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Article in *European journal of dermatology: EJD* · December 2021

DOI: 10.1684/ejd.2021.4168

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Atopic dermatitis associated with autoimmune, cardiovascular and mental health comorbidities: a systematic review and meta-analysis

Background: Previous studies have reported conflicting estimates of associations between atopic dermatitis (AD) and autoimmune, cardiovascular and mental health comorbidities. **Objectives:** Our objective was to determine and report these global associations based on a systematic literature review. **Materials & Methods:** A systematic search of studies published in PubMed/MEDLINE and Cochrane Library (January 1990 - April 2020) including patients with physician-diagnosed AD and concurrent populations, were identified. The metaanalysis (random-effect model) included 37 studies. Studies originated from Europe, UK, Asia, The USA and Canada, including 237,226,993 patients and subjects with 20 autoimmune, eight cardiovascular and eight mental illnesses. **Results:** Pooled analyses revealed significantly higher overall odds of autoimmune diseases (OR: 1.74; 95% CI: 1.55-1.94, $p < 0.001$; I²: 98.39%) and mental illnesses (OR: 1.62; 95% CI: 1.53-1.72; $p < 0.001$; I²: 98.86%) and a smaller increased risk for cardiovascular diseases (OR: 1.08; 95% CI: 0.01-1.16, $p < 0.001$; I²: 99.45%). **Conclusion:** Our systematic review highlights that AD patients are at significantly increased risk for many autoimmune diseases and mental illnesses and at a relatively lower risk for cardiovascular diseases. Updated global estimates should encourage physician/patient empowerment to seek further medical and wellness interventions for optimal patient care

Key words: atopic dermatitis, eczema, autoimmune diseases, systemic diseases, mental health, epidemiology

Article accepted on 02/05/2021

Atopic dermatitis (AD) is a chronic inflammatory disorder [1], which usually begins in childhood [2] and has a lifetime prevalence between 7% and 13% [1-3]. The etiopathogenesis of AD is commonly accepted to be multifactorial, including a genetic predisposition to skin barrier deficiency, immune-mediated inflammation and environmental factors [1]. Gene mapping studies have identified *FLG* as a dominant risk gene involved in skin barrier function, as well as numerous loci associated with immune dysregulation [4]. These loci are not specific to AD and are shared with several other immune inflammatory diseases that are thought to be TH1/TH17 mediated, such as psoriasis, rheumatoid arthritis and alopecia areata.

AD has been associated with numerous cardiovascular (CV) risk factors [5-7] and is reportedly at a general higher risk for many CV diseases [8]. AD has also been associated with numerous other systemic diseases, including allergic, metabolic [9-11], rheumatological [12], and inflammatory and mental illnesses [13, 14]. These previously unrecognized disease associations have promoted the hypothesis of an autoimmune mechanism in AD pathogenesis [14] and that AD is itself a systemic disease [2].

The relationship between AD and comorbid diseases has implications for the understanding of underlying mecha-

nisms. However, previous metaanalyses and observational studies have found conflicting results, and pooled estimates are often reported independently or as a group of disorders associated with a single etiopathogenesis or national population.

This study aimed to systematically analyse the incidence of physician-diagnosed AD with non-atopic disorders, grouped according to aetiopathogenetics, particularly cardio-vascular, autoimmune and mental health disorders, compared to concurrent control populations in published studies over the last 30 years.

Materials and methods

We report a systematic review and meta-analysis according to the recommendations indicated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15].

Search strategy and selection criteria

We systematically searched the electronic PubMed/ MEDLINE database and the Cochrane Central Register of

doi: 10.1684/ejd.2021.4168

Controlled Trials (CENTRAL) with the following search terms (MeSH): (“atopic dermatitis” OR “atopic eczema”) AND (“cardiovascular” OR “heart” OR “myocardial” OR “stroke” OR “hypertension” OR “ischemia” OR “angina” OR “diabetes” OR “mortality” OR “death” OR “mental disorders” OR “depression” OR “attention deficit hyperactivity disorder” OR “autism” OR “autoimmune” OR “comorbidities”). The last search was run in April 2020.

We considered observational, case-control and cohort studies including a concurrent control population, according to the following criteria: (1) human subjects of any age, published in English or French from 1990 to April 2020; (2) enrolled patients with self-reported/registered clinical diagnosis of systemic AD and “non-atopic” comorbidities; (3) topical and/or systemic therapies or without any therapy; (4) any study regardless of duration of follow-up; and (5) any study regardless of AD severity or presence/absence of genetic analysis.

We excluded studies according to the following criteria: (1) a non-AD condition as the primary focus; (2) general symptoms and un-codified diseases; (3) unsuitable statistical risk comparison for meta-analysis methodology; (4) physiopathological mechanisms and atopic or therapy-linked comorbidities; (5) no population control; (6) case reports/small populations (<30 cases), meta-analyses, surveys, and short communications; and (7) manuscripts without abstract(s) or full article(s) available online.

To identify any additional studies, reference lists of included articles were also screened and evaluated according to the above selection criteria.

Study selection and data extraction

From selected studies, relevant data were extracted independently (SL and SK). AD was the dependent variable, defined by patient self-reports of physician diagnosis, physician-diagnosed reports and/or previous physician reporting in medical records, databases and registries. Non-atopic comorbidities were included when clinically diagnosed, self-reported or assessed according to questionnaires for symptoms over a period of >12 months. In the case of multiple data sets, each set was assessed according to inclusion criteria. Additional information was requested from authors by email, when required.

Any disagreements were resolved with other authors. Data extracted from each study included: (1) study characteristics- author, year, country of patient residence, number of involved centres/registries, type of study; (2) population characteristics- median age, gender, total sample size; and (3) non-atopic comorbidities- cardiovascular, autoimmune, and psychiatric. Non-specific disease information (e.g. “diabetes”, “arthritis” or “autoimmune disease”) were not considered. All individual comorbidities were analysed with meta-analysis.

Quality assessment

Methodological quality was assessed by adapting the quality assessment tool of the National Institute of Health in an ad hoc checklist to evaluate the risk of bias [16]. Checklist questions and assessment are outlined in *supplementary table 1*.

