Health Science Reports

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SYSTEMATIC REVIEW OPEN ACCESS

Etiology of Adult Female Acne–Systematic Review

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Received: 31 October 2024 | **Revised:** 26 March 2025 | **Accepted:** 3 April 2025

Funding: The authors received no specific funding for this work.

Keywords: acne | diet | female acne | genes | hormones | pathogenesis

ABSTRACT

Background: Acne vulgaris is a common inflammatory disease of the skin. Acne occurring in > 25 years old is called "adult acne," and it occurs more commonly in women than in men.

Purpose: The aim of this study was to examine the recent findings of the connection between genetic factors, hormones and diet with adult female acne.

Methods: The study was conducted as a systematic literature review. For the review, data searches were made on the PubMed and Scopus databases. Finally, 20 articles met the inclusion criteria.

Results: According to this systematic literature review, several different hormones may be linked to the development of adult acne. Androgens play a particularly important role, as they can stimulate growth of the sebaceous glands and increase the secretion of sebum, thus promoting the formation of skin changes associated with acne. A high glycemic diet increases the secretion of insulin, which in turn causes an increase in the amount of insulin-like growth factor (IGF)-1. IGF-1 increases the growth of the sebaceous gland, sebum production, keratinocyte proliferation and it activates androgen synthesis, thus contributing to acne pathogenesis. Adults with acne have a positive familial history more often than healthy controls, which indicates the genetic nature of adult acne.

Conclusion: This literature review highlighted that especially hyperandrogenism, a positive familial history and a high-glycemic diet may be linked to the development of adult acne. Understanding the pathogenesis of adult acne is crucial for effective treatment.

1 | Introduction

Acne refers to an inflammatory disease in the duct connecting the hair follicle and the sebaceous gland. It occurs in areas with densely packed hair follicles, such as the face, neck, chest, back and shoulders. Acne typically begins during puberty, when androgens activate the sebaceous gland [1]. According to many studies, adult acne is more common among women than in men [2, 3]. The incidence of acne decreases with age [2, 3]; Acne occurs in 7.5% of women aged 16–29, about 5% of women aged 30–39 and less than 2% of women aged 40–49 [2].

Acne in women over 25 years of age is called adult female acne. It can be divided into persistent, late-onset and recurring subtypes based on when it starts. However, in many studies, acne has been categorized into two types: persistent acne and late-onset acne [4]. Clinically, adult female acne differs from that of adolescents as adult women present more frequently with mild

Abbreviations: DHEAS, dehydroepiandrosterone; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment for insulin resistance; IGFBP-3, insulin-like growth factor-binding protein 3; IGF-1, insulin-like growth factor 1; LDL, low density lipoprotein.

to moderate lesions and few deep inflammatory cysts on the mandibular zone [5]. The overall severity of adult acne varies from mild to moderate [6], but a cohort study from Finland has demonstrated that most middle-aged women suffer from mild acne [3].

The development of acne is linked to several causal factors: increase in sebum production, hyperkeratinization abnormalities of the pilosebaceous follicles, hyperproliferation of Propionibacterium acnes (*P. acnes*), inflammation and DNA Methylation. [7]. Genetic factors, hormones, eating habits and many other lifestyle factors have also been found to play a role in the development of acne [7, 8]. In adult female acne, premenstrual flare-ups triggered by hormonal factors are common [9].

This study aimed to use a systematic literature review to determine the significance of hormones, nutrition and genetic factors in the onset of adult female acne. Although complex inflammatory mechanisms play a role in the pathogenesis of acne in general [8], those at the molecular level were outside the scope of this systematic review. The study focuses on studies published in 2018 or later, which allows us to create an overall picture of what we know now and where we should focus research in the future.

2 | Materials and Methods

2.1 | Search Strategy and Selection Criteria

The systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10]. An electronic literature searches were made on the PubMed/Medline and Scopus databases using the medical subject headings on September 2023. A full list of search terms is available online in Supplementary methods.

The search words were to be found either in the title, keywords or in the summary. No manual data searches were made in related journals and no unpublished studies were sought, either.

