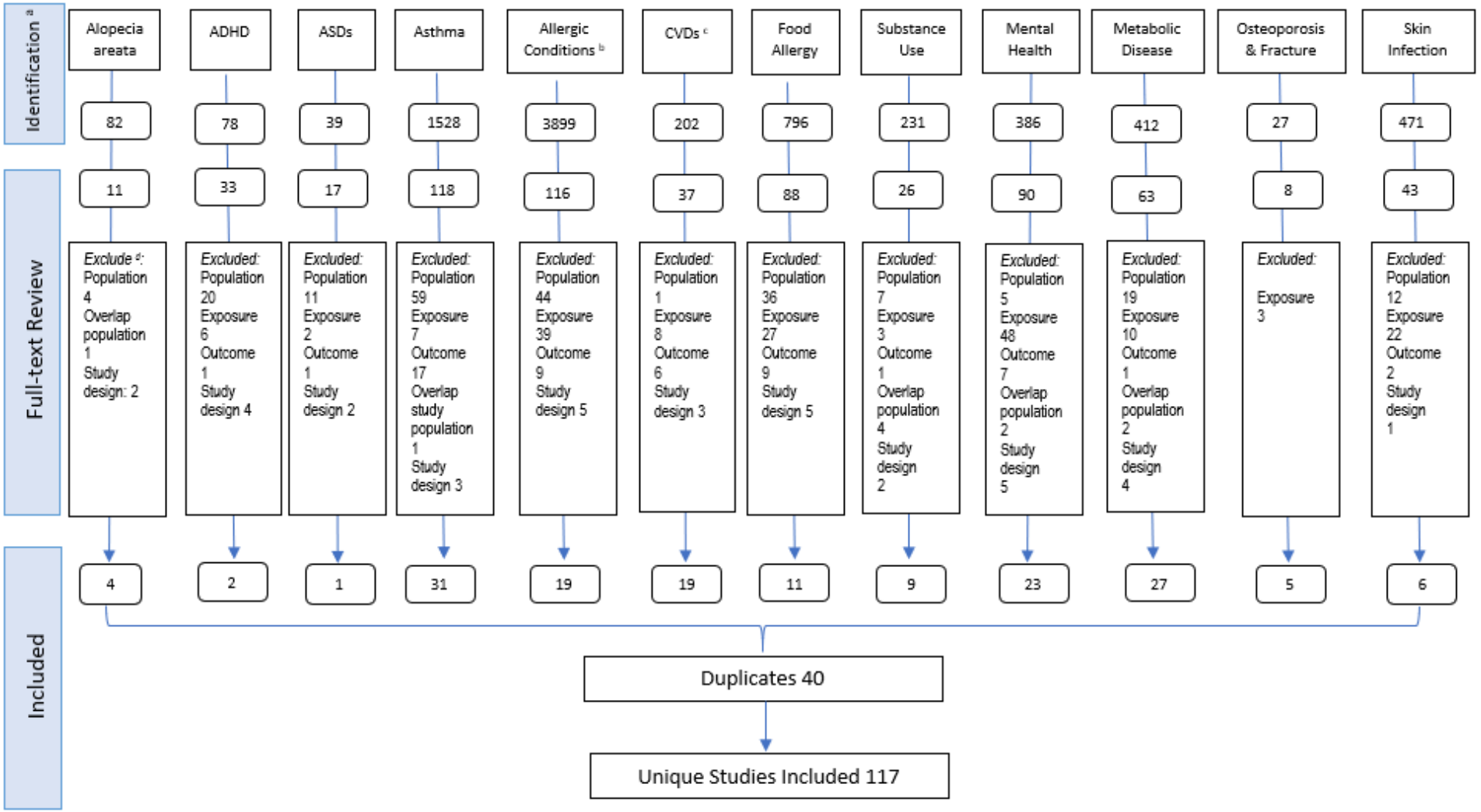
e-Appendix 1. MEDLINE (via PubMed) Search Strategy

((((((("dermatitis, atopic"[MeSH Terms] OR "Eczema"[MeSH Terms]) OR "Neurodermatitis"[MeSH Terms]) OR ("atopic"[Title/Abstract] AND ("dermatitis"[Title/Abstract] OR "dermatitides"[Title/Abstract]))) OR "Eczema"[Title/Abstract]) OR ("Neurodermatitis"[Title/Abstract] AND ("atopic"[Title/Abstract] OR "disseminated"[Title/Abstract]))) AND (((((("Osteoporosis"[MeSH Terms] OR (("Osteoporosis"[Title/Abstract] OR "osteopenia"[Title/Abstract]) OR "osteoporoses"[Title/Abstract])) OR ("osteoporotic fracture"[Title/Abstract] OR "osteoporotic fractures"[Title/Abstract])) OR ("bone"[Title/Abstract] AND ((("density"[Title/Abstract] OR "mass"[Title/Abstract]) OR "loss"[Title/Abstract]) OR "losses"[Title/Abstract]))) OR ("metabolic bone disease"[Title/Abstract] OR "metabolic bone diseases"[Title/Abstract])) OR (("fractures, bone"[MeSH Terms] OR ((((((((((((("bone"[Title/Abstract] OR "bones"[Title/Abstract]) OR "hip"[Title/Abstract]) OR "femoral"[Title/Abstract]) OR "ulna"[Title/Abstract]) OR "ulnar"[Title/Abstract]) OR "spinal"[Title/Abstract]) OR "vertebral"[Title/Abstract]) OR "vertebrae"[Title/Abstract]) OR "skull"[Title/Abstract]) OR "rib"[Title/Abstract]) OR "radius"[Title/Abstract]) OR "humeral"[Title/Abstract]) OR "ankle"[Title/Abstract]) OR "stress"[Title/Abstract]) AND (("Fracture"[Title/Abstract] OR "fractures"[Title/Abstract]) OR "broken"[Title/Abstract]))) OR ("Fracture"[Title/Abstract] OR "fractures"[Title/Abstract])))) AND ((((((("Comorbidity"[MeSH Terms] OR (("Comorbidity"[Title/Abstract] OR "comorbidities"[Title/Abstract]) OR "comorbid"[Title/Abstract])) OR ("multimorbidity"[Title/Abstract] OR "multimorbidities"[Title/Abstract])) OR (("risk factor"[Title/Abstract] OR "risk factors"[Title/Abstract]) OR "associated risk"[Title/Abstract])) OR ("coexist"[Title/Abstract] OR "coexists"[Title/Abstract])) OR ((("co-occurrence"[Title/Abstract] OR "cooccurrence"[Title/Abstract]) OR "co-occur"[Title/Abstract]) OR "co-occurs"[Title/Abstract])) OR ((((((((((((((((("prevalence"[Title/Abstract] OR "odds"[Title/Abstract]) OR "hazard"[Title/Abstract]) OR "association"[Title/Abstract]) OR "associated"[Title/Abstract]) OR "risk"[Title/Abstract]) OR "relationship"[Title/Abstract]) OR "relation"[Title/Abstract]) OR "predict"[Title/Abstract]) OR "predicting"[Title/Abstract]) OR "predicts"[Title/Abstract]) OR "interrelationship"[Title/Abstract]) OR "interrelationships"[Title/Abstract]) OR "protective"[Title/Abstract]) OR "incidence"[Title/Abstract]) OR "correlate"[Title/Abstract]) OR "correlates"[Title/Abstract]) OR "correlated"[Title/Abstract]) OR "correlation"[Title/Abstract]))

e-Appendix 2. Study Identification Flow Diagram



a. Identification included database searching in MEDLINE via PubMed and the Cochrane Library. Bibliographic handsearching was also conducted.
b. Allergic conditions search and literature review included urticaria but not food allergy.
c. Search and literature review for hypertension conducted with metabolic diseases.

d. Exclusion categories: Exposure: main exposure not AD or comorbid condition of interest; Outcome: does not quantitatively evaluate the prevalence, incidence, or risk of comorbid condition in AD patients, or vice versa, or the association between AD and comorbid condition; Population: not adults (≥ 18 years old)

e-Table 1. GRADE EVIDENCE PROFILE- Asthma

Question: Is asthma associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Asthma (follow up: Cross-sectional; assessed with: rate of asthma in AD)									
28 [1-28]	observational studies	serious [a]	serious [b]	not serious [c]	not serious	none	Based on the incidence of asthma in 116,571 adults with AD reported in 28 studies, the pooled prevalence of asthma in AD is **24.8% (95%CI 22.2%- 27.5%)**.[1-28]	⊕⊕◯◯ LOW	IMPORTANT
Occurrence of Asthma (follow up: Cross-sectional; assessed with: risk of asthma in AD)									
15 [1-4, 9, 11, 13, 18, 21, 23, 26-30]	observational studies	serious [d]	not serious [e]	not serious	not serious	dose response gradient [f] *(not upgraded)*	Based on the pooling of adjusted ORs of the association of self-reported or physician-diagnosed asthma in adults with AD compared to non-AD controls reported in 5 studies (including 6 study populations), AD is associated with increased odds of asthma [1, 3, 4, 29, 30]: **pooled OR** 3.04 (95% CI 1.65-5.62) Based on the pooling of incidence of asthma in 28,615 adults with AD and 209,133 non-AD controls reported in 9 studies, AD is associated with increased odds of asthma [2, 9, 11, 13, 21, 23, 26-28]: **OR 2.61** (95% CI 1.93-3.53) Based on data from 602 adults reporting current AD (symptomatic within the last 12 months) and 1,471 non-AD controls, AD is associated with increased risk of a history of asthma and increasing risk was associated with increasing AD severity [18]: <u>Overall Risk</u> **aRR** 1.68 (95%CI 1.48-1.80), p<0.0001 <u>Risk by AD Severity*</u>	⊕⊕⊕◯ MODERATE	CRITICAL

							Mild AD **aRR** 1.34 (95%CI 1.12-1.56), p=0.0008 *Moderate AD* **aRR** 1.94 (95%CI 1.66-2.21), p<0.0001 *Severe AD* **aRR** 2.38 (95%CI 1.91-2.85), p<0.00001		
Occurrence of Asthma (follow up: 12 months and 3 years; assessed with: risk of asthma in AD)									
2 [12, 31]	observational studies	serious [g]	not serious [h]	not serious	not serious [i]	none	Based on data from 231 adult males with a history of AD and 123,623 controls without a history of AD, allergic rhinitis, or allergic conjunctivitis, the risk of developing asthma during a 3-year follow up period was increased in those with AD [12]: **RR** 1.45 (95%CI 0.61-3.45) Based on data from 83,106, 31,060, and 5,550 adults with AD and their matched (1:1) non-AD controls included in commercial, Medicare, and Medical databases, respectively, followed for 12 months, AD was associated with an increased risk of asthma in all populations [31]: *Commercial cohort* **aOR** 2.51 (CI not reported) *Medicare cohort* **aOR** 1.65 (CI not reported) *Medi-Cal cohort* **aOR** 2.78 (CI not reported) p<0.0001 for all	⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis; **OR:** Odds ratio; **CI:** Confidence interval; **RR:** Risk ratio; **NOS:** Newcastle Ottawa Scale

*AD severity determined by Patient Oriented Eczema Measure scores.

Explanations

a. Cross-sectional evidence; Majority of studies rely on self-reported or unvalidated exposure and/or outcome assessment; Majority of the included studies scored below a 7 on the standard or modified NOS suggesting a moderate risk of bias (range 4-7; average 5.3).

b. Rates of asthma in AD vary widely across the included studies (I^2 of 99.1%).

c. Two studies include individuals under the age of 18 (as young as 10yo) but the average age of participants in these studies was over 18 suggesting the study samples are aligned with the research question.

d. Cross-sectional evidence; Majority of studies rely on self-reported or unvalidated exposure and/or outcome assessment; Majority of studies scored below a 7 on the modified or standard NOS suggesting a moderate risk of bias (range 4-7; average 5.6).

e. Studies consistently suggest an increased risk of asthma in AD; however the magnitude of effects varies across studies suggesting borderline inconsistency.

f. Effect estimates based on the data in these studies suggest increasing magnitude of risk of asthma is associated with increasing AD severity. However, the certainty of the evidence was not upgraded due to concerns of risk of bias.

g. One study included a non-representative population (limited to male soldiers) and did not ensure comparability of study cohorts; One study relied on unvalidated exposure and outcome assessment and minimally reported outcome measures.
h. All reported effect estimate are consistent in direction and magnitude as all estimates from one study fall within the CI for the estimate reported by the other included study.
i. Effect estimate for one study includes a CI consistent with no risk difference and both important decreased and increased risk; One study does not provide CIs for effect estimates making an assessment of precision unclear but this study reports on 3 populations ranging in size from 11,100 to 166,212 suggesting optimal information size was met; this suggests borderline imprecision.

e-Figure 1a. Occurrence of asthma in AD (pooled adjusted ORs)

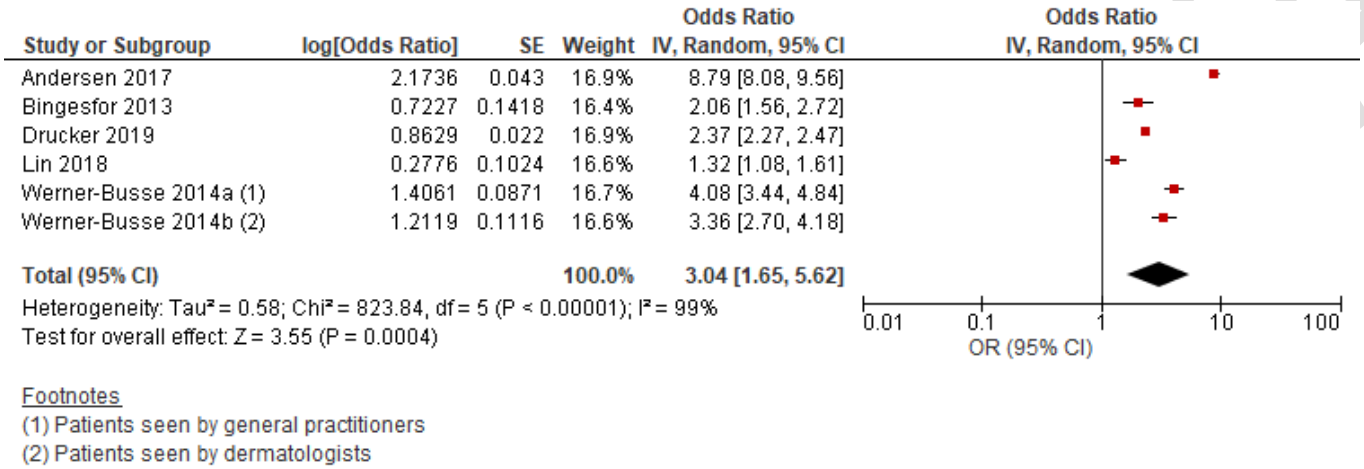


Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of any self-reported or physician-diagnosed asthma in individuals with AD compared to non-AD controls.

e-Figure 1b. Occurrence of Asthma in AD (pooled incidence of asthma in AD vs non-AD controls)

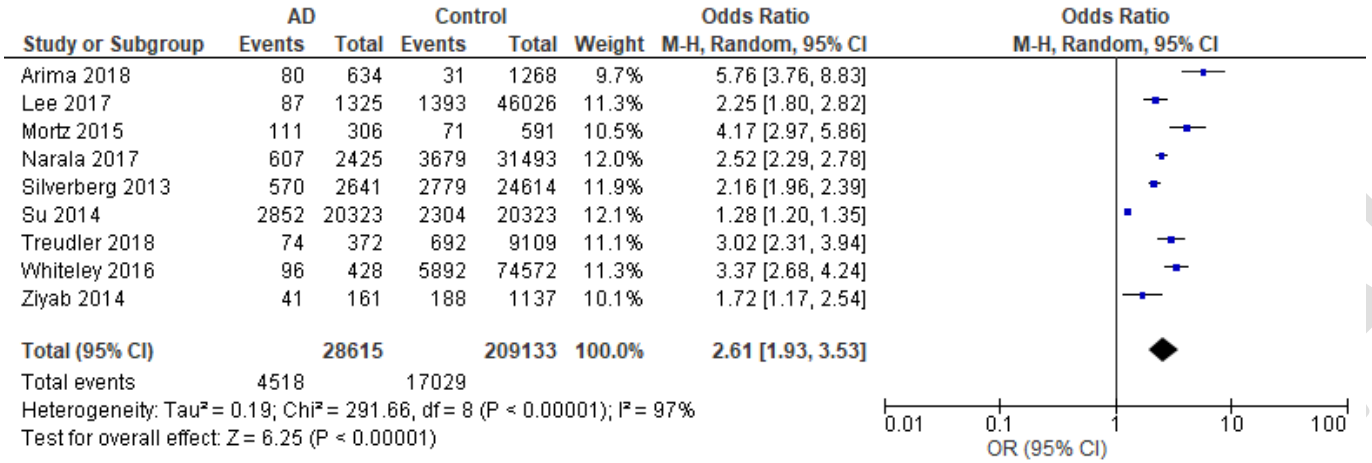


Figure: Pooled analysis of prevalence of any self-reported or physician-diagnosed asthma in individuals with AD compared to non-AD controls.

e-Figure 1c. Prevalence of Asthma in AD (pooled rates of asthma in AD)

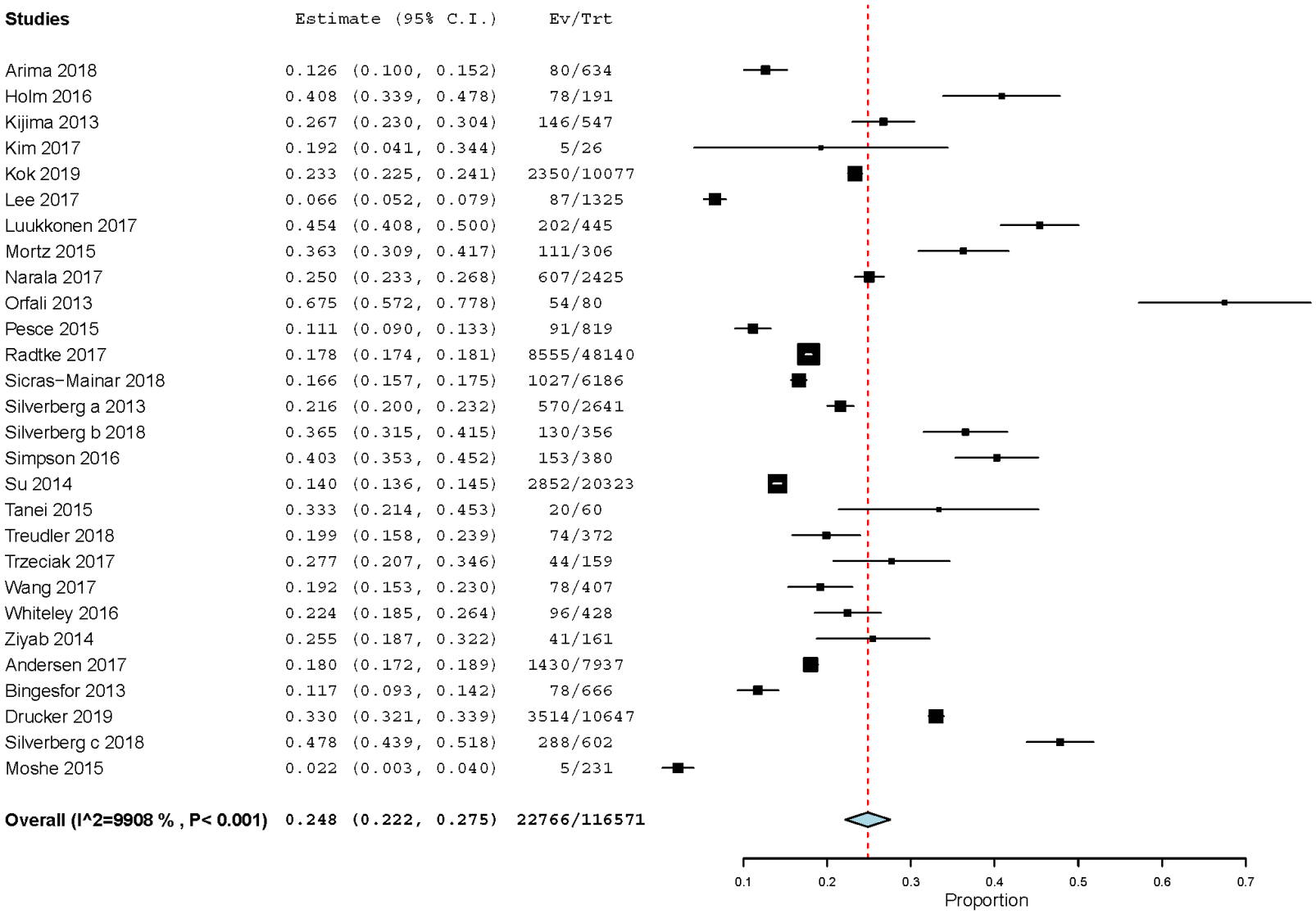


Figure: Pooled analysis of rates of any self-reported or physician-diagnosed asthma in individuals with AD.

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e-Table 2. GRADE EVIDENCE PROFILE- Food Allergy

Question: Are food allergies associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Food Allergy (follow up: Cross-sectional; assessed with: rate of FA in AD)									
7 [1-7]	observational studies	serious [a]	serious [b]	not serious [c]	not serious	none	Based on data from 11,816 adults with AD reported in 7 studies, the pooled prevalence of any food allergy in individuals with AD was **11.2% (95%CI 6-16.4%)**.[1-7]	⊕⊕◯◯ LOW	IMPORTANT
Occurrence of Food Allergy (follow up: Cross-sectional; assessed with: risk of FA in AD)									
2 [8, 9]	observational studies	serious [d]	not serious [e]	not serious	not serious	dose response gradient [f] *(not upgraded)*	Based on data from 547 adults (age 18 -41yo) with AD, the odds of a personal history of food allergy were [8]: **aOR** 5.22 (95%CI 3.89-7.01), p<0.001 Based on data from 601 adults (≥18 yo) with AD in the past year and 2,107 non-AD controls, AD was associated with higher risk of FA in the past year and increasing risk was associated with increasing AD severity[9]: <u>Overall risk of FA</u> **aRR** 2.45 (95%CI 1.79-3.06), p<0.001 <u>Risk of FA by AD Severity*</u> *Mild AD* **aRR** 1.48 (95%CI 0.89-2.07), p=0.08 *Moderate AD* **aRR** 2.40 (95%CI 1.54-3.27), p<0.0001 *Severe AD* **aRR** 8.49 (95%CI 5.44-11.54), p<0.0001	⊕⊕⊕◯ MODERATE	CRITICAL
Occurrence of Food Allergy (follow up: up to14 years; assessed with: risk of developing AD in individuals with food allergy)									
2 [10, 11]	observational studies	not serious [g]	not serious	not serious [h]	not serious	strong association [i]	Based on data from 2,851 individuals with FA and 11,404 individuals without FA followed up over 14 years, FA was associated with an increased risk of developing AD [11]:	⊕⊕⊕⊕ HIGH	CRITICAL

							aHR 2.49 (95%CI 1.91-3.25), p<0.0001 Based on survey data from 480 individuals with food allergy and 4,950 non-food allergic controls, a reported history of AD in the first 2 years of life and a history of ever having been diagnosed with AD were associated with a higher risk of food allergy [10]: *AD in first 2-years* **aOR** 2.3 (95%CI 1.6-3.5) *AD Ever Diagnosed* **aOR** 1.6 (95%CI 1.1-2.3)		

AD: Atopic dermatitis**; FA:** Food allergy**; OR:** Odds ratio; **CI:** Confidence interval; **RR:** Risk ratio; **NOS:** Newcastle Ottawa Scale

*****AD severity determined via Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD) index.

Explanations

a. Cross-sectional evidence; Majority of studies did not provide details necessary to ascertain the representativeness of the sample or included non-representative samples; Most scored below a 6 on the modified NOS scale suggesting a moderate-to-high risk of bias (NOS scores ranging from 3 to 6; mean score 4.7).
b. Prevalence of any food allergy in the AD populations varied greatly in magnitude across the included studies (I^2=98.5%).
c. Two of the studies included in the prevalence analysis include individuals aged 14 to 63 yo but the mean age of included participants in these studies was 26.2±9.5yo and 25.2 ± 9.2yo, suggesting the study populations are aligned with the research questions focused on AD in adults.
d. Cross-sectional evidence; Both studies relied on self-reported exposure and outcome assessment; One study included a non-representative sample; modified NOS scores of 3 and 5 suggest moderate-to-high risk of bias.
e. The risk of food allergy in AD varied in magnitude across the included studies but consistently indicates increased risk of FA in AD.
f. Effect estimates based on the data in these studies suggest increasing magnitude of risk of FA is associated with increasing AD severity. However, the certainty of the evidence was not upgraded due to concerns of risk of bias.
g. Both studies relied on unvalidated or self-report exposure and/or outcome assessment; One longitudinal study received an NOS of 8 suggesting a low risk of bias; The second study scored 6, suggesting borderline risk of bias across the evidence base.
h. One study included individuals ≥12yo with food allergies at baseline but documented a mean age of 41.5±18.1yo in the food allergy cohort and 41.4± 17.9yo in the control cohort suggesting the age of the study population is aligned with the research question focused on adults with AD; One study included participants of all ages but reported a median age of individuals with FA of 38yo and a median age of controls of 43.4yo, suggesting the age of the study population is aligned with the research question focused on AD in adults.
i. Evidence from the low risk of bias, longitudinal study (14-year follow-up) suggests a large magnitude of association (CI is precise supporting the large magnitude of effect); Large magnitude of effect supported by the moderate risk of bias evidence from the included case-control study.

e-Figure 2. Prevalence of Any Food Allergy in Individuals with AD

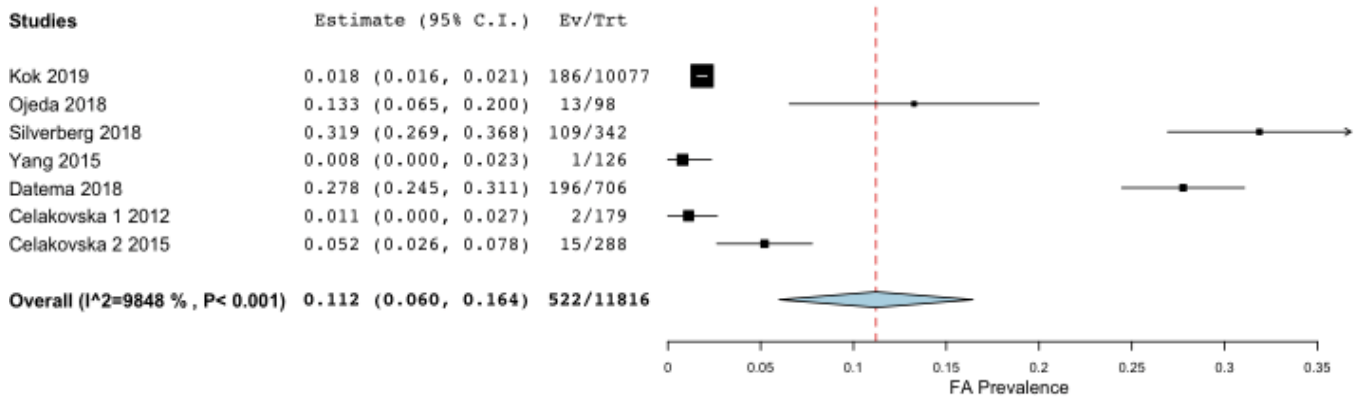

Figure: Pooled prevalence of any food allergy in adults with AD.

