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An Unblemished Look: Understanding the Role of Acne in Internalizing Problems

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ABSTRACT OF THE DISSERTATION

An Unblemished Look: Understanding the Role of Acne in Internalizing Problems

by

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Several studies have shown an association between acne vulgaris and depression and anxiety. Some evidence suggests that these associations may be influenced by moderating factors such as sex, clinical acne severity, and perceptions of acne severity. Overarching these questions are those pertaining to the developmental salience of these factors. The current investigation addressed these gaps based on an examination of literature to assess data from 40 studies retrieved from PubMed, PsycINFO, MEDLINE, and Cochrane databases.

A 2-step hierarchical meta-analytic approach was utilized in order to perform random effects model analyses to determine associations (1) between individuals with acne and without acne, and (2) among individuals with acne. Step 1 analyses across 1,028,893 participants from 33 studies found a significant association between acne vulgaris and depression, $r = 0.210$ (95% CI: 0.143-0.253, $p < .00001$). Similarly, across 21,634 participants from 22 studies sample sizes, results revealed a significant association with anxiety, $r = 0.258$ (95% CI: 0.187-0.323, $p < .00001$).

It is of note that acne, which is often disregarded as a cosmetic concern, explains 4.41% and 6.66% of the variation in depression and anxiety, respectively. Sensitivity analyses underscored the robustness of these results. Subgroup analyses and comparisons showed influences on these associations such that females, adults, and those with more severe acne were at greater risk.

Limitations included marked heterogeneity and inconsistencies between publications regarding acne and outcome ascertainment, data reporting, and studies with no control group. These considerations posed considerable barriers to synthesizing all available literature. Still, because of increased risk for depression and anxiety among individuals with acne, clinicians should consider screening patients with acne for psychiatric morbidity.

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CHAPTER 1 – INTRODUCTION AND THEORETICAL FRAMEWORK

In 1948, Sulzberger and Zaidems conducted a study of the psychogenic factors in cutaneous disorders. They concluded the following: "There is no single disease which causes more psychic trauma… more general insecurity and feelings of inferiority and greater sums of psychic suffering than does acne vulgaris (pp. 671)." To some, this assertion may seem overly dramatic. Yet accumulating evidence suggests that these clinicians may have captured something of the essence of the psychological effect of acne. For years, researchers have found that acne can impair psychological wellbeing in younger and older individuals of both sexes (e.g., Shuster et al., 1978; van der Meeren et al., 1985; Koo & Smith, 1991; Thomas, 2005). Recently, the psychological effects of acne have been studied in some detail. Acne is associated with decreased appearance-related satisfaction, self-esteem, and self-confidence (e.g., Nguyen, Koo, & Cordoro, 2016; Hassan et al., 2009; Fried & Wechsler, 2006), and increased internalizing problems such as social isolation, anxiety, anger, depression, and suicidal ideation (e.g., Wu, Kinder, & Trunnell, 1998; Cotterill & Cunliffe, 1997; Gupta & Gupta, 1998; Purvis et al., 2006). Several literature reviews (e.g., Tan, 2004; Dunn, O'Neill & Feldman, 2011) and one meta-ethnography of qualitative literature (Ablett & Thompson, 2016) have borne out these associations, but no quantitative review has been conducted to date. A meta-analysis would advance knowledge by quantifying the effect of acne on internalizing problems and helping to concretize our understanding of the psychosocial effect of acne.

Acne vulgaris is a chronic inflammatory skin disease characterized by lesions, such as pilosebaceous gland comedones, papules, pustules, and nodules (Aktan et al.,

2000). These lesions are localized in areas with well-developed sebaceous glands such as the face, back, chest, and upper arms (Hanna, Sharma, & Klotz, 2003). Epidemiological studies have found that acne affects a majority of adolescents world-wide (e.g., Law et al., 2010; Yahya, 2009; Wei et al., 2010). Prevalence rates of acne estimate that it affects approximately 50 million American anually (Bickers et al., 2006), and in approximately 15-20% of those cases, acne is moderate to severe.

Individuals present with acne throughout the life course: in infancy, prevalence rates are approximately 20% (Mancini et al., 2011), though infantile acne and pediatric acne in prepubertal children are often considered special cases of acne (Friedlander et al., 2010; for review, see Lucky, 1998). Post-pubertal acne, or adult acne, continues across the life course, particularly into the 30s and 40s (Holzmann & Shakery, 2014; Khunger & Kumar, 2012), though individuals in excess of 60 years of age present with acne (for review, see Bhate & Williams, 2013). For example, a German population study by Schafer, Nienhaus, and Vieluf (2001) found that 64% of the population of adults aged 20-29 years and 43% of the population aged 30-39 years had visible acne. Even among men and women aged 40-49, prevalence rate estimates are 3% and 5%, respectively (e.g., Cunliffe & Gould, 1979). Further, some research suggests that adult acne is increasing, particularly among women, according to some estimates, by as much as 15% (Tanghetti et al., 2014).

In contrast, peak occurrence for acne is during adolescence, with an 85% prevalence rate in those between the ages of 12 and 24 years (for a review, see Bhate & Williams, 2013). Thus acne is a relatively developmentally normative phenomenon

during adolescence as puberty heralds the onset of various morphological changes. Yet some of these changes deviate from sociocultural appearance ideals (i.e., acne, weight gain, body hair). Skin changes (i.e., increased sebum production) and acne are often the first visible signs of pubertal onset, and these changes are at odds with the cultural ideal of smooth, clear, unblemished skin (Magin et al., 2011). Adolescence marks a period of increasing sensitivity to physical appearance, and a growing body of research shows that acne is a risk factor for internalizing problems among adolescents.

Except in cases of severe cystic acne where individuals experience physical symptoms such as pain and bleeding, the most prominent morbidity of mild to moderate acne is its psychosocial effect. Since the majority of those with acne have no direct physical impairment, acne runs the risk of being dismissed as a mere cosmetic condition (e.g., Barankin & Dekoven, 2002). Yet studies on the psychological impact of acne in comparison to other dermatological and non-dermatological illnesses, for example, tell a different narrative. One such study by Mallon et al. (1999) found that acne patients reported levels of social, psychological, and emotional problems that were as great or greater than those reported by patients with serious non-dermatological illnesses including epilepsy, diabetes, or coronary artery disease. Another study that compared the psychological symptoms of individuals with acne to those with other dermatological conditions of alopecia, atopic dermatitis, and psoriasis found that those with acne had significantly higher scores for depression (Gupta & Gupta, 2003). Among individuals with acne, there is some evidence that factors such as sex and acne severity, both from

the perspective of a clinician and from the perspective of the individual, differentially influence the riskiness of acne as well (e.g., CITE).

The unifying purpose of this dissertation was to explore the role of acne in internalizing problems. A quantitative synthesis of available literature addressed the gaps and inconsistencies in current knowledge reviewed above. Specifically, I utilized a meta-analytic approach to quantify the magnitude of the association between acne and internalizing problems, and to determine whether this association varies by key moderating factors of sex and acne severity both from the perspective of a clinician and from the perspective of the individual. I used a broadly developmental and contextual lens in this investigation to examine whether age and context (i.e., study context) influenced associations at all levels of analysis. What follows is a review of relevant extant literature. First, I will provide an overview of sensitivity to appearance in adolescence including the development of body image awareness and the larger context of cultural appearance norms in which body image develops. Next, I will review literature on acne in adolescence, highlighting the intersection of pubertal development and acne, and the salience of acne as a highly visible feature of puberty. Third, I will discuss findings from literature exploring the relationship between acne and internalizing problems.

Emergence of Sensitivity to Appearance During Adolescence

Appearance-related concerns may be central to understanding the negative psychological impact of dermatological conditions in general and acne in particular. A person's perception of his or her attractiveness is mostly formed through social

experience, and by cultural values or ideals (Thompson, Heinberg, Altabe, & Tantleff-Dunn, 1999). Western appearance ideals include clear, unblemished skin (e.g., Magin et al., 2011), and deviations from these ideals, such as acne, can lead to negative reactions from others (e.g., Ablett & Thompson, 2016). The cumulative effect of the internalization of negative skin-based reactions, together with the socio-cultural influence and stereotypes associated with the appearance of the skin, may put individuals with a dermatological condition such as acne at increased risk for developing appearance-related distress and internalizing problems (Thompson, 2011). The high visibility of acne lesions or spots, often localized on the face, may be particularly traumatic. Prior research has found that facial acne in particular is related to shame, negative body image (Kellett & Gawkrodger, 1999), increased feelings of appearance-related concern, withdrawal from social interaction, and poorer psychological functioning (Motley & Finlay, 1992).

Developmental researchers have long been aware that body image concerns become particularly salient in early adolescence (e.g., Kostanski, 1998; Petroski, Pelegrini, & Glaner, 2012), which coincides with the time adolescents begin to experience puberty-related skin changes. As puberty unfolds, adolescent body image must develop to accommodate physical changes. Adolescents may compare their evolving physicality to more stable cultural standards of desired physical appearance (e.g., Faust, 1983) at a time when many pubertal changes (i.e., weight gain, body hair, acne) place them further from these standards. Additionally, youth may be more sensitive to social feedback regarding their appearance given that both social comparisons and physical appearance become increasingly important in adolescence (Hart, 1988).

Development of Body Image Awareness. According to the literature on body image, increasing cognitive abilities and capacities for introspection in adolescence may render youth particularly vulnerable to excessive concern over, and negative perception of, their changing appearance (e.g., Simmons, Blyth, & McKinney, 1983). The psychological construct of body image includes a person's perceptions, thoughts, and feelings about his or her body (Grogan, 2016). Body image awareness emerges quite early in development, and from as young as around 3 years of age, children begin to learn and be influenced by cultural and social representations about the value of appearance (Thompson, 2011). However, body image is not likely to be self-evaluative until 6 years of age, becoming increasingly so into adolescence (Smolak, 2011).

Ideas about one's image come from a variety of sources, including family, peers, and social and cultural attitudes about the value of appearance (Kearney-Cooke, 2002). Cultural attitudes in Western society place great emphasis on outward appearance, and thus it is likely that children draw on these internalized representations of socio-cultural standards and stereotypes in forming evaluations of themselves (Thompson, 2012). Additionally, outward appearance serves as a powerful stimulus for social evaluation (Cash, 1995), and it is likely that social feedback makes important contributions to the development of body image over time (e.g., Sorrell & Nowak, 1981; Fisher, 1990). Youth who deviate from culturally determined standards related to physical attractiveness (i.e., acne) may evoke negative social evaluations and feedback (Burns & Farina, 1992), and internalize these negative appearance-based reactions from others (Harter, 1991). For example, in a meta-ethnography of childhood and adolescent experiences with skin

conditions (including acne), Ablett and Thompson (2016) found that youth were extremely distressed by stigmatization, the receipt of negative comments, and even fears of receiving such comments. These results suggest that negative appearance-related feedback, and even the fear of it, are salient influences which shape body image over time. This is particularly concerning given that body image is related to self-concept (Pruzinsky & Cash, 1990), and research has found that physical self-concept is related to depression among adolescents (e.g., Dishman et al., 2006). Given such findings, it is important to understand the particular impact of visible signs such as skin change and acne on youth well-being.

Moreover, it is even possible that appearance concerns may leave lasting psychological impacts. For example, in a longitudinal study of adolescents at ages 13, 15, and 18 years of age, Rosenblum and Lewis (1999) found that, particularly among adolescent girls, those who received unfavorable feedback about their appearance in early adolescence were at increased risk of developing poor body image which persisted over time. Further, their poor body image was resistant to change despite future gains in attractiveness. This pattern of findings highlights early adolescence as a salient period for the development of body image, which, once developed, may remain relatively constant across this developmental period. Persistent poor body image may be particularly detrimental as research that shows negative body image places youth at risk for a number of adverse psychological sequelae, including low self-esteem (Blyth et al., 1981) and depression (Noles, Cash, & Winstead, 1985).

Acne and Puberty

Puberty runs in the background of the aforementioned changes such as the emergence of acne, heightened self-introspection, and self-awareness of appearance. Puberty is a gradual series of neuroendocrine events which typically unfolds across a span of 3 to 5 years (Papadimitriou, 2016), though the tempo, or rate of pubertal development, can span from 1 year to 7 years or more (e.g., Mendle, 2014). The first of two pubertal processes is adrenarche, or the maturation of the hypothalamic-pituitary-adrenal (HPA) axis, during which the secretion of adrenal androgen precursors increases (Dorn, Dahl, Woodward, & Biro, 2006). These increases begin at some point in middle childhood, from 5 to 8 years of age (Utriainen et al., 2014). Gonadarche begins later at approximately 9 to 11 years of age, though onset in boys is typically 1 year later than girls (Dorn et al., 2006). It involves the reactivation of the hypothalamic-pituitary-gonadal (HPG) axis (relatively dormant since infancy) which results in the secretion of gonadal estradiol and testosterone. This process sets in motion a series of events in which gonadotropin-releasing hormone (GnRH) secreted from the hypothalamus stimulates the pituitary gland to secrete luteinizing hormone (LH) and follicle-stimulating hormones (FSH) which in turn stimulate the ovaries and testes to secrete estradiol and testosterone. These complex changes in the HPA and HPG axes set in motion a series of morphological changes (Dorn & Biro, 2011).

Skin change and acne can be an early, visible sign of HPA axis activation or adrenarche onset. The clinical signs of adrenal androgen action (e.g., body odor, acne, greasy hair) begins at similar ages for girls and boys, typically at 8 or 9 years of age (see

Styne & Grumbach, 2011 for review). These signs begin to emerge following an early childhood period of inactivity of sebaceous (sebum-producing) glands. Spanning approximately 7 to 10 years of age, androgens stimulate increasing activity of the sebaceous glands (Stewart et al., 1992). During this time, there are significant changes in the microbiome, or the microorganisms which normally reside on human skin (Oh et al., 2012). These fluctuations can interact to produce skin change and acne, where increases in sebum production occurs as micriobiome changes produce increases in lipophilic (oil-loving) bacteria on sebaceous skin regions such as the scalp, face and upper trunk.