2.1.1 | Inclusion Criteria

- Peer-reviewed studies examining the effect of hormones, genome and nutrition on acne pathogenesis.
- Women across all age groups with consideration given to age in the analyses.
- Both women and men with consideration given to gender in the analyses.
- Publication year 2018–2023.
- English language publications with no restrictions imposed on location.

2.1.2 | Exclusion Criteria

- Studies focusing on the treatment of acne and scarring, inflammatory mediators or other diseases or conditions.
- Studies on men only.
- Studies in which the subjects suffered from an acne-linked disease.
- Full text not available.
- Abstracts, case reports, reviews, comments and editorials.

2.1.3 | Study Selection

The search results were imported to the Covidence program for systematic assessment. Literature search results were screened independently by two reviewers (A.T. and L.H.) to identify all citations that met the inclusion criteria. Discrepancies in the selection were reviewed by a third reviewer (S.P.S.) for arbitration. The PRISMA flow diagram of the search progress is shown in Figure 1.

2.1.4 | Summary Measures and Synthesis of Results

Characteristics of the included studies were described and results discussed in narrative synthesis.

2.1.5 | Risk of Bias and Level of Evidence

The risk of bias for the studies included in the review was assessed following the "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" of the National Institutes of Health (Supporting Information S1: Table SI). The level of evidence was recorded according to the Center for Evidence-Based Medicine (CEBM). Levels of evidence were recorded as follows: 1a: Evidence obtained of systematic reviews or meta-analysis of randomized control trials; 1b: Evidence obtained from individual randomized control trials; 2a: Evidence obtained from systematic reviews or meta-analysis of cohort studies; 2b: Evidence obtained from individual cohort studies; 3a: Evidence obtained from systematic reviews or meta-analysis of case-control studies; 3b: Evidence obtained from individual case-control studies; 4: Evidence obtained from case series; and 5: Evidence obtained from expert opinions.

2.1.6 | Assessment of Review Reliability

The study aims to address adult female acne. However, when selecting the material, studies involving men had to be approved to include articles covering the desired areas in the final report.

3 | Results

3.1 | Study Selection

A total of 20 studies met the inclusion criteria (Figure 1). A total of 10 studies addressed the link between hormones and/or metabolic factors (e.g., lipids) and acne. Four studies focused on researching the use of certain food or diet in acne patients. Only

