Biomedical Dermatology

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Meta-analyses of associations of obesity with risk of melanoma and acne based on case-control studies

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Abstract

Background: Melanoma and acne are highly prevalent dermatological diseases. A meta-analysis of case-control studies was performed to explore obesity as a risk factor for the same.

Objective: The relationship between increased BMI and melanoma incidence has been investigated in the past. We utilized recent epidemiological evidence to study this association and confirm previous findings. Moreover, to date, no meta-analysis evaluating the relationship between obesity and acne has been performed. We conducted this analysis to cast light on the same.

Methods: PubMed database was searched systematically to identify relevant literature related to the associations of obesity with risk of melanoma and acne respectively. Meta-analyses were performed using Review Manager 5.3, and the resulting risk ratios and 95% confidence intervals (CIs) were analyzed.

Results: A total of 2304 melanoma patients and corresponding 2468 controls, and 983 acne patients and corresponding 1313 controls from 5 and 4 case-control studies respectively were finally enrolled in the meta-analysis. The results showed a weak positive association between increasing BMI ($\geq 25 \text{ kg/m}^2$) and melanoma (OR = 1.36; 95% CI = 1.20–1.55), and a null association between increasing BMI ($\geq 25 \text{ kg/m}^2$) and acne (OR = 1.27; 95% CI = 0.98–1.65).

Conclusions: The result from the first meta-analysis showed that as BMI increases, there is an increased risk of melanoma incidence. The second meta-analysis revealed the absence of any significant relationship between obesity and acne. However, larger and more high-quality studies are needed to confirm this result.

Keywords: Meta-analysis, Obesity, Melanoma, Acne, Case-control studies

Key points

- There is a need to study the impact of obesity on dermatological diseases like melanoma and acne.
- The meta-analysis revealed that people with BMI $\geq 25 \text{ kg/m}^2$ are at a higher risk of melanoma than those with BMI $\leq 25 \text{ kg/m}^2$.
- The meta-analysis also showed that an increase in BMI beyond 25 kg/m^2 did not impact acne incidence significantly.

Introduction

Obesity is an escalating global epidemic, and its prevalence has increased dramatically in children by 47% and in adults by 28% between 1980 and 2013 (The GBD 2013 Obesity Collaboration et al. 2014). By 2030, it is estimated that 20% of the world's adult population will be inflicted with obesity and another 38% will be overweight if current trends persist (Kelly et al. 2008).

Affecting at least 300 million people worldwide (Tobin et al. 2013a), this complex disease is now a major health problem. A contributing factor to the aforesaid is the association of this multifactorial disease with numerous comorbidities such as cardiovascular disease (Jokinen, 2015), cancer (Park et al., 2014), diabetes (Garg et al. 2014), hypertension (Becton et al. 2012), osteoarthritis

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(Berenbaum et al. 2013; Bliddal et al. 2014), and sleep apnea (Tuomilehto et al. 2013).

Obesity also leads to metabolic changes that have dermatological manifestations (Guerra-Segovia and Ocampo-Candiani, 2015), but they have received minimal attention and have not been studied extensively (Yosipovitch et al. 2007). Recently, researchers have developed an interest in studying the role of obesity in psoriasis (Jensen and Skov, 2016; Carrascosa et al. 2014), but obesity is implicated in many other dermatoses as well (Tobin et al. 2013b).

Melanoma is the deadliest form of skin cancer (Ingraffea, 2013) and its incidence continues to increase worldwide at a pace much faster than any other type of solid cancer (Owens, 2014). Acne too, as evidenced by epidemiological data demonstrating a predominance of 9.4%, is one of the most common skin diseases (Stein Gold, 2016) and the eighth most prevalent disease all over the world (Tan and Bhate, 2015).

A previously conducted meta-analysis (Sergentanis et al. 2013) evaluated the association between obesity and melanoma risk. However, it included case-control studies published from 1984 to 2008. We believe that lifestyle factors have changed over the years and hence, it is important to conduct the meta-analysis again utilizing recent reports as they are better indicators of the current scenario. Moreover, no meta-analysis has been conducted so far to study the association between obesity and acne risk.

Hence, the aim of this meta-analysis was to comprehensively examine case-control studies published from 2011 to 2017 that link body mass index (BMI), a marker of obesity, with highly prevalent dermatological diseases like melanoma and acne.

