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META-ANALYSIS

# Low Glycemic Load or Index Diet in Association with Acne Vulgaris: A Systematic Review and Meta-analysis

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**Received:** 28 March 2019 **Accepted:** 2 August 2019
Published 2020, Volume 1, Issue 1,

## ABSTRACT

**Background:** Social life can be affected by skin condition. Acne Vulgaris (AV) is a multi-factorial skin disorder that affects many people. Several dietary factors are associated with AV.

**Objectives:** Different findings on glycemic indices led us to investigate the effect of the dietary glycemic index (GI) and glycemic load (GL) on AV by a systematic review and meta-analysis.

**Methods:** Observational studies and clinical trials were extracted from PubMed, EMBASE, Scopus, and Google Scholar. The mean ± Standard division (SD) for acne grading in clinical trials and the mean ± SD GI or GL of the diet for observational studies were used for meta-analysis.

**Results:** We found that nine out of 15 studies were eligible for systematic review clinical trials (N = 3) and observational studies (N = 6) designs. The meta-analysis of three studies clinically assessed the effect of GI/GL on acne and showed that a diet with lower GI/GL reduced the acne severity (Hedges'g = -0.91, 95% CI: -1.57, -0.25, P = 0.007). The analysis of six observational studies showed that dietary habit with higher GI might not affect the acne severity in patients with AV (Hedges'g = 0.07, 95%CI: -0.23, 0.38, P = 0.636), but individuals with higher acne severity had a diet with higher GL (Hedges'g = 0.64, 95%CI: 0.01, 1.26, P = 0.045).

**Conclusions:** Diet, as a part of life style, is associated with AV. Adherence to lower GL diet may reduce the severity of AV. Further well-designed clinical trials are required to confirm these results.

**Key words:** Acne Vulgaris; Glycemic Index; Glycemic Load; Diet

**How to Cite:** Sakhaei R, Mohsenpour MA. Low glycemic load or index diet in association with acne vulgaris: a systematic review and meta-analysis. Critical Comments in Biomedicine. 2020; 1(1): e10001.

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## Introduction

Acne vulgaris (AV) is known as a chronic skin abnormality *[1, 2]*, which might affect everyone at the age of 15 to 17 years *[3-5]*. It was estimated that about 40 to 50 million Americans were suffering from acne *[6]*. It is proposed that AV affects mental health *[7]*, as patient with AV are more depressed *[7]* and show higher behavioral and emotional symptoms*[8]*. Thus, treatment or prevention measures are needed to reduce effect of AV.

Published online: Dec. 2019

Acne is considered as a multifactorial disorder associated with several genetic factors *[9]*, hormonal change *[10]*, as well as lifestyle determinants like stress *[11]* and diet *[12]*. It is not fully understood how diet might affect the risk of AV *[13]*. Various aspects of diet including the amount and the type of dietary oils *[14, 15]* as well as the intake of fruits and vegetables *[14, 16]*, fish *[16]*, dairy products *[17]*, meat, chocolate *[18]*, and fast food *[19]* were investigated in relation with acne. In addition to all these factors, association of the glycemic index (GI) and glycemic load (GL) were investigated in association with the development of AV and its aggravation *[20-28]*. The concept of GI represents the relative ability of existing carbohydrates in foods that induce responses to increased blood glucose *[29, 30]*. Since GI can be used in the case that the amounts of carbohydrates in foods are equal, another concept was introduced: GL considers not only the types, but also the amount of carbohydrates in diet. Therefore, it can be used for the individuals' whole diet or meal *[31]*. It is proposed that high GI diet might increase the risk of AV through some hormonal effects of consumed carbohydrates. Increase in IGF-1 and reduction of IGFBP-3 are the consequences of hyper-insulinemia followed by carbohydrates consumption. These changes led to sebum production and keratinization of the epithelial cells *[16]* and development AV.

Several studies have tried to assess the association of dietary GI and/or GL with AV. The researches over the effect of low GI and/or GL diets on the disease status have led to inconsistent results. For instance, some available observational studies indicated that participants with AV had a diet with significantly higher GI and/or GL *[23-25]*, while the others could not support this finding *[27, 28]*. Furthermore, some clinical trials revealed that adherence to low GI or low GL diets by patients with AV might improve the disease *[20, 22]*, while the others could not replicate the same results *[21]*.