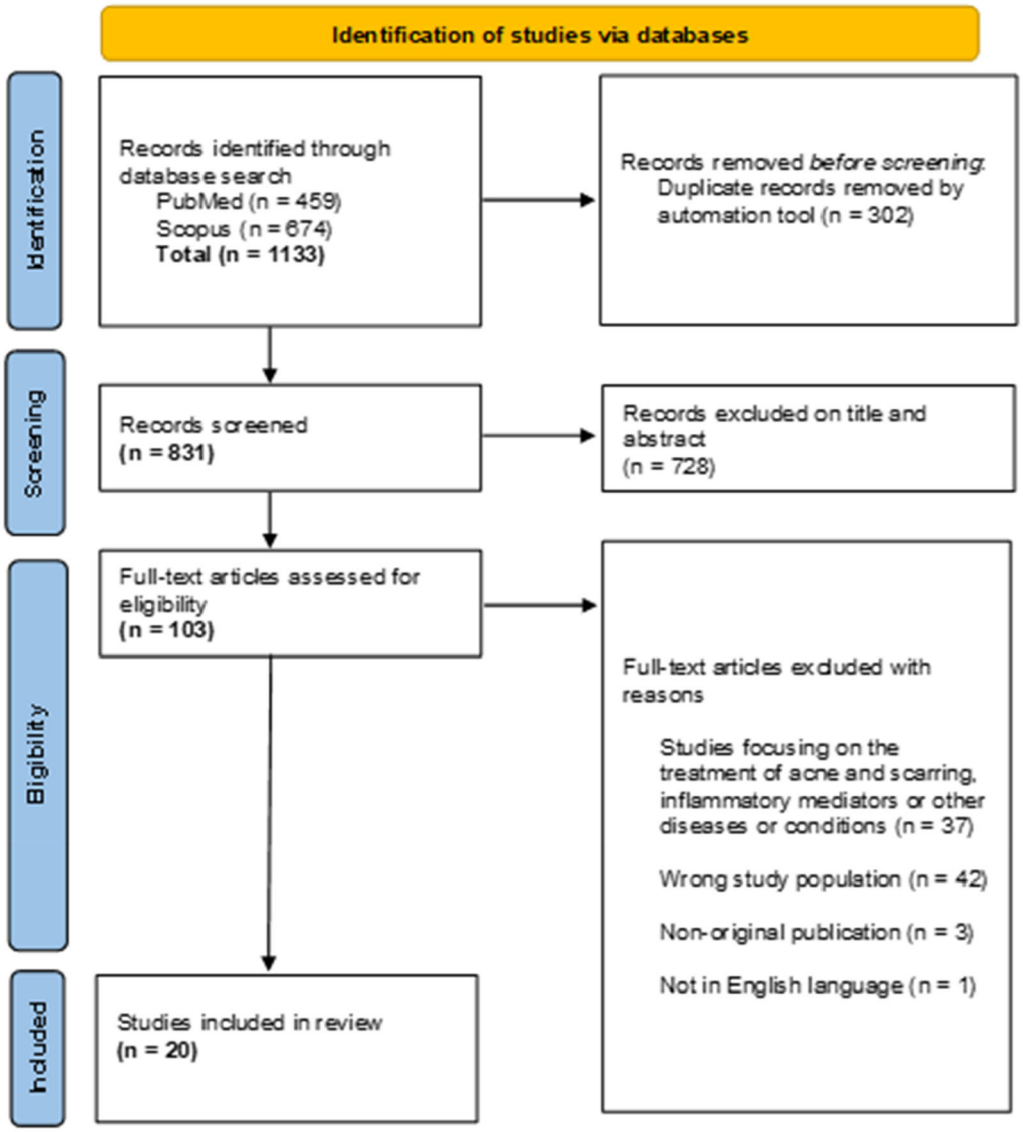

FIGURE 1 | Flow diagram of systematic literature search progress.

two studies, whose aim was to explain the inheritance of acne, met the criteria. There were four studies on the link between several different variables and acne. Methods and populations of the included studies are outlined in Table 1. All reported data is from the original papers.

3.2 | Nutrition

In their study, Penso et al. (2020) reported the significant consumption of sweets and sugary beverages by acne patients [11]. They also found that acne patients consume significantly more dairy products and fatty foods than the controls. Juhl et al. (2018) analysed the possible link between milk consumption and acne in adulthood in subjects having lactose intolerance or not. They did not find a link between dairy products and adult acne, and their finding was not associated with lactose tolerance status [12].

Burris et al. (2018) studied the impact of a low glycemic diet on biochemical factors linked to adult acne [13]. The aim of sampling was to monitor possible changes in blood sugar, insulin, insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGFBP-3) concentrations. IGF-1 levels were found to be significantly decreased in those who follow a low glycemic diet. Due to the short duration of the study ($t = 2$ weeks), authors were unable to conclude whether the decrease in IGF-1 levels had a clinical impact on acne.

The search produced several studies related to vitamin D and acne. However, only the study carried out by Kemeriz et al. (2020) met the required criteria [14]: The purpose of their study was to investigate the link between vitamin D levels in serum and acne and its severity. They found that vitamin D deficiency was significantly more common among acne patients compared to the controls. It was also noted that there was a significant link between the severity of acne and vitamin D deficiency. Gender and age did not affect vitamin D levels in this study [14]. Penso et al. (2020) also studied vitamin D concentrations in acne patients and controls as one of the variables [11]. Unlike Kemeriz and co-workers [14], they did not notice any significant differences in the concentration of vitamin D in acne patients and controls.

TABLE 1 | Overview of the studies included in the systematic review.