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e-Table 3. GRADE EVIDENCE PROFILE- Allergic Rhinitis

Question: Is allergic rhinitis associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Allergic Rhinitis (follow up: Cross-sectional; assessed with: rate of AR in AD)									
3 [1-3]	observational studies	very serious [a]	serious [b]	not serious	not serious	none	In a study of 149 adults with AD, 58 (38.9%) had concomitant AR.[1] A study of 407 individuals with adult-onset AD (AD diagnosed at or after age 18) and 275 adults with onset of AD before age 18 reports 87 (21.4%) and 60 (21.8%), respectively, had a history of AR.[3] In a study of 4,130 adults (≥18yo) with AR, 425 (10.5%) had concomitant AD.[2] An additional study of 18,617 individuals* reports 192 (1.03%) had concomitant AD and AR.[4]	⊕◯◯◯ VERY LOW	IMPORTANT
Occurrence of Allergic Rhinitis (follow up: Cross-sectional; assessed with: odds of AR in AD)									
5 [4-8]	observational studies	serious [c]	not serious	not serious	not serious	strong association [d] *(not upgraded)*	An analysis of 36,184,761 adults (≥20yo) found a history of AD was positively associated with AR[6]: **aOR**: 1.55 (1.31-1.84), p<0.001 A study of individuals** seen in general practice and dermatology practice settings reports that of 2,762 individuals with AD and 2,762 non-AD controls seen by GPs, 488 (17.7%) of AD patients had a co-diagnosis of AR compared to 176 (6.4%) of controls[7]: **aOR** 3.24 (95%CI 2.69-3.89), p<0.0001. Of 5,606 individuals with AD and 5,606 non-AD controls seen in dermatology practices, 1,053 (19.1%) AD patients had a co-diagnosis of AR compared to 401 (7.3%) of controls[7]:	⊕⊕⊕◯ MODERATE	CRITICAL

							aOR 3.07 (2.71-3.47), p<0.0001 In a study of 17,734 adults (≥ 19yo) with AD and 63,492 adults with nonatopic eczema, urticaria, or psoriasis, 6,231 (35.1%) of those with AD had AR compared to 27,928 (44%) individuals with non-AD dermatological conditions[5]: **OR**: 0.69 (95%CI 0.67-0.71), p<0.0001 In a study of 634 adults with AD and 1,268 controls without AD, eczema, or dermatitis, 234 (36.9%) of AD patients had nasal allergies/hay fever compared to 188 (14.8%) controls [8]: **OR:** 3.36 (95%CI 2.69- 4.20), p<0.0001		
Occurrence of Allergic Rhinitis (follow up: range 10 years to 20 years; assessed with: risk of AR in AD)									
2 [9, 10]	observational studies	serious [e]	not serious	not serious	not serious	none	In a cohort of 1,435 individuals aged 23 to 25 followed up over 10 years to document the occurrence of new AR (no AR at baseline in 2002 but report of AR during the follow up period between 2002 and 2012), AD was a risk factor for AR[9]: **aRR** 1.51 (95%CI 1.11-2.06) In a cohort of 941 individuals followed from birth to 20yo to examine determinants of AR in the first 2 decades of life, eczema in the first 3 years of life was associated with AR by 20 years old[10]: **aHR** 1.83 (95%CI 1.38-2.42)	⊕⊕⊕◯ MODERATE	CRITICAL

AR: Allergic rhinitis; **AD:** Atopic dermatitis; **CI:** Confidence interval; **OR**: Odds ratio; **GP:** General practitioner; **RR:** Risk ratio; **HR**: Hazard Ratio; **NOS**: Newcastle Ottawa Scale

* This study included children ages 6-7 yo and 13-14 yo and adults. Adults comprise 50.4% of the study population (n=9,386).
**This study included patients of all ages. The mean age of patients seen in general practice was 52.4± 20.2 and the mean age of patients seen by dermatologists was 47.4 ± 19.0.

Explanations
a. Cross-sectional evidence; Studies do not clearly describe exposure and/or outcome assessment or rely on unvalidated or self-reported assessment; Studies scored between a 4 and 5 on the modified NOS suggesting a high-to-moderate risk of bias.
b. Rates of concomitant AR and AD vary in magnitude across the included studies.

c. Cross-sectional evidence; Majority of studies rely primarily on self-reported and/or unvalidated exposure and outcome assessment; Modified NOS scores ranged from 3 to 7 suggesting a high-to-moderate risk of bias.
d. Majority of studies reporting on the association between AD and AR report a large magnitude of effect. However, the certainty of the evidence was not upgraded due to concerns of risk of bias.
e. These studies rely on self-reported exposure and outcome assessment and had considerable loss to follow up (>20%) over the study periods (NOS scores 5 and 6).

Study	Allergic Rhinitis Definition
Bekić 2020	ICD codes for allergic rhinitis
Izquierdo-Dominguez 2017	Physician-diagnosed allergic rhinitis
Wang 2017	Self-reported of and "rhinitis" – data presented separately from self-reported allergic conjunctivitis
Sybilski 2015	Self-reported "allergic rhinitis"- Allergic rhinitis (AR) was diagnosed when the subjects answered "yes" to the question "do you have any nasal allergies, including hay fever?"
Ahn 2019	Diagnostic codes (ICD code) for allergic rhinitis
An 2015	Self-reported allergic rhinitis (A participant was considered to have had AR when a runny nose, sneezing, and nasal blockage, without fever or a sore throat, were reported)
Werner-Busse 2014	Diagnostic codes (ICD codes) for allergic rhinitis
Arima 2018	Self-reported "nasal allergies or hay fever"
Arnedo-Pena 2017	Self-reported "nasal allergy including hay fever" or "medication for allergic rhinitis"
Grabenhenrich 2015	Self-reported allergic rhinitis based on responses to survey questions based on ISAAC questionnaire

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e-Table 4. GRADE EVIDENCE PROFILE- Allergic Conjunctivitis

Question: Is allergic conjunctivitis associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Allergic Conjunctivitis (follow up: Cross-sectional; assessed with: rate of allergic conjunctivitis in AD)									
1 [1]	observational studies	serious [a]	not serious	not serious	serious [b]	none	In a study of 407 individuals with adult-onset AD (AD diagnosed at or after age 18) and 275 adults with onset of AD before age 18, 89 (21.9%) and 41 (14.9%), respectively, had a history of allergic conjunctivitis.[1]	⊕⊕◯◯ LOW	IMPORTANT
Occurrence of Allergic Conjunctivitis (follow up: Cross-sectional; assessed with: incidence and odds of allergic conjunctivitis in AD)									
1 [2]	observational studies	serious [c]	not serious	serious [d]	not serious	none	In a study of 17,734 adults (≥19yo) with a history of AD and 63,492 controls with nonatopic eczema, urticaria, or psoriasis, 2,123 (12%) individuals with AD had allergic conjunctivitis compared to 9,797 (15.4%) controls[2]: **OR:** 0.75 (95%CI 0.71- 0.78)	⊕⊕◯◯ LOW	CRITICAL

AD: Atopic dermatitis; **CI:** Confidence interval; **OR**: Odds ratio; **NOS**: Newcastle Ottawa Scale

Explanations

a. Cross-sectional evidence: Study relies on self-reported and unvalidated exposure and outcome assessment and does not control for outcome-important factors by design or analysis (modified NOS score 4).

b. Small sample does not meet optimal information size criteria and is concerning for imprecision.

c. Cross-sectional evidence: Study relies on unvalidated exposure and outcome assessment (modified NOS scores 6).

d. Study includes only samples with dermatological conditions: comparing occurrence of allergic conjunctivitis in individuals with AD to individuals with non-AD dermatologic conditions.

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e-Table 5. GRADE EVIDENCE PROFILE- Eosinophilic Esophagitis

Question: Is eosinophilic esophagitis associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of EoE (follow up: Cross-sectional; assessed with: rate of AD in EoE)									
3 [1-3]	observational studies	very serious [a]	serious [b]	not serious [c]	serious [d]	none	Based on data from 670 adults with EOE reported in 3 studies, rates of concomitant AD in the EoE populations ranged from 10% to 46.1% (mean rate 28.1%).[1-3]	⊕◯◯◯ VERY LOW	IMPORTANT
Occurrence of EoE (follow up: 2 years; assessed with: risk of EoE)									
1 [4]	observational studies	very serious [e]	not serious	not serious [f]	not serious	none	Based on data from 7,722 individuals with EoE and 10,600,000 controls (mean age 37.6 ± 19.0yo) without EoE, there was an increased risk of AD in patients with EoE: **RR**: 1.53 (95%CI 1.47-1.60) AD was diagnosed an average of 169.4±14.8 (95%CI 140.2-198.5) days prior to the diagnosis of EoE in the EoE cohort.	⊕⊕◯◯ LOW	CRITICAL

EoE: Eosinophilic esophagitis; **AD:** Atopic dermatitis; **RR**: Risk ratio; **CI:** Confidence interval; **NOS:** Newcastle Ottawa Scale

Explanations

a. Cross-sectional evidence; These small, single cohort studies relied on self-reported or unvalidated exposure and/or outcome assessment and minimally reported outcome data (modified NOS scores 3 to 5) suggesting high risk of bias.

b. Rates of AD in the EoE populations ranged from 10% in the smallest study (n=50) to 46.1% in the largest study population (n=449) suggesting inconsistency.

c. One study did not report the age range of included participants but documented a mean age of EoE onset in the study population of 30.52 ± 17.54 yo, suggesting the age of the population is aligned with the research question focused on adults.

d. The event rate across the three studies is 260 and the pooled EoE population is 670, suggesting imprecision.

e. This study relied on unvalidated exposure and outcome assessment and did not adjust for confounding factors by design or analysis. NOS score of 4 suggests a high risk of bias.

f. This study included participants of all ages, but the mean age of included individuals was 37.6 ± 19.0 yo, suggesting the age of the population is aligned with the research question focused on adults.

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e-Table 6. GRADE EVIDENCE PROFILE- Alopecia Areata

Question: Is alopecia areata associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Occurrence of Alopecia Areata (follow up: Cross-sectional; assessed with: odds of AA in AD or odds of AD in AA)									
3 [1-3]	observational studies	serious [a]	not serious [b]	not serious [c]	not serious	strong association *(not upgraded)* [d]	Based on data from 8,112 adults (≥18yo) with AD and 40,560 non-AD controls, AD was associated with increased odds of AA [1]: **aOR** 26.31 (95%CI 14.48-47.80), p<0.001 Based on data from 1,751 individuals (mean age 34.9±17.8yo) with AA and 3,502 non-AA, AA was associated with increased odds of AD [3]: **aOR** 4.17 (95%CI 3.18-5.47), p<0.001 Based on data from 584 individuals (mean age 35.54±19.28yo) with AA and 172 non-AA controls with seborrheic dermatitis, AA was associated with increased odds of AD [2]: **OR** 3.91 (95%CI 1.77- 8.62), p<0.001	⊕⊕⊕◯ MODERATE	CRITICAL
Occurrence of Alopecia Areata (follow up: 2 years; assessed with: odds of AA after diagnosis of AD)									
1 [4]	observational studies	serious [e]	not serious	not serious	not serious	none	Based on data from 9,234 individuals (mean age 54.4±4.6yo) with AD and 78,172 non-AD controls (mean age 54.5±4.7yo) the odds of AA following a diagnosis of AD were: **aOR** 1.80 (95%CI 1.18-2.76)	⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis; **AA:** Alopecia areata; **CI:** Confidence interval; **OR:** Odds ratio; **NOS:** Newcastle Ottawa

Explanations

a. Cross-sectional evidence; Studies rely on unvalidated exposure and outcome assessment: One study provides an unadjusted risk assessment; NOS scores range from 4 to 7 suggesting a moderate-to-high risk of bias.
b. All studies report positive association between AA and AD in adults, with varying magnitudes of effect.
c. One study compares the odds of AD in individuals with AA to individuals with seborrheic dermatitis: not further downgraded as downgrade for borderline risk of bias.
d. Studies uniformly suggest a very large or large magnitude of effect with consistent CIs but the evidence was not upgraded for this outcome due to risk of bias.
e. This study relies on self-reported exposure and assessment and the study sample is limited to female registered nurses (NOS score 6).

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e-Table 7. GRADE EVIDENCE PROFILE- Urticaria

Question: Is urticaria associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Occurrence of Urticaria (unspecified)^ (follow up: Cross-sectional; assessed with: rate and odds of urticaria (type unspecified) in AD)									
2 [1, 2]	observational studies	serious [a]	not serious [b]	not serious [c]	not serious	none	Based on data from 2,762 individuals* with AD and 2,762 non-AD controls seen in a general practice setting, 162 (5.9%) AD patients had a co-diagnosis of urticaria compared to 31 (0.1%) of the controls[2]: **aOR**: 5.50 (95%CI 3.73-8.11), p<0.0001 Based on data from 5,606 individuals with AD and 5,606 non-AD controls seen in dermatology practices, 315 (5.7%) AD patients had a co-diagnosis of urticaria compared to 197 (3.6%) controls[2]: **aOR**: 1.64 (95%CI 1.36-1.96), p<0.0001 Based on data from 666 adults with self-reported childhood AD and 4,209 controls not reporting AD in childhood, childhood AD was associated with self-reported current urticaria (within the past 12 months)[1]: **aOR** 2.50 (95%CI 1.73-3.62)	⊕⊕⊕◯ MODERATE	CRITICAL
Prevalence of Chronic Urticaria^ (follow up: Cross-sectional; assessed with: rate of AD in individuals with chronic urticaria (itchy wheals lasting at least 6 weeks)()									
1 [3]	observational studies	serious [d]	not serious	not serious	serious [e]	none	For 37 elderly (>= 60yo) and 800 non-elderly (mean age 38.0 +/- 10.5yo) with chronic urticaria, 14 (37.8%) and 169 (21.7%) had a physician-diagnosis of AD.	⊕⊕◯◯ LOW	IMPORTANT
Occurrence of Chronic Urticaria^ (follow up: Cross-sectional; assessed with: odds or chronic urticaria in AD)									
2 [4, 5]	observational studies	not serious [f]	not serious	not serious	not serious	none	Based on data from 8,112 adults with AD and 40,560 matched controls, AD was associated with increased odds of chronic urticaria[4]: **aOR** 9.92 (95%CI 6.43-15.32)	⊕⊕⊕⊕ HIGH	CRITICAL

							Based on data from 9,332 adults (mean age 37.7 + 17.6yo) with chronic urticaria and 37,328 matched controls, urticaria was associated with increased odds of AD[5]: **aOR:** 1.94 (95%CI 1.81-2.08)		
Occurrence of Chronic Urticaria (follow up: up to 21 years; assessed with: Cox proportional hazards regression for subsequent diagnosis of AD after diagnosis of CU)									
1[6]	observational studies	not serious[g]	not serious	not serious	not serious	strong association	Based on data from 12,185 adults (mean age at inclusion 38.4) first diagnosed with chronic urticaria between 1994 and 2015 and 104,007 controls without CU, CU is associated with increased risk of subsequent AD diagnosis (AD dx at least 1 year after CU dx): **HR** 3.1 (95%CI 2.0-4.8)	⊕⊕⊕⊕ HIGH	CRITICAL

AD: Atopic dermatitis; **CI:** Confidence interval; **OR**: Odds ratio; **HR**: Hazard ratio; **CU**: Chronic urticaria **NOS**: Newcastle Ottawa Scale

^Study Definitions of Urticaria

Study	Definition of Urticaria
Andersen 2017	ICD-10 code L50.8A "Chronic Urticaria"
Ban 2014	Physician-diagnosed chronic urticaria defined as itchy wheals lasting at least 6 weeks
Bingefors 2013	Self-report in response to: "Have you had urticaria in the past 12 months?"
Chiu 2018	ICD-9 code 708.8 "Chronic Urticaria"
Ghazanfar 2020	ICD-10 codes DL50,563,282A, DO268 (study definition=hives and itch lasting 6 weeks or longer)
Werner-Busse 2014	ICD-10 L50 "Urticaria, unspecified"

Explanations

a. Cross-sectional evidence; Both studies rely on unvalidated or self-reported exposure and outcome assessment; one study is of a low risk of bias (modified NOS 7) and one study is of a high risk of bias (NOS 3).

b. Results are consistent in direction across samples and studies; A large magnitude of the effect is reported for the subgroup of patients seen in general practice. This magnitude of effect is not reported for the subgroup of patients seen in dermatology practices. However, as the study design indicates, this inconsistency may be explained by the differences between AD patients seeking specialized care and those treated in general practice settings.

c. One study includes individuals of all ages. The mean age of patients seen in general practice was 52.4± 20.2 and the mean age of patients seen by dermatologists was 47.4 ± 19.0, suggesting the evidence is aligned with the question is focused on adults with AD.

d. Cross-sectional evidence; Sample derived from a single specialized center (NOS 4).

e. A small event rate (n=183) suggests imprecision.

f. Cross-sectional evidence; Both studies rely on unvalidated exposure and/or outcome measures but are otherwise of low risk of bias (standard and modified NOS scores of 7).

g. The study relies on unvalidated outcome and exposure assessment but is otherwise at low risk of bias (NOS 7).

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e-Table 8. GRADE EVIDENCE PROFILE- Clinician-diagnosed Depression

Question: Is clinical depression associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Depression (follow up: Cross-sectional; assessed with: rate of physician-diagnosed or self-reported clinical depression in individuals with AD)									
16 [1-16]	observational studies	serious [a]	serious [b]	not serious [c]	not serious	none	Based on data from 138,057 individuals with AD reported in 15 studies, the pooled prevalence of physician-diagnosed or self-reported clinical depression in AD was **17.5% (95%CI 14.4%- 20.6%)**.[1-15] Based on data from 602 individuals with AD, incidence of depression increased with increasing AD severity* from 8.8% in mild AD to 19.5% and 19.7% in moderate and severe AD, respectively.[16]	⨁⨁◯◯ LOW	IMPORTANT
Occurrence of Depression (follow up: Cross-sectional; assessed with: odds of depression in AD)									
13 [1-7, 10, 11, 13-15, 17]	observational studies	serious [d]	not serious [e]	not serious	not serious	none	Based on the pooling of adjusted ORs of the association of self-report or physician-diagnosed clinical depression in individuals with AD compared to non-AD controls reported in 4 studies including 11,244 individuals with AD and 149,713 non-AD controls, AD is associated with increased odds of depression in AD [3, 5, 15, 17]: **pooled OR** 1.99 (95%CI 1.53-2.59) Based on analysis of incidence of self-reported or physician-diagnosed clinical depression in individuals with AD compared to individuals without AD reported in 8 studies including 21,451 individuals with AD and 154,420 controls, AD is associated with increased odds of depression [1, 2, 4, 7, 10, 11, 13, 14]: **OR** 1.60 (95%CI 1.01-2.52) Based on data from 57,690 individuals with AD and 40,363 individuals with melanocytic nevi, odds of major depression (as identified by diagnostic codes) was higher in AD patients[6]:	⨁⨁⨁◯ MODERATE	CRITICAL

							OR 1.33 (95%CI 1.27-1.39)		
Occurrence of Depression (follow up: up to 15 years; assessed with: incidence and risk of developing depression in AD)									
2[13, 18]	observational studies	serious [f]	not serious	not serious [g]	not serious	strong association & dose response gradient [h] *(not upgraded)*	Based on data from 8,208 individuals with AD and 8,208 non-AD controls followed for up to 13 years, individuals with AD had a higher incidence and increased risk of developing major depression or any depressive disorder** during the study period[18]: <u>Major Depression</u> *Incidence* 1.42 vs 0.20 per 1,000 PY, p<0.001 *Risk* **aHR** 6.56 (95%CI 3.64-11.84) <u>Any Depressive Disorder</u> *Incidence* 4.32 vs 0.74 per 1,000 PY, p<0.001 *Risk* **aHR** 5.44 (95%CI 3.99- 7.44) Based on data from 5,766 adults with mild AD*** diagnosed at or after age 18 followed up for 46,770 PY, 4,272 adults with moderate-severe AD*** diagnosed at or after age 18 followed-up for 32,463 PY and 4,259,457 adult general population controls followed-up for 38,999,055 PY, incidence of depression diagnosed during follow-up was higher in the AD cohorts than in the general population[13]: <u>Incidence Rates</u> *General population* 0.80 (95%CI 0.79-0.81) per 1,000 PY *Mild AD* 0.86 (95%CI 0.63-1.17) per 1,000 PY *Moderate-severe AD* 1.08 (95%CI 0.77-1.50) per 1,000 PY	⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis**; OR:** Odds ratio**; CI:** Confidence interval; **HR:** Hazard ratio; **PY:** Person-years; **NOS:** Newcastle Ottawa Scale

*AD severity classified using Patient-Oriented Eczema Measure (POEM); For this study, a score of 0-7 was considered mild, 8-16 as moderate, and 7-28 as severe.
**Any depressive disorders identified via the following diagnostic codes: ICD-9-CM codes: 296.2X, 296.3X, 300.4 and 311.
*** AD severity determined by prescription of systemic therapy; Mild AD = no systemic therapy; Severe AD= Patients were classified with severe disease if they received systemic therapy for AD (methotrexate, azathioprine, mycophenolate mofetil, systemic corticosteroids, psoralen plus ultraviolet A [PUVA], or cyclosporine).