Statistical analysis

Data were analysed with OpenMetaAnalyst and Opine statistical software. Heterogeneity was assessed using Dorsmanin and Laird test (Q-statistic) and inconsistency index (I²) with >25%, >50%, and >75% designated as small, medium, and high heterogeneity, respectively. A random-effects model (REM) was used to ascertain pooled-effect estimates, and robustness was determined with sensitivity analysis (leave-one-out analysis). Evidence of publication bias was assessed using funnel plots and visually examined. Subgroup analysis was performed for reported individual disorders in AD patients and control populations.

Results

Literature search

The initial database search generated 2,794 records, screened according to inclusion and exclusion criteria. The PRISMA flowchart outlines the study selection process (*figure 1*). A total of 37 studies (including 237,226,993 people; 3,741,101 patients) and 36 comorbid disorders (20 autoimmune, eight CV and eight psychiatric) were finally included [17-53]. Data concerning the incidence of any autoimmune, CV or mental health comorbidity for AD patients and concurrent control subjects were extrapolated and stored in a dedicated database.

Study characteristics

Selected studies were mostly published after 2010 (two were published prior) and included patients and subjects from Europe (Denmark [6], mixed [1], Germany [6], Sweden [1]), UK [3], Asia (Japan [1], Korea [5], Taiwan [7]), USA [6] and Canada [1]. Reported non-atopic comorbidities included autoimmune diseases from 13 studies [20-22, 27, 28, 33-36, 38, 41, 43, 46, 52], CV diseases from 16 studies [17, 22, 24, 27-29, 32, 33, 36, 37, 39, 41, 44-46, 50] and mental illnesses from 17 studies [17-19, 22, 23, 25, 30, 31, 36, 40-42, 47-49, 51, 53]. Study characteristics are outlined in *table 1* and *supplementary table 2*.

Methodological quality

Overall methodological quality was classified as good in >80% (30), fair in 16% (6) and poor in a single study (*supplementary table 1*). All studies clearly defined the research question and control subjects were selected from a concurrent population.

AD and autoimmune diseases

Autoimmune diseases were reported in 13 studies (eight dedicated to autoimmune diseases only), involving 93,620,378 subjects, of whom 1,969,765 were AD patients (2.1%) from six countries (Denmark, Germany, Japan, Taiwan, UK and USA).

Overall, AD was significantly associated with autoimmune disorders (OR: 1.74; 95% CI: 1.55 -1.94; $p < 0.001$) with high heterogeneity among the studies (I²: 98.39%). The

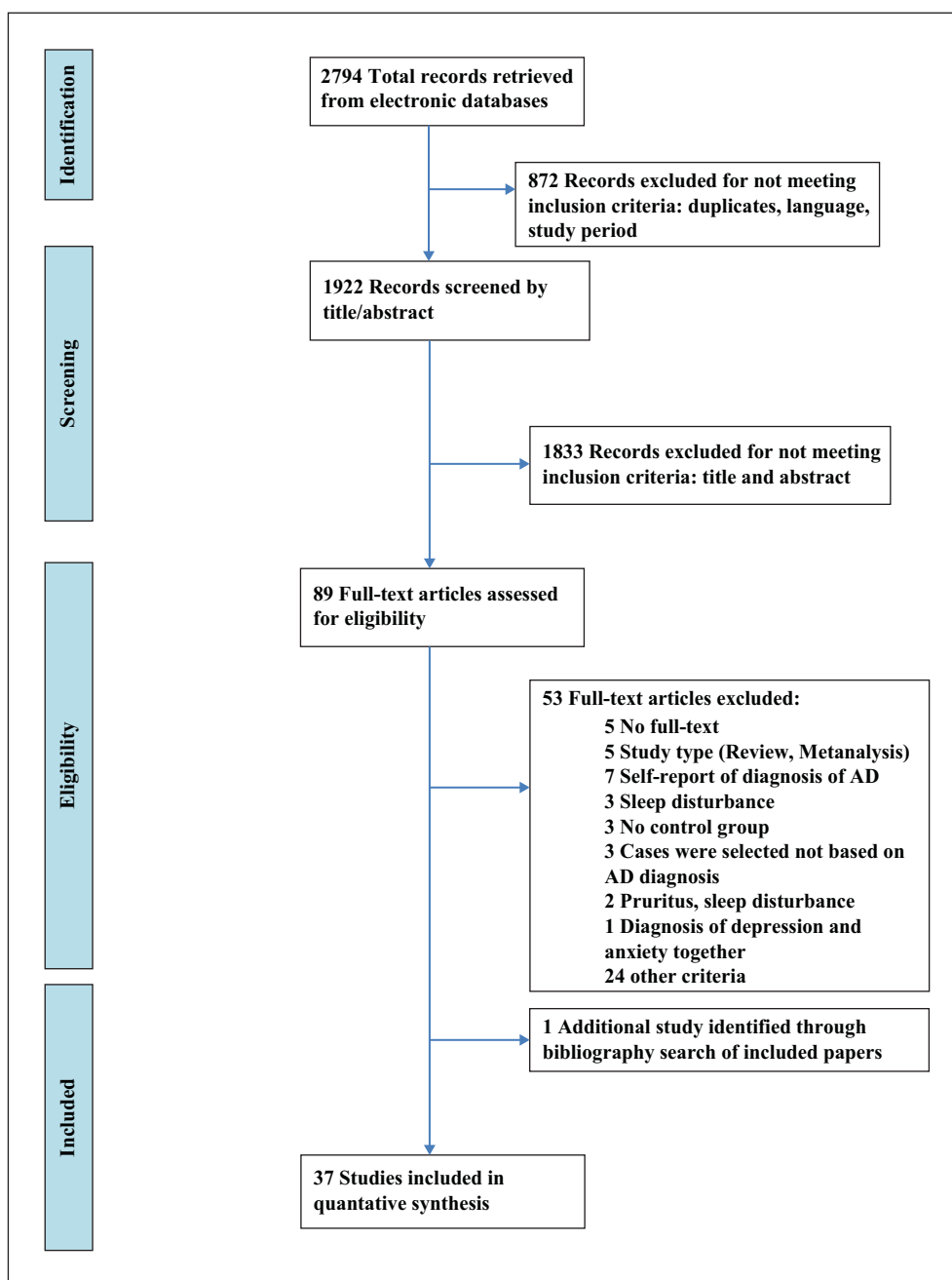


Figure 1. Workflow diagram describing the systematic search of papers and inclusion for meta-analysis.

