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Cardiovascular risk factors and confounders in severe atopic dermatitis: a scoping review

Fatores de risco cardiovascular e confundidores na dermatite atópica grave: revisão de escopo

Factores de riesgo cardiovascular y factores de confusión en la dermatitis atópica grave: revisión de alcance

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Abstract
Atopic dermatitis (AD) is a chronic and recurrent inflammatory skin disease that could be associated with cardiovascular diseases (CVDs). Interest in determining whether the chronic inflammation of AD is a risk factor for CVD has been growing in recent years, although there are few studies available on this topic, and the results are quite controversial. The purpose of this scoping review was to understand whether severe atopic dermatitis and its chronic systemic inflammatory process contribute, or not, as a risk factor for the development of CVD. Following the development of a study protocol, a scoping review was carried out based on the structure outlined by Arksey and O'Malley, Levac *et al*., the Joanna Briggs Institute and the PRISMA-ScR guidelines. PubMed, Cochrane, EMBASE, CINAHL, LILACS, Web of Science, Biblioteca Virtual em Saúde (BVS), Scopus and SciELO were the selected databases. Results: Fifty-two studies were included in this review (18 review studies, 16 cross-sectional studies, 15 cohort studies and three meta-analyses). We found that 36 studies could associate AD with CVD, while 16 studies found no relationship between AD and CVD. Conclusions: It is possible that cardiovascular risk in moderate to severe atopic disease is in confounding factors, and not necessarily because AD and CVDs share the same chronic systemic inflammatory pathway. There is no robust evidence that AD is a risk factor for CVD. To reduce CVD risk in patients with AD, we must pay attention to the risk factors commonly present in these patients and strongly recommend a healthy lifestyle.
Keywords: Dermatitis, Atopic; Cardiovascular diseases; Inflammasomes; Inflammation; Atherosclerosis; Metabolic syndrome; Myocardial infarction; Stroke.

Resumo
A dermatite atópica (DA) é uma doença inflamatória crônica e recidivante que pode estar associada a doenças cardiovasculares (DCV). É crescente o interesse na DA como um fator de risco para DCV, embora existam poucos estudos disponíveis sobre esse tema e os resultados sejam ainda controversos. Objetivo: Entender se a dermatite atópica grave e os mecanismos inflamatórios envolvidos nessa doença são um fator de risco para DCV. Metodologia: Após o desenvolvimento de um protocolo de estudo, foi realizada uma revisão de escopo com base na estrutura delineada por Arksey e O'Malley, Levac et al., o Joanna Briggs Institute e as diretrizes PRISMA-ScR. PubMed, Cochrane, EMBASE, CINAHL, LILACS, Web of Science, Biblioteca Virtual em Saúde (BVS), Scopus e SciELO foram as bases de dados selecionadas. Resultados: Cinquenta e dois estudos foram incluídos nesta revisão (18 estudos de revisão, 16 estudos transversais, 15 estudos de coorte e três meta-análises). Encontramos 36 estudos que correlacionaram a DA com DCV, enquanto outros 16 estudos não encontraram relação entre DA e DCV. Conclusões: É possível que o risco cardiovascular na doença atópica moderada a grave esteja nos fatores de confusão, e não necessariamente porque DA e DCV compartilham a mesma via inflamatória sistêmica crônica. Não há evidências robustas de que a DA seja um fator de risco para DCV. Para reduzir o risco de DCV em pacientes com DA, deve-se dar maior atenção aos fatores de risco cardiovascular comumente presentes nesses pacientes e recomendar fortemente um estilo de vida saudável.
Palavras-chave: Dermatite atópica; Doenças Cardiovasculares; Inflamassomos; Inflamação; Acidente vascular cerebral; Aterosclerose; Síndrome metabólica; Infarto do miocárdio.

Abstracto
El interés en la dermatitis atópica (DA), enfermedad inflamatoria crónica y recurrente, como un factor de riesgo de enfermedades cardiovasculares (ECV) ha ido en aumento últimamente, aunque existen pocos estudios disponibles al respecto y los resultados son controvertidos. El propósito de esta revisión fue comprender si los mecanismos inflamatorios en la DA grave la convierten en un factor de riesgo para las ECV. Después del desarrollo de un protocolo de estudio, se llevó a cabo una revisión de alcance basada en la estructura delineada por Arksey y O'Malley, Levac et al., el Instituto Joanna Briggs y las guías PRISMA-ScR. PubMed, Cochrane, EMBASE, CINAHL, LILACS, Web of Science, Biblioteca Virtual em Saúde (BVS), Scopus y SciELO fueron las bases de datos seleccionadas.Resultados: Cincuenta y dos estudios se incluyeron en esta revisión (18 estudios de revisión, 16 estudios transversales, 15 estudios de cohortes y tres metanálisis). Encontramos que 36 estudios asocian la DA con la ECV, mientras que 16 estudios no encontraron relación entre la DA y la ECV. Conclusiones: Es posible que el riesgo cardiovascular en la enfermedad atópica moderada a grave se encuentre en factores de confusión, y no necesariamente porque la DA y las ECV comparten la misma vía inflamatoria sistémica crónica. No hay pruebas sólidas de que la DA sea un factor de riesgo de ECV. Para reducir el riesgo de ECV en pacientes con DA debemos prestar atención a los factores de riesgo comúnmente presentes en estos pacientes y recomendar encarecidamente un estilo de vida saludable.
Palabras clave: Dermatitis atópica; Enfermedades Cardiovasculares; Inflamasomas; Inflamación; Accidente cerebrovascular; Aterosclerosis; Síndrome metabólico; Infarto de miocardio.