Explanations

a. Cross-sectional evidence; Majority of studies relied on self-reported or unvalidated exposure and/or outcome assessment; 7/16 included studies scored below a 6 on the modified or standard NOS suggesting at least a moderate-to-high overall risk of bias.
b. Reported prevalence of depression in the AD populations varied across the included studies (I^2= 99.7%).
c. Some studies included participants under the age of 18, however all included studies had a mean age of participants over 18yo suggesting the age of the study populations is aligned with the research question focused on adults with AD.
d. Cross-sectional evidence; Majority of studies relied on self-reported or unvalidated exposure and/or outcome assessment; 7/13 studies scored below a 6 on the modified NOS suggesting a moderate-to-high risk of bias.
e. Studies consistently report increased odds of clinical depression in AD: 11/13 studies report increased odds (10/11 report significant association; 1/11 report non-significant association).
f. Both studies rely on self-reported and/or unvalidated exposure and outcome assessment; NOS scores 5 and 6 suggest moderate risk of bias.
g. One study enrolled participants aged 12 and older but the mean age of study participants was 32.60yo and the 13-year follow-up period suggest the age of the study population is aligned with the research question focused on adults with AD.
h. A very large magnitude of effect for the association of depressive disorders and AD is reported and incidence rates of depression in mild and moderate-severe AD suggest a dose-response gradient. However, the moderate risk of bias of the evidence base precluded upgrading for these factors.

e-Figure 3a. Prevalence of Clinical Depression in Individuals with AD

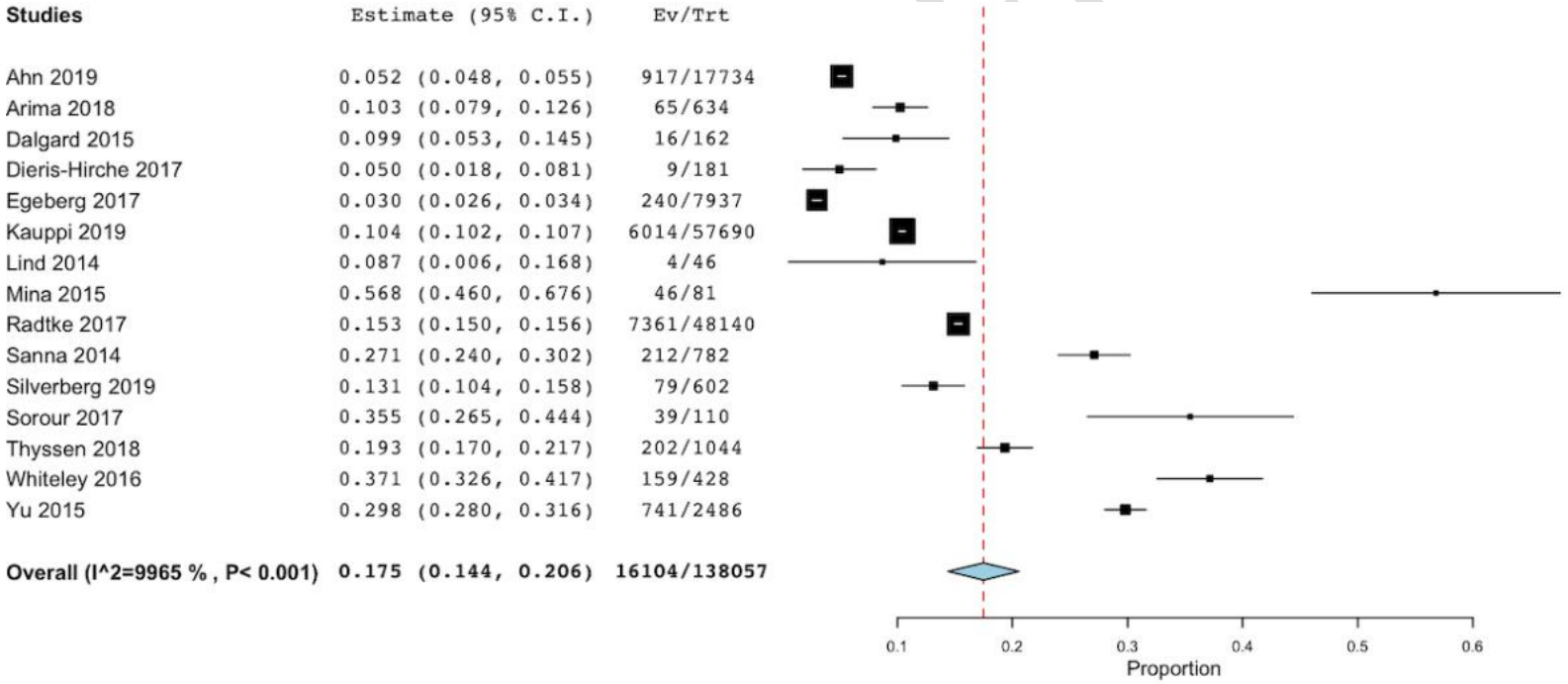

Figure: Pooled prevalence rates of self-reported or physician-diagnosed clinical depression in individuals with AD**.**

e-Figure 3b. Occurrence of Clinician-diagnosed Depression in AD (pooled adjusted ORs)

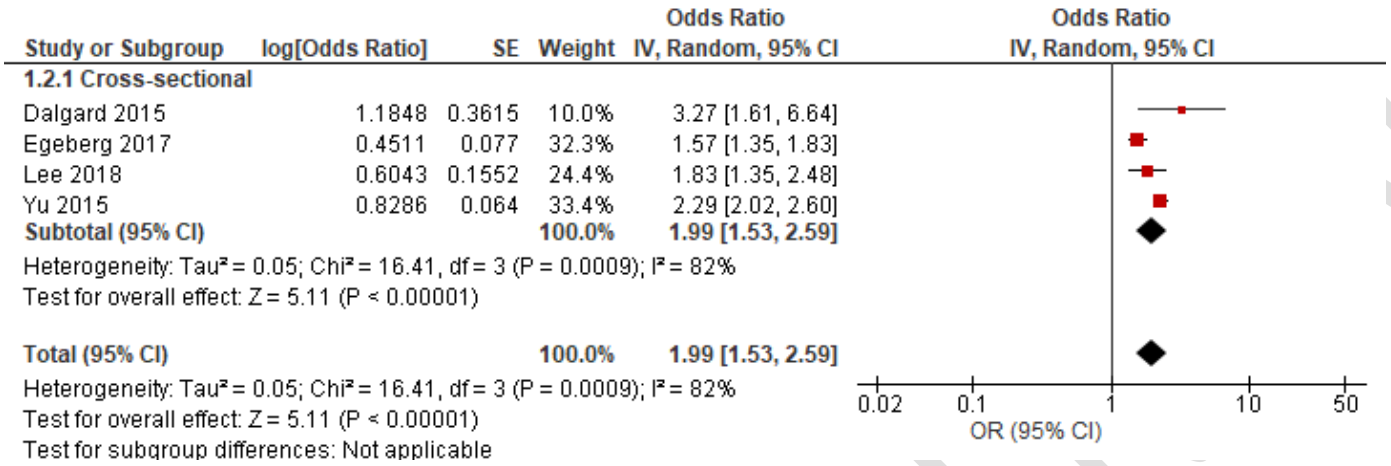

Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of self-reported or physician diagnosed clinical depression in individuals with AD compared to non-AD controls.

e-Figure 3c. Occurrence of Clinician-diagnosed Depression in AD (prevalence in AD vs non-AD controls)

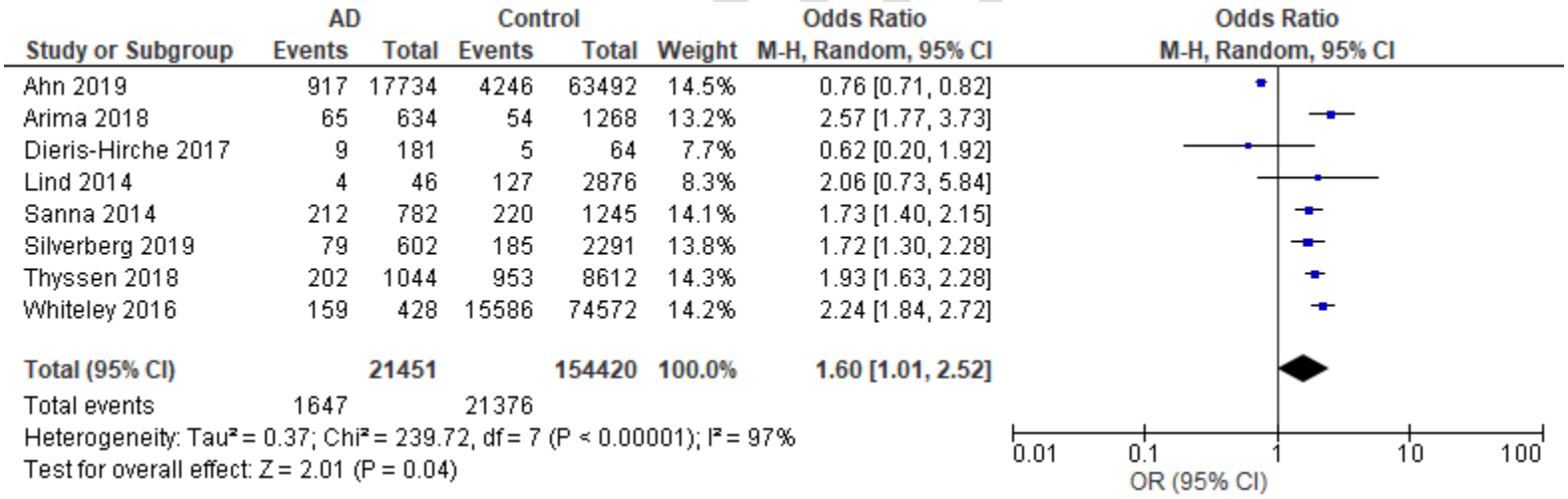

Figure: Pooled rates of self-reported or physician diagnosed clinical depression in individuals with AD compared to non-AD controls.

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e-Table 9. GRADE EVIDENCE PROFILE- Clinician-diagnosed Anxiety

Question: Is clinical anxiety associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Anxiety (follow up: Cross-sectional; assessed with: rate of physician-diagnosed or self-reported clinical anxiety in individuals with AD)									
12 [1-12]	observational studies	serious [a]	serious [b]	not serious [c]	not serious	none	Based on data from 86,487 individuals with AD reported in 11 studies, the pooled prevalence of self-reported or physician-diagnosed clinical anxiety was **14.1% (95%CI 11.7% - 16.5%)**.[1-11] Based on data from 602 individuals with AD, rate of clinical anxiety* increased with increasing AD severity** from 16.0% in mild AD to 32.2% and 54.6% in moderate and severe AD, respectively.[12]	⨁⨁◯◯ LOW	IMPORTANT
Occurrence of Anxiety (follow up: Cross-sectional; assessed with: odds of anxiety in AD)									
11 [1-6, 8, 10, 11, 13, 14]	observational studies	serious [d]	not serious [e]	not serious [c]	not serious	none	Based on the pooling of adjusted ORs of the association of self-reported or physician-diagnosed clinical anxiety in individuals with AD compared to non-AD controls reported in 4 studies including 157,222 individuals with AD and 300,719,113 non-AD controls, there are increased odds of anxiety in AD[4, 5, 13, 14]: **pooled OR** 1.40 (95% CI 1.12-1.75) Based on the analysis of incidence of self-reported or physician-diagnosed clinical anxiety in individuals with AD compared to individuals without AD reported in 7 studies including 20,669 individuals with AD and 153,175 non-AD controls, AD was associated with increased odds of anxiety [1-3, 6, 8, 10, 11]: **OR** 1.97 (95%CI 1.04-3.74) Based on data from 3,317 individuals with mild AD*** compared to 33,170 general population controls and 4,620 individuals with severe AD compared to 46,200	⨁⨁⨁◯ MODERATE	CRITICAL

							general population controls, the odds of clinical anxiety were significantly increased severe but not mild AD [4]: *Mild AD* **aOR** 1.39 (95%CI 0.97-1.98), p=0.0711 *Severe AD* **aOR** 1.48 (95%CI 1.09-1.99), p=0.011		
Occurrence of Anxiety (follow up: up to 15 years; assessed with: incidence and risk of developing anxiety in AD)									
2[10, 15]	observational studies	serious [f]	not serious	not serious [g]	not serious	strong association [h] (*not upgraded)*	Based on data from 8,208 individuals with AD and 8,208 non-AD controls followed for up to 13 years, individuals with AD had a higher incidence and increased risk of developing anxiety disorder during the study period [15]: *Incidence* 2.83 vs 0.7 per 1,000 PY, p<0.001 *Risk* **aHR** 3.57 (95%CI 2.55- 4.98) Based on data from 5,766 adults with mild AD*** diagnosed at or after age 18 followed up for 46,960 PY, 4,272 adults with moderate-severe AD*** diagnosed at or after age 18 followed-up for 32,629 PY and 4,259,457 adult general population controls followed-up for 39,154,394 PY, rates of clinical anxiety diagnosed during follow-up was higher in the AD cohorts than in the general population[10]: <u>Incidence Rates</u> *General population* 0.30 (95%CI 0.29-0.30) per 1,000 PY *Mild AD* 0.45 (95%CI 0.29-0.69) per 1,000 PY *Moderate-severe AD* 0.49 (95%CI 0.30- 0.80) per 1,000 PY	⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis**; OR:** Odds ratio**; CI:** Confidence interval; **HR:** Hazard ratio; **PY:** Person-years; **NOS:** Newcastle Ottawa Scale

*****Anxiety assessed via the Hospital and Anxiety Depression scale (HADS): anxiety subscores between 11 and 21 were considered as clinical diagnosis of anxiety
******AD severity classified using Patient-Oriented Eczema Measure (POEM); For this study, a score of 0-7 was considered mild, 8-16 as moderate, and 7-28 as severe.
*** AD severity determined by prescription of systemic therapy; Mild AD = no systemic therapy; Severe AD= Patients were classified with severe disease if they received systemic therapy for AD (methotrexate, azathioprine, mycophenolate mofetil, systemic corticosteroids, psoralen plus ultraviolet A [PUVA], or cyclosporine)

Explanations
a. Cross-sectional evidence; Majority of studies relied on self-reported or unvalidated exposure and/or outcome assessment; All studies scored a 5 or 6 on the modified or standard NOS suggesting a moderate risk of bias.
b. Reported prevalence of anxiety in the AD populations varied greatly across the included studies (I^2= 99.4%).

c. Some studies included participants under the age of 18, however all included studies had a mean age of participants over 18yo suggesting the age of the study populations is aligned with the research question focused on adults with AD.
d. Cross-sectional evidence; Majority of the included studies relied on self-reported or unvalidated exposure and/or outcome assessment and scored a 6 or below on the modified or standard NOS scale (range 1 to 8) suggesting a moderate risk of bias..
e. Evidence consistently reports increased odds of clinical anxiety in AD: 11/12 included studies report increased odds of clinical anxiety in AD (9/11 report significant association; 2/11 report not significant findings).
f. Both studies rely on self-reported and/or unvalidated exposure and outcome assessment; NOS scores 5 and 6 suggest moderate risk of bias.
g. One study enrolled participants aged 12 and older but the mean age of study participants was 32.60yo and the 13-year follow-up period suggest the age of the study population is aligned with the research question focused on adults with AD.
h. A large magnitude of effect for the association of anxiety and AD is reported and incidence rates of anxiety in mild and moderate-severe AD suggest a dose-response gradient. However, the moderate risk of bias of the evidence base precluded upgrading for these factors.

e-Figure 4a. Prevalence of Clinical Anxiety in Individuals with AD

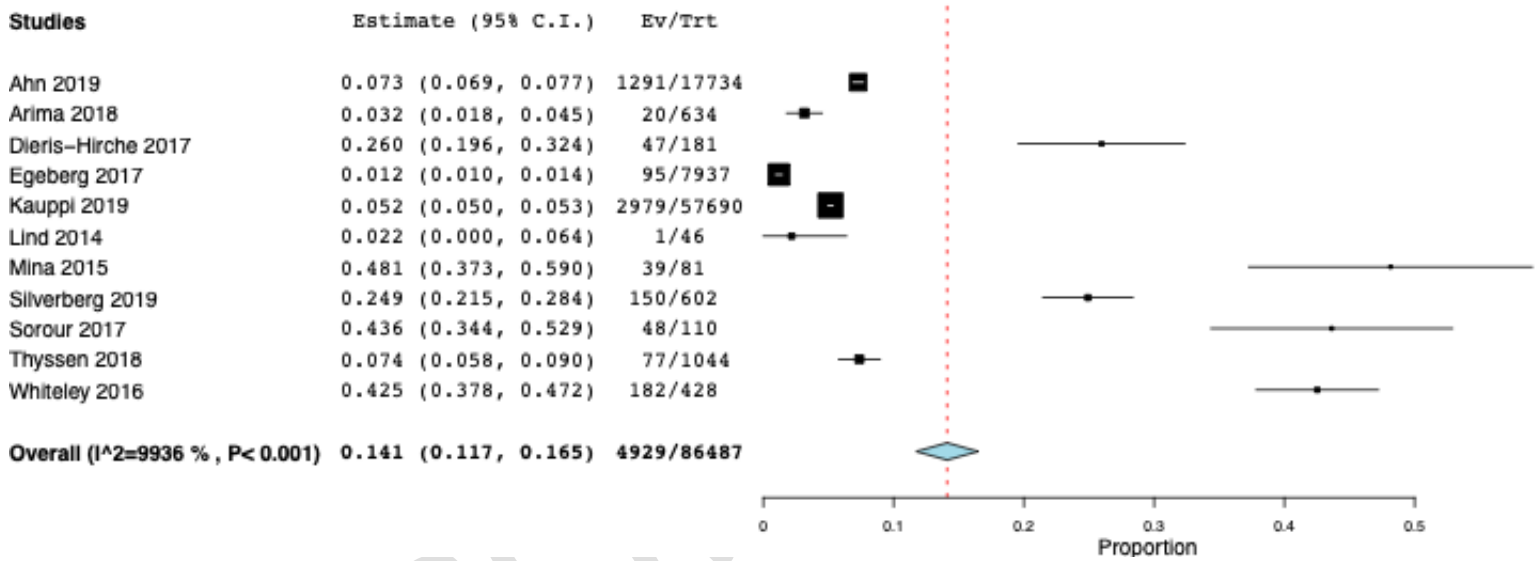

Figure: Pooled rates of self-reported or physician diagnosed clinical anxiety in individuals with AD**.**

e-Figure 4b. Occurrence of Clinical Anxiety in AD (pooled adjusted ORs)

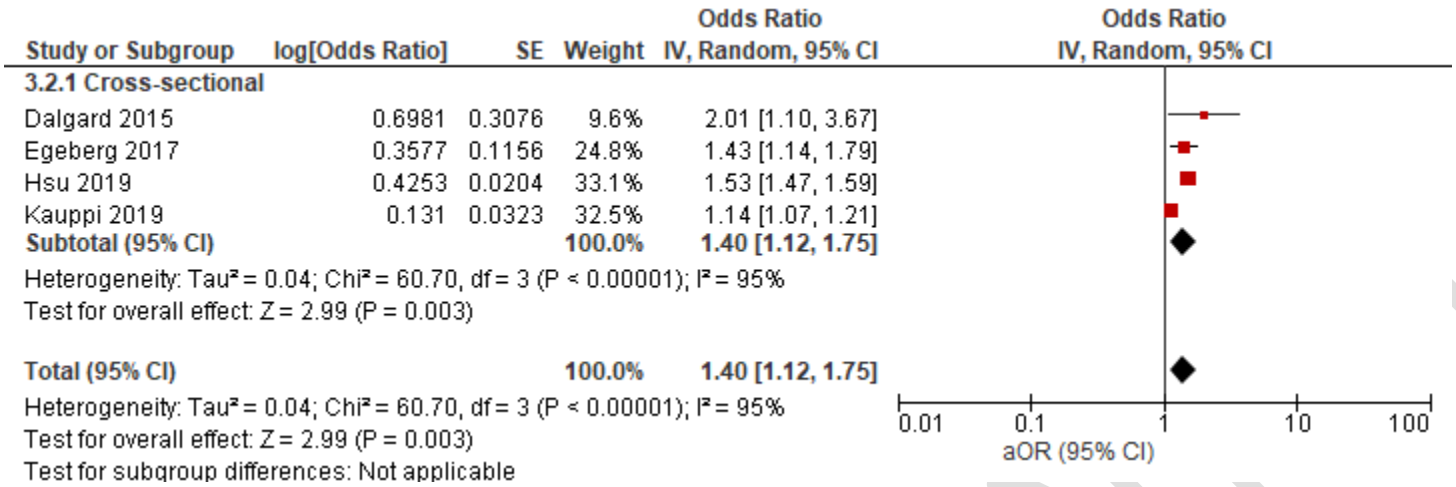

Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of self-reported or physician diagnosed clinical anxiety in individuals with AD compared to non-AD controls.

e-Figure 4c. Occurrence of Clinical Anxiety in AD (pooled prevalence in AD vs non-AD controls)

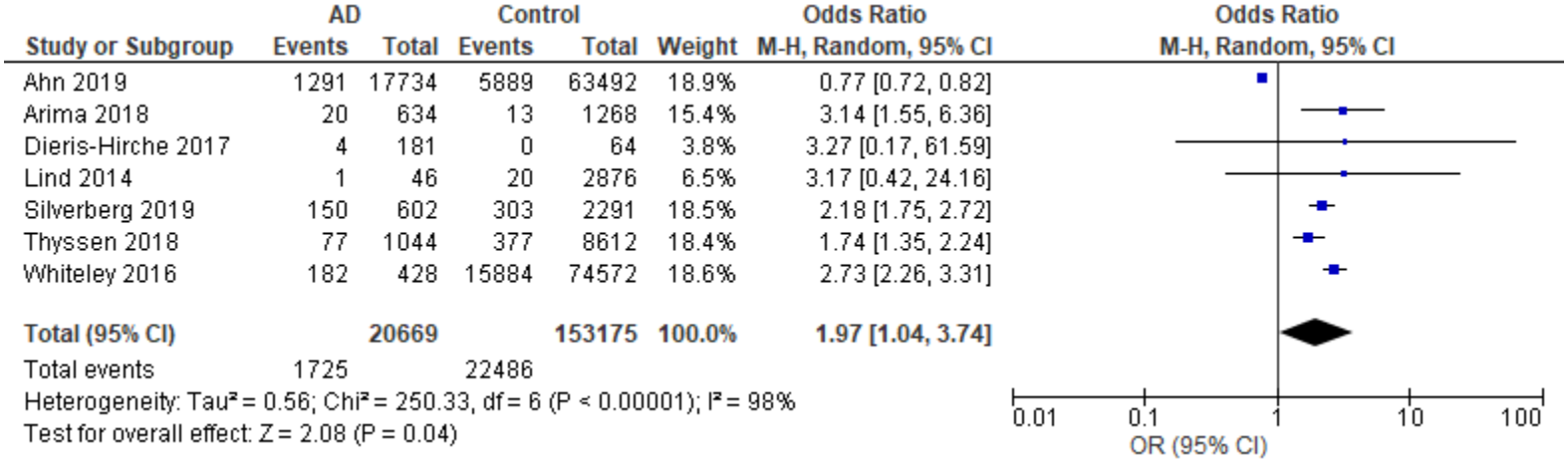

Figure: Pooled prevalence of self-reported or physician diagnosed clinical anxiety in individuals with AD compared to non-AD controls.

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e-Table 10. GRADE EVIDENCE PROFILE- Suicide

Question: Is suicidality and death from suicide associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Suicidal Ideation (follow up: Cross-sectional; assessed with: odds of self-reported or physician-assessed suicidal ideation in individuals with AD)									
5 [1-5]	observational studies	serious [a]	serious [b]	not serious [c]	serious [d]	none	Based on data from 18,448 individuals with AD reported in 5 studies, the pooled prevalence of self-reported or physician-assessed suicidal ideation in AD is **10.4% (95%CI 3.6%- 17.2%)**.[1-5]	⊕◯◯◯ VERY LOW	IMPORTANT
Occurrence of Suicidal Ideation (follow up: Cross-sectional; assessed with: odds of self-reported or physician-assessed suicidal ideation in individuals with AD)									
3 [3, 6, 7]	observational studies	not serious	not serious	not serious [c]	not serious	none	Based on the pooling of adjusted ORs of the association of self-reported or physician-assessed suicidal ideation in individuals with AD compared to non-AD controls reported in 3 studies including 1,181 individuals with AD and 40,781 non-AD controls, AD was associated with increased odds of suicidal ideation [3, 6, 7]: **pooled OR** 1.71 (95%CI 1.43- 2.03)	⊕⊕⊕⊕ HIGH	IMPORTANT
Occurrence of Suicide (follow up: up to 15 years; assessed with: rate and risk of suicide in individuals with AD)									
4 [8-11]	observational studies	serious [e]	serious [f]	not serious [g]	not serious [h]	none	In a case-control study of 18,441 cases of suicide and 36,882 alive matched controls, 174 (0.98%) of cases and 285 (0.77%) of controls had a history of persistent eczema*. Persistent eczema was associated with increased odds of suicide [8]: **aOR** 1.22 (95%CI 1.01- 1.48), p=0.037 In a case-control study of 618 cases of suicide among individuals with AD and 54,364 matched general population controls with AD, AD was not associated with death by suicide[9]: **aOR** 0.77 (95%CI 0.48 - 1.24), p=0.28	⊕⊕◯◯ LOW	CRITICAL

							Based on data from 267,788 individuals with AD compared to a reference cohort of individuals** (n not reported), an increased rate of death from suicide during the 12 year study period was associated with AD [10]: **adjusted Rate Ratio** 1.4 (95%CI 1.1 - 1.18) Based on data from 5,766 adults with mild AD*** diagnosed at or after age 18 followed up for 46,770 PY, 4,272 adults with moderate-severe AD*** diagnosed at or after age 18 followed-up for 32,629 PY and 4,259,457 adult general population controls followed-up for 39,154,394 PY, incidence of death from suicide during follow-up was lower in the AD cohorts than in the general population [11]: <u>Incidence Rates</u> *General population* 0.15 (95%CI 0.14 - 0.15) per 1,000 PY *Mild AD* 0.11 (95%CI 0.04-0.26) per 1,000 PY *Moderate-severe AD* 0.12 (95%CI 0.05-0.33) per 1,000 PY		

AD: Atopic dermatitis**; OR:** Odds ratio**; CI:** Confidence interval; **PY:** Person-years; **NOS:** Newcastle Ottawa Scale

*****Persistent eczema defined as five or more physician visits for eczema over the 5 years preceding study inclusion.
**A reference cohort was constructed of individuals seen as day cases or inpatients at the same institutions as the identified cases with a wide range of other, mainly minor, surgical and medical conditions and injuries (including appendectomy, adenoidectomy, hip replacement, squint, cataract, otitis, head injury, bunion, dislocations, sprains, strains, etc.).
*** AD severity determined by prescription of systemic therapy; Mild AD = no systemic therapy; Moderate-Severe AD= Patients were classified with severe disease if they received systemic therapy for AD (methotrexate, azathioprine, mycophenolate mofetil, systemic corticosteroids, psoralen plus ultraviolet A [PUVA], or cyclosporine).

