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ORIGINAL ARTICLE

Association between Homocysteine Levels and Psoriasis: A Meta-Analysis

Jung Eun Kim, Ho Jung Lee, Jong Suk Lee, Kyu Uang Whang[1], Young Lip Park[2], Sung Yul Lee, Hyun Jung Kim[3]

Department of Dermatology, Soonchunhyang University Cheonan Hospital, Cheonan, [1]Department of Dermatology, Soonchunhyang University Seoul Hospital, Seoul, [2]Department of Dermatology, Soonchunhyang University Bucheon Hospital, Bucheon, [3]Department of Preventive Medicine, Korea University College of Medicine, Seoul, Korea

Background: Psoriasis is a multifactorial disease associated with an increased risk for metabolic syndrome and cardiovascular diseases. Elevated levels of homocysteine (Hcy) are a marker of cardiovascular risk. Several studies have evaluated the associations between psoriasis and Hcy levels; however, the results remain inconclusive. **Objective:** We performed a systematic review of the literature and a meta-analysis to better understand the relationship between psoriasis and Hcy. **Methods:** Five scientific databases (MEDLINE, Embase, Cochrane Library, Scopus, and Web of Science) were searched to identify relevant studies. A review of 307 publications identified 16 studies that directly assessed plasma levels of Hcy in psoriasis patients. **Results:** A total of 16 studies including 2,091 subjects were included in the meta-analysis. Hcy levels were significantly higher in psoriasis patients relative to healthy controls (weighted mean difference [WMD], 3.30; 95% confidence interval [CI], 1.58～5.02; I^2=82.1%). Subgroup analyses revealed that patients with higher mean psoriasis area severity index (PASI) scores (PASI＞10) had significantly higher Hcy levels compared to healthy controls (WMD, 4.17; 95% CI, 1.18～7.16; I^2=88.3%), whereas patients with lower mean PASI scores (PASI ≤10) had not (WMD, 0.76; 95% CI, −1.84～3.35; I^2=72.2%). **Conclusion:** This meta-analysis found that psoriasis patients, in particular those with PASI ＞10, had significantly higher Hcy levels compared to healthy controls. Further research is needed to determine the association between Hcy levels and psoriasis severity. **(Ann Dermatol 31(4) 378～386, 2019)**

-Keywords-
Homocysteine, Meta-analysis, Psoriasis

INTRODUCTION

Psoriasis is a common chronic inflammatory disease of the skin affecting 2% to 3% of the general population, with varying prevalence among different ethnic groups[1]. The characteristic skin lesion is a sharply demarcated erythematous scaly plaque, with evidence of abnormal epidermal thickening and inflammatory cell infiltrates, predominated by T lymphocytes. Recent advances in immunology and genetics have significantly altered our understanding of the disease, with many now regarding psoriasis as a systemic inflammatory disease, as opposed to a localized skin condition. Although psoriasis primarily manifests at the skin, recent studies have identified several serious comorbidities associated with this disease, including atherosclerosis, chronic ischemic heart disease, diabetes mellitus, and metabolic syndrome[2,3]. As understanding of the pathogenesis of psoriasis has evolved, dysregulation of the im-

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Corresponding author: Sung Yul Lee, Department of Dermatology, Soonchunhyang University Cheonan Hospital, 31 Suncheonhyang 6-gil, Dongnam-gu, Cheonan 31151, Korea. Tel: 82-41-570-2270, Fax: 82-41-570-2271, E-mail: dermsung@schmc.ac.kr
ORCID: https://orcid.org/0000-0002-6995-4561

Hyun Jung Kim, Department of Preventive Medicine, Korea University College of Medicine, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Korea. Tel: 82-2-2286-1351, Fax: 82-2-927-7220, E-mail: moole02@naver.com
ORCID: https://orcid.org/0000-0003-2018-2385

mune system in disease pathology has taken center stage, characterized by systemic inflammatory processes resulting from the release of inflammatory cytokines, including tumor necrosis factor-α, interleukin (IL)-17, and IL-22[4]. As these inflammation processes also play an important role in the pathogenesis of other diseases including atherosclerosis, cardiovascular diseases (CVDs), and metabolic syndrome, it is not surprising that many of these conditions are more common in psoriatic patients than in the general population[5]. Moreover, cardiovascular risk factors including diabetes, hypertension, hyperlipidemia, and obesity have been revealed to be more strongly associated with severe psoriasis than with mild psoriasis[1,6,7]. Accordingly, recent studies have sought to assess systemic inflammation in psoriasis using inflammatory biomarkers to measure psoriasis disease severity and to explain its comorbidities[8,9].

Homocysteine (Hcy) is a sulfur-containing amino acid that is generated as a result of the metabolism of methionine. The metabolism of Hcy occurs through two biochemical pathways; remethylation to methionine or conversion to cysteine via coenzymes such as vitamin B6, vitamin B12 and folic acid[10,11].

