ORIGINAL ARTICLE

Association between rosacea and cardiometabolic disease: A systematic review and meta-analysis

Qi Chen, MD,[a,b,c] Xiao Shi, MD,[d] Yan Tang, MD, PhD,[a,b,c] Ben Wang, MD, PhD,[a,b,c] Hong-fu Xie, MD, PhD,[a,b,c] Wei Shi, MD, PhD,[a,b,c] and Ji Li, MD, PhD[a,b,c]
Changsha, China

Background: Rosacea is recognized as a chronic inflammatory cutaneous disorder associated with multiple systemic illnesses. However, the association between rosacea and cardiometabolic disease (CMD) remains controversial.

Objective: To evaluate the association between rosacea and CMD by a systematic review and meta-analysis.

Methods: A comprehensive search of studies published before October 16, 2019, was performed in databases of PubMed, Embase, Cochrane Library, and Web of Science. The pooled risk ratios or standardized mean differences were calculated.

Results: Thirteen studies were included, representing 50,442 patients with rosacea. Patients with rosacea had higher prevalence of dyslipidemia, higher prevalence of hypertension, higher total cholesterol, higher low-density lipoprotein, higher triglycerides, higher systolic blood pressure, higher diastolic blood pressure, and higher fasting blood glucose. Rosacea was not associated with ischemic heart disease, stroke, diabetes, and high-density lipoprotein.

Limitations: No subgroup analysis could be performed according to the subtypes and severity of rosacea.

Conclusions: Rosacea showed a correlation with hypertension and dyslipidemia but not with ischemic heart disease, stroke, or diabetes. We advocate screening for CMD indicators among patients with rosacea, which may be helpful for diagnosis and appropriate treatment at an early stage of disease. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2020.04.113.)

Key words: cardiometabolic disease; cardiovascular disease; diabetes; dyslipidemia; hypertension; meta-analysis; rosacea.

Rosacea is recognized as a chronic inflammatory cutaneous disorder mainly affecting the centrofacial region.[1-3] Rosacea usually occurs in people aged 20 to 50 years.[4] The exact pathogenesis of rosacea remains poorly understood. However, substantial evidence supports the involvement of immune dysregulation, genetic factors, neurovascular dysregulation, micro-organisms, and

From the Department of Dermatology, Xiangya Hospital, Central South University[a]; National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University[b]; Key Laboratory of Organ Injury, Aging and Regenerative Medicine of Hunan Province[c]; and Department of Gastroenterology, The Third Xiangya Hospital, Central South University, Changsha.[d]
Drs Chen and Shi contributed equally to this paper.
Funding sources: Supported by the National Natural Science Foundation of China (grant nos. 81874251), the National Natural Science Foundation of China (grant nos. 81673086), the National Natural Science Foundation of China (grants nos. 81602784), and the National Natural Science Foundation of China (the Major Research Plan, Training Program, grant nos. 91749114).
Conflicts of interest: None disclosed.
IRB approval status: Not applicable.

Accepted for publication April 20, 2020.
Reprints not available from the authors.
Correspondence to: Ji Li, MD, PhD, Department of Dermatology, Xiangya Hospital, Central South University, 87 Xiangya Rd, Changsha, Hunan, People's Republic of China 410008. E-mail: liji_xy@csu.edu.cn.
Wei Shi, MD, PhD, Department of Dermatology, Xiangya Hospital, Central South University, 87 Xiangya Rd, Changsha, Hunan, People's Republic of China 410008. E-mail: shiwei@csu.edu.cn.
Published online September 14, 2020.
0190-9622

https://doi.org/10.1016/j.jaad.2020.04.113

environmental factors as promoting features of rosacea.[5,6] A number of risk factors to aggravate rosacea symptoms have also been proposed, such as diet, smoking, alcohol consumption, and stress.[7,8] So far, mounting comorbidities of rosacea have been identified, suggesting that rosacea is not simply a skin disease but has links to multiple systemic illnesses.[9,10]

Cardiometabolic disease (CMD) is defined as a cluster of diseases and risk factors including diabetes, cardiovascular disease (CVD), hypertension, dyslipidemia, and obesity.[11-13] CMD has become a growing threat to public health.[14] Most recently, chronic inflammation activated by the renin-angiotensin system and immune dysregulation have been recognized as major components contributing to the development of CMD.[15] Smoking, excessive alcohol consumption, and unhealthy diet are also known risk factors for CMD.[16]

CAPSULE SUMMARY

- Previous studies have yielded a controversial association between rosacea and cardiometabolic disease.
- This meta-analysis suggests that rosacea showed correlation with hypertension and dyslipidemia; therefore, patients with rosacea are encouraged to be screened for indicators identified with cardiometabolic disease, which may be helpful for diagnosis and appropriate treatment at an early stage.

Some risk factors, such as smoking, alcohol consumption, and diet, along with chronic inflammation activated by immune dysregulation, are shared in the pathogenesis of both rosacea and CMD. Meanwhile, in patients, the age at onset of rosacea occurs at a comparatively earlier age than CMD. Hence, it is worth exploring their relationship, as well as whether rosacea, which has a predilection for highly visible symptoms on facial skin, could become a potential early indicator of CMD.

