

REVIEW ARTICLE

Is atopic dermatitis associated with obesity? A systematic review of observational studies

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Abstract

Obesity has been associated with atopic dermatitis (AD); however, the results have been conflicting. Our aim was to provide an update on current knowledge from observational studies addressing the possible association between obesity and AD. Systematic literature review was performed by identifying studies addressing a possible link between AD and overweight/obesity from PubMed, EMBASE and the Cochrane Library in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The quality of the included studies was assessed using the Newcastle–Ottawa Scale. A total of 45 studies (comprising more than 90 000 individuals with AD) fulfilled the criteria and were included in the present review. The available studies revealed inconsistencies, but the majority indicated that obesity is associated with AD. Studies addressing obesity in infancy or early childhood (age < 2 years) and AD reported a positive association. From childhood into adulthood, there is a discrepancy in the observations, as the more recent prospective studies found a positive association, whereas this was not observed in older cross-sectional studies. The inconsistency might be explained by the difference in study design, the diagnostic criteria of AD, regional differences, and by the varied definitions of overweight and obesity used in the studies. In Conclusion, overweight/obesity is associated with an increased risk of AD. Large prospective cohort studies are required to confirm the association between AD and obesity and the possibility that weight control in childhood may help to mitigate or reverse AD symptoms.

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Introduction

Atopic dermatitis (AD) is an inflammatory, chronically relapsing and intensely pruritic skin disease characterized by dry skin.¹ The prevalence of AD has increased in the past three decades and is now as high as 20% in industrialized countries.^{2–8} Furthermore, it is the highest ranked skin disease with respect to disability-adjusted life years and years lived with a disease.⁹

The prevalence of obesity has also increased over the last few decades.¹⁰ Research on the association between obesity and atopic diseases has mostly focused on asthma and asthma-like symptoms. Obesity-related reductions in pulmonary function, as well as leptin and tumour necrosis factor production by adipose tissue, have been suggested as the mechanisms underlying asthma development in obese individuals.^{11,12} With the complex aetiology of AD, involving both genetic factors, such as *filaggrin*

(*FLG*) mutations, and environmental factors,^{9,13} the increased prevalence of obesity and overweight could contribute to the AD epidemic.¹⁴ However, little is known about the relationship of body mass index (BMI) to other atopic disorders in children, such as AD, and the available information is conflicting.^{15,16} The association between AD and obesity has a great clinical importance as obesity may be a modifiable risk factor for AD or a comorbidity of AD. The identification of modifiable risk factors for AD enables development of novel strategies for prevention and management of AD. Several modifiable risk factors for AD have previously been identified, including stress, irritants, food, inhalant and contact allergens.¹⁷ Furthermore, obesity has been associated with increased morbidity and mortality and is, therefore, an important comorbidity to be aware of when consulting patient with AD.

The aim of this systematic review was, therefore, to provide an update on current knowledge from population studies addressing the possible association between adiposity and AD.

Methods

We conducted a systematic literature review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement¹⁸ searching the PubMed database, EMBASE and the Cochrane Library, last updated September 2017. The searches were carried out using the following terms: 'obesity' or 'overweight' or 'adiposity' or 'body mass index' AND 'atopic dermatitis' or 'eczema'. Papers were included in the present review provided that they fulfilled the following inclusion criteria: (i) studies (either prospective or retrospective in design) containing data of the association between AD and overweight/obesity, and (ii) BMI as main measure of overweight/obesity. Non-English papers and studies in abstract form or meeting reports were excluded. A total of 257 articles in the PubMed database, 802 in EMBASE and 179 in the Cochrane Library were identified and reviewed for possible inclusion. Studies were excluded based on content of the abstract if there was no clear indication that they were investigating characteristics of overweight/obesity or AD. Furthermore, duplicate articles were excluded. A total of 78 articles were reviewed for possible inclusion in this study, and all studies with primary epidemiologic data reporting the relationship between AD and overweight/obesity were included in the present review ($n = 45$) (Fig. 1). The quality of the studies was assessed using the Newcastle–Ottawa Scale (NOS).¹⁹ NOS is a tool for assessing the quality of non-randomized studies included in a systematic review and/or meta-analyses. Using the tool, each study is

judged on eight items, categorized into three groups based on the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome. Stars are awarded for each numbered item within the selection and outcome categories, and a maximum of two stars for comparability. The highest quality studies are awarded up to nine stars.