The plasma Hcy level can be influenced by genetic factors, nutrition, chronic diseases and drugs. It was reported that hyperhomocysteinemia, an elevated plasma total Hcy concentration (the normal range is 5 to 15 μmol/L) is related to the occurrence and development of many diseases, for example, atherosclerotic CVDs, stroke, peripheral arterial occlusive disease, and venous thrombosis[12,13], although the underlying mechanisms responsible for these associations are only partially understood. Among the prevailing theories, a leading hypothesis is that Hcy can increase oxidative stress, resulting in increased endothelial dysfunction[5,14].

Several studies reported that patients with psoriasis have elevated levels of Hcy in the plasma in combination with lower levels of folate[15-18]. However, the correlation between Hcy levels and the severity of psoriasis remains controversial, with some studies having demonstrated a direct proportional relationship between them. Additional correlations have also been seen between Hcy levels and psoriasis duration[10,13,14]. To address this apparent divergence among published studies, we performed a systematic review of the literature and a meta-analysis to assess plasma levels of Hcy in patients with psoriasis, and their relationship to disease severity. We compared Hcy levels between psoriasis patients and controls, and tried to evaluate the correlation between Hcy levels and severity of psoriasis.

MATERIALS AND METHODS

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Supplementary Table 1)[19].

Search strategy

A systematic search of the literature was performed using five major scientific databases (MEDLINE, Embase, Cochrane Library, Scopus, and Web of Science) up to June 2017 to assess the potential association between Hcy levels and psoriasis. The search was not restricted based on language or publication year. The following keywords and medical subject headings were used for the MEDLINE search: "psoriasis" and "homocysteine." Search strategies for the other databases were developed based on the MEDLINE strategy (Supplementary Table 2). In addition to the initial electronic search, a manual search for additional relevant publications was also performed.

Study selection

Two reviewers independently assessed the eligible of each study for this meta-analysis using the inclusion and exclusion criteria. The study inclusion criteria consisted of the following: 1) studies evaluating the association between plasma levels of Hcy and psoriasis; 2) Hcy levels of psoriasis were presented as means with either standard deviations or standard errors; and 3) availability of a full-text article. Study exclusion criteria consisted of the following: 1) reviews and case reports with fewer than 10 subjects; and 2) studies without control groups. Final 16 studies [5,12,13,15-17,20-29] were selected for further analysis.

Data extraction

Two reviewers independently extracted data from the 16 studies using a predefined data extraction form. Disagreements over data extraction were resolved by consensus. The following variables were assessed for each study: authors, year of publication, demographic characteristics of the study population (country, age, sex, and number), inclusion criteria for psoriasis, the plasma levels of Hcy in both the case and control groups, and psoriasis area severity index (PASI) score.

Statistical analyses

Hcy levels were compared using weighted mean differences (WMDs) and 95% confidence interval (CI) and are presented as μmol/L. Heterogeneity was assessed using the I^2 static, which indicates the proportion of variation across trials attributable to heterogeneity, rather than sampling error. I^2 values $>50\%$ and p-values from the χ^2 test

<0.10 were considered indicative of significant heterogeneity among the included studies. If substantial statistical heterogeneity was noted ($I^2>50\%$), a more detailed assessment of individual study characteristics and subgroups was planned to better understand the main body of evidence. The results were presented in a forest plot. In addition, potential publication bias was assessed by funnel plot and Egger test. Moreover, we also performed "trim and fill" analysis to further assess the possible influence of unpublished studies on the results of our meta-analysis. All calculations were performed using Stata MP version 13.0 (STATA Corp., College Station, TX, USA) and a *p*-value less than 0.05 indicated a significant difference. This study is based on Cochrane Review Methods.

Quality assessment and sensitivity analysis

The quality assessment was performed independently by two reviewer, using the Quality In Prognosis Studies (QUIPS) tool to assess the methodological quality of included studies[30]. The following six domains were assessed and recorded in all included studies: study participation; study attrition; prognostic factor measurement; outcome measurement; study confounding; and statistical analysis and reporting. Risk of bias in each of these six domains was categorized as 'low', 'moderate', or 'high'. We considered "study confounding" as an important bias domain in this study and thus, sensitivity analyses was done by the "study confounding" bias domain status.

RESULTS

Identification of studies

The database search yielded 484 articles. After excluding duplicates and studies that are not eligible according to inclusion and exclusion criteria, 23 articles remained. Of those, seven studies were excluded after detailed assessment of the full text because they did not provide sufficient data (Fig. 1). The last remaining 16 studies were included in the meta-analysis.