1. Introduction

Atopic dermatitis (AD) is a chronic and recurrent inflammatory disease that affects the skin surface. It has a multifactorial aetiology involving genetic factors and immunological and non-immunological changes. Its prevalence has been increasing in the last 30 years, and approximately 30% of AD patients can be classified as having moderate to severe disease.(Silverwood et al., 2018; Weidinger et al., 2016)

AD can have an extremely negative impact on the quality of life of patients and their families, with socioeconomic implications and personal consequences.(Aaron M. Drucker et al., 2017; Oliveira et al., 2019; Sehra et al., 2008; Silverwood et al., 2018) In recent years, it has been discussed whether AD is an exclusively cutaneous disease or whether it is a systemic inflammatory disease. Some research suggests that AD is predominantly a systemic disease influenced by the T helper (Th) 2 inflammatory axis and its biomarkers and not just a skin-limited disease.

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. Approximately 17 million deaths in 2013 were due to CVD.(Roth et al., 2015) Over the years, many studies have shown an increased risk of CVD in a series of chronic inflammatory diseases, where CVD-related mortality increases by approximately 50%. (Lindhardsen et al., 2016) Endothelial damage, difficulty in vascular remodelling, atherosclerosis and insulin resistance are often related to mild and chronic inflammatory status and ageing. (Ferrucci et al., 2018; Franceschi et al., 2006) Epidemiological studies have confirmed that chronic inflammatory diseases play a fundamental role in endothelial dysfunction and, consequently, in atherosclerosis. Cardiovascular risk factors (CVRFs), such as metabolic syndrome (MS), obesity, diabetes, chronic renal failure and sleep apnoea syndrome, accelerate arterial ageing and increase the risk of cardiovascular (CV) outcomes. (Castellon et al., 2016; Cuende et al., 2016; Kahlenberg et al., 2013; Manzi et al., 2000)

Myocardial infarction (MI) is the most commonly reported CVD in patients with chronic inflammatory disease. The risk of MI among patients with rheumatoid arthritis and severe psoriasis is increased, and an estimated 11,500 CV events per year in the United States are related to these diseases.(Ahlehoff et al., 2011; Armstrong et al., 2013; Lindhardsen et al., 2011) Research on the association of AD with CVD, autoimmune diseases and skin and/or extracutaneous infections has accelerated in recent years, although the correlation is not well established. (Oliveira et al., 2019) Because the correlation between chronic inflammatory disease in severe psoriasis and increased CVD is already well established, currently, increasing attention has been given to severe AD, whose chronic inflammation could be related to an increased risk of CVD and poor outcomes. However, studies have found conflicting results.

To address topics that are controversial, a scoping review can be a good tool, as it is an interactive process. (Arksey & O'Malley, 2005) They are very useful for providing an overview of the available evidence. As there are not very many double-blind high-quality studies on the association of severe AD with CVD, a meta-analysis cannot be conducted at this time.

2. Objective

This study aimed to review the scope of publications on the inflammatory mechanisms of severe AD and its relationship with CVD. It is not yet well established whether severe AD and its chronic systemic inflammatory process contribute, or not, as a risk factor for the development of CVD.

3. Justification

Recently, a possible relationship between CVD and dermatological diseases has received greater attention. An increased prevalence of CV events is observed in patients with severe psoriasis, possibly due to the pro-inflammatory mediators existing in the pathophysiology of skin disease. For this reason, it has been hypothesized that severe AD and its chronic systemic inflammatory state may also be associated with an increased risk of atherosclerosis and CVD, although there are still relatively few studies on this topic.

Recent studies suggest that severe and active AD is associated with a higher risk of CV events and increased mortality. (Hjuler et al., 2015; Silverwood et al., 2018) Patients with AD seem prone to have risk factors for CVD, such as physical inactivity, alcoholism, smoking, obesity, high blood pressure, diabetes and dyslipidaemia. (Brunner et al., 2017; Drucker, 2018; Egeberg et al., 2017; Kantor et al., 2016; Jonathan I. Silverberg et al., 2015; Jonathan I. Silverberg et al., 2015; Zhang et al., 2015)

Several serum biomarkers can be correlated with AD activity and cytokine activation, suggesting a systemic inflammatory disease. In the acute phase of AD, there is a predominance of the T helper cytokine 2 (Th2) axis, with increased activation of cytokines IL4, IL13 and IL31. In the chronic phase, there is polarization to the T helper cytokine 1 (Th1) axis, with increased IL12 and IFNγ. The severity of AD is significantly correlated with the Th2 axis and IL4 and IL13, in addition to the accumulation of Th22 cells in skin lesions.(Furue et al., 2017)

Patients with chronic diseases seem to strongly express Th1 and have an increased Th17-mediated inflammatory response.(Ivert et al., 2019) This could explain the association of coronary heart disease and stroke with severe and chronic AD, whereas mild forms of AD are not associated with stroke. (V. Y. F. Su et al., 2014) It is likely that patients with severe and recalcitrant AD may have an increased risk of comorbidities compared to patients with mild AD. (A. M. Drucker & Flohr, 2018)