Results

A total of 45 studies, comprising more than 90 000 individuals with AD, were included in the present review. Two studies investigated the association between obesity and AD in early childhood, 35 in children and adolescents, and eight in adults.

Obesity and atopic dermatitis in early childhood

In a secondary analysis of a randomized clinical trial investigating treatment for airway obstruction in acute bronchiolitis from 2010 to 2014 in Norway, Berents *et al.*²⁰ investigated the association between BMI in infancy and the development of AD in early life (2-year follow-up). In the original study,²¹ children hospitalized for acute bronchiolitis before 12 months of age were included as cases ($n = 404$) and controls were children recruited from the general population ($n = 238$). The 2-year follow-up visit was attended by 294 children from the bronchiolitis group (follow-up rate 73%, lost to follow-up $n = 110$) and 205 children recruited from the general population (follow-up rate 85%, lost to follow-up $n = 33$). Data on weight and length were obtained from 473 children at the 2-year follow-up visit. AD was diagnosed clinically by experienced physicians based on the diagnostic criteria of Hanifin & Rajka,²² and the severity of AD was assessed using the SCORing Atopic Dermatitis index (SCORAD index).²³ At the 2-year follow-up visit, AD was diagnosed in 106 of 473 children (22%), of whom 72 (68%) fulfilled the Hanifin & Rajka's diagnostic criteria. BMI was positively associated with an increased risk of being classified as having AD at the follow-up visit, whereas no association was found between BMI and the severity of AD (Table 1).

In a non-interventional, single-centre birth cohort study, O'Donovan *et al.*²⁴ sought to describe risk factors for AD in the first year of life. All women participating in the Screening for Pregnancy Endpoints (SCOPE) study²⁵ (a global multicentre longitudinal cohort study of low-risk primiparous women, with the main aim of developing screening tests for the major diseases of late pregnancy) were invited to partake in the study of risk factors for AD in the first year of life. Clinical assessments were carried out at day 2 and at 2, 6 and 12 months of age. AD was diagnosed using The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis.²⁶ From 2008 to 2011, 1,537 infants were recruited; however, only 709 attended and completed the 12-month assessment. The prevalence of persistent AD at 12 months was 7.5% (99% CI, 5.0% to 9.9%). Fat mass (in kilograms) at the 80th percentile or greater at day 2 was significantly associated with persistent AD at twelve months of age (OR 2.31;

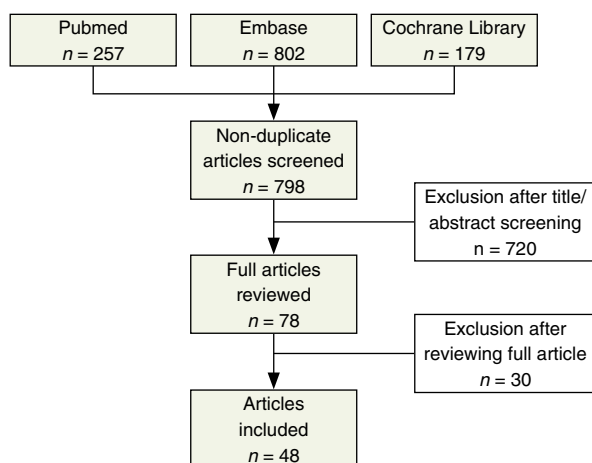


Figure 1 Flow diagram of literature search and study selection for the association between atopic dermatitis and overweight/obesity.

