Bone mineral density, osteopenia, osteoporosis, and fracture risk in patients with atopic dermatitis: a systematic review and meta-analysis

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Background: The relationship between atopic dermatitis (AD) and abnormal bone metabolism remains unclear. We performed a systematic review and meta-analysis to determine whether patients with AD were associated with increased risks of low bone mineral density (BMD), osteopenia, osteoporosis, and related fractures.

Methods: We searched PubMed, Embase, and the Cochrane Library through December 2019 to identify studies that investigated the association between AD and abnormal bone metabolism (including BMD, osteopenia, osteoporosis, and related fractures). The predefined primary outcome was related fractures; secondary outcomes included osteoporosis, osteopenia, and BMD. We calculated the summary odds ratios (ORs) and 95% confidence intervals (CIs) using a random-effects model.

Results: Ten studies were included in this systematic review. In children and adolescents, four studies investigated the association between AD and BMD; three studies indicated that children and adolescents with AD were associated with an increased risk of low BMD; one study found similar BMD between AD and control groups. In adults, three studies assessed the risk of fracture and were included in the meta-analysis, comprising 562,405 AD patients among 3,171,268 participants. Adults with AD were associated with an increased risk of fracture (OR 1.13; 95% CI, 1.05–1.22; P=0.001). Three studies investigated the association between AD and osteoporosis, which suggested that patients with AD were associated with an increased risk of osteoporosis (OR 1.95; 95% CI, 1.18–3.23; P=0.009). Further, patients with AD were associated with increased risks of osteopenia (OR 1.90; 95% CI, 1.51–2.38; P<0.001) and low BMD at the femur and spine.

Conclusions: Patients with AD were associated with increased risks of low BMD, osteopenia, osteoporosis, and related fractures. Both clinical studies and basic research are needed to clarify the mechanisms of association between AD and abnormal bone metabolism.

Keywords: Atopic dermatitis (AD); bone mineral density (BMD); osteopenia; osteoporosis; fracture

Introduction

Atopic dermatitis (AD) is a common chronic, pruritic inflammatory skin disease, which afflicts not only 10–20% of children and adolescents, but also 2–10% adults around the world (1-4). With an increasing prevalence of AD and its manifestation in developed and developing countries, together with more supporting evidence of the progression to other long-term sequelae, AD has developed into a worldwide public health problem and burden.

During the past years, there is growing evidence that suggests that people who suffer from AD are more likely to have a lower bone mineral density (BMD), higher prevalence of osteopenia, osteoporosis, and related fractures when compared with those without AD (5-9). However, evidence of the potential association between AD and abnormalities in the bone mineral metabolism remains fragmented (10-14). As osteoporosis and fracture are associated with increased morbidity and mortality, which also represents a significant public health challenge, a better understanding of the relationship between AD and abnormal bone metabolism would help to clarify this issue and intervene earlier, if needed.

To date, several previous studies have evaluated the abnormalities in bone mineral metabolism with disease progression in AD patients. However, they have reported inconsistent results, and a comprehensive review and analysis of the existing evidence to elaborate on the relation between AD and abnormal bone metabolism is lacking. In order to clarify this issue, we performed this systematic review and meta-analysis, aiming to integrate the growing body of evidence, clarify the association between AD and abnormal bone metabolism, and to provide direction for future research in this domain. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4708).

Methods

Study design

This systematic review and meta-analysis were conducted following the Cochrane Handbook for Systematic Reviews of Interventions and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (15,16).

Search strategy

We systematically searched PubMed, Embase, and the Cochrane Library from inception to December 2019. The exploded Medical Subject Heading (MeSH) terms and corresponding keywords were used in the electronic searches (MeSH exp "Dermatitis, Atopic", "Eczema", and keywords "Atopic dermatitis", "Eczema") and (MeSH exp"Bone Density", "Bone Diseases, Metabolic", "Osteoporosis", "Fractures, Bone" and keywords "Bone mineral density", "Osteopenia", "Osteoporosis", "Fracture"). Details of the search strategy are available in Table S1. We also searched unpublished studies and ClinicalTrials.gov registry (https://clinicaltrials.gov/), and manually checked the reference lists of included studies and related reviews to identify any potentially eligible articles. No language restriction was imposed. In addition, we also tried to contact the authors for detailed information of primary studies. The obtained study records were exported from medical databases and imported into a software package (EndNote, version X8; Thomson Reuters) for records management.

Eligibility criteria

We included any observational studies (e.g., cohort, case-control, and cross-sectional studies) that investigated and reported a risk estimate for the abnormal bone metabolism (including BMD, osteopenia, osteoporosis, and related fractures) in patients with AD compared with a control group (e.g., patients without AD or general population). Notably, there was no limitation on age or disease duration. The predefined primary outcome measure was a fracture. Secondary outcomes included osteoporosis, osteopenia, and BMD.

Study selection

Two authors independently undertook electronic searches, removed the duplicated records, and screened the titles and abstracts for potentially eligible studies. The full-text articles were accessed and reviewed to identify eligibility. Selection discrepancies were resolved by discussion and involvement of a third reviewer, if necessary.