However, there are studies that suggest that AD is not an independent risk factor for CVD. (Andersen et al., 2016; A M Drucker et al., 2016, 2017; Egeberg et al., 2017; Marshall et al., 2016; Standl et al., 2017; J P Thyssen et al., 2018) Many skin and joint disorders are associated with CV comorbidities because they share aetiological elements. The complexity of the immune system and its role in defending the body requires an arsenal to accurately identify and selectively control inflammatory processes or cells that promote atherosclerosis. It has also been observed that inflammation in skin diseases seems to be an active source of several pro-inflammatory cytokines and chemokines that may predispose patients to CV comorbidities. (Kerkhof & Khamaganova, 2018)

Inflammation is known to play a central role in CVD. In the inflammatory cascade, a macromolecular structure called the "inflammasome" stands out. The inflammasome is a signalling platform that detects a variety of triggers of the innate immune system.(Li et al., 2014) For this reason, this complex structure is currently being extensively studied in different epitheliums, including the skin epithelium, and atherogenic inflammasomes are also of great interest. (Palazon-Riquelmeet al., 2018)

Secretion of the pro-inflammatory cytokines interleukin-1β and interleukin-18 by inflammasomes triggers an inflammatory cascade that results in a strong immune response and can culminate in the progression of diseases such as atherosclerosis, ischaemic injury, cardiomyopathy and skin diseases such as psoriasis and AD.(Li et al., 2014)

4. Methodology

In this study, a scoping review was carried out. The methodology was based on the structure outlined by Arksey and O'Malley and the methodological improvement made by Levac *et al*. and the Joanna Briggs Institute. (Arksey et al., 2005; Levac et al., 2010; Peters et al., 2020)

STEP 1: Formulation of the research question.

This scoping review was guided by the question: 'Does chronic inflammation in severe atopic dermatitis make it a risk factor for cardiovascular disease?'

STEP 2: Identification of the relevant studies

The descriptors used in this research to identify the eligible studies are as follows:

• ("Dermatitis, Atopic" OR "Atopic Dermatitis" OR "Atopic Eczema") AND ("cardiovascular diseases" OR stroke OR "metabolic syndrome" OR "coronary disease" OR "myocardial infarction" OR atherosclerosis).

• inflammasomes AND ("atopic eczema" OR "dermatitis, atopic" OR "atopic dermatitis") AND "cardiovascular diseases"

The selected databases were PubMed, Cochrane, EMBASE, CINAHL, LILACS (BIREME), Web of Science, Biblioteca Virtual em Saúde (BVS - Regional Portal), Scopus and SciELO.

STEP 3: Study Selection

The review process consists of 3 levels of screening: (1) title review, (2) summary review and (3) full text review. For the first level of screening, two researchers independently screened the title of the 849 eligible articles found with the search strategy. Subsequently, the abstracts of all 712 citations retrieved for inclusion were screened against a set of minimum inclusion criteria. In the third stage, the two researchers independently evaluated the 52 articles selected from the analysis of the abstracts in full text to determine whether they met the inclusion/exclusion criteria.

Inclusion criteria:

1. Articles published in English, Italian, Spanish, French or Portuguese.
2. Published since the year 2000.
3. Human studies.
4. Studies on chronic systemic inflammation and inflammasomes in cardiovascular and skin diseases.
5. Studies correlating cardiovascular diseases with moderate to severe atopic dermatitis.

Exclusion criteria:

1. Analysis of subgroups from articles that were already included.
2. Experimental studies.
3. Studies in which the methodological design was not clear or presented a high risk of bias.
4. Studies involving other types of dermatitis, inflammation or cardiovascular diseases.