Table 1 Population studies of the association between overweight/obesity and atopic dermatitis in early childhood

No	First author, year published	Study design	Location	n	AD (n)	Age (months)	Assessment of AD	Assessment of adiposity	Conclusion	NOS Score
1	Berents, 2017 ²⁰	Prospective	Norway	642	72	0–14 at enrolment and 18–35 at 2-year follow-up	Hanifin & Rajka	WHO cut point	Overweight is positively associated with the development of AD.	8
2	O'Donovan, 2016 ²⁴	Prospective	Australia	709	53	6–12	The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis.	Fat mass	Neonatal adiposity is positively associated with persistent AD at twelve months of age.	6

NOS, Newcastle–Ottawa Scale; WHO, World Health Organization; IOTF, International Obesity Task Force; BMI SDS, body mass index standard deviation score; CDC, The Centers for Disease Control and Prevention; ECOG, European Childhood Obesity Group.

99% CI 1.02–5.25; $P = 0.009$) compared with infants who never had AD (27% vs 15%).

Both cohort studies are published very recently and found a positive association between AD and obesity (comprising 125 individuals with AD). None of the studies investigating the association between obesity and AD in early childhood has a representative cohort of the general population. In the study by Berents *et al.*,²⁰ more than 50% of the cohort consist of children hospitalized for acute bronchiolitis. Children with acute bronchiolitis do not represent the general population or the common population with AD. In the study by O'Donovan *et al.*,²⁴ only primiparous women with a singleton pregnancy from the Cork region of Australia were recruited. The cohort was not nationally representative, as a higher number of tertiary educated mothers were recruited in this cohort. AD has been associated with higher levels of the mother's education.²⁷ Furthermore, a limited percentage (around 50%) of the recruited cohort attended the 12-month assessment and were included in the final analysis.

Obesity and atopic dermatitis in children and adolescents

D'Auria *et al.*²⁸ conducted a case–control study over a 12-month period in children with AD selected among those consecutively referred for evaluation at the Department of Pediatrics, Unit of Allergy or to the Unit of Dermatology, in Milan. Among the children referred, 54 children aged 1–11 years were considered eligible of whom 52 parents accepted the invitation. During the same period, 43 healthy children without AD (age 1–14 years) consecutively evaluated at the same department before undergoing minor surgical procedures (dental extraction, cyst excision, circumcision) were enrolled as non-matched controls. AD was diagnosed according to the Hanifin and Rajka criteria,²² and the severity was assessed by means of the SCORAD index.²³ AD was classified as mild (SCORAD < 25), moderate (SCORAD 25–40) and severe (SCORAD > 40). BMI z scores were calculated using World Health Organization (WHO) growth standards. Among children with AD, 12 had mild AD, 25 moderate and 15 severe. The mean SCORAD was 33.6 (SD = 12.4). BMI was not significantly different between AD children and controls, and furthermore, BMI z scores did not correlate with the SCORAD index ($r = 0.131$). However, a positive correlation between BMI and AD severity was observed when the analysis was limited to male children with AD ($r = 0.426$).

In a US multicentre, cross-sectional study by Silverberg *et al.*²⁹ conducted from 2009 to 2012, 132 individuals with AD aged 4–17 years were included. Children attending the same dermatology centres for other skin problems (e.g. naevi, molluscum contagiosum, warts and acne) with similar age, sex and ethnicity without skin or systemic inflammatory or allergic diseases were recruited as controls ($n = 143$). Hanifin and Rajka criteria were used to diagnose AD, and the severity was classified using a physician's global assessment score as moderate, severe and very severe. Overweight and obesity cut-offs for BMI percentile were defined according to the recommendations of The Centers for

Disease Control and Prevention (CDC) (85th–94th, and ≥ 95 th percentiles)³⁰ and the European Childhood Obesity Group (ECOG) (90th–96th, and ≥ 97 th percentiles).³¹ Overweight and obesity were further defined using the international cut-offs proposed by the International Obesity Task Force (IOTF) that correspond to BMIs of 25 and 30 in adulthood.³²

AD prevalence was associated with BMI in the 97th percentile or higher when the classification of the ECOG was used (OR, 2.64; 95% CI, 1.15–6.06). Similarly, AD was associated with obesity as defined by the IOTF cut-offs (OR, 2.38; 95% CI, 1.06–5.34) but not by the CDC criteria (OR, 1.64; 95% CI, 0.82–3.29). The associations remained significant after controlling for age, race/ethnicity and sex. Furthermore, AD prevalence was associated with central obesity as judged by a waist circumference in the 85th percentile or greater (OR, 3.92; 95% CI, 1.50–10.26) and a waist-to-height ratio in the 5th percentile or greater (OR, 2.22; 95% CI, 1.10–4.50).