Such changes can herald the onset of pubertal maturation-related visible skin changes ranging from oily skin to the onset of conditions such as acne vulgaris, seborrheic dermatitis, and psoriasis (Wong et al., 2014). Therefore, puberty-related skin change and acne can occur earlier than many parents, and even clinicians, expect (e.g., Bhate & Williams, 2013). For example, Lucky (1998) notes that girls can have onset of acne at the age of 8 years. Some dermatologists theorize that secular decreases in the age of adrenarche onset is the reason for younger children ranging from 8 to 11 years with acne presenting in their clinics (Friedlander et al., 2010). While these trends are worthy of note, they are as of yet the exception rather than the norm.

Consequently, the highly visible nature of skin change and acne may be particularly distressing for the adolescents who experience them as unfamiliar and ugly at a time when social comparison is of increasing importance and when they are experiencing these visible changes before their peers (Hart, 1988). By the time the first children begin to show visible signs of adrenarche such as skin change and acne at age 8

or 9, they have internalized socio-cultural values associated with ideal skin appearance and are likely to internalize negative skin-based reactions from others (Thompson, 2011). Though acne can occur across the life course from infancy through adulthood (for a review, see Bhate & Williams, 2012), for adolescents, its psychological significance may be magnified both because of its novelty and its departure from appearance ideals at a time when conforming to these ideals is increasingly important.

Research on the psychosocial experience of skin change and acne in childhood and adolescence has shown a host of associated negative interpersonal and psychopathological consequences. A review of studies by Dunn et al. (2011) concluded that acne negatively impacts quality of life, self-esteem, and mood, and increases the risk of anxiety, depression, and suicidal ideation among adolescents. A more recent meta-ethnography by Ablett and Thompson (2016) on child and adolescent experiences with skin conditions including acne found that common experiences across studies were feelings of difference, powerlessness, and stigmatization. Others have found that adolescents with acne struggle with anxiety in social situations, dissatisfaction with appearance, and experience social isolation and constriction of activities (Koo & Smith, 1991; Law, Chuh, & Molinari, 2010; Fried & Wechsler, 2006).

Visibility of Acne. The face is arguably the most visible and socially relevant part of the human body. As such, facial appearance may occupy a particularly salient niche in the development of body image. Indeed, in one study of early adolescents ($N = 157$, $M_{age} = 11.79$ years), Perkins and Lerner (1995) found that facial attractiveness was more predictive of overall psychological functioning than multiple measures of bodily

attractiveness combined. Historically, some psychologists have long acknowledged the psychological importance of facial appearance. In their California Adolescent Study, Stolz and Stolz (1944) pointed out that, "As with other physical characteristics, boys and girls become increasingly aware of individual facial appearance during the cycle of puberty (p. 81)." Almost a decade later, Roff and Brody (1953) warned of the potential lasting psychological effects of facial appearance disturbances during adolescence.

In more recent decades, however, many investigations of body image in children and adolescents have focused on aspects of weight and shape, and tended to ignore concerns about the face or appearance of the skin (Smolak, 2011). Yet cultural emphasis on facial appearance is high (Landsdown et al., 1997) and it is theorized that children and adolescents internalize facial appearance ideals and social feedback similarly to how they develop other aspects of body image: namely, that they internalize both reactions from their social environment and at the same time socio-cultural appearance expectations for skin (e.g., Magin et al., 2011). As a consequence, youth with acne may be at particular risk for developing image-related distress (Thompson, 2011, 2012).

Research into psychological distress associated with dermatological conditions or physical disfigurement has emphasized the psychosocial weight of facial appearance. For example, in a study comparing older children with cleft palates to those with disfigured hands, the children with cleft palates were significantly less socially competent and more withdrawn compared to those with hand problems (Bradbury & Hewison, 1994). In the case of acne, lesions typically develop on the facial or truncal (chest and back) regions. Approximately 50% of facial acne cases present with truncal acne (e.g., Del Rosso, 2006)

but there is evidence that facial lesions are often more distressing because of their relatively higher visibility. For example, in a study of psychological morbidity among individuals with facial acne compared to those with truncal (i.e., back, chest) acne, Papadopoulos, Walker, Aitken, & Bor (2000) found that individuals with facial acne reported significantly greater psychological distress. The authors interpreted these findings, and those of others (e.g., Wessley & Lewis, 1989), as suggestive of a causal relationship between between the visibility of a facial skin condition such as acne and the development of a psychological disorder.

Acne and Internalizing Problems

Given the high visibility, high undesirability, and widespread cultural condemnation surrounding acne, it is unsurprising that it has been linked to internalizing problems. Studies with comparison groups (e.g., Yazici et al., 2004; Sayar et al., 2001; Khan, Naeem, & Mufti, 2001) and without comparison groups (e.g., Polengi, Zizak, & Molinari, 2002; Gupta & Gupta, 1998; Woodruff et al., 1997) have established associations between acne and symptoms of depression and anxiety. One large-scale study of nearly 10,000 adolescents in New Zealand found that those with acne have significantly higher rates of depression, anxiety, and suicide attempts (Purvis et al., 2006). Another large study of Australian adolescents (n = 2,525) by Kilkenny et al. (1997) found that those with moderate acne reported significantly greater depression and anxiety symptoms. In a similar sized study of approximately 2,600 Turkish high school students, those with acne (n = 615) reported significantly higher anxiety but not depressive symptoms (Aktan, Ozmen, & Sanli, 2000).

Smaller-scale studies have found comparable results. For example, Yarpuz et al. (2008) found that 83 acne patients from a university dermatology center reported significantly more social anxiety, general anxiety, depression, and negative automatic thoughts in comparison to a sample of 58 healthy controls. Others have found similar patterns of results among those with acne in Canada, Turkey, South Korea, Hong Kong, and the United States (e.g., Klassen et al., 2000; Yazici et al., 2004; Do et al., 2009; Hedden et al., 2008). Another set of studies has taken a different approach, examining the association between effective treatment of acne and alleviation of depression and anxiety symptoms. These investigations have shown that depression and anxiety symptoms decrease when acne is successfully treated (e.g., Schulpis et al., 1999; Grahame et al., 2002; Rubinow, Peck, Squillace, & Gantt, 1987; Ferahbas et al., 2004; Strauss et al., 2001; Gupta et al., 1990).

These studies paint a compelling picture of acne as a risk factor for internalizing problems of depression and anxiety. However, findings from individual studies and qualitative reviews have several limitations that can be overcome using quantitative synthesis techniques such as a meta-analysis (Rosenthal, 1984). First, by pooling the results of multiple studies, a meta-analysis helps to overcome the problem of low statistical power that affects most dermatology-psychopathology research. Many investigations on the psychological impact of acne have been conducted using community samples with individuals who may not be experiencing clinically significant symptoms. Among clinical studies, researchers face limitations due to typically small clinical sample sizes. It is therefore important for theoretical and practical purposes to

gain an overall estimate of the effect of acne on internalizing problems by conducting a quantitative synthesis of the evidence. Second, meta-analysis enables a statistical assessment of the extent to which certain hypothesized moderators influence the effect of acne on internalizing problems. This information is particularly useful given substantial gaps in knowledge regarding the effect of several key factors on the association between acne and internalizing problems.

Moderators of the Acne Effect

Though previous studies have shown a link between acne and internalizing problems, the strength of this association varies. Some studies report effect sizes that are quite small (e.g., $r = .06$; Mallon et al., 1999; $r = .12$, Do et al., 2009), while others report moderate to large effects (e.g., $r = .43$; Kurek et al., 2013). To explain the heterogeneity in these effect sizes, the current study will focus on four potential moderators: age, sex, acne severity, and reporter of acne severity (clinician-report versus self-report). Thus, a secondary aim of the current meta-analysis is to examine how these potential moderators contribute to the mixed results in the literature.

Developmental stage. Though there is evidence that acne has negative psychological impact on individuals both young (e.g., Purvis et al., 2006) and old (e.g., Lasek & Churn, 1998), the age of acne occurrence may have implications for internalizing problems. While some have found no age differences (e.g., Klassen, Newton, & Mallon, 2000), others have found that acne is particularly risky for internalizing problems among youth in comparison with older populations. For example, in a controlled study of 83 acne patients aged 15-40 years ($M = 21.8$, $SD = 5.1$), Yarpuz

et al. (2008) found that age and internalizing problems were significantly negatively correlated such that as patient age decreased, the severity of depressive and anxiety symptoms increased. The authors expected this pattern of results given the increasing importance of appearance during adolescence coupled with the relative novelty of acne and limited cognitive and emotional coping capacities in comparison with older populations.

Indeed, as children enter adolescence, peer relationships and peer acceptance become a central concern (Bukowski et al., 1993), and the desire to conform to peer-sanctioned appearance ideals and norms can result in the experience of stress, isolation, and feelings of inferiority among those who deviate either from their peers or from peer-sanctioned ideals (e.g., Dwyer & Mayer, 1969). In a meta-ethnography of the experiences of children and adolescents with skin conditions including acne, Ablett and Thompson (2016) highlighted themes of child and adolescent sense of stigmatization, negative social reactions, and feelings of difference relating to the appearance of the skin. These findings align with the previously outlined literature regarding heightened body image, introspection, and sensitivity to social evaluation during adolescence. In this light, paradoxically, adolescence emerges as a particularly risky period for the emergence of acne despite its developmentally normative increases in prevalence (Bhate & Williams, 2013).

This picture is complicated by others who have found greater acne-related psychological distress among older populations. In a medical database study of approximately 9.6 million patients in the U.S., Uhlenhake et al. (2010) found that, acne-

related depression was higher in those over 18 years of age, with the highest rates in the age group of 36-64 years. Smaller-scale studies have found similar patterns of results. For example, a study of dermatological quality of life in 60 acne patients found that those aged 30-39 reported significantly higher depressive symptoms, fear, and social effects in comparison with those aged 17-19 years. Another study by Hassan et al. (2009) found that patients 20 years and above were significantly more likely to suffer appearance-related distress in comparison with 16 to 19 year olds. These authors argued that acne may present a particular challenge for older populations because their symptoms deviate from a cultural belief that acne is a condition affecting only adolescents. Given the lack of clarity reviewed above, this meta-analysis took a broadly developmental lens to examine whether associations between acne and internalizing problems was influenced depending on the developmental stage of the participants.

Sex. Although the general literature on poor body image suggests heightened female vulnerability, extant literature on the differential psychological and emotional impact of acne according to gender is inconclusive. Some have found no evidence to suggest that the association of acne with depressive symptoms and anxiety differs by gender (e.g., Purvis et al., 2006; Yazici et al., 2004; Gupta & Gupta, 1998). Others have shown patterns of results which suggest that the psychological impact of acne may be greater for females than males. In their population based study, Uhlenhake et al. (2010) found that depression prevalence among all acne patients (aged 0-65 years) was twice as high among females (10.6% females versus 5.3% males).

In a study of adolescents, Atkan et al. (2000) found that depression scores of boys and girls with acne were not significantly different, but anxiety scores among girls with acne were significantly higher than boys with acne. Others have found that adolescent females with acne reported increased difficulty with stress and interpersonal relationships (Do et al., 2009) and decreased self-esteem and self-confidence (Nguyen, Koo, & Cordoro, 2016) in comparison with adolescent males. Similarly, in a questionnaire-based cross-sectional study of 3,775 late adolescents (aged 18-19 years), girls with substantial (versus little acne) acne reported a threefold increase in suicidal ideation in comparison to boys with the same severity of acne. Several studies of adult acne have found similar patterns of results (e.g., Dalgard et al., 2004). I therefore examined the role of sex as a potential moderator of the association between acne and internalizing problems.

Acne Severity. Researchers often investigate whether acne severity is associated with psychiatric morbidity, yet the evidence is inconclusive. Several studies have found no correspondence between acne severity and the degree of internalizing problems (e.g., Yarpuz et al., 2008; Magin et al., 2011; Yazici et al., 2004; Law et al., 2010). Some (e.g., Gupta et al., 1990) argue that mild to moderate acne may be just as psychologically salient for some individuals as more severe acne. Yet others find that acne severity is related to internalizing problems such that moderate or severe acne is related to increased depressive and anxiety symptoms in comparison with mild acne (e.g., Do et al., 2009; Lee & Ahn, 2003; Kilkenny et al., 1997). As such, the present investigation included acne severity as a potential moderator of the effect of acne on depression and anxiety.

Clinical Severity and Self-Rated Severity. There are four different approaches to assessment of acne severity: lesion counting, global acne severity grading, multimodal digital imaging, and via self-report (Agnew, 2016). Of these, the first three are clinical approaches to the assessment of acne severity. Investigations into the association between acne severity and internalizing problems have found that matters are complicated by the fact that the *reporter* of acne severity is often a salient risk factor – sometimes even a more salient risk factor – for internalizing problems than clinical ratings of acne severity alone (e.g., Gupta & Gupta, 2003). For example, Do et al. (2009) found that self-report but not clinician-report of acne severity was significantly related to negative self-image, interpersonal impairments, and depression.

Similarly, Motley and Finlay (1992) found no linear relationship between clinician gradings of acne severity and psychological distress. Rather these authors found that the individual's own perception of acne severity was predictive of increased embarrassment, frustration, depression, and acne-related behavior changes. Thus while some contend that clinical assessments of acne severity are more precise and valuable, others find that self-reported assessments of acne severity are likely a more important consideration in the evaluation of psychological outcomes associated with acne. Mallon et al. (1999) hypothesized that the extent to which acne is related to psychological morbidity is less dependent on clinical severity than by the individual's own perception of severity, which is likely influenced by his or her personal, social, and occupational environment. In light of these assertions, the current study sought to clarify the relative

influence of clinical ratings of acne severity versus self-rated acne severity on the strength of the relation between acne and internalizing problems.

Current Study

Several gaps in current understanding remain. First, there are inconsistencies in extant literature regarding the magnitude of the effect of acne on internalizing problems. Second, there is no consensus regarding whether the association between acne and internalizing problems is stronger among adolescent or adult populations. Third, it is unknown whether there is a differential psychological impact of acne according to sex. Fourth, it is unclear whether clinical ratings of acne severity are associated with psychological morbidity. Finally, the association with self-perceptions of acne severity is even more poorly understood.

Together, extant theory and research has not painted a consisted picture of the effect of acne on depression and anxiety. As such, the computation of an aggregated effect size across studies will represent a contribution to existing knowledge. There is growing consensus regarding several important limitations of the heavy reliance by prior experimental studies on null hypothesis significance testing (NHST) which has recently been criticized for its dependence on sample size, its insufficient consideration of effect size, and for the risk of (often unintentional) data manipulation in order to achieve statistical significance, $p < .05$ (e.g., Cumming, 2014). To address these issues, Cumming (2014) and others suggest the use of both small and large scale meta-analyses to help avoid dependence on single studies with the aim of building a cumulative and replicable body of results. To this end, the benefits of utilizing a meta-analytic technique include its

estimation of an overall trend in the data, and an examination of study features that may moderate these effects.