To the best of our knowledge, no systematic review and meta-analysis is published regarding the association of dietary GI and GL with AV. Therefore, we aimed to find the studies that examined the association of dietary GI or GL with AV and to conduct meta-analyses in order to derive the overall estimates and to explore any heterogeneity between the study results and the possible resources.

## Materials and Methods

The present study was reported based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines *[32]*. Authors registered this study in the international prospective register of systematic reviews (PROSPERO) under registration code of: CRD42016039182.

### Search strategy

We searched for publications indexed in PubMed, Scopus, and Google Scholar up to September 2018. The following sets of MeSH and non-MeSH Keywords and their combinations were used to find the related papers: 1) "glycemic", "glycemic load", "GL", "glycemic index", "GI", "glycemic diet", "GL diet", "GI diet", "glyceamic", and 2) "acne", and "acne vulgaris". In order to maximize the related articles, no limitation was applied for date and language. Moreover, reference lists of related publications were checked to ensure that no article has been neglected unintentionally.

### Eligibility criteria

We aimed to include the original clinical trials or observational studies, which investigated the association of dietary GI or GL with acne vulgaris. The clinical trials were included if: 1) they were conducted on human participants, 2) were randomized clinical trial (RCT), 3) included mild to severe acne patients, and 4) used low GI or GL diet for the intervention.

On the other hand, observational the studies were eligible if 1) compared GI or GL of diet for acne patients with healthy control group and 2) compared the chance of developing acne between participants with highest dietary GI or GL to those with the lowest dietary GI or GL. The retrieved studies were assessed for their eligibility by one of the authors (RS), the

included articles were double checked by the second author (MAM), and any differences were resolved by group discussion.

**Data extraction**

The general characteristics of the studies and participants were extracted: the first author's last name, publication year, location, sample size, participants' gender, age range, recruitment procedure, acne grading system, variables adjusted in the statistical analysis and the dietary assessment method. For the RCTs, we obtained the mean ±SD for acne severity before and after the intervention or its change for both the intervention and control groups. For the observational studies, mean ± SD for dietary GI and/or GL reported by the AV cases and the healthy controls were extracted.

**Quality assessment**

The quality of RCTs was checked by Cochrane collaboration's tool *[33]*. For every single study, randomization allocation of participants and its concealment, incomplete outcome data, and selective reporting were assessed. Considering that the intervention in these studies focused on the change in the diet, blinding for participants and investigators was impossible. Therefore it was not considered as a key domain in the quality assessment. In this method, each domain was categorized as: 1) low risk of bias, 2) high risk of bias, and 3) unclear. If any of the studies achieved low grade in two domains, it was considered as high quality. The studies that were low risk for only two fields or lower, were regarded as middle and low quality, respectively.

The Newcastle-Ottawa scale (NOS) *[34]* was used in order to evaluate the quality of observational studies. This scale was designed to assess the case-control studies in three major domains: 1) selection (population representativeness): each study can earn maximum 4 stars, 2) comparability of cases and control groups based on the design or analysis: maximum 2 stars can be allocated in this domain, and 3) ascertainment of the outcome with maximum 3 stars. The studies were categorized as low, moderate, and high quality if they received 0-3, 3-6, and 7-9 points, respectively.

**Statistical analysis**

The pre and post intervention mean ± standard deviation (SD) values for acne severity were used to calculate the mean changes from the baseline and their corresponding SDs were calculated for the intervention and the control groups in RCTs. The difference in mean changes [± standard error (SE)] between the intervention and the control groups were calculated and converted to Hedges' g and its corresponding standard error to be used as effect size for the meta-analysis. For observational studies, mean ± SD of the dietary GI/GL score were extracted for patients with AV and healthy participants. These values were used to calculate the mean difference and its corresponding SE. Later, the mean differences ± SEs were converted to Hedges' g and its corresponding SE to be used for meta-analysis of the observational studies. DerSimonian and Liard's random effects model was applied to conduct the meta-analysis *[35]* because this all meta-analyses hypothesis considerers the between-study variability. The heterogeneity was checked using Cochran's Q test and I-squared ($I^2$) *[35]*. The possible sources of heterogeneity were explored using subgroup analysis. Sensitivity analysis was done by sequentially excluding each study from the overall meta-analysis. Publication bias was also assessed by visual inspection of funnel plots, Egger's regression, and Begg's adjusted rank correlation tests *[36]*. All analyses were conducted using STATA software, version 11.2 (Stata Corp, College Station, TX). $P \leq 0.05$ was considered as statistically significant.