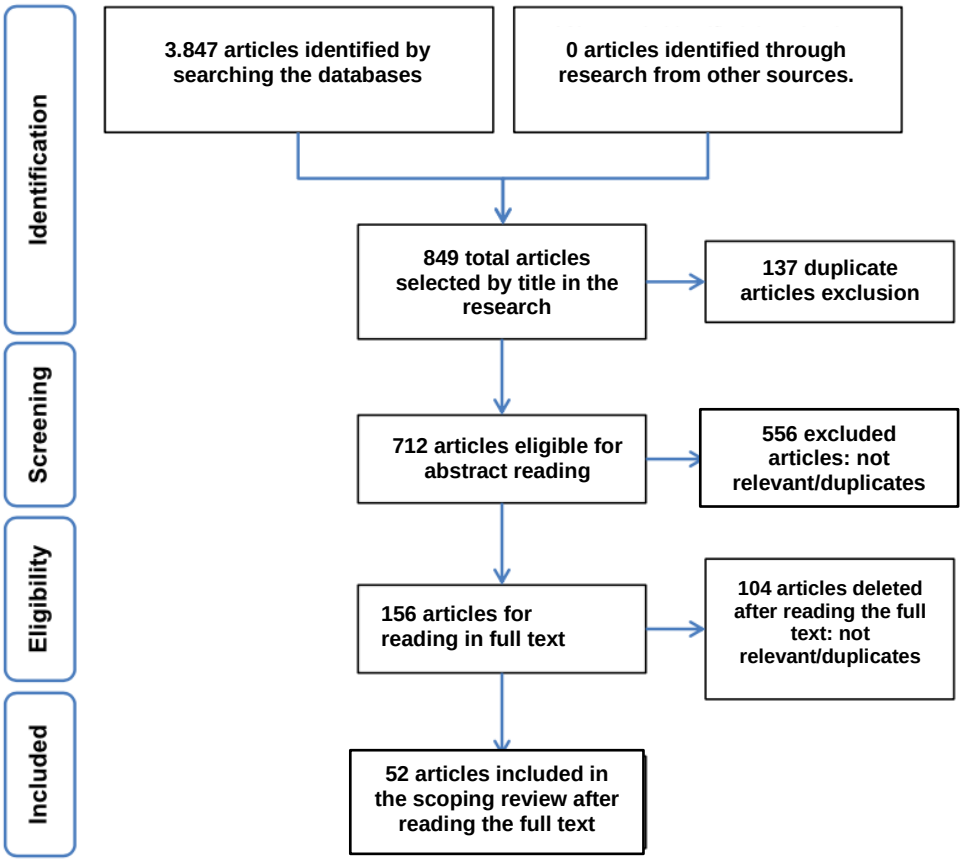
STEP 4: Data mapping

The results obtained after analysing the full-text articles and the excluded data were reviewed a second time, and any disagreements about the study's eligibility in the text review phase were resolved through discussion among the researchers. The search results were imported into the Mendeley® quote manager and grouped into a single library.

STEP 5: Collection, summarization and reporting of the results

Critical assessment of the risk of bias was carried out by researchers FWR and ELJ. The PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines were followed to report the findings of this scoping review (Figure 1). (Tricco et al., 2018).

Figure 1: Flowchart of the scoping review adapted from PRISMA.



Source: Authors.

5. Results

In this review, 52 studies were included (18 review studies, 16 cross-sectional studies, 15 cohort studies and three meta-analyses). According to the analysis of the results, 36 studies could associate AD with CVD (Table 1, Table 2, Table 3 and Table 4).

Table 1. Review studies: Positive results of an association between AD and DCV. Total: 11.

Author, Year (references)	***Country***	***Study Design***	***Publication/ Impact Factor 2020***	***Main Findings***
Cribier B 2019 (Cribier, 2019)	*France*	*Review*	*Annales de dermatologie et de vénéréologie IF2020: 0,777*	*Positive association between obesity and the MS in severe AD. Many studies are contradictory.*
Silverberg JI 2019 (Jonathan I Silverberg, 2019)	*USA*	*Review*	*Annals of Allergy, Asthma & Immunology IF2020: 6,347*	*AD seems to have a higher risk of infection and a higher CV risk.*
Fujiyoshi A 2019 (Fujiyoshi, 2019)	*Japan*	*Review*	*Journal of Atherosclerosis and Thrombosis IF2020: 4,928*	*Risk of death due to CVD was 30% higher in an adjusted multivariate model. An association with stroke was not observed.*
Oliveira C, Torres T 2019 (Oliveira & Torres, 2019)	*Portugal*	*Review*	*European Journal of Dermatology IF2020: 3,328*	*Risk factors for CVD and poor health habits may cause CV events instead of systemic inflammation associated with AD.*
Hu et al. 2019 (Hu et al., 2019)	*USA China*	*Review*	*Frontiers in Endocrinology IF2020: 5,555*	*Insulin resistance and chronic inflammation possibly contribute to the positive association of some skin diseases with MS.*
Silverberg JI 2018 (Jonathan I Silverberg, 2018)	*USA*	*Review*	*F1000 Research IF2020: 2,445*	*Evidence of an association between AD and CVD. It is closely linked to several CV risk factors.*
Zarqa et al. 2018 (Ali et al., 2018)	*Denmark*	*Systematic review*	*Dermatology IF2020: 5,366*	*Positive association AD x MS. It is more intense in women. Conflicting results AD x arterial hypertension and dyslipidaemia. Inverse association between AD and type 2 diabetes.*
Paller et al. 2018 (Paller et al., 2018)	*USA*	*Systematic Review*	*American Journal of Clinical Dermatology IF2020: 7,403*	*AD and CVD share several risk factors, especially obesity and mental health.*
Andersen et al. 2017 (Andersen et al., 2017)	*Denmark*	*Review*	*Current Dermatology Reports IF2020: 1,066*	*AD appear to be at increased risk of CVD, cancer, autoimmune and psychiatric diseases.*
Nijsten T 2017 (Nijsten, 2017)	*Netherlands*	*Review*	*Journal of Investigative Dermatology IF2020: 8,551*	*Modest association of AD and CVD.*
Brunner et al. 2017 (Brunner, Silverberg, et al., 2017)	*USA Japan Germany Austria*	*Review*	*Journal of Investigative Dermatology IF2020: 8,551*	*Poor health behaviours and increased CV risk factors are the main factors in CVD/CV events and AD, not necessarily chronic systemic inflammation.*

Source: Authors.