First author, year (reference)	Epidemiological design	Country	Research material	Purpose of the trial	Relevant results	CEBM level of evidence
Nutrition						
Burris et al. 2018 [13]	Randomized controlled trial	USA	A total of 66 acne patients aged 18–40 divided into two groups. Patients in group 1 followed a low glycemic diet and patients in group 2 followed a normal diet. Women accounted for 82% of the subjects.	Changes in biochemical factors associated with acne that are caused by low glycemic diets among adults suffering from acne.	IGF levels decreased significantly among those following a low glycemic diet. No changes in blood sugar, insulin and IGFBP-3 were observed.	1b
Juhl et al. 2018 [12]	Cross-sectional population study (Mendelian randomization)	Denmark	A total of 20,416 Danish respondents filled out the questionnaire. 1.5% of the respondents suffered from acne. Of the acne patients, 141 were aged 20–39 and 162 were over 40 years of age. Women accounted for 54.5% of the acne patients.	Link between adult acne and milk consumption and lactose intolerance.	No link was found between the consumption of dairy products and acne, regardless of whether the patient suffered from lactose intolerance or not.	2b
Penso et al. 2020 [11]	Cross-sectional study, Prospective cohort study	France	A total of 24,452 men and women participated in the study. The average age of the participants was 57 years and 75% of them were women. 1762 participants suffered from acne.	To study the connection between diet and acne.	The multivariable analysis found that the consumption of dairy products, sugary beverages, fatty and sugary products was significantly more common among those with acne than those who had never had acne. No differences were observed in vitamin D levels between the two groups.	2b
Kemeriz et al. 2020 [14]	Case-control study	—	134 acne patients from 18 to 65 years of age. Women accounted for 61.9% of the subjects. The control group included 129 controls of a suitable age and gender.	To examine the connection of serum vitamin D levels with acne and its severity.	It was found that vitamin D deficiency was significantly more common among acne patients compared to the controls. Vitamin D deficiency was significantly more common among those with severe or very severe acne than in other groups.	3b

(Continues)

TABLE 1 | (Continued)

First author, year (reference)	Epidemiological design	Country	Research material	Purpose of the trial	Relevant results	CEBM level of evidence
Hormones and metabolic factors						
Bansal et al. 2021 [22]	Case-control study	India	A total of 120 women, who were at least 25 years of age and suffering from acne, participated in the study.	To assess participants with regard to acne, hormones, logistics, and androgenic hair loss.	More than 70% of the women suffered from acne with hyperandrogenic features. However, only 18% of these had biochemically measured hyperandrogenism.	3b
Borzyszkowska et al. 2022 [15]	Case-control study	Poland	A total of 99 women between the ages of 18 and 31 suffering from acne. There were 69 controls of a suitable age and gender.	To assess the hormone profile of acne patients and its connection to the acne.	Testosterone, androstenedione, androgen index, prolactin and cortisol had significantly increased in the acne patients. SHBG and ACTH had dropped significantly in patients with acne.	3b
Dhaher et al. 2022 [16]	Case-control study	Iraq	In the study, female patients (total = 160) were divided into three groups: AA (47%): average age 17.2 years EA (23.5%): average age 21.4 years PA (29.4%): average age 28.7 years	To find differences between acne patients in different age groups.	Hyperandrogenic features were more common in the EA and PA groups than in the AA group. Before menstruation, acne worsened most frequently in the PA group. Total testosterone, DHEAS, LH, FSH and prolactin were higher in the EA and PA groups than in the AA group.	3b
Kim et al. 2020 [19]	Cross-sectional study	South Korea	The study included 60 men and women aged 19–35 suffering from acne. The control group included 40 controls of a suitable age and gender. There were equal numbers of women and men in both groups.	Link between metabolic factors and acne and its severity.	DHEAS and serum fatty acid concentrations were significantly higher among women than in the controls. The number of essential and non-essential amino acids was also significantly reduced in women with acne.	4
Meena et al. 2023 [17]	Cross-sectional study	India	A total of 60 women suffering from acne. The	To examine biochemical and hormonal parameters in acne patients.	25% had elevated fasting blood sugar, 10% had elevated insulin levels, 55% had a disturbance in	4

(Continues)

TABLE 1 | (Continued)

