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Original Article

Circulating leptin and its correlation with rheumatoid arthritis activity: a meta-analysis

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Objective: The aim of the study was to investigate the association between the levels of leptin in the circulating of individuals with rheumatoid arthritis (RA) and the severity of the disease.

Methods: We looked through the databases of Embase, Medline, and the Cochrane Library. We conducted a meta-analysis on the correlations between circulating leptin and the Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) and C-reactive protein (CRP) levels in RA patients, as well as a meta-analysis of circulating or circulating leptin levels in RA patients.

Results: This meta-analysis study analyzed 42 different comparisons from 37 different publications, including a total of 2,350 patients with RA and 1,815 controls. The RA group had substantially higher leptin levels than the control group (standardized mean difference [SMD]=0.507, 95% confidence interval [CI]=0.309~0.704, p<0.001). The finding that RA patients had higher leptin levels was unaffected by sample size. The correlation between circulating leptin levels and DAS28 is statistically significant (correlation coefficient=0.247, 95% CI=0.087~0.396, p=0.003). Leptin levels are also correlated with CRP levels (correlation coefficient=0.203, 95% CI=0.048~0.349, p=0.010).

Conclusion: This comprehensive meta-analysis demonstrates that the circulating leptin levels of RA patients are elevated, and provides compelling evidence of the significant relationship between leptin levels and the activity of RA. The findings of this research suggest that leptin plays a significant role in the pathophysiology of this disease.

Keywords: Leptin, Rheumatoid arthritis, Meta-analysis

INTRODUCTION

Rheumatoid arthritis (RA) is a persistent and debilitating autoimmune disease that affects the joints and causes inflammation and damage to the surrounding tissue. The disease is initiated by the invasion of the synovium by various immune system cells, including T cells, B cells, macrophages, dendritic cells, and neutrophils. This leads to a chronic state of inflammation that can have a significant impact on the individual's quality of life and life expectancy.

Leptin, a hormone produced primarily by white adipose tissue cells, was initially believed to play a role in regulating hunger and energy levels. However, recent research has revealed that leptin has a much broader role in the regulation of inflammation. Leptin and its receptors are similar in structure and function to cytokines of the IL-6 family and play a role in mediating the immune response. Leptin has both pro-inflammatory and anti-inflammatory effects, and it can activate the Th1 phenotype of T cells, leading to the production of pro-inflammatory cytokines such as TNF-[Symbol - a] and IL-6. However, it can also increase the production of anti-inflammatory molecules, such as IL-1 receptor antagonists and IL-4.

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Leptin levels have been found to increase in conditions that cause inflammation and play a role in the regulation of the immune response in autoimmune diseases. Despite the potential importance of leptin in RA, the relationship between leptin levels and disease activity has produced conflicting results. Some studies have shown a positive relationship between leptin levels and RA, while others have shown no relationship or even a negative correlation. This discrepancy in the literature may be due to small sample sizes, low statistical power, clinical heterogeneity, or leptin gene expression owing to the energy or fat status [1]. The purpose of this research is to examine the relationship between circulating leptin levels and RA patients using a meta-analytic approach.

MATERIALS AND METHODS

Examining academic literature and gathering data

We searched for studies that compared circulating leptin levels between RA patients and healthy controls, or that examined the relationship between leptin levels and RA disease activity. Publications were discovered by searching Medline (from 1971), Embase (from 1946), and Cochrane databases (from 1993) (up to December 2022). The terms, "rheumatoid arthritis" and "leptin" were used for the literature search. References of available articles were thoroughly investigated in order to discover research that the aforementioned key phrases had missed. To be included, studies had to be case-control or cohort studies, and give leptin levels in both RA and controls, or provide pertinent information on the relationship between circulating leptin levels and RA activity, as defined by Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) or C-reactive protein (CRP) level. Each study's authors, publication years, ethnicities, numbers, means and standard deviations, and correlation coefficients were gathered. Using the Newcastle–Ottawa scale, we evaluated the overall quality of the meta-analysis studies. Six to nine points imply high methodological quality, with nine being the highest possible score.