Table 2. Cross-sectional studies: Positive results about the association between AD and CVD. Total:12

Author, Year (references)	***Country***	***Study Design***	***Publication/ Impact Factor 2020***	***Main Findings***
He et al. 2020 (He et al., 2020)	*USA*	*Cross-sectional case-control*	*Annals of Allergy, Asthma & Immunology IF2020: 6,347*	*Elderly people with AD have increased levels of systemic inflammatory markers for CVD and atherosclerosis.*
Agón-Banzo et al. 2020 (Agón-Banzo et al., 2020)	*Spain*	*Cross-sectional Case-control*	*Australasian Journal of Dermatology IF2020: 2,875*	*AD is associated with a higher metabolic risk in childhood, similar to the risk of other chronic skin inflammatory diseases such as psoriasis.*
Shalom et al. 2019 (Shalom et al., 2019)	*Israel*	*Cross-sectional observational Case-control*	*Journal European Academy of Dermatology and Venereology IF2020: 6,166*	*Moderate to severe AD was associated with a higher prevalence of MS.*
Kok et al. 2019 (Kok et al., 2019)	*Singapore*	*Cross-sectional*	*Acta Dermato-Venereologica IF2020: 4,437*	*Metabolic and atopic conditions were significantly related to the severity of AD. Severe AD increases CV morbidity and mortality.*
Silverberg et al. 2018 (Jonathan I Silverberg et al., 2018)	*USA*	*Cross-sectional*	*Annals of Allergy, Asthma & Immunology IF2020: 6,347*	*Strong positive relationship between the severity of AD and allergic, autoimmune and CV comorbidities.*
Szolnoky et al. 2018 (Szolnoky et al., 2018)	*Hungary*	*Cross-sectional*	*American Journal of Clinical Dermatology IF2020: 7,403*	*The increase in aorta stiffness index and the decrease in aortic tension in patients with AD maintain that AD in adults is associated with increased CV risk.*
Brunner et al. 2017 (Brunner, Suárez-Fariñas, et al., 2017)	*USA*	*Cross-sectional*	*Scientific Reports IF2020: 4,379*	*The inflammatory mediators involved in atherosclerosis are significantly increased in severe AD, making it a risk factor for CVD.*
Varbo et al. 2017 (Varbo et al., 2017)	*Denmark*	*Cross-sectional observational Case-control*	*Journal of Thrombosis and Haemostasis IF2020: 5,824*	*AD was associated with an increased risk of ischaemic stroke. However, the association was not statistically significant after the multifactorial adjustment. Residual confusion is a possibility.*
Sicras-Mainar et al. 2017 (Sicras-Mainar et al., 2018)	*Spain*	*Cross-sectional observational retrospective*	*Actas Dermo-Sifiliograficas IF2019-2020: 0,726*	*Severe AD had a higher risk of comorbidities: MI 10%, stroke 16.6% and CV event 22.9%.*
Silverberg et al. 2015 (Jonathan I. Silverberg et al., 2015)	*USA*	*Cross-sectional Case-control*	*JAMA Dermatology IF2020: 10,282*	*AD was associated with central obesity. Severe AD was associated with arterial hypertension.*
Silverberg et al. 2015 (Jonathan I. Silverberg & Greenland, 2015)	*USA*	*Cross-sectional Case-control*	*Journal of Allergy and Clinical Immunology IF2020: 10,793*	*Adults with AD have an increased risk of metabolic syndrome and cardiovascular diseases.*
Hjuler et al. 2015 (Hjuler et al., 2015)	*Denmark*	*Cross-sectional Case-control*	*American Journal of Medicine IF2020: 4,965*	*Atherosclerotic plaques in patients with AD were significantly higher. This suggests that AD is associated with an increased prevalence of disease coronary artery.*

Source: Authors.

Table 3. Cohort studies: Positive results of the association between AD and CVD. Total: 11.

Author, Year (references)	***Country***	***Study Design***	***Publication/ Impact Factor 2020***	***Main Findings***
Ivert et al. 2019 (Ivert et al., 2019)	*Sweden*	*Retrospective case-control Descriptive cohort*	*Acta Dermato-Venereologica IF2020: 4,437*	*Women cohort. Smoking as a risk factor among severe cases of AD. Diabetes mellitus, hyperlipidaemia and hypertension were more prevalent in severe AD. Hyperlipidaemia and hypertension were more prevalent in non-severe AD. There was a positive association between AD and CVD.*
Nishida et al. 2019 (Nishida et al., 2019)	*Japan*	*Prospective descriptive cohort*	*Journal of Atherosclerosis and Thrombosis IF2020: 4,928*	*Frequent self-reported eczema was associated with an increased risk of mortality from coronary heart disease, but not from other major CVDs, in the Japanese population.*
Silverwood et al. 2018 (Silverwood et al., 2018)	*United Kingdom*	*Retrospective case-control cohort*	*BMJ IF2020: 39,890*	*Severe AD: 22% increased risk of stroke; 40% to 50% risk of MI, angina and atrial fibrillation and CV death; 69% increase in ICC.*
Kwa MC, Silverberg JI 2017 (Kwa & Silverberg, 2017)	*USA*	*Retrospective cohort*	*American Journal of Clinical Dermatology IF2020: 7,403*	*Positive association between AD and CVD or cerebrovascular disease. In a study of hospitalized patients, the severity of AD was greater in this sample. No adjustment of variables.*
Thyssen JP, Skov L, Egeberg A. 2017 (Jacob P Thyssen et al., 2018)	*Denmark*	*Prospective observational descriptive cohort*	*Journal of the American Academy of Dermatology IF2020: 11,527*	*The risk of death from any of the causes studied was significantly increased in patients with AD.*
Radtke et al. 2017 (Radtke et al., 2017)	*Germany*	*Retrospective cohort*	*Journal European Academy of Dermatology and Venereology IF2020: 6,166*	*Metabolic syndrome was more prevalent in patients with psoriasis when compared with patients with AD.*
Sung et al. 2017 (Sung et al., 2017)	*China*	*Longitudinal retrospective cohort*	*Journal of Medical Sciences IF2020: 2,523*	*AD is an independent risk factor for the development of ischaemic stroke, but not for haemorrhagic stroke.*
Riis et al. 2016 (Riis et al., 2016)	*Denmark*	*Prospective cohort*	*BMJ Open IF2020: 2,692*	*This study concludes that hospital diagnosed AD was associated with an increased risk of MI compared to the general population.*
Andersen et al. 2016 (Andersen et al., 2016)	*Denmark*	*Retrospective case-control cohort*	*Journal of Allergy and Clinical Immunology IF2020: 10,793*	*Severe AD: a higher risk of CVD, an increased prevalence of CVD risk factors in patients with AD due to the inflammatory nature of atopic disease.*
Silverberg JI 2015 (J I Silverberg, 2015)	*USA*	*Retrospective cohort*	*Allergy IF2020: 13,146*	*Patients with AD may have increased CVD, MI and stroke.*
Su et al. 2014 (V. Y.-F. Su et al., 2014)	*China*	*Retrospective case-control cohort*	*Annals of Medicine IF2019-2020: 4,709*	*AD can be an independent risk factor for ischaemic stroke, and the risk of ischaemic stroke increases with the severity of AD.*