First author, year (reference)	Epidemiological design	Country	Research material	Purpose of the trial	Relevant results	CEBM level of evidence
			women were between 26 and 41 years of age.		their HOMA-IR index, 6.7% had an elevated testosterone level, 18.3% had an elevated FSH level, 3.3% had an elevated LH level, 15% had an elevated TSH level, 20% had high triglycerides, 38.3% had an elevated total cholesterol, 50% had and elevated LDL and 66.7% had a low HDL.	
Mohammed et al. 2023 [18]	Case-control study	—	100 acne patients from 18 to 45 years of age participated. Women accounted for 44% of the subjects. The control group included 100 controls of a suitable age and gender.	To assess lipid and hormone levels in acne patients and link them to acne severity.	The total cholesterol, triglycerides, LDL, HDL, estradiol, total testosterone and free testosterone of women with acne had significantly increased compared to the controls.	3b
Romańska-Gocka et al. 2018 [26]	Case-control study	Poland	A total of 60 women between the ages of 20 and 64 suffering from acne. The control group included 20 controls of a suitable age and gender.	Examine the connection between a lipid profile and acne.	Acne patients had significantly higher total cholesterol, triglyceride and LDL levels compared to controls. No significant deviations were found in HDL levels.	3b
Sardana et al. 2020 [20]	Cross-sectional study	—	120 women over 25 years of age and suffering from acne participated.	To compare the clinical and hormonal profile of female acne.	Clinical features of hyperandrogenism were found in 71.6% of the subjects. Biochemical hyperandrogenism was found in only 18.3% of the subjects.	2b
Shrestha 2018 [24]	Cross-sectional study	Nepal	A total of 78 women aged over 25 suffering from acne participated in the study	To examine the connection between acne and hormonal factors and lipid profile.	Hyperandrogenism was found in 17.9% of the participants, abnormal TSH values in 15.4%, high C-peptide levels in 10.3%, elevated total cholesterol in 7.6%, elevated LDL in 3.8%, high	2b

(Continues)

TABLE 1 | (Continued)

First author, year (reference)	Epidemiological design	Country	Research material	Purpose of the trial	Relevant results	CEBM level of evidence
					triglycerides in 3.8%, and decreased HDL in 10.2%.	
Zhang et al. 2022 [21]	Cross-sectional study	China	693 acne patients between the ages of 20 and 30 participated. Women accounted for 81.5% of the subjects.	To determine the link between gender hormones and the severity of acne.	The testosterone levels of acne patients did not differ from those of the controls. As the levels of estradiol and progesterone decreased in women, their acne worsened. An increase in FSH alleviated the acne, and an increase in the ratio of androgen to estrogen aggravated the acne.	2b
Genetic factors						
Aydingoz et al. 2021 [29]	Case-control study	—	156 men and women suffering from acne. The control group included 154 controls of a suitable for age and gender.	To examine the role of EGFR and EGF volume, expression and EGFR gene polymorphism in acne pathogenesis.	None of the different allele forms of EGFR presented a greater risk of developing acne over the others.	3b
El-Beah et al. 2022 [28]	Case-control study	Egypt	A total of 118 men and women aged 19–24 suffering from acne. Women accounted for 84.7% of the subjects. The control group included 120 controls of a suitable age and gender.	To determine the connection of survivin gene polymorphism (C/G) on the development of acne.	Acne patients had significantly higher levels of Survivin than healthy controls. Those with the C allele were 1.6 times more likely to develop acne than those with the G allele. The C/C genotype was also found with far greater frequency in acne patients than in the controls.	3b
Several different variables						
Kaminsky et al. 2019 [25]	Cross-sectional study	Latin America and Iberian Peninsula	1384 men and women aged 25–60 suffering from acne participated in the study. Women accounted for 80% of the subjects.	To examine the link between demographic, biological, social and environmental factors and adult acne.	59.8% of those with acne had a history of acne in their family. Symptoms of hyperandrogenism presented in people with severe acne more frequently than in others. 61.5% felt that there was a link between stress and the development of acne.	2b

(Continues)

TABLE 1 | (Continued)