autoimmune diseases with the largest effect sizes were AA (OR: 8.56; 95% CI: 1.5-48.79, $p < 0.001$, I²: 98.96), vitiligo (OR: 3.48; 95% CI: 1.66 - 7.3, $p < 0.001$; I²: 98.47%) and celiac disease (OR: 2.18; 95% CI: 1.35-3.47; $p < 0.001$; I²: 93.42); all included studies reported positive associations between AD and the respective autoimmune disorder. AD was also significantly associated with inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), systemic sclerosis, thrombocytopenia, and autoimmune thyroiditis; all included studies reported positive associations between AD and the respective comorbidities. Other significant positive associations with a smaller effect size included Sjogrens syndrome, chronic glomerulonephritis,

and rheumatoid arthritis (RA). Significant negative associations included multiple sclerosis (MS), type I diabetes, giant cell arthritis, and myasthenic gravis (see figure 2A).

AD and cardiovascular (CV) diseases

CV diseases were reported in 16 studies (10 dedicated to CV diseases only), involving 77,943,272 subjects, of which 812,141 were AD patients (1.04%) from eight countries (Canada, Denmark, Germany, Japan, South Korea, Sweden, UK and USA). Overall, a slight significant association was found with CV disorders (OR: 1.08; 95% CI: 1.01-1.16, $p < 0.001$) with high heterogeneity among the studies

Table 1. Characteristics of included studies.

Author	Country	Total no. subjects included	Comorbid disorder	Data set	AD ascertainment	Control selection	Co-pathology ascertainment	Co-pathologies
Schmitt <i>et al.</i> 2009 [17]	Germany	7538	Cardio-vascular Psychiatric	Interdisciplinary outpatient German database of approximately 250,000 individuals between 2003-2004	Physician-registered AD diagnosis and topical treatment prescription (> 15 years) between 2003-2004	Sex and age-matched (1:1) via random selection of patients without AD	Interdisciplinary outpatient German database	MI, hypertension, type 2 diabetes, affective disorders, schizophrenia
Schmitt <i>et al.</i> 2009 [18]	Germany	2872	Psychiatric	Population-based administrative health care (600,000 individuals) children (6-17 years) in 2003-2004	Physician-registered AD diagnosis	Subjects without physician-diagnosed AD	Physician-registered diagnosis	ADHD, affective disorders, personality and behaviour disorders
Yaghmaie <i>et al.</i> 2012 [19]	USA	79496	Psychiatric	USA 2007 National Survey of Children's Health (NSCH)	Self-reported physician AD diagnosis	Self-report no physician diagnosed AD	Self-reported physician diagnosis of	Depression, anxiety, autism, adhd, conduct disorder
Wei <i>et al.</i> 2014 [20]	Taiwan	961785	Autoimmune	National Insurance database (NHIRD Taiwan population) children (<18 years) between 2000-2007	Physician-registered AD diagnosis before 2009	Sex, age, residential area, socio-economic status, and index year matched (1:4) via random selection of patients without AD	Physician-registered diagnosis (board-certified) before 2009	SLE
Wu <i>et al.</i> 2014 [21]	Taiwan	209750	Autoimmune	National Insurance database (NHIRD Taiwan population) children (<18 years) between 2000-2007	Physician-registered AD diagnosis before 2009	Sex, age, residential area, socio-economic status, and index year matched (1:4) via random selection of patients without AD	Physician-registered diagnosis	IBD, type i diabetes, RA, SLE, vitiligo, pernicious anaemia
Augustin <i>et al.</i> 2015 [22]	Germany	293181	Autoimmune, cardio-vascular, psychiatric	German Statutory Health Insurance database children (<18 years) in 2009	Self-reported physician AD diagnosis	Subjects without physician-diagnosed AD or psoriasis	Self-report	Depression, ADHD, vitiligo, AA, IBD
Cheng <i>et al.</i> 2015 [23]	Taiwan	16416	Psychiatric	National Insurance database (NHIRD Taiwan population) individuals > 12 years between 1998-2008	Physician-registered AD diagnosis between 1998-2008	Sex, age matched (1:1) via random selection of subjects without AD diagnosis	Physician-registered diagnoses between 2009 and 2011	Depression, anxiety
Kim <i>et al.</i> 2015 [24]	Korea	2604	Cardio-vascular	National KNHANES database of survey 2007-2012- selected adults (>18 years) without chronic illness	Self-report of physician diagnosed AD	Age and sex matched (1:10) randomly selected population without AD	Self-reported physician diagnosed	Hypertension
Kim <i>et al.</i> 2015 [25]	Korea	120508	Psychiatric	Military Manpower Administration for conscription in Incheon (population of 3 million) 2008-2012	Conscription officers, medical specialists, face-to-face interviews, and medical work-ups.	Subjects without physician-diagnosed AD	Conscription officers, medical specialists, face-to-face interviews, and medical work-up.	Depression, anxiety

Table 1. (Continued).