A cross-sectional study conducted in France by Saadeh *et al.*³³ from 2000 to 2001 with 6,733 schoolchildren aged 9–11 years did not find any association between high BMI and AD. AD was diagnosed based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire,³⁴ and overweight and obesity were based on The International Obesity Task Force (IOTF) cut-offs. Furthermore, a Canadian study by Wang *et al.*³⁵ also using the ISAAC questionnaire found no association between obesity and AD. The study was conducted from April to December 2003, and 8334 children aged 13–14 were included. Age- and sex-specific BMI cut points by Cole *et al.*³² were used. The overall prevalence rate of current AD was 9.4%. Another cross-sectional study from Australia by Tai *et al.*³⁶ conducted between August and December 2006 also using the ISAAC questionnaire with 1509 preschool children 4–5 years of age found no association between obesity and AD. The prevalence of AD was 18.8%.

A total of 35 studies have investigated the association between AD and obesity in children and adolescents (<18 years of age) comprising around 86 000 individuals with AD (Table 2). Twelve studies were conducted in Asia, 15 in Europe, four in America, one in Australia and two were multinational studies. Twenty-one studies of 35 found a positive association. Overall, the majority (nine of 12) of the prospective and case-control studies found a positive association between obesity and AD in children and adolescents, of which two studies found a positive association between obesity and AD severity. Furthermore, a greater number of these studies are of recent date and conducted in Europe. However, they are limited by a small sample size. The cross-sectional and retrospective studies are larger studies comprising more than 80 000 individuals with AD. More than half of these studies found no association, and around 50% of them are conducted in Asia.

Obesity and atopic dermatitis in adulthood

In a cross-sectional study by Silverberg *et al.*,³⁷ cardiovascular risk factors for doctor-diagnosed AD were determined in 34 525

adults aged 18–85 years living in the United States. The prevalence of AD was estimated to be 7.2% and those with AD had a significantly higher BMI than did those without (adjusted β , 0.86, 95% CI 0.37–1.36; $P < 0.001$). In particular, AD was associated with class II/III obesity (body mass index of 35 or more) even after controlling for sociodemographic factors (OR, 1.54, 95% CI 1.16–2.05; $P = 0.003$) and comorbid asthma and hay fever (OR, 1.22, 95% CI 1.03–1.46; $P = 0.02$). Another retrospective case-control study by Silverberg *et al.*³⁸ with 2090 adults aged 19–60 also found an association between obesity (BMI > 30 kg/m²) and AD prevalence based on Hanifin and Rajka criteria²² (OR 1.43, 95% CI 1.08–1.89; $P = 0.01$).

In a cross-sectional study with national representative data of 5202 Korean adults aged 19–40 years, Lee *et al.*³⁹ only found a positive association between BMI ≥ 25 kg/m² and doctor-diagnosed AD in women (OR 4.08, 95% CI 1.53–10.93), but not in men. Furthermore, Kilpeläinen *et al.*⁴⁰ have shown that the risk of physician-diagnosed AD increased linearly with BMI in women but not men in a questionnaire study among 10 667 Finnish first-year university students aged 18–25 years.

In a recent questionnaire-based survey by Rönmark *et al.*,⁴¹ 30 000 randomly selected individuals in West Sweden aged 16–75 years received a mail to fill out a questionnaire. BMI was defined as normal (20–25 kg/m²), underweight (<20 kg/m²), overweight (25–30 kg/m²) and obesity (>30 kg/m²). The prevalence of self-reported current AD was 13.5%, and obesity was not a risk factor for AD (OR 1.43, 95% CI 0.89–2.31). Additionally, another questionnaire-based survey by Sybilski *et al.*¹⁶ with 8,617 participants (24.2% aged 6–7 years, 25.4% aged 13–14 years and 50.4% adults aged 20–44 years) also found no association between obesity and AD.