Study characteristics and patients

All sixteen studies finally included for the meta-analysis were cross-sectional observational studies. Sixteen studies were comprised of a total of 2,091 participants, which included 1,172 patients with psoriasis and 919 healthy or hospital-based patients with other mild skin diseases. The sample sizes ranged from 13 to 200 psoriasis patients. All studies assessed and defined psoriasis using specific tools or by measuring clinical findings. With the exception of fives studies[13,15,17,21,29], all used the PASI scoring system to evaluate psoriasis severity. The range of the mean Hcy levels was 11 to 24.73 μmol/L in psoriasis patients and 9.99 to 17.3 μmol/L in controls. Of the 16 included studies, 8 were carried out in Turkey, 4 in Italy, 2 in Spain, 1 in Norway, and 1 in Malaysia. The main characteristics of the studies are shown in Table 1[5,12,13,15-17,20-29].

Plasma levels of homocysteine and psoriasis

This meta-analysis demonstrated that Hcy levels were significantly higher in psoriasis patients relative to controls (WMD, 3.30; 95% CI, 1.58~5.02; $I^2=82.1\%$; Fig. 2A)[5,12,13,15-17,20-28]. Subgroup analyses showed that patients with higher mean PASI scores (PASI>10) had significantly higher Hcy levels compared to healthy controls (WMD, 4.17; 95% CI, 1.18~7.16; $I^2=88.3\%$), whereas patients with lower mean PASI scores (PASI≤10) had not (WMD, 0.76; 95% CI, −1.84~3.35; $I^2=72.2\%$; Fig. 2B)[5,12,16,20,22-28]. In addition, there were two studies[12,29] which individually

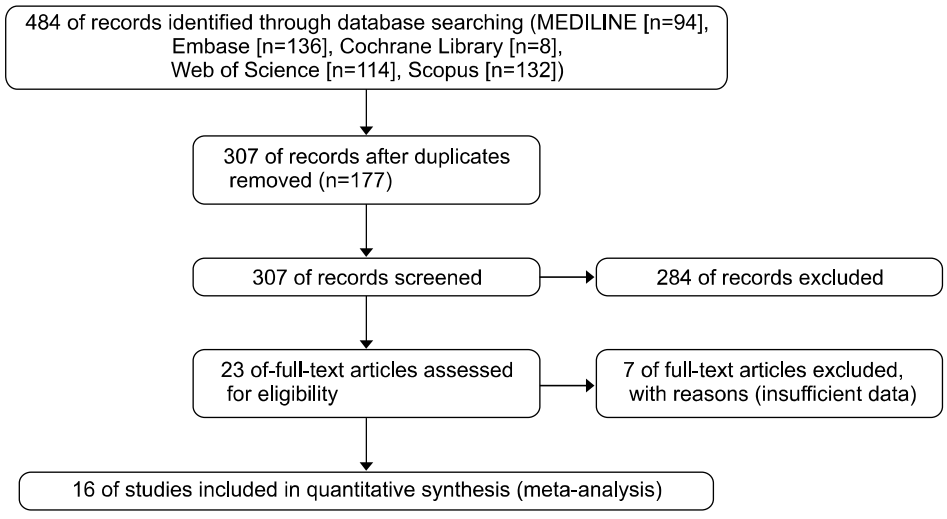

Fig. 1. Flow diagram of study identification, inclusion, and exclusion.

Table 1. Characteristics of the 16 studies included in the final analysis

Study	No. of patient		Age (yr)	PASI score	Plasma homocysteine level	
	Psoriasis group (n=1,172)	Control group (n=919)			Psoriasis group (n=1,172)	Control group (n=919)
Akcali et al., 2014[26]	50	40	≥18	20.32±5.9	13.64±7.97	13.8±9.77
Ataseven et al., 2014[27]	56	33	≥18	8.3±6.5	13.55±8.3	16.04±9.3
Bilgiç et al., 2015[28]	42	48	≥18	10.64±6.77	24.73±12.96	17.3±7.65
Brazzelli et al., 2010[12]	98	98	-	19.51±16.26	19.6±15.1	13.7±5.56
Cakmak et al., 2009[21]	70	70	18~60	-	16.76±16.62	12.86±6.45
Curcó et al., 2018[29]	178	-	≥20	-	11±12	-
Dogan and Atakan, 2010[22]	45	45	-	22.44±9.28	12.64±5.54	9.99±2.88
Erturan et al., 2014[5]	56	53	≥18	6.65±6.7	14.33±7.61	14.96±8.81
Giannoni et al., 2015[13]	52	24	-	-	19.71±11.16	13.9±11.2
Gisondi et al., 2010[23]	172	198	≥18	10.3±9.3	16.3±12.7	10.3±4.6
Karabudak et al., 2008[20]	20	20	-	13±7	21±8	11±2
Vanizor Kural et al., 2003[16]	30	30	-	5.52±3.63	15.91±6.18	11.36±4.46
Liew et al., 2012[24]	200	167	-	8.92±7.64	15.67±4.37	14.89±3.69
Malerba et al., 2006[15]	40	30	≥18	-	16±5.6	10.4±4.7
Refsum et al., 1989[17]	13	13	-	-	14.4±4.8	10.8±2.9
Romaní et al., 2012[25]	50	50	≥18	15.6±5.4	12.1±5.1	13.7±5.4