The primary aim of the current study was to examine the association between the acne and internalizing problems. A secondary aim is to examine whether several factors including sex, clinical acne severity, and self-rated acne severity moderate the magnitude of this association. Overarching these questions related to the developmental salience of these factors, and whether adolescents or adults are at greater risk.

This dissertation was guided by the following overarching research questions:

RQ1: Do individuals with acne have elevated levels of depression and anxiety compared to individuals without acne? Does age influence this association? Are adolescents or adults at particular risk?

RQ2: Among those with acne, do factors of sex, clinical severity, and self-perception of severity influence its riskiness? Does age influence these associations? Are adolescents or adults at particular risk?

Based on the literature reviewed above, the following hypotheses were investigated:

H1: Individuals with acne are more depressed and anxious than individuals without acne.

H2: Age qualifies the magnitude of the association between acne and internalizing symptoms.

H2a: The association between acne and internalizing problems will be stronger among adolescents such that adolescents with acne will be significantly more likely to be

depressed than their acne-free peers relative to adults with acne in comparison to *their* acne-free peers.

H3: Sex and severity indices influence the riskiness of acne such that:

H3a: Females with acne are more depressed and anxious than males with acne.

H3b: Adolescent females with acne are more depressed than adolescent males with acne.

H4: Clinical severity influences the riskiness of acne such that more severe acne is more strongly related to depression and anxiety than less severe acne.

H4a: Adolescents with more clinically severe acne are more depressed and anxious than adolescents with less clinically severe acne.

H5: Self-perceptions of severity influences the riskiness of acne such that those who perceive their acne as more severe are more depressed and anxious than those who perceive their acne as less severe.

H5a: Adolescents who perceive their acne as more severe will be more depressed and anxious than adolescents who perceive their acne as less severe.

It should be noted that limited quantity of available studies and information contained therein prevented the investigation of hypotheses drawing direct comparisons between adolescents and adults who have acne with regard to factors of sex, clinical acne severity, and self-rated acne severity.

CHAPTER 2 – META-ANALYSIS

Acne vulgaris and risk of depression and anxiety: A meta-analytic review

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***Background*:** Several studies have shown an association between acne vulgaris and depression and anxiety but a quantitative review has not yet been conducted.

Objective: To conduct a systematic review and meta-analysis that elucidates the relationship between acne vulgaris and depression and anxiety.

Method: A systematic review and meta-analysis of literature published prior to May 1, 2018 from PubMed, PsycINFO, MEDLINE, and Cochrane databases was conducted. We used a 2-step hierarchical meta-analytic approach to perform a random effects analysis of those with and without acne, and among those with acne. Subgroup analyses between studies included geographic region and study setting; subgroup analyses within studies included sex, acne severity, and severity reporter.

Results: In all, 40 studies were included. Of these, 11 used a derived control group. We found a significant association between acne vulgaris and depression, $r = 0.210$ (95% CI: 0.163-0.257, $p < .00001$) and anxiety, $r = 0.258$ (95% CI: 0.192-0.321, $p < .00001$). Subgroup analyses and comparisons showed influences based on the following factors: age, sex, clinical severity, self-rated severity, and study setting.

Limitations: Inconsistency between publications regarding acne and outcome ascertainment, data reporting, and studies with no control group posed considerable barriers to synthesizing all available literature.

Conclusions: Because of increased risk for depression and anxiety, clinicians should consider screening patients with acne for psychiatric morbidity.

Key words: acne; depression; anxiety; adolescence; meta-analysis

Acne vulgaris is a chronic inflammatory skin condition characterized by lesions, such as pilosebaceous gland comedones, papules, pustules, and nodules (Aktan et al., 2000). Acne presents throughout the life course yet prevalence peaks in adolescence and affects a majority of adolescents worldwide (e.g., Bhate & Williams, 2003; Law et al., 2010; Yahya, 2009; Wei et al., 2010). Except in cases of severe cystic acne where individuals experience physical symptoms such as pain and bleeding, the most prominent morbidity of acne is its psychosocial effect. Since the majority of those who have acne have no direct physical impairment that affects daily functioning, acne runs the risk of being dismissed as a mere cosmetic condition (e.g., Barankin & Dekoven, 2002).

Yet acne constitutes a significant risk factor for impaired psychological wellbeing in younger and older individuals of both sexes (e.g., Shuster et al., 1978; van der Meeren et al., 1985; Koo & Smith, 1991; Thomas, 2005). Acne is associated with decreased appearance-related satisfaction, self-esteem, and self-confidence (e.g., Nguyen, Koo, & Cordoro, 2016; Hassan et al., 2009; Fried & Wechsler, 2006), and increased internalizing problems such as social isolation, anxiety, anger, depression, and suicidal ideation (e.g., Wu, Kinder, & Trunnell, 1998; Cotterill & Cunliffe, 1997; Gupta & Gupta, 1998; Purvis et al., 2006). Several population-based studies show increased prevalence of depression and anxiety among those with acne compared with their acne-free counterparts (e.g., Vallerand, 2018; Uhlenhake, 2010).

Acne is risky even in comparison to other dermatological and non-dermatological illnesses. A study of depression among dermatology patients (acne, alopecia areata, atopic dermatitis, psoriasis) found that those with mild acne had the highest prevalence of depression second only to severe psoriasis inpatients (Gupta & Gupta, 1998). Another study found that acne patients report levels of psychosocial and emotional problems as great or greater than those reported by patients with serious non-dermatological illnesses (epilepsy, diabetes, coronary artery disease) (Mallon et al., 1999).

Yet others have found no significant association between acne and internalizing problems (e.g., Golchai et al., 2010) and still others have found considerable variation in the strength of the association (e.g., Mallon et al., 1999; Do et al., 2009; Kurek et al., 2013). Indeed, among those with acne, several factors may influence its riskiness. The developmental period of acne occurrence may have unique implications for internalizing problems, though evidence is mixed. Some researchers have found that acne is particularly risky during adolescence (Yarpuz et al., 2008) which aligns with marked sensitivity to physical appearance in the context of rapid multilevel changes during this period. Others have found that adults with acne struggle more (e.g., Hassan et al., 2009) and still others have found no age differences (Klassen et al., 2000). Similarly, some researchers find that the association between acne and internalizing problems is stronger for females than males (e.g., Uhlenhake et al., 2010), while others have found comparable associations between sexes (e.g., Purvis et al., 2006).

Acne severity is also often considered, though evidence is inconclusive. Some find no correspondence between acne severity and internalizing problems (e.g., Yazici et

al., 2004), whereas others find that individuals whose acne is moderate or severe are more depressed and anxious than those whose acne is mild (Kilkenny et al., 1997). This picture is complicated by evidence suggesting that this association is influenced by the perspective of the reporter whereby some find evidence of an association between either self- or clinician-rated acne severity, but not both. For example, in a study of adolescents, Do et al. (2010) found that self-perceptions of acne severity, but not clinical grading, were associated with depression. While many contend that clinical ratings of acne severity are more precise and valuable, others contend that self-perceptions are more salient when evaluating psychological outcomes (Mallon et al., 1999).

These studies paint a compelling picture of the association between acne vulgaris and depression and anxiety. Yet there is a gap in the literature due to limitations of findings from individual studies. The present systematic review and meta-analysis aims to synthesize the available literature on the relation between acne and internalizing problems. Based on prior research, we hypothesized that individuals with acne would be more depressed and anxious than those without acne, and that among those with acne, females and those with more severe acne, particularly when severity is self-reported, will be more depressed and anxious than males and those with less severe acne. We also hypothesized that developmental differences may exist such that these associations would be stronger among adolescents relative to adults given the unique challenges of this period.

METHODS

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was registered with the Prospective International Register for Systematic Reviews (PROSPERO).

Data sources and search strategy

We identified studies indexed in PubMed, PsycINFO, MEDLINE, and the Cochrane Library databases prior to May 1, 2018. The search parameters included all pairwise combinations of *acne* and the following terms: *depress**, *anx**, *psychiat**, *psycholog**, *psychosoc**. We used * to include other variations of the words (i.e., *depress** includes depression or depressive). Additional relevant articles were identified by manual inspection of reference lists and contacting authors.

Eligibility criteria

We focused on noninterventional studies (e.g., case-control, cross-sectional, cohort), both retrospective and prospective, that described associations between acne vulgaris and depression and anxiety. The following inclusion criteria were applied: English language (or translated); participants aged 12 years or older; depression or anxiety included as outcomes; and authors reported Pearson *r* correlation coefficient or sufficient information to compute the desired effect size (group means and standard deviations; *t*, *F*, or χ^2 values from between-group analyses; exact *p*-values and df; frequencies; Cohen's *d*; or Hedge's *g*). We contacted authors to obtain statistics that had not been reported in their published articles.

Studies conducted in clinical (e.g., dermatology clinic) and community (e.g., high school) settings in all available countries were included. We excluded interventional studies because our interest was in assessment of harms generated by the presence of acne (e.g., prevalence of depression and anxiety) rather than change in response to acne interventions. Studies that assessed variants of acne other than acne vulgaris (e.g., acne inversa, acne fulminans) were excluded.

Data extraction

All titles and abstracts were screened by the primary author to identify those that potentially met the inclusion criteria. The full text of each eligible study was retrieved and assessed for inclusion. Any uncertainties or ambiguities were brought to an independent reviewer and resolved through discussion. The following data was extracted from included studies: author and publication year; study design and setting; geographic location and characteristics; number and age of participants; number of acne cases; acne severity ascertainment; and outcome ascertainment (Appendix A).

Analytic approach

Our analyses sought to answer the following overarching questions: (1) Between individuals with acne and without acne, who is more depressed and anxious? (2) Within those with acne, who is more depressed and anxious? These between- and within-group comparisons structured a 2-step hierarchical meta-analytic approach. Step 1 involved comparisons between those with acne and those without acne to obtain an overall effect size for each outcome. Step 2 involved comparisons within individuals with acne by sex,

clinical acne severity, and self-rated acne severity. This approach was advantageous because it enabled us to answer different levels of questions.

Differences should be noted between two types of study factors: (1) those that apply equally to all participants in a study (e.g., study setting), and (2) those that summarize individual participant-level data (e.g., acne severity). Step 2 meta-analyses were based upon these participant-level factors. In addition, both Step 1 and Step 2 meta-analyses included subgroup analyses according to two theoretically and methodologically relevant study-level factors: age and study setting. In accordance with recommendations (Fu et al., 2010), comparisons between subgroups were conducted only when there were sufficient studies for categorical subgroup variables ($k \geq 4$)[1]. As such, we were unable to conduct several Step 2 comparisons between subgroups, yet independent subgroup analyses were conducted whenever there were at least 3 studies ($k = 3$), which were informative without drawing comparisons per se (Fu et al., 2010; Cooper, 2003).

Heterogeneity among the included studies was considered on the basis of methodological, clinical, and statistical variation (Higgins, 2002; Rao, 2017) to gauge the significance of the meta-analysis results. In line with guidelines on informative presentation of statistical heterogeneity indices (Higgins, 2002), we examined measures of uncertainty (p-value of Cochrane Q, 95% CI for τ^2), inconsistency (I^2), and magnitude (τ^2) (Fu et al., 2010; Borenstein, 2009). The statistical significance of Cochran's Q is an indication of variation among the study effect sizes, though it yields no information about

[1] Though Cochrane Handbook guidelines suggest ($k = 10$) studies for each subgroup analysis, others (e.g., Fu et al., 2010) contend that that is a somewhat arbitrary number and instead that additional factors should determine the number of studies.

the magnitude of their dispersion. Rather a significant *Q* indicates either (1) a substantial amount of observed dispersion, or (2) a minor amount of observed dispersion within the context of precise studies (Borenstein, 2009) where precision increases as sample sizes increase (Higgins, 2002). Since *Q* is influenced by high precision, it is of note that 40% of studies in the present meta-analysis included N > 500.

I^2 describes the degree of inconsistency across study findings and is also influenced by precision, though in a different manner (Higgins et al., 2003). A large I^2 indicates that a high proportion of the observed variance (τ^2) is reflective of real between-study differences rather than within-study variance (V_Y) (Borenstein et al., 2009). Borenstein and colleagues (2009) note that one caveat is the absence of any single meta-analytic indicator of within-study variance (V_Y) for V_Y varies from study to study. Moreover, within-study precision decreases as sample sizes increase, thus I^2 is vulnerable to inflation with many large studies.

As such, we also examined τ^2, an indicator of the magnitude of heterogeneity that is not influenced by sample size. It is within the same metric of the effect size and is the point estimate of the variance of observed effect sizes yet since τ^2 gives no information about the proportion of variance that can be attributed to dispersion relative to within-study error. Using the combined picture given by these indices, when heterogeneity was determined to be high ($I^2 > 50\%$[25], high τ^2, significant *Q*), we conducted subgroup analyses by factors identified a priori as potential sources of between-study variation including participant age and study setting in attempt to explain it.

The effect size *r* was the statistical basis for this meta-analysis. As noted earlier, for studies reporting effect sizes other than *r*, information in the published article was computed into the desired effect size. Effect sizes were transformed via Fisher's *Zr* transformation, and back-transformed to *r*'s for interpretability. To synthesize these results, we computed mean and median *r*'s. We used a random effects approach because (1) our aim was to estimate the mean of a distribution of effect sizes rather than assume that there is one true mean effect size (i.e. fixed effects approach); and (2) the included studies were performed by independent researchers operating in different contexts (Borenstein et al., 2009). All statistical analyses were conducted using MIX 2.0 software (Bax, 2006), Excel Professional Plus 2013, and by-hand.