Explanations
a. Cross-sectional evidence; Majority of studies relied on self-reported or unvalidated exposure and/or outcome assessment and scored a 6 or below on the modified NOS (range 5-7) suggesting a moderate risk of bias.
b. Rates of suicidal ideation varied greatly across the included studies (I^2= 96%).
c. Some studies included participants under the age of 18, however all included studies had a mean age of participants over 18yo suggesting the age of the study populations is aligned with the research question focused on adults with AD.
d. Imprecision is apparent as the CI for the effect estimate includes small and moderate magnitude of effect.
e. Majority of studies relied on unvalidated exposure and/or outcome assessment; Two studies minimally reported study information including sample sizes and age of participants making a full assessment of the applicability of the evidence unclear; Studies scored between 5 and 8 on the NOS suggesting a moderate-to-low risk of bias.

f. Findings on the association of AD and suicide vary in direction across the evidence base; Two studies suggest increased risk of suicide in AD, while two studies did not find an increased risk of suicide in AD compared to the general population.
g. One study included participants aged 15 to 55yo but documented a mean age of participants of 38yo; Two studies did not report the age of included participants; One study included adults 18yo and older; suggesting borderline indirectness with the research question focused on AD in adults.
h. One of the 4 studies reports an effect estimate consistent with the possibility of no risk difference, reduced risk, and increased risk. The results of the other 3 studies are precise.

e-Figure 5a. Prevalence of Suicidal Ideation in Individuals with AD

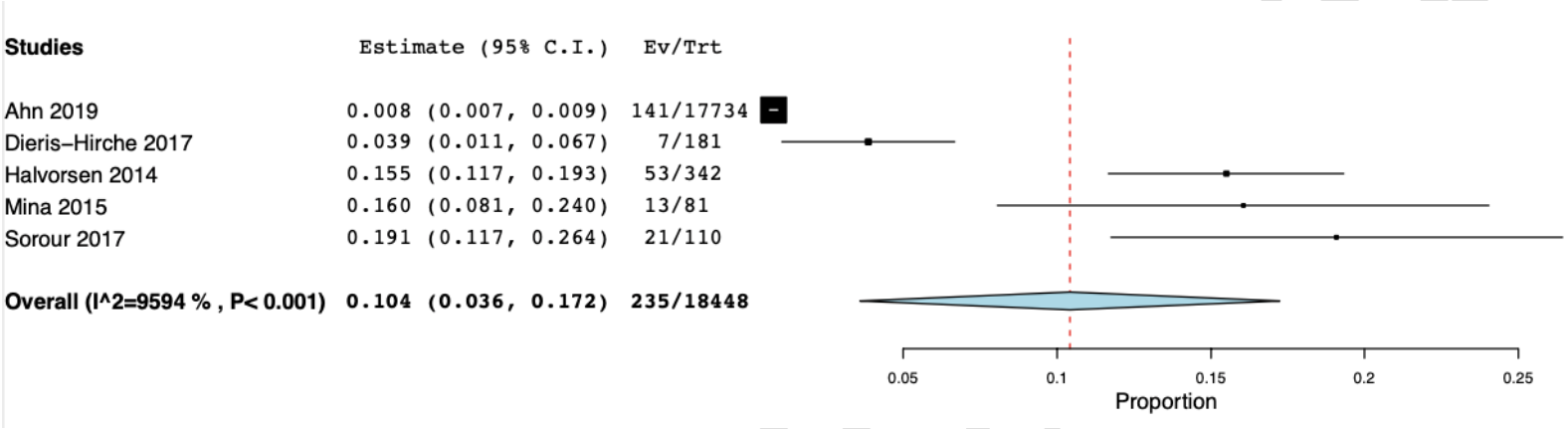

Figure: Pooled prevalence rates of self-reported or physician-assessed suicidal ideation in individuals with AD.

e-Figure 5b. Occurrence of Suicidal Ideation in AD (pooled adjusted ORs)

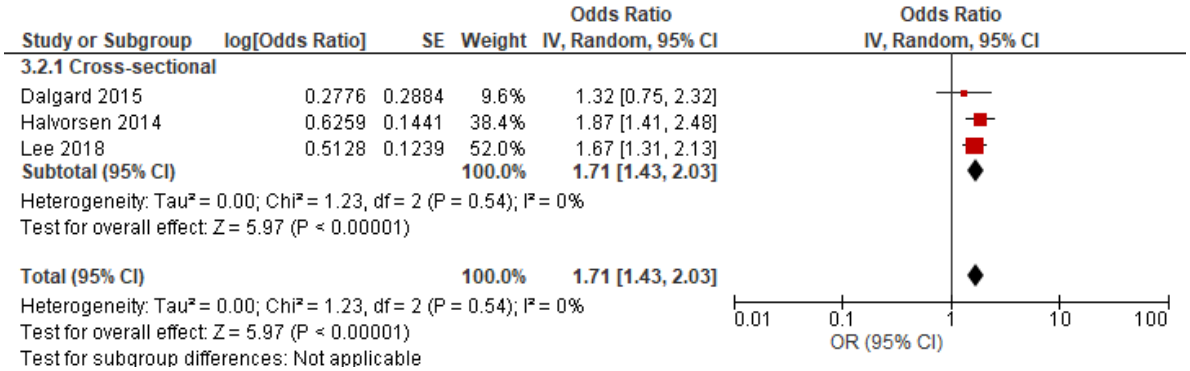

Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of self-reported or physician-assessed suicidal ideation in individuals with AD compared to non-AD controls.

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e-Table 11. GRADE EVIDENCE PROFILE- Alcohol Abuse Disorders

Question: Are alcohol use disorders associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Alcoholism (follow up: Cross-sectional; assessed with: rate of alcoholism in AD)									
2 [1, 2]	observational studies	serious [a]	serious [b]	not serious	not serious	none	Based on data from 278 adults (aged 20-60yo) with physician diagnosed alcoholism and 271 non-alcoholic controls, there was no significant^ difference in the prevalence of AD between the groups, 0.36% and 0.37%, respectively.[1] Based on baseline data from a cohort of 6,186 adults with AD, the rate of physician diagnosed alcoholism in the cohort was 4.2%. The rate of alcoholism increased with increasing AD severity* from 3.5% in mild AD to 5.1% and 5.5% in moderate and severe AD, respectively.[2]	⊕⊕◯◯ LOW	IMPORTANT
Occurrence of Alcohol Use Disorders (follow up: Cross-sectional; assessed with: odds of alcohol use disorders in AD)									
2 [3, 4]	observational studies	serious [c]	not serious	not serious	not serious	none	Based on data from 114 adults with AD and 175 adults with non-inflammatory skin conditions (including BCC, SCC, AK, warts, and lipoma), AUD** was more prevalent in AD (33.3% vs 14.3%, respectively) , but was not significantly associated with increased odds of AD based on adjusted analysis [3]: **aOR** 1.61 (95%CI 0.80-3.21) Based on data from 7,937 adults with AD and 79,370 healthy general population controls, alcohol abuse*** was associated with higher odds of AD [4]: **aOR** 1.38 (95%CI 1.24-1.53), p<0.001	⊕⊕⊕◯ MODERATE	CRITICAL
Alcohol Consumption (follow up: Cross-sectional; assessed with: rate and association of rates of alcohol consumption in AD)									
3 [5-7]	observational studies	serious [d]	serious [e]	not serious	not serious	none	Based on data from 8,069 adults with AD and 72,027 non-AD controls, alcohol consumption at any rate	⊕⊕◯◯ LOW	IMPORTANT

							(measured in grams consumed per day) was not associated with AD [5]: *1-4g/day* **aOR** 0.94 (95%CI 0.89-1.00) *5-9g/day* **aOR** 0.93(95%CI 0.86-1.00) *10-14g/day* **aOR** 0.97(95%CI 0.88-1.07) *15-29g/day* **aOR** 0.93 (95%CI 0.85-1.03) ≥*30g/day* **aOR** 1.09 (95%CI 0.96-1.24) Based on data from 70 adults with AD and 70 healthy controls, alcohol consumption (measured as the % of energy intake per day) was negatively associated with AD [6]: **aOR** 0.91 (95%CI 0.83-0.98), p=0.018 Based on data from 2,488 adults with AD and 32,100 non-AD controls, AD was associated with increased odds of current moderate and heavier alcohol consumption**** [7]: *Moderate intake* **aOR** 1.33 (95%CI 1.09-1.62), p=0.005 *Heavier intake* **aOR** 1.58 (95%CI 1.23-2.03), p<0.001		

AD: Atopic dermatitis; **AUD:** Alcohol Use Disorder; **OR:** Odds ratio; **CI:** Confidence interval**; NOS:** Newcastle Ottawa Scale

^No p-value provide but noted in study as "not significant".
* AD severity determined by prescribed treatment: Mild AD based on prescription of emollients or low/medium potency topical corticosteroids; Moderate AD based on prescription of calcineurin inhibitors, high potency topical or oral corticosteroids, or UV radiation; Severe AD based on prescription of immunosuppressants, biologics, or hospitalization.
**Alcohol use disorder determined via Alcohol Use Disorders Identification Test (AUDIT)- total test scores ranging from 0 to 40; A score of ≥ 8 indicates an AUD.
***Alcohol abuse was determined via diagnoses in medical records of alcohol abuse or conditions strongly related to alcohol abuse (e.g., alcoholic liver disease), treatment with drugs used for alcohol dependence, and treatment interventions for alcohol dependence.
**** Current moderate alcohol intake defined as ≥12 drinks in lifetime, and (male) >3 drinks per week up to 14 drinks per week or (female) >3 drinks per week up to 7 drinks per week); Heavier alcohol intake defined as ≥12 drinks in lifetime, and (male) >14 drinks per week in past year or (female) >7 drinks per week in past year) alcohol intake.

Explanations
a. Cross-sectional evidence; One study included a non-representative sample (restricted to military police) and minimally reported outcome analysis and assessment suggesting a high risk of bias (modified NOS score 3); One study relied on unvalidated exposure assessment and limited outcome data reporting (NOS score 7).
b. Prevalence of concomitant alcoholism and AD varied in magnitude across studies.
Majority of the included studies rely on small samples and/or low event rates which is concerning for imprecision.
c. Cross-sectional evidence; Studies relied on self-reported and/or unvalidated exposure and/or outcome assessment; Studies scored 5 and 6 on the modified NOS suggesting a moderate risk of bias.

d. Cross-sectional evidence; All studies rely on self-reported exposure and outcome assessment; The studies scored between 5 and 6 on the modified NOS with a mean score of 5.7, suggesting a moderate risk of bias.
e. One study suggests no association between AD and alcohol consumption; One study reports a negative association between AD and alcohol consumption; One study reports a positive association between AD and both current moderate and heavier alcohol consumption.

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e-Table 12. GRADE EVIDENCE PROFILE- Cigarette Smoking

Question: Is cigarette smoking associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Smoking (follow up: Cross-sectional; assessed with: rate of smoking in AD)									
1 [1]	observational studies	not serious	not serious	not serious	not serious	dose-response gradient	Based on baseline data from a cohort of 6,186 adults with a history of AD, the rate of current smoking was 21.1% and rates of active smoking decreased with increasing AD severity* from 22.4% to 19.0% and 18.4% for mild, moderate, and severe AD, respectively (p=0.013).[1]	⨁⨁⨁⨁ HIGH	IMPORTANT
Occurrence of Smoking (follow up: Cross-sectional; assessed with: risk of smoking in AD)									
4 [2-5]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	Based on data from 8,069 adults with AD and 72,027 non-AD controls, past but not current smoking was significantly associated with increased odds of AD [2]: <u>Past smoker</u> **aOR** 1.10 (95%CI 1.05-1.16) <u>Currently smoke:</u> *≤15 cigarettes per day* **aOR** 0.93 (95%CI 0.81-1.07) *15-20 cigarettes per day* **aOR** 1.10 (95%CI 0.93-1.30) *≥25 cigarettes per day* **aOR** 1.06 (95%CI 0.79-1.42) Based on data from 7,937 adults with AD and 79,370 healthy general population controls, a history of smoking (past or current) was associated with increased odds of diagnosis of AD [3]: **aOR** 1.32 (95%CI 1.22-1.42), p<0.001 Based on data from 1,318 adults with AD and 44,370 non-AD controls neither past nor current smoking was significantly associated with self-reported history of AD [4]: *Past smoker* **OR** 0.86 (95%CI 0.69-1.07) *Current smoker* **OR** 0.92 (95%CI 0.79-1.07)	⨁⨁⨁◯ MODERATE	CRITICAL

							Based on data from 2,488 adults with AD and 32,100 non-AD controls, adults with current (symptomatic in the past 12 months) AD had higher odds of ever smoking 100 cigarettes in their lifetime and of being current smokers [5]: *100 cigarettes ever* **aOR** 1.32 (95%CI 1.18-1.47), p<0.001 *Current smoker* **aOR** 1.28 (95%CI 1.12-1.45), p<0.001		
Occurrence of Smoking (follow up: up to 18 years; assessed with: association between smoking status and AD)									
1 [6]	observational studies	serious [c]	not serious	not serious	serious [d]	none	Based on data from 76,701 adults, 463 with AD, followed up over 1,357,932 person years, neither current nor past smoking was associated with AD. Among current smokers, there was no dose-response relationship for number of cigarettes smoked daily and risk of AD: *Past smoker* **aHR** 1.02 (95%CI 0.82-1.26) *Current smoker* **aHR** 1.21 (95%CI 0.86-1.68) *Currently smoke 1-14 cigarettes per day* **aHR** 1.25 (95%CI 0.81-1.94) *Currently smoke 15 or more cigarettes per day* **aHR** 1.15 (95%CI 0.72-1.86)	⊕⊕◯◯ LOW	CRITICAL

AD: Atopic dermatitis; **OR:** Odds ratio; **CI:** Confidence interval**; HR:** Hazard ratio; **NOS:** Newcastle Ottawa Scale

*****AD severity determined by prescribed treatment: Mild AD based on prescription of emollients or low/medium potency topical corticosteroids; Moderate AD based on prescription of calcineurin inhibitors, high potency topical or oral corticosteroids, or UV radiation; Severe AD based on prescription of immunosuppressants, biologics, or hospitalization.

Explanations

a. Cross-sectional evidence; Studies relied on self-reported or unvalidated exposure and outcome assessment; One study use non-representative sample; Modified and standard NOS scores ranged from 4 to 6 with a mean score of 5.3 suggesting a moderate risk of bias.

b. Three of four studies report an association between AD and smoking, an additional study reports no significant association: borderline inconsistency.

c. Study relies on self-reported exposure and outcome assessment and the study population was restricted to female nurses (NOS score 6), suggesting a moderate risk of bias

d. All CIs consistent with both the possibility of no difference and important risk increases.

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e-Table 13. GRADE EVIDENCE PROFILE- ADHD

Question: Is ADHD associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Occurrence of ADHD (follow up: Cross-sectional; assessed with: odds of ADHD in AD)									
2 [1, 2]	observational studies	serious [a]	not serious [b]	serious [c]	not serious	none	In a study of 17,734 adults (≥19yo) with AD and 63,492 adults with nonatopic eczema, urticaria, or psoriasis, 24 (0.14%) individuals with AD had ADHD compared to 81 (0.13%) individuals with non-AD dermatological conditions[1] : **OR**: 1.06 (95%CI 0.67-1.67), p=0.80 Based on data from 2,483 adults (≥18yo) with AD and 32,072 adults without AD, AD was associated with increased odds of ADHD[2] : **aOR** 1.61 (95%CI 1.25-2.06)	⊕⊕◯◯ LOW	CRITICAL

ADHD: Attention deficit hyperactivity disorder; **AD:** Atopic dermatitis; **CI:** Confidence interval; **OR**: Odds ratio; **NOS**: Newcastle Ottawa Scale

Explanations

a. Cross-sectional evidence: Studies rely on self-reported and unvalidated exposure and outcome assessment; One study minimally reports outcome important data (modified NOS scores 5).

b. The CI of the unadjusted OR suggests imprecision as the it is compatible with no difference and both important reduction and increase in odds. However, the magnitude and direction of the effect measures are similar across the two studies and the CIs overlap, suggesting borderline imprecision.

c. The largest included study compares odds of ADHD in individuals with AD to odds in individuals with other dermatologic conditions.

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e-Table 14. GRADE EVIDENCE PROFILE- Autism Spectrum Disorders

Question: Are ASDs associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Occurrence of ASDs (follow up: Cross-sectional; assessed with: incidence and odds of ASDs in AD)									
1 [1]	observational studies	serious [a]	not serious	serious [b]	serious [c]	none	In a study of 17,734 adults (≥19yo) with AD and 63,492 adults with nonatopic eczema, urticaria, or psoriasis, 19 (0.12%) individuals with AD had concomitant ASDs compared to 46 (0.07%) individuals with non-AD dermatological conditions: **OR** 1.48 (95%CI 0.87-2.52), p=0.15	⊕◯◯◯ VERY LOW	CRITICAL

ASDs: Autism spectrum disorders; **AD:** Atopic dermatitis; **CI:** Confidence interval; **OR**: Odds ratio; **NOS**: Newcastle Ottawa Scale

Explanations

a. Cross-sectional evidence; Study relies on unvalidated outcome and exposure assessment; modified NOS score of 5 suggests moderate risk of bias.

b. Study includes only populations with dermatological conditions.

c. Crude OR calculation includes a CI compatible with no difference in risk and an important increase in risk.

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e-Table 15. GRADE EVIDENCE PROFILE- Hypertension

Question: Is hypertension associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Hypertension (follow up: Cross-sectional; assessed with: rate of hypertension in AD)									
3 [1-3]	observational studies	very serious [a]	not serious	not serious	not serious	none	Based on data from 1,349,671 adults, 48,140 with a diagnosis of AD, hypertension was significantly more prevalent in adults with AD[2]: **Prevalence Ratio** 1.17 (95%CI 1.13-1.20) Based on data from 253 adults with persistent AD (diagnosed at <18yo and persisting into adulthood) or adult onset AD (diagnosed at ≥18yo), prevalence of hypertension was 1.2% in the AD cohort.[1] Based on data from 3,445 adults with mild AD****, 2,361 adults with moderate AD and 380 adults with severe AD, prevalence of physician-diagnosed hypertension increased significantly with increasing AD severity[3]: *Mild AD* prevalence 19.6% *Moderate AD* prevalence 29.2% *Severe AD* prevalence 48.7% (p<0.001 also significant for pairwise comparisons)	⊕⊕◯◯ LOW	IMPORTANT
Occurrence of Hypertension (follow up: Cross-sectional; assessed with: odds of hypertension in AD)									
16 [4-19]	observational studies	serious [b]	not serious	not serious	not serious [c]	none	Based on the pooling of adjusted ORs of the association of self-reported or physician-diagnosed hypertension in adults with AD compared to non-AD controls reported in 6 studies (including 7 study populations), AD is not associated with significantly increased odds of hypertension[4-8, 19]:	⊕⊕⊕◯ MODERATE	CRITICAL

							pooled OR 1.06 (95%CI 1.00-1.13) Based on the pooling of adjusted RRs of the association of self-reported or physician diagnosed hypertension in adults with AD compared to non-AD controls reported in 2 studies, AD is associated with increased risk of hypertension[9, 10]: **pooled RR** 1.07 (95%CI 1.06-1.08) Based on the pooling of crude incidence rates of hypertension in 165,334 adults with AD and in 4,837,526 non-AD controls reported in 7 studies, AD is not associated with hypertension[11-17]: **OR** 1.00 (95%CI 0.82-1.22) Based on data from 7,471 adult males with mild AD* and 2,606 males with moderate-to-severe AD, those who with a diagnosis of hypertension were more likely to have moderate-to-severe AD[18]: **aOR** 1.65 (95%CI 1.16-2.34), p=0.005 Based on data from 3,317 adults with mild AD** compared to 33,170 general population controls and 4,620 adults with severe AD compared to 46,200 general population controls, severe but not mild AD was associated with increased odds of hypertension[5]: *Mild AD* **aOR** 0.83 (95%CI 0.72-0.95) *Severe AD* **aOR** 1.28 (95%CI 1.16-1.42)		
Occurrence of Hypertension (follow up: up to 7 years; assessed with: risk of hypertension diagnosis in AD)									

1 [10]	observational studies	not serious	not serious	not serious	not serious	none	Based on the longitudinal analysis of 33,816 adults (≥40yo) with AD in 2005 and 1,180,317 controls without AD between 2005 and 2007, AD was associated with an increased risk of subsequent hypertension diagnosis between 2008 and 2014: **aRR** 1.04 (95%CI 1.02-1.06), p=2.71 X 10-3	⊕⊕⊕⊕ HIGH	CRITICAL

AD: Atopic dermatitis**; OR:** Odds ratio**; CI:** Confidence interval; **RR:** Risk ratio; **NOS:** Newcastle Ottawa Scale

* Classification of AD severity according to prescribed treatment: Mild AD- prescription of emollients or low/medium potency topical corticosteroids; Moderate AD-prescription of calcineurin inhibitors, high-potency topical corticosteroids, monotherapy with UV radiation, or oral corticosteroids; Severe AD-prescription of immunosuppressants, biologics, or hospitalization for AD.
** Physician-based AD severity classification was global and based on the body surface area affected, frequency of disease flare, treatments required, and functional impact of those affected. For example, mild cases of AD had limited involvement, requiring only topical therapy with infrequent flares, while moderate AD has more frequent intermittent flares. Severe cases of AD were those with extensive involvement, requiring systemic immunosuppressants and/or significant impact to function.

Explanations
a. Cross-sectional evidence; Majority of studies relied on unvalidated exposure and outcome assessment; One study restricted cases of AD to those diagnosed by a physician with >15 years' experience; modified NOS scores from 4 to 6 suggest high risk of bias.
b. Cross-sectional evidence; Majority of included studies scored between 4 and 6 on the modified or standard NOS (range 5-8) suggesting a moderate risk of bias.
c. The majority of effect estimates include CIs consistent with increased odds or risk of hypertension in AD; The OR based on the pooled crude incidence data has a CI that spans no risk difference suggesting borderline imprecision as do the effect estimates specific to mild AD, but the overall evidence base is precise.

e-Figure 6a. Occurrence of Hypertension in AD (pooled adjusted ORs)

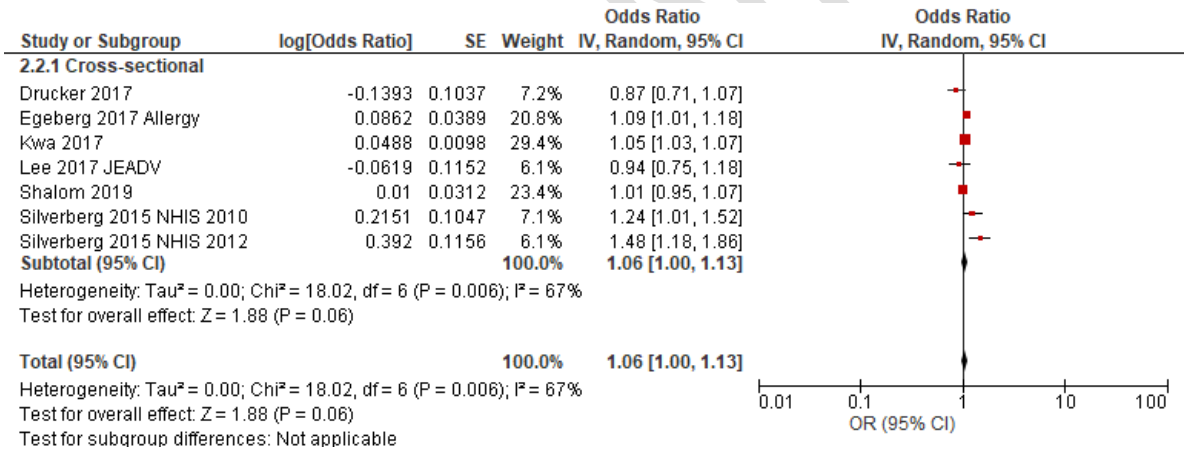

Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of any self-reported or physician-diagnosed hypertension in individuals with AD compared to non-AD controls.

e-Figure 6b. Occurrence of Hypertension in AD (pooled adjusted RRs)

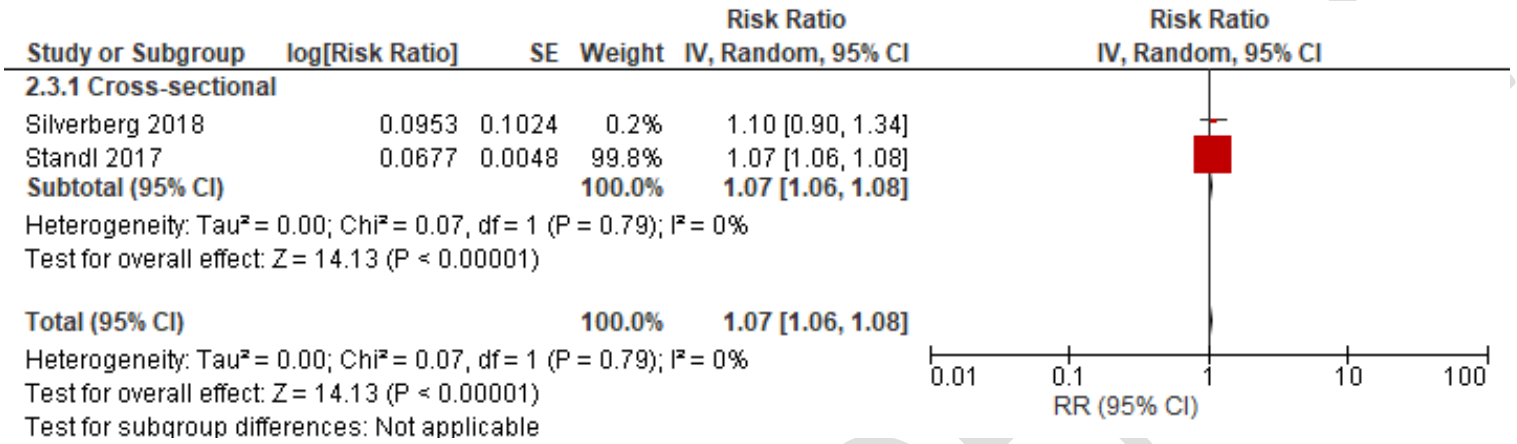

Figure: Pooled analysis of adjusted risk ratios and 95% CIs of the association of any self-reported or physician-diagnosed hypertension in individuals with AD compared to non-AD controls.

e-Figure 6c. Occurrence of Hypertension in AD (pooled prevalence in AD vs non-AD controls)

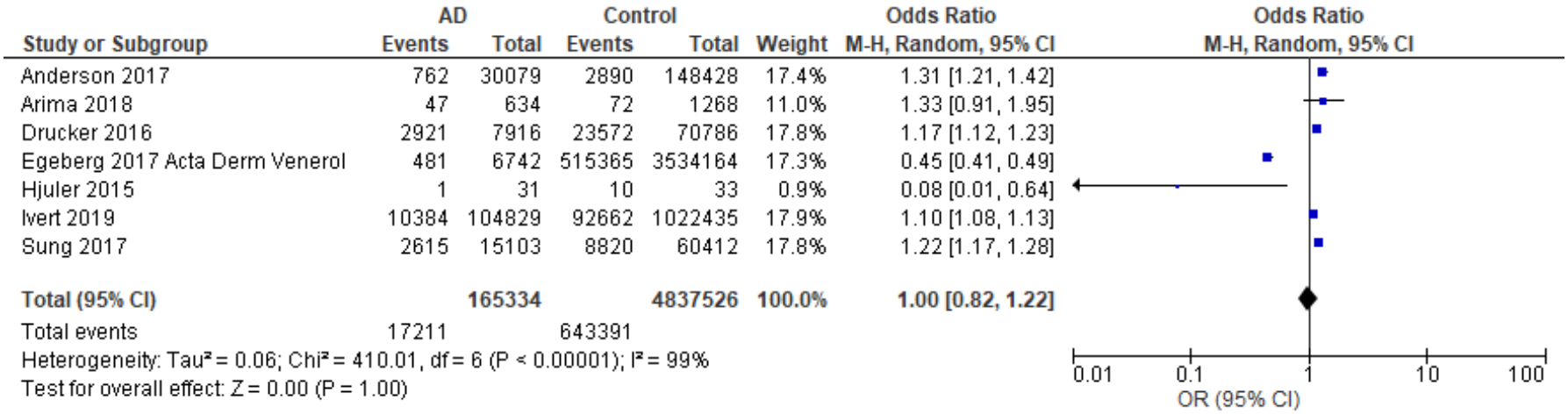

Figure: Pooled analysis of rates of any self-reported or physician-diagnosed hypertension in individuals with AD compared to non-AD controls.