Statistical analyses

We gathered data from studies to look for associations between leptin and RA, as well as to determine if leptin is linked to DAS28 or CRP. Results were consistently presented as standard deviations of the mean and 95% confidence intervals (Cis). Using Cochran's Q-statistics, we examined both within- and between-trial heterogeneity and variance [2]. If the Q-statistic indicated trial heterogeneity, the random-effects model was used ($p<0.10$). Elsewhere, a fixed-effects model was used. For statistical analysis, a comprehensive meta-analysis was used (Biostat, Englewood, NJ, USA). p-values less than 0.05 were regarded statistically significant.

Test of heterogeneity

In a meta-regression analysis, ethnicity, publication year, and sample size were used to better comprehend the observed het-

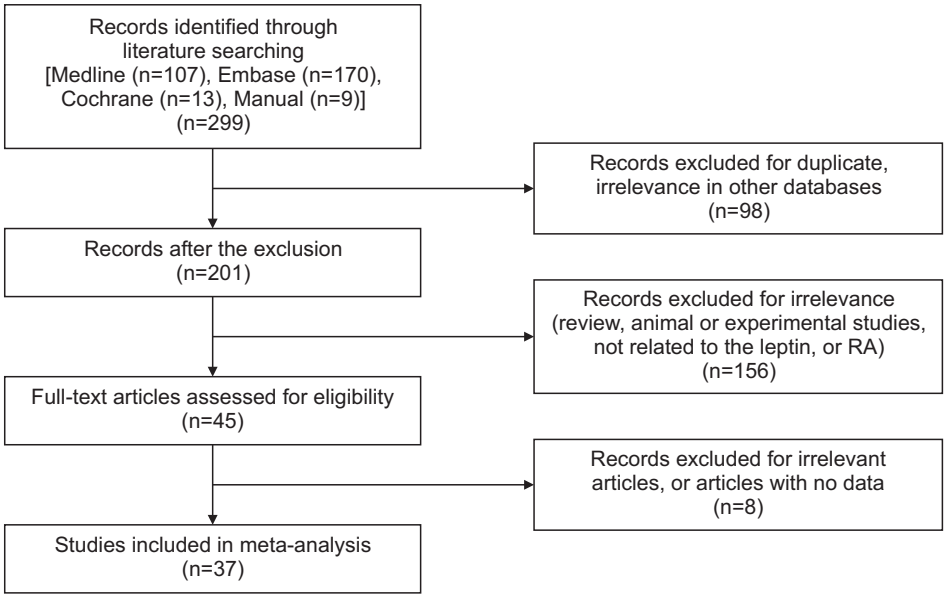

Figure 1. The procedure for selecting the studies included in this meta-analysis. RA: rheumatoid arthritis.