Author	Country	Total no. subjects included	Comorbid disorder	Data set	AD ascertainment	Control selection	Co-pathology ascertainment	Co-pathologies
Schmitt <i>et al.</i> 2015 [26]	Germany	655815	Autoimmune	German national insurance database - individuals <40 years with consistent insurance between 2005-2011	Physician-registered AD diagnosis	Subjects without physician-diagnosed AD	Physician-registered diagnosis	IBD, type I diabetes, RA
Silverberg <i>et al.</i> 2015 [27]	USA	34567	Cardio-vascular	National USA NHIS survey 2012	Self-report of physician-diagnosed AD	Self-report no physician-diagnosed AD	Self-report	Stroke, CAD, angina pectoris
Andersen <i>et al.</i> 2016 [28]	Denmark	48672	Autoimmune, Cardio-vascular	National Danish registry of all in-and out-patient contacts > 15 years between 1997-2012	Physician-registered AD diagnosis	Sex, age and index year matched (1:5) via random selection of patients without AD	Physician-registered diagnosis	IBD, celiac disease, MS, giant cell arthritis, chronic glomerulonephritis, autoimmune thyroiditis, Sjogren's syndrome, type I diabetes, systemic sclerosis, RA, SLE, vitiligo, thrombocytopenia, ankylosing spondylitis, AA, chronic urticaria
Andersen <i>et al.</i> 2016 [29]	Denmark	174797	Cardio-vascular	National Danish registry of all in-and out-patient contacts > 15 years between 1997-2012	Physician-registered AD diagnosis	Sex, age and calendar time matched (1:5) subjects without AD	Physician-registered diagnosis	IBD, hypertension, arrhythmia
Lee <i>et al.</i> 2016 [30]	Taiwan	36946	Psychiatric	National Insurance database (NHIRD Taiwan population) children between 1998-2008	Physician-registered AD diagnosis before age 3	Age and gender-matched (1:1) toddlers without AD diagnosis through lifetime	Physician-registered diagnosis	Autism, ADHD
Liao <i>et al.</i> 2016 [31]	Taiwan	774524	Psychiatric	National Insurance database (NHIRD Taiwan population) children born between 2000-2010	Physician-registered AD diagnosis before age 2	Birth year, birth season and residential region-matched (1:1) without AD diagnosis	Physician-registered diagnosis (before 2012)	Autism, ADHD
Riis <i>et al.</i> 2016 [32]	Denmark	53210	Cardio-vascular	Population based-medical registries of all hospital admissions in Denmark between 1977 - 2013	Physician-registered AD diagnosis	Sex and birth year-matched (10:1) from a civil registry of the general population without AD	Physician-registered diagnosis	Stroke, hypertension
Standl <i>et al.</i> 2016 [33]	Germany	1180678	Cardio-vascular	Prospective AOK cohort from German National Health Insurance beneficiaries (> 40 years in 2005) 2005 and 2007 and 2012-2014	Physician-registered diagnosis	Subjects without physician-diagnosed AD	Physician-registered diagnosis	Angina pectoris, MI, stroke, hypertension

Table 1. (Continued).

Author	Country	Total no. subjects included	Comorbid disorder	Data set	AD ascertainment	Control selection	Co-pathology ascertainment	Co-pathologies
Wei <i>et al.</i> 2016 [34]	Taiwan	285624	Autoimmune	National Insurance database (NHIRD Taiwan population) individuals >18 years between 2000-2007	Physician-registered AD diagnosis	Sex, age, residential area, socio-economic status, and index year-matched (1:2) via random selection of subjects without AD diagnosis	Physician-registered diagnosis (before 2009)	Vasculitis
Wei <i>et al.</i> 2016 [35]	Taiwan	362112	Autoimmune	National Insurance database (NHIRD Taiwan population) between 2000-2007	Physician-registered AD diagnosis	Sex, age, residential area, socio-economic status, and index year-matched (1:2) via random selection of patients without AD	Physician-registered diagnosis (before 2009)	Thrombocytopenia
Egeberg <i>et al.</i> 2017 [36]	Denmark	87307	Autoimmune, Cardio-vascular, Psychiatric	The Danish National Patient Register of adult patients (>18 years) with inpatient or outpatient diagnosis 1995-2012	Physician-registered diagnosis	Age and sex-matched (1:10) randomly selected population without AD	Physician-registered diagnosis	Hypertension, MI, stroke, IBD, depression, anxiety
Drucker <i>et al.</i> 2017 [37]	Canada	259119	Cardio-vascular	Volunteer questionnaire (sample from CPTP - 5 Canadian regions) residents aged 30-74 years from 2009	Self-reported clinical AD diagnosis	Self-report no physician diagnosed AD	Self-reported physician diagnosis	Stroke, MI, hypertension, type 2 diabetes
Drucker <i>et al.</i> 2017 [38]	USA	87406	Autoimmune	Nurses Health Study (NHS2) cohort of female nurses in USA 2009, follow-up 2013	Self-reported physician-diagnosed AD prior to 2009	Subjects without physician-diagnosed AD	Self-reported physician diagnosed	AA, vitiligo
Kwa <i>et al.</i> 2017 [39]	USA	72651487	Cardio-vascular	USA Nationwide Inpatient Sample (NIS) adult patients 2002-2012	Physician-registered diagnosis	Subjects without any physician-diagnosed inflammatory skin disease	Physician-registered diagnosis	Hypertension, type 2 diabetes, CAD, heart failure, MI
Thyssen <i>et al.</i> 2017 [40]	Denmark	4269495	Psychiatric	Population based Danish administrative and health registries of adults (>18 years) in 1997 follow-up 2012	Physician-registered AD therapies	Subjects without physician-registered AD therapies	Physician-registered diagnosis	Depression, anxiety
Arima <i>et al.</i> 2018 [41]	Japan	1902	Autoimmune, cardio-vascular, psychiatric	Japanese population survey (NHWS) of adult population	Self-reported physician diagnosed AD	Age, sex, marital status, education, income, insurance status, body mass index, smoking status and the Charlson comorbidity index (CCI) propensity score-matched (1:2) for patients without AD	Self-reported physician-diagnosed	Hypertension, depression, anxiety

Table 1. (Continued).