Methods
Search strategy
A comprehensive literature search was performed using PubMed to evaluate the incidence of melanoma and acne in obese and overweight subjects. Our search strategy included terms of "Obesity" (e.g., "body mass index," "body surface area," "BMI," "overweight," "body weight," "obese," "diet," "adiposity," "body size"), "Melanoma" (e.g., "skin cancer," "skin neoplasm," "malignancy"), and "Acne" (e.g., "acne vulgaris," "pimple").

Study selection
All scientific papers published through 2017 were examined. Studies with insufficient data for estimating HR and 95% CI were excluded, as were texts written in languages other than English and those with duplicate data. In case study populations overlapped, only the study of larger size was considered. Scientific papers that did not mention melanoma and acne were eliminated. Other studies that did not use BMI as an obesity index or involve a case-control study were also eliminated. The decision of inclusion or exclusion of each study was made independently by the investigator (A.M).

Data extraction
All candidate articles were evaluated, and data were independently extracted by the investigator (A.M.). For each study, information regarding baseline characteristics (first author's name, year of publication, country, age range, sex, number of cases and controls, sources of cases and controls, adjustment factors) was extracted. The corresponding authors were contacted at least twice in case the data required for the meta-analyses were incomplete, not available, or insufficient in the published study.
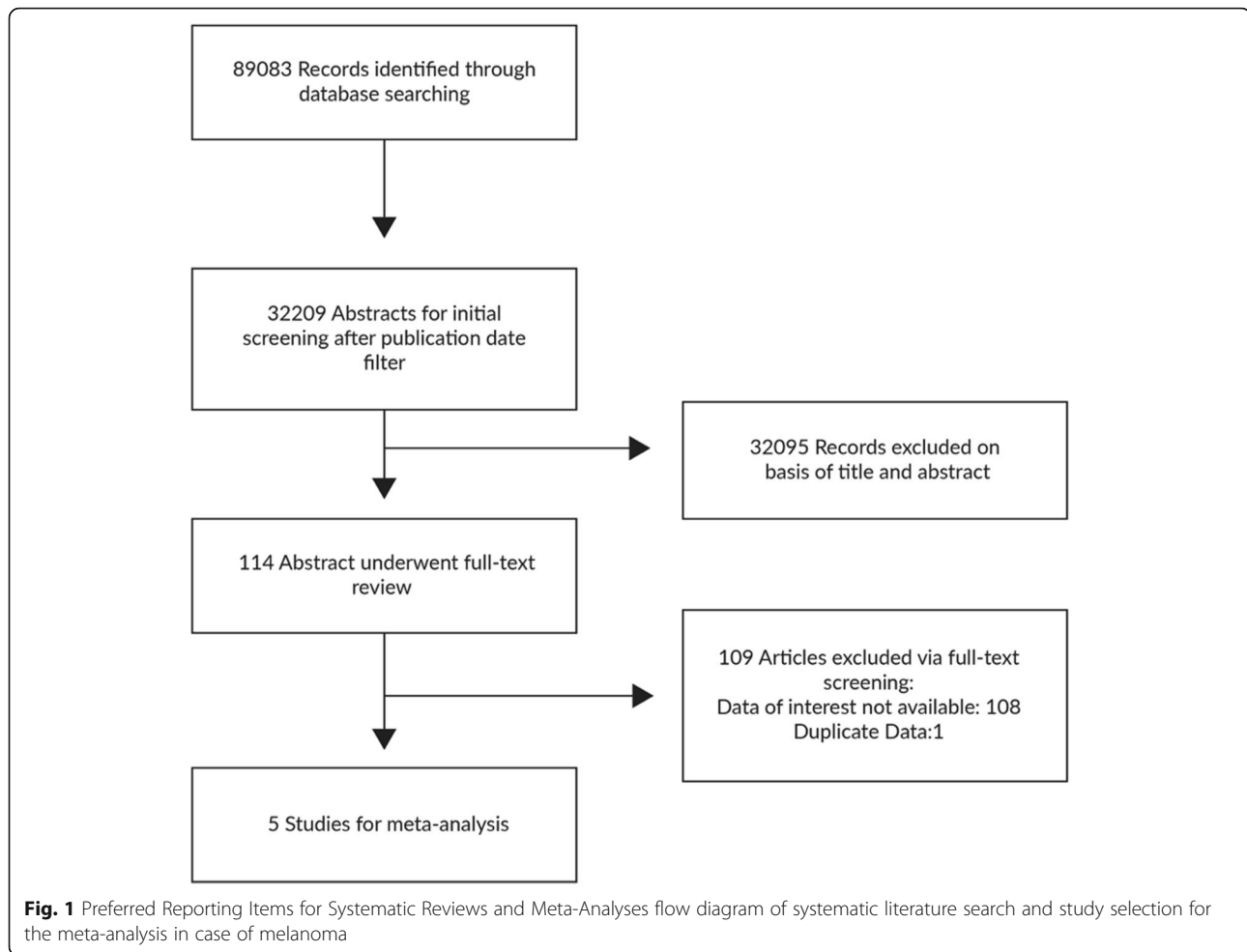
Statistical analyses
Statistical analyses were performed using Review Manager 5.3. The odd ratios (ORs) were used as a measure of the association between the particular dermatological disease and obesity. The I^2 statistic was undertaken as an objective measure to quantify the heterogeneity of the included studies. Fixed-effect meta-analysis (Mantel-Haenszel method) was performed on the studies. $P < 0.1$ was indicative of the presence of clear heterogeneity and vice-versa. The condition of being overweight was defined as having BMI ≥ 25 and < 30 km/m2 while that of being obese was defined as having BMI $\geq 30 \, kg/m^2$.