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e-Table 16. GRADE EVIDENCE PROFILE- Heart Disease

Question: Is heart disease associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Occurrence of Heart Disease (follow up: Cross-sectional; assessed with: risk of heart failure and heart disease in AD)									
3 [1-3]	observational studies	serious [a]	not serious	not serious	not serious	none	Based on the pooling of adjusted ORs of the association of self-reported or physician-diagnosed CHF in adults with AD compared to non-AD controls reported in 2 studies, AD is associated with increased odds of CHF[1, 2]: **pooled OR** 1.03 (95%CI 1.01- 1.05) Based on data from 602 adults with AD and 7,615 non-AD controls, AD was associated with increased risk of self-reported heart disease and risk increased with increasing AD severity[3]: <u>Overall Odds</u> **aRR** 2.01 (95%CI 1.24- 2.78), p=0.0004 <u>Odds by AD Severity*</u> *Mild AD* **aRR** 1.48 (95%CI 0.74- 2.21), p=0.13 *Moderate AD* **aRR** 2.60 (1.37 - 3.82), p=0.0001 *Severe AD* **aRR** 3.88 (1.13-6.62), p=0.0009	⊕⊕⊕◯ MODERATE	CRITICAL
Occurrence of Heart Disease (follow up: up to 9 years)									
3 [4-6]	observational studies	not serious [b]	not serious [c]	not serious	serious [d]	none	Based on the pooling of adjusted HRs of the association of physician-diagnosed HF in adults with AD compared to non-AD controls reported in 2 studies (followed up for 1-5 years or for a median of 5.1 years), AD was associated with increased risk of HF[4, 5]: **pooled HR** 1.25 (95% CI 1.03- 1.53) Based on data from 285,661 adults with mild AD** (1,545,238 PY at risk), 145,614 (900,749 PY at risk) adults with moderate AD, 19,624 adults with severe AD (124,425 PY at risk), and 1,528,477 non-AD controls (9,375,383 PY at risk), increased risk of HF increased with AD severity[4]:	⊕⊕⊕◯ MODERATE	CRITICAL

							Mild AD **aHR** 1.12 (95%CI 1.02-1.24) *Moderate AD* **aHR** 1.20 (95%CI 1.09- 1.33) *Severe AD* **aHR** 1.67 (95%CI 1.36-2.05) Based on data from 622 adults (aged 30-64yo) with AD and 4,263 controls without AD, rosacea, or psoriasis followed for 1 year following AD diagnosis, the odds of cardiovascular disease events*** were not significantly higher in individuals with AD[6]: **aOR** 1.03 (95%CI 0.74- 1.43), p=0.85		

AD: Atopic dermatitis**; CHF:** Congestive heart failure**; HF:** Heart failure**; OR:** Odds ratio**; CI:** Confidence interval; **RR:** Risk ratio**; HR:** Hazard ratio; **PY:** Person-years; **NOS:** Newcastle Ottawa Scale

***** AD severity was assessed using the Patient-Oriented Scoring AD scale.
** AD severity determined by prescribed treatments: Mild AD as default severity if not meeting the following criteria for moderate or severe AD; Moderate AD- prescription of two potent topical corticosteroid treatments within 1 year or calcineurin inhibitor treatment; Severe AD- prescription of systemic treatment, phototherapy, or referral for AD.
***Cardiovascular disease events include ischemic heart disease, transient cerebral ischemia, heart failure, occlusion and stenosis of pre-cerebral arteries, and occlusion of cerebral arteries.

Explanations
a. Cross-sectional evidence; All studies relied on self-reported or unvalidated outcome and exposure assessment; One study included self-reported skin allergy or inflamed skin in addition to self-report of eczema in the AD exposure cohort; All studies scored between 5 and 6 on the modified NOS scale.
b. All studies relied on unvalidated exposure and/or outcome assessment; One study included a highly selective cohort of AD patients (newly diagnosed at or after 30yo and not receiving treatment 180 days prior to the study); Studies scored between 6 and 7 on the NOS suggesting low risk of bias.
c. Pooled HR analysis has I^2 of 54% suggesting moderate heterogeneity but the effect estimates are consistent in direction and magnitude across the included studies, so the evidence was not downgraded for this borderline inconsistency as if was downgraded for borderline imprecision.
d. Majority of reported estimates of effect include CIs consistent with the possibility of no risk difference.

e-Figure 7a. Occurrence of Congestive Heart Failure in AD (pooled adjusted ORs)

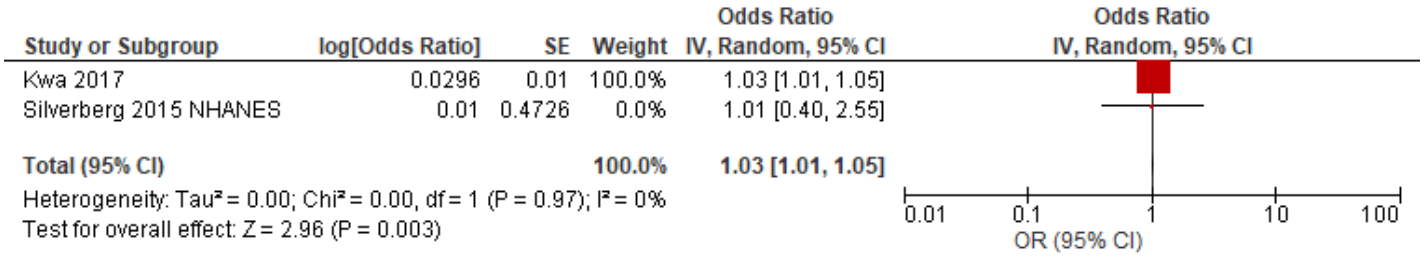

Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of self-reported or physician-diagnosed congestive heart failure in individuals with AD compared to non-AD controls.

e-Figure 7b. Occurrence of Heart Failure in AD (pooled adjusted HRs)

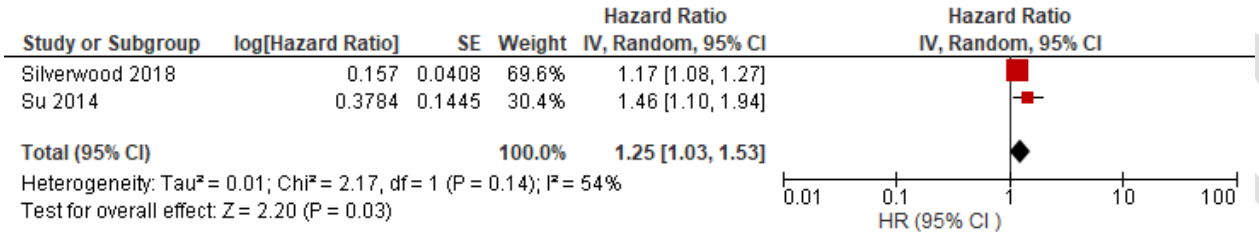

Figure: Pooled analysis of adjusted hazards ratios and 95% CIs of the association of physician-diagnosed heart failure in individuals with AD compared to non-AD controls.

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e-Table 17. GRADE EVIDENCE PROFILE- Coronary Artery Disease

Question: Is coronary artery disease associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Coronary Artery Disease (follow up: Cross-sectional; assessed with rate of CAD in AD									
1[1]	observational studies	serious [a]	not serious	not serious	not serious	none	Based on data from 1,349,671 adults, 48,140 with a diagnosis of AD, CAD was less prevalent in individuals with AD[1]: **Prevalence Ratio** 0.83 (95%CI 0.80-0.86)	⊕⊕⊕◯ MODERATE	IMPORTANT
Occurrence of Coronary Artery Disease (follow up: Cross-sectional; assessed with: risk of CAD in AD)									
4 [2-5]	observational studies	serious [b]	not serious	not serious	serious [c]	none	Based on the pooling of adjusted ORs of the association of self-reported or physician-diagnosed CAD in adults with AD compared to non-AD controls reported in 3 studies (including 5 populations), AD is not significantly associated with CAD [2-4]: **pooled OR** 1.25 (95%CI 0.77- 2.03) Based on baseline incidence data from a longitudinal study including 15,103 adults with AD and 60,412 non-AD controls, AD was associated with increased odds of physician-diagnosed CAD[5]: **OR** 1.33 (95%CI 1.24-1.41)	⊕⊕⊕◯ MODERATE	CRITICAL
Occurrence of Angina (follow up: Cross-sectional; assessed with: risk of angina in AD)									
2 [3, 6]	observational studies	serious [d]	not serious	not serious	not serious	none	Based on the pooling of adjusted ORs of the association of self-reported angina in adults with AD compared to non-AD controls in three populations reported in a single study, AD was associated with increased odds of angina[3]: **pooled OR** 1.72 (95%CI 1.37-2.15)	⊕⊕⊕◯ MODERATE	IMPORTANT

							Based on data from 36,606 adults (≥40yo) with AD and 1,144,072 non-AD controls, AD was associated with increased risk of diagnosis of angina[6]: **aRR** 1.32 (95%CI 1.26-1.38), p<0.0001		
Occurrence of Angina (follow up: up to 48 years; assessed with: risk of angina in AD)									
3 [6-8]	observational studies	not serious [e]	not serious	not serious [f]	not serious	none	In a case-control study of 104,823 individuals with a diagnosis of AD at ≥15yo and 1,022,435 matched controls followed from 1968 to 2016, AD was associated with increased risk of physician-diagnosed angina[7]: <u>Overall Odds</u> **aOR** 1.13 (95%CI 1.08- 1.19) <u>Odds by AD Severity*</u> *Non-severe AD (n= 95,274)* **aOR** 1.13 (95%CI 1.08-1.19) *Severe AD (n= 9,558*) **aOR** 1.11 (95%CI 1.00- 1.24) Based on the longitudinal analysis of 33,090 adults (≥40yo) with AD in 2005 and 1,152,607 controls without AD between 2005 and 2007, AD was associated with an increased risk of subsequent diagnosis of angina between 2008 and 2014[6]: **aRR** 1.17 (95%CI 1.12-1.23), P<0.000314 Based on data from 285,661 adults with mild AD (1,545,238 PY at risk), 145,748 adults with moderate AD (904,975 PY at risk), 19,661 adults with severe AD (125,012 PY at risk), and 1,528,477 non-AD controls (9,392,370 PY at risk), AD was associated with increased risk of unstable angina[8]: <u>Overall Risk</u> **aHR** 1.17 (95%CI 1.03- 1.32)	⊕⊕⊕⊕ HIGH	IMPORTANT

							Risk by AD Severity** *Mild AD* **aHR** 1.19 (95%CI 1.04-1.37) *Moderate AD* **aHR** 1.11 (95%CI 0.96-1.29) *Severe AD* **aHR** 1.41 (95%CI 1.02-1.95)		

AD: Atopic dermatitis**; CAD:** Coronary artery disease; **OR:** Odds ratio**; CI:** Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio; **PY:** Person-years; **NOS:** Newcastle Ottawa Scale

Explanations

a. Cross-sectional evidence; modified NOS score of 6 suggests moderate-to-low risk of bias.

b. Cross-sectional evidence; Majority of studies rely on self-reported and/or unvalidated exposure and outcome assessment and scored 6 on the modified or standard NOS suggesting moderate-to-low risk of bias (range 5-6).

c. The majority of studies report precise effect estimates consistent in magnitude and direction. A single study of hospitalized patients reports divergent results.

d. Cross-sectional evidence; Studies rely on self-reported and unvalidated exposure and outcome assessment and scored a 6 and 7 on the modified or standard NOS suggesting low-to-moderate risk of bias.

e. Majority of studies rely on self-reported and or unvalidated exposure and outcome assessment and all studies scored a 7 on the modified or standard NOS suggesting low risk of bias.

f. One study included participants aged ≥15yo at baseline but noted an average age at the end of the study of 41.0 + 16.7yo suggesting alignment with the research question focused on AD in adults.

e-Figure 8a. Occurrence of CAD in AD (pooled adjusted ORs)

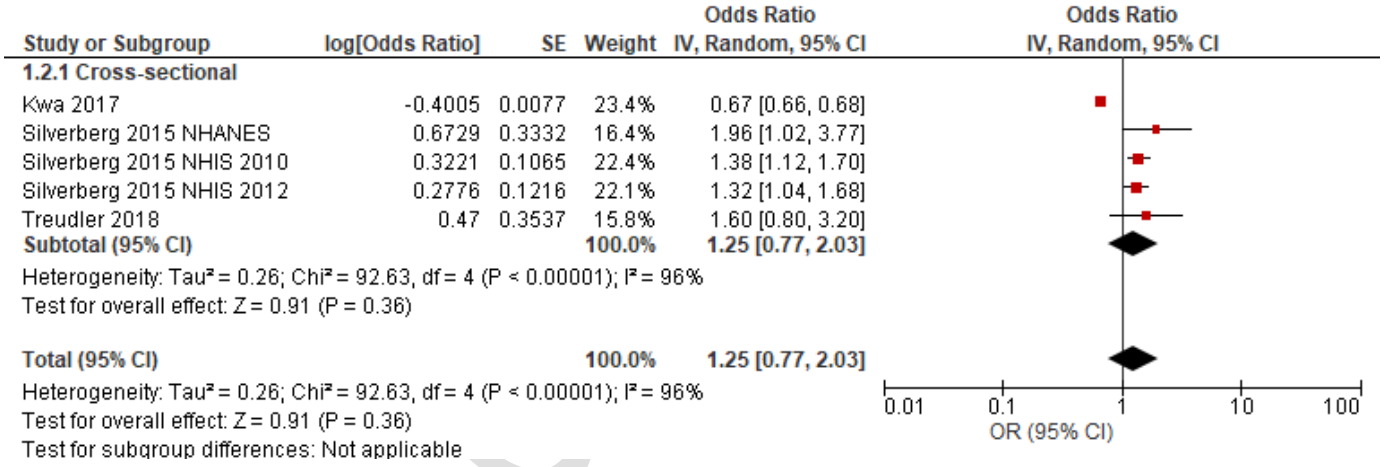
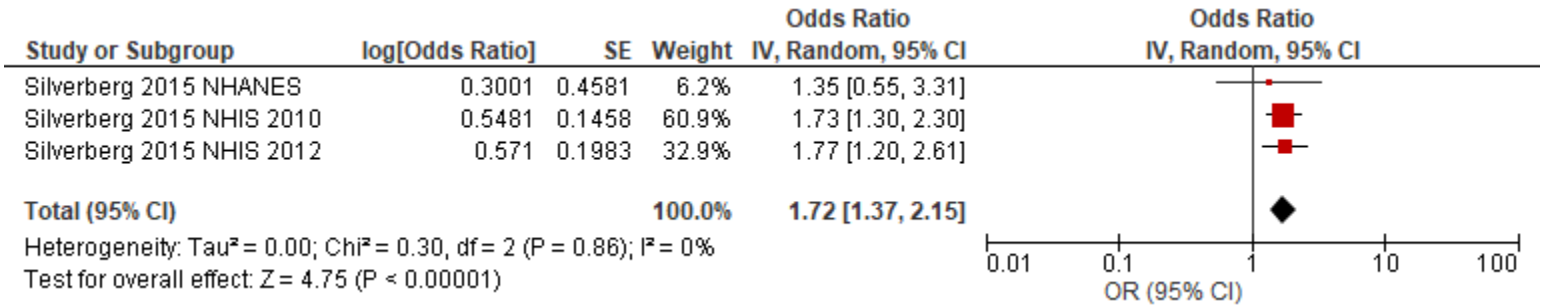


Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of self-reported or physician-diagnosed coronary artery disease in individuals with AD compared to non-AD controls.



e-Figure 8b. Occurrence of Angina in AD (pooled adjusted ORs)

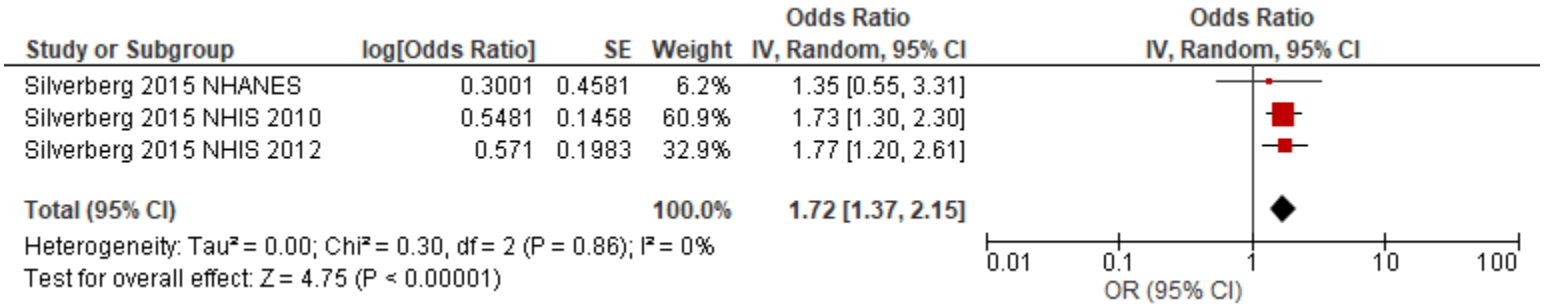


Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of self-reported angina in individuals with AD compared to non-AD controls.

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e-Table 18. GRADE EVIDENCE PROFILE- Circulatory Disease

Question: Is circulatory disease associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Occurrence of Circulatory Disease (follow up: Cross-sectional; assessed with: risk of PVD or PAD in AD)									
2 [1-3]	observational studies	serious [a]	not serious	not serious	not serious	none	Based on data from 72,651,487 adult discharges from US hospitals (weighted frequency of admissions for AD was 789,488), adults hospitalized with a primary or secondary diagnosis of AD had increased odds of physician-diagnosed PVD[1]: **aOR** 1.07 (95%CI 1.04- 1.11), p<0.0001 Based on data from 2,485 adults (≥20yo) with AD and 32,067 non-AD controls, adults with AD had increased odds of a history of PVD[3]: **aOR** 2.07 (1.79-2.40), p<0.0001 Based on data from 36,606 adults (≥40yo) with AD and 1,144,072 non-AD controls, AD was associated with increased risk of PAD[2]: <u>Overall Risk</u> **aRR** 1.16 (95%CI 1.13- 1.20), p<1.00 x 10^{-16} <u>Risk by AD Severity*</u> *Mild AD (n= 11,921)* **aRR** 1.15 (95%CI 1.09-1.22), p= 6.74 x 10^{-7} *Moderate AD (n=18,399)* **aRR** 1.14 (95%CI 1.09-1.19), p=5.18 x 10^{-9} *Severe AD (n=6,286)* **aRR** 1.26 (95%CI 1.17-1.35), p=2.63 x 10^{-10}	⊕⊕⊕◯ MODERATE	CRITICAL
Occurrence of Circulatory Disease (follow up: 6 years; assessed with: risk of PAD in AD)									
1 [2]	observational studies	serious [b]	not serious	not serious	not serious	none	Based on the longitudinal analysis of 31,150 adults (≥40yo) with AD in 2005 and 1,100,250 controls without AD between 2005 and 2007, AD was	⊕⊕⊕◯ MODERATE	CRITICAL

							associated with an increased risk of subsequent PAD diagnosis between 2008 and 2014: **aRR** 1.15 (95%CI 1.11-1.19), p= 3.18 x 10^{-13}		
Occurrence of Venous Thromboembolism (follow up: Cross-sectional; assessed with: odds of thrombosis and embolism in AD)									
1 [4]	observational studies	serious [c]	not serious	not serious	not serious	none	Based on data from 72,512,581 adult hospitalizations, including 164,822 with a primary or secondary diagnosis of AD, AD was associated with increased risk of VTE, including DVT and PE: *VTE* **aOR** 1.22 (1.17-1.27) *DVT* **aOR** 1.28 (1.22-1.33) *PE* **aOR** 1.08 (1.02-1.15)	⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis**; PVD:** Peripheral vascular disease; **PAD:** Peripheral arterial disease; **OR:** Odds ratio**; CI:** Confidence interval; **RR:** Risk ratio; **VTE:** Venous thromboembolism; **DVT:** Deep vein thrombosis; **PE:** Pulmonary embolus; **NOS:** Newcastle Ottawa Scale

***** AD severity determined by prescribed treatments: Mild AD- No anti-inflammatory treatment prescribed; Moderate AD- Topical treatment prescribed; Severe AD: Both topical & systemic treatment prescribed.

Explanations

a. Cross-sectional evidence; Studies rely on unvalidated or self-reported exposure and outcome assessment; modified and standard NOS scores of 6 suggest a moderate risk of bias.
b. Study relied on unvalidated exposure and outcome assessment, included a short follow-up period, and did not have data necessary to adjust for all outcome important factors, suggesting a moderate risk of bias (NOS score of 6).
c. Cross-sectional evidence; Study relied on unvalidated exposure and outcome assessment; modified NOS score of 6 suggests a moderate risk of bias.