Author	Country	Total no. subjects included	Comorbid disorder	Data set	AD ascertainment	Control selection	Co-pathology ascertainment	Co-pathologies
Choi <i>et al.</i> 2018 [42]	Korea	42222	Psychiatric	Korea Community Health Survey for the years 2010-2013	Self-reported physician AD diagnoses	Age, sex, current smoking status, preference for low sodium intake, BMI, and year propensity score-matched (1:1) without AD diagnosis	Self-reported physician diagnosed	Depression
Narla <i>et al.</i> 2018 [43]	USA	87053155	Autoimmune	USA Nationwide Inpatient Sample (NIS)	Physician-registered AD diagnoses	Subjects without physician-registered AD diagnosis	Physician-registered AD diagnoses	MS, vasculitis, pernicious anaemia, IBD, myasthenia gravis, celiac disease, ankylosing spondylitis, RA, SLE, systemic sclerosis, Sjogren's syndrome, AA, chronic urticaria, vitiligo, haemolytic anaemia, thrombocytopenia, thyroiditis, giant cell arthritis, type I diabetes, chronic glomerulonephritis
Silverwood <i>et al.</i> 2018 [44]	UK	1915916	Cardio-vascular	UK Clinical Practice Research Datalink (CPRD) of prospectively collected primary care records of adults (> 18 years) from 1998 - 2015	Physician-registered AD diagnoses	Age (within 15 years), sex, general practice, and calendar time-matched (1:5) for patients without AD	Physician-registered diagnosis	Stroke, MI, hypertension, angina pectoris, heart failure, CAD, arrhythmia, depression, anxiety
Thyssen <i>et al.</i> 2018 [45]	Denmark	95546	Cardio-vascular	Danish National Patient and Cause of Death Registries of adults (> 18 years) in 2011, follow up 2015	Physician-registered AD diagnoses	Sex, age and calendar time matched (1:10) with controls without AD diagnosis	Physician-registered diagnosis	Hypertension
Treudler <i>et al.</i> 2018 [46]	Germany	9481	Autoimmune, Cardio-vascular	LOIFE-Adult-Study gender-stratified, random sample of 10,000 residents in the city of Leipzig in a target age range 40-79 (some 18-39)	Physician-diagnosed AD	Subjects without physician-diagnosed AD	Medical examinations, laboratory examinations, self-administered questionnaires, interviews for diagnosis	Stroke, MI, CAD, IBD
Ahn <i>et al.</i> 2019 [47]	Korea	182127	Psychiatric	Korean National Health Insurance Research Database 2015: patients of all ages after surgery during 2015	Physician-registered diagnosis	Subjects without physician-diagnosed AD	Physician-registered diagnosis	ADHD, autism, conduct disorder, depression, anxiety, schizophrenia

Table 1. (Continued).

Author	Country	Total no. subjects included	Comorbid disorder	Data set	AD ascertainment	Control selection	Co-pathology ascertainment	Co-pathologies
Eckert <i>et al.</i> 2019 [48]	France, Germany, Italy, Spain, UK	3720	Psychiatric	NHWS General population survey of adults (>18 years) in 5 European countries 2016	Self-reported physician AD diagnosis	Country, age, sex, education, income, employment status, body mass index, smoking status, and Charlson Comorbidity Index propensity score-matched (1:1) with controls without AD diagnosis	Self-reported physician diagnosis	Depression, anxiety
Hsu <i>et al.</i> 2019 [49]	USA	57961464	Psychiatric	USA Nationwide Inpatient Sample (NIS)	Physician-registered AD diagnosis	Subjects without physician-diagnosed AD	Physician-registered diagnosis	Anxiety, ADHD, personality and behaviour disorder, schizophrenia
Ivert <i>et al.</i> 2019 [50]	Sweden	1127267	Cardio-vascular	Swedish Nationwide health care registries of population (>15 years) from 1968- 2016.	Physician-registered AD	Age and sex matched (1:10) randomly selected population without AD	Physician-registered diagnosis	Hypertension, angina pectoris, MI, stroke
Kim <i>et al.</i> 2019 [51]	Korea	371191	Psychiatric	Korean Nationwide, school based, web survey (KYRBWS) of adolescents (12-18 years) 2007-2016	Self-reported physician diagnosed AD	Subjects without physician-diagnosed AD	Self-report	Depression
Krishna <i>et al.</i> 2019 [52]	UK	3564188	Autoimmune	The Health Improvement Network (THIN) all age patients 1990-2018	Physician-registered AD diagnoses	Age and sex-matched (1:2) patients from same clinic without any allergic disease diagnosis	Physician-registered diagnosis	SLE, MS, Sjogren's syndrome, vitiligo, RA, pernicious anaemia, myasthenia gravis, IBD, celiac disease, autoimmune thyroiditis
Schonmann <i>et al.</i> 2019 [53]	UK	1980710/2242905	Psychiatric	UK Clinical Practice Research Datalink linked to Hospital Episode Statistics (HES) database in adults (>18 years) 1998-2016	Physician-registered AD diagnosis	Age, sex, general practice and calendar time-matched (1:5) patients without AD	Physician-registered diagnosis	Depression, anxiety

AA: alopecia areata; ADHD: attention deficit hyperactivity disorder; CAD: coronary artery disease; IBD: inflammatory bowel disease; ITP: immune thrombocytopenia; MI: myocardial infarction; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus.