**Results**

Database search resulted in 226 articles. After omitting the duplicate findings, 169 papers were remained. By reading the titles and abstracts, 154 articles were excluded and 15 clinical and observational studies were remained *[20-28, 37-42]*. The remaining articles were checked manually and 5 other related papers were added to the initial search *[43-47]*. After reading the

articles' full-text, one article was removed, since its participants used medications along their diet *[39]*, another research was omitted because it was duplicate *[42]*, and three publications were excluded since they were based on the same research *[40-42]*. Thus, we selected the publications with higher number of the participants and omitted a pilot study *[40]*, a research conducted on specific outcome with less participants *[41]*, and one review study *[45]*. Furthermore, a study *[47]*, found in manual search was also omitted since it did not use randomized controlled clinical trial design. Overall, 14 articles were included in our systematic review *[20-28, 37, 38, 43, 44, 46]*. **Figure 1** depict the study selection process. **Table 1** summarizes the studies with clinical trials design and **Table 2** provides data on observational studies.

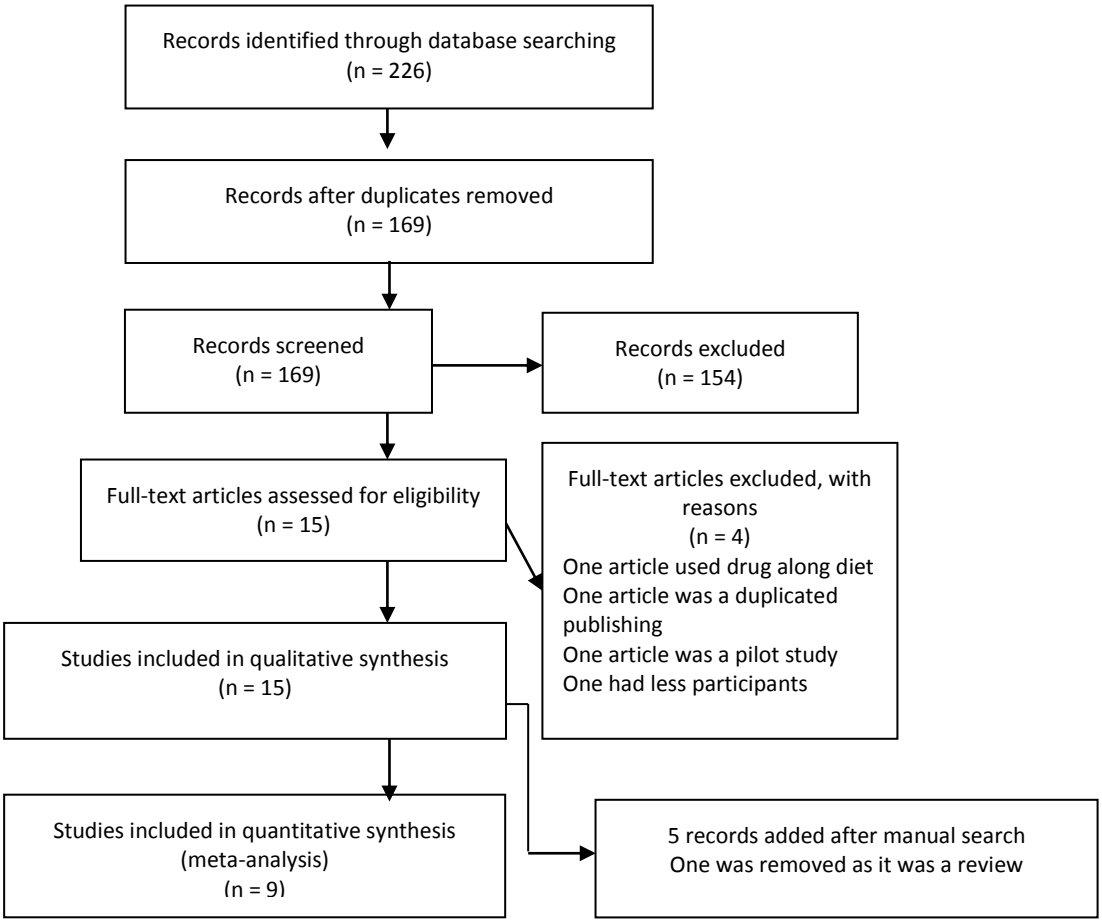


**Figure 1**. PRISMA flow diagram of included studies

**Table 1**. Characteristic of randomized controlled trials that evaluated the effect of the low GI/GL diet on acne severity and were eligible to be included in systematic review.