Table 1. Individual study characteristics analyzed in the meta-analysis

Reference	Country	Ethnicity	Number		Result		
			Case	Control	SMD	Magnitude*	p-value
Magali Chamorro-Melo, 2022 [3]	Colombia	Hispanic	51	51	0.853	Large	<0.001
Cheleschi, 2022 [4]	UK	Caucasian	50	50	0.643	Large	0.002
Zhang. 2021 [5]	Sweden	Caucasian	82	88	0.055	Small	0.718
Turgunova, 2021a [6]	Kazaklstan	Asian	48	63	0.126	Small	0.512
Turgunova, 2021b [6]	Kazaklstan	Asian	82	63	−0.131	Small	0.435
Chen, 2020 [7]	China	Asian	150	48	0.336	Medium	0.044
Tao, 2020 [8]	China	Asian	103	95	−0.197	Small	0.168
Chihara, 2020 [9]	Japan	Asian	136	78	0.331	Medium	0.021
Hoffman, 2019 [10]	Israel	Caucasian	40	40	0.134	Small	0.550
Dervišević, 2018 [11]	Bosnia	Caucasian	55	25	0.374	Medium	0.123
Angel-Chávez, 2018 [12]	Mexico	Hispanic	70	74	0.251	Medium	0.134
Rodríguez-Carrio, 2017a [13]	Spain	Caucasian	84	83	0.333	Medium	0.033
Rodríguez-Carrio, 2017b [13]	Spain	Caucasian	29	83	0.889	Large	<0.001
Najafizadeh, 2016 [14]	Iran	Arab	75	40	0.794	Large	<0.001
Gülkesen, 2016 [15]	Turkey	Caucasian	33	24	0.272	Medium	0.312
Gómez-Bañuelos, 2015 [16]	Mexico	Hispanic	64	66	0.905	Large	<0.001
Oner, 2015 [17]	Turkey	Caucasian	106	52	0.136	Small	0.421
Abdalla, 2014 [18]	Egypt	Arab	60	30	0.454	Medium	0.045
Toussirot, 2013 [19]	France	Caucasian	30	31	0.426	Medium	0.100
Olama, 2012 [20]	Egypt	Arab	40	30	1.228	Large	<0.001
Allam, 2012 [21]	Egypt	Arab	37	34	0.973	Large	<0.001
Kopec-Medrek, 2012 [22]	Poland	Caucasian	16	16	0.020	Small	0.955
Yoshino, 2011 [23]	Japan	Asian	141	146	1.146	Large	<0.001
Ismail, 2011 [24]	Egypt	Arab	40	30	3.355	Large	<0.001
El-Batch, 2010 [25]	Turkey	Caucasian	30	15	2.263	Large	<0.001
Seven, 2009 [26]	Turkey	Caucasian	20	15	0.836	Large	0.019
Rho, 2009 [27]	USA	Caucasian	167	91	1.791	Large	<0.001
Canoruç, 2009 [28]	Turkey	Caucasian	52	52	1.163	Large	<0.001
Hizmetli, 2007 [29]	Turkey	Caucasian	41	25	−0.165	Small	0.517
Gunaydin, 2006 [30]	Turkey	Caucasian	50	34	0.967	Large	<0.001
Otero, 2006 [31]	Spain	Caucasian	31	18	0.618	Large	0.041
Popa, 2005a [32]	Netherlands	Caucasian	11	9	0.461	Medium	0.311
Popa, 2005b [32]	Netherlands	Caucasian	20	9	0.236	Medium	0.558
Toussirot, 2005 [33]	France	Caucasian	38	32	0.512	Large	0.036
Härle, 2004a [34]	Greece	Caucasian	8	28	−0.854	Large	0.039
Härle, 2004b [34]	Greece	Caucasian	22	26	−0.937	Large	0.002
Bokarewa, 2003 [35]	Sweden	Caucasian	49	34	0.720	Large	0.002
Nishiya, 2002a [36]	Japan	Asian	14	10	−0.224	Medium	0.589
Nishiya, 2002b [36]	Japan	Asian	35	10	0.238	Medium	0.509
Tokarczyk-Knapik, 2002 [37]	Poland	Caucasian	52	24	−0.869	Large	0.001
Salazar-Páramo, 2001 [38]	Mexico	Hispanic	30	27	0.634	Large	0.020
Anders, 1999 [39]	Greece	Caucasian	58	16	0.273	Medium	0.335

UK: United Kingdom, SMD: standardized mean difference. *Magnitude of Cohen's d effect size: small effect, 0.2~0.5; medium effect, 0.5~0.8; large effect, ≥0.8.

erogeneity in the meta-analysis. We ran a sensitivity analysis to see how the pooled standardized mean difference (SMD) would change if individual trials were omitted. We used the "trim and fill" procedure to address the publication bias in the summary estimates.

RESULTS

Papers included into the meta-analysis

We discovered 37 articles for this meta-analysis [3-39] (Figure 1). Five of the studies reported data pertaining to two distinct groups. For the meta-analysis, 2,350 RA patients and 1,815 controls were selected from 42 comparisons (Table 1). The quality of research was similarly high across the board (all studies obtained scores between 6 and 8). Table 1 contains the demographic information for each participant.