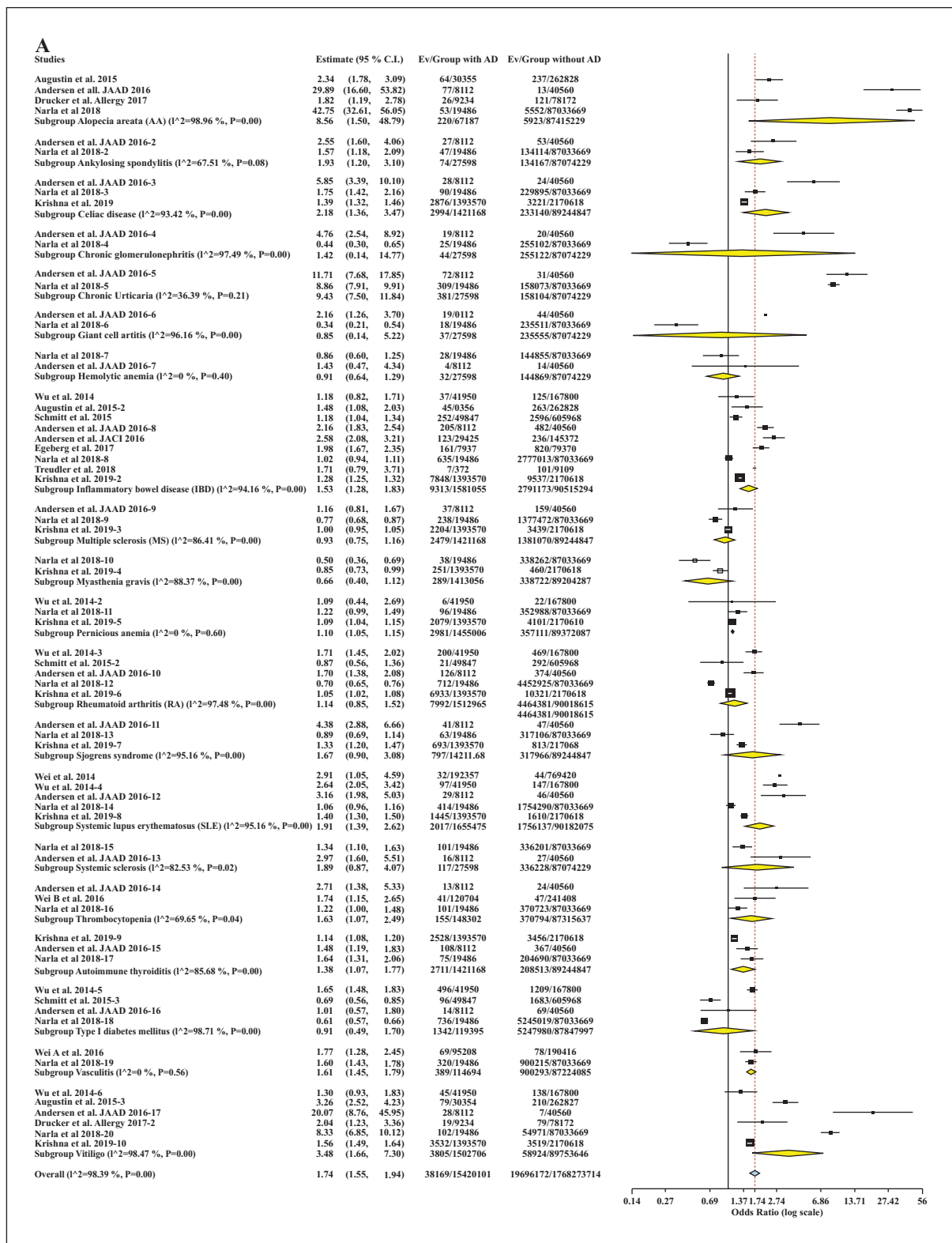


Figure 2. Forest plot for autoimmune diseases meta-analysis. A random-effects model (REM) was used to ascertain a pooled-effect estimates compared to control populations with within-studies and between-studies variance plus sampling error for non-atopic disorders according to autoimmune diseases (A), cardiovascular diseases (B) and mental illnesses (C). For each listed study, estimates and 95% CI are represented by squares and horizontal lines; the size of each square is proportional to the weight of the individual study. The yellow diamond symbolizes the overall pooled estimate for each disorder and according to grouped disorders.