Although numerous observational studies have been conducted to investigate the correlation between rosacea and CMD, the published outcomes are controversial. Additionally, to the best of our knowledge, no conclusions involving full-scale indicators of CVD, diabetes, hypertension, and dyslipidemia have been recapitulated in the same study. Perhaps this is why their relationships have not been comprehensively discerned. As such, we performed a systematic review and meta-analysis to convincingly and thoroughly elucidate the association between rosacea and CMD.

METHODS

Search strategy

This systematic review and meta-analysis was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines. A comprehensive search of studies published before October 16, 2019, was performed the PubMed, Embase, Cochrane Library, and Web of Science electronic databases. The combined search terms "rosacea" AND ("cardiometabolic disease" or "cardiovascular disease" or "stroke" or "diabetes mellitus" or "hypertension" or "dyslipidemia") were used. Our retrieval strategy is shown in the supplemental material (available via Mendeley at http://doi.org/10.17632/g6czhcpkdy.2).

Study selection

All study selections were conducted independently by 2 reviewers (QC, XS), with discrepancies discussed with the research group. Original cohort, case-control, or cross-sectional trials reporting the risk of CMD in patients with rosacea with the full text were eligible for inclusion. Exclusion criteria were articles published in the form of reviews, editorials, nonresearch letters, or protocols.

Data extraction

Two independent investigators (QC, XS) evaluated the titles and abstracts and resolved differences through discussion and consensus. The following data were extracted and recorded from each eligible study: (1) first author,; (2) year of publication, (3) country, (4) study design, (5) number of case patients (female/male), (6) age of case patients (mean ± standard deviation),; (7) number of control individuals (female/male), (8) age of control individuals (mean ± standard deviation), and (9) outcomes. If measurements of mean values among different studies were not the same, they would be converted (eg, from mmol/L to mg/dL).

Outcomes

For our large-scale database search (see Results section), only parameters identified in 3 or more sources were analyzed. The outcomes based on population samples were ischemic heart disease (IHD), stroke, diabetes, hypertension, and dyslipidemia. The outcomes based on calculated values were total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), systolic and diastolic blood pressure, and fasting blood glucose (FBG) levels.

Abbreviations used:

CCB: calcium channel blocker
CI: confidence interval
CMD: cardiometabolic disease
CVD: cardiovascular disease
FBG: fasting blood glucose
HDL: high-density lipoprotein
IHD: ischemic heart disease
LDL: low-density lipoprotein
RR: pooled risk ratio
SMD: standardized mean difference
TC: total cholesterol
TG: triglycerides

Assessment of study quality

For each included study, 2 researchers (QC, XS) explored the methodologic quality through the Newcastle-Ottawa Scale.[17] Every single question received 1 point (marked as a star *) for a semi-quantitative assessment, except for the comparability item, which could be awarded with 2 points. The maximum total score is 9 points. In total, scores of 7 to 9 scores considered as high quality.[18]

Statistical analysis

The pooled risk ratios (RRs) and corresponding 95% confidence intervals (CIs) were calculated within outcomes based on population samples. In terms of outcomes according to calculated values, standardized mean differences (SMDs) and 95% CIs were determined to compare differences between the rosacea and control groups. We assessed the degree of heterogeneity using an inconsistency index (I^2). I^2 values of 0%, 25%, 50%, and 75% represent no, low, moderate, and high heterogeneity, respectively.[19] If values of I^2 were less than 50%, a fixed-effects model was applied; otherwise, a random-effects model was used.[20] To explore the sources of heterogeneity, sensitivity analysis was undertaken to demonstrate the overall influence of an individual study where I^2 was >50%. If the related studies to assess the same outcome were adequate, we planned to evaluate publication bias using a funnel plot.

All statistical meta-analyses were conducted with Stata, version 14.0 (Stata Corp, College Station, TX) to generate forest plots of pooled RRs and SMDs with 95% CIs. All P values reported were 2-sided, with P <.05 considered statistically significant.

RESULTS

Literature search

A total of 404 references were identified, including 44 articles from PubMed, 89 articles from Embase, 9 articles from Cochrane Library, and 262 articles from Web of Science. Of these, 101 duplicate references were excluded from the analysis. After the independent evaluation of titles and abstracts, 282 articles were subsequently excluded for being irrelevant. Twenty-one possible full-text studies were carefully reviewed, of which 7 studies were excluded because of no available data and 1 study was conducted only on specific populations. As a result, a total of 13 studies were included in the final analysis. The flow diagram of the literature search is shown in Fig 1.

Study characteristics and quality assessment

The total population of recruited studies covered 50,442 patients with rosacea and 1,525,864 control individuals. Among them, diagnoses of rosacea and metabolic diseases were made according to the National Rosacea Society criteria by experienced dermatologists or cardiologists or from a database using International Classification of Diseases records. Most patients with rosacea were female, accounting for 71.44%, and male patients accounted for the remaining 28.56%. Of the involved articles, 5 recruited patients from the general population,[21-25] and 8 collected data from a dermatology department.[26-33] With regard to the distribution of patient samples across continents, 8 studies were conducted in Asia,[22-25,27,29-31] 3 in Northern Europe,[21,26,28] and 2 in North America.[32,33] Detailed characteristics of these articles are summarized in Table I. In accordance with these characteristics, studies may differ from each other in many respects. Thus, a random-effects model was used in each analysis to obtain conservative outcome data.

On the basis of the Newcastle-Ottawa Scale, all of the eligible studies were graded as high quality (scores of 7 or greater) (Table II).