| First author | Publication year | No of participants | Gender | Design | Study duration (week) | Subjects characteristic | Intervention diet | control diet | Outcome measured |
|---|---|---|---|---|---|---|---|---|---|
| Smith [22] | 2007 | 43 | M | Parallel | 12 | Mild to moderate facial acne | LGL diet CHO: 45% Fat: 30% Pro: 25% CHOs used, was low glycemic | CHO dense diet | Total lesion count |
| Reynolds [21] | 2010 | 43 | M | Parallel | 8 | Healthy adolescents with acne | Low GI diet | High GI diet | Facial acne score |
| Kwon [20] | 2012 | 32 | M/F | Parallel | 10 | Mild to moderate acne | LGL diet CHO: 45% Fat: 30% Pro: 25% CHOs used, was low glycemic | Regular diet CHO-rich foods daily | Inflamma-tory and non-inflamma-tory acne |

M: male; F: female; LGL: Low Glycemic Load; CHO: Carbohydrate; Pro: Protein; GI: Glycemic Index

**Low glycemic load/index diet and acne vulgaris**

Three studies with (randomized clinical trial design) investigated the effect of low glycemic load/index diet on acne *[20-22]*. Kwon et al. *[20]* and Smith et al. *[22]* used glycemic load and Reynolds et al. *[21]* applied the glycemic factors to plan diet for their interventions. Kwon et al. [20] and Smith et al. *[22]* used lesion count but Reynolds et al. *[21]* used acne scoring to show the changes in acne severity. In contrast, Reynolds et al. *[21]* did not see any improvement after consuming low glycemic diet. The quality assessment showed that all included studies were low risk in 3 or more domains out of seven. Therefore, all publications included in the meta-analysis of clinical trials were of high quality regarding the Cochrane collaboration's tool. **Table 3** shows the quality assessment results for the studies with clinical trial design.

**Table 2**. Characteristics of the observational studies over the effect of low GI/GL diet on acne severity included in the systematic review

| First author | Publication year | No. of participants | Gender | Design | Country | Outcome measured | Questionnaire | Study quality |
|---|---|---|---|---|---|---|---|---|
| Adebamowo *[43]* | 2005 | 47355 | F | Nested case-control | US | GL | FFQ | 7 |
| Kaymak *[27]* | 2007 | 91 | M/F | Case - control | Turkey | GI/GL | FFQ | 7 |
| Jung *[26]* | 2010 | 1285 | M/F | Case - control | Korea | GI/GL | Food record | 7 |
| Ismail *[25]* | 2012 | 88 | M/F | Case - control | Malaysia | GL | Food record | 7 |
| Salomone *[38]* | 2012 | 80 | M/F | Analytic study | India | GI | ------ | ----- |
| Aghasi *[44]* | 2013 | 140 | F | Case - control | Iran | GI | FFQ | 6 |
| Burris *[23]* | 2014 | 248 | M/F | Case - control | US | GI | FFQ | 8 |
| Okoro *[46]* | 2016 | 464 | M/F | Case - control | Nigeria | GI | FFQ | 7 |
| Cerman *[24]* | 2016 | 86 | M/F | Case - control | Turkey | GI/GL | Food recall | 7 |
| LaRosa *[28]* | 2016 | 225 | M/F | Case - control | US | GI/GL | Food recall | 8 |
| Burris *[37]* | 2017 | 64 | M/F | Case - control | US | GI/GL | Food record | 8 |

F: female, M: male, GL: Glycemic Load; GI: Glycemic Index; FFQ: Food frequency questionnaire

**Table 3**. Study quality and risk of bias assessment for RCT using Cochrane collaboration tool

| First author (year) | Random Sequence generation | Allocation concealment | Blinding | blinding of outcome assessment | Incomplete outcome data | Selective reporting | Score | Overall quality |
|---|---|---|---|---|---|---|---|---|
| Smith (2007) |  |  |  |  |  |  | 5 | Good |
| Reynolds (2010) |  |  |  |  |  |  | 3 | Good |
| Kwon (2012) |  |  |  |  |  |  | 4 | Good |

Eleven observational studies were found, which were case-control in design *[23-28, 37, 38, 43, 44, 46]*; eight studies were found in database search *[23-28, 37, 38]*, and 3 were found during the manual search *[43, 44, 46]*. Among these studies, four *[23, 38, 44, 46]* used GI to assess the diet, 2 applied GL *[25, 43]*, while 5 studies *[24, 26-28, 37]* assessed both GI and GL. Almost all included publications had high quality (**Table 2** shows the quality scoring). Of all these 11 studies, 5 were not included in the meta-analysis; they were included in the systematic review, because their data were not appropriate to be used in the meta-analysis.