Circulating leptin concentrations in rheumatoid arthritis patients and healthy persons.

The RA group had substantially higher leptin levels than the control group (SMD=0.507, 95% CI=0.309~0.704, p<0.001) (Table 2, Figure 2). Leptin levels in the RA group were also higher in Caucasians, Arabs, and Hispanics (SMD=0.418, 95% CI=0.145~0.692, p=0.003; SMD=1.317, 95% CI=0.554~2.081, p=0.001; SMD=0.652, 95% CI=0.317~0.988, p=0.001, respectively) (Table 2, Figure 2). The fact that RA patients had higher leptin levels was unaffected by sample size (Table 2).

The correlation between circulating leptin levels and RA activity.

The link between circulating leptin levels and DAS28-ESR is statistically significant (correlation coefficient=0.247, 95% CI=0.087~0.396, p=0.003) (Figure 3, Table 3). Leptin levels are also associated with CRP levels (correlation coefficient=0.203, 95% CI=0.048~0.349, p=0.010) (Table 3).

Heterogeneity and publication bias

A meta-analysis of leptin levels in RA patients revealed heterogeneity across studies (Table 2). In a meta-analysis of leptin levels in RA patients, ethnicity and sample size did not impact heterogeneity, but publication year was a significant predictor. As the publication year becomes more recent, there was a decrease in the heterogeneity of the study's findings, indicating a trend towards greater consistency and reliability in research over time. A sensitivity analysis found that the omission of a single study did not significantly impact the meta-findings analyses. The funnel plot was asymmetrical, thus, the "trim and fill" method was used to correct this (Figure 4). In spite of the modification, the substantial SMD (SMD=0.774, 95% CI=0.565~0.975) remained unaltered.

DISCUSSION

Leptin regulation is crucial for maintaining optimal immunological and neuroendocrine function. As previously documented, leptin has the ability to suppress the development of T-cells into the Th1 phenotype, activate monocytes/macrophages and stimulate the production of proinflammatory cytokines. Moreover, it has been observed that proinflammatory cytokines can increase the levels of leptin in circulation. Leptin plays a significant role in T-cell-mediated inflammation by regulating T-helper cell activity. This regulation results in the induction of

Table 2. Meta-analysis of the relationship between circulating leptin levels and rheumatoid arthritis

Groups	Population	No. of Studies	Test of association			Test of heterogeneity		
			SMD*	95% CI	p-value	Model	p-value	I^2
All	Overall	42	0.507	0.309~0.704	<0.001	R	<0.001	88.4
Ethnicity	Caucasian	25	0.418	0.145~0.692	0.003	R	<0.001	87.9
	Asian	8	0.226	−0.156 to 0.608	0.246	R	<0.001	89.2
	Arab	5	1.317	0.554~2.081	0.001	R	<0.001	91.5
	Hispanic	4	0.652	0.317~0.988	0.001	R	0.036	64.8
Sample size (n)	<100	24	0.474	0.152~0.796	0.004	R	<0.001	86.7
	>100	18	0.545	0.286~0.084	<0.001	R	<0.001	90.5

SMD: standard mean difference, CI: confidence interval, F: fixed effects model, R: random effects model. *Magnitude of Cohen's d effect size (SMD): small effect, 0.2~0.5; medium effect, 0.5~0.8; large effect, ≥0.8.

macrophages and granulocytes, two cell types that contribute to lymphopoiesis and myelopoiesis, leading to an increase in phagocytosis and the production of proinflammatory cytokines. Interactions between the immune system and neuroendocrine system may also contribute to the development of RA. However, the specific role of leptin in chronic inflammatory diseases such as RA is still uncertain.