Data collection

The following items were extracted from the included

studies: first author, publication year, study location, study design, study period, AD identification, sample size, patient characteristics, covariates used in adjustment model, and multivariate-adjusted risk estimates for the association between AD and abnormal bone metabolism. Extracted data were entered into a predefined standardized Excel (Microsoft Corporation, WA, USA) file. The supplementary files of the included studies were also examined for data extraction, and corresponding authors were contacted to verify the extracted data or request the missing data. Data extraction was performed by one author and confirmed independently by another two authors.

Quality assessment

Two authors assessed the risk of bias of included studies. The quality of the included cohort study or case-control study was evaluated using the Newcastle-Ottawa Scale (NOS), which is a validated assessment tool for the quality of non-randomized studies in meta-analyses (17). This scale allocates a maximum of nine stars to comprises three domains (selection of participants and measurement of exposure, comparability outcomes, adequacy of follow-up) through which bias might be introduced. Studies were categorized as low (score 0–3), moderate (score 4–6), or high quality (score 7–9). The quality of included cross-sectional study was evaluated using the Agency for Healthcare Research and Quality (AHRQ), which is a validated assessment tool that includes an 11-item questionnaire to explore the quality of patient recruitment, outcome measurement, blinding of the observers and follow-up of patients. Each item of the checklist was scored with "Yes", "No", or "Unclear" (18,19). Any discrepancy was resolved by discussion and consensus, with the opinion of a third reviewer sought where necessary. Poor study quality was not an exclusion criterion.

Statistics analysis

The risk estimates for osteopenia, osteoporosis, and related fracture incidence observed in studies were weighted using the inverse variance method, and pooled using the DerSimonian and Laird random-effects model to produce odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity was assessed by using the Cochran Q statistic, a two-sided P<0.05 was considered statistically significant. Heterogeneity was also quantified using the I^2 statistic, I^2 values of 0%, 25%, 50%, and 75% indicate no,

low, moderate, and high heterogeneity, respectively (20). Publication bias was assessed using Egger's regression test (21). A P value <0.05 was considered statistically significant, except where otherwise specified. Data analysis was conducted using Stata software, version 13.0 (Stata Corporation, College Station, TX, USA).

Results

Study selection

The PRISMA flow diagram of study selection is shown in *Figure 1*. A total of 1,109 potentially relevant records were identified through the initial electronic search, and six additional records were identified through other sources. After removing duplicates, 963 records remained, and 943 records were further excluded after reviewing their titles and abstracts. The full texts of the remaining 20 records were carefully scrutinized for eligibility, and ten studies met the inclusion criteria and were included in the qualitative synthesis (5-14).

Study characteristics and risk of bias assessment

The main characteristics of the included studies are presented in *Table 1*, and more details are shown in Table S2. Of the ten included studies, seven were cross-sectional studies and three were retrospective cohort studies; four studies recruited children and adolescents and six studies reporting on adult patients. These ten studies were published between 1997 and 2019. More than half of the studies are from North America and Europe, and the others are from Asia, South America, and Australia. The number of participants in these studies ranged from 29 to 61,065,660.

The quality of the included studies is shown in Tables S3,S4. The average NOS score was 7.5, and the score for all cohort studies was 7 or above, which suggested that all the studies were of high quality, while the general quality of the cross-sectional studies was poor, but most of the cross-sectional studies were not included in the meta-analysis.

Children and adolescents

Four studies, including 3,436 participants, investigated the BMD changes in children and adolescents with AD (4-8). Three studies measured lumbar and femur using dual-energy X-ray absorptiometry (DEXA) and found that

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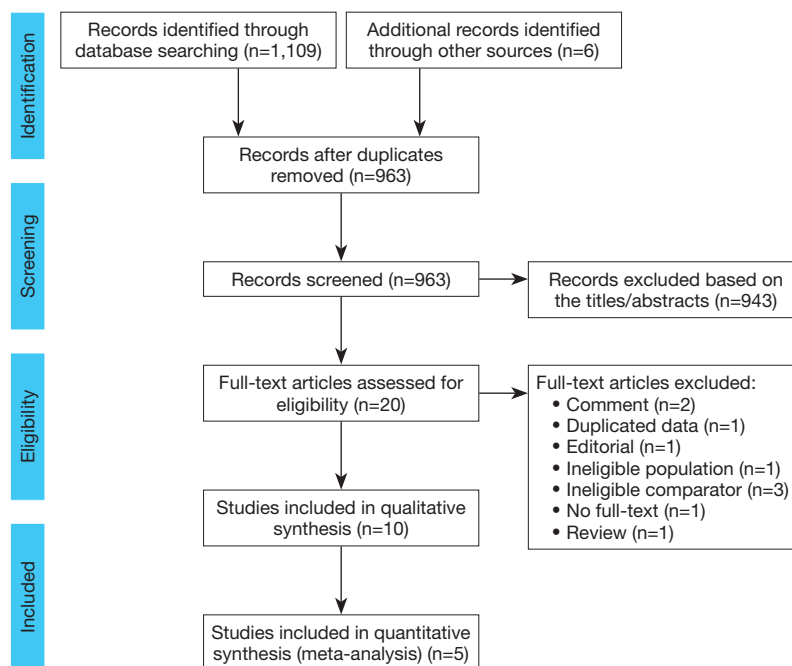
Figure 1 Flow diagram showing the process of literature screening, study selection, and reasons for exclusion.

children and adolescents who were diagnosed with AD had a higher rate of lower BMD (Z-score). In contrast, one study measured radius and tibia using quantitative ultrasound bone sonometry (QUBS) and detected similar BMD (Z-score) between AD and control groups.