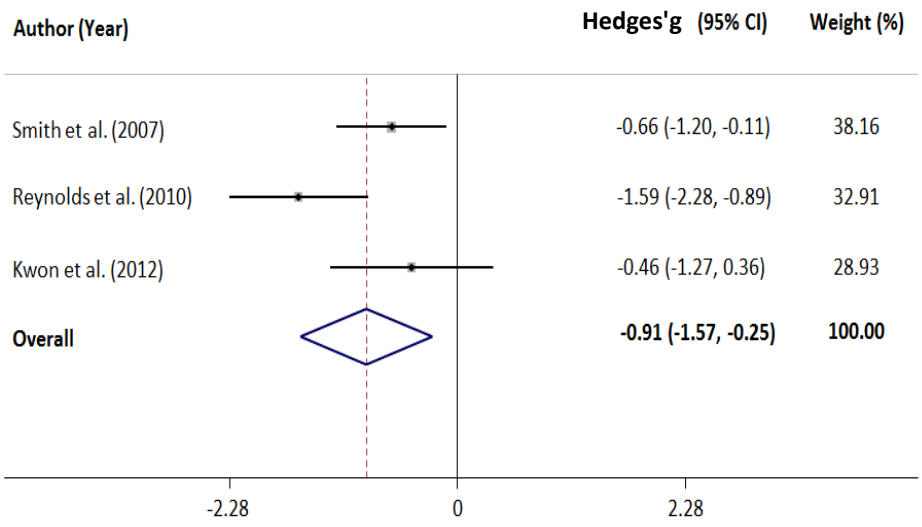


**Figure 2**: Forest plot for the effect of low glycemic diet on the acne severity

**Meta-analysis**

**Randomized controlled clinical trials**

Three studies with 118 participants were included in the meta-analysis. Results indicated that adherence to diet with lower GI/GL decreased the acne severity compared to the control diet (Hedges'g = -0.91, 95%CI:-1.57,-0.25, P = 0.007). The heterogeneity among included studies was moderate (Q statistic = 5.65 Cochrane Q test, P = 0.059, $I^2$ = 64.6%). **Figure 2** shows the meta-analysis of controlled clinical trials.

**Observational studies**

Among 11 eligible studies, 6 studies were included in the meta-analysis. Data for the 5 remaining studies were not available *[26, 38, 43, 44, 46]*. In our meta-analysis, we assessed the observational studies in 2 groups based on the index used to assess the diet (GI or GL).

**GI and Acne**

The meta-analysis of 5 studies *[23, 24, 27, 28, 37]* with 714 participants showed that diet's GI might not be significantly different between participants with acne vulgaris and healthy controls (Hedges'g = 0.07, 95%CI: -0.23, 0.38, P = 0.636). A high heterogeneity was observed between the included studies (Q statistic = 14.61 Cochrane Q test, P = 0.006, $I^2$ = 72.6%). A subgroup analysis based on the diet evaluation method investigated the possible sources of heterogeneity. As a result, we found that three studies *[23, 27, 28]* with 564 individuals used retrospective questionnaires (24 hr. recall, and food frequency questionnaire Hedges'g = 0.01, 95%CI: -0.41, 0.44, P = 0.951). The heterogeneity found among studies was very high (Q statistic = 11.57 Cochrane Q test, P = 0.003, $I^2$ = 82.7%). The meta-analysis of studies that used questionnaires and were not based on the participants' memory (food records) [24, 37] (150 participants) led to the same finding (Hedges'g = 0.18, 95%CI: -0.36, 0.71, P = 0.519). The heterogeneity between studies was not significant (Q statistic = 2.67 Cochrane Q test, P = 0.102, $I^2$ = 62.5%). Moreover, no significant difference was observed between subgroup analysis results (P value = 0.539). **Figure 3** indicates the meta-analysis results for the association between GI and acne severity in observational design.