This meta-analysis showed that the RA group had significantly higher leptin levels in the circulating compared to the control group. The study also discovered a connection between leptin levels and RA activity using the DAS28 and CRP. It was noted that the clinical improvement of individuals with RA who

A

Study name	Std diff in means	Lower limit	Upper limit	p-value
Magali Chamorro-Melo, 2022 [3]	0.853	0.448	1.259	<0.001
Cheleschi, 2022 [4]	0.643	0.241	1.045	0.002
Zhang. 2021 [5]	0.055	−0.246	0.356	0.718
Turgunova, 2021a [6]	0.126	−0.250	0.502	0.512
Turgunova, 2021b [6]	−0.131	−0.460	0.198	0.435
Chen, 2020 [7]	0.336	0.009	0.663	0.044
Tao, 2020 [8]	−0.197	−0.476	0.083	0.168
Chihara, 2020 [9]	0.331	0.051	0.611	0.021
Hoffman, 2019 [10]	0.134	−0.305	0.573	0.550
Dervišević, 2018 [11]	0.374	−0.102	0.851	0.123
Angel-Chávez, 2018 [12]	0.251	−0.077	0.579	0.134
Rodríguez-Carrio, 2017a [13]	0.333	0.028	0.639	0.033
Rodríguez-Carrio, 2017b [13]	0.889	0.451	1.328	<0.001
Najafizadeh, 2016 [14]	0.794	0.396	1.191	<0.001
Gülkesen, 2016 [15]	0.272	−0.256	0.801	0.312
Gómez-Bañuelos, 2015 [16]	0.905	0.544	1.266	<0.001
Oner, 2015 [17]	0.136	−0.196	0.468	0.421
Abdalla, 2014 [18]	0.454	0.011	0.897	0.045
Toussirot, 2013 [19]	0.426	−0.082	0.933	0.100
Olama, 2012 [20]	1.228	0.713	1.744	<0.001
Allam, 2012 [21]	0.973	0.480	1.465	<0.001
Kopec-Medrek, 2012 [22]	0.020	−0.673	0.713	0.955
Yoshino, 2011 [23]	1.146	0.897	1.396	<0.001
Ismail, 2011 [24]	3.355	2.625	4.085	<0.001
El-Batch, 2010 [25]	2.263	1.486	3.039	<0.001
Seven, 2009 [26]	0.836	0.138	1.533	0.019
Rho, 2009 [27]	1.791	1.492	2.089	<0.001
Canoruç, 2009 [28]	1.163	0.748	1.579	<0.001
Hizmetli, 2007 [29]	−0.165	−0.663	0.334	0.517
Gunaydin, 2006 [30]	0.967	0.508	1.427	<0.001
Otero, 2006 [31]	0.618	0.024	1.211	0.041
Popa, 2005a [32]	0.461	−0.431	1.354	0.311
Popa, 2005b [32]	0.236	−0.553	1.025	0.558
Toussirot, 2005 [33]	0.512	0.034	0.990	0.036
Härle, 2004a [34]	−0.854	−1.664	−0.043	0.039
Härle, 2004b [34]	−0.937	−1.535	−0.339	0.002
Bokarewa, 2003 [35]	0.720	0.269	1.171	0.002
Nishiya, 2002a [36]	−0.224	−1.038	0.590	0.589
Nishiya, 2002b [36]	0.238	−0.467	0.942	0.509
Tokarczyk-Knapik, 2002 [37]	−0.869	−1.372	−0.366	0.001
Salazar-Páramo, 2001 [38]	0.634	0.101	1.167	0.020
Anders, 1999 [39]	0.273	−0.282	0.828	0.335
	0.507	0.309	0.704	<0.001