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e-Table 19. GRADE EVIDENCE PROFILE- Myocardial Infarction

Question: Is myocardial infarction associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Occurrence of Myocardial Infarction (follow up: Cross-sectional; assessed with: risk of MI in AD)									
7 [1-7]	observational studies	serious [a]	not serious [b]	not serious	serious [c]	none	Based on the pooling of adjusted ORs of the association of self-reported or physician-diagnosed MI in adults with AD compared to non-AD controls reported in 6 studies (including 8 study populations), AD is not associated with MI[1-6]: **pooled aOR** 0.98 (95%CI 0.68- 1.41) Based on data from 36,606 adults (≥40 yo) with AD and 1,144,072 non-AD controls, AD was not associated with MI[7]: <u>Overall Risk</u> **aRR** 0.98 (95%CI 0.91-1.06), p=0.66 <u>Risk by AD Severity*</u> *Mild AD (n= 11,921)* **aRR** 0.95 (95%CI 0.82-1.09), p=0.42 *Moderate AD (n=18,399)* **aRR** 0.95 (95%CI 0.86-1.06), p=0.38 *Severe AD (n=6,286)* **aRR** 1.12 (95%CI 0.94-1.33), p=0.192 Based on data from 3,317 adults with mild AD compared to 33,170 general population controls and 4,620 adults with severe AD compared to 46,200 general population controls, AD of any severity** was not significantly associated with MI[3]: *Mild AD* **aOR** 0.88 (95%CI 0.63- 1.23), p=0.47 *Severe AD* **aOR** 1.23 (95%CI 0.98- 1.54), p=0.07	⊕⊕◯◯ LOW	CRITICAL
Occurrence of Myocardial Infarction (follow up: up to 15 years; assessed with: risk of MI in AD)									
6 [7-12]	observational studies	serious [d]	not serious [e]	not serious [f]	serious [g]	none	Based on the pooling of adjusted HRs of the association of physician-diagnosed MI in individuals with AD compared to non-AD controls reported in 3 studies with follow-up ranging from one to 15 years, AD was not associated with an significant increased risk of MI [8-10]:	⊕⊕◯◯ LOW	CRITICAL

							pooled aHR 1.29 (95%CI 0.92- 1.79) Based on the longitudinal analysis of 33,534 adults (≥40 yo) with AD in 2005 and 1,173,679 controls without AD between 2005 and 2007, AD was not significantly associated with an increased risk of subsequent MI between 2008 and 2014 [7]: **aRR** 1.05 (95%CI 0.99 - 1.12), p=0.127 In a case-control study of 104,823 individuals with a diagnosis of AD at ≥15 yo and 1,022,435 matched controls followed from 1968 to 2016, AD was associated with increased odds of non-fatal MI. Increased odds of MI were not associated with increasing AD severity[11]: <u>Overall Odds</u> **aOR** 1.07 (95%CI 1.02- 1.12) <u>Odds by Severity***</u> *Non-severe AD (n= 95,274)* **aOR** 1.07 (95%CI 1.02 - 1.13) Severe AD (n= 9,558) **aOR** 1.03 (95%CI 0.92 - 1.15) Based on data from 285,661 adults with mild AD (1,544,463 PY at risk), 145,648 adults with moderate AD (900,472 PY at risk), 19,635 adults with severe AD (124,279 PY at risk)****, and 1,528,477 non-AD controls (9,361,522 PY at risk), severe AD was associated with an increased risk of MI[9]: *Mild AD* **aHR** 1.00 (95%CI 0.91 - 1.10) *Moderate AD* **aHR** 1.07 (95%CI 0.97 - 1.18) *Severe AD* **aHR** 1.37 (95%CI 1.12 - 1.68) Based on data from 26,898 individuals with mild AD** diagnosed at ≥15 yo, 2,527 individuals with severe AD** diagnosed at ≥15 yo, and 145,372 non-AD controls followed for 15 years, incidence of MI was reduced in patients with mild AD but increased in patients with severe AD compared to controls[12]: <u>Incidence Rates</u> *Controls* 4.75 (95%CI 4.39-5.14) per 10,000 PY *Mild AD* 4.58 (95%CI 3.75-5.58) per 10,000 PY		

							Severe AD 20.3 (95%CI 14.02- 29.42) per 10,000 PY <u>Incidence Rate Ratios</u> *Mild AD* **aIRR** 0.73 (95%CI 0.59-0.91), p<0.05 *Severe AD* **aIRR** 1.06 (95%CI 0.72-1.56), p=0.761		

AD: Atopic dermatitis**; MI:** Myocardial infarction**; OR:** Odds ratio**; CI:** Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio; **IRR:** Incidence rate ratio; **PY:** Person-years; **NOS:** Newcastle Ottawa Scale

*****AD severity determined by prescribed treatments: Mild AD- No anti-inflammatory treatment prescribed; Moderate AD- Topical treatment prescribed; Severe AD: Both topical & systemic treatment prescribed.
** AD severity determined by prescription of systemic therapy; Mild AD - no systemic therapy; Severe AD- Patients were classified with severe disease if they received systemic therapy for AD.
*** AD classified as severe if the patient was prescribed systemic treatment or treated in a dermatological ward with AD as main diagnosis; All other AD classified as non-severe
**** AD severity determined by prescribed treatments: Mild AD as default severity if not meeting the following criteria for moderate or severe AD; Moderate AD- prescription of two potent topical corticosteroid treatments within 1 year or calcineurin inhibitor treatment; Severe AD- prescription of systemic treatment, phototherapy, or referral for AD.

Explanations
a. Cross-sectional evidence; All studies relied on self-reported or unvalidated exposure and outcome assessment; Studies scored between 5 and 6 on the standard or modified NOS scales suggesting a moderate-to-low risk of bias.
b. I^2 of 96% for the pooled OR analysis suggests heterogeneity, but all effect estimates are consistent in magnitude and direction, suggesting borderline inconsistency.
c. All reported effect estimates include CIs consistent with the possibility of no risk difference and increased risk.
d. Most studies relied on self-reported or unvalidated exposure and/or outcome assessment; modified and standard NOS scores ranged from 6-7 suggesting moderate-to-low risk of bias.
e. Pooled HR analysis has an I^2 of 76% suggesting moderate heterogeneity, but the effect estimates, and associated CIs, reported across the majority of included studies are similar in magnitude and direction, suggesting borderline inconsistency.
f. One study included participants aged ≥15 yo at baseline but noted an average age at the end of the study of 41.0 + 16.7 yo; One study included participants aged ≥15 yo at baseline but noted an average age of at least 23.8 yo across the 3 study cohorts; One study followed a birth cohort for a median of 15.1 years but recorded the median age of MI in the AD cohort of 48.2 yo; Mean age of participants in these studies suggests alignment with the research question focused on AD in adults.
g. Majority of effect estimates include CIs consistent with no difference and important difference in risk.

e-Figure 9a. Occurrence of MI in AD (pooled adjusted ORs)

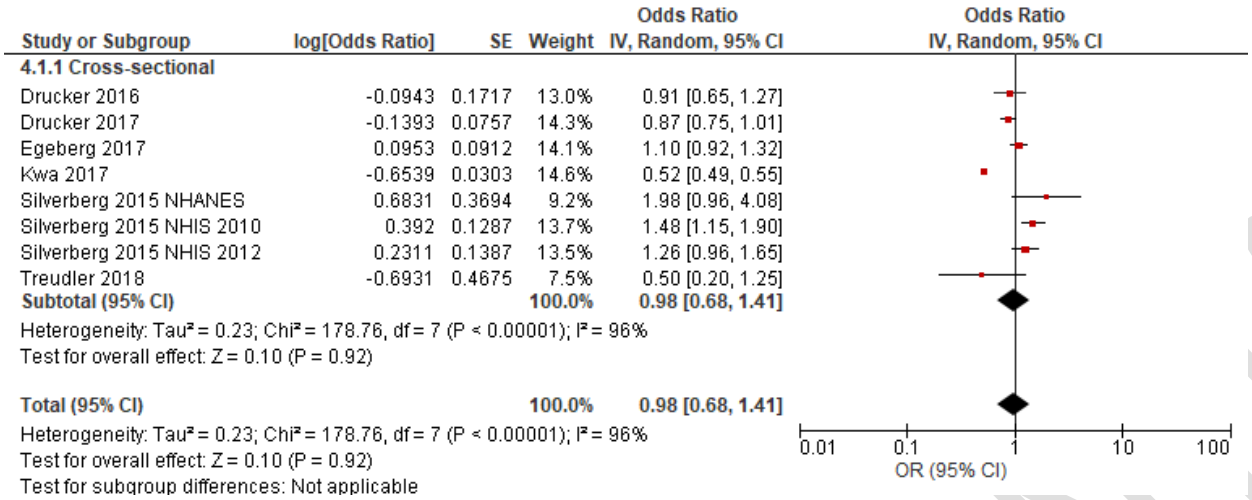

Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of self-reported or physician-diagnosed MI in individuals with AD compared to non-AD controls.

e-Figure 9b. Occurrence of MI in AD (pooled adjusted HRs)

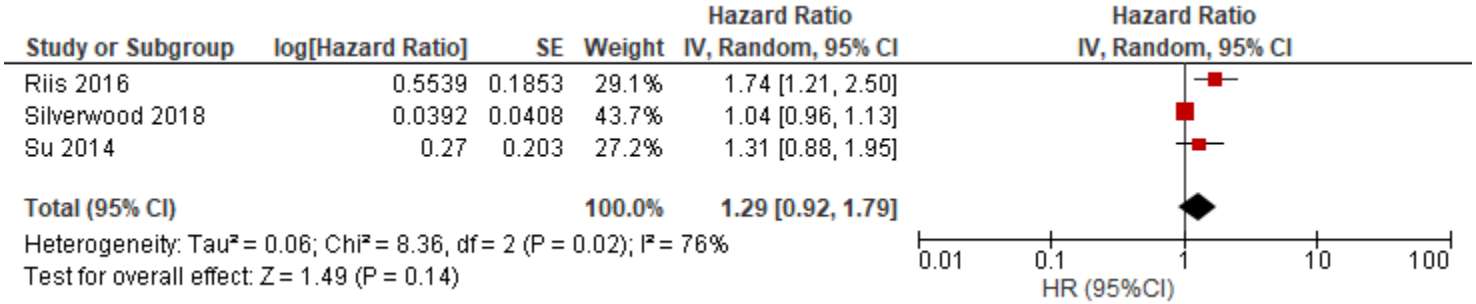

Figure: Pooled analysis of adjusted hazard ratios and 95% CIs of the association of physician-diagnosed MI in individuals with AD compared to non-AD controls.

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e-Table 20. GRADE EVIDENCE PROFILE- Stroke

Question: Is stroke associated with AD in adults?

№ of studies	Certainty assessment					Impact		Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Occurrence of Stroke (follow up: Cross-sectional; assessed with: risk of stroke in AD)									
7 [1-7]	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	Based on the pooling of adjusted ORs of the association of self-reported or physician-diagnosed stroke in adults with AD compared to non-AD controls reported in 6 studies (including 8 populations), AD is not associated with significantly increased odds of stroke[1-6]: **pooled OR** 1.12 (95%CI 0.80- 1.55) Based on data from 36,606 adults (≥40yo) with AD and 1,144,072 non-AD controls, AD was not significantly associated with increased risk of non-fatal stroke[7]: <u>Overall Risk</u> **aRR** 1.05 (95%CI 1.00 -1.11), p=0.032 <u>Risk by AD Severity*</u> *Mild AD (n= 11,921)* **aRR** 1.03 (95%CI 0.94-1.12), p=0.032 *Moderate AD (n=18,399)* **aRR** 1.05 (95%CI 0.99-1.13), p=0.118 *Severe AD (n=6,286)* **aRR** 1.08 (95%CI 0.96-1.21), p=0.209 Based on data from 3,317 adults with mild AD** compared to 33,170 general population controls and 4,620 adults with severe AD compared to 46,200 general population controls, severe but not mild AD was associated with significantly increased odds of stroke[3]: *Mild AD* **aOR** 1.23 (95%CI 0.94 - 1.60), p=0.134 *Severe AD* **aOR** 1.45 (95%CI 1.19- 1.77), p=0.0002	⊕◯◯◯ VERY LOW	CRITICAL
Occurrence of Stroke (follow up: up to 12 years; assessed with: risk of stroke in AD)									
7 [7-13]	observational studies	serious [d]	not serious [e]	not serious [f]	serious [g]	dose response gradient [h] (*not upgraded)*	Based on the pooling of adjusted HRs of the association of physician-diagnosed stroke in adults with AD compared to non-	⊕⊕◯◯ LOW	CRITICAL

							AD controls reported in 3 studies with follow-up ranging from 1 to 12 years, AD was associated with an increased risk of stroke[8-10]: **pooled HR** 1.13 (95%CI 1.10- 1.16) Based on the longitudinal analysis of 33,090 adults (≥40yo) with AD in 2005 and 1,152,607 controls without AD between 2005 and 2007, AD was not associated with a significantly increased risk of subsequent non-fatal stoke between 2008 and 2014[7]: **aRR** 1.02 (95%CI 0.98-1.07), p=0.35 Based on data from 20,323 adults (≥20yo) newly diagnosed with AD between 2005 and 2008 and 20,323 matched controls without an AD diagnosis followed through 2009, individuals with AD had an increased risk of ischemic stroke during follow up and and increasing risk of stroke was associated with increasing AD severity[11]: <u>Overal Risk</u> **aHR** 1.33 (95%CI 1.12-1.59), p=0.001 <u>Risk by AD Severity***</u> *Mild AD (n=17,328)* **aHR** 1.20 (95%CI 1.00-1.45), p=0.052 *Moderate AD (n=2,256)* **aHR** 1.64 (1.23- 2.19), p=0.001 *Severe AD (n=739)* **aHR** 1.71 (95%CI 1.15-2.56), p=0.008 In a case-control study of 104,823 individuals with a diagnosis of AD at ≥15yo and 1,022,435 matched controls followed from 1968 to 2016, overall, AD was not associated with significantly increased odds of non-fatal ischemic stroke, but severe AD was associated with increased odds of stroke[12]: <u>Overall Odds</u> **aOR** 1.04 (95%CI 0.99- 1.09) <u>Odds by Severity****</u> *Non-severe AD (n= 95,274)* **aOR** 1.00 (95%CI 0.94 - 1.06) *Severe AD (n= 9,558*) **aOR** 1.19 (95%CI 1.07 - 1.33)		

							Based on data from 15,103 individuals diagnosed with AD between 2000 and 2006 and 60,412 matched controls without AD followed through 2011, individuals diagnosed with AD had an increased risk of subsequent ischemic stroke but not hemorrhagic stroke. Severity of AD was significantly correlated with risk of stroke (ischemic or hemorrhagic)[9]: <u>Overall Risk</u> *Ischemic stroke* **aHR** 1.21 (95%CI 1.08-1.36) *Hemorrhagic stroke* a**HR** 0.97 (95%CI 0.74-1.29) *All Stroke* a**HR** 1.17 (1.06-1.30), p<0.01 <u>Risk by AD Severity*****</u> *Mild AD* **aHR** 1.08 (95%CI 0.97-1.20), p<0.01 *Moderate AD* **aHR** 6.02 (95%CI 4.13-8.76), p<0.001 *Severe AD* **aHR** 19.82 (95%CI 12.23-32.13), p<0.001 Based on data from 285,661 adults with mild AD (1,543,768 PY at risk), 145,627 (900,587 PY at risk) adults with moderate AD******, 19,622 adults with severe AD (124,394 PY at risk), and 1,528,477 non-AD controls (9,361,252 PY at risk), moderate and severe AD were associated with increased risk of stroke[8]: *Mild AD* **aHR** 1.06 (95%CI 0.97-1.15) *Moderate AD* **aHR** 1.09 (95%CI 1.00-1.20) *Severe AD* **aHR** 1.20 (95%CI 0.99-1.46) Based on data from 26,898 individuals with mild AD** diagnosed at ≥15yo, 2,527 individuals with severe AD diagnosed at ≥15yo, and 145,372 non-AD controls followed for 15 years, incidence of ischemic stroke was reduced in patients with mild AD but increased in patients with severe AD compared to controls[13]: <u>Incidence Rates</u> *Controls* 6.74 (95%CI 6.31-7.21) per 10,000 PY *Mild AD* 6.95 (95%CI 5.91-8.17) per 10,000 PY *Severe AD* 26.98 (95%CI 19.55- 37.242) per 10,000 PY <u>Incidence Rate Ratios</u> *Mild AD* **aIRR** 0.82 (95%CI 0.68-0.98), p<0.05		

							Severe AD **aIRR** 1.19 (95%CI 0.85-1.65), p=0.32		

AD: Atopic dermatitis**; OR:** Odds ratio**; CI:** Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio; **IRR:** Incidence rate ratio; **PY:** Person-years; **NOS:** Newcastle Ottawa Scale

*****AD severity determined by prescribed treatments: Mild AD- No anti-inflammatory treatment prescribed; Moderate AD- Topical treatment prescribed; Severe AD: Both topical & systemic treatment prescribed.
** AD severity determined by prescription of systemic therapy; Mild AD - no systemic therapy; Severe AD- Patients were classified with severe disease if they received systemic therapy for AD.
*** AD severity classified by Defined Daily Dose (DDD) and/or the number of DDs, total amount of drug/amount of drug in a DDD of oral antihistamines and corticosteroids (the average daily adult maintenance dose of a drug recommended for a given indication); Mild AD= <28 DDDs; Moderate AD= greater than or equal to 28 DDs of oral antihistamines and < 28 DDs of oral corticosteroids; Severe AD= at least 28 DDDs of oral corticosteroids.
**** AD classified as severe if the patient was prescribed systemic treatment or treated in a dermatological ward with AD as main diagnosis; All other AD classified as non-severe.
*****AD severity classified by the number of clinical visits for AD; Mild AD= <10 clinical visits for AD; Moderate AD= 10-19 clinical visits for AD; Severe AD= 20 or more clinical visits for AD.
****** AD severity determined by prescribed treatments: Mild AD as default severity if not meeting the following criteria for moderate or severe AD; Moderate AD- prescription of two potent topical corticosteroid treatments within 1 year or calcineurin inhibitor treatment; Severe AD- prescription of systemic treatment, phototherapy, or referral for AD.

Explanations
a. Cross-sectional evidence; Majority of studies rely on self-reported or unvalidated exposure and/or outcome assessment; All studies scored between a 5 and 6 on the modified or standard NOS suggesting a moderate risk of bias.
b. Estimates of risk of stroke in AD varied in direction across studies included in the pooled OR analysis (I^2= 95%).
c. Reported effect estimates include CIs consistent with the possibility of no risk difference and increased risk.
d. Studies relied on self-reported or unvalidated exposure and/or outcome assessment; Studies scored between 5 and 7 on the standard or modified NOS suggesting a moderate-to-low risk of bias.
e. Studies largely report consistent magnitude of effects and consistent trends in the association between AD severity and risk of stroke; I^2 for pooled HRs in 0% suggesting limited heterogeneity among the studies pooled in the analysis.
f. One study included participants aged ≥15yo at baseline but noted an average age at the end of the study of 41.0 + 16.7yo; One study included participants aged ≥15 yo at baseline but noted an average age of at least 23.8yo across the 3 study cohorts; Mean age of participants in these studies suggests alignment with the research question focused on AD in adults; One study included individuals with newly diagnosed dermatitis which may include conditions other than atopic dermatitis, suggesting borderline indirectness.
g. Estimates of the association of AD severity with risk of stroke are imprecise across the included studies largely providing effect estimates with CIs consistent with the possibility of no risk difference and both decreased and increased risk.
h. Increasing magnitude of risk of stroke with increasing AD severity documented across the studies in the evidence base suggests a dose response gradient; However, the imprecision of reported effect estimates precluded upgrading.

e-Figure 10a. Occurrence of Stroke in AD (pooled adjusted ORs)

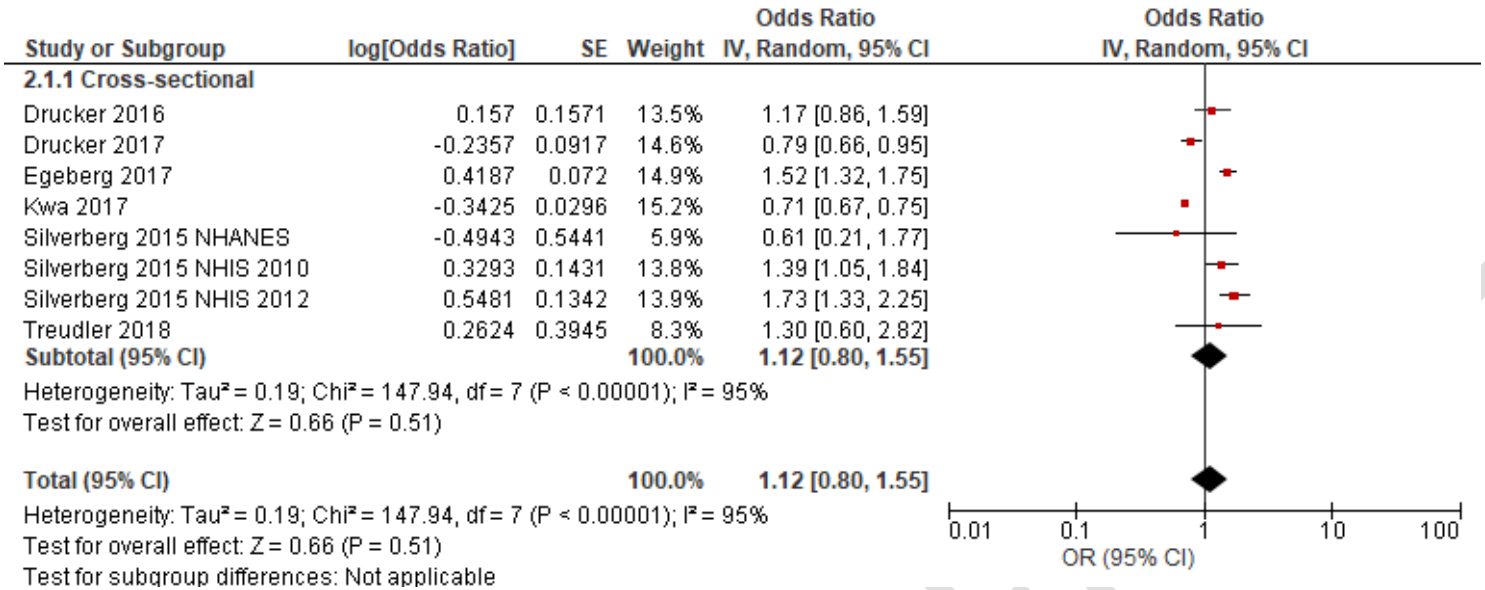

Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of any self-reported or physician-diagnosed stroke in individuals with AD compared to non-AD controls.

e-Figure 10b. Occurrence of Stroke in AD (pooled adjusted HRs)

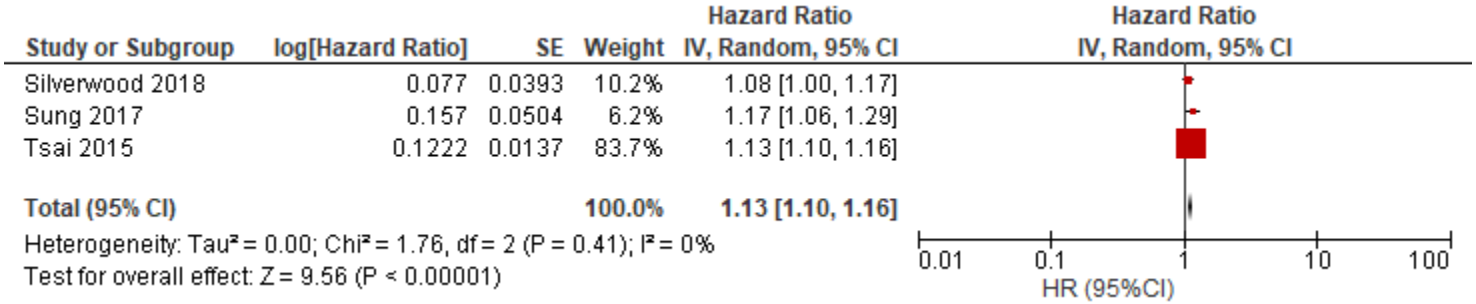

Figure: Pooled analysis of adjusted hazard ratios and 95% CIs of the association of any physician-diagnosed stroke in individuals with AD compared to non-AD controls.

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e-Table 21. GRADE EVIDENCE PROFILE- Cardiovascular Death

Question: Is cardiovascular death associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Occurrence of Cardiovascular Death (follow up: up to 15 years; assessed with: risk of cardiovascular death in AD)									
4 [1-4]	observational studies	not serious [a]	serious [b]	not serious [c]	serious [d]	none	Based on the pooling of adjusted HRs of the association of physician-diagnosed cardiovascular death in adults with AD compared to non-AD controls reported in 2 studies (follow up of up to 4 years and a median of 5.1 years), AD is not significantly associated with increased odds of cardiovascular death[1, 2]: **pooled HR** 1.15 (95%CI 0.77-1.71) Based on data from 285,661 adults with mild AD* (1,554,072 PY at risk), 145,947 adults with moderate AD(910,385 PY at risk), 19,696 adults with severe AD (125,849 PY at risk), and 1,528,477 non-AD controls (9,427,420 PY at risk), only severe AD was significantly associated with increased risk of physician-diagnosed cardiovascular death[1]: *Mild AD* **aHR** 0.90 (95%CI 0.83-0.98) *Moderate AD* **aHR** 1.01 (95%CI 0.93-1.10) *Severe AD* **aHR** 1.30 (95%CI 1.10-1.53) In a case-control study of 104,823 individuals with a diagnosis of AD at ≥15yo and 1,022,435 matched controls followed from 1968 to 2016, AD was not significantly associated with increased odds of death from MI or stroke[3]: Overall Odds **aOR** 1.01 (95%CI 0.93- 1.10) Odds by AD Severity** *Non-severe AD (n= 95,274)* **aOR** 0.99 (95%CI 0.90 - 1.10)	⊕⊕◯◯ LOW	CRITICAL

							Severe AD (n= 9,558) **aOR** 1.04 (95%CI 0.88 - 1.23) Based on data from 26,898 individuals with mild AD*** diagnosed at ≥15yo, 2,527 individuals with severe AD diagnosed at ≥15yo, and 145,372 non-AD controls followed for 15 years, incidence of physician-diagnosed cardiovascular death was increased in patients with mild and severe AD compared to controls[4]: <u>Incidence Rates</u> *Controls* 5.60 (5.21-6.03) per 10,000 PY *Mild AD* 7.66 (6.57-8.94) per 10,000 PY *Severe AD* 29.35 (21.65-39.87) per 10,000 PY <u>Incidence Rate Ratios</u> *Mild AD* **aIRR** 0.71 (95%CI 0.60-0.84), p<0.001 *Severe AD* **aIRR** 1.06 (95%CI 0.77-1.46), p=0.72		

AD: Atopic dermatitis**; OR:** Odds ratio**; CI:** Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio; **IRR:** Incidence rate ratio; **PY:** Person-years; **NOS:** Newcastle Ottawa Scale

***** AD severity determined by prescribed treatments: Mild AD as default severity if not meeting the following criteria for moderate or severe AD; Moderate AD- prescription of two potent topical corticosteroid treatments within 1 year or calcineurin inhibitor treatment; Severe AD- prescription of systemic treatment, phototherapy, or referral for AD.
** AD classified as severe if the patient was prescribed systemic treatment or treated in a dermatological ward with AD as main diagnosis; All other AD classified as non-severe.
*** AD severity determined by prescription of systemic therapy; Mild AD - no systemic therapy; Severe AD- Patients were classified with severe disease if they received systemic therapy for AD.