Results
Study selection
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is demonstrated in Fig. 1 to show the study selection process. Our PubMed literature search for melanoma yielded 83,083 citations, out of which 32,209 had been published during the preferable time period between 2011 and 2017. Records that were not case-control studies and did not mention the keywords related to melanoma in their title or abstract were excluded to give 114 articles that were eligible for a full-text review. All the studies were published in peer-reviewed journals. Five eligible studies (Antoniadis et al. 2011; Davies et al. 2011; Fortes et al. 2013; De Giorgi et al. 2017; Malagoli et al. 2015) were included in the final meta-analysis after excluding 108 records that had insufficient, incomplete, or irrelevant data. The data from a case-control study by Malagoli et al. (Malagoli et al. 2015) was used in another one (Malavolti et al. 2017) and hence the latter was also excluded from the meta-analysis.

Similarly, for acne, as shown in Fig. 2, a total of 1192 manuscripts were identified from PubMed, out of which 447 had been published between 2011 and 2017. An

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of systematic literature search and study selection for the meta-analysis in case of melanoma

additional article was identified from other sources. Records that did not mention keywords related to acne in their title or abstract were excluded along with those that did not involve case-control studies. This yielded 26 abstracts for a full-text review. Manuscripts that gave insufficient information on the effect of acne on obesity were rejected. A case-control study by Grossi et al. (Grossi et al. 2016) was also excluded from the meta-analysis since it had the same data as that by Landro et al. (Di Landro et al. 2012). After careful screening, four studies (Di Landro et al. 2012; Di Landro et al. 2016; Lu et al. 2017; Al-Shobaili et al. 2012) were selected for final inclusion in the meta-analysis. This literature search was also conducted according to PRISMA guidelines.

Study characteristics

The main characteristics of the studies included in the meta-analysis for melanoma are listed in Additional file 1. The meta-analysis included 2304 patients with melanoma and 2468 uninfected controls to study the effect of obesity on melanoma. BMI was used as an indicator of obesity. Three studies were performed in Italy, one in Greece, and one in the UK. All the five studies were case-control studies, encompassing participants of all ages, both male and female. The studies were published from 2011 to 2017.

In case of acne, the meta-analysis included a total of 2296 participants of all ages—983 acne patients and 1313 unaffected controls. Two studies were performed in Italy, one in China, and one in Saudi Arabia. These four case-control studies were published between 2012 and 2017 and helped study the association between obesity and acne. BMI was used as an index for obesity. Barring one study that included only female participants, the rest had both male and female participants. The main characteristics of the studies included in the meta-analysis for acne are listed in Additional file 2.