Values are presented as number only or mean±standard deviation. PASI: psoriasis area severity index, -: data not collected.

recorded Hcy levels in two groups of patients which was divided based on psoriasis severity; mild psoriasis and moderate-severe psoriasis. One study considered a moderate-severe psoriasis as a PASI score of 10 or more[12]. The other study defined it when PASI >10 and/or body surface area >10 or systemic treatment of psoriasis were performed[29]. Meta-analysis of these two studies showed that patients with moderate-severe psoriasis had significantly higher Hcy levels compared to that of patients with mild disease (WMD, 4.50; 95% CI, 1.30~7.70; I^2=0.0%; Fig. 2C)[12,29]. The characteristics of these two studies are shown in Table 2[12,29].

Quality assessment

The six QUIPS domains with risk of bias for each of the 16 included studies are shown in Table 3[5,12,13,15-17,20-29]. "Study confounding" was thought to be the most important bias domain in this study. As for this domain, six studies were considered at low risk of bias, three studies at moderate risk of bias, and seven studies at high risk of bias.

Sensitivity analysis

We conducted sensitivity analysis among studies showing low risk of bias at "study confounding" QUIPS domain. We individually analyzed studies according to the mean PASI score, thus we excluded one study[15] not presenting mean PASI score. The sensitivity analysis outcomes are shown in Fig. 3[5,20,24,27,28]. Sensitivity analysis outcomes of two studies with higher mean PASI scores (PASI>10) had significantly higher Hcy levels (WMD, 8.99; 95% CI, 6.17~11.80; I^2=0%; Fig. 3). However, three studies with lower PASI scores (PASI<10) havent' shown significantly higher Hcy levels.

Publication bias

Although visual inspection of the funnel plot suggested some asymmetry (Fig. 4), the result of Egger test did not reveal any significant publication bias (p=0.37). Additional trim and fill analysis indicated that two more studies would be required to produce a symmetrical funnel plot. However, even after adjustment of effect size for potential publication bias, the corrected analysis continued to show a statistically higher serum Hcy levels in psoriasis patients relative to healthy controls (WMD, 2.56; 95% CI, 0.79~4.33). Thus, these results indicate there might be a publication bias, but it is unlikely that publication bias poses a significant threat to the current meta-analysis.

DISCUSSION

The results of our meta-analysis demonstrated that patients with psoriasis had higher plasma levels of Hcy than healthy controls, which was significant only in studies with high PASI scores. So far, several studies have examined Hcy levels in psoriasis patients, with most observing hyperhomocysteinemia in these patients. However, the role of Hcy in the pathophysiology of psoriasis and the exact mechanism causing hyperhomocysteinemia in psoriasis