Source: Authors.

Table 4. Meta-analyses. Total: 2

Author, Year (references)	*Country*	*Study Design*	*Publication/ Impact Factor 2020*	*Main Findings*
Ascott et al. 2019 (Ascott et al., 2019)	*United Kingdom Canada USA*	*Meta-analysis*	*Journal of Allergy and Clinical Immunology IF2020: 10.793*	*There is an association between stroke and MI in cohort studies. Association with the severity of AD and CV outcomes. Heterogeneous and inaccurate results with low quality of evidence for such associations. Outcomes were at a low risk of bias.*
Yuan et al. 2018 (Yuan et al., 2018)	*China*	*Meta-analysis*	*Medicine (Baltimore) IF2020: 1,889*	*14 studies on stroke and 12 on MI. Significant increase in stroke risk in patients with AD. AD is associated with a greater risk of stroke and MI. The risk was higher in men. The results indicated that the risk was greater for stroke and that there is an influence of the severity of AD.*

Source: Authors.

This scoping review also found 16 studies that there was no relationship between AD and CVD (Table 5, Table 6, Table 7 and Table 8).

Table 5. Review studies: Negative results of an association between AD and DCV. Total: 7.

Author, Year (references)	*Country*	*Study Design*	*Publication/ Impact Factor 2020*	*Main Findings*
Steele et al. 2019 (Steele et al., 2019)	*USA*	*Review*	*Current Opinion in Pediatrics IF2020: 2,856*	*The relationship between AD and MS remains unclear. Overweight and obesity are strongly related to childhood AD.*
Hale et al. 2019 (Hale et al., 2019)	*United Kingdom*	*Review*	*Clinical and Experimental Dermatology IF2020: 3,470*	*AD is not related to type 2 diabetes, arterial hypertension, stroke or MI.*
Drucker, AM Harvey, PJ 2019 (Aaron M. Drucker & Harvey, 2019)	*Canada*	*Review*	*Journal of Allergy and Clinical Immunology IF2020: 10,793*	*Correlates the findings of the few studies on AD, CVD and associated risk factors. Conflicting results.*
Hong et al. 2018 (Hong et al., 2018)	*Canada*	*Review*	*Journal of Cutaneous Medicine and Surgery IF2020: 1,218*	*There is no consistent evidence of CV risk in patients with AD.*
Standl et al. 2017 (Standl et al., 2017)	*Germany*	*Review*	*Journal Investigative Dermatology IF2020: 8,551*	*Even for severe AD, the increase in risk factors for CVD was modest, of little clinical relevance.*
Wollina Uwe 2017 (Wollina, 2018)	*Germany*	*Review*	*Clinics in Dermatology IF2020: 3,541*	*The association of AD with MS is unclear. Lifestyle and genetic factors may be important. The risk is low in Europe, higher in Asia and USA.*
Furue et al. 2017 (Furue & Kadono, 2017)	*Japan*	*Review*	*Inflammation Research IF2020: 4,575*	*The results of the studies are still controversial about an association of AD and psoriasis with MS, autoimmune diseases and chronic systemic inflammatory disease.*

Source: Authors.

Table 6. Cross-sectional studies: Negative results of the association between AD and CVD. Total: 4.

Author, Year (references)	***Country***	***Study Design***	***Publication/ Impact Factor 2020***	***Main Findings***
Jachiet et al. 2019 (Jachiet et al., 2019)	*France*	*Cross-sectional*	*Journal of the European Academy of Dermatology and Venereology IF2020: 6,166*	*High frequency of neuropsychic disorders and a low frequency of CVD in French adults with AD. Smoking and skin infections are associated with a worse quality of life in this sample.*
Treudler et al. 2018 (Treudler et al., 2018)	*Germany*	*Cross-sectional*	*Journal of the European Academy of Dermatology and Venereology IF2020: 6,166*	*Increased risk of autoimmune disease in AD. No significant independent association between AD and CVD.*
Lee et al. 2017 (Lee et al., 2017)	*Korea*	*Cross-sectional*	*Acta Dermato-Venereologica IF2020: 4,437*	*In adjusted models, women with AD were more likely to have MS, central obesity, or hypertriglyceridemia.*
Drucker et al. 2017 (A M Drucker et al., 2017)	*Canada USA*	*Cross-sectional*	*British Journal of Dermatology IF2020: 9,302*	*No evidence was found for a positive association between AD and hypertension, type 2 diabetes mellitus, MI or stroke. AD is not a risk factor for CVD.*

Source: Authors.