An additional feature of our analytic approach should be noted. Because there were a substantial number of studies whose design did not include a comparison group (k = 11), we devised a method to include them in Step 1 analyses (R. Rosenthal, personal communication). We determined the proportion of those with and without acne who were depressed and anxious across all studies. Specifically, we computed the following: (1) the proportion of participants with acne who were depressed or anxious across all studies (k = 40), and (2) the proportion of participants without acne who were depressed or anxious across only those studies which included a comparison group (k_{total} = 29; $k_{depression}$ = 24; $k_{anxiety}$ = 18). We used these proportions to determine whether to take a fine-tuned approach to matching studies with and without comparison groups or impute an average theoretical control across studies without comparisons according to both the degree of relation between acne and no-acne groups, and the similarity between acne only groups

across study types (Appendix B). Based on a high correlation betwen those groups with and without acne and a nonsignificant difference between acne groups from both study designs, we decided to proceed with fine-tuned matching in which we used computed proportions of control group prevalence of depression and anxiety to calculate these frequencies for unmatched studies. From these, we computed correlation coefficients to obtain overall effects.

Quality assessment

We assessed study quality on the basis of domains including the selection of participants, comparability between groups, the way in which confounds were controlled, conflicts of interest, statistical methods, and assessment of outcomes. We followed recommendations for quality assessment procedure for noninterventional studies which uses a checklist rather than scoring method (e.g., Rao et al., 2017).

Sensitivity analysis

We used a random effects model for sensitivity analyses to explore heterogeneity based on a priori hypotheses via subgroup analyses. Additionally we repeated analyses using only those studies with comparison groups ($k_{total} = 29$; $k_{depression} = 24$; $k_{anxiety} = 18$) in order to to affirm our results.

Publication bias

To detect possible publication bias, we visually inspected funnel plots for asymmetry and conducted two formal statistical tests of asymmetry including the regression-based Egger test and the rank correlation Begg test. We also computed a fail-safe *N* (Rosenthal, 1979), or the number of new, unpublished, or otherwise unretrieved

studies that would need, on average, no effect in order to reduce our findings to non-significance at the $p \leq .05$ level; and its partner, the tolerance level or file-drawer effect, an estimation of the number of unpublished null studies that may possibly exist.

RESULTS

We identified a total of 2,609 references, and after application of the selection criteria, 40 studies were included in the meta-analysis (Figure 1). All studies included participants in whom acne was recently diagnosed or self-reported. Table I summarizes study and participant characteristics, and Table II summarizes study findings.

Step 1: Comparing Individuals with and without Acne

Depression. In total, 1,028,893 participants from 33 studies with sample sizes that ranged from 24 to 1,000,000 (median and mean sample sizes of 225 and 31,178, respectively[2]) were included in the main outcome meta-analysis for depression. Of these, 9 studies were included on the basis of matched controls. Across the 33 effect sizes, we found that those with acne were significantly more likely to be depressed than those without acne, with a median correlation of $r = 0.138$ and mean correlation of $r = 0.210$, 95% CI: 0.163-0.257, $p < .00001$ (Figure 2). We used a more conservative approach and replicated these results in sensitivity analyses by including only those studies with control groups[3].

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[2] The discrepancy between median and mean sample sizes can be attributed at least in part to a population-based study where $N = 1{,}000{,}000$ (Yang et al., 2014).

[3] This pattern of results does not substantially change when 9 studies using matched control proportions are omitted from the analyses (k = 24), $r = 0.155$, 95% CI: 0.114-0.195, $p < .00001$, $N_{failsafe} = 2{,}975$, $N_{tolerance} = 130$, $Q_{23} = 454.69$, $p = 0$, $I^2 = 94.94$, $\tau^2 = 0.007$, 95% CI: 0.005-0.01.

Visual inspection of a funnel plot suggested some publication bias (Figure 3). Formal statistical tests of funnel plot asymmetry yielded contradictory results such that Egger's regression test (H_0: symmetry exists in the funnel plot) indicated bias, $p < .05$, but Begg's rank correlation test did not ($p = .609$). Still, according to the fail-safe N (Rosenthal, 1979) these findings would be disputed only if there were over 10,661 studies showing that there is no association between acne and depression; this well exceeds the tolerance level of $N = 175$. Heterogeneity indices suggested significant ($Q_{32} = 913.7$, $p = 0$) moderate dispersion ($\tau^2 = 0.016$, 95% CI: 0.013-0.019) and considerable inconsistency ($I^2 = 96.50$) across these effect sizes though high precision should be noted (> 33% of studies have $N > 500$). We proceeded with subgroup analyses by a priori between-study factors to explore indicators of heterogeneity.

Contrary to our expectations, subgroup comparisons by age revealed that adult-only samples with acne, $r = 0.449$, 95% CI: 0.206-0.639, $p = 0.0006$, $I^2 = 96.85$, $\tau^2 = 0.145$, rather than adolescent-only samples with acne, $r = 0.109$, 95% CI: 0.079-0.139, $p < 0.00001$, $I^2 = 58.03$, $\tau^2 = 0.001$, were significantly more depressed than their acne-free peers, $z = 2.40$, $p = 0.016$ (Figure 4). Additional subgroup comparisons indicated that studies conducted in settings that were clinical, $r = 0.302$, 95% CI: 0.198-0.400, $p < .00001$, $I^2 = 92.74$, $\tau^2 = 0.063$, rather than community, $r = 0.105$ (95% CI: 0.075-0.134, $p < .00001$ $I^2 = 54.26$, $\tau^2 = 0.0008$, reported a significantly higher association with depression, $z = 2.872$, $p < 0.004$ (Figure 5). In these subgroup analyses, we observed marked declines in heterogeneity when we separately grouped studies by adolescence and by community setting. It is additionally worth noting that adolescent-only samples were

overrepresented in community studies and adult-only samples were overrepresented in clinical studies.

Anxiety. In total, 21,634 participants from 22 studies with sample sizes that ranged from 56 to 9,008 (median and mean sample sizes of 198 and 829, respectively) were included in the main outcome meta-analysis for anxiety. Of these, 4 studies were included on the basis of matched controls. Across the 22 effect sizes, we found that those with acne were significantly more likely to be anxious than those without acne, with a median correlation of $r = 0.269$ and mean correlation of $r = 0.258$, 95% CI: 0.192-0.321, $p < .00001$, $I^2 = 92.93$, $\tau^2 = 0.021$ (Figure 6). Sensitivity analyses including only those studies with control groups yielded similar results[4].

Visual inspection of a funnel plot suggested moderate publication bias (Figure 7).

Again, formal statistical tests of funnel plot asymmetry yielded contradictory results such that Egger's regression test (H_0: symmetry exists in the funnel plot) indicated bias, $p < .05$, but Begg's rank correlation test did not ($p = .052$). Still, these findings would be disputed only if there were over 3,091 studies (i.e., fail-safe N) showing that there is no association between acne and depression; this well exceeds the tolerance level of $N = 120$. Heterogeneity indices suggested significant ($Q_{21} = 297.02$, $p = 0$) moderate dispersion ($\tau^2 = 0.020$, 95% CI: 0.016-0.029) and considerable inconsistency ($I^2 = 92.930$), though there was relatively high precision. We proceeded with subgroup

[4] This pattern of results does not substantially change when 4 studies using matched controls are omitted from the analyses (k = 18), $r = 0.257$ 95% CI: 0.187-0.323, $p < .00001$, $N_{failsafe} = 1{,}916$ studies, $N_{tolerance} = 100$, $Q_{17} = 257.89$, $p = 0$, $I^2 = 93.55$, $\tau^2 = 0.019$, 95% CI: 0.013-0.027.

analyses by a priori between-study factors to explore these indices of statistically significant heterogeneity in magnitude and uncertainty.

Similarly to depression results, subgroup comparisons by age revealed that adult-only samples with acne, $r = 0.409$, 95% CI: 0.218-0.570, $p = 0.00006$, $I^2 = 96.08$, $\tau^2 = 0.04$, rather than adolescent-only samples with acne, $r = 0.102$, 95% CI: -0.004-0.205, $p = .059$, $I^2 = 95.56$, $\tau^2 = 0.008$, were significantly more likely to be anxious relative to their acne-free peers, $z = 2.04$, $p = 0.041$. Additional subgroup comparisons indicated that studies conducted in settings that were clinical, $r = 0.317$, 95% CI: 0.218-0.409, $p < 0.00001$, $I^2 = 89.25$, $\tau^2 = 0.045$, rather than community, $r = 0.08$, 95% CI: -0.01-0.163, $p = 0.08$, $I^2 = 95.33$, $\tau^2 = 0.007$, reported a higher association with anxiety, $z = 2.54$, $p = 0.011$ (Figure 8).

Step 2: Within-Acne Sample: Sex and Severity of Acne as Moderators

Females with acne were significantly more likely than males with acne to be depressed (k = 9), $r = 0.114$ (95% CI: 0.019-0.207, $p = .019$) (Figure 9) and anxious (k = 6), $r = 0.150$ (95% CI: 0.043-0.253, $p = .006$) (Figure 10). With regard to statistical heterogeneity, when depression was the outcome, indices of magnitude ($I^2 = 88.46$, $\tau^2 = 0.015$) and uncertainty (95% CI: 0.007-0.027; $Q_8 = 69.33$, $p = 0$) were quite high, but when anxiety was the outcome, these were more moderate, $I^2 = 58.90$, $\tau^2 = 0.012$, 95% CI: 0-0.04; $Q_5 = 12.17$, $p = 0.03$. We found a similar pattern of results in sex differences in depression among adolescents with acne (k = 3), $r = .167$ (95% CI: 0.095-0.318, $p = .038$) though these results should be interpreted with caution given the small number of studies.

Regarding acne severity, results show that across all ages, those with more clinically severe acne were more likely to be depressed, $r = 0.160$ (95% CI: 0.015-0.298, $p = .030$) and anxious, $r = 0.193$ (95% CI: 0.103-0.342, $p = .017$) than those with less clinically severe acne (Figure 11). We found a similar relation between self-rated acne severity and depression, $r = .259$ (95% CI: 0.086-0.417, p = 0.004). There were insufficient studies (k = 2) to perform these analyses with anxiety as the outcome.

Interestingly, when we performed adolescent subgroup analyses (k = 4), clinical acne severity was not related to depression, $r = .028$, n.s., and these results indicated homogeneity, $I^2 = 0$, $\tau^2 = 0$. Direct comparisons with self-ratings of acne severity were prevented given that only 3 studies of adolescent-only samples reported their association with depression, however we were able to conduct a subgroup meta-analysis. We found the opposite pattern of results such that when adolescent perceptions of their acne severity was considered, there was a statistically significant association with depression, $r = 0.130$ (95% CI: 0.091-0.168, $p < 0.0001$). Moreover, statistical heterogeneity was quite low, $I^2 = 15.67$, $\tau^2 = 0.0003$, which bolsters confidence in these results.

DISCUSSION

Extant literature has posited an association between acne and internalizing problems. Some evidence suggests these associations may be influenced by moderating factors. Based on an examination of literature to assess data from 40 studies, this meta-analysis sought to establish a consensus of what is known. We found that individuals with acne are more depressed ($r = 0.210$) and anxious ($r = 0.258$) than those without acne. Though these effect sizes are modest according to published guidelines (e.g.,

Cohen, 1988) it would be unwise to conclude that they are unimportant (Rosenthal & Rosnow, 2008). Rather it is of note that acne, which is often disregarded as a cosmetic concern, explains 4.41% and 6.66% of the variation in depression and anxiety, respectively. Sensitivity analyses yielded negligible changes in these estimates and did not affect conclusions. Thus the robustness of these estimates lend added confidence to the findings of this quantitative review.

In contrast to our hypothesis, subgroup comparisons suggested that acne is riskier for adults than adolescents. However, these results must be interpreted with caution for the following reasons: (1) limitations inherent in drawing definitive conclusions from subgroup comparisons (see Cochrane Handbook, 9.6.2), and (2) the potential confounding relationship between moderating factors in the present study. To the latter, age was somewhat conflated with study setting such that adolescent-only samples were overrepresented among studies conducted in community settings and adult-only samples were overrepresented among studies conducted in clinical settings. Thus we may interpret these results as indicative of a greater likelihood that those seeking treatment for their acne within a clinical setting are already experiencing a potentially higher degree of dissatisfaction.

It should also be noted that heterogeneity indices were high across adult subgroup analyses in comparison to marked decreases in heterogeneity when adolescent subgroup analyses were conducted. This is somewhat unsurprising considering the magnitude of the difference developmentally between approximately a decade of adolescence in comparison with several decades of adulthood represented in the included studies (20s-

60s). Still, consistently high heterogeneity among adult subgroup analyses limit the interpretability of these results to some degree.

Among those with acne, we found that females are significantly more depressed and anxious than males. This aligns with prior population-based studies (Vallerand, 2018; Uhlenhake, 2010). Subgroup analyses of sex within the adolescent sample confirmed this pattern when depression was the outcome, though these results must be interpreted cautiously as they are based on 3 studies. At the same time, meta-analyses are technically able to be performed on as little as 2 studies (e.g., Cooper, 2003). However, we were unable to investigate sex moderation in anxiety due to insufficient studies. Another key finding from our analyses among individuals with acne (including both adults and adolescents) is that those with more severe acne are significantly more depressed and anxious than those with less severe acne regardless of whether the severity determination is made by a clinician or by oneself.

However, a closer look at the adolescent-only sample showed no association between clinical acne severity and depression, but a significant relation when self-rated acne severity was considered. These findings must be interpreted with caution but are perhaps suggestive of the particular salience of perceptions of oneself during adolescence as consequential for psychological outcomes. Adolescence is a developmental period uniquely characterized by normative increases in the importance of physical appearance, self-awareness, and egocentrism. Regardless of how mild acne severity is in a clinical sense, some adolescents may perceive any degree of acne as severe insofar as its presence constitutes a departure from culturally sanctioned appearance ideals and norms, which

can result in the experience of stress, isolation, and feelings of inferiority among those who deviate. Moreover, these results align with findings from several other studies (e.g., Do et al., 2009).

These and the larger pattern of findings in the present study suggest that appearance-related concerns may be central to understanding the negative psychological impact of dermatological conditions in general and acne in particular. A person's perception of his or her attractiveness is mostly formed through social experience, and by cultural values or ideals (Thompson, Heinberg, Altabe, & Tantleff-Dunn, 1999). Western appearance ideals include clear, unblemished skin (Magin et al., 2011) and deviations from these ideals, such as acne, can lead to negative reactions from others (e.g., Ablett & Thompson, 2016).