Adults

Three studies evaluated the risk of fracture and were included in the meta-analysis, comprising 562,405 AD patients among 3,171,268 participants (11-13). Compared with patients without AD, patients with AD were at a higher risk of fracture (OR 1.13; 95% CI, 1.05–1.22; P=0.001), and there was high heterogeneity (I^2=79.9%; P<0.001) (*Figure 2*). Three studies involving 105,566,867 participants were included in the meta-analysis of AD and osteoporosis (11,12,14). Patients with AD were associated with an increased risk of osteoporosis (OR 1.95; 95% CI, 1.18–3.23; P=0.009) when compared with those without AD (*Figure 3*). Similarly, patients with AD were associated with an increased risk of osteopenia (OR 1.90; 95% CI, 1.51–2.38; P<0.001) (*Figure 4*). In addition, patients with AD were also associated with decreased BMD (Z-score) at the femur and spine.

Publication bias

For the primary outcome, publication bias was indicated by the Egger regression asymmetry test (P=0.028), which might be derived from the limited amount of included studies.

Discussion

Main findings

To our knowledge, this is the first systematic review and meta-analysis that comprehensively reviewed the currently available evidence to investigate the association between AD and abnormal bone metabolism. However, there is still a lack of high-quality evidence for a comprehensive assessment. We found that children and adolescents with AD were associated with diminished BMD, and this effect may be accumulated and aggravated in adult patients, who suffered from AD were associated with increased risks of low BMD, osteopenia, osteoporosis, and related fractures.
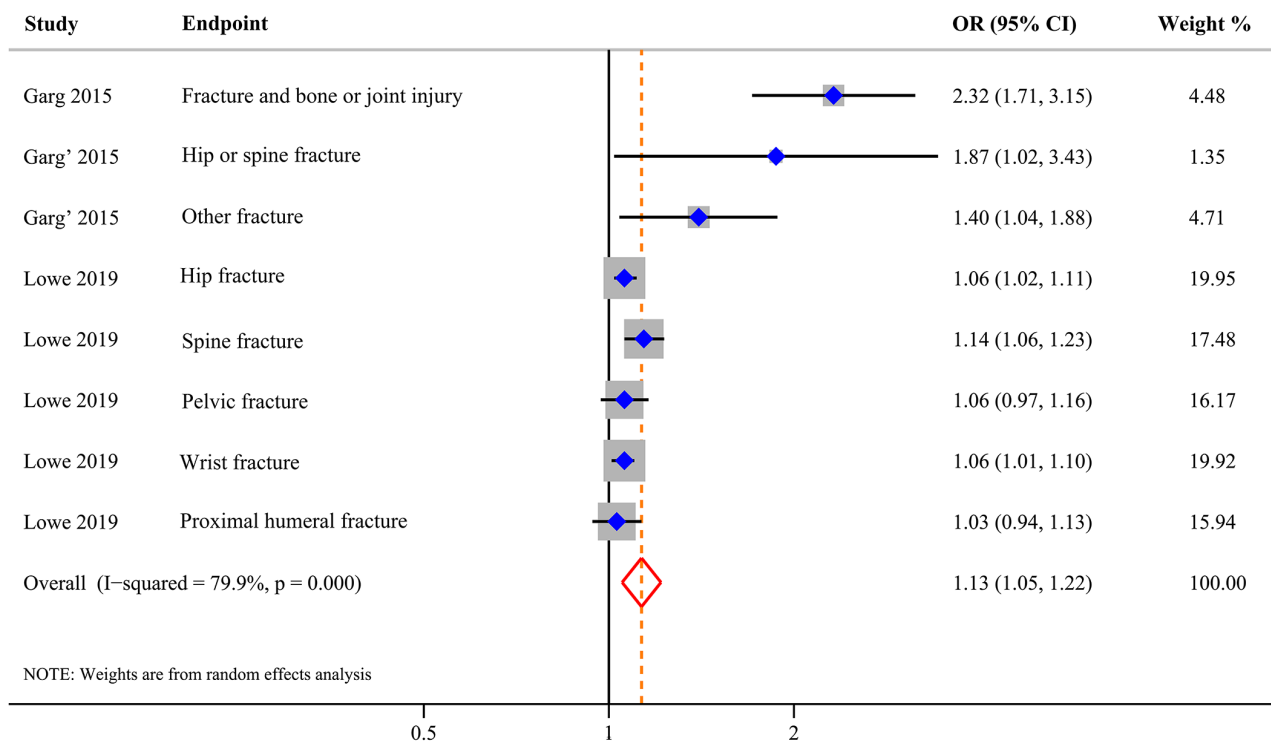
Possible mechanisms