Table 7. Cohort studies: Negative results of the association between AD and CVD. Total: 4.

Author, Year (references)	***Country***	***Study Design***	***Publication/ Impact Factor 2020***	***Main Findings***
Egeberg et al. 2017 (Egeberg et al., 2017)	*Denmark*	*Retrospective cohort*	*Allergy IF2020: 13,146*	*The risk of MI, stroke, arterial hypertension, kidney disease, diabetes, cancer, and Crohn's disease was significantly lower in AD compared to psoriasis in the adjusted models.*
Marshall et al. 2016 (Marshall et al., 2016)	*USA*	*Retrospective cohort*	*Dermatology and Therapy IF2020: 3,264*	*No increased risk of CVD was detected in AD, psoriasis or rosacea after adjusted for the confounding factors.*
Drucker et al. 2016 (A M Drucker et al., 2016)	*USA*	*Prospective cohort*	*Allergy IF2020: 13,146*	*AD was not independently associated with nonfatal MI or stroke among US women.*
Schmitt et al. 2008 (Schmitt et al., 2008)	*Germany*	*Retrospective cohort*	*Italian Journal of Public Health IF2010: 0,43 IF2020: not available*	*Chronic inflammation in AD does not appear to be a cause of morbidity and mortality, unlike in psoriasis.*

Source: Authors.

Table 8. Meta-analyses. Total: 1

Author, Year (references)	***Country***	***Study Design***	***Publication/ Impact Factor 2020***	***Main Findings***
Thyssen et al. 2018 (J. P. Thyssen et al., 2018)	*Denmark*	*Systematic review and meta-analysis*	*British Journal of Dermatology IF2020: 9,302*	*16 cohort studies analysed. Did not find significant evidence to corroborate the association between AD and stroke, MI, type 2 diabetes or arterial hypertension. It is unlikely that AD represents an independent and clinically relevant risk factor for CVD.*

Source: Authors.

6. Discussion

The inflammatory nature of AD could be responsible for an association with CVD, as in other chronic inflammatory diseases such as psoriasis and rheumatoid arthritis, whose evidence is well established. However, alcoholism, smoking, dyslipidaemia, sleep disorders, metabolic syndrome, mood disorders, obesity, overweight, physical inactivity, and diabetes, which are known to be factors predisposing to CVD, are present in most AD patients and are considered confounding factors.(Ali et al., 2018) Most comorbidities associated with AD are apparently caused by the interaction between genetic predisposition, environmental exposure, chronic inflammation due to AD, medication use and lifestyle.(Andersen et al., 2017)

In fact, the heterogeneity found in the studies can be attributed to variations in the studied populations, the study design, the follow-up time and adjustment for confounding factors. These factors seem to be of great relevance for the interpretation of the results of the studies and the scientific data analysed.

Under a critical epidemiological view, it is possible to explain, in large part, the possible associations between AD and CVD with respect to these confounding factors. The literature points out that AD is associated with sleep disorders and obesity, and both are strongly related to CV events.(Aaron M. Drucker & Harvey, 2019) Some studies concluded that being male is associated with AD and an increased risk of stroke and myocardial infarction (MI), but it should be considered that in men, the occurrence of factors such as smoking, alcoholism, and sleep disorders is more prevalent.(Yuan et al., 2018)

In addition, some studies have identified AD through questionnaires and self-reports. This fact could lead to a risk of bias, which could certainly lead to an incorrect classification of AD, psoriasis and other pruritic diseases of the skin. Misclassification bias may be responsible for an increased risk of CV outcomes in atopic patients, as those with severe disease are often defined by receiving systemic therapies, and some of these therapies increase the CV risk, such as systemic corticosteroids.(Wei et al., 2004) The time of onset of AD, whether in childhood or adulthood, has been little reported in the literature, but it can be a significant problem due to the timing of progression of the disease and the timing of the exposure to CV risk factors or medications. (Ascott et al., 2019)

In an arbitrary way, in many studies analysed in this review, they considered that an HR (hazard ratio) or (odds ratio) less than two (2), which is a “small” variation, can be explained only by confounding factors or biases in the different types of study designs and their heterogeneity.(Cribier, 2019) This increases the risk of a false positive. Studies that intend to assess the risk of CV events and that have fewer than two years of follow-up of patients are not considered adequate to assess the risk of more serious outcomes, such as MI, stroke and mortality. This is due to the time required for the progression of this outcome in the studied groups, which evolves insidiously and probably requires more than 18 months to 24 months. Therefore, studies with a longer follow-up time can present more robust data to be analysed.

There is a possibility that studies that found a positive association between AD and CVD are making a type I error or an alpha (α) error because they do not take into account confounding factors. In statistics, an alpha error or type I error occurs when a hypothesis is rejected when it is true. This can occur in research when a different result is found randomly or due to the

confounding factors existing in the studied population. Thus, what could be causing CVD would be CV risk factors, which are often present in patients with moderate to severe AD. This does not make it an isolated risk factor for CVD but a possible residual risk factor or risk marker.