Association between obesity and melanoma

Five studies were included to investigate the relationship between obesity and the risk of melanoma. Two studies reported a higher risk of melanoma in "obese and overweight people" (BMI $\geq 25 \, kg/m^2$) while the other three did not show a significant relationship individually. The
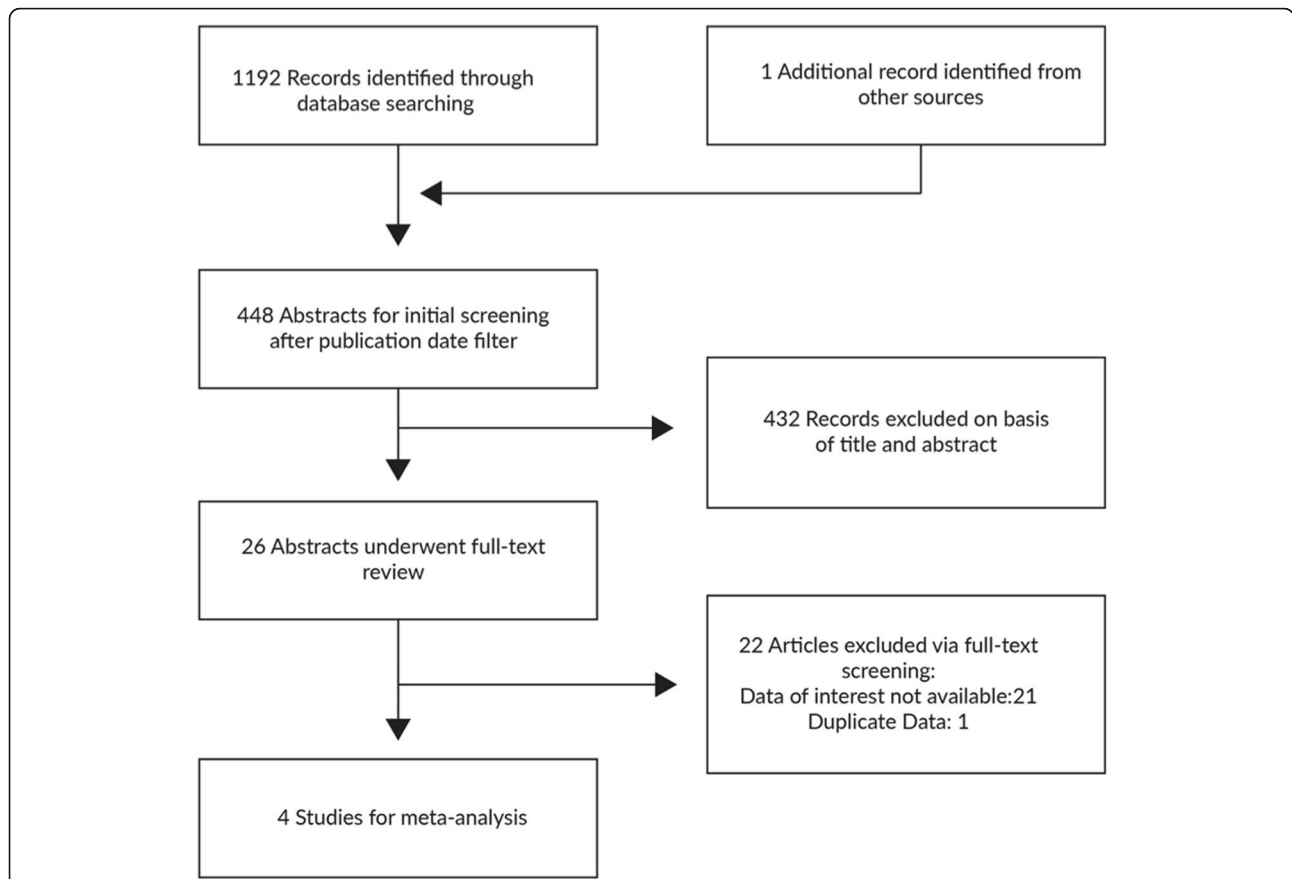
Fig. 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of systematic literature search and study selection for the meta-analysis in case of acne

pooled estimate was significant (OR = 1.36; 95% CI = 1.20–1.55), with significant heterogeneity (I^2 = 93%; P < 0.00001) (Fig. 3). The analyses for incidence of melanoma in overweight people (25 kg/m² ≤ BMI < 30 kg/m²) (OR = 0.94; 95% CI = 0.8–1.10) and obese people (BMI ≥ 30 kg/m²) (OR = 1.32; 95% CI = 1.06–1.64) individually have been shown in Additional file 3: Figure S1 and Additional file 4: Figure S2 respectively. The study by Grossi et al. (Grossi et al. 2016) has not been included in these individual analyses

since data specific for BMI ranges 25–30 kg/m² and ≥ 30 kg/m² was unavailable.