IHD

Four studies (1,534,511 participants) assessed the risk of IHD among patients with rosacea and control individuals. Rosacea was not associated with IHD: RR, 0.89; 95% CI, 0.59-1.34; P = .575 (I^2 = 91.1%; P < .001) (Fig 2).

Stroke

The relative risk of stroke for individuals with rosacea was measured in 3 studies (1,528,158 participants). The rosacea group showed no obvious difference in incidence of stroke: RR, 0.94; 95% CI, 0.70-1.27; P = .705 (I^2 = 80.7%; P = .006) (Fig 2).

Diabetes

The prevalence of diabetes and the values of FBG were both counted in 5 studies (1,528,463

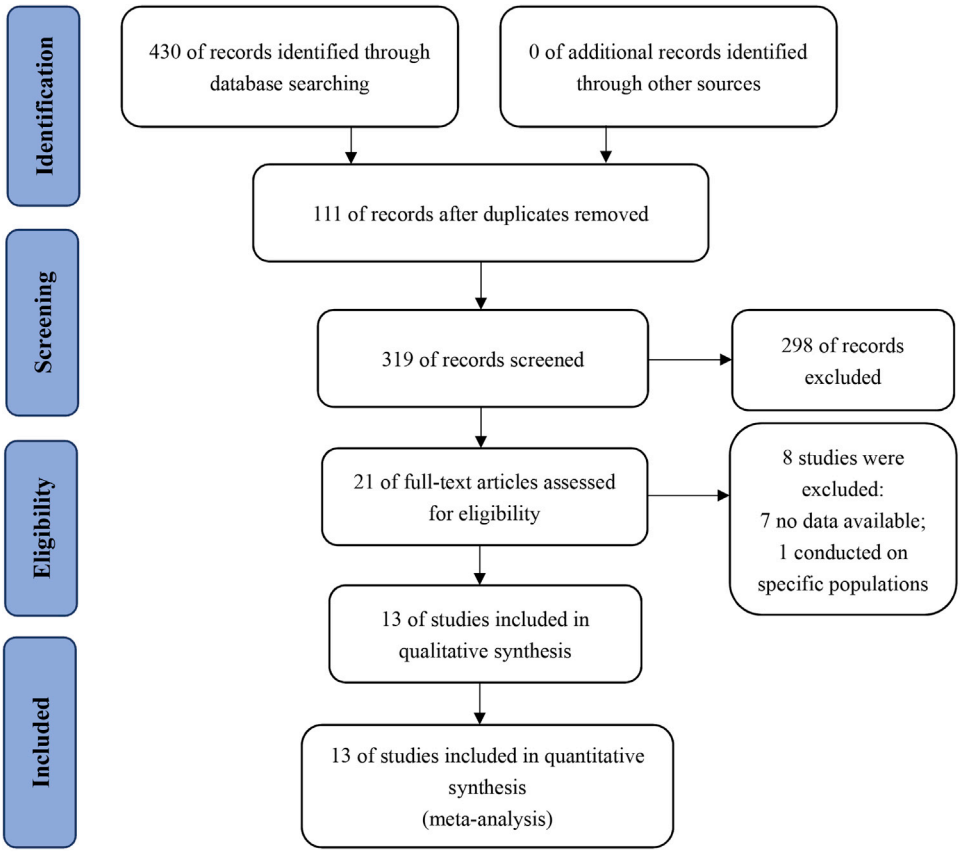

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart of the literature search.

participants and 826 participants). The rosacea group was at significantly increased risk of higher FBG: SMD, 0.24; 95% CI, 0.03-0.46; P = .026 (I^2 = 48.8%; P = .098) (Fig 3). However, the relationship between rosacea and the prevalence of diabetes failed to reach statistical significance: RR, 1.15; 95% CI, 0.92-1.42; P = .216 (I^2 = 85.5%; P < .001) (Fig 2).

Hypertension

Four trials reported systolic and diastolic blood pressure (722 participants, and 5 of the 13 trials reported prevalence of hypertension (1,528,463 participants). Participants with rosacea had elevated SMDs of systolic and diastolic blood pressure: SMD, 0.40; 95% CI, 0.19-0.62; P = .000 (I^2 = 39.9%, P = .172) and SMD, 0.50; 95% CI, 0.19-0.81; P = .002 (I^2 = 69.3%; P = .021), respectively) (Fig 3). A statistically significant association was seen for hypertension in patients with rosacea: RR, 1.20; 95% CI, 1.08-1.34; P = .001 (I^2 = 68.5%; P = .013) (Fig 2).

Dyslipidemia

Three studies (1,528,158 samples) reported dyslipidemia, and 7 studies (1111 participants) measured its related parameters, including TC, HDL, LDL, and TG. Rosacea was associated with dyslipidemia: RR, 1.32; 95% CI, 1.10-1.58; P = .002 (I^2 = 86.9%; P < .001) (Fig 2); higher TC: SMD, 0.42; 95% CI, 0.17-0.68; P = .001 (I^2 = 73.8%; P = .001) (Fig 3); higher LDL: SMD, 0.37; 95% CI, 0.18-0.56; P < .001 (I^2 = 55.2%; P = .037) (Fig 3); and higher TG: SMD, 0.28; 95% CI, 0.08-0.49; P = .006 (I^2 = 60.1%; P = .020) (Fig 3). No significant correlation between rosacea and HDL was found: SMD, -0.01; 95% CI, -0.14 to 0.11; P = .859 (I^2 = 5.2%; P = .387) was found (Fig 3).