Explanations
a. All studies relied on self-reported or unvalidated exposure and/or outcome assessment; Two studies included minimal follow up; All studies scored a 7 on the NOS suggesting a low risk of bias.
b. Results across the evidence base differ in direction.
c. One study included participants aged ≥15yo at baseline but noted an average age at the end of the study of 41.0 + 16.7yo; One study included participants aged ≥15 yo at baseline but noted an average age of at least 23.8yo across the 3 study cohorts; Mean age of participants in these studies suggests alignment with the research question focused on AD in adults.
d. The pooled HR and most effect estimates reported across the included studies include CIs consistent with the possibility of no risk difference, increased risk, and decreased risk.

e-Figure 11. Occurrence of Cardiovascular Death in AD (pooled adjusted HRs)

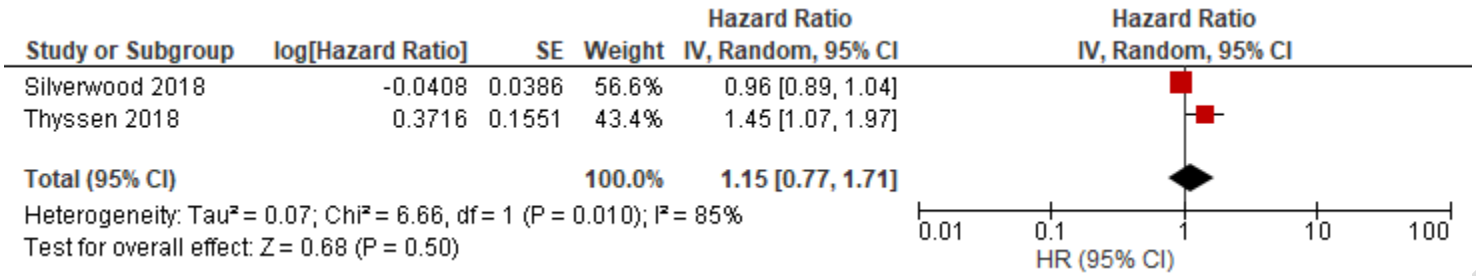

Figure: Pooled analysis of adjusted hazards ratios and 95% CIs of the association of physician-diagnosed cardiovascular death in individuals with AD compared to non-AD controls.

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e-Table 22. GRADE EVIDENCE PROFILE- Obesity

Question: Is obesity associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Obesity (follow up: Cross-sectional; assessed with: rate of obesity^ in AD)									
3 [1-3]	observational studies	serious [a]	serious [b]	not serious	not serious	none	Based on data from 1,349,671 adults, 48,140 with a diagnosis of AD, obesity was more prevalent in individuals with AD[2]: **Prevalence Ratio** 1.17 (95%CI 1.13-1.20) Based on data from 253 adults with persistent AD (diagnosed at <18yo and persisting into adulthood) or adult onset AD (diagnosed at ≥18yo), prevalence of obesity was 1.6% in the AD cohort.[1] Based on data from 3,445 adults with mild AD*, 2,361 adults with moderate AD and 380 adults with severe AD, prevalence of physician-diagnosed obesity increased significantly with increasing AD severity[3]: *Mild AD* 13.6% *Moderate AD* 19.3% *Severe AD* 32.9% p<0.001 (also significant for pairwise comparisons)	⊕⊕◯◯ LOW	IMPORTANT
Occurrence of Obesity (follow up: Cross-sectional; assessed with: risk of obesity^ in AD)									
9 [4-12]	observational studies	serious [c]	not serious [d]	not serious	not serious	none	Based on the pooling of adjusted ORs of the association of self-reported or physician-diagnosed obesity in adults with AD compared to non-AD controls reported in 5 studies (including 6 study populations), AD is associated with increased odds of obesity[4-7, 12]:	⊕⊕⊕◯ MODERATE	CRITICAL

							pooled OR 1.36 (95%CI 1.01-1.83) Based on data from 602 adults with AD and 7,615 non-AD controls, AD was not significantly associated with increased risk of current obesity[8]: **aRR** 1.11 (95%CI 0.95-1.26), p=0.15 Based on data from 1,319 adults (≥19yo) with AD and 45,770 non-AD controls, AD was not associated with obesity[9]: **OR** 0.89 (95% CI 0.76- 1.04) In a case-control study of 2,090 adults, including 277 obese individuals, obesity was associated with increased odds of AD[10]: **aOR** 1.43 (95%CI 1.08- 1.89), p=0.01 Based on data from 785 obese adults (aged 20-44yo) and 8,601 non-obese adults, obesity was not associated with AD[11]: **OR** 0.99 (95%CI 0.49-1.97)		

AD: Atopic dermatitis**; OR:** Odds ratio**; CI:** Confidence interval; **RR:** Risk ratio; **NOS:** Newcastle Ottawa Scale

^ Study Definitions of Obesity

Study	**Definition of Obesity**
Kwa 2017	Diagnostic codes (AHRQ comorbidity measures and ICD 9)
Lee 2017	BMI ≥25 kg/m^2
Luo 2013	BMI≥ 28.0 kg/m^2
Megna 2017	undefined
Radtke 2017	ICD 10 Diagnostic Code
Ronmark 2016	BMI ≥30 kg/m^2
Shalom 2019	Appendix S2 provides an incomplete definition of obesity (sentence containing BMI parameter for obesity is incomplete)
Sicras-Mainar 2018	International Classification of Primary Care, Second Edition code T82
Silverberg 2012	BMI ≥30 kg/m^2

Silverberg 2015	Class I obesity (BMI 30-34); Class II obesity (BMI ≥35)
Silverberg 2018	Self-reported physician-diagnosis of obesity
Sybilski 2015	BMI ≥30 kg/m^2

*Classification of AD severity according to prescribed treatment: Mild AD- prescription of emollients or low/medium potency topical corticosteroids; Moderate AD-prescription of calcineurin inhibitors, high-potency topical corticosteroids, monotherapy with UV radiation, or oral corticosteroids; Severe AD-prescription of immunosuppressants, biologics, or hospitalization for AD.

Explanations

a. Cross-sectional evidence; Majority of studies relied on unvalidated exposure and outcome assessment; One study restricted cases of AD to those diagnosed by a physician with >15 years' experience; modified NOS scores from 4 to 6 suggest moderate-to-high risk of bias.
b. Reported prevalence of obesity varies across studies.
c. Cross-sectional evidence; Majority of included studies relied on self-reported or unvalidated exposure and/or outcome assessment; studies scored between a 5 and 6 on the modified or standard NOS suggesting moderate risk of bias.
d. Findings on the association of AD and obesity varied across the included studies with 6/9 studies reporting increased risk of obesity in AD and 3/9 studies reporting decreased risk; these findings suggest borderline imprecision.

e-Figure 12. Occurrence of Obesity in AD (pooled adjusted ORs)

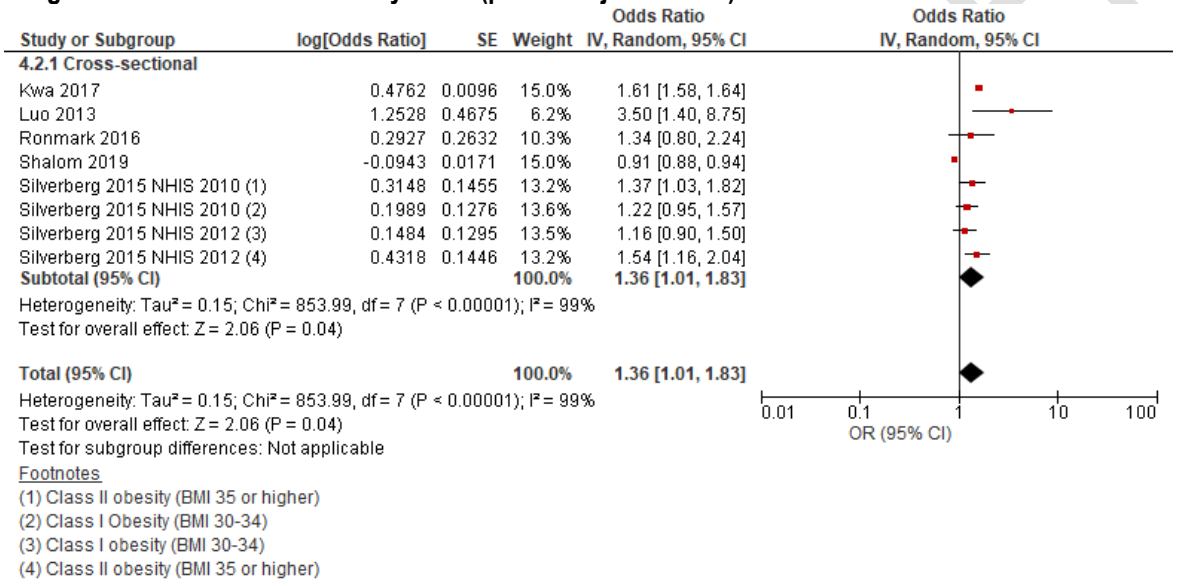

Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of self-reported or physician-diagnosed obesity in individuals with AD compared to non-AD controls.

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e-Table 23. GRADE EVIDENCE PROFILE- Dyslipidemia

Question: Is dyslipidemia associated with AD in adults?

№ of studies	Certainty assessment						impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Dyslipidemia (follow up: Cross-sectional; assessed with: rate of hyperlipidemia or dyslipidemia in AD)									
3 [1-3]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	Based on data from 1,349,671 adults, 48,140 with a diagnosis of AD, hyperlipidemia was significantly less prevalent in individuals with AD[1]: **Prevalence Ratio** 0.94 (95%CI 0.91-0.95) Based on data from 3,445 adults with mild AD*, 2,361 adults with moderate AD and 380 adults with severe AD, prevalence of physician-diagnosed dyslipidemia increased significantly with increasing AD severity[2]: *Mild AD* prevalence 28.6% *Moderate AD* prevalence 39.1% *Severe AD* prevalence 53.7% p<0.001 (also significant for pairwise comparisons) Based on data from 252 adults with persistent AD (diagnosed at <18yo and persisting into adulthood) or adult onset AD (diagnosed at ≥18yo), prevalence of hypercholesterolemia and hypertriglyceridemia were 2.4% and 1.2%, respectively in the AD cohort.[3]	⊕⊕⊕◯ MODERATE	IMPORTANT
Occurrence of Hypercholesterolemia (follow up: Cross-sectional; assessed with: odds of high cholesterol and/or hyperlipidemia in AD)									
11 [4-14]	observational studies	serious [c]	not serious [d]	not serious	not serious [e]	none	Based on the pooling of adjusted ORs of the association of self-reported or physician-diagnosed hypercholesterolemia in adults with AD compared to non-AD controls reported in 3 studies, AD is associated with	⊕⊕⊕◯ MODERATE	CRITICAL

							increased odds of hypercholesterolemia[4, 5, 14]: **pooled OR** 1.13 (95%CI 1.09- 1.18) Based on the pooling of crude incidence data from 135,255 adults with AD and 4,689,098 non-AD controls reported in 6 studies, AD was not significantly associated with increased odds of hypercholesterolemia[6-10, 13]: **OR** 1.08 (95%CI 0.84- 1.40) Based on data from 94 men with AD and 128 women with AD compared to 4,785 non-AD controls, decreased HDL (< 40 mg/dl in men and < 50 mg/dl in women) was not significantly associated with AD in either sex [11]: *Women* a**OR** 1.31 (95%CI 0.86-1.99) *Men* **aOR** 1.01 (95%CI 0.53-1.89) Based on data from 3,317 adults with mild AD** compared to 33,170 general population controls and 4,620 adults with severe AD compared to 46,200 general population controls, severe but not mild AD was associated with increased odds of hypercholesterolemia[4]: *Mild AD* **aOR** 0.96 (95%CI 0.84-1.09) *Severe AD* **aOR** 1.22 (95%CI 1.11-1.34) Based on data from 7,471 adult males with mild AD*** and 2,606 males with moderate-to-severe AD, those with hyperlipidemia were more likely to have moderate-to-severe AD[12]: **aOR** 1.51 (95%CI 1.13-2.02), p=0.005		

Occurrence of Hypertriglyceridemia (follow up: Cross-sectional; assessed with: odds of hypertriglyceridemia [(≥ 150 mg/dl or taking medications for hypertriglyceridemia] in AD)									
1 [11]	observational studies	serious [f]	not serious	not serious	serious [g]	none	Based on data from 94 men with AD and 128 women with AD compared to 4,785 non-AD controls, AD was associated with increased odds of hypertriglyceridemia in women[11]: *Women* a**OR** 2.20 (95%CI 1.20-4.03) *Men* **aOR** 1.12 (95%CI 0.67- 1.86)	⊕⊕◯◯ LOW	CRITICAL

AD: Atopic dermatitis**; OR:** Odds ratio**; CI:** Confidence interval; **RR:** Risk ratio; **NOS:** Newcastle Ottawa Scale

* Classification of AD severity according to prescribed treatment: Mild AD- prescription of emollients or low/medium potency topical corticosteroids; Moderate AD-prescription of calcineurin inhibitors, high-potency topical corticosteroids, monotherapy with UV radiation, or oral corticosteroids; Severe AD-prescription of immunosuppressants, biologics, or hospitalization for AD.
**AD severity determined by prescription of systemic therapy: Mild AD- received no systemic therapy; Severe AD- received systemic therapy.
*** Physician-based AD severity classification was global and based on the body surface area affected, frequency of disease flare, treatments required, and functional impact of those affected. For example, mild cases of AD had limited involvement, requiring only topical therapy with infrequent flares, while moderate AD has more frequent intermittent flares. Severe cases of AD were those with extensive involvement, requiring systemic immunosuppressants and/or significant impact to function.

Explanations
a. Cross-sectional evidence; Majority of studies relied on unvalidated exposure and outcome assessment; One study restricted cases of AD to those diagnosed by a physician with >15 years' experience; modified NOS scores from 4 to 6 suggest moderate-to-high risk of bias.
b. Studies report varied outcomes making an assessment of the consistency of findings unclear.
c. Cross-sectional evidence base; Majority of included studies relied on self-reported or unvalidated exposure and/or outcome assessment; studies scored a between a 5 and 8 on the modified or standard NOS suggesting a moderate-to-low risk of bias.
d. Heterogeneity is suggested by the I^2 of 98% for the pooled crude incidence analysis but the I^2 of 0% for the pooled adjusted OR analysis suggests no heterogeneity. The majority of the evidence is consistent in direction and magnitude.
e. Pooled crude incidence data is imprecise as the CI is consistent with the possibility of no risk difference and important risk increase. The remainder of the evidence appears precise. This suggests borderline imprecision.
f. Cross-sectional evidence; Study relied on self-reported exposure and outcome assessment; modified NOS score of 5 suggests moderate risk of bias.
g. CI for the effect estimate for males is consistent with no risk difference and both important decrease and increase in risk.

e-Figure 13a. Occurrence of Hypercholesterolemia in AD (pooled adjusted ORs)

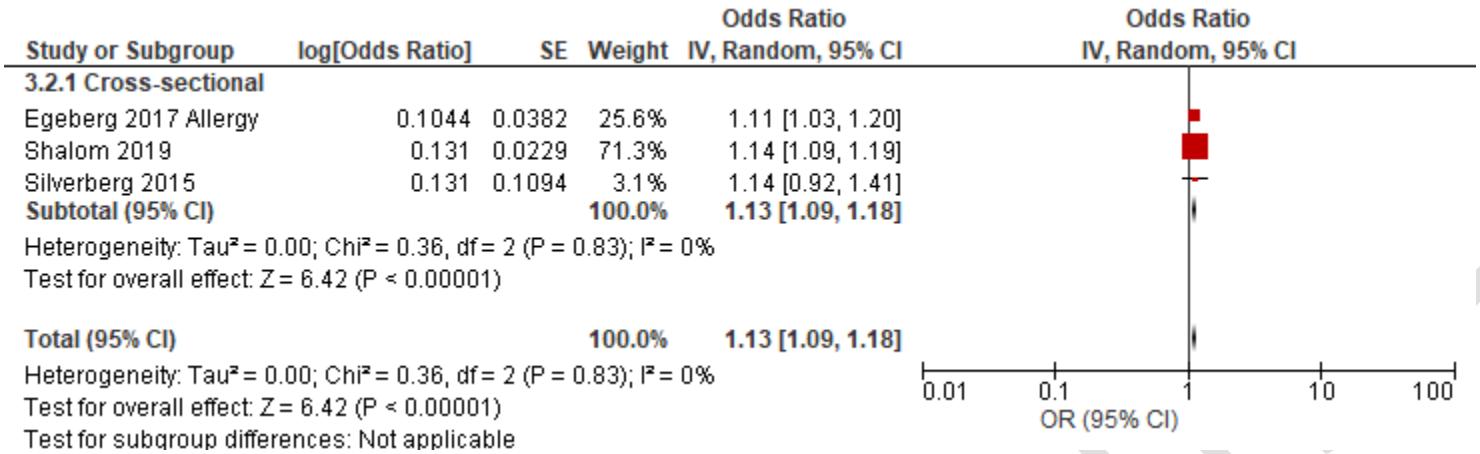

Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of self-reported or physician-diagnosed hypercholesterolemia in individuals with AD compared to non-AD controls.

e-Figure 13b. Occurrence of Hypercholesterolemia in AD (pooled crude prevalence data)

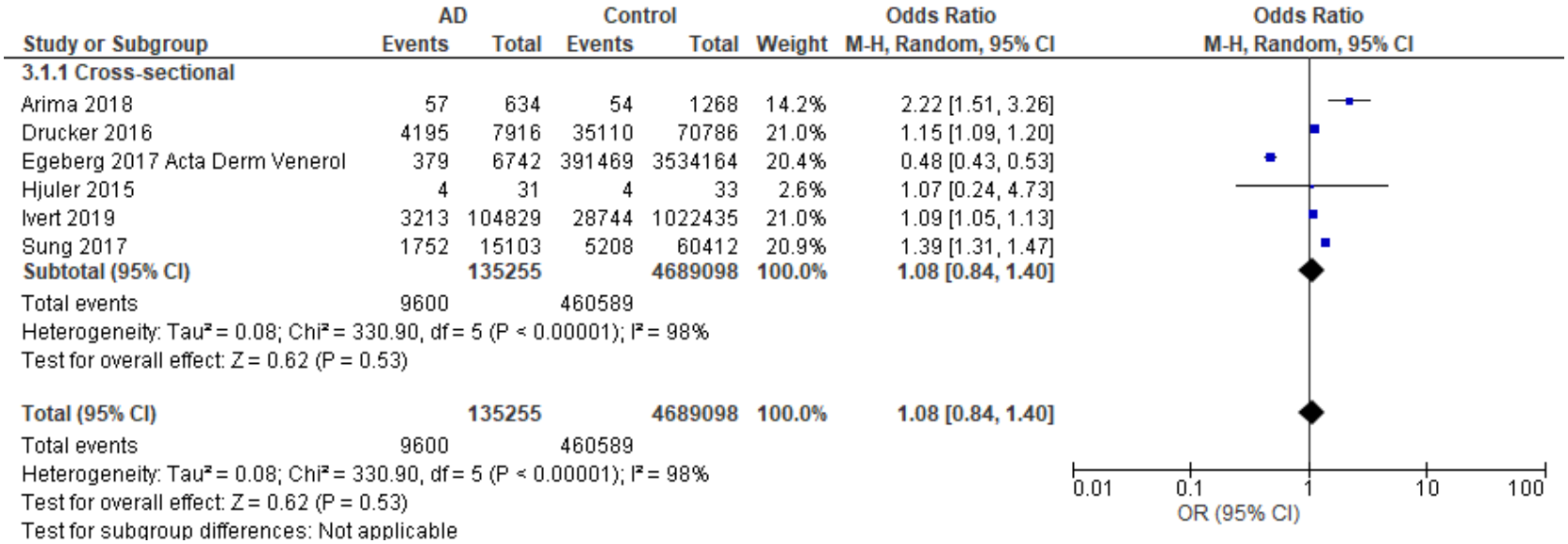

Figure: Pooled analysis of rates of self-reported or physician-diagnosed hypercholesterolemia in individuals with AD compared to non-AD controls.

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e-Table 24. GRADE EVIDENCE PROFILE- Diabetes

Question: Is diabetes associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Occurrence of Prediabetes (follow up: Cross-sectional; assessed with: odds of lifetime history of prediabetes-self-reported clinical history of prediabetes, impaired fasting glucose, impaired glucose tolerance, borderline diabetes, or high blood sugar)									
1 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	Based on data from 4,896 adults reporting symptomatic AD in the past 12 months and 54,373 non-AD controls from 2 study population reported in a single study, AD was associated with increased odds of a lifetime history of prediabetes in both populations: *Population 1* **aOR** 1.57 (95%CI 1.07-2.30), p=0.02 *Population 2* **aOR** 1.71 (95%CI 1.19-2.45), p=0.04	⊕⊕⊕◯ MODERATE	CRITICAL
Occurrence of Hyperglycemia (follow up: Cross-sectional; assessed with: odds of hyperglycemia [≥ 100 mg/dl or taking medications for increased glucose] in AD)									
1 [2]	observational studies	serious [c]	not serious [b]	not serious	serious [d]	none	Based on data from 94 adult males and 128 adult females (aged 19-40yo) with self-reported AD and 4,785 non-AD controls, AD was not significantly associated with hyperglycemia in either sex: *Males* **aOR** 0.83 (95%CI 0.61-1.92) *Females* **aOR** 1.42 (95%CI 0.63-3.19)	⊕⊕◯◯ LOW	CRITICAL
Prevalence of Diabetes^ (follow up: Cross-sectional; assessed with: rate of diabetes in AD)									
3 [3-5]	observational studies	serious [e]	serious [f]	not serious	not serious	none	Based on data from 1,349,671 adults, 48,140 with a diagnosis of AD, diabetes was less prevalent in individuals with AD [4]: **Prevalence Ratio** 0.82 (95%CI 0.80-0.85) Based on data from 253 adults with persistent AD (diagnosed at <18yo and persisting into adulthood) or adult-onset AD (diagnosed at ≥18yo), prevalence of diabetes was 1.2% in the AD cohort.[3]	⊕⊕◯◯ LOW	IMPORTANT

							Based on data from 3,445 adults with mild AD***, 2,361 adults with moderate AD, and 380 adults with severe AD, prevalence of physician-diagnosed type 1 or T2D increased with increasing AD severity [5]: *Mild AD* prevalence 7.0% *Moderate AD* prevalence 11.7% *Severe AD* prevalence 22.9%, p<0.001 (also significant for pairwise comparisons)		
Occurrence of Diabetes^ (follow up: Cross-sectional; assessed with: risk of diabetes in AD)									
16 [1, 6-20]	observational studies	serious [g]	serious [h]	not serious	not serious [i]	none	Based on the pooling of adjusted ORs of the association of self-reported or physician-diagnosed diabetes in adults with AD compared to non-AD controls reported in 7 studies (including 8 study populations), AD is associated with decreased odds of diabetes [1, 6-11]: **pooled OR** 0.89 (95% CI 0.80-0.99) Based on the pooling of incidence rates of diabetes in 135,874 adults with AD and 4,693,361 non-AD controls reported in 7 studies, AD is not significantly associated with diabetes [12-18]: **OR** 0.92 (95%CI 0.74-1.16) Based on data from 8,217 adults, 602 with AD, AD was not significantly associated with increased risk of diagnosis of diabetes in the past 12 months [19]: **aRR** 1.31 (95%CI 0.96-1.13), p=0.08 Based on data from 7,471 adult males with mild AD* and 2,606 males with moderate-to-severe AD, having T2D was significantly associated with an increased risk of moderate-to-severe AD [20]: **aOR** 5.62 (95%CI 2.15- 14.6), p<0.001	⊕⊕◯◯ LOW	CRITICAL

							Based on data from 3,317 adults with mild AD** compared to 33,170 general population controls and 4,620 adults with severe AD compared to 46,200 general population controls, both mild and severe AD were associated with decreased odds of T2D [7]: *Mild AD* **aOR** 0.82 (95%CI 0.68-0.98) *Severe AD* **aOR** 0.80 (95%CI 0.69-0.93)		
Occurrence of Type II Diabetes (follow up: up to 14 years; assessed with: T2D defined as the first claimed prescription of a glucose-lowering drug excluding insulin.)									
1 [21]	observational studies	serious [j]	not serious	not serious [k]	not serious	none	Based on data from 30,079 adults (≥18yo) with a hospital diagnosis of adult AD and 148,428 non-AD controls followed for up to 14 years, adult AD was associated with decreased risk of developing T2D: **aHR** 0.76 (95%CI 0.68-0.83) <u>Incidence Rates</u> *AD* 1.96 (95% CI 1.80-2.13) per 1,000 PY *Controls* 1.92 (95%CI 1.86-2.00) per 1,000 PY	⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis**; OR:** Odds ratio**; CI:** Confidence interval; **RR:** Risk ratio; **T2D:** type II diabetes; **HR:** Hazard ratio; **PY:** Person years**; NOS:** Newcastle Ottawa Scale

^Included studies varied in assessment and definition of diabetes and often do not distinguish between type 1 and type 2 diabetes. See below for the per study definition of diabetes:

Study	**Definition of Diabetes**
Andersen 2017	Type II diabetes was defined by first claimed prescription of a glucose-lowering drug excluding insulin
Arima 2018	Self-reported lifetime history of diagnosis of diabetes (type not specified)
Drucker 2016	Self-reported history of diagnosis of diabetes (type not specified)
Drucker 2017	Self-reported history of physician-diagnosed type II diabetes
Egeberg 2017 *Allergy*	Type II diabetes assessed via ICD-10 codes
Egeberg 2017 *Acta Derm*	Diabetes assessed via ICD-8 and ICD-10 codes (type not specified)
Hjuler 2015	Medically treated type II diabetes
Ivert 2019	Diabetes mellitus-type not specified- assessed by treated with insulin or oral hypoglycaemic agents, or documented hyperglycaemia with dietary restrictions
Kok 2019	Physician-diagnosed type II diabetes
Kwa 2017	Type II diabetes assessed via ICD-9 codes
Lee 2017 *JEADV*	Self-reported “diabetes mellitus” (type not specified)
Marshall 2016	Diabetes assessed via ICD-9 codes (type not specified)
Megna 2017	Diabetes (type and method of assessment not specified)
Radtke 2017	Diabetes assessed via ICD-10 codes (type not specified)

Shalom 2019	Diabetes diagnosed according to one of the following criteria: 1) two random tests of blood glucose greater than 200 mg/dL, 2) one random test of blood glucose over 200 mg/dL with proven target organ damage, or 3) two fasting glucose tests over 126 mg/dL
Sicras-Mainar 2018	Type I or type II diabetes assessed via ICPC-2 codes
Silverberg 2015	Self-reported lifetime history of diabetes (type not specified)
Silverberg 2018	Self-reported diabetes diagnosis in the past 12 months (study restricted to adults)
Sung 2017	ICD-9 code 250 (Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled)
Thyssen 2011	Self-reported lifetime history of diabetes (type not specified))

* Global physician-based AD severity classification based on the body surface area affected, frequency of disease flare, treatments required, and functional impact of those affected. For example, mild cases of AD had limited involvement, requiring only topical therapy with infrequent flares, while moderate AD has more frequent intermittent flares. Severe cases of AD were those with extensive involvement, requiring systemic immunosuppressants and/or significant impact to function.
** AD severity determined by prescription of systemic therapy: Mild AD- received no systemic therapy; Severe AD- received systemic therapy.
*** Classification of AD severity according to prescribed treatment: Mild AD- prescription of emollients or low/medium potency topical corticosteroids; Moderate AD-prescription of calcineurin inhibitors, high-potency topical corticosteroids, monotherapy with UV radiation, or oral corticosteroids; Severe AD-prescription of immunosuppressants, biologics, or hospitalization for AD.
**** AD classified as severe if patients received systemic pharmacotherapy for AD or had been treated in a dermatological ward with AD as the main diagnosis. Other AD was classified as non-severe.