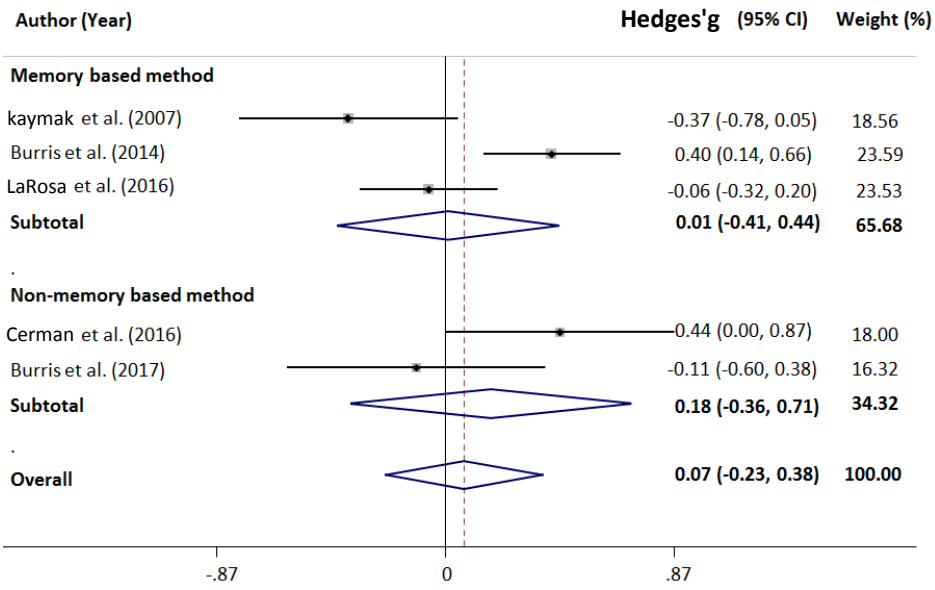


**Figure 3:** Forest plot for the effect of GI on the acne severity

### GL and Acne

In order to find the relationship between GL and AV, 5 studies *[24, 25, 27, 28, 37]* with 554 participants were entered in our meta-analysis. The overall analysis showed that individuals with higher acne severity had higher GL diets (Hedges'g = 0.64, 95%CI: 0.01, 1.26, P = 0.045). The heterogeneity was high in the included studies (Q statistic = 46.50 Cochrane Q test, P < 0.001, $I^2$ = 91.4%). the subgroup analysis showed that GL was not significantly different between those with AV and healthy participants in studies which used retrospective methods to assed diet *[27, 28]* (316 participants) (Hedges'g = -0.03, 95%CI: -0.37, 0.32, P = 0.878). The heterogeneity between studies was not significant (Q statistic = 2.09 Cochrane Q test, P = 0.148, $I^2$ = 52.2%). In contrast, analysis of studies that used food records *[24, 25, 37]* (238 participants) showed that participants with higher acne severity had a higher GL diet compared to the healthy controls (Hedges'g = 1.13, 95%CI: 0.57, 1.68, P < 0.001); however, a high heterogeneity was observed between studies (Q statistic = 7.91 Cochrane Q test, P=0.019, $I^2$ = 74.7%). The between -groups heterogeneity was significant (P value < 0.001). **Figure 4** illustrates the meta-analysis results for the association between GL and acne severity in observational studies.