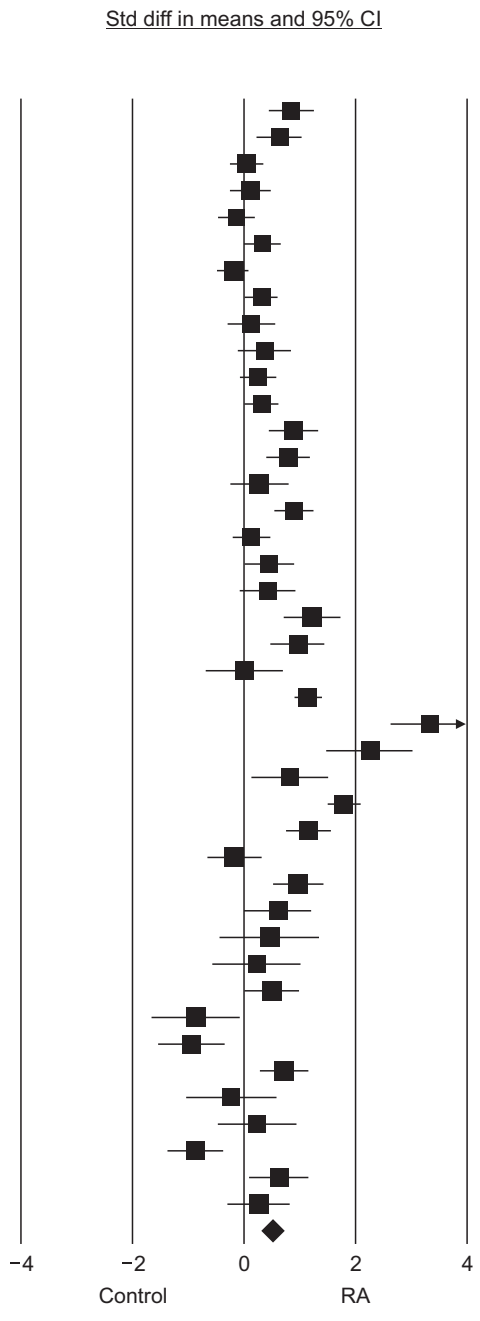

Figure 2. Meta-analysis investigating the relationship between leptin and RA, taking into account all study participants (A) and considering any racial groups (B). CI: confidence interval, RA: rheumatoid arthritis.

B

Group by Ethnicity	Study name	Std diff in means	Lower limit	Upper limit	p-value
Arab	Najafizadeh, 2016 [14]	0.794	0.396	1.191	<0.001
Arab	Abdalla, 2014 [18]	0.454	0.011	0.897	0.045
Arab	Olama, 2012 [20]	1.228	0.713	1.744	<0.001
Arab	Allam, 2012 [21]	0.973	0.480	1.465	<0.001
Arab	Ismail, 2011 [24]	3.355	2.625	4.085	<0.001
Arab		1.317	0.554	2.081	0.001
Asian	Turgunova, 2021a [6]	0.126	−0.250	0.502	0.512
Asian	Turgunova, 2021b [6]	−0.131	−0.460	0.198	0.435
Asian	Chen, 2020 [7]	0.336	0.009	0.663	0.044
Asian	Tao, 2020 [8]	−0.197	−0.476	0.083	0.168
Asian	Chihara, 2020 [9]	0.331	0.051	0.611	0.021
Asian	Yoshino, 2011 [23]	1.146	0.897	1.396	<0.001
Asian	Nishiya, 2002a [36]	−0.224	−1.038	0.590	0.589
Asian	Nishiya, 2002b [36]	0.238	−0.467	0.942	0.509
Asian		0.226	−0.156	0.608	0.246
European	Cheleschi, 2022 [4]	0.643	0.241	1.045	0.002
European	Zhang. 2021 [5]	0.055	−0.246	0.356	0.718
European	Hoffman, 2019 [10]	0.134	−0.305	0.573	0.550
European	Dervišević, 2018 [11]	0.374	−0.102	0.851	0.123
European	Rodríguez-Carrio, 2017a [13]	0.333	0.028	0.639	0.033
European	Rodríguez-Carrio, 2017b [13]	0.889	0.451	1.328	<0.001
European	Gülkesen, 2016 [15]	0.272	−0.256	0.801	0.312
European	Oner, 2015 [17]	0.136	−0.196	0.468	0.421
European	Toussirot, 2013 [19]	0.426	−0.082	0.933	0.100
European	Kopec-Medrek, 2012 [22]	0.020	−0.673	0.713	0.955
European	El-Batch, 2010 [25]	2.263	1.486	3.039	<0.001
European	Seven, 2009 [26]	0.836	0.138	1.533	0.019
European	Rho, 2009 [27]	1.791	1.492	2.089	<0.001
European	Canoruç, 2009 [28]	1.163	0.748	1.579	<0.001
European	Hizmetli, 2007 [29]	−0.165	−0.663	0.334	0.517
European	Gunaydin, 2006 [30]	0.967	0.508	1.427	<0.001
European	Otero, 2006 [31]	0.618	0.024	1.211	0.041
European	Popa, 2005a [32]	0.461	−0.431	1.354	0.311
European	Popa, 2005b [32]	0.236	−0.553	1.025	0.558
European	Toussirot, 2005 [33]	0.512	0.034	0.990	0.036
European	Härle, 2004a [34]	−0.854	−1.664	−0.043	0.039
European	Härle, 2004b [34]	−0.937	−1.535	−0.339	0.002
European	Bokarewa, 2003 [35]	0.720	0.269	1.171	0.002
European	Tokarczyk-Knapik, 2002 [37]	−0.869	−1.372	−0.366	0.001
European	Anders, 1999 [39]	0.273	−0.282	0.828	0.335
European		0.418	0.145	0.692	0.003
Latin American	Magali Chamorro-Melo, 2022 [3]	0.853	0.448	1.259	<0.001
Latin American	Angel-Chávez, 2018 [12]	0.251	−0.077	0.579	0.134
Latin American	Gómez-Bañuelos, 2015 [16]	0.905	0.544	1.266	<0.001
Latin American	Salazar-Páramo, 2001 [38]	0.634	0.101	1.167	0.020
Latin American		0.652	0.317	0.988	<0.001