Eight studies investigated the association between AD and obesity in adulthood (7000 individuals with AD) of whom five studies found a positive association (Table 3). There are four prospective and case-control studies, and three of these studies found a positive association. A prospective study by Shaheen *et al.*⁴² did not find any association; however, it was conducted in 1999. Furthermore, two of four cross-sectional studies found a positive association.

Discussion

The limited number of studies addressing AD and obesity in infancy or early childhood (age < 2 years) concluded that there is a positive association between overweight/adiposity in infancy (and the development of AD in early life. However, studies addressing AD and obesity in infancy and early childhood do not have a representative cohort. Conversely, there was an inconsistency in the studies from childhood and adulthood due to varying definitions of overweight and obesity, differences in the diagnostic criteria of AD and regional differences. However, the majority of the studies found a positive association between obesity/overweight and AD in childhood and adulthood.

Table 2 Population studies of the association between overweight/obesity and atopic dermatitis in children and adolescents

No	First author, year published	Study design	Location	N	AD (n)	Age (years)	Assessment of AD	Assessment of adiposity	Conclusion	NOS Score
1	Hesketh, 2016 ⁴⁹	Prospective	United Kingdom	11 399	3585	11	Parent-reported	IOTF cut points	Overweight was positively associated with AD prevalence	6
2	Byberg, 2016 ⁴⁴	Prospective	Norway	617	544	12–13	Doctor-diagnosed	BMI SDS	BMI in childhood was positively associated with AD in late childhood.	8
3	Lei, 2016 ⁷⁴	Prospective	China	3327	493	2–14	Hanifin & Rajka	Local age- and sex-specific cut points	Obesity was associated with an increased prevalence of AD	7
4	Koutroulis, 2015 ⁴⁶	Prospective	Philadelphia	104	104	0–18	SCORAD	CDC standards	BMI > 24 kg/m ² was significantly associated with SCORAD severity categories for children over the age of 2 years	6
5	Sidoroff, 2012 ⁷⁵	Prospective	Finland	82	68	7–13	Doctor-diagnosed	BMI SDS using the British Growth Reference	Obesity was associated with a decreased risk of AD	5
6	Kajbaf, 2011 ⁵²	Prospective	Iran	903	–	7–11	ISAAC questionnaire	Age- and sex-specific BMI cut points by Cole <i>et al.</i> ³²	No association	6
7	Murray, 2011 ⁶⁸	Prospective	United Kingdom	731	49–66 (according to age)	3–8	Parent-reported	BMI SDS using the British Growth Reference and Cole <i>et al.</i> ³²	Being overweight at age 3 years was significantly associated with persistent AD	8
8	Mai, 2007 ⁵⁵	Prospective	Sweden	2869	624	4	ISAAC questionnaire	IOTF cut points	No association	7
9	D'Auria, 2017 ²⁸	Case-control	Italy	95	52	1–14	Hanifin & Rajka	WHO cut point	BMI was not associated with AD; however, a positive correlation was observed between BMI and the AD severity in males.	8
10	Silverberg, 2015 ²⁹	Case-control	United States	275	132	4–17	Hanifin & Rajka	CDC, ECOG and IOTF	AD was positively associated with BMI	8
11	Silverberg, 2011 ⁷⁶	Case-control	United States	1242	414	1–21	ICD-9 codes	CDC and WHO percentiles	Prolonged obesity in early childhood is a risk factor for AD	8
12	Mai, 2003 ⁷⁷	Case-control	Sweden	2505	199	11–13	ISAAC questionnaire	Local age- and sex-specific cut points	High BMI tended to be associated with ever AD	7
13	Lim, 2017 ⁴³	Cross-sectional	Korea	53769	3546	12–18	Doctor-diagnosed	Obesity ≥95th percentile and overweight ≥85th percentile	Overweight and obesity were positively associated with AD prevalence	6
14	Lee, 2016 ⁴⁸	Cross-sectional	Korea	75 643	17 474	13–18	Doctor-diagnosed	Local age- and sex-specific cut points	Obesity was not a significant risk factor for AD. However, after adjusting for socio-economic and sociodemographic variables, it became significant.	6
15	Saadeh, 2014 ³³	Cross-sectional	France	6733	1725	9–11	ISAAC questionnaire	IOTF cut points	No association	7
16	Weinmayr, 2014 ⁷⁸	Cross-sectional	Multicountry	10 652	4292	8–12	ISAAC questionnaire	Age- and sex-specific BMI cut points by Cole <i>et al.</i> ³²	Overweight and obesity were positively associated with AD in affluent countries but not in non-affluent countries.	8