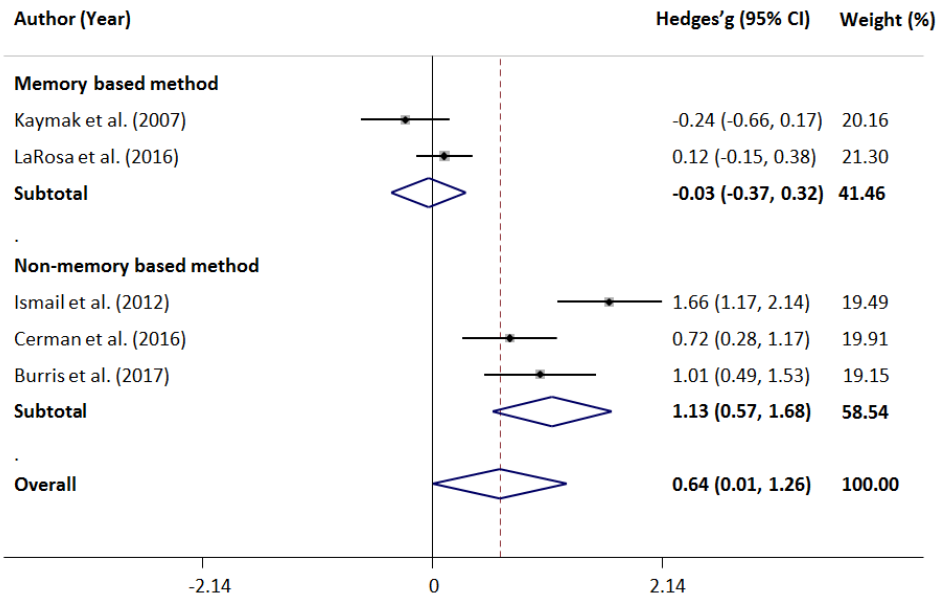


**Figure 4**: Forest plot for the effect of GL on the acne severity

**Publication bias and sensitivity analysis**

The Begg's funnel plot was almost symmetric for the trial studies **Figure 5A**. On the other hand, a slight asymmetry was seen in Begg's funnel plot for studies that investigated the difference in GI **Figure 5B** and GL **Figure 5C** between participants with acne vulgaris and healthy participants, but the results of the asymmetry tests did not show any evidence of publication bias for the meta-analysis regarding the association of GI (Begg's test, P = 0.806, Egger's test, P = 0.630) and GL (Begg's test, P = 0.221, Egger's test, P = 0.226) with acne vulgaris.

Sensitivity analysis showed that omission of the studies from the analysis with regard to the effect of diet's GI or GL on AV severity did not apparently alter the summary effects.

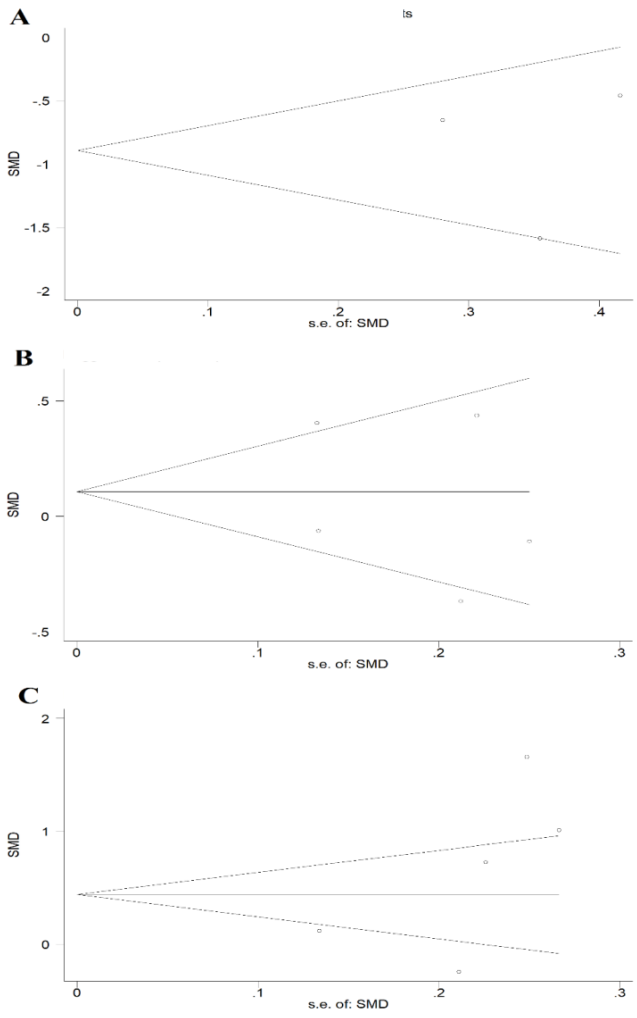


**Figure 5:** Begg's funnel plot for the publication bias, A: Trial studies, B: Studies investigated the GI, and C: studies investigated the GL

## Discussion

The Current systematic review and meta-analysis indicated that consuming a low glycemic diet might decrease the severity of AV. However, the meta-analysis of observational studies suggested that diet's GL could establish a better relationship than GI. In the other words, results showed that healthy participants followed a diet with lower GL compared to the patients suffering from AV.

The trials included in the meta-analysis *[20-22]* also confirmed our findings. Moreover, the same result was seen in a study by Tayel et al. *[47]*. As this study did not use randomization and was a before–after study, we did not include this study in our systematic review and meta-analysis. Tayel et al. reported that concordance with a low GL diet for 12 weeks might alleviate the acne in comparison with the baseline.