B

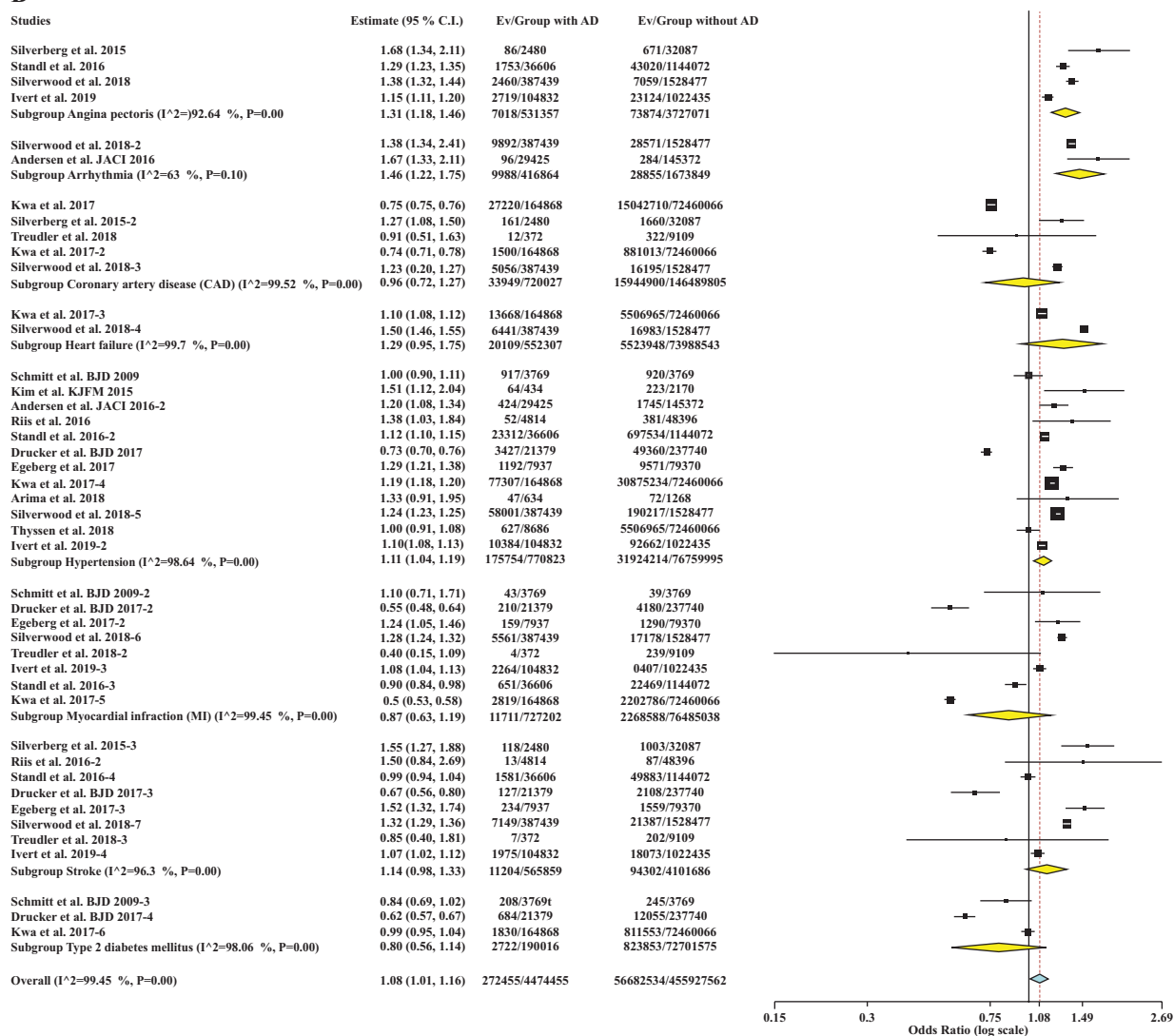


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($I^2: 99.45\%$). CV diseases with the largest effect sizes included angina pectoris (OR: 1.31; 95% CI: 1.18-1.46, $p < 0.001$; $I^2: 92.64\%$) and heart failure (OR: 1.29; 95% CI: 0.95-1.75; $p < 0.001$; $I^2: 99.7\%$); all included studies reported positive associations between AD and the respective CV disorder. Other positive associations were found for stroke and hypertension and negative associations were estimated for carotid artery disease (CAD), myocardial infarction (MI) and type 2 diabetes. A negative association between AD and type 2 diabetes was reported in all included studies (figure 2B).

AD and mental illnesses

Mental illnesses were reported in 17 studies (13 dedicated to mental illnesses only), involving 68,474,524 subjects, of whom 1,441,731 were AD patients (2.1%) from eight countries (Denmark, France, Germany, Italy, Japan, Korea, Spain, Taiwan, UK and USA). Overall, a significant association was estimated with mental illnesses (OR: 1.62; 95% CI: 1.53-1.72; $p < 0.001$), with high heterogeneity among the studies ($I^2: 98.85\%$). All included studies, with the exception of Ahn *et al.* [47] reported a positive

C

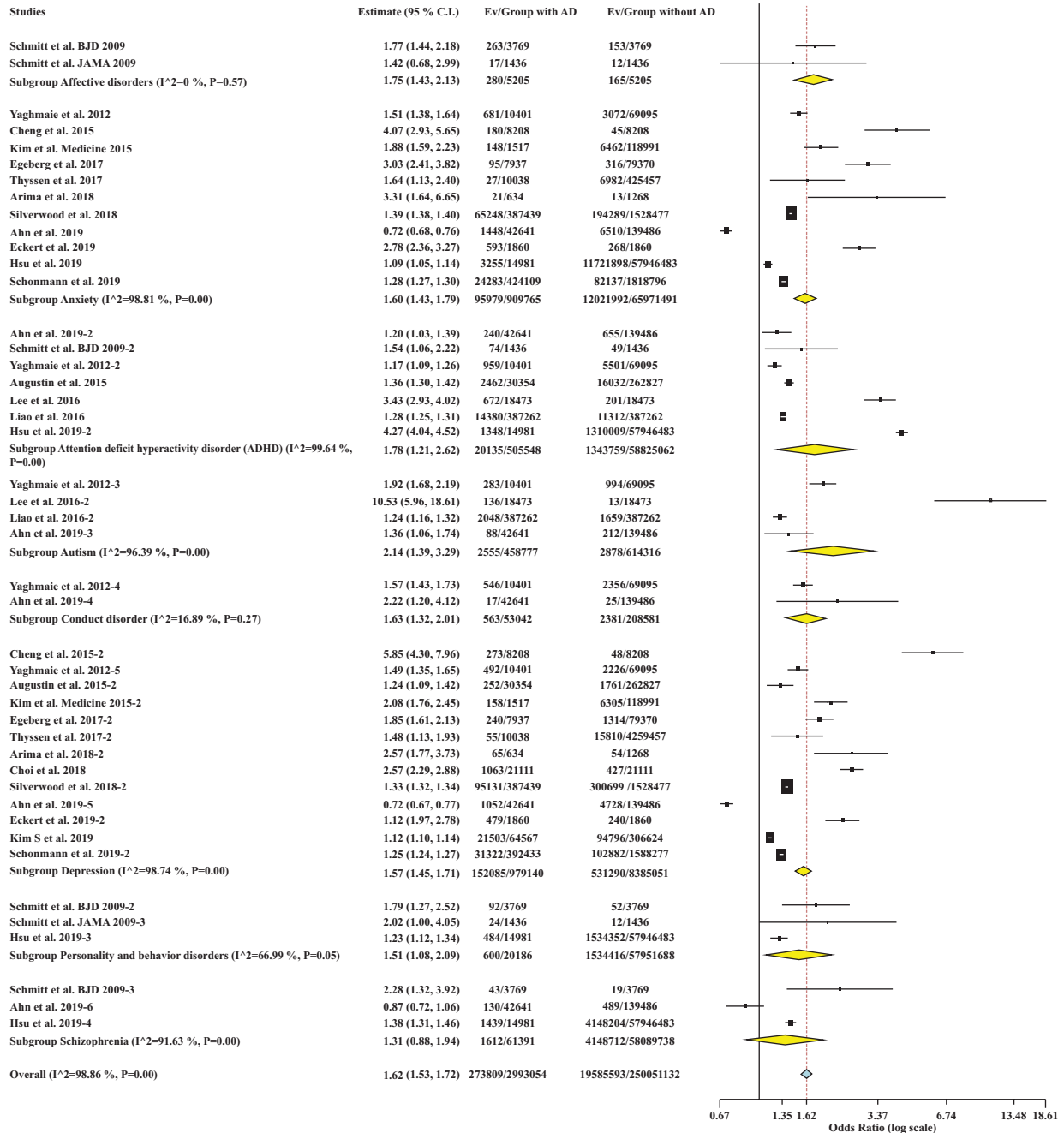


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association between AD and all mental illnesses. Disorders with the greatest effect sizes were autism (OR: 2.14; 95% CI: 1.39-3.29; $p < 0.001$; I²: 96.39%) and ADHD (OR: 1.78; 95% CI: 1.21-2.62; $p < 0.001$; I²: 99.64%). AD was also significantly associated with anxiety, depression, personality and behavioural disorders and schizophrenia (figure 2C).

Publication bias

Publication bias was not detected (plots are close to symmetrical), as a relatively large number of unpublished studies would be required to change statistically significant effects (supplementary figure 1).