The mechanisms that predispose AD patients to low

Table 1 Characteristics of the included studies

Author	Year	Region	Study design	Population	Atopic dermatitis identification	Database	Study period	Number of participants	Age, years	Endpoints			
										Low BMD	Osteopenia	Osteoporosis	Fracture
Pedreira et al. (5)	2007	Australia	Cross-sectional	Children with moderate to severe AD	UK diagnostic criteria	NA	2003	116	4–10.9	↑	–	–	–
Penterich et al. (6)	2018	Brazil	Cross-sectional	Children with AD	Outpatient	NA	2012	97	4–12	↑	–	–	–
Silverberg et al. (7)	2015	USA	Cross-sectional	Children and adolescents with AD	Self-report	2005–2006 National Health and Nutrition Examination Survey	2005–2006	3,049	8–19	↑	–	–	–
Leung et al. (8)	2017	Hong Kong	Cross-sectional	Children with moderate to severe AD	Hanifin and Rajka criteria	NA	2012	174	<18	↔	–	–	–
Aalto-Korte et al. (9)	1997	Finland	Cross-sectional	Adult with chronic AD	Outpatient	NA	1996	29	21–73	↔	–	–	–
Garg et al. (10)	2015	USA	Cross-sectional	Adults with AD	Self-report	2012 National Health Interview Survey	2012	34,500	18–85	–	–	–	↑
Garg et al. (11)	2015	USA	Cross-sectional	Adults with AD	Self-report	2005–2006 National Health and Nutrition Examination Survey	2005–2006	4,972	20–85	↑	↑	↑	↑
Wu et al. (12)	2017	Taiwan	Retrospective cohort	Adults with AD	Administrative coding	Taiwan National Health Insurance Research Database (NHIRD)	1996–2010	70,458	20–49	–	–	↑	–
Lowe et al. (13)	2020	UK	Retrospective cohort	Adults with AD	Administrative coding	UK primary care (CPRD Gold 1998–2016) and hospital admissions	1998–2016	3,095,838	>18	–	–	–	↑
Shaheen et al. (14) (NEDS)	2019	USA	Retrospective cohort	Older adults with AD	Administrative coding	2006–2012 NEDS database	2006–2012	61,065,660	>50	–	↑	↑	–
Shaheen et al. (14) (NIS)	2019	USA	Retrospective cohort	Older adults with AD	Administrative coding	2002–2012 NIS	2002–2012	44,425,777	>50	–	↑	↑	–

AD, atopic dermatitis; BMD, bone mineral density; CPRD, clinical practice research datalink; NA, not available; NEDS, nationwide emergency department sample; NIS, national inpatient sample; –, not reported; ↔, no difference; ↑, increased risk.

Study	Endpoint	OR (95% CI)	Weight %
Garg 2015	Fracture and bone or joint injury	2.32 (1.71, 3.15)	4.48
Garg' 2015	Hip or spine fracture	1.87 (1.02, 3.43)	1.35
Garg' 2015	Other fracture	1.40 (1.04, 1.88)	4.71
Lowe 2019	Hip fracture	1.06 (1.02, 1.11)	19.95
Lowe 2019	Spine fracture	1.14 (1.06, 1.23)	17.48
Lowe 2019	Pelvic fracture	1.06 (0.97, 1.16)	16.17
Lowe 2019	Wrist fracture	1.06 (1.01, 1.10)	19.92
Lowe 2019	Proximal humeral fracture	1.03 (0.94, 1.13)	15.94
Overall (I−squared = 79.9%, p = 0.000)		1.13 (1.05, 1.22)	100.00

NOTE: Weights are from random effects analysis

0.5　　　　　　1　　　　　　2

Figure 2 Forest plot showing the risk of fracture in patients with AD. CI, confidence interval; OR, odds ratio.

BMD, osteopenia, osteoporosis, and related fractures are multifactorial and complicated, which may not only relate to the disease pathogenesis but also close to the AD-related pattern. In essence, AD is a kind of systematic chronic inflammatory diseases, just like inflammatory bowel disease, rheumatoid arthritis, and systemic lupus erythematosus (22). The relationship between chronic inflammatory diseases with bone loss and fracture risk has been well established (23-28). Inflammation-induced bone loss of these diseases was resulted from elevated numbers of bone-resorbing osteoclasts, which may help explain why the bone loss started as early as in children and adolescents (29,30). There is also growing knowledge regarding the immune-mediated pathomechanism of AD, and the osteoimmunology has highlighted the cross-regulation of bone and the immune system, which involving various cell types, signaling pathways, cytokines, and chemokines, under both homeostatic and pathogenic conditions (31-33). Since many cytokines and immune cell types have been found to be active in AD and play a role in bone remodeling, which may help to elaborate on how immune-associated diseases affect osteoimmunology and lead to bone loss (32-38). Besides, a number of studies have found

that Vitamin D deficiency is more prevalent in patients with AD and correlated with the severity of the disease, and extra supplementation of Vitamin D could result in a clinically meaningful AD severity reduction (39). As Vitamin D also increases intestinal calcium absorption and related to bone metabolism, it seems reasonable to expect that patients with AD have low BMD (40).