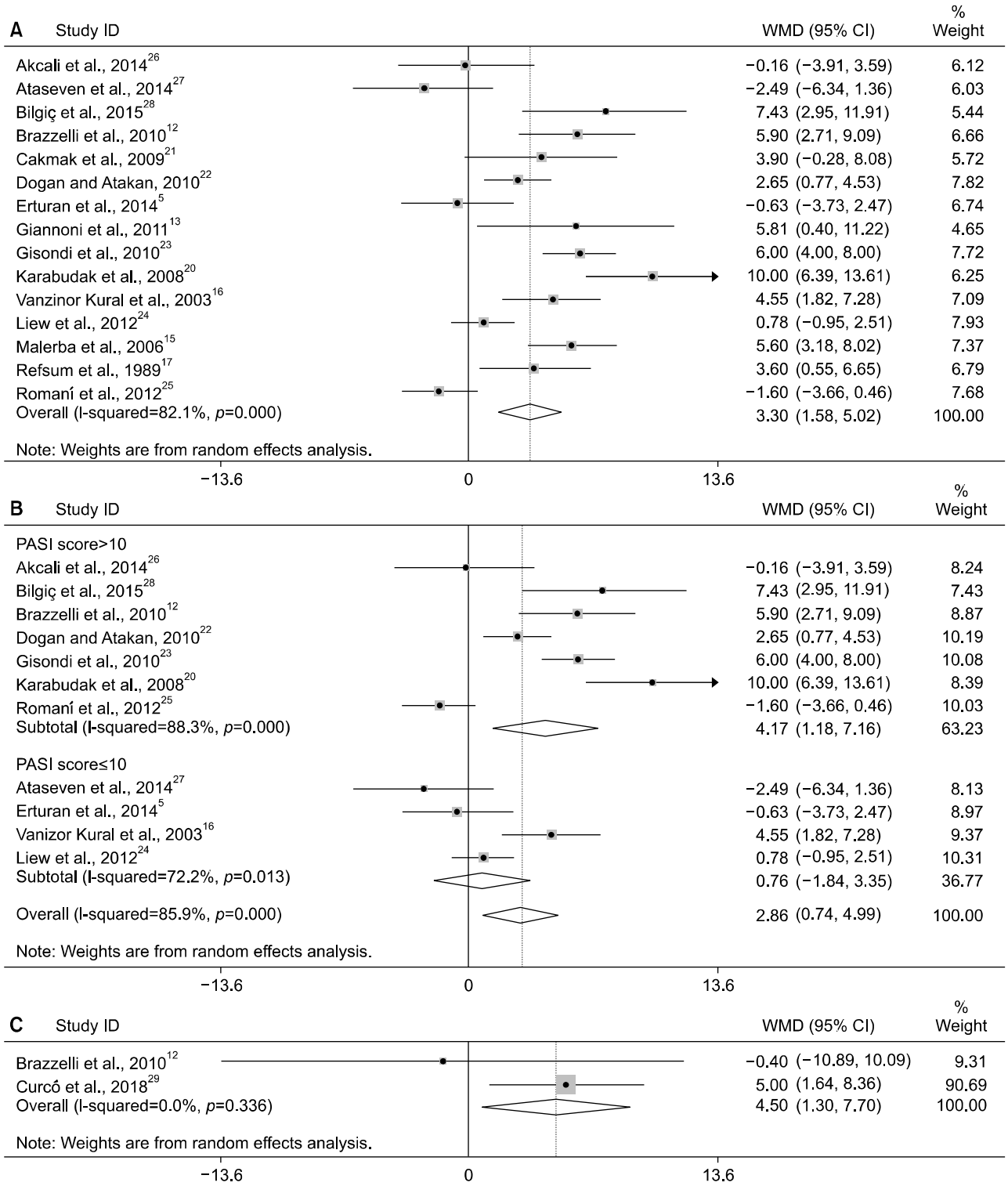

Fig. 2. Forest plot of the meta-analysis for homocysteine levels. (A) Homocysteine levels in psoriasis patients and controls. (B) Subgroup analysis according to mean psoriasis area severity index (PASI) scores. (C) Meta-analysis of two studies which directly compared homocysteine levels according to psoriasis severity within studies. WMD: weighted mean difference, CI: confidence interval.

has not been fully established.

Psoriasis is a chronic inflammatory skin disease with complex pathophysiology. The inflammatory reactions in psoriasis may be associated with increased reactive oxygen species. Oxidative stress, an imbalance between oxidants and antioxidants, can disrupt redox signaling and lead mo-

Table 2. Characteristics of the 2 studies separately evaluated homocysteine (Hcy) levels based on psoriasis severity

Study	No. of patient		Plasma Hcy level	
	Mild psoriasis (n=115)	Moderate-severe psoriasis (n=161)	Mild psoriasis (n=115)	Moderate-severe psoriasis (n=161)
Brazzelli et al., 2010[12]	16	82	19.9±20.5	19.5±13.9
Curcó et al., 2018[29]	99	79	9±3	14±18

Values are presented as number only or mean±standard deviation.

Table 3. Quality assessment of included studies (risk of bias in six different domains according to the Quality In Prognosis Studies [QUIPS] tool [Hayden et al, 2013[30]])

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis
Akcali et al., 2014[26]	Low	Low	Low	Low	High	Low
Ataseven et al., 2014[27]	Low	Low	Low	Low	Low	Low
Bilgiç et al., 2015[28]	Low	Low	Low	Low	Low	Low
Brazzelli et al., 2010[12]	Low	Low	Low	Low	Moderate	Low
Cakmak et al., 2009[21]	Low	Low	Low	Low	Moderate	Low
Curcó et al., 2018[29]	Low	Low	Low	Low	High	Low
Dogan and Atakan, 2010[22]	Low	Low	Low	Low	High	Low
Erturan et al., 2014[5]	Low	Low	Low	Low	Low	Low
Giannoni et al., 2015[13]	Low	Low	Low	Low	High	Low
Gisondi et al., 2010[23]	Low	Low	Low	Low	Moderate	Low
Karabudak et al., 2008[20]	Low	Low	Low	Low	Low	Low
Vanizor Kural et al., 2003[16]	Low	Low	Low	Low	High	Low
Liew et al., 2012[24]	Low	Low	Low	Low	Low	Low
Malerba et al., 2006[15]	Low	Low	Low	Low	Low	Low
Refsum et al., 1989[17]	Low	Low	Low	Low	High	Low
Romaní et al., 2012[25]	Low	Low	Low	Low	High	Low