The cumulative effect of the internalization of negative skin-based reactions, together with the socio-cultural influence and stereotypes associated with the appearance of the skin, may put individuals with a dermatological condition such as acne at increased risk for developing appearance-related distress and internalizing problems (Thompson, 2011). Moreover, the high visibility of acne lesions or spots, often localized on the face, may be particularly traumatic. Prior research has found that facial acne in particular is related to shame, negative body image (Kellett & Gawkrodger, 1999) increased feelings of appearance-related concern, withdrawal from social interaction, and poorer psychological functioning (Motley & Finlay, 1992).

Limitations

This meta-analysis needs to be interpreted within the context of the available studies. There was a high degree of inter-study variability in study design, operationalization and measurement of key study constructs, and statistics reported. These differences posed considerable barriers to synthesizing all available literature. Relatedly, despite our effort to streamline the types of study designs by excluding interventional studies (e.g., randomized clinical trials) or studies focusing on less common variants of acne such as acne inversa, acne fulminans, or pediatric acne, heterogeneity was still noted in most analyses. Though it is advantageous to include studies of different populations because of increased validity and generalizability (Zlowodoski, 2007), substantial heterogeneity and potential for unclear findings often accompanies such broad inclusion criteria (Rao et al., 2017).

Additionally, the exclusion of clinical intervention studies was intended to minimize heterogeneity in study designs and potential psychiatric side effects of medication (e.g., isotretinoin), but this criterion also had the effect of limiting the breadth of available clinical acne literature. An additional limitation concerns interpretation of subgroup analyses. We encountered a limited number of studies when conducting specific, fine-tuned subgroup analyses which is not unusual (e.g., Cochrane Handbook, 9.6.2), and there were a couple instances of potential confounding factors in these subgroup analyses (e.g., study setting and sample age), which may complicate interpretation.

In conclusion, this meta-analysis suggests a higher prevalence of depression and anxiety among individuals with acne in comparison to those without acne. Females and

those with greater acne severity are especially at risk. These results present an emerging picture of acne as a condition with the potential to significantly impact psychological functioning. Our findings stress the importance of screening patients with recently diagnosed acne for internalizing problems, and identifies certain subgroups which might be at greater risk. More broadly, the present study adds to a historic call (e.g., Sulzberger & Zaidems, 1948) for the legitimization of acne as more than a cosmetic problem.

CHAPTER 4 – GENERAL DISCUSSION

Dermatologists have long acknowledged that acne can impair psychological wellbeing. This is problematic given the widespread prevalence of acne, particularly among adolescents (e.g., Bhate & Williams, 2013), though some evidence suggests increasing prevalence among adults as well (Tanghetti et al., 2014). Acne occupies a unique status among skin disorders for although it is common and causes minimal functional impairment, there are significant psychic costs left in its sebaceous wake.

Yet significant gaps have persisted in our understanding of the precise nature of the psychological impact of acne. Broadly, extant literature has not established a consensus regarding the association between acne and internalizing problems. It is possible that such a gap has influenced the common perception of acne as a cosmetic condition with minimal implications for substantial psychological suffering. Such a claim has often been lamented and refuted by dermatologists (e.g., Picardi et al., 2000).

As such, the primary purpose of this dissertation was to examine the magnitude of the association between acne and internalizing problems. This broad aim paved the way for increasingly detailed questions such that I structured a hierarchical meta-analytic approach to proceed from wide to narrow, general to fine-tuned. The second aim of this investigation was to explore the factors among individuals with acne that influence associations with depression and anxiety. Based on a careful review of the literature, several factors emerged as solid candidates including sex and acne severity, both from the perspective of the clinician and from the perspective of the individual.

Across these primary and secondary study aims, I applied a developmental and contextual lens. Prior research has yielded inconsistent findings regarding whether and how developmental stage (adolescence versus adulthood) impacts relations between acne and internalizing problems. Some researchers find heightened risk among adolescents (e.g., Yarpuz et al., 2008), others among adults (e.g., Uhlenhake et al. 2010), and still others find no association (e.g., Klassen et al., 2000). As such, questions of developmental salience overarched this study.

In fulfillment of its primary aim, this meta-analysis found that individuals with acne are more depressed and anxious than individuals without acne. These results were robust to replication and were based on data from 40 studies with a total of 1,028,893 participants from across 33 studies which reported associations between acne and depression, and 21,634 participants across 22 studies which reported associations between acne and anxiety. Given the lack of an established consensus to date, the present findings fill an important gap.

Findings in regard to developmental and contextual influences were more nuanced. In fact, the most interesting results in the current study centered on developmental differences. First, associations between acne and internalizing problems were magnified among adults in comparison to adolescents. I had hypothesized the reverse given the developmental significance of adolescence as a period of heightened attunement to peers and increased appearance sensitivity, particularly in the realm of deviations in physicality.

Though such empirical evidence reviewed in Chapter 1 substantiates this logic, in light of the current findings, it is useful to apply a similarly developmental rationale albeit to adulthood. It may be the case that adults with acne face unique challenges in that their appearance is not only deviant in the sense that it violates cultural ideals of smooth, unblemished skin (e.g., Magin et al., 2011), but is in fact doubly deviant since these individuals are out of step developmentally from the majority of their peers. Specifically, in comparison with adolescents who have an 85% prevalence rate of acne at some point (Bhate & Williams, 2013), the adult prevalence rate of acne pales in comparison with peak estimates around 30-40%, though it should be noted that there is some degree of variability according to geography and decade (e.g., Khunger & Kumar, 2012). It follows that an adult with acne is arguably more physically deviant in comparison to his or her peers than is an adolescent with acne in comparison to his or her peers. As such, if associations between acne and depression are at least in part driven by feelings of inferiority and physical deviation from one's peers, then adults may experience compounded risk.

Relatedly, adults with acne may encounter marked skepticism in the face of cultural beliefs that acne is a skin disorder relegated to adolescence. There is some empirical support for this idea. For example, a study comparing acne patients aged 16-19 years with those aged 20 and above found heightened appearance-related distress in the older group. In fact, the study authors explained these findings in terms of developmental deviation – that older populations with acne face additional challenges due to their symptoms representing a departure from cultural beliefs that relegate acne to a teenage

problem (Hassan et al., 2009). As such, though adolescents and adults with acne are both out step with cultural appearance ideals, adult deviations from their peers and from sociocultural beliefs about the relative normalization of acne during the teenage years may compound this effect.

The present study found that subjective assessments of acne severity are related to depression such that a person's experience of their acne as more severe corresponds to increased reporting of depressive symptoms. Further, adolescent perception of the severity of their acne rather than their clinical severity per se was found to be salient in relation to depression. It is imprudent to infer greatly based on results of subgroup analyses (e.g., Rao et al., 2017), (and there were insufficient studies to draw comparisons to adult samples), yet it may be tentatively concluded that subjective assessments of acne severity are particularly weighty psychologically in adolescence. This is supported by the finding that objective acne severity was unrelated to depression among adolescents and these results were homogenous.

Here it may not be that objective severity per se but rather adolescent perception of severity is what matters. This view is bolstered theoretically by work on depression among dermatological patients from Gupta and Gupta (2003) that concluded that it is not acne severity itself but perception that matters in psychological outcomes. Their study found that those with mild acne were among the most psychologically disturbed of dermatology patients. Moreover, this conclusion is underscored by empirical evidence from adolescent-only samples where statistically significant associations between self-

perceptions of severity (rather than clinical gradings of severity) were uniquely related to internalizing outcomes (e.g., Do et al., 2009).

Limitations

An elaboration on several key limitations outlined in Chapter 2 is warranted here. First, analyses revealed substantial heterogeneity across study findings. On the one hand, it is advantageous to include studies of different populations because of increases in validity and generalizability of meta-analytic findings to those populations (Zlowodoski, 2007). Yet the cost of such inclusiveness is increases in heterogeneity. Though heterogeneity is to be expected in meta-analytic contexts (Higgins, 2008), there are various approaches for dealing with it ranging from guidelines that caution against pooling effect sizes in the presence of marked heterogeneity (e.g., Rao et al., 2017) to those who instead use heterogeneity as an opportunity for exploration of its causes (e.g., Higgins, 2002).

The latter approach includes two options: subgroup analyses and comparisons, and meta-regression. In the context of the present study, meta-regression was determined to be ill-advised for several reasons, chief among them its assumption of equal heterogeneity (Higgins, 2008), while subgroup analyses and comparisons allow for separate heterogeneity estimates. Since my interest lay in understanding how heterogeneity was influenced by partitioning subgroups, I chose the latter. Further, my decision to use an overarching random effects analytic approach in subgroup analyses was guided in part by an awareness and expectation that true variation of effects was

likely to exist according to a priori factors among subgroups of studies (Borenstein, 2009).

In addition, it should be noted that a high degree of heterogeneity among adult-only studies was not surprising when viewed with a developmental lens. In the absence of more theoretically or empirically precise criteria, adulthood is typically defined (as in the present study) as a period spanning several decades. In comparison with adolescence, this opens quite a range of variability for the experiences of individuals in their 20s, for example, are likely markedly different from markedly from experiences of individuals in their 50s. Future research should include more precise adult age ranges for theoretical and statistical clarity.

A second limitation is that the present study did not include randomized controlled trials. These interventional studies were excluded because my interest was in assessment of harms generated by the presence of acne (e.g., prevalence of depression and anxiety) rather than change in response to acne interventions. Moreover systematic reviews (e.g., Bremner et al., 2012) have concluded that isotretinoin, the most effective treatment for acne, may induce depressive symptoms. The hypothesized mechanism of action stems from the fact that isotretinoin is a fat-soluble compound that crosses the blood-brain barrier and affects dopaminergic and serotonergic systems among others (O'Reilly, Trent & Bailey, 2007). However, a recent meta-analysis by Huang and Cheng (2017) did not support the association between depression and isotretinoin. As such, future researchers may consider including these trials in analyses of the association between acne and internalizing problems.

This meta-analysis also excluded studies of infantile and childhood (prepubertal) acne, and those that assessed variants of acne other than acne vulgaris (e.g., acne inversa, acne fulminans) were excluded. These other types of acne and other populations with acne were excluded primarily because the aim of the current study was to gain a better understanding of the relationship between acne and depression and anxiety as it commonly manifests in individuals with more developed capacities for self-reflection and evaluation. Moreover, other variants of acne, while certainly distressing, present in a physically different manner (i.e., acne inversa presents in genitoanal and axillary regions and rarely in facial regions; Wollina et al., 2013) and may be more or less distressing than acne vulgaris.

Finally, there were potentially confounding factors within subgroup analyses such that adolescent-only samples were overrepresented in studies conducted in community settings and adult-only samples were overrepresented in those conducted in clinical settings. While this is understandable given the typical settings a researcher might find individuals of these ages, it represents a significant gap in the literature and a barrier to interpretation in the present analysis. Future research should seek to ameliorate this.

Implications and Conclusions

The current meta-analysis addressed several gaps in the existing literature on the association between acne and internalizing problems. Overall, study findings revealed a higher prevalence of depression and anxiety among individuals with acne in comparison to those without acne. Females and those with more severe acne are at particular risk. In addition, results suggest that particular attention should be paid to indicators of

psychiatric disturbance in adult patients who seek acne treatment in clinical settings. Among adolescents, perceptions of acne severity may be an especially important indicator of the potential for psychological problems.

A notable strength of this study was the utilization of a statistical strategy to include data from studies without control groups that would have been otherwise excluded as additional studies increase the generalizability of meta-analytic findings (e.g., Fitzpatrick-Lewis et al., 2009). Sensitivity analyses that excluded these studies affirmed the robustness of the overall pattern of results as well as the effective implementation of this strategy. Another strength of the present study was the creation and use of a hierarchical meta-analytic approach such that questions regarding both study-level and participant-level factors could be included within a single quantitative synthesis.

This meta-analysis has the potential to make significant epistemological and clinical contributions. The former is more straightforward particularly in light of the robustness of the overarching findings. Of note, this study interweaves two distinct content areas that are ripe for collaborations and interdisciplinary efforts. It is timely given growing recognition that psychological and physical (including cutaneous) health are interrelated, a call evidenced by the emerging discipline of psychodermatology (Koo & Lebwohl, 2001). Dermatologists focus on the most visible aspect of the human body, and its visibility evokes both the reactions of others and of ourselves in response to those others, either real or imagined. Thus the present study focused on a common

dermatological affliction with theoretical and practical reaches into aspects of self-perception, identity development, cultural norms of beauty, and psychopathology.

Finally, in terms of clinical contributions, several findings of this investigation are applicable. Foremost are the overarching associations between acne and internalizing problems. That these associations exist is a noteworthy clinical finding, broadly construed. Moreover, results of subgroup analyses suggested that adolescents' own perceptions of their acne severity is uniquely associated with depression. Though it is typically unwise to invest heavily in a new treatment or in other consequential medical decisions based on the results of subgroup analyses (Rao et al., 2017), the stakes here are comparatively low in terms of potential costs outweighing potential substantial benefit. Specifically, I will proceed by suggesting that the aforementioned pattern of results may yield particular recommendations for clinicians and researchers whose goal is to understand the psychic toll of acne, especially among adolescents: that is, it is recommended that these parties supplement typical clinical grading of acne severity by gathering information regarding the individual's own assessment of the severity of the condition. After all, perception lends a window into the individual experience of acne.

Further, the initiation of a dialogue around an individual's own perception of the severity of their acne may open a degree of influence for clinical intervention. For example, clinicians may engage in brief patient education detailing the relative normalization of acne, for both adolescents and adults, though adolescents may particularly benefit given their particular attunement to deviations from social and cultural norms. This recommendation is based on research in other areas such as

adolescent female experience of menarche, or first menstruation, which can be distressing. However, there is evidence that education and normalization of menarche mitigates these effects. Here the intersection of dermatology and psychology is readily apparent for if further research bears out this association between subjective assessment of acne severity and internalizing problems, a target for intervention beyond the acne itself may be the person's own perception of it. Again, the risks here are quite low and the potential gain in terms of human suffering are quite high.

Another clinical implication is based on results which revealed that acne patients in clinical contexts are significantly likely to be depressed. In general, dermatologists and practitioners in these settings are uniquely situated to recognize and screen for psychiatric problems such as depression and anxiety and to take appropriate actions such as providing referral resources. In fact several dermatologists have been variously outspoken over the years advocating for routine psychiatric screening of dermatological patients. For example, Picardi et al. (2009) have proposed that dermatologists routinely administer the Global Health Questionnaire (GHQ) given its clinical ease and efficiency of use for patients, nurses, and practitioners alike. The results of the present study underscore this need.