The AD-related pattern also plays an important role in bone metabolism on several fronts. (I) Corticosteroids can have profound, pluripotent effects on bone mineral turnover, particularly during developmental phases, but recent studies have demonstrated that topical corticosteroids have no effect on BMD in AD patients, yet, the accumulative effect could not be ruled out (5,6,9,41). (II) AD patients are liable to food allergy and may have dietary restrictions, which could also lead to malnutrition and low BMD (42,43). (III) AD patients are inclined to low levels of physical activity, which may contribute to decreased skeletal calcification and strength (44,45). (IV) AD patients are vulnerable to depression, stress, anxiety, and sleep disturbance, all of which could further lead to low BMD and a higher risk of osteoporosis (46-49). (V) A growing body of evidence indicated that AD is also associated with
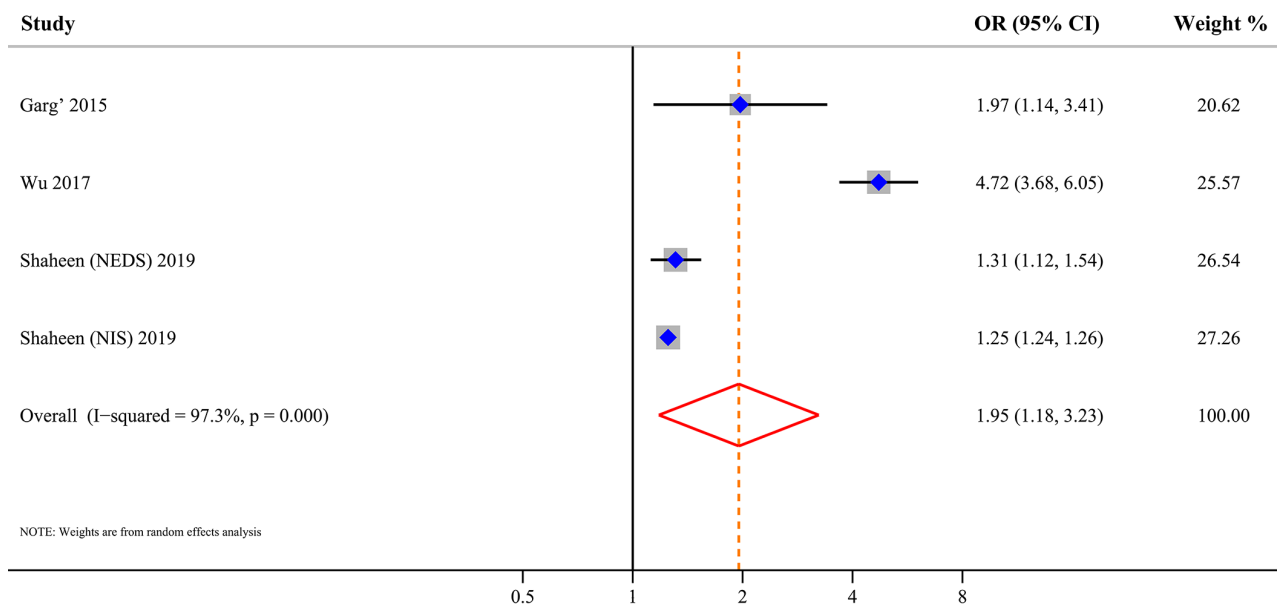
Figure 3 Forest plot showing the risk of osteoporosis in patients with AD. CI, confidence interval; OR, odds ratio.
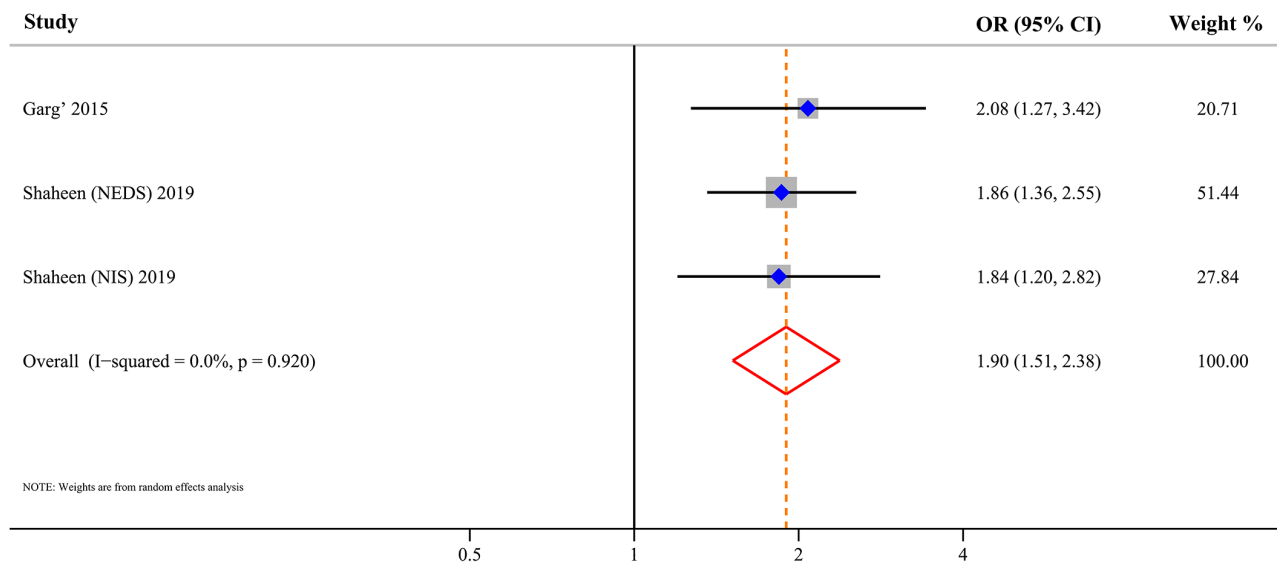
Figure 4 Forest plot showing the risk of osteopenia in patients with AD. CI, confidence interval; OR, odds ratio.