First author, year (reference)	Epidemiological design	Country	Research material	Purpose of the trial	Relevant results	CEBM level of evidence
Kozłowski et al. 2023 [27]	Case-control study	Poland	A total of 168 women aged 18–31 suffering from acne participated. The control group included 69 controls of a suitable age and gender.	To determine the link between selected metabolic and nutritional parameters and acne.	Serum cholesterol, insulin and HDL levels had decreased significantly compared to the controls. The HOMA-IR index had significantly increased in acne patients. The consumption of sweets was linked to the severity of acne.	3b
Kutlu et al. 2023 [5]	Case-control study	Turkey	1066 acne patients from 25 to 65 years of age. Women accounted for 89% of the patients. The control group also included 960 controls of a suitable age and gender.	To examine the medical history, hereditary tendency, and alcohol, tobacco and nutritional factors of acne patient.	Hyperandrogenic features were found in 28% of the acne patients, which was a statistically significant difference compared to the controls. More than half of acne patients associated phases of exacerbation with stressful life situations. Those with adult acne had acne in their immediate circle about two times more often than the controls. The consumption of high glycemic foods was statistically more common in the acne group.	3b
Shah et al. 2021 [23]	Cross-sectional study	—	A total of 180 men and women over 25 years of age participated in the study. 81.7% of the participants were women.	To assess the prevalence of acne in the adult population and identify potential factors that cause or aggravate acne.	Of the acne patients, 23.9% reported suffering from chronic stress, 62.8% had acne in their immediate family, 42% said they consumed high glycemic food, 61.9% felt that their acne grew worse before menstruation, 16.3% reported having hirsutism, and 5.5% reported suffering from androgenic hair loss.	2b

Note: CEBM, Center for Evidence-Based Medicine. 1a: Evidence obtained of systematic reviews or meta-analysis of randomized control trials; 1b: Evidence obtained from individual randomized control trials; 2a: Evidence obtained from systematic reviews or meta-analysis of cohort studies; 2b: Obtained from individual cohort studies; 3a: Obtained from systematic reviews or meta-analysis of case-control studies; 3b: Obtained from individual case-control studies; 4: Obtained from case series; and 5: Obtained from expert opinions.

Abbreviations: AA, adolescent acne; ACTH, adrenocorticotropic hormone; DHEAS, dehydroepiandrosterone sulfate; EA, early adult acne; EGFR, epidermal growth factor receptor; EGF, epidermal growth factor; FSH, follicle stimulating hormone; HDL, high density lipoprotein; HOMA-IR, homeostatic Model Assessment for Insulin Resistance; IGF, insulin-like growth factor; IGFBP-3, insulin-like growth factor-binding protein 3; LDL, low density lipoprotein; LF, luteinizing hormone; PA, post adolescent acne; SHBG, sex hormone-binding globulin.

3.3 | Hormones and Metabolic Factors

The link between androgens and acne has been studied for a long time and is generally considered to be part of the pathogenesis of acne. The included studies reported, for example, significant increases in testosterone [15–18] and dehydroepiandrosterone (DHEAS) levels [16, 19, 20] in acne patients compared to healthy acne patients. Contrary reports were also found, as the testosterone levels of women with acne in a study conducted by Zhang and co-workers were within the reference limits [21], and Borzyszkowska and co-workers did not notice any difference in DHEAS values for acne patients compared to the controls [15].

Clinical hyperandrogenism in acne patients was reported in several studies [5, 16, 20, 22–25]. Depending on the study, hirsutism, androgenic hair loss, menstrual disorders and/or seborrhea were considered of the clinical features of hyperandrogenism. Interestingly, the study conducted by Sardana on the relationship between clinical and hormonal hyperandrogenism found clinical features of hyperandrogenism in 71.6% of acne patients, but only 18.3% of the patients had biochemically verified hyperandrogenism [20].

Other hormones associated with acne included thyrotrophin secreted by the pituitary gland [17, 24] and cortisol (stress hormone) secreted from the adrenal gland [15]. Patients' self-reported stress was also commonly reported as a triggering or aggravating factor among acne patients [5, 23, 25].

Elevated low density lipoprotein (LDL) [17, 18, 24, 26, 27], high triglycerides [17, 18, 24, 26] and low high density lipoprotein (HDL) [17, 24] were most seen changes in the lipid profile of acne patients. However, Romanska-Gocka et al. did not notice any differences in HDL levels between acne patients and the controls [26]. In the study conducted by Mohammed et al. the HDL values of acne patients were above the reference values [18].

Meena et al. studied the glucose metabolism of acne patients [17]. They found that one fourth of acne patients had elevated fasting blood sugar levels and elevated serum insulin levels, and 55% had insulin resistance in the body (assessed using the homeostasis model assessment for insulin resistance [HOMA-IR]).