Sensitivity analysis and publication bias

In general, most meta-analyses showed comparatively low to moderate statistical heterogeneity (I^2 < 75%). Therefore, the results from these parts can be considered to be stable and reliable. To explore the sources of heterogeneity, sensitivity analyses where I^2 was less than 50% were conducted. The results showed that after removing articles with significant heterogeneity, the heterogeneity decreased to a low level (I^2 < 50%). The trend and final conclusions derived from most meta-analyses were not affected (supplemental material and

Table I. Characteristics of eligible articles

Authors	Year of publication	Country	Study design	Number of case patients, female/male	Age of case patients, y, mean ± SD	Number of control individuals, female/male	Age of control individuals, y, mean ± SD	Outcomes
Sinikumpu et al[21]	2019	Finland	Cohort	146/0	46	278/0	46	TC, LDL, HDL, TG, SBP, DBP, FBG
Gürel and Turan[29]	2019	Turkey	Case-control	23/29	50.69 ± 7.88	23/29	50.29 ± 8.42	TC, LDL, HDL, TG, FBG
Son et al[28]	2018	Korea	Case-control	1745/791	47.21 ± 15.01	N/A	N/A	Diabetes, hypertension, dyslipidemia, IHD, stroke
Akin Belli et al[31]	2017	Turkey	Case-control	31/9	50.35	30/10	50.52	TC, LDL, HDL, TG, SBP, DBP, FBG
Akin Belli A et al[30]	2017	Turkey	Case-control	45/16	50.46 ± 8.58	47/13	49.80 ± 9.70	TC, LDL, HDL, TG, SBP, DBP, FBG
Akin Belli and Altun[22]	2017	Turkey	Case-control	65/20	50.63 ± 8.45	67/23	50.79 ± 9.02	TC, LDL, HDL, TG, hypertension
Marshall et al[32]	2016	United States	Case-control	1588/502	49.2 ± 9.1	2866/1397	49.9 ± 8.3	Diabetes, IHD
Egeberg et al[25]	2016	Denmark	Cohort	3160/1788	49.2 ± 14.5	15,477/7546	48.7 ± 14.2	Hypertension, dyslipidemia, IHD, stroke, diabetes
Egeberg et al[26]	2016	Denmark	Case-control	4270/2489	40.2 ± 16.3	21,350/12,445	40.2	Diabetes
Akin Belli et al[23]	2016	Turkey	Case-control	35/12	50.8	39/11	50.9	TC, LDL, HDL, TG, SBP, DBP, FBG
Rainer et al[33]	2015	United States	Case-control	43/22	50.6	43/22	50.4	Hypertension
Hua et al[24]	2015	Taiwan	Case-control	24,947/8606	44	49,894/17,212	44	Hypertension, dyslipidemia, IHD, stroke, diabetes
Duman et al[27]	2015	Turkey	Case-control	40/20	44.65 ± 12.9	33/17	42.3 ± 12.3	TC, LDL, HDL, TG

DBP, Diastolic blood pressure; *FBG,* fasting blood glucose; *IHD,* ischemic heart disease; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *N/A,* not available; *SBP,* systolic blood pressure; *SD,* standard deviation; *TC,* total cholesterol; *TG,* triglycerides.

Supplemental Figs S1-S7; available via Mendeley at http://doi.org/10.17632/g6czhcpkdy.2), except for diabetes and dyslipidemia.

It is unlikely that the assessment of publication bias could be completed by using a funnel plot because of the small numbers of studies in each subgroup.

DISCUSSION

This systematic review and meta-analysis provides systematic assessment of the association and risk estimates of rosacea with CMD.

Our systematic assessment determined that patients with rosacea had a remarkably higher probability of experiencing hypertension. Research has supplied ample evidence that activation of the sympathetic nervous system and vascular changes caused by transient receptor potential ion channels might contribute to the development of hypertension.[34,35] Given the fact that many rosacea triggers, such as temperature changes and spicy food, could activate sensory nerves, neurovascular dysregulation is emerging as another pathophysiology characteristic of rosacea.[36] An enhanced immunoreactivity for transient receptor potential vanilloid subfamily (TRPV) was also proven in patients with rosacea.[36] Therefore, neurovascular dysfunction tends to be the shared mechanism encompassed by rosacea and

Table II. Newcastle-Ottawa Scale quality assessment table

First author	Year of publication	Selection	Comparability	Exposure	Total Newcastle-Ottawa Scale score
Sinikumpu et al[21]	2019	****	**	**	8
Gürel and Turan[29]	2019	***	**	**	8
Son et al[28]	2018	***	**	***	8
Akin Belli et al[31]	2017	***	**	***	8
Akin Belli et al[30]	2017	***	**	***	8
Akin Belli et al[22]	2017	***	**	***	8
Marshall et al[32]	2016	****	**	***	9
Egeberg et al[25]	2016	****	**	***	9
Egeberg et al[26]	2016	****	**	***	9
Akin Belli et al[23]	2016	***	**	***	8
Rainer et al[33]	2015	***	**	***	8
Hua et al[24]	2015	****	**	***	9
Duman et al[27]	2015	***	**	***	8

Asterisk represents one score for each item.