Analyses of the observational studies showed a high heterogeneity between studies; therefore, we separated the publications based on the factor used to assess the dietary carbohydrate (GI or GL). The subgroup analysis based on the dietary assessment method (memory based and non-memory based methods) could partly explain the heterogeneity; the meta-analysis showed that a higher GL diet was associated with AV. However, we could not see the same association for GI. The GI assesses the types and quality of food carbohydrates using the presence of fiber, fat protein, or other factors such as food processing method, but GL considers the amount of carbohydrate in diet. Therefore, GL is more useful to assess the effect of food on postprandial glycaemia and insulin demands and level *[48, 49]*. A lower GL diet has a lower amount of glucose, which can decrease subcutaneous glands glycogen concentration; thus, decreases the lipogenesis in these glands *[41]*. According to the results, we can hypothesize that the amount of carbohydrate in the diet may affect severity of AV more than the types of the carbohydrates.

The relationship between GL and AV was clearer in the publications which used non-memory based dietary assessment method (dietary record). Food records, as a non-memory-based method are a better tool for calculating the GL of a diet compared to food recalls, FFQ, or other memory-based diet assessing tools *[50]*. It can be said that recording the diet after each meal *[51]* leads to a better record of the portion size and amount of food, especially when the food is consumed at home and weighted

before and after the meal *[52]*. However, in memory-based tools, such as 24-hour recall *[53]*, the diet is reported after a while; so, the portion size and the amount of food are likely to be forgotten *[54, 55]*. It was observed that reporting energy intake using 24-hour recalls was 16% lower than using food records *[52]*. Thus, non-memory-based tools are better choices to assess GL, which depends on the amount of foods. In a study by Adebamowo et al. *[43]*, results did not show any relationship between higher GL diet and AV severity, but we have to consider that in this study, researchers used FFQ questionnaire, which is a memory based assessing tool. *[56]*.

Previously, some reviews investigated the possible effect of GI/GL on the acne, but they did not systematically review the literature and meta-analysis was not used to achieve a comprehensive conclusion. Berra et al. *[57]* also suggested that life style factors like diet and GI may influence the AV. Romanska-Gocka et al. [58] stated that the same relationship exists between GL and AV severity.

It is proposed that the elevated serum insulin increases Insulin growth factor-1 (IFG-1) and reduces Insulin Growth Factor Binding Protein-3 (IGFBP-3) when high amounts of carbohydrate is consumed *[45]*. It is suggested that IGF-1 has a dual role in the pathogenesis of AV: first, it increases the keratinocyte and sebum production; second, it increases blood androgens by inducing the synthesis. The blood androgens also increase sebum production. The proliferation of keratinocytes and the increased sebum production are associated with aggravating AV; moreover, reduced IGFBP-3 leads to higher binding of IGF-1 to receptors; thus, it increases the effects of IGF-1 *[26]*.

Kwon et al. *[20]* found that consuming low GL diet for 10 weeks, leads to a considerable dwindling in the size of sebaceous glands and reduces the production of SREBP-1 protein, which is the main protein to regulate the synthesis of lipids. Subsequently, the sebum production decreases.

To the best of our knowledge, the present study was the first one which systematically reviewed the existing publications on the relationship between dietary GI/GL and the AV severity. It also used a quantitative method to summarize the effects. A number of limitations exist that should be considered when interpreting our results: the number of existing studies was low and more clinical trials with higher quality are still needed. Furthermore, since life style factors, such as diet are related to acne vulgaris, prospective investigations are highly needed to confirm the association between dietary GI/GL and AV.

Furthermore, the observational studies only provided crude data for comparison of the diet between participants with AV and healthy controls. In conclusion, the present systematic review and meta-analysis suggested that low GI/GL diets might improve AV. Furthermore, it seems that dietary GL might predict AV better than the dietary GI. Future well-designed prospective investigations are still needed to confirm these results.

**Acknowledgments**

The authors thank the research council of the Nutrition and Food Research Center, Shahid Sadoughi University of Medical Sciences, for financial support of this study.

**Authors' contributions**

The authors' cooperation was as follows: MAM and RS developed the study concept and designed the research; electronic searches, study selection, data extraction, data analysis, interpretation of the results, and composition of the first draft of the manuscript were done by both authors. All authors read and approved the final version.

**Funding source**

The study was supported by Nutrition and Food Security research center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

## Conflict of Interest

The authors state that there is no conflict of interests in this study.

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