Association between obesity and acne

Four studies were included to investigate the relationship between obesity and the risk of acne. One study reported a higher risk of acne in obese and overweight people (BMI ≥ 25 kg/m²) while the other three did not show a significant relationship individually. No significant association
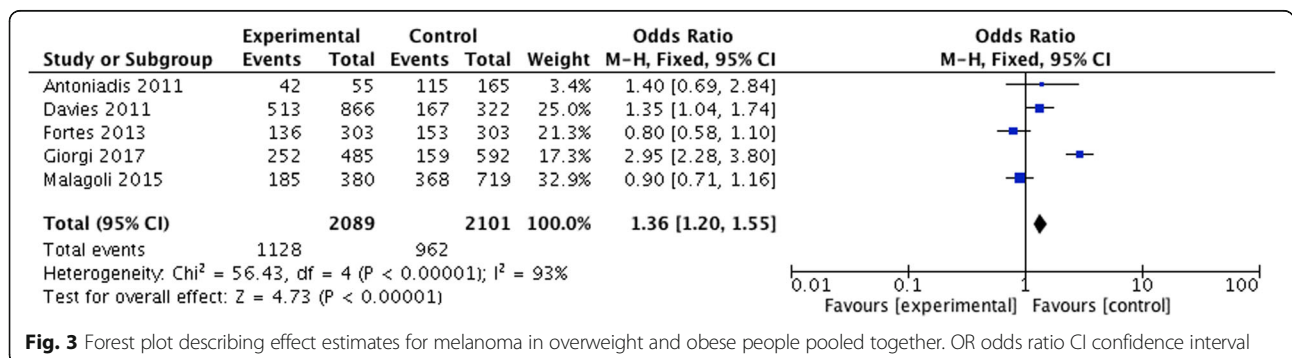
Fig. 3 Forest plot describing effect estimates for melanoma in overweight and obese people pooled together. OR odds ratio CI confidence interval

was documented after a pooled analysis (OR = 1.27; 95% CI = 0.98–1.65; I^2 = 24%) (Fig. 4). Meta-analyses were not conducted for overweight and obese people specifically due to the lack of sufficient data and studies.

Exploration of heterogeneity
Heterogeneity was assessed by visually studying the forest plots. Non-overlapping CIs and *P* values obtained via the chi-square test were used to make the assessment. $P < 0.1$ denotes statistical significance while $I^2 > 50\%$ indicates substantial heterogeneity.

Publication bias
Since each meta-analysis includes less than 10 studies, publication bias cannot be assessed.

Discussion
This is the first meta-analysis aiming to investigate the relationship between obesity and the risk of acne and also the most recent one to include up-to-date evidence related to the association between obesity and melanoma risk.

Five studies were included to summarize the effect of obesity on the risk of melanoma. The analysis pointed to a weak positive association between increased BMI ($\geq$ 25 kg/m^2) and melanoma (OR = 1.36; 95% CI = 1.20–1.55) with significant heterogeneity between studies. This result is coherent with the result from a meta-analysis conducted in 2008 (Renehan et al. 2008) that involved cohort studies only. It is also concomitant with a meta-analysis conducted in 2011 (Sergentanis et al. 2013) in which 45% of the studies were cohorts and the rest were case-control studies. This meta-analysis also included an unpublished case-control dataset, the numbers of which do not correspond with those in the published version (Antoniadis et al. 2011) that has been included in our meta-analysis.