3.4 | Genetic Factors

In their study, Kutlu et al. reported that patients with adult acne had a close relative with acne approximately twice as often as healthy controls [5]. In the study conducted by Shah et al. more than 60% of those with adult acne had acne in their family [23]. Similar results were found by Kaminsky et al. which reported in their study that 59.8% of those suffering from acne had inherited the disease [25].

El-Beah et al. examined the connection of Survivin gene polymorphism (C/G) on the development of acne [28]. They found that acne patients had significantly higher levels of survivin than healthy controls. Those with the C allele were 1.6 times more likely to develop acne than those with the G allele. Those with a C/C genotype had an acne risk 2.8 times higher than those with a G/G genotype.

4 | Discussion

According to this systematic literature review, especially hyperandrogenism, a positive familial history and a high-glycemic diet may be linked to the development of adult acne. The mechanism of action of androgens is unclear in adult acne, as most patients have normal androgen levels. Research findings on the link between milk and acne are contradictory.

4.1 | Nutrition

The association between adult acne and diet has been studied widely, and, many expert consider Western diet with high-glycemic-index food (high-fat, high-sugar foods) to worsen acne. In a large French study by Penso et al. [11] it was shown that acne patients consumer more high-sugar foods than those without acne. The link between diet and acne has been explained e.g. by a study conducted by Burris et al. in which a low glycemic diet reduced the IGF-1 levels of acne patients [13]. IGF-1 contributes to acne pathogenesis, increasing the growth of the sebaceous gland, sebum production, keratinocyte proliferation and activating androgen synthesis. The increase in IGF-1 also reduces the amount of IGFBP-3, which increases the concentration of free IGF-1, thus exacerbating the acne [30, 31].

Although the relationship between dairy products and acne has been studied for a long time, no convergent opinion on its contribution to acne development has been stated. For example, Penso et al. found that subjects with high consumption of milk intake have a higher risk of adult acne [11], however, in a large Danish study Juhl et al. did not found that association [12]. More, even though milk has a low glycemic index, it is thought that it can cause acne with the same mechanism as high glycemic foods - in other words it increases the production of IGF-1 [32–35].

A recent systematic review by Meixiong and co-workers reports that high-glycemic-index food may exacerbate acne and acne severity [36]. All the reviewed studies about milk and acne were observational in nature and varied widely in terms of exposure assessment and reported results [36]. Like us, they conclude that studies investigating the association between diet and acne face several challenges: in many studies sample sizes are inadequate or with too short exposure period, and large surveys rely on food diaries and participant self-assessment of acne, which are prone to bias [36].

Vitamin D is necessary for optimal health and vitamin D deficiency has been implicated in various skin diseases [37]. Interestingly, some studies have reported the relationship between acne and D vitamin, too. For example in a small Turkish study by Kemeriz et al. acne patients showed significantly lower D vitamin levels than acne-free controls [14]. Corresponding findings were reported in South-Korean [38] and in an Australian studies too [39]. The role of vitamin D in acne pathogenesis could be explained by its ability to regulate the growth of the sebaceous gland, the distribution of keratinocytes and the expression of inflammatory mediators [40]. However, the association between acne and D-vitamin is not indisputable either and studies with contradictory findings exist

as well [41]. For example age is seldom taken into account when reporting results. Geographical location also affects vitamin D levels in people with acne; Northern location has a negative effect on vitamin D levels in acne patients [42]. Also, it would be important to investigate how vitamin D supplementation affects vitamin D levels and clinical manifestations of acne in adult women living in the North.

Thus, more studies among various ethnicities, among different age groups and geographical areas are still needed before recommendations about the D vitamin intake can be given for patients with acne.

4.2 | Hormones and Metabolic Factors

In some studies glucose and fat metabolism disorders have been associated with acne. However, the mechanism linking elevated triglycerides, LDL, total cholesterol, low HDL and acne is not precisely understood. In addition to glucose, a high glycemic diet often contains a lot of saturated fatty acids, which increase the triglycerides, total cholesterol and LDL circulating in the blood [43]. Therefore, the link between the lipid profile and acne could also be explained by the consumption of high glycemic foods.