Table 2 Continued

No	First author, year published	Study design	Location	N	AD (n)	Age (years)	Assessment of AD	Assessment of adiposity	Conclusion	NOS Score
17	Silverberg, 2014 ⁴⁷	Cross-sectional	United States	45 897	4108	10–17	Doctor-diagnosed	CDC standards	BMI was significantly associated with AD prevalence. Obesity was associated with increased severity of AD	6
18	Song, 2014 ⁵⁰	Cross-sectional	China	10 338	1219	6–18	ISAAC questionnaire	BMI	No association	5
19	Mitchell, 2013 ⁷⁹	Cross-sectional	Multicountry	277 534	–	6–14	ISAAC questionnaire	Age- and sex-specific BMI cut points by Cole <i>et al.</i> ³²	Overweight and obesity were positively associated with AD symptoms	6
20	Vicedo-Cabrera, 2012 ⁸⁰	Cross-sectional	Spain	21 355	1276	6–7	ISAAC questionnaire	Age- and sex-specific BMI cut points by Cole <i>et al.</i> ³²	A higher prevalence of AD was found in obese children	6
21	Tanaka, 2011 ⁵¹	Cross-sectional	Japan	24 399	1684	6–15	ISAAC questionnaire	Local age- and sex-specific cut points	No association	6
22	Yao, 2011 ⁸¹	Cross-sectional	Taiwan	5351	1124	4–18	ISAAC questionnaire	IOTF cut points	Elevated BMI was associated with greater prevalence of AD	6
23	Yoo, 2011 ⁸²	Cross-sectional	Korea	717	142	15–17	Doctor-diagnosed	Local age- and sex-specific cut points	No association	8
24	Wang, 2010 ³⁵	Cross-sectional	Canada	8334	783	13–14	ISAAC questionnaire	Age- and sex-specific BMI cut points by Cole <i>et al.</i> ³²	No association	6
25	Tai, 2009 ³⁶	Cross-sectional	Australia	1509	284	4–5	ISAAC questionnaire	IOTF cut points	No association	6
26	Leung, 2009 ⁵³	Cross-sectional	China	486	76	14–16	ISAAC questionnaire	Local age- and sex-specific cut points	No association	7
27	Van Gysel, 2009 ⁵⁴	Cross-sectional	Belgium	1576	363	3–15	ISAAC questionnaire	Age- and sex-specific BMI cut points by Cole <i>et al.</i> ³² and WHO cut point	No association	7
28	Kusunoki, 2008 ⁸³	Cross-sectional	Japan	45 520	3014	7–15	ISAAC questionnaire	Obesity ≥95th percentile and overweight ≥85th percentile	Childhood obesity was associated with AD severity	7
29	Silva, 2007 ⁸⁴	Cross-sectional	Portugal	228	6	5–16	ISAAC questionnaire	CDC standards	No association	7
30	Vlaski, 2006 ⁵⁶	Cross-sectional	Republic of Macedonia	2926	198	13–14	ISAAC questionnaire	Age- and sex-specific BMI cut points by Cole <i>et al.</i> ³²	No association	6
31	Lee, 2001 ⁸⁵	Cross-sectional	Korea	38 955	2439	6–15	ISAAC questionnaire	BMI	High BMI increases the risk of AD	6
32	Von Kries, 2001 ⁸⁶	Cross-sectional	Germany	9317	–	5–6	Doctor-diagnosed	Local age- and sex-specific cut points	No association	6
33	Lin, 2015 ⁴⁵	Retrospective	Taiwan	74 688	5676	13–15	Doctor-diagnosed	Local age- and sex-specific cut points	Adolescents with high BMI measures (>23 kg/m ²) were more likely to develop AD	6
34	Augustin, 2015 ⁸⁷	Retrospective	Germany	293 181	30 354	0–18	ICD-10 codes	ICD-10 codes	Obesity is positively associated with AD prevalence	6
35	Ellison, 2006 ⁸⁸	Retrospective	United Kingdom	–	110	5–7	ISAAC questionnaire	Cole U.K. references	Overweight is positively associated with AD prevalence	7