hypertension. In addition, beta-blockers, diuretics, and calcium-channel blockers (CCBs) are widely proven in antihypertensive therapy. Prior studies also indicated that they may aggravate or alleviate symptoms of rosacea.[37] CCBs are powerful vasodilators, so the prevailing notions claim that they are commonly discouraged for individuals with rosacea.[38] Although it remains to be clarified, it is worth noticing that CCBs are generally not recommended for patients with rosacea, especially those presenting with symptoms of flushing, whereas carvedilol and spironolactone prescriptions were suggested as primary options for patients displaying rosacea combined with hypertension.[38-40]

In our analysis, patients with rosacea were more subject to dyslipidemia with elevated levels of TC, LDL, and TG. Dyslipidemia is an important CVD risk factor because excess cholesterol deposition leading to plaque formation could occur in the endothelial lining, resulting in atherosclerosis.[41,42] Studies confirm that activation of nucleotide binding oligomerization domain–like receptor 3 may cause interleukin 1β liberation, inducing lipoprotein structural alterations (eg, LDL and HDL), impeding their abilities to break down and transport cholesterol. Therefore, chronic inflammation in patients with rosacea could be one possible explanation for dyslipidemia.[27] Strong signs indicate that statin therapy may exert favorable anti-inflammatory effects by other means than simply lowering lipid levels.[43] Statins could suppress monocyte-to-macrophage activation by inhibiting monocyte chemotaxis, lipopolysaccharide-mediated tumor necrosis factor release, and T helper type 1 cell development and expansion.[44,45] The upregulation of macrophages and T helper type 1 cells might also evoke rosacea immune dysfunction.[4] Accordingly, whether statins could ameliorate rosacea skin lesions is still to be determined.

Diabetes was found to play a slight but nonsignificant role in rosacea. Also, although FBG levels in patients with rosacea were in the normal range (<100 mg/dL), they were consistently higher than in control individuals. Hence, patients with rosacea are more likely to develop diabetes.[46] Previous studies implicated metabolic interactions, such as insulin resistance caused by increased oxidative stress, might participate in the physiology of rosacea, which may be a probable mechanism linking rosacea and diabetes.[23,47] However, this correlation emerging from our study could be attributed to other complicated pathogenesis involved in rosacea and diabetes, which needs to be reassessed in the context of experimental research.

Atherosclerosis is a generalized disease, and its major clinical manifestations include IHD and ischemic stroke.[48,49] Our results illustrate that rosacea is not associated with IHD and stroke. The population recruited covered a wide range of continents, including Asia, Northern Europe, and North America, which may reduce the impact of ethnic variations. Notably, a few obvious shortcomings in the literature that met our enrollment criteria might influence the outcome of our study. For instance, 2 studies mentioned that they might omit patients with diagnosed rosacea who had incomplete records of ICD diagnostic codes.[24,30] In addition, some articles excluded previous history of CVD,[25] whereas others included both new onset and previous diagnosis with CVD.[24,28,32]