Explanations
a. Cross-sectional evidence; Study relied on self-reported exposure and outcome assessment and received a modified NOS score of 6 suggesting a moderate risk of bias.
b. Effect estimates consistent in direction and magnitude across study populations.
c. Cross-sectional evidence; Study relied on self-reported exposure and outcome assessment and received a modified NOS score of 5 suggesting moderate risk of bias.
d. Small sample; CIs consistent with the possibility of no risk difference and both important risk increase and decrease.
e. Cross-sectional evidence; majority of studies relied on self-reported or unvalidated exposure and outcome assessment; modified NOS scores ranged from 4 to 6 suggesting high-to-moderate risk of bias.
f. Prevalence rates vary across the included studies from 1.2% to an average of 14%.
g. Cross-sectional evidence; Majority of studies relied on self-reported or unvalidated exposure and/or outcome assessment and scored below a 7 on the standard or modified NOS suggesting a moderate risk of bias (range 4-8).
h. Studies inconsistently report increased and decreased odds of diabetes in AD; Estimates of association varied across included studies and the pooled adjusted ORs analysis has an I^2=80%; Pooled analysis of reported incidence of diabetes in individuals with AD compared to non-AD controls had an I^2 of 96% suggesting inconsistency.
i. Two reported estimates of effect have CIs consistent with no risk difference and increased risk; other reported estimates are precise, suggesting borderline imprecision.
j. Study relies on unvalidated exposure and outcome assessment and AD cases were restricted to hospital diagnosis of adult AD, suggesting a overall moderate risk of bias (NOS score 7).
k. AD cases restricted to hospital diagnosis of adult AD (diagnosed at or after age 18). Not downgraded for this domain as the evidence was downgraded for risk of bias including consideration of the restricted study population.

e-Figure 14a. Occurrence of Diabetes (pooled adjusted ORs)

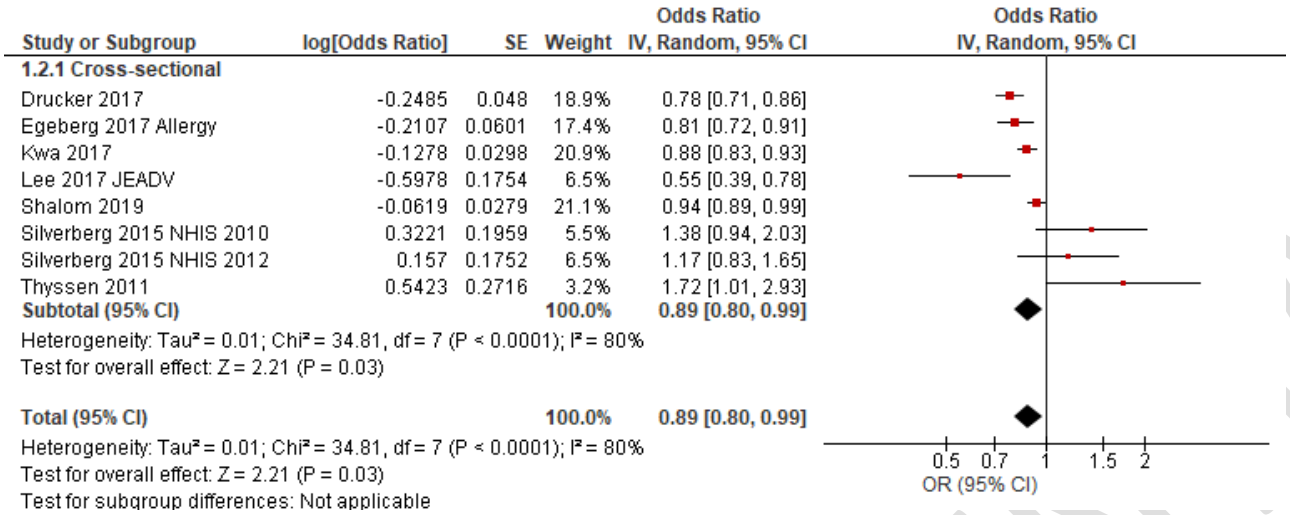

Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of self-reported or physician-diagnosed diabetes in individuals with AD compared to non-AD controls.

e-Figure 14b. Sensitivity Analysis: Occurrence of Type II Diabetes (pooled adjusted ORs)

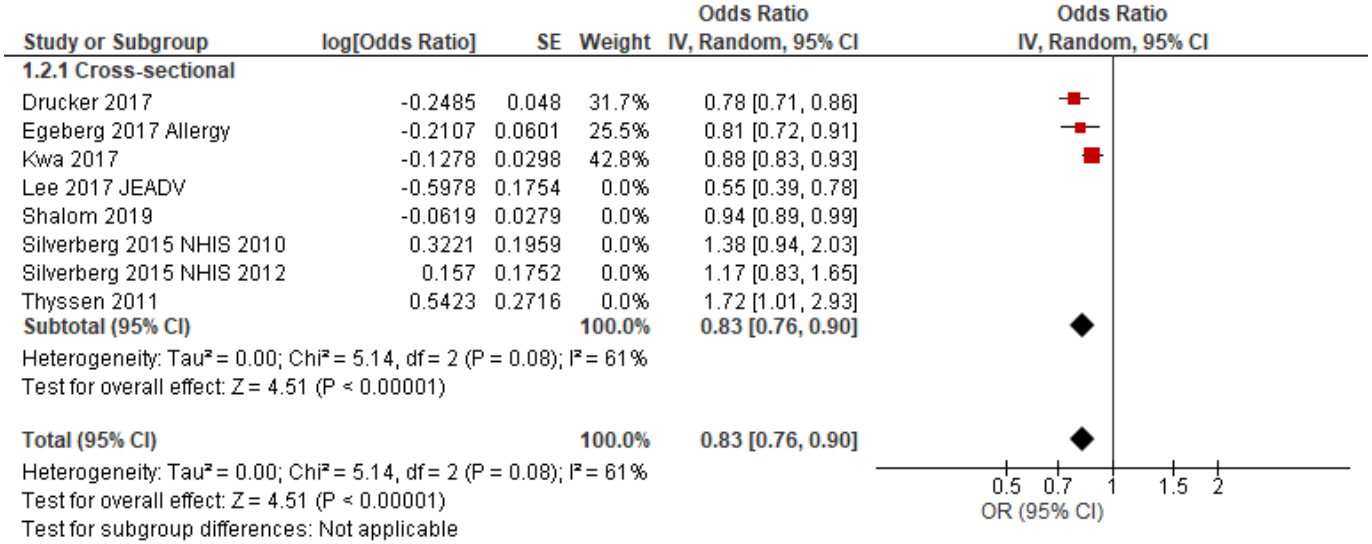

Figure: Pooled analysis of adjusted odds ratios and 95% CIs of the association of self-reported or physician-diagnosed type II diabetes in individuals with AD compared to non-AD controls. Analysis restricted to studies explicitly defining inclusion criteria as self-reported or physician diagnosed type II diabetes.

e-Figure 14c. Occurrence of Diabetes (pooled prevalence)

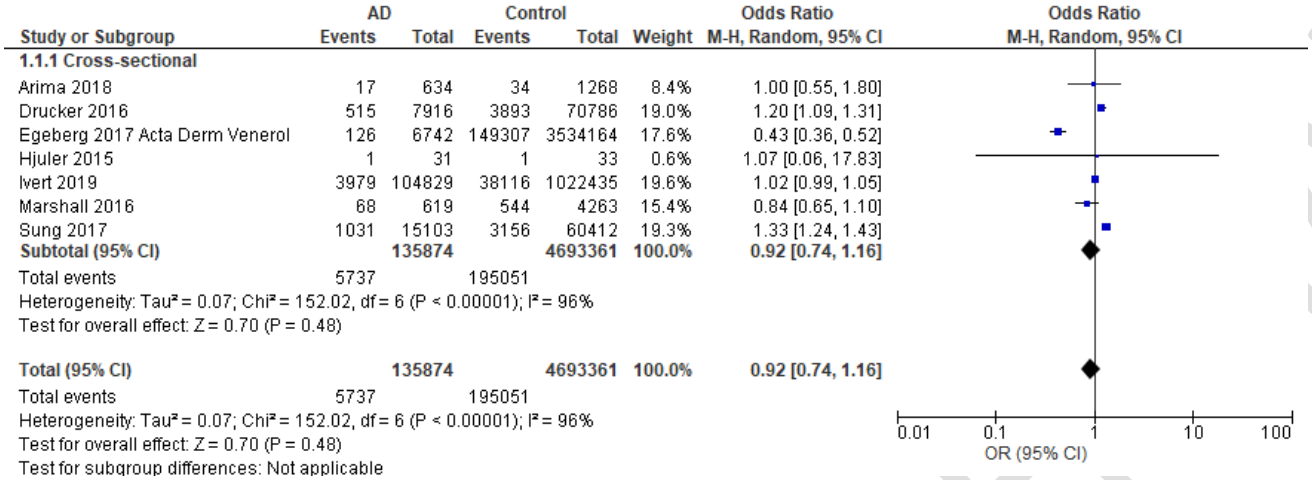

Figure: Pooled analysis of rates of self-reported or physician-diagnosed diabetes in individuals with AD compared to non-AD controls.

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e-Table 25. GRADE EVIDENCE PROFILE- Metabolic Syndrome

Question: Is metabolic syndrome associated with AD in adults?

№ of studies	Certainty assessment						impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Metabolic Syndrome (follow up: Cross-sectional; assessed with: incidence of metabolic syndrome^ in AD)									
1 [1]	observational studies	very serious [a]	not serious	not serious	serious [b]	none	Based on data from 195 adults with AD seen at a single, family medicine center, the prevalence of metabolic syndrome in the AD cohort was 8.7%.[1]	⊕◯◯◯ VERY LOW	IMPORTANT
Occurrence of Metabolic Syndrome (follow up: Cross-sectional; assessed with: odds of metabolic syndrome^ in AD)									
3 [2, 3]	observational studies	serious [c]	serious [d]	not serious	not serious [e]	none	Based on data from 45,157 adults with AD and 45,157 matched non-AD controls, AD was associated with decreased odds of metabolic syndrome[3]: **aOR** 0.88 (95%CI 0.85-0.95) Based on data from 94 men with AD and 128 women with AD compared to 4,785 non-AD controls, AD was associated with increased odds of metabolic syndrome in women but not men[2]: *Women* a**OR** 2.82 (95%CI 1.45-5.52) *Men* **aOR** 0.75 (95%CI 0.34-1.66)	⊕⊕◯◯ LOW	CRITICAL

AD: Atopic dermatitis; **OR:** Odds ratio; **CI:** Confidence interval; **NOS:** Newcastle Ottawa Scale

^Study Definitions of Metabolic Syndrome

Study	Definition of Metabolic Syndrome
Bekic 2020	Undefined
Lee 2017	Presence of at least 3 of the following: (i) elevated WC (≥ 90 cm for men and ≥ 85 cm for women, according to the Korean Society for the Study of Obesity's cut-off point for central or abdominal obesity); (ii) elevated TG level (≥ 150 mg/dl or taking medications for hypertriglyceridemia); (iii) reduced HDL (< 40 mg/dl in men and < 50mg/dl in women); (iv) elevated blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥ 85 mmHg, or receiving antihypertensive treatment); and (v) elevated fasting glucose (≥ 100 mg/dl or taking medications for increased glucose).
Shalom 2019	Presence of at least three of the following: diabetes, dyslipidemia, hypertension or obesity.

Explanations

a. Cross-sectional evidence; Small, single, family medicine practice study with minimal outcome reporting; NOS score of 4 suggests high risk of bias

b. Total sample of 195 adults does not meet optimal information size thresholds (> 400 events), suggesting imprecision.

c. Cross-sectional evidence; One study relied on self-reported exposure and outcome assessment; studies scored 5 and 8 on the modified NOS suggesting moderate risk of bias.

d. Metabolic syndrome defined differently across included studies; effect estimates vary.
e. Effect estimate for metabolic syndrome in men includes a CI consistent with no risk difference and both important decrease and increase in risk, suggesting borderline imprecision as the other effect estimates are precise.

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e-Table 26. GRADE EVIDENCE PROFILE- Osteoporosis

Question: Is osteoporosis associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Osteoporosis (follow up: Cross-sectional; assessed with: rate of osteoporosis in AD)									
1 [1]	observational studies	serious [a]	not serious	serious [b]	not serious	none	Based on data from 634 adults (≥18yo) with current AD (AD experienced in the past 12 months) and 1,268 non-AD controls, the incidence of self-reported osteoporosis/osteopenia was 1.42% in individuals with AD and 0.47% in individuals without AD (p=0.028).[1]	⊕⊕◯◯ LOW	IMPORTANT
Occurrence of Osteoporosis (follow up: Cross-sectional; assessed with: odds of osteoporosis in AD)									
1 [2]	observational studies	not serious [c]	not serious	not serious	not serious	none	Based on data from 105,491,437 adult (≥50yo) emergency department and inpatient encounters in one study reporting on 2 study populations, AD was associated with higher odds of osteoporosis in both populations [2]: *Cohort 1* **aOR** 1.31 (95%CI 1.12-1.54), p=0.0008 *Cohort 2* **aOR** 1.25 (95%CI 1.24-1.26), p<0.0001	⊕⊕⊕⊕ HIGH	CRITICAL
Occurrence of Osteoporosis (follow up: 14 years; assessed with: incidence and risk of developing osteoporosis in individuals with AD)									
1 [3]	observational studies	not serious [d]	not serious	not serious	not serious [e]	strong association [f]	Based on data from 35,229 adults (aged 20 to 49yo) with AD and 35,229 non-AD controls, the risk of developing osteoporosis during the 14-year follow-up period was increased in individuals with AD:	⊕⊕⊕⊕ HIGH	CRITICAL

							aHR 4.72 (95%CI 3.68-6.05) **Absolute Effect** 1.82 per 1,000 person years in AD 0.24 per 1,000 person years in non-AD controls		

AD: Atopic dermatitis; **CI:** Confidence interval; **HR:** Hazard ratio; **OR:** Odds ratio; **NOS:** Newcastle Ottawa Scale

Explanations

a. Cross-sectional evidence; Study relied on self-reported exposure and outcome assessment and had a low response rate, suggesting moderate risk of bias (modified NOS scores 5).

b. One included study reports on the compound outcome of incidence of osteoporosis or osteopenia, which differs importantly from the research question focused on the association between AD and osteoporosis.

c. Cross-sectional evidence; Studied relied on unvalidated outcome and exposure assessment but was otherwise of low risk of bias (modified NOS score 6).

d. This study scored 9 on the NOS suggesting a low risk of bias.

e. The event rate was 360 in the AD cohort and 127 in the non-AD cohort, suggestive of borderline imprecision. However, the CI is inclusive of a meaningful association of AD and osteoporosis, so the evidence was not rated down for this domain.

f. Large magnitude of effect with consistent CI.

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e-Table 27. GRADE EVIDENCE PROFILE- Bone Fracture

Question: Are bone fractures associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Risk of Fracture (follow up: Cross-sectional; assessed with: odds of any fracture after age 20 years)									
1 [1]	observational studies	serious [a]	not serious	serious	not serious	none	Based on data from 4,972 individuals aged 20 to 85yo (rate of AD 7.4% [95%CI 6.5%-8.3%]) the odds of any fracture after age 20 were higher in those with AD: **OR** 1.48 (95%CI 1.10-1.99), p=0.01	⊕⊕⊕◯ MODERATE	CRITICAL
Risk of Fracture (follow up: median 5.0 years; assessed with: risk of any hip, pelvis, spine, wrist, or proximal humerus fracture)									
1 [2]	observational studies	not serious [b]	not serious	not serious	not serious	dose response gradient [c]	Based on data from 509,769 individuals (≥18yo) with AD and 2,568,889 matched non-AD controls followed until their first fracture diagnosis*, risk of fracture was higher in those with AD and risk increased with increasing AD severity: <u>Overall Risk</u> **HR** 1.07 (99%CI 1.05-1.09) **Unadjusted Absolute Rate** 1,428 fractures per 100,000 person-years in AD 1,264 fractures per 100,000 person-years in non-AD controls <u>Risk by AD Severity**</u> *Mild AD* (n=321,523) **HR** 1.03 (99%CI 1.01-1.06) *Moderate AD* (n=159,818) **HR** 1.11 (99%CI 1.08-1.14)	⊕⊕⊕⊕ HIGH	CRITICAL

							Severe AD (n=28,428) **HR** 1.22 (99%CI 1.14-1.30)		

AD: Atopic dermatitis; **CI:** Confidence interval; **HR:** Hazard ratio; **OR:** Odds ratio; **NOS:** Newcastle Ottawa Scale

*AD cohort followed for a median of 5.0 years and control cohort followed for a median of 4.4 years.
**Mild AD: Default if not meeting requirements for moderate or severe AD as follows; Moderate AD: Prescription for potent topical steroids or calcineurin inhibitors; Severe AD: Prescription for systemic drug and/or record of phototherapy treatment.

Explanations
a. Cross-sectional evidence; Study relied on self-reported exposure and outcome assessment and did not report on completeness of data collection and outcome-important data (modified NOS score 4).
b. This study scored a 9 on the NOS suggesting a low risk of bias.
c. An increased magnitude of risk of fracture is seen with increased AD severity, suggesting increased confidence in the study's findings of increased risk of fracture in AD.

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e-Table 28. GRADE EVIDENCE PROFILE- Skin Infections

Question: Are skin infections associated with AD in adults?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of Skin Infections (follow up: Cross-sectional; assessed with: rate of secondary bacterial infections in AD)									
1 [1]	observational studies	serious [a]	not serious	not serious	not serious	none	A study of 1,174 individuals with AD found secondary bacterial infection* to be common, occurring in 752 (64.1%) AD patients.[1]	⊕⊕⊕◯ MODERATE	IMPORTANT
Occurrence of Skin Infection (follow up: Cross-sectional; assessed with: odds of varied skin infections in AD)									
2 [2, 3]	observational studies	serious [b]	not serious	not serious	not serious	strong association [c] *(not upgraded)*	Based on data from 72,108,077 adult (≥18yo) hospital discharges, including 791,091 (wtd frequency) AD discharges (identified as a primary and/or secondary discharge diagnosis), AD was associated with increased odds of *serious cutaneous infections*** (defined as infections that led to hospitalization, were life threatening, or required treatment in an inpatient setting) [2]: **aOR** 4.62 (95%CI 4.51-4.74), p=0.0002 Based on data from ED visits of 196,599 adults (wtd frequency) with a primary diagnosis of AD and 25,738,111 (wtd frequency) without a primary diagnosis of AD, AD was associated with higher odds of *1 or more skin infections**** [3]: **aOR** 1.93 (95%CI 1.89-1.97), p<0.0001.	⊕⊕⊕◯ MODERATE	CRITICAL
Occurrence of Skin Infections (follow up: mean 13.7 years; assessed with: odds of skin infection in AD)									
1 [4]	observational studies	not serious [d]	not serious	not serious	not serious	none	Based on data from 448,311 individuals with AD and 2,664,306 without AD followed for a mean of 13.7 years, AD was associated with increased odds of all cutaneous infections studied: *Cutaneous Warts* **aOR** 1.98 (95%CI 1.96-2.00) *Dermatophyte Infection* **aOR** 2.54 (95%CI 2.47-	⊕⊕⊕⊕ HIGH	CRITICAL

							2.61) *HSV* **aOR** 2.08 (95%CI 2.04-2.12) *Impetigo* **aOR** 1.55 (95%CI 1.47-1.64) *Molluscum Contagiosum* **aOR** 3.11 (95%CI 3.07-3.14)		
Occurrence of Specific Skin Infections (follow up: Cross-sectional; assessed with: incidence and odds of specific skin infections in AD)									
2 [5, 6]	observational studies	serious [e]	not serious	not serious [f]	serious [g]	none	A study comparing 190 adults (≥18 yo) with AD to 202 healthy controls found no difference between the groups in incidence of tinea pedis (rate of tinea pedis was 8.4% and 7.4% =, respectively) [6]: **OR** 1.15 (95%CI 0.55-2.39), p=0.72 A study of 62 individuals with gram-negative toe-web infection found eczema to be common concomitant condition and a predisposing factor for GNTWI as 41 (66%) of 62 GNTWI patients had eczema and eczema occurred prior to intertrigo in 25 of the 41 patients.[5]	⨁⨁◯◯ LOW	IMPORTANT

AD: Atopic dermatitis; **OR:** Odds ratio; **CI:** Confidence interval; **HSV:** Herpes simplex virus; **GNTWI:** Gram-negative toe-web infection; **NOS:** Newcastle Ottawa Scale

* Secondary bacterial infection identified as very likely or suspected: Very likely bacterial infection was considered if pustules, prudent exudation, or yellow colored crust was detected. Bacterial infection was suspected if multiple scratches, oozing, erosion, or ulceration was found.
**Specific skin infections studied via diagnostic codes include eczema herpeticum, erysipelas, cellulitis, HSV, and any skin infection
***Specific skin infections studied via diagnostic codes include Carbuncle/furuncles, Impetigo, Cellulitis , Erysipelas, MSSA , MRSA , Molluscum contagiosum , Cutaneous warts, Herpes Simplex Virus infection of skin, Herpes Zoster virus infection, Eczema herpeticum, Genital warts, Genital herpes, Fungal infection, Dermatophytosis, Candidiasis of skin and nails, Candidiasis of vulva and urogenitals, any skin infection)

Explanations
a. Cross-sectional evidence; Study relied on unvalidated exposure and outcome assessment; modified NOS score 5 suggests moderate risk of bias.
b. Cross-sectional evidence; One study relies on unvalidated outcome and exposure assessment; Both studies include only hospitalized or emergency department samples; modified NOS scores range from 5 to 8 suggesting moderate-to-low risk of bias.
c. The largest included study, restricted to hospitalized patients, reports a very large magnitude of effect but the evidence was not upgraded for this outcome due to risk of bias.
d. Study relied on unvalidated exposure and outcome assessment; NOS score of 7 suggests moderate-to-low risk of bias.
e. Studies scored 6 on the standard and modified NOS suggesting a moderate risk of bias.
f. One study includes participants aged 10 to 94 years old but documents a median age of 52.5 years suggesting the age of the population is aligned with the research question focused on the adults with AD.
g. The event rates across both studies of 31 and 41 suggest imprecision; The effect estimate reported includes a CI consistent with the possibility of no difference in risk and both important increased and decreased risk.

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