NOS, Newcastle–Ottawa Scale; WHO, World Health Organization; IOTF, International Obesity Task Force; BMI SDS, body mass index standard deviation score; CDC, The Centers for Disease Control and Prevention; ECOG, European Childhood Obesity Group.

Table 3 Population studies of the association between overweight/obesity and atopic dermatitis in adulthood

No.	First author and year published	Study design	Location	N	AD (n)	Age (year)	Assessment of AD	Assessment of adiposity	Conclusion	NOS Score
1	Lee, 2016 ³⁹	Prospective	Korea	5202	230	19–40	Doctor-diagnosed	Obesity: BMI ≥ 25 kg/m ²	Obesity was positively related to the presence of AD in women.	7
2	Shaheen, 1999 ⁴²	Prospective	United Kingdom	8960	1032	26	Self-reported	Overweight: BMI 25–29.99 kg/m ² . Obesity BMI > 30 kg/m ²	No association	6
3	Luo, 2013 ⁸⁹	Case-control	China	798	90	Mean 38.5	Doctor-diagnosed	Obesity: BMI ≥ 28 kg/m ²	Obesity is significantly associated with AD	7
4	Silverberg, 2012 ³⁸	Case-control	United States	2090	951	19–60	Hanifin & Rajka	Obesity: BMI ≥ 30 kg/m ²	Obesity in adulthood is positively associated with AD	8
5	Rönmark, 2016 ⁴¹	Cross-sectional	Sweden	1172	158	18–77	Self-reported	Overweight: BMI 25–30 kg/m ² , obesity: BMI > 30 kg/m ²	No association	7
6	Silverberg, 2015 ³⁷	Cross-sectional	United States	34 525	2486	18–85	Doctor-diagnosed	BMI	AD was associated with higher BMI	8
7	Sybilski, 2015 ¹⁶	Cross-sectional	Poland	18 617	728	6–44	Hanifin & Rajka	Local age- and sex-specific cut points	No association	6
8	Kilpeläinen, 2006 ⁴⁰	Cross-sectional	Finland	10 667	1350	18–25	Doctor-diagnosed	BMI	Higher BMI is associated with AD in women but not men	5

NOS, Newcastle-Ottawa Scale; WHO, World Health Organization; IOTF, International Obesity Task Force; BMI SDS, body mass index standard deviation score; CDC, The Centers for Disease Control and Prevention; ECOG, European Childhood Obesity Group.

In general, recent studies have found that prevalence of AD is positively associated with obesity, overweight or high BMI. The studies are based on doctor-diagnosed AD,^{37,43–47} and few studies adjust for possible confounders.^{43,48,49} Older studies have not been able to find this association. However, they often use ISAAC criteria to diagnose AD,^{33,36,50–56} and the most commonly used questions are “Have you ever had an itchy rash which was coming and going for at least 6 months? Have you had this itchy rash at any time in the past 12 months?” Nevertheless, these questions have been validated with a high sensitivity and specificity.²⁶ The difference in the diagnostic criteria along with the increased prevalence of obesity over the last few decades¹⁰ might explain the inconsistency in newer and older studies.