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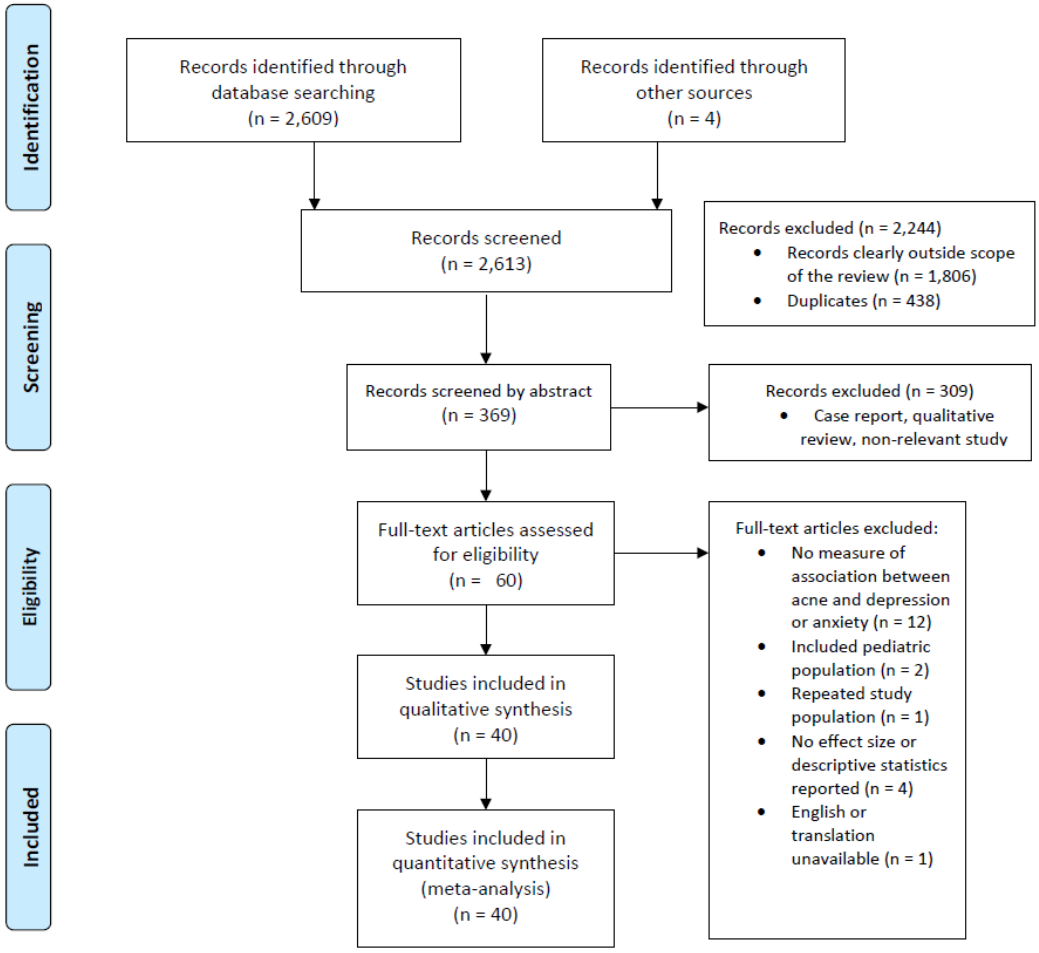

Figure 1. Selection of studies included in the systematic review and meta-analysis.

Author	N	r	95% CI		p
UNSAL	846	0.0904	0.02314	0.15685	0.00849
WEN	2284	0.085	0.04414	0.12558	0.00005
SMITHARD	317	0.1242	0.01424	0.2312	0.02695
YARPUZ	141	0.1988	0.03463	0.35253	0.01794
YAZICI	99	0.2571	0.06288	0.43256	0.00997
BEHNAM	209	0.2265	0.09366	0.35141	0.00094
BEZ	238	0.0889	-0.0387	0.21365	0.17181
GOLCHAI	164	0.0275	-0.12628	0.17999	0.72707
SALMAN	74	0.4699	0.27044	0.63068	0.00002
REHN	315	0.057	-0.05385	0.16646	0.3135
AWAD	100	0.3931	0.21314	0.54726	0.00004
PURVIS	9167	0.1114	0.09114	0.13157	<0.00001
YANG	1000000	0.006	0.00404	0.00796	<0.00001
OZTURK	87	0.312	0.10848	0.49042	0.0031
HALVORSEN	3628	0.0982	0.06587	0.13033	<0.00001
AKTAN	615	0.0278	-0.05137	0.10663	0.49151
GUL	80	0.7709	0.66358	0.84713	<0.00001
KUBOTA	1443	0.1773	0.12686	0.22683	<0.00001
BASHIR	24	0.4303	0.03255	0.71039	0.03493
KANG	574	0.6692	0.62139	0.71204	<0.00001
ANTUNA	36	0.4961	0.20019	0.70907	0.00177
JOWETT	60	0.1214	-0.13674	0.3641	0.357
KOCAK	88	0.042	-0.16893	0.24925	0.69842
KOSARUJU	26	0.4336	0.05558	0.7029	0.02596
LUKAVICIUTE	510	0.2735	0.19121	0.35197	<0.00001
GAO	4658	0.0352	0.00649	0.06385	0.01628
KAHN	100	0.1063	-0.09204	0.29653	0.2933
ARSLAN	822	0.091	0.02276	0.15839	0.00902
SAYAR	56	0.2883	0.02748	0.51237	0.03077
POLENGHI	66	0.6428	0.47461	0.76571	<0.00001
KLASSEN	1415	0.2611	0.21187	0.30901	<0.00001
DALGARD	426	0.0352	-0.06001	0.12978	0.46891
DUMAN	225	0.108	-0.02312	0.23546	0.10621
	1028893	0.20968	0.16142	0.25694	<0.00001

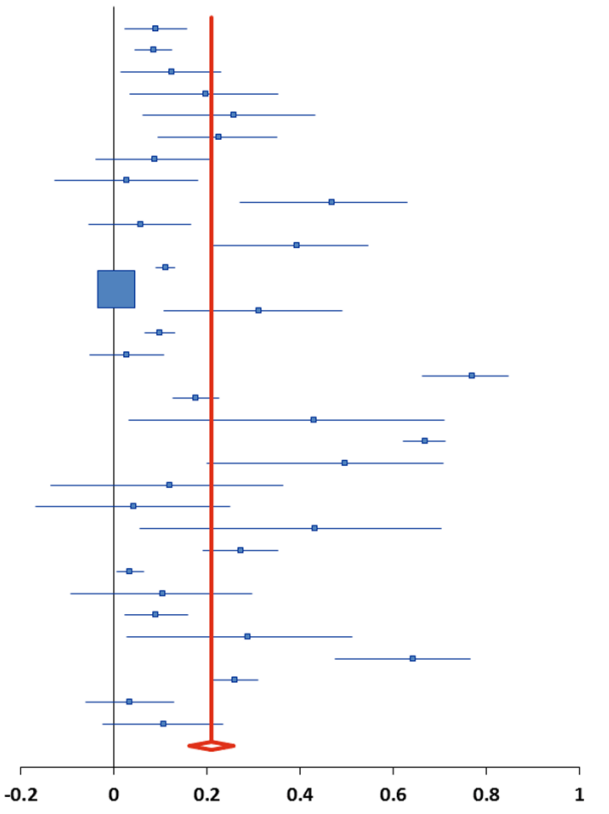

Figure 2. Step 1: Meta-analysis of the association between acne and depression across individuals of all ages (k = 33). *CI*, Confidence Interval.

Note. Forest plots show the estimate and CI for each study where the size of the squares are proportional to the relative study weights. The diamond shape at the bottom is a summary estimate whose points extend to the confidence limits.

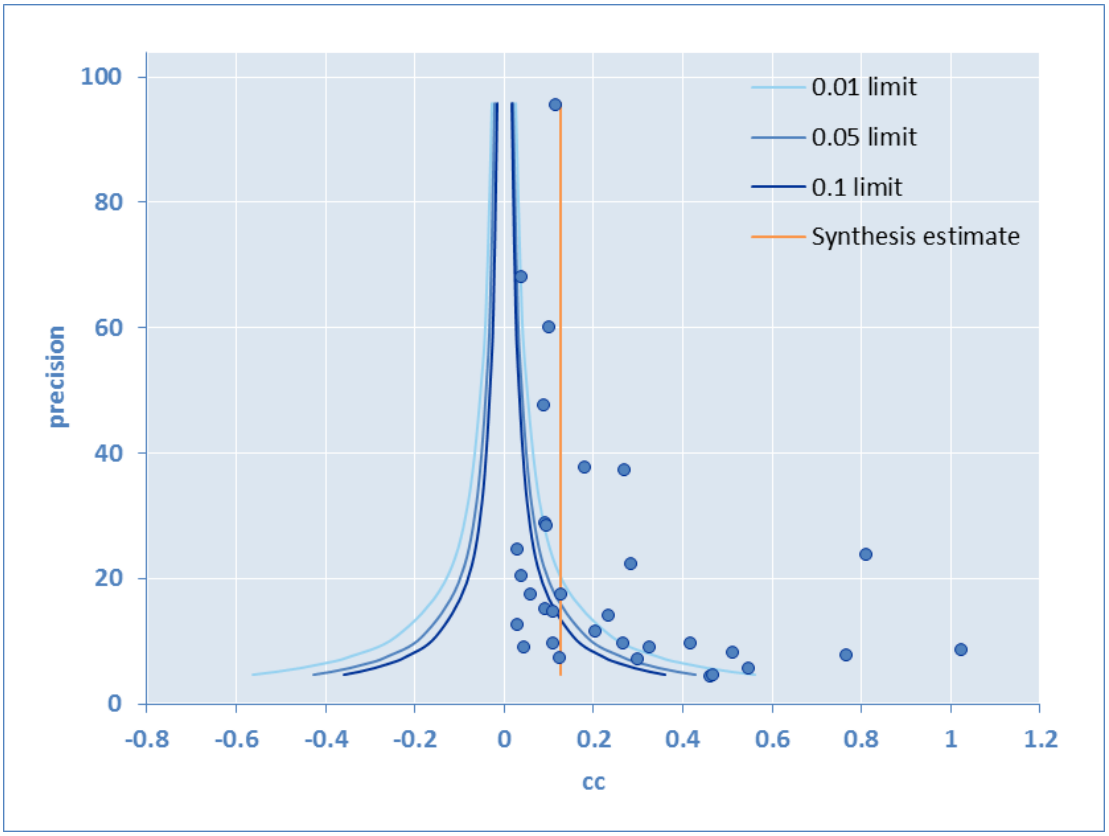

Figure 3. Funnel plot analysis for potential publication bias for meta-analysis on the association between acne and depression.

Note. Results of individual studies are plotted on the x-axis against a measure of precision on the y-axis (sample size divided by 100). Missingness between *p*-value limit reference lines indicates the possibility of selective evidence dissemination in that smaller studies with findings that are not statistically significant normally occupy the bottom-left side of the graph.

Author	N	r	95% CI		p
UNSAL	846	0.0904	0.02314	0.15685	0.00849
SMITHARD	317	0.1242	0.01424	0.2312	0.02695
PURVIS	9167	0.1114	0.09114	0.13157	<0.00001
HALVORSEN	3628	0.0982	0.06587	0.13033	<0.00001
AKTAN	615	0.0278	-0.0514	0.10663	0.49151
KUBOTA	1443	0.1773	0.12686	0.22683	<0.00001
Adolescents	16016	0.10919	0.07905	0.13912	<0.00001
GOLCHAI	164	0.0275	-0.1263	0.17999	0.72707
SALMAN	74	0.4699	0.27044	0.63068	0.00002
GUL	80	0.7709	0.66358	0.84713	<0.00001
BASHIR	24	0.4303	0.03255	0.71039	0.03493
KANG	574	0.6692	0.62139	0.71204	<0.00001
LUKAVICIUTE	510	0.2735	0.19121	0.35197	<0.00001
POLENGHI	66	0.6428	0.47461	0.76571	<0.00001
DALGARD	426	0.0352	-0.06	0.12978	0.46891
Adults	1918	0.44867	0.20591	0.63941	0.00055

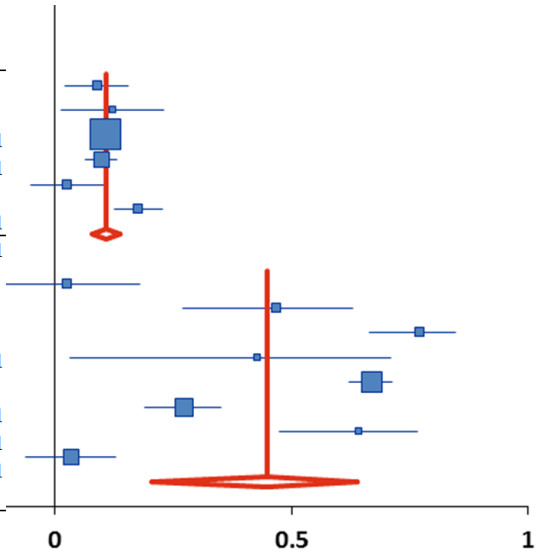

Figure 4. Step 1: Subgroup comparison of the association between acne and depression by age.