The study design that could best answer the question "Is severe atopic dermatitis a risk factor for cardiovascular disease?" would be two study groups, the first group of which would be patients with MS and severe AD and the second group would be with MS without severe AD. Both groups were treated for MS and followed for three to five years. If the group of patients with MS and severe AD had more fatal CV outcomes, it could be concluded that severe AD is an independent risk factor for CVD. Thus, it would define the burden of AD in CVD, which could be considered a neglected residual risk factor.

The CV mortality rates, despite having suffered a significant reduction in recent years, are still considered high, possibly due to the residual risk of CV events.(Hermans & Fruchart, 2010)

Residual risk is comprised of modifiable risk factors, such as lipid changes, diabetes, hypertension, physical inactivity and smoking, and nonmodifiable risk factors, such as age, sex, previous CVD and genetic factors. (Thomas et al., 2018) Since the major components of residual risk are related to dyslipidaemia and hypertension, changes in lifestyle associated with usual drug therapy can strongly contribute to the reduction of CVD and fatal outcome events.(Hermans & Fruchart, 2010)

Recent studies suggest, although still with conflicting results, that AD-related comorbidities increase morbidity and mortality in paediatric and adult patients with both psoriasis and AD. Many of the pathophysiological mechanisms of these comorbidities associated with AD are still not fully understood. However, AD itself and the associated lifestyle contribute to mechanisms to trigger such comorbidities. It is possible that adequate and early treatment of AD, in addition to reducing risk factors, can contribute to the prevention of these comorbidities.(Andersen et al., 2017)

What is the importance of these studies for the patient and the doctor? For patients with moderate to severe AD, the evidence points to the need to map risk factors for CVD. Age-appropriate cardiometabolic screening should be performed. There is insufficient evidence to state that the treatment of systemic inflammation in AD would have an effect on the patient's cardiometabolic profile. It is likely that the appropriate treatment of AD, with an improvement of symptoms, may, in turn, improve the quality of sleep, mood and the ability to tolerate physical exercise, thus being able to contribute to a reduction in the general CV risk.(Aaron M. Drucker & Harvey, 2019)

The severity of atopic disease and the patient's lifestyle are closely associated, as well as comorbidities, and perhaps more attention should be given to those patients with moderate to severe disease.(Vestergaard, 2019) The origin of these comorbidities is probably multifactorial, including rupture of the skin barrier, immunological dysregulation, extensive symptoms and iatrogenic complications. Many of these comorbidities are directly related to the underlying severity of AD and to inadequate disease control, and they could be avoided or mitigated by optimizing AD management.(Jonathan I Silverberg, 2018) Due to the prevalence of adults with eczema or AD, any reduction in the risk of CVD is important from the point of view of public health.(Fujiyoshi, 2019)

Therefore, physicians must rethink whether interventions in this group of patients could prevent fatal outcomes. Evidence from new treatment perspectives that could contribute to reducing CV events would be an important advance to guide the clinical conduct of health professionals.(Ingram, 2018)

Epidemiological studies aim to reduce bias and confounding effects, but the statistical associations have not yet been sufficient to prove the causality of the relationship between AD and CVD. It is possible that monitoring patients longitudinally to determine the impact of new therapeutic approaches on comorbidities associated with AD, in addition to its cutaneous manifestations, might raise new hypotheses about the mechanisms of the associations between these diseases.(Brunner, Silverberg, et al., 2017)

Although there are contradictory results, together, these findings suggest that an increase in risk factors for CVD and poor health behaviour, lifestyle factors such as smoking, drinking and physical inactivity, may be important factors for cardiovascular events instead of considering only the systemic inflammation associated with AD.

Patients should be encouraged to modify these habits and acquire a healthier lifestyle. The growing body of evidence for potential comorbidities associated with AD and its related systemic immune activation reflects the disease burden and supports the concept of AD as a systemic disease, reinforcing the importance of considering the general health of patients, not just their skin disease.(Oliveira et al., 2019)

7. Conclusion

It is possible that cardiovascular risk in moderate to severe atopic disease is in confounding factors, not necessarily because AD and CVD share the same chronic systemic inflammatory pathway. There is no robust evidence that AD alone is a risk factor for CVD.

For future studies, it is necessary to identify and adjust the confounding factors and mediators to address this unanswered question: whether the inflammatory burden of AD contributes to CVD independently. This would help to outline the contribution of the increased burden of CV risk factors and the increased risk of CVD conferred by AD.(Ascott et al., 2019) For now, perhaps the main objective is to improve the general health status of patients with AD.

Strengths and limitations of our study:

►To address topics that are still controversial, such as the inflammatory mechanisms involved in severe atopic dermatitis and cardiovascular diseases, a scoping review is a good first approach.

►This scoping review included a large volume of literature on a broad topic, and the results highlight the possibility of cardiovascular risk in moderate to severe atopic disease is in confounding factors, and not necessarily because AD shares the same chronic systemic inflammatory pathway with CVD.

►The scoping review approach has some limitations, as it does not formally assess the quality of the evidence and generally collects information from a wide variety of study models and methods.

►Scoping reviews do not provide a synthesized result or answer to a specific question, but they do provide a more general view of the available literature.

Patient and Public Involvement

No patients were directly involved.

Ethics and Dissemination

This study does not require ethical approval.

Author's Contribution FWR conducted the literature review, data collection, data analysis and writing of the manuscript. ELJ was responsible for the idea and design of the study and conceived the research question. He was involved in data verification, student supervision, and editing of the manuscript. Both authors had full access to all of the data in this study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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