Furthermore, regional differences in risk factors such as industrialization, urban living, race, educational levels, household incomes and family sizes could confound the association and explain why the association is significant in some regions but not others.⁵⁷

Lastly, the inconsistent results could be explained by the varying definitions of overweight and obesity used in studies. There are no universally agreed definitions for high BMI in children or adolescents. Children’s BMI varies with age, gender and ethnicity. Children grow in height and weight at different speeds, their BMI will rise in the first years of life, drop in the early school years and raise again towards adulthood.³² Consequently, different national and international references are used to classify childhood obesity. Children and adolescents are categorized as obese by comparing their BMI with a statistical distribution in a reference population. If the child’s BMI is higher than a specific age and sex-specific cut-off value in the particular reference population, the child is classified as obese. As the reference populations and the associated cut-off values are different, the prevalence of the investigated disease will also vary depending on the reference used.

The underlying mechanisms between obesity and AD are not straightforward and only incompletely understood. Obesity is associated with persistent low-grade systemic inflammation and by that regarded as a pro-inflammatory state.¹² Visceral adipose tissue is an important source of cytokine production, whereby adiposity contributes to the pro-inflammatory milieu and is responsible for the formation of low-grade chronic inflammation.¹² Adipose tissue produces a number of mediators, termed adipokines, which have significant metabolic effects. The two important adipokines are leptin and adiponectin. Leptin stimulates the production of inflammatory mediators such as TNF and IL-6 from the adipose tissue.^{58,59} TNF establishes a positive feedback mechanism by promoting the expression and release of leptin from the adipose tissue.^{60,61} Furthermore, Leptin promotes CD4 (+) T lymphocyte activation towards the Th1 phenotype with increased production of interferon γ ⁶² and thereby leads to production of pro-inflammatory cytokines, including TNF, IL-6 and interferon γ , well known to be associated with AD.⁶³

Adiponectin levels decrease in obesity and are inversely related to BMI.⁶⁴ The anti-inflammatory effects of adiponectin are inhibition of the production of the pro-inflammatory cytokines IL-6 and TNF.⁶⁵ Low adiponectin levels have also been associated with increased prevalence of AD in population studies.⁶⁶

In addition, obesity has been shown to alter the skin’s epidermal barrier, leading to increased transepidermal water loss and dry skin,⁶⁷ which may aggravate underlying barrier defects in AD.

Some studies^{39, 40, 68} only found the association between obesity or high BMI and AD in females. The same trend has also been observed in the association between obesity and asthma.¹² The observed gender difference may be related to the sex hormone oestrogen as adipose tissue is recognized as metabolically active, and in obesity, androgen levels are increased.¹² Oestrogen is associated with collagen synthesis, increased skin thickness and dermal water content (through hyaluronic acid production), and improved barrier function.⁶⁹ However, peripheral aromatization of androstenedione to oestrone and testosterone to oestradiol occurs within the stroma of adipose tissue.⁷⁰ Studies on mice have shown that administration of β -oestradiol in female mice results in a shift in the immunological reaction from a Th1 to a Th2 type. Studies have demonstrated that γ -oestradiol increases IL-4 and IL-13 production from blood monocytes and increases both eosinophil recruitment and degranulation.¹² Furthermore, BMI is known indicator for adiposity; however, the level of body fat varies widely and is not linearly correlated to BMI. Women tend to have more body fat than men at a given BMI⁷¹ and are expected to have a higher exposure to inflammation than men at a given BMI. Additionally, women have greater intramuscular fat infiltration in their lean mass compared to men, which results in high systemic leptin levels, low systemic adiponectin levels and increased expression of TNF.^{72,73} This may also explain a stronger association in women.

In conclusion

There is an inconsistency in the reported observations; however, the majority of the studies indicate that obesity is associated with AD. This has great clinical importance as obesity may be a modifiable risk factor for AD, and it is well known that obesity is related to many health issues. Further large-cohort, prospective studies are required to confirm the association between AD and obesity and the possibility that weight control early in life may help to mitigate or reverse AD symptoms. The mechanism for the association between obesity and AD is only incompletely understood. Understanding of the underlying mechanisms would have significant implications for patients suffering from AD.

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