Author	N	r	95% CI		p
UNSAL	846	0.0904	0.02314	0.15685	0.00849
WEN	2284	0.085	0.04414	0.12558	0.00005
SMITHARE	317	0.1242	0.01424	0.2312	0.02695
PURVIS	9167	0.1114	0.09114	0.13157	<0.00001
AKTAN	615	0.0278	-0.05137	0.10663	0.49151
KUBOTA	1443	0.1773	0.12686	0.22683	<0.00001
ARSLAN	822	0.091	0.02276	0.15839	0.00902
Community	15494	0.10483	0.07548	0.134	<0.00001
YARPUZ	141	0.1988	0.03463	0.35253	0.01794
YAZICI	99	0.2571	0.06288	0.43256	0.00997
BEHNAM	209	0.2265	0.09366	0.35141	0.00094
BEZ	238	0.0889	-0.0387	0.21365	0.17181
GOLCHAI	164	0.0275	-0.12628	0.17999	0.72707
SALMAN	74	0.4699	0.27044	0.63068	0.00002
REHN	315	0.057	-0.05385	0.16646	0.3135
AWAD	100	0.3931	0.21314	0.54726	0.00004
OZTURK	87	0.312	0.10848	0.49042	0.0031
GUL	80	0.7709	0.66358	0.84713	<0.00001
BASHIR	24	0.4303	0.03255	0.71039	0.03493
KANG	574	0.6692	0.62139	0.71204	<0.00001
ANTUNA	36	0.4961	0.20019	0.70907	0.00177
JOWETT	60	0.1214	-0.13674	0.3641	0.357
KOCAK	88	0.042	-0.16893	0.24925	0.69842
KOSARAJU	26	0.4336	0.05558	0.7029	0.02596
LUKAVICI	510	0.2735	0.19121	0.35197	<0.00001
KAHN	100	0.1063	-0.09204	0.29653	0.2933
SAYAR	56	0.2883	0.02748	0.51237	0.03077
POLENGHI	66	0.6428	0.47461	0.76571	<0.00001
KLASSEN	1415	0.2611	0.21187	0.30901	<0.00001
DALGARD	426	0.0352	-0.06001	0.12978	0.46891
DUMAN	225	0.108	-0.02312	0.23546	0.10621
Clinical	5113	0.30237	0.19787	0.40008	<0.00001

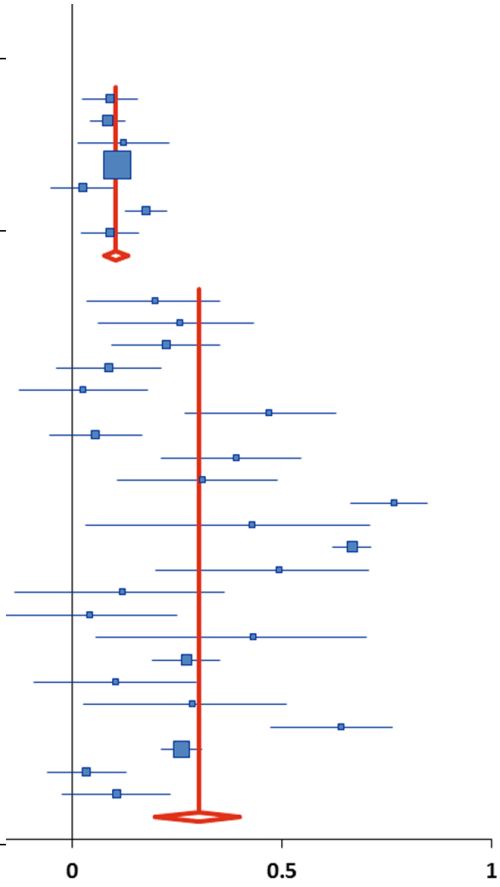

Figure 5. Step 1: Subgroup comparison of the association between acne and depression by study setting.

Author	N	*r*	95% CI		*p*
WEN	2284	0.0042	-0.03682	0.04521	0.84102
YARPUZ	141	0.3824	0.23174	0.51515	<0.00001
YAZICI	99	0.3465	0.16004	0.50909	0.0004
UKONU	112	0.5748	0.43572	0.68707	<0.00001
BEHNAM	209	0.4204	0.30191	0.5261	<0.00001
BEZ	238	0.0111	-0.11623	0.13807	0.86488
GOLCHAI	164	0.2935	0.14686	0.42752	0.00012
SALMAN	74	0.4937	0.29892	0.64899	0.00001
AWAD	100	0.4722	0.30398	0.61187	<0.00001
PURVIS	9008	0.0762	0.05564	0.0967	<0.00001
OZTURK	87	0.3954	0.20154	0.55945	0.00013
AKTAN	616	0.0075	-0.07154	0.08645	0.85268
GUL	80	0.7725	0.66579	0.84824	<0.00001
KOUTOU	362	0.0738	-0.0295	0.17554	0.16126
KANE	186	0.379	0.24868	0.49584	<0.00001
LUKAVICIUTE	510	0.3182	0.23795	0.39414	<0.00001
DING	2891	0.207	0.17184	0.24163	<0.00001
KAYMAK	298	0.0705	-0.04347	0.18266	0.22517
SAYAR	56	0.2309	-0.03407	0.46554	0.08693
POLENGHI	66	0.1905	-0.05402	0.41347	0.12583
DALGARD	426	0.0556	-0.03962	0.14982	0.25233
DUMAN	225	0.056	-0.07534	0.18543	0.40357
	18232	0.25829	0.1928	0.32149	<0.00001

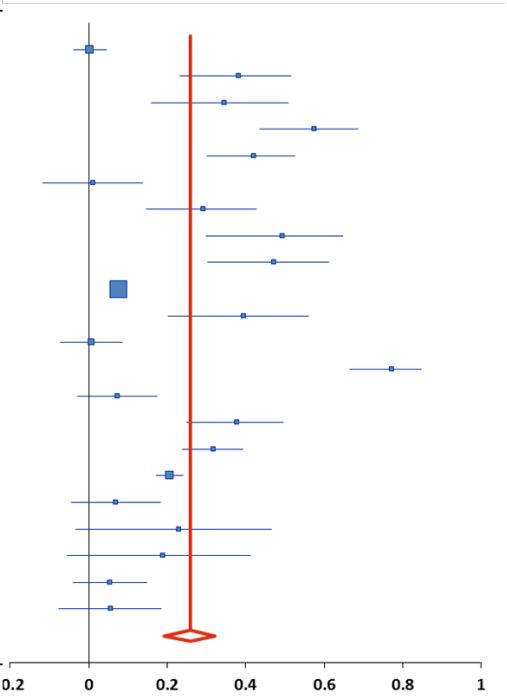

Figure 6. Step 1: Meta-analysis of the association between acne and anxiety across individuals of all ages (k = 22).

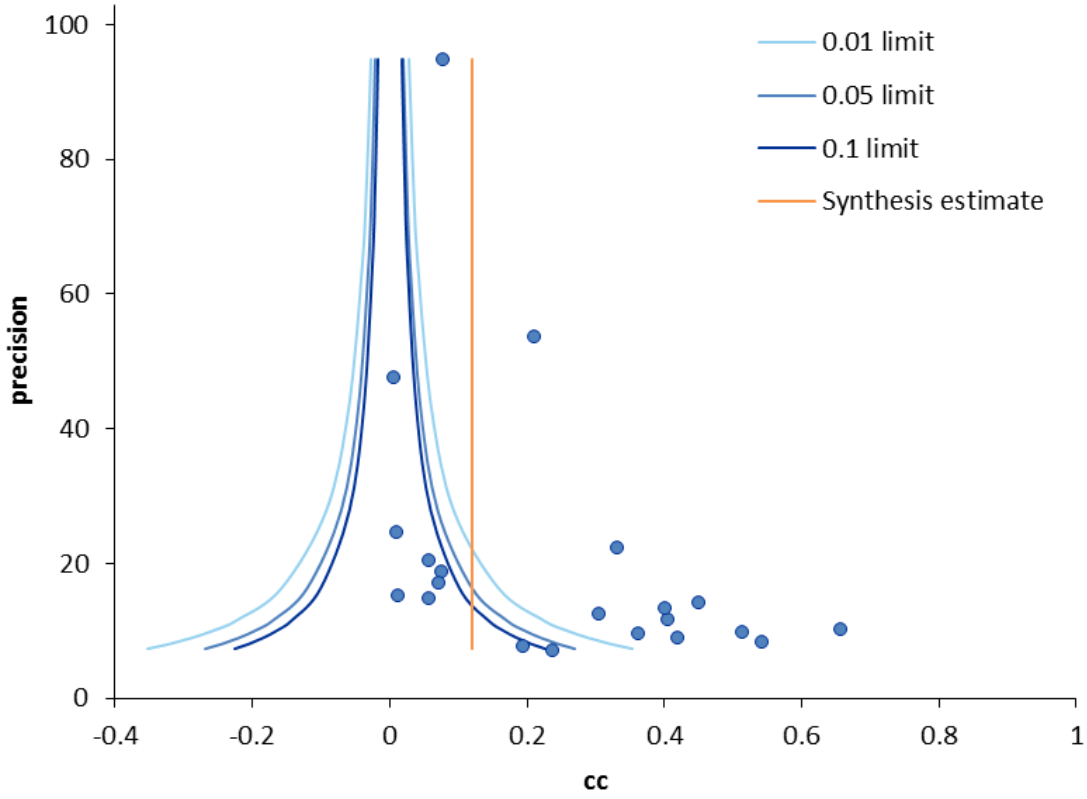

Figure 7. Funnel plot analysis for potential publication bias for meta-analysis on the association between acne and anxiety.

Author	N	r	95% CI		p
WEN	2284	0.0042	-0.03682	0.04521	0.84102
PURVIS	9008	0.0762	0.05564	0.0967	<0.00001
AKTAN	616	0.0075	-0.07154	0.08645	0.85268
DING	2891	0.207	0.17184	0.24163	<0.00001
Community	14799	0.07708	-0.00994	0.16294	0.08247
YARPUZ	141	0.3824	0.23174	0.51515	<0.00001
YAZICI	99	0.3465	0.16004	0.50909	0.0004
UKONU	112	0.5748	0.43572	0.68707	<0.00001
BEHNAM	209	0.4204	0.30191	0.5261	<0.00001
BEZ	238	0.0111	-0.11623	0.13807	0.86488
GOLCHAI	164	0.2935	0.14686	0.42752	0.00012
SALMAN	74	0.4937	0.29892	0.64899	0.00001
AWAD	100	0.4722	0.30398	0.61187	<0.00001
OZTURK	87	0.3954	0.20154	0.55945	0.00013
GUL	80	0.7725	0.66579	0.84824	<0.00001
KOUTOU	362	0.0738	-0.0295	0.17554	0.16126
KANE	186	0.379	0.24868	0.49584	<0.00001
LUKAVICIUTE	510	0.3182	0.23795	0.39414	<0.00001
KAYMAK	298	0.0705	-0.04347	0.18266	0.22517
SAYAR	56	0.2309	-0.03407	0.46554	0.08693
POLENGHI	66	0.1905	-0.05402	0.41347	0.12583
DALGARD	426	0.0556	-0.03962	0.14982	0.25233
DUMAN	225	0.056	-0.07534	0.18543	0.40357
Clinical	3433	0.31683	0.21801	0.40922	<0.00001

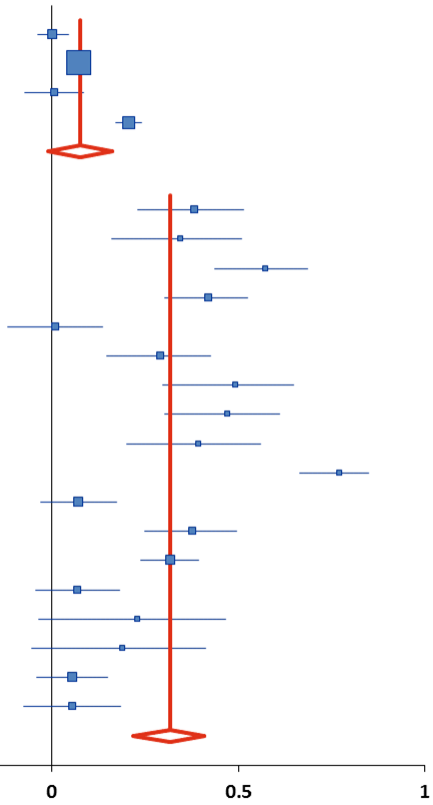

Figure 8. Step 1: Subgroup comparison of the association between acne and anxiety by study setting.

Author	N	r	95% CI		p
YAZICI	61	0.081	-0.17438	0.32617	0.53642
GOLCHAI	82	0.0878	-0.13172	0.29911	0.43398
AWAD	60	0.0759	-0.18152	0.32359	0.56588
YANG	47111	0.0134	0.00437	0.02243	0.00363
HALVORSEN	490	0.317	0.23502	0.3945	<0.00001
AKTAN	308	0.0093	-0.10257	0.12093	0.87097
KUBOTA	847	0.1592	0.09283	0.22416	<0.00001
KOCAK	44	0.3035	0.00728	0.55076	0.0448
LUKAVICIUTE	255	0.0234	-0.09973	0.14582	0.71024
	49258	0.11391	0.01888	0.20689	0.0189

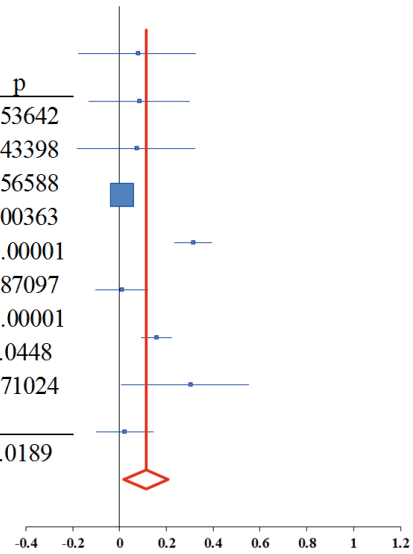

Figure 9. Step 2: Meta-analysis of the association between sex and depression among individuals of all ages with acne.

Author	N	r	95% CI		p
YAZICI	61	0.076	-0.17925	0.32166	0.56197
UKONU	62	0.025	-0.22618	0.27306	0.84769
GOLCHAI	82	0.444	0.2512	0.60292	0.00002
AWAD	60	0.2514	-0.0027	0.475	0.05243
AKTAN	308	0.1207	0.00906	0.22936	0.03415
LUKAVICIUTE	255	0.0686	-0.0547	0.18984	0.2754
	828	0.15996	0.04228	0.27326	0.0079

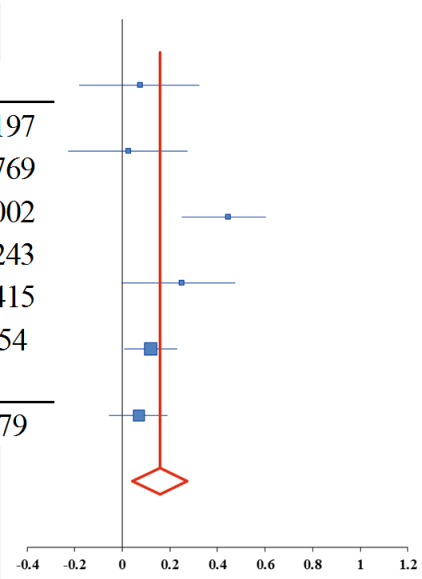

Figure 10. Step 2: Meta-analysis of the association between sex and anxiety among individuals of all ages with acne.