Sensitivity analysis

Leave-one-out meta-analysis revealed that individual studies included in the present meta-analysis did not influence the outcomes based on the primary analysis (supplementary figure 2).

Discussion

Overall significant positive associations were established for autoimmune and mental health comorbidities and to a lesser extent, cardiovascular disorders. The mechanism of the association between autoimmunity and AD is unclear [54]. Recently, positive correlations between immunoglobulin (Ig)E autoreactivity and T-helper cell dysregulation have been suggested, supporting the hypothesis that there is an autoimmune mechanism of involvement in AD [15, 43]. Further, AD and autoimmune disorders share a chronic relapsing-remitting pattern of disease, supporting the hypothesis of a pathogenic link [15]. Gene mapping has associated many loci with AD, which are not AD-specific but are shared with many other immune-related inflammatory diseases, and the effects of these loci may be agonistic or opposing [26].

The largest association effect between AD and immune diseases in the current study was estimated for AA (OR: 8.56) and vitiligo (OR: 3.48) and all included studies reported positive associations. A previous meta-analysis [55], which included studies with self-reported AD, smaller cohorts and only 12% of the studies included control groups, reported considerably different effect estimates (2.57 and 7.82, respectively). More recently, Acharya *et al.* [56] reported similar estimates of association with vitiligo in their analysis of case-control/cross-sectional studies (OR: 3.21), but not for those reported in cohort studies (OR: 1.64).

Shi *et al.* [57] very recently reported a significant bidirectional association between AD and IBD based on a meta-analysis of 14 studies. Despite issues of heterogeneity among the studies, a similar risk ratio was estimated (RR: 1.44) in comparison to our current meta-analysis (OR: 1.53). Further, AD as a potential protective factor for the development of type I diabetes has been reported in many single studies and a metanalysis [9, 58, 59]. Our study confirms this inverse relationship. Further, the current study presents other estimates previously not included in meta-analyses, including positive associations with celiac

disease, SLE, systemic sclerosis, Sjorgens's syndrome, thrombocytopenia, chronic glomerulonephritis, autoimmune thyroiditis and RA, and negative associations with MS, giant cell arthritis and myasthenic gravis.

There are inconsistent associations between AD and CV in the literature, which may be heavily influenced by ethnic group, patient age and race, and risk estimates seem greater in more severe and persistent disease [59, 60]. Explanations for these findings include differences in dose-response effect, pathogenesis of disease severity, or effects of systemic therapies used for AD treatment [59, 61]. Some authors have also hypothesized that the main drivers for this association are often poor health behaviours of AD patients, and in studies in which outcomes are adjusted for these factors, generally no augmented CV risks for AD patients are reported [29, 37, 62]. Ascott *et al.* [60] suggests that AD is a chronic inflammatory disease associated with a greater prevalence of some mediators involved in the pathway of CV diseases. Disease-specific estimates in our meta-analysis confirm previously reported meta-analysis results for heart failure [60] and stroke [8, 60, 61]. However, current estimates for angina pectoris (OR: 1.31) and hypertension (OR: 1.11) were lower than previous estimates reported by meta-analyses [60, 61]. Interestingly, this is the first meta-analysis to report significant negative associations between AD and MI and type 2 diabetes [60, 61], and to report pooled negative association estimates for CAD (0.96).

Recently, the concept of psycho-neuro-immune-endocrinology has been used to explain the many associations between atopy, immune dysregulation and the mind [63]. AD has been constantly associated with significantly impaired levels of quality of life, sleep disturbance [64], perceptions of stigmatization [65], anxiety [65-67] and suicide [3]. Any association may be explained by shared inflammatory pathways, over secretion of pro-inflammatory Th1 cytokines (IL-1, IL-6 and TNF α , INF γ) and Th1-related mechanisms (increased INF γ production), contributing to the risk of mental illnesses by penetrating the blood-brain barrier [68, 69]. Other shared biological factors, such as excessive histamine production, genetic predisposition [70] and finally, the psychological impact of such disorders, may also explain this shared comorbidity [63], without a definite role of cause and effect [71]. The 2019 meta-analysis investigating risk estimates for multiple mental illnesses in children (<18 years) [72] reported overall risk estimates similar to those reported in the current study (1.65 vs 1.62, respectively), despite study design differences. For specific mental illnesses, current anxiety and depression estimates (1.60 and 2.14 respectively) were within estimate ranges reported by Roonstad *et al.* [13] for adults and Xie *et al.* [72] for children. Xie *et al.* [72] concluded higher current estimates for ADHD, lower estimates for autism and significant associations for conduct disorder, which in the current study was assessed as insignificant; marked differences in meta-analysis design may account for these singular estimate differences. The temporal relationship needs to be investigated in prospective studies and the impact of AD on quality of life is not restricted to mental illnesses alone, and recent estimates suggest that AD patients have a 36% higher likelihood of attempting suicide [3].

The present study has several limitations. Information regarding time of disease and comorbidity onset was gen-

erally unavailable and cause and effect or different risks of adult or juvenile-onset AD cannot be hypothesized. Given the stigmatization and often underdiagnosis of mental health, current estimates may not represent the full psychological impact of AD. However, this meta-analysis reports high heterogeneity amongst the included studies from 12 countries with low publication bias, including an extremely large AD patient and concurrent control population. Such pooled data in a single meta-analysis provides an important update of global estimations for some AD-associated disorders, previously not included in meta-analyses. The data provided by this study are important for future association studies and guidelines for the role of the dermatologist in managing AD.

Conclusions

Global pooled estimates of 3.7 million AD patients from 12 countries confirm the association of AD with many autoimmune and mental illnesses and limited associations with some CV diseases. The pooled estimates for many associated illnesses may assist the dermatologist and patient in considering further medical and wellness interventions for optimal patient care. ■

Disclosure. *Acknowledgements: none. Financial support: none. Conflicts of interest statement: none. Data availability statement: The data that support the findings of this study are openly available in Mendeley Data at <http://dx.doi.org/10.17632/3xc4rjx6wj.1> Chester, Johanna; Kaleci, Shaniko [2020].*

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1684/ejd.2021.4168.

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