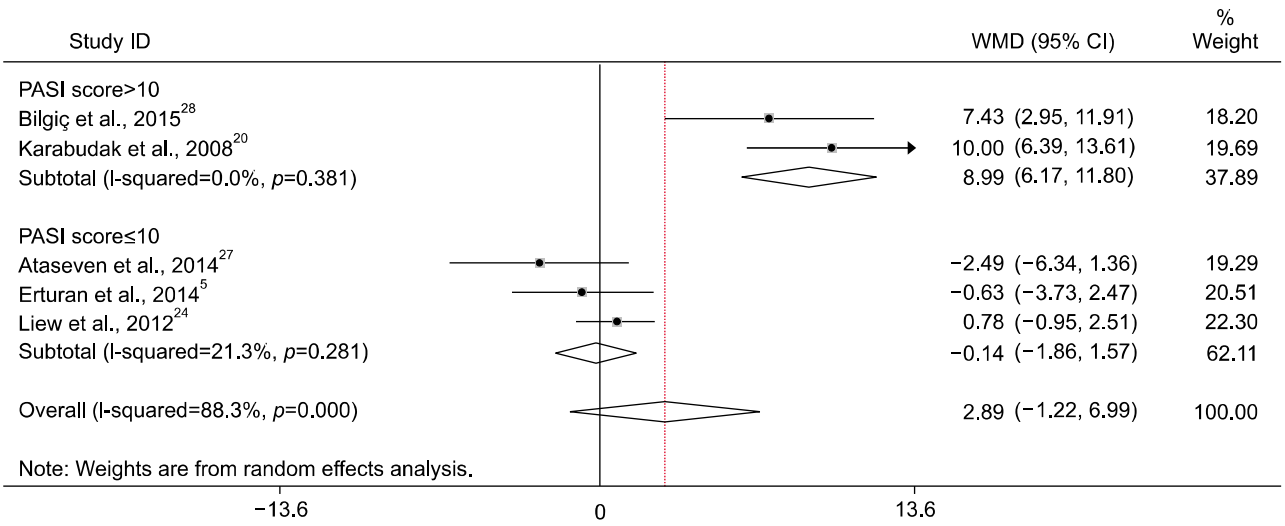

Fig. 3. Forest plot of the meta-analysis for sensitivity analysis. PASI: psoriasis area severity index, WMD: weighted mean difference, CI: confidence interval.

lecular damage. This also impacts dendritic cells, T lymphocytes, keratinocytes, angiogenesis, and inflammatory signaling[31]. Hcy has a highly reactive sulfhydryl group, which easily self-oxidizes. More than 98% of Hcy is in oxidized state. Hcy acts as a pro-oxidant and has been implicated in decreased antioxidant capacity in patients with

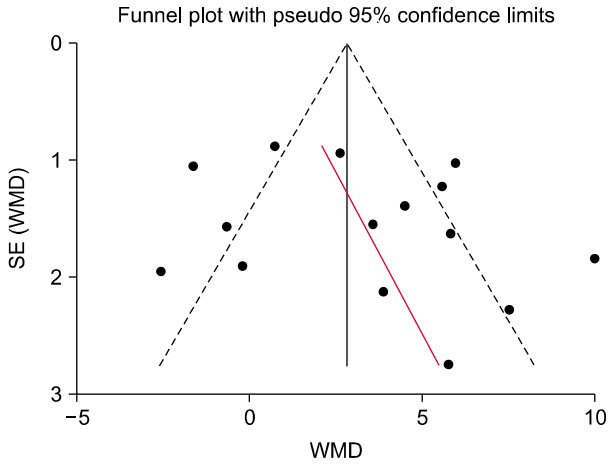

Fig. 4. Funnel plot of included studies. SE: standard error, WMD: weighted mean difference.

inflammatory bowel disease[10,32,33]. In addition, there is a close relationship between CVD and oxidative stress[32].

Patients with psoriasis have an increased prevalence of CVD compared to the general population[34]. This was originally reported by McDonald and Calabresi[35], who found that patients with psoriasis had almost twice the incidence of cardiovascular or cerebrovascular disease. Since then, several epidemiological studies have provided evidence supporting the link between psoriasis and CVD[36-38] and showing increased prevalence of coronary artery calcification in psoriasis patients[39]. Possible factors underlying the increased risk for CVD in psoriasis patients include hypertension, smoking, excess alcohol intake, dyslipidemia, diabetes mellitus, hyperhomocysteinemia, and inflammation[40]. Elevated levels of Hcy are an independent risk factor for the development of CVD[41]. Hyperhomocysteinemia (>15 μmol/L) is associated with increased aortic stiffness, a parameter of the stiffness of central arteries indicative of endothelial dysfunction[42]. In a multicenter European study, Hcy levels >12 μmol/L were shown to double the risk for CVD, independent of conventional risk factors. The magnitude of the risk for CVD was equivalent to that of smoking or hyperlipidemia[41]. Hcy is believed to cause endothelial dysfunction by causing accumulation of asymmetrical dimethyl arginine, a natural inhibitor of nitric oxide synthase. This results in reduction of the vasodilator nitric oxide which helps protect vessel walls against vascular pathologies, such as atherosclerosis and thrombosis[18].