Author	N	r	95% CI		p
YARPUZ	83	0.034	-0.18303	0.24787	0.76096
SALMAN	37	-0.217	-0.50548	0.11511	0.19853
AWAD	60	0.2625	0.00919	0.48415	0.04242
OZTURK	47	0.341	0.05968	0.57214	0.01846
AKTAN	308	0.066	-0.0461	0.17646	0.24837
KOUTOU	181	0.291	0.15158	0.41907	0.00006
LUKAVICIUTE	255	0.423	0.31661	0.51888	<0.00001
NOTE: Weights are from random effects analyses.					
	971	0.19328	0.03468	0.34238	0.01721

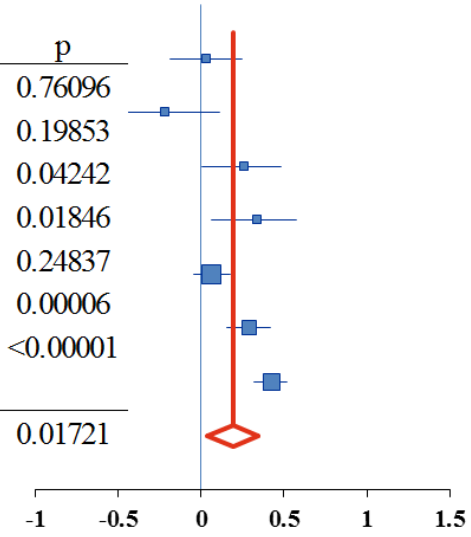

Figure 11. Step 2: Meta-analysis of the association between clinical acne severity and depression across individuals of all ages with acne.

Table I. Summary of participant and study characteristics.

Study	Country	Study Setting	Participants			Age classification
			N	Acne (n)	Control (n)	
META-ANALYSIS						
Unsal & Ayranci 2008	Turkey	Community	846	95	451	Adolescent
Wen et al. 2014	China	Community	2284	1156	1128	Mixed
Smithard et al. 2001	UK	Community	317	88	229	Adolescent
Yarpuz et al. 2008	Turkey	Clinical	141	83	58	Mixed
Yazici et al. 2004	Turkey	Clinical	99	61	38	Mixed
Ukonu et al. 2016	Nigeria	Clinical	112	62	50	Adult
Behnam et al. 2013	Iran	Clinical	209	103	106	Mixed
Bez et al. 2011	Turkey	Clinical	238	140	98	Mixed
Golchai et al. 2010	Iran	Clinical	164	82	82	Adult
Salman et al. 2016	Turkey	Clinical	74	37	37	Adult
Rehn et al. 2008	Finland	Clinical	315	165	150	Mixed
Awad et al. 2018	Egypt	Clinical	100	60	40	Mixed
Purvis et al. 2006	New Zealand	Community	9657	1329	8328	Adolescent
Yang et al. 2014	Taiwan	Population	1000000	47111	952889	Mixed
Öztürk et al. 2013	Turkey	Clinical	87	47	40	Mixed
Halvorsen et al. 2009	Norway	Population	3628	490	3138	Adolescent
Aktan et al. 2000	Turkey	Community	616	308	308	Adolescent
Gül & Çölgeçen 2015	Turkey	Clinical	80	40	40	Adult
Uslu et al. 2007	Turkey	Community	550	459	91	Adolescent
Do et al. 2009	South Korea	Community	504	398	106	Adolescent
Kubota et al. 2010	Japan	Community	1443	859	584	Adolescent
Koutou et al. 2016	Cameroon	Clinical	362[I]	181	NC	Mixed
Bashir et al. 2010	India	Clinical	24[I]	12	NC	Adult
Kang et al. 2015	China	Clinical	574[I]	287	NC	Adult
Antuña Bernardo et al. 2	Spain	Clinical	36[I]	18	NC	Mixed
Jowett & Ryan 1985	UK	Clinical	60[I]	30	NC	Mixed
Kane et al. 2007	Senegal	Clinical	186[I]	93	NC	Mixed
Kocak et al. 2007	Turkey	Clinical	88[I]	44	NC	Mixed
Kosaraju et al. 2015	India	Clinical	26[I]	13	NC	NR
Lukaviciute et al. 2017	Lithuania	Clinical	510[I]	255	NC	Adult
Ding et al. 2008	China	Community	2891	701	2190	Adolescent
Kaymak et al. 2007	Turkey	Clinical	426	93	205	Mixed
Gao et al. 2017	U.S.	Population	4658	202	4456	Mixed
Kahn, Naeem, & Mufti,	Pakistan	Clinical	100[I]	50	NC	Mixed
Arslan et al. 2009	Turkey	Community	822	330	492	Mixed
Sayar et al. 2000	Turkey	Clinical	56	31	25	Mixed
Polenghi et al. 2002	Italy	Clinical	66[I]	33	NC	Adult
Klassen et al. 2000	UK	Clinical	1415	111	1304	Mixed
Dalgard et al. 2015	Multinational*	Clinical	1572	213	1359	Adult
Duman et al. 2016	Turkey	Clinical	225	125	100	Mixed

NOTE. NR = Not reported; NC = No control; Imputation denoted by [I]

Table II. Summary of study outcomes.

			Depression			Anxiety		
Study	**Outcome ascertainment**	**Acne ascertainment**	***r***	***p***	**Conclusion**	***r***	***p***	**Conclusion**
Unsal & Ayranci 2008	BDI	Presence or Absence	0.0904	0.0085	A > NA	0.0904	0.0085	A > NA
Wen et al. 2014	HADS	Pillsbury Grading	0.085	0.000024	A > NA	0.085	0.000024	A > NA
Smithard et al. 2001	SDQ	Leeds Grading System	0.1242	0.027	A > NA	0.1242	0.027	A > NA
Yarpuz et al. 2008	HADS	GAGS	0.1988	0.0181	A > NA	0.1988	0.0181	A > NA
Yazici et al. 2004	HADS	Clinical diagnosis	0.2571	0.011	A > NA	0.2571	0.011	A > NA
Behnam et al. 2013	SCL-90	AAD Guidelines	0.2265	0.0011	A > NA	0.2265	0.0011	A > NA
Bez et al. 2011	HADS	GAGS	0.0889	0.947	A ≈ NA	0.0889	0.947	A ≈ NA
Golchai et al. 2010	HADS	GAGS	0.0275	0.7245	A ≈ NA	0.0275	0.7245	A ≈ NA
Salman et al. 2016	HADS	European Guidelines	0.4699	<.00001	A > NA	0.4699	<.00001	A > NA
Rehn et al. 2008	BDI	Leeds Grading System	0.057	0.311	A ≈ NA	0.057	0.311	A ≈ NA
Awad et al. 2018	HADS	Combined Classificatio	0.3931	<.00001	A > NA	0.3931	<.00001	A > NA
Purvis et al. 2006	RADS, ADI	Acne problematic or n	0.1114	<.00001	A > NA	0.1114	<.00001	A > NA
Yang et al. 2014	ICD-9-CM	ICD-9-CM	0.006	<.000001	A > NA	0.006	<.000001	A > NA
Öztürk et al. 2013	HADS	Presence or Absence	0.312	0.00033	A > NA	0.312	0.00033	A > NA
Halvorsen et al. 2009	HSCL-10	Pimples in last week	0.0982	<.000001	A > NA	0.0982	<.000001	A > NA
Aktan et al. 2000	HADS	GAGS	0.0278	0.4896	A ≈ NA	0.0278	0.4896	A ≈ NA
Gül & Çölgeçen 2015	SCL 90-R	Presence or Absence	0.7709	<.00001	A > NA	0.7709	<.00001	A > NA
Kubota et al. 2010	MHI	Presence or Absence	0.1773	<.00001	A > NA	0.1773	<.00001	A > NA
Bashir et al. 2010	ICD-10	Clinical diagnosis	0.3162	0.000041	A > NA	0.3162	0.000041	A > NA
Kang et al. 2015	BDI	Pillsbury Grading	0.633	<.000001	A > NA	0.633	<.000001	A > NA
Antuña Bernardo et al. 2	Zung	Skindex	0.2414	<.00001	A > NA	0.2414	<.00001	A > NA
Jowett & Ryan 1985	Clincal Interview	Clinical diagnosis	0.0455	0.096707	A ≈ NA	0.0455	0.096707	A ≈ NA
Kocak et al. 2007	BDI, BAI	GAGS	0.0214	0.848962	A ≈ NA	0.0214	0.848962	A ≈ NA
Kosaraju et al. 2015	PHQ-9	Clinical diagnosis	0.1924	<.00001	A > NA	0.1924	<.00001	A > NA
Lukaviciute et al. 2017	HADS	European Guidelines	0.2654	<.000001	A > NA	0.2654	<.000001	A > NA
Gao et al. 2017	CES-D	Rx in past year	0.0352	0.008	A > NA	0.0352	0.008	A > NA
Kahn et al. 2001	ICD-10	Clinical diagnosis	0.1036	0.236977	A ≈ NA	0.1036	0.236977	A ≈ NA
Arslan et al. 2009	BDI	Clinical diagnosis	0.091	0.005	A > NA	0.091	0.005	A > NA
Sayar et al. 2000	BDI, STAI	Cook Scale	0.2883	0.0156	A > NA	0.2883	0.0156	A > NA
Polenghi et al. 2002	STAI	Clinical diagnosis	0.3904	<.000001	A > NA	0.3904	<.000001	A > NA
Klassen et al. 2000	EQ-5D	Leeds Grading System	0.2611	<.000001	A > NA	0.2611	<.000001	A > NA
Dalgard et al. 2015	HADS	Clinical diagnosis	0.023	0.362132	A ≈ NA	0.023	0.362132	A ≈ NA
Duman et al. 2016	HADS	GAGS	0.108	0.053	A > NA	0.108	0.053	A > NA

NOTE. A = acne; NA = no acne

Appendix A

Details of Outcome Ascertainment Scales

Scale	Scale description	Clinical cut-offs
HADS	Self-administered screening scale for symptoms of anxiety and depression. There are 14 items: 7 refer to symptoms of anxiety and 7 refer to depression. Intensity and frequency of symptoms measured on a 4-point Likert scale, rated 0-3.	8-10 points indicates mild disorder, 11+ points indicates clinically significant disorder
SCL-90	90-item inventory of psychiatric symptoms for ppl > 17 yrs, rated 0-4.	Subscales include depression and anxiety scales where scores are converted to standard T-scores to determine clinical cut-off points (> 60 points)
BDI	Reporting instrument including 21 groups of 4 statements in which patients are asked to select the statement that most clearly describes the way they felt in the previous week. Scores are used for measuring symptoms of depression.	10-18 indicates mild depression, 19-29 indicates moderate to severe depression 30-63 indicates severe depression
BAI	Reporting instrument including 21 groups of 4 statements in which patients are asked to select the statement that most clearly describes the way they felt in the previous week. Scores are used for measuring symptoms of anxiety.	10-18 indicates mild anxiety 19-29 indicates moderate to severe anxiety, 30-63 indicates severe anxiety
HRSD-17	This scale gives a rating of depression and changes in violent behavior. There are 17 questions, rated 0-4.	14-27 points indicates mild depression; 28-41 points indicates moderate depression; 42-53 points indicates severe depression
HSCL-10	This 10-item scale gives a rating of depression and anxiety where intensity and frequency of symptoms are evaluated on a 4-point scale (1-4).	Higher scores indicate greater psychological distress
STAXI	Scale assesses severity of state and trait anxiety using 20 items each on a 4-point scale.	Scores range from 20 to 80 where higher scores indicate a greater degree of anxiety
SDQ	Self-report screening questionnaire with 5 subscales scored 0-10 points including Emotional Symptoms Subscale which indicates internalizing problems	Score ranges from 0-20 points where higher scores indicate a greater degree of internalizing problems
ICD-9-CM	Internationally adapted scale with standard list of six-character alphanumeric codes to describe diagnoses.	Codes for depression and anxiety diagnoses require fifth digit indicator for severity where 1 = mild, 2 = moderate, 3 = severe without mention of psychosis, 4 = severe with mention of psychosis, 5 = partial or unspecified remission
RADS	Screening tool designed to measure severity of symptoms of depression in adolescents	Empirically derived clinical cutoff score helps to identify adolescents who may be at risk for a depressive disorder or a related disorder
MASC ADI	Self-report instrument to identify children and adolescents with anxiety disorder	Scores of 48 for boys and 56 for girls using total scores, or scores of 15 for boys and 17 for girls using the Anxiety Disorders Index could be employed (both represent 90th percentiles)
CES-D	Consists of 20 items, addressing depression symptoms across 4 dimensions of depressed affect. It is a self-reported scale, and participants indicate how often they experienced each symptom in the preceding week.	Scores range from 0 to 60 where scores > 16 indicate depression

HADS, Hospital Anxiety and Depression Scale; *BDI*, Beck Depression Inventory; *BAI*, Beck Anxiety Inventory; *SCL-90*, Symptom Checklist-90; *HSCL-10*, Hopkins Symptoms Checklist-10; *STAI,* State-Trait Anxiety Inventory; *SDQ,* Strengths and Difficulties Questionnaire; *RADS,* Reynolds Adolescent Depression Scale; *ICD-9-CM* International Classifications of Diseases, Ninth Revision, Clinical Modification; *CESD,* Center for Epidemiological Studies Depression scale; *MHI,* Mental Health Inventory; *MASC ADI*, Multidimensional Anxiety Scale for Children Anxiety Disorder Index; EQ-5D, EuroQoL; *HRSD*, Hamilton Rating Scale for Depression.

Appendix B

Decision procedure for control group construction (k = 11)

If…	*Then*	Evidence	Fine-tuned Matching	Impute Mean
Within-study proportions of acne and controls who were depressed and anxious were highly correlated ($r \geq .50$)	Groups were effectively matched	$r_D = 0.6172$, $p < .001$ $r_A = 0.6664$, $p < .001$	X	
Between-study proportions of acne participants from studies with and without control groups did not significantly differ from each other	No indication of systematic differences between the two types of studies	$t_D(18) = .691$, $p = .50$ $t_A(30) = 1.4$, $p = .17$	X	