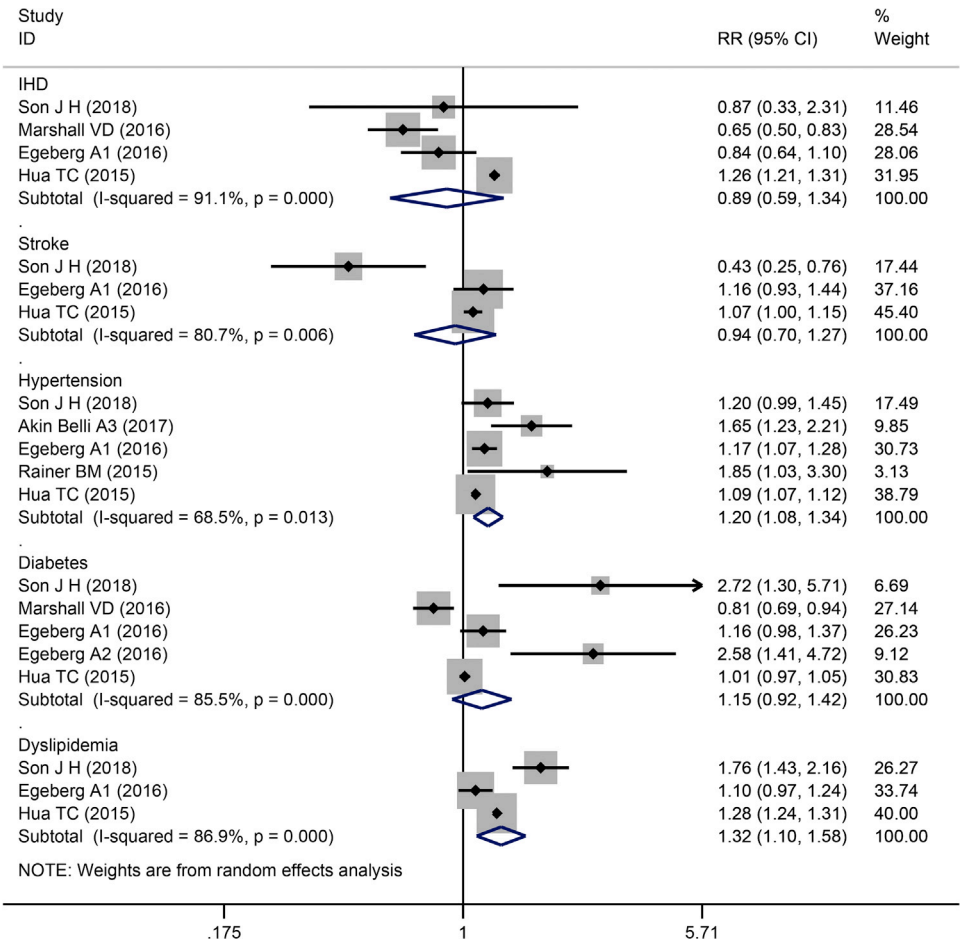

Fig 2. Comparison of (**A**) IHD, (**B**) stroke, (**C**) hypertension, (**D**) diabetes, and (**E**) dyslipidemia between patients with rosacea and control individuals. The squares indicate individual studies. The diamonds represent pooled effect sizes. The dashed lines represent the 95% CIs. Data were analyzed separately by using a random-effects model. *CI,* Confidence interval; *CVD,* cardiovascular disease; *IHD,* ischemic heart disease; *RR,* risk ratio; *SMD,* standardized mean difference.

Of note, the majority of patients with rosacea were outpatients, failing to represent general populations. Thus, doctors treating patients with diabetes or CVD with more serious conditions might have focused primarily on the highly fatal diseases and taken no notice of patients' skin diseases. Further investigations are warranted to identify the relationship between rosacea and CMD in general populations to further validate the significance of our findings.

Our current results were hampered by several limitations. First, there were inevitable inherent shortcomings of observational studies, such as unmeasured confounders and heterogeneity between different studies. Second, because of the absence of clinical data, we were unable to perform subgroup analyses according to the subtypes and severity of rosacea. Furthermore, analysis of publication bias was not available because of the small research sample size. Finally, bias in diagnostic test accuracy may exist because rosacea diagnosis in several articles was extracted from ICD codes rather than obtained directly from dermatologists.[24,28,32]

In aggregate, rosacea showed a correlation with hypertension and dyslipidemia but not with IHD, stroke, or diabetes. We advocate screening for CMD indicators among patients with rosacea, which may be helpful for diagnosis and appropriate treatment at an early stage of disease. To provide more solid evidence, future studies exploring underlying mechanisms and interactions are necessary.

We are grateful to Randall Bruce Widelitz, PhD, Department of Pathology, from Keck School of Medicine for help with native English expression.