Keratinocyte turnover may be accelerated in patients with psoriasis, and folate, used to methylate DNA in actively dividing cells, may be consumed, leading to higher levels of Hcy[43-45]. Psoriasis patients often present with low levels of folic acid as a result of increased vitamin utilization in the skin and/or reduced gut absorption[15,18]. As dietary nutrients such as folic acid, vitamin B6, and vitamin B12 are all involved in Hcy metabolism in the blood, supplementation with these compounds is recommended in psoriasis patients[14].

In our meta-analysis, Hcy levels were significantly higher in psoriasis patients than in healthy controls. Furthermore, subgroup and sensitivity analyses revealed that patients with psoriasis showed significantly higher Hcy levels compared with controls only in studies with high mean PASI score (PASI>10). In addition, meta-analysis of two studies[12,29] which separately evaluated Hcy levels based on psoriasis severity showed that patients with moderate-severe psoriasis had significantly higher Hcy levels compared to those with mild psoriasis.

This study had several limitations that should be considered. First, all studies included in this meta-analysis were retrospective studies, and did not include blinding or randomization, which may have resulted in bias. Second, although Egger's test showed no evidence of significant publication bias, but possible publication bias was still existed in our meta-analysis. There could be unpublished negative studies or incomplete raw data which might influence the results. Third, the geographic regions were limited to Turkey, Italy, Malaysia, Norway, and Spain, and thus our results may not be indicative of other populations. Fourth, the sample size was small and there was heterogeneity existed in the eligible studies. Lastly, plasma levels of Hcy can be influenced by a variety of other factors including age, sex, and systemic disease, which was not controlled for in all studies. And also the positive associations of psoriasis and serum Hcy level which was shown in this study may not be due to psoriasis itself and may be due to CVDs that can concurrently occur in psoriasis. Additional well-designed longitudinal epidemiological studies with larger sample sizes representing a more diverse patient population are required. Such studies may be used to determine whether serum levels of Hcy can be used as a predictive and prognostic marker for disease severity in psoriasis patients.

Although our study confirmed elevated levels of Hcy are significantly associated with psoriasis, particularly in patients with a mean PASI score greater than 10, the pathophysiological connections are complex and remain unclear. It is likely that these changes involve mechanisms that underlie chronic inflammatory conditions of psoriasis including inflammatory cytokines, and metabolic, immune, and endocrine changes. Also, higher plasma levels of Hcy are likely an important factor underpinning increased cardiovascular comorbidities in patients with psoriasis. Future studies are needed to investigate the pathogenetic mechanisms of Hcy on psoriasis and association between Hcy

levels and psoriasis severity.

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SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad-31-378-s001.pdf.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

ORCID

Jung Eun Kim, https://orcid.org/0000-0002-8399-8456
Ho Jung Lee, https://orcid.org/0000-0001-9674-6429
Jong Suk Lee, https://orcid.org/0000-0002-6554-7598
Kyu Uang Whang, https://orcid.org/0000-0002-5483-8410
Young Lip Park, https://orcid.org/0000-0002-6532-3156
Sung Yul Lee, https://orcid.org/0000-0002-6995-4561
Hyun Jung Kim, https://orcid.org/0000-0003-2018-2385

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Supplementary Table 1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	#1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	#2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	#3, #4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	#4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	#4, #5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	#4, #5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	#4, #5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	#5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	#5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	#5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	#6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	#5, #6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	#5, #6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	#6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	#5, #6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	#6, #7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	#7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	#8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	#7, #8, #9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	#7, #8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	#9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	#7, #8

Supplementary Table 1. Continued

Section/topic	#	Checklist item	Reported on page #
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	#9, #10, #11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	#11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	#9, #10, #11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	#11, #12

Supplementary Table 2. Search strategy on MEDLINE, EMBASE, Cochrane Library, SCOPUS, and Web of Science

MEDLINE

1. Psoriasis[TIAB] OR Psoriases[TIAB] 33437
2. "Psoriasis"[MeSH] 34085
3. 1 OR 2 42937
4. "Homocysteine"[Mesh] OR "Methylenetetrahydrofolate Reductase (NADPH2)"[Mesh] 17989
5. Homocysteine[TIAB] OR "2-amino-4-mercaptobutyric acid"[TIAB] OR "2 amino 4 mercaptobutyric acid"[TIAB] OR "NADPH"[TIAB] OR "Methylene-THF Reductase"[TIAB] OR "Methylenetetrahydrofolate Reductase"[TIAB] OR "5,10-Methylenetetrahydrofolate Reductase"[TIAB] OR "Methylene Tetrahydrofolate Reductase"[TIAB] OR "MTHFR"[TIAB] 62740
6. Hyperhomocysteinemia"[Mesh] 5422
7. Hyperhomocysteinemia[TIAB] OR Hyperhomocysteinemias[TIAB] 4880
8. 4-7/OR 68231
9. 3 AND 8 94