For the association between obesity, indicated here by BMI $\geq$ 25 kg/m^2, and the risk of acne, four studies were studied. The meta-analysis showed a null association (OR = 1.27; 95% CI = 0.98–1.65). However, in the future, more prospective, well-designed, and large-scale studies along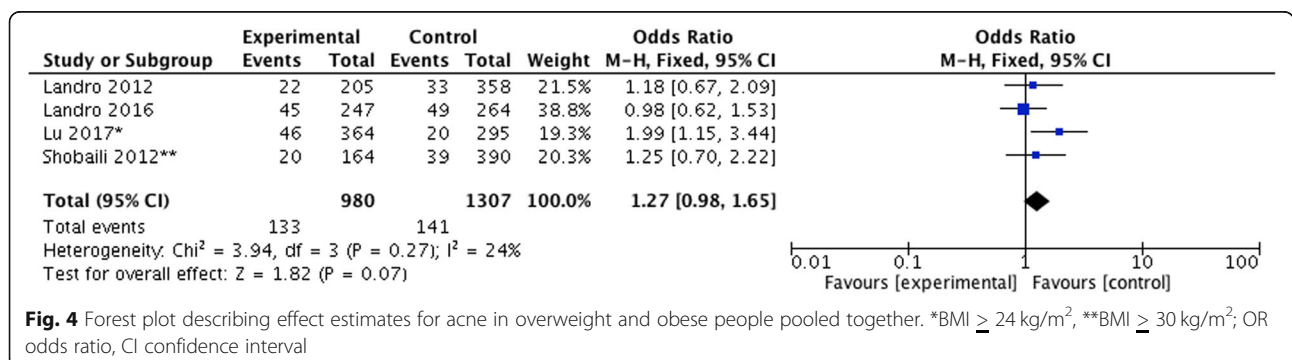 with basic research need to be conducted to properly explore and validate the relationship between increased BMI and risk of acne.

There are several limitations to our meta-analyses. Most of them hail from the shortcomings of individual studies, but there are other factors that need to be considered as well. Firstly, the pooled studies had varying inclusion or exclusion criteria, geographical locations, sample sizes, etc. Secondly, the confounding factors were not properly adjusted in the individual case-control studies, hence subjecting the associations to confounding bias. Thirdly, the fact that only five studies were included in case of melanoma and four in case of acne point to the high probability of a publication bias. Next, the meta-analyses were constrained to articles published in PubMed, in English, and those that used body mass index as an indicator of obesity. Also, since the enrolled studies were retrospective, the meta-analysis is subject to certain methodical limitations like selection bias and information bias. Lastly, it does not give gender-specific results due to inadequate data availability. The authors of such studies were contacted at least twice for the same.

Our study has several strengths. A comprehensive literature search of PubMed was performed to study the relationship between obesity, as denoted by increased BMI, and dermatological diseases like melanoma and acne. The studies included in the meta-analysis were of high quality. Another merit of this article lies in the fact that it involves the first meta-analysis to evaluate the association between obesity and acne risk.

Conclusions
Our findings from the first meta-analysis support the notion that increased BMI has a weak positive association with incidence of melanoma. This result is congruous with previously conducted meta-analyses that evaluated a different set of studies. The second meta-analysis demonstrated a null association between obesity and acne risk. However, since this is the first meta-analysis to evaluate the relationship between increased BMI and incidence of acne, this result needs to be confirmed by future studies and meta-analyses as more literature accumulates.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI	Odds Ratio M–H, Fixed, 95% CI
Landro 2012	22	205	33	358	21.5%	1.18 [0.67, 2.09]	
Landro 2016	45	247	49	264	38.8%	0.98 [0.62, 1.53]	
Lu 2017*	46	364	20	295	19.3%	1.99 [1.15, 3.44]	
Shobaili 2012**	20	164	39	390	20.3%	1.25 [0.70, 2.22]	
Total (95% CI)		980		1307	100.0%	1.27 [0.98, 1.65]	
Total events	133		141				
Heterogeneity: Chi² = 3.94, df = 3 (P = 0.27); I² = 24%							
Test for overall effect: Z = 1.82 (P = 0.07)							

Fig. 4 Forest plot describing effect estimates for acne in overweight and obese people pooled together. *BMI $\geq$ 24 kg/m^2, **BMI $\geq$ 30 kg/m^2; OR odds ratio, CI confidence interval

Additional files

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Not applicable.

Availability of data and materials
Not applicable

Authors' contributions
YH conceived the idea of the study. AM designed the study. AM and YH wrote the manuscript. Both the authors approved the final manuscript.

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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