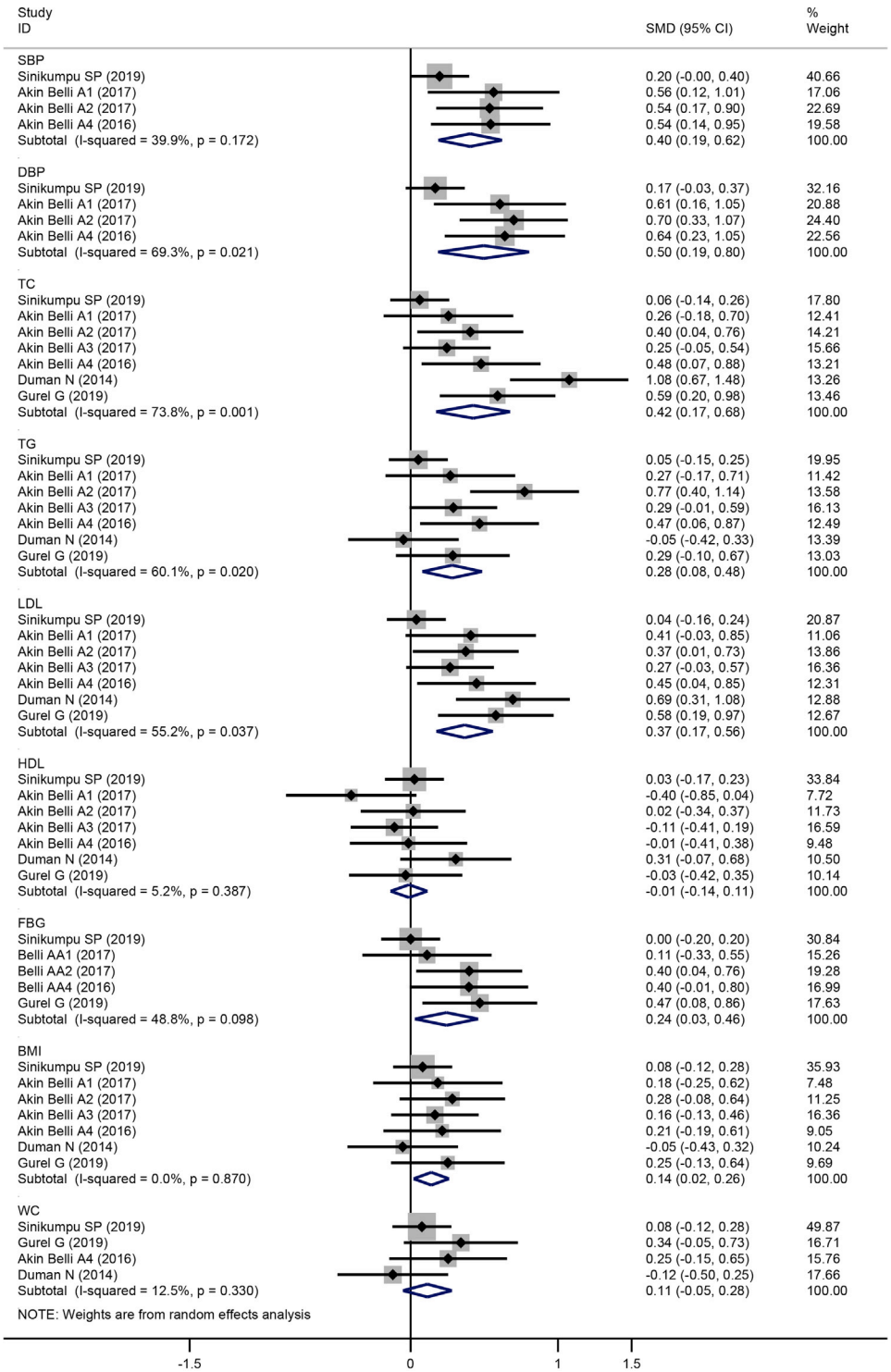

Fig 3. Comparison of (**A**) SBP, (**B**) DBP, (**C**) TC, (**D**) TG, (**E**) LDL, (**F**) HDL, and (**G**) FBG between patients with rosacea and control individuals. The squares indicate individual studies. The diamonds represent pooled effect sizes. The dashed lines represent the 95% CIs. *CI,* Confidence interval; *DBP,* diastolic blood pressure; *FBG,* fasting blood glucose; *HDL,* high-density lipoprotein; *ID,* identification; *LDL,* low-density lipoprotein; *SBP,* systolic blood pressure; *SMD,* standardized mean difference; *TC,* total cholesterol; *TG,* triglycerides. Data were analyzed separately using a random-effects model.