Embase

1. Psoriasis:ab,ti OR Psoriases:ab,ti 48390
2. 'psoriasis'/exp 72500
3. 1 OR 2 76613
4. 'homocysteine'/exp OR 'methylenetetrahydrofolate reductase (nadph2)'/exp OR 'hyperhomocysteinemia'/exp OR '5,10 methylenetetrahydrofolate reductase (fadh2)'/exp 34795
5. homocysteine:ab,ti OR '2-amino-4-mercaptobutyric acid':ab,ti OR '2 amino 4 mercaptobutyric acid':ab,ti OR 'nadph':ab,ti OR 'methylene-thf reductase':ab,ti OR 'methylenetetrahydrofolate reductase':ab,ti OR '5,10-methylenetetrahydrofolate reductase':ab,ti OR 'methylene tetrahydrofolate reductase':ab,ti OR 'mthfr':ab,ti OR hyperhomocysteinemia:ab,ti OR hyperhomocysteinemias:ab,ti 77357
6. 4 OR 5 85693
7. 3 AND 6 226
8. 7 NOT ('animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'in vitro study'/de OR 'nonhuman'/de) 184
1. 9. 8 NOT ('conference review'/it OR 'review'/it) 136

Cochrane Library

1. Psoriasis OR Psoriases :ti,ab,kw 4487
2. MeSH descriptor: [Psoriasis] explode all trees 2192
3. 1 OR 2 4621
4. MeSH descriptor: [Homocysteine] explode all trees 97
5. MeSH descriptor: [Methylenetetrahydrofolate Reductase (NADPH2)] explode all trees 174
6. Homocysteine OR "2-amino-4-mercaptobutyric acid" OR "2 amino 4 mercaptobutyric acid" OR "NADPH" OR "Methylene-THF Reductase" OR "Methylenetetrahydrofolate Reductase" OR "5,10-Methylenetetrahydrofolate Reductase" OR "Methylene Tetrahydrofolate Reductase" OR "MTHFR":ti,ab,kw 2272
7. Hyperhomocysteinemia OR Hyperhomocysteinemias:ti,ab,kw 459
8. 4-7/OR 2333
9. 3 AND 8 8
10. 9/TRIALS 8

Scopus

1. TITLE-ABS-KEY (psoriasis OR psoriases) 60233
2. INDEXTERMS (Psoriasis) 50891
3. 1 OR 2 60233
4. INDEXTERMS(Homocysteine) OR INDEXTERMS(Methylenetetrahydrofolate Reductase) OR INDEXTERMS(Hyperhomocysteinemia) 31448
5. TITLE-ABS-KEY (homocysteine OR "2-amino-4-mercaptobutyric acid" OR "2 amino 4 mercaptobutyric acid" OR nadph) OR TITLE-ABS-KEY ("Methylene-THF Reductase" OR "Methylenetetrahydrofolate Reductase" OR "5,10-Methylenetetrahydrofolate Reductase") OR TITLE-ABS-KEY ("Methylene Tetrahydrofolate Reductase" OR "MTHFR" OR hyperhomocysteinemia OR hyperhomocysteinemias) 96561
6. 4 OR 5 96584
7. 3 AND 6 190
8. 7 AND (EXCLUDE (DOCTYPE, "re")) 132

Supplementary Table 2. Continued

Web of Science
1. TOPIC: (Psoriasis OR Psoriases) OR TITLE: (Psoriasis OR Psoriases) 39566
2. TOPIC: (Homocysteine OR "2-amino-4-mercaptobutyric acid" OR "2 amino 4 mercaptobutyric acid" OR "NADPH" OR "Methylene-THF Reductase" OR "Methylenetetrahydrofolate Reductase" OR "5,10-Methylenetetrahydrofolate Reductase" OR "Methylene Tetrahydrofolate Reductase" OR MTHFR OR Hyperhomocysteinemia OR Hyperhomocysteinemias) OR TITLE: (Homocysteine OR "2-amino-4-mercaptobutyric acid" OR "2 amino 4 mercaptobutyric acid" OR "NADPH" OR "Methylene-THF Reductase" OR "Methylenetetrahydrofolate Reductase" OR "5,10-Methylenetetrahydrofolate Reductase" OR "Methylene Tetrahydrofolate Reductase" OR MTHFR OR Hyperhomocysteinemia OR Hyperhomocysteinemias) 79105
3. 1 AND 2 114