obesity, cardiovascular disease, and high alcohol and tobacco consumption, all of which are risk factors for bone loss and osteoporosis (50-53). (VI) Long-term sequelae of AD are essential to consider, and atopic march such as asthma is also associated with low BMD (54). These AD-related medical and behavioral factors, at least partially, explain the relationship between AD and bone loss.

Implications for clinical practice

So far, limited evidence suggested that the bone loss initiates as early as in children, although only a marginal decline in BMD. However, the difference in bone metabolism expands gradually with age and presents varied from osteopenia, osteoporosis, to related fractures.

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Previous epidemiological studies have demonstrated that the incidence of fractures in general populations increases steadily with age in females, and in males over 70 years old (55-57). Considering the female gender is a predisposing factor to AD (58-60), and females are at higher risk for osteoporosis and fractures than males, it is reasonable that the incidence of osteoporosis was higher in females than in males in both the AD cohort and non-AD cohort (12). However, there is varying evidence about the age modified fracture risk in patients with AD (10,12,13). Garg *et al.* reported that the prevalence of fracture among adults with AD increased gradually with age and peaked at ages 50 to 69 years, then decreased substantially after that (10). While Lowe *et al.* indicated that the fracture risk reached a plateau at ages 50 or older, the risks of hip fractures and wrist fractures decreased with age, the risk of spine fractures increased with age, and the risk of pelvic fractures peaked at ages 50 to 69 years and decreased thereafter (13). Based on the currently available evidence, different measures should be taken to alleviate the age-related effect of AD on fracture risk. For children, adolescents, and young adults, modify the AD-related patterns, including dietary, physical activity, psychological intervention, and improve their lifestyle, should be taken as a high priority. While for adults and older adults, early targeted screening of osteoporosis, and intervene early if necessary, would benefit individuals with AD.

Furthermore, the standard therapy for patients with AD remains limited, which often have insufficient efficacy and causes many side effects. Therefore, other innovative alternative therapies with promising efficacy and acceptable safety should be considered (61,62). The emerging biological therapeutics are focused on intervening in the inflammatory pathway by targeting specific molecules or their receptors, which may not only provide new prospects for the optimal treatment of AD, but also prevent bone loss and fragility fractures induced by AD (63,64). Meanwhile, large prospective cohort studies are still needed to confirm these associations and identify potential risk factors. Additional research focus on determining the possible biological mechanisms linking AD to abnormal bone metabolism are also warranted.

Limitations

The main limitation of this study is the lack of high-quality studies, which limited the assessment of abnormal bone metabolism, risk of osteopenia and osteoporosis, and related fractures in patients with AD. Moreover, although studies have adjusted for major confounders, the results still could have been biased due to the retrospective nature, and the control for confounding variables was often not comprehensive. Besides, other factors, including data source, study population, AD diagnosis confirmation, and study design, could also affect the results.

Conclusions

In conclusion, compared with patients without AD, patients with AD were associated with increased risks of low BMD, osteopenia, osteoporosis, and related fractures. To clarify the association between AD and abnormal bone metabolism, but also for better prevention and treatment of bone loss in patients with AD, both clinical studies and basic research are warranted.

Acknowledgments

Footnote

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Table S1 Details of the database search strategy (searched on: December 15, 2019)