REFERENCES

1. Yuka A, Jerry T, Akerke B, et al. Canadian clinical practice guidelines for rosacea. *J Cutan Med Surg*. 2016;20:432-445.
2. Xie HF, Huang YX, He L, et al. An observational descriptive survey of rosacea in the Chinese population: clinical features based on the affected locations. *PeerJ*. 2017;5:e3527.
3. Zhou M, Xie H, Cheng L, Li J. Clinical characteristics and epidermal barrier function of papulopustular rosacea: a comparison study with acne vulgaris. *Pak J Med Sci*. 2016;32(6):1344-1348.
4. Kyriakis KP, Palamaras I, Terzoudi S, et al. Epidemiologic aspects of rosacea. *J Am Acad Dermatol*. 2005;53(5):918-919.
5. Kim JY, Kim YJ, Lim BJ, et al. Increased expression of cathelicidin by direct activation of protease-activated receptor 2: possible implications on the pathogenesis of rosacea. *Yonsei Med J*. 2015;55:1648-1655.
6. Ahn CS, Huang WW. Rosacea pathogenesis. *Dermatol Clin*. 2018;36:81-86.
7. Vieira ACC, Höfling-Lima AL, Mannis MJ. Ocular rosacea: a review. *Arq Bras Oftalmol*. 2012;75:363-369.
8. Yuan X, Huang X, Wang B, et al. Relationship between rosacea and dietary factors: a multicenter retrospective case-control survey. *J Dermatol*. 2019;46:219-225.
9. Holmes AD, Spoendlin J, Chien AL, et al. Evidence-based update on rosacea comorbidities and their common physiologic pathways. *J Am Acad Dermatol*. 2017;78:156-160.
10. Haber R, Gemayel M. Comorbidities in rosacea: a systematic review and update. *J Am Acad Dermatol*. 2018;78:786-792.
11. Yang PT, Yuan H, Wang YQ, et al. Correlations between brachial endothelial function and cardiovascular risk factors: a survey of 2,511 Chinese subjects. *J Thorac Dis*. 2014;6(10):1441-1451.
12. Hou X, Chen P, Hu G, et al. Distribution and related factors of cardiometabolic disease stage based on body mass index level in Chinese adults—The National Diabetes and Metabolic Disorders Survey. *Diabetes Metab Res Rev*. 2018;34(2):e2963.
13. Gromovsky AD, Schugar RC, Brown AL, et al. Δ-5 fatty acid desaturase FADS1 impacts metabolic disease by balancing proinflammatory and proresolving lipid mediators. *Arterioscler Thromb Vasc Biol*. 2018;38(1):218-231.
14. Zhang D, Tang X, Shen P, et al. Multimorbidity of cardiometabolic diseases: prevalence and risk for mortality from one million Chinese adults in a longitudinal cohort study. *BMJ Open*. 2019;9(3):e024476.
15. International Diabetes Federation. IDF diabetes atlas. 8th ed.; 2017. Available at: https://www.idf.org/component/attachments/attachments.html?id=1405&task=download. Accessed August 14, 2020.
16. Reed RM, Dransfield MT, Eberlein M, et al. Gender differences in first and secondhand smoke exposure, spirometric lung function and cardiometabolic health in the old order Amish: a novel population without female smoking. *PLoS One*. 2017;12(3):e0174354.
17. Wells G, Shea B, O'Connell D, et al. New Castle-Ottawa Quality Assessment Scale—cohort studies. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed August 14, 2020.
18. de Aquino Moura KB, Behrens PMP, Pirolli R, et al. Anticoagulant-related nephropathy: systematic review and meta-analysis. *Clin Kidney J*. 2019;12:400-407.
19. Higgins J, Green S. *Cochrane Collaboration: Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. Available at: www.training.cochrane.org/handbook. Accessed August 14, 2020.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
21. Sinikumpu SP, Jokelainen J, Auvinen J, et al. Increased risk of cardiovascular diseases in female rosacea patients: a nested case-control study. *Acta Derm Venereol*. 2019;99:705-706.
22. Akin Belli A, Altun I. Assessment of Framingham risk score and systemic coronary risk evaluation in rosacea patients. *Dermatologica Sin*. 2017;35:127-130.
23. Akin Belli A, Ozbas Gok S, Akbaba G, et al. The relationship between rosacea and insulin resistance and metabolic syndrome. *Eur J Dermatol*. 2016;26:260-264.
24. Hua TC, Chung PI, Chen YJ, et al. Cardiovascular comorbidities in patients with rosacea: a nationwide case-control study from Taiwan. *J Am Acad Dermatol*. 2015;73:249-254.
25. Egeberg A, Hansen PR, Gislason GH, et al. Assessment of the risk of cardiovascular disease in patients with rosacea. *J Am Acad Dermatol*. 2016;75:336-339.
26. Egeberg A, Hansen PR, Gislason GH, et al. Clustering of autoimmune diseases in patients with rosacea. *J Am Acad Dermatol*. 2016;74(4):667-672.e1.
27. Duman N, Ersoy Evans S, Atakan N. Rosacea and cardiovascular risk factors: a case control study. *J Eur Acad Dermatol Venereol*. 2014;28:1165-1169.
28. Son JH, Chung BY, Jung MJ, et al. The risk of rosacea according to chronic diseases and medications: a 5-year retrospective, multi-institutional case-control study. *Ann Dermatol*. 2018;30:676-687.
29. Gürel G, Turan Y. Noninvasive assessment of subclinical atherosclerosis in patients with rosacea [e-pub ahead of print]. *G Ital Dermatol Venereol*. https://doi.org/10.23736/S0392-0488.19.06218-7.
30. Akin Belli A, Kara A, Ozbas Gok S. Can hematologic parameters be an indicator of metabolic disorders accompanying rosacea? *Acta Dermatovenerol Croat*. 2017;25:145-150.
31. Akin Belli A, Altun I, Altun I, et al. Thickness of carotid intima and epicardial fat in rosacea: a cross-sectional study. *An Bras Dermatol*. 2017;92:820-825.
32. Marshall VD, Moustafa F, Hawkins SD, et al. Cardiovascular disease outcomes associated with three major inflammatory dermatologic diseases: a propensity-matched case control study. *Dermatol Ther (Heidelb)*. 2016;6:649-658.
33. Rainer BM, Fischer AH, Luz Felipe da Silva D, et al. Rosacea is associated with chronic systemic diseases in a skin severity-dependent manner: results of a case-control study. *J Am Acad Dermatol*. 2015;73:604-608.
34. Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. *J Exp Med*. 2018;215:21-33.
35. Touyz RM, Alves-Lopes R, Rios FJ, et al. Vascular smooth muscle contraction in hypertension. *Cardiovasc Res*. 2018;114(4):529-539.
36. Two AM, Wu W, Gallo RL, et al. Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors. *J Am Acad Dermatol*. 2015;72(5):749-758.
37. National Institute for Health and Care Excellence. *Hypertension—Clinical Management of Primary Hypertension in Adults*. London, UK: National Institute for Health and Care Excellence; 2011.
38. Natale F, Cirillo C, Granato C, et al. Worsening of rosacea in patients treated with dihydropyridine calcium channel blockers: a clinical observation. *Hypertens Res*. 2011;34(6):790-791.
39. Hsu CC, Lee JY. Carvedilol for the treatment of refractory facial flushing and persistent erythema of rosacea. *Arch Dermatol*. 2011;147:1258-1260.
40. Spoendlin J, Voegel JJ, Jick SS, et al. Spironolactone may reduce the risk of incident rosacea. *J Invest Dermatol*. 2013;133:2480-2483.

41. Wild SH, Byrne CD, Tzoulaki I, et al. Metabolic syndrome, haemostatic and inflammatory markers, cerebrovascular and peripheral arterial disease: the Edinburgh Artery Study. *Atherosclerosis*. 2009;203:604-609.
42. Zhao S, Wang Y, Mu Y, et al. Prevalence of dyslipidaemia in patients treated with lipid-lowering agents in China: results of the DYSlipidemia International Study (DYSIS). *Atherosclerosis*. 2014;235(2):463-469.
43. Koh KK. Effects of statins on vascular wall: vasomotor function, inflammation, and plaque stability. *Cardiovasc Res*. 2000;47:648-657.
44. Davignon J, Mabile L. [Mechanisms of action of statins and their pleiotropic effects]. *Ann Endocrinol*. 2001;62:101-112.
45. Palinsk W. New evidence for beneficial effects of statins unrelated to lipid lowering. *Arterioscler Thromb Vasc Biol*. 2001;21:3-5.
46. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. *J Am Coll Cardiol*. 2012;59:635-643.
47. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature*. 2006;440(7086):944-948.
48. Herrington W, Lacey B, Sherliker P, et al. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. *Circ Res*. 2016;118:535-546.
49. Cai JJ, Wen J, Jiang WH, et al. Androgen actions on endothelium functions and cardiovascular diseases. *J Geriatr Cardiol*. 2016;13(2):183-196.