It is well demonstrated that sex hormones - and especially androgens -have a remarkable role in the pathogenesis of adult acne. Androgens can stimulate growth of the sebaceous glands and increase the secretion of sebum, which promotes changes in the skin associated with acne [44]. The role of androgens in the development of acne is also supported by research evidence that antiandrogenic therapies often successfully treat acne in women [45, 46]. Based on our systematic review, it could be concluded that the androgen levels of acne patients are more often abnormal and that clinical features of hyperandrogenism occur more frequently than in healthy controls. However in fact, most women suffering from adult acne have normal androgen levels [1, 3, 20, 22, 47, 48].

Sebaceous gland is able to transform weak hormone precursors into potent androgens as testosterone and dihydrotestosterone [49, 50]. These androgens stimulate increased sebum production, which favors colonization by *P. acnes* [51]. Normoandrogenic acne patients have been reported to have higher level of androsterone glucoronate, an androgenic metabolite, than healthy controls [52]. This result may indicate that local androgen production in sebaceous gland is more active in acne patients than in healthy controls. In addition, the inflammation associated with acne also appears to be localized to the skin [53]. This further supports the use of topical treatments, such as azelaic acid, which has an acne-promoting effect by decreasing toll-like-receptor 2 expression in sebaceous glands [54].

Many women report that stress is aggravating their acne. In addition, some studies have found an association between more severe form of acne and reported stress [55]. The connection between acne and stress has been explained e.g. by the secretion of different neurotransmitters, cytokines and hormones such as cortisol, which are known to affect acne [56]. New insights into the association between acne in women and professional stress are needed, particularly to understand the correlation between acne in adult women and potential job situation or unemployment.

However, these studies about these associations have their limitations since many aspects are contributing simultaneously both acne and stress.

4.3 | Genetic Factors

Based on our review, patients with acne have other acne sufferers in their first-degree relatives more often than healthy controls. This finding is further supported by other studies (from United Kingdom and Nigeria) which reported an increase in the risk of adult acne among those with a positive familial history of acne [57, 58]. In addition, those with a positive familial history have a greater risk of developing a severe form of acne and acne scars as well [58]. Therefore, when planning the comprehensive treatment of acne patients it is important to be aware of the possible family history of the disease.

Unfortunately, our review does not provide a broad understanding of how genetic factors can be part of acne pathogenesis. However, the survivin –noted in our review–can be integrated into a larger framework of innate immunity to understand the role of genetic factors in the development of acne: Rocha & Bagatin have suggested that factors activating the innate immune system seem to explain the persistence of acne lesions [59] as survivin indirectly supports the activation of innate immune responses by promoting e.g. the function of dendritic cells [60].

5 | Conlusions

Acne is a complex condition influenced by a variety of factors including diet, hormones, metabolism and genetics. However, there are still contradiction of the role of diet in adult acne whereas low D-vitamin levels might have an association with acne and this relationship requires more research. Androgens, in turn, has a major role in pathogenesis – interestingly, androgen levels may be normal in adult acne patients but in some individuals hormonal receptors in sebaceous glands and keratinocytes seems to react to even low androgen levels. More, patients with adult acne have more often first-degree relatives with acne than those without adult acne which strengthens the role of genome in adult acne. Nevertheless, the complexity of the pathogenesis in acne, creates a great challenge for studies investigating these association. Due to this, it is understandable that also this review included many studies with contradictory results. Thus, more studies taking this bias into consideration are needed. Moreover, the population size in many studies in this review were moderately small which can be considered as a limitation, and more larger scale studies among various ethnicities are needed.

Author Contributions

Anni Telkkälä: writing – original draft. **Suvi-Päivikki Sinikumpu:** conceptualization, investigation, writing – review and editing, supervision,

methodology, project administration. **Laura Huilaja:** conceptualization, investigation, writing – review and editing, supervision, methodology, project administration.

Acknowledgments

The authors thank the Senior Information Specialists of the Faculty of Medicine at the University of Oulu for expert help when conducting the data search.

Ethics Statement

The authors have nothing to report. This study did not collect data from human or animal subjects.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Transparency Statement

The lead author Suvi-Päivikki Sinikumpu affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

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