Search	Query	Results
PubMed		
#1	"Dermatitis, Atopic"[Mesh]	19,244
#2	Atopic dermatitis[Title/Abstract]	19,937
#3	"Eczema"[Mesh]	11,011
#4	Eczema[Title/Abstract]	17,014
#5	#1 OR #2 OR #3 OR #4	41,880
#6	"Bone Density"[Mesh]	51,908
#7	Bone mineral density[Title/Abstract]	39,312
#8	"Bone Diseases, Metabolic"[Mesh]	74,848
#9	Osteopenia[Title/Abstract]	9,298
#10	"Osteoporosis"[Mesh]	54,425
#11	Osteoporosis[Title/Abstract]	66,883
#12	"Fractures, Bone"[Mesh]	179,463
#13	Fracture[Title/Abstract]	167,622
#14	#6 OR #7 OR #8 OR #9 #11 OR #12 OR #13	358,541
#15	#5 AND #14	135
Cochrane		
#1	MeSH descriptor: [Dermatitis, Atopic] explode all trees	1,650
#2	(Atopic dermatitis):ti,ab,kw	4,211
#3	MeSH descriptor: [Eczema] explode all trees	951
#4	(Eczema):ti,ab,kw	3,545
#5	#1 or #2 or #3 or #4	6,174
#6	MeSH descriptor: [Bone Density] explode all trees	4,526
#7	(Bone mineral density):ti,ab,kw	8,041
#8	MeSH descriptor: [Bone Diseases, Metabolic] explode all trees	4,329
#9	(Osteopenia):ti,ab,kw	1,132
#10	MeSH descriptor: [Osteoporosis] explode all trees	3,824
#11	(Osteoporosis):ti,ab,kw	10,093
#12	MeSH descriptor: [Fractures, Bone] explode all trees	5,577
#13	(Fracture):ti,ab,kw	21,383
#14	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	31,074
#15	#5 and #14	51
Embase		
#1	'atopic dermatitis'/exp	43,424
#2	'eczema'/exp	33,908
#3	'atopic dermatitis':ti,ab,kw	32,821
#4	eczema:ti,ab,kw	29,957
#5	#1 OR #2 OR #3 OR #4	80,612
#6	'bone density'/exp	89,969
#7	'osteopenia'/exp	18,656
#8	'osteoporosis'/exp	130,081
#9	'fracture'/exp	330,981
#10	'bone mineral density':ti,ab,kw	56,625
#11	osteopenia:ti,ab,kw	15,712
#12	osteoporosis:ti,ab,kw	110,324
#13	fracture:ti,ab,kw	220,411
#14	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	522,926
#15	#5 AND #14	923

Table S2 Additional details of the included studies

Endpoint	Author	Year	Region	Outcomes	Crude HR/OR/β (95% CI)	Multivariate OR/HR/adjusted β (95% CI)	Covariates in a fully adjusted model
Fracture	Garg et al. (11)	2015	USA	Any fracture	OR 1.49 (1.12–1.96)	OR 1.48 (1.10–1.99)	Not available
	Lowe et al. (13)	2019	UK	Any fracture	HR 1.13 (1.11–1.14)	HR 1.07 (1.05–1.09)	Age, sex, general practice, and date of cohort entry, time-updated asthma, index of multiple deprivations, calendar time, BMI, smoking status, harmful alcohol use, oral glucocorticoid exposure
	Garg et al. (10)	2015	USA	Fracture and bone or joint injury	–	OR 2.32 (1.71–3.15)	Age, sex, race/ethnicity, Hispanic origin, household income, highest level of household education, family structure, birthplace in the United States, health insurance coverage
	Garg et al. (11)	2015	USA	Hip or spine fracture	OR 1.80 (1.00–3.24)	OR 1.87 (1.02–3.43)	Not available
	Lowe et al. (13)	2019	UK	Hip fractures	HR 1.11 (1.07–1.16)	HR 1.06 (1.02–1.11)	Age, sex, race/ethnicity, Hispanic origin, household income, highest level of household education, family structure, birthplace in the United States, health insurance coverage
	Lowe et al. (13)	2019	UK	Spine fractures	HR 1.22 (1.14–1.30)	HR 1.14 (1.06–1.23)	Age, sex, race/ethnicity, Hispanic origin, household income, highest level of household education, family structure, birthplace in the United States, health insurance coverage
	Lowe et al. (13)	2019	UK	Pelvic fractures	HR 1.12 (1.04–1.21)	HR 1.06 (0.97–1.16)	Age, sex, race/ethnicity, Hispanic origin, household income, highest level of household education, family structure, birthplace in the United States, health insurance coverage
	Lowe et al. (13)	2019	UK	Wrist fractures	HR 1.09 (1.05–1.13)	HR 1.06 (1.01–1.10)	Age, sex, race/ethnicity, Hispanic origin, household income, highest level of household education, family structure, birthplace in the United States, health insurance coverage
	Lowe et al. (13)	2019	UK	Proximal humeral fractures	HR 1.08 (0.99–1.17)	HR 1.03 (0.94–1.13)	Age, sex, race/ethnicity, Hispanic origin, household income, highest level of household education, family structure, birthplace in the United States, health insurance coverage
	Garg et al. (11)	2015	USA	Other fracture	OR 1.42 (1.07–1.89)	OR 1.40 (1.04–1.88)	Not available
Osteoporosis	Shaheen et al. (14) (NEDS)	2019	USA	Osteoporosis	–	OR 1.31 (1.12–1.54)	Age, sex, race/ethnicity (white, nonwhite), insurance (private, government, self-pay, no charge, other), and household income quartile
	Shaheen et al. (14) (NIS)	2019	USA	Osteoporosis	–	OR 1.25 (1.24–1.26)	Age, sex, race/ethnicity (white, nonwhite), insurance (private, government, self-pay, no charge, other), and household income quartile
	Wu et al. (12)	2017	Taiwan	Osteoporosis	HR 8.01 (6.32–10.16)	HR 4.72 (3.68–6.05)	Age, sex, comorbidities (hypertension, diabetes mellitus, hyperlipidaemia, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, depression), and use of systemic corticosteroids
	Garg et al. (11)	2015	USA	Trochanter	OR 1.86 (1.10–3.15)	OR 1.97 (1.14–3.41)	Not available
Osteopenia	Shaheen et al. (14) (NEDS)	2019	USA	Osteopenia	–	OR 1.86 (1.36–2.55)	Age, sex, race/ethnicity (white, nonwhite), insurance (private, government, self-pay, no charge, other), and household income quartile
	Shaheen et al. (14) (NIS)	2019	USA	Osteopenia	–	OR 1.84 (1.20–2.82)	Age, sex, race/ethnicity (white, nonwhite), insurance (private, government, self-pay, no charge, other), and household income quartile
	Garg et al. (11)	2015	USA	Trochanter	OR 2.03 (1.24–3.33)	OR 2.08 (1.27–3.42)	Not available
Bone mineral density	Garg et al. (11)	2015	USA	Total femur	β –0.29 (–0.49 to –0.10)	Adjusted β –0.27 (–0.46 to –0.08)	Not available
	Silverberg et al. (7)	2015	USA	Total femur	β –0.50 (–0.80 to –0.19)	Adjusted β –0.42 (–0.68 to –0.16)	Age, gender, race/ethnicity, household income, birthplace in the United States, the highest level of education in the household, body mass index percentile (ordinal), and milk consumption in the past 30 days (binary)
	Garg et al. (11)	2015	USA	Trochanter	β –0.26 (–0.43 to –0.09)	Adjusted β –0.25 (–0.42 to –0.08)	Not available
	Silverberg et al. (7)	2015	USA	Trochanter	β –0.31 (–0.57 to –0.05)	Adjusted β –0.29 (–0.54 to –0.05)	Age, gender, race/ethnicity, household income, birthplace in the United States, the highest level of education in the household, body mass index percentile (ordinal), and milk consumption in the past 30 days (binary)
	Garg et al. (11)	2015	USA	Femoral neck	β –0.18 (–0.37 to 0.01)	Adjusted β –0.13 (–0.31 to 0.04)	Not available
	Silverberg et al. (7)	2015	USA	Femoral neck	β –0.31 (–0.60 to –0.02)	Adjusted β –0.29 (–0.53 to –0.05)	Age, gender, race/ethnicity, household income, birthplace in the United States, the highest level of education in the household, body mass index percentile (ordinal), and milk consumption in the past 30 days (binary)
	Garg et al. (11)	2015	USA	Total lumbar spine	β –0.18 (–0.37 to 0.01)	Adjusted β –0.22 (–0.41 to –0.03)	Not available
	Silverberg et al. (7)	2015	USA	Total lumbar spine	β –0.51 (–0.86 to –0.17)	Adjusted β –0.31 (–0.52 to –0.11)	Age, gender, race/ethnicity, household income, birthplace in the United States, the highest level of education in the household, body mass index percentile (ordinal), and milk consumption in the past 30 days (binary)

CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

Table S3 Methodological quality assessment (risk of bias) of included studies by Newcastle-Ottawa Scales (NOS)

Study	Selection				Comparability	Outcome			Total score
	Case definition	Representativeness	Control selection	Control definition		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
Wu *et al.* (12), 2017	*	*	*	*	**	*	*	–	8
Lowe *et al.* (13), 2019	*	*	*	*	**	*	*	–	8
Shaheen *et al.* (14), 2019 (NEDS)	*	*	*	*	**	*	–	–	7
Shaheen *et al.* (14), 2019 (NIS)	*	*	*	*	**	*	–	–	7

The asterisks represent a score, each asterisk represents one star.

Table S4 Quality assessment (risk of bias) of included studies by the Agency for Healthcare Research and Quality (AHRQ) checklist

Item	Pedreira *et al.* (5), 2007	Penterich *et al.* (6), 2012	Silverberg *et al.* (7), 2015	Leung *et al.* (8), 2017	Aalto-Korte *et al.* (9), 1997	Garg *et al.* (10), 2015	Garg *et al.* (11), 2015
1) Define the source of information (survey, record review)	R	R	R	R	R	R	R
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	R	U	R	R	R	R	R
3) Indicate time period used for identifying patients	R	U	R	R	Q	R	R
4) Indicate whether or not subjects were consecutive if not population-based	U	U	R	U	U	R	R
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Q	Q	Q	Q	U	R	R
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	R	U	R	R	Q	R	R
7) Explain any patient exclusions from analysis	R	U	R	R	Q	R	R
8) Describe how confounding was assessed and/or controlled	Q	U	R	R	U	R	R
9) If applicable, explain how missing data were handled in the analysis	Q	U	R	Q	U	R	R
10) Summarize patient response rates and completeness of data collection	Q	Q	R	Q	Q	R	Q
11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	Q	Q	Q	Q	Q	Q	Q

ARHQ methodology checklist for cross-sectional study (http://www.ncbi.nlm.nih.gov/books/NBK35156/). R, yes; Q, no; U, unclear.