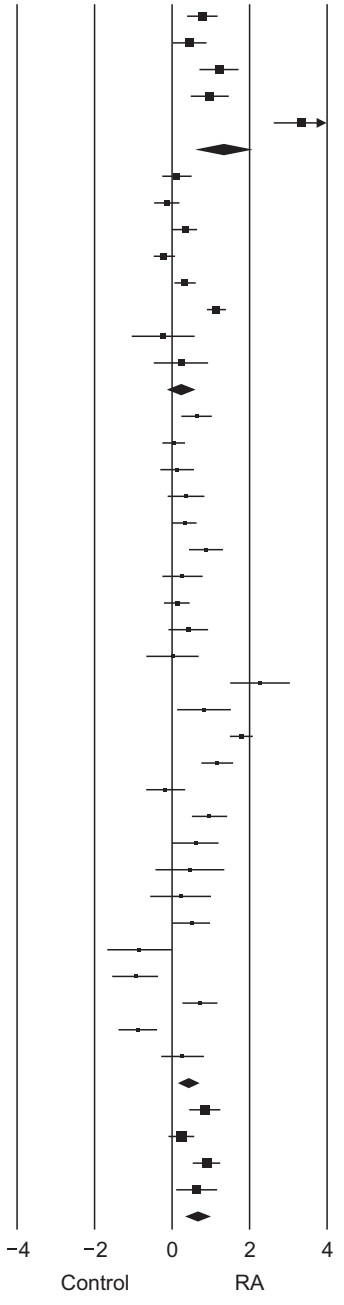

Figure 2. Continued.

fasted was associated with a decrease in circulating leptin levels and a transition to Th2 cytokine production, further emphasizing the impact of adipocytokines on the proinflammatory state in RA. These findings suggest that leptin might have the ability to induce a Th1 response and change the inflammatory process in RA. Leptin levels in the RA group were not statistically differentto those seen in Asians. There are several possible reasons for the lack of noticeable statistical differences in leptin levels between the RA and control groups among individuals of Asian descent. These could include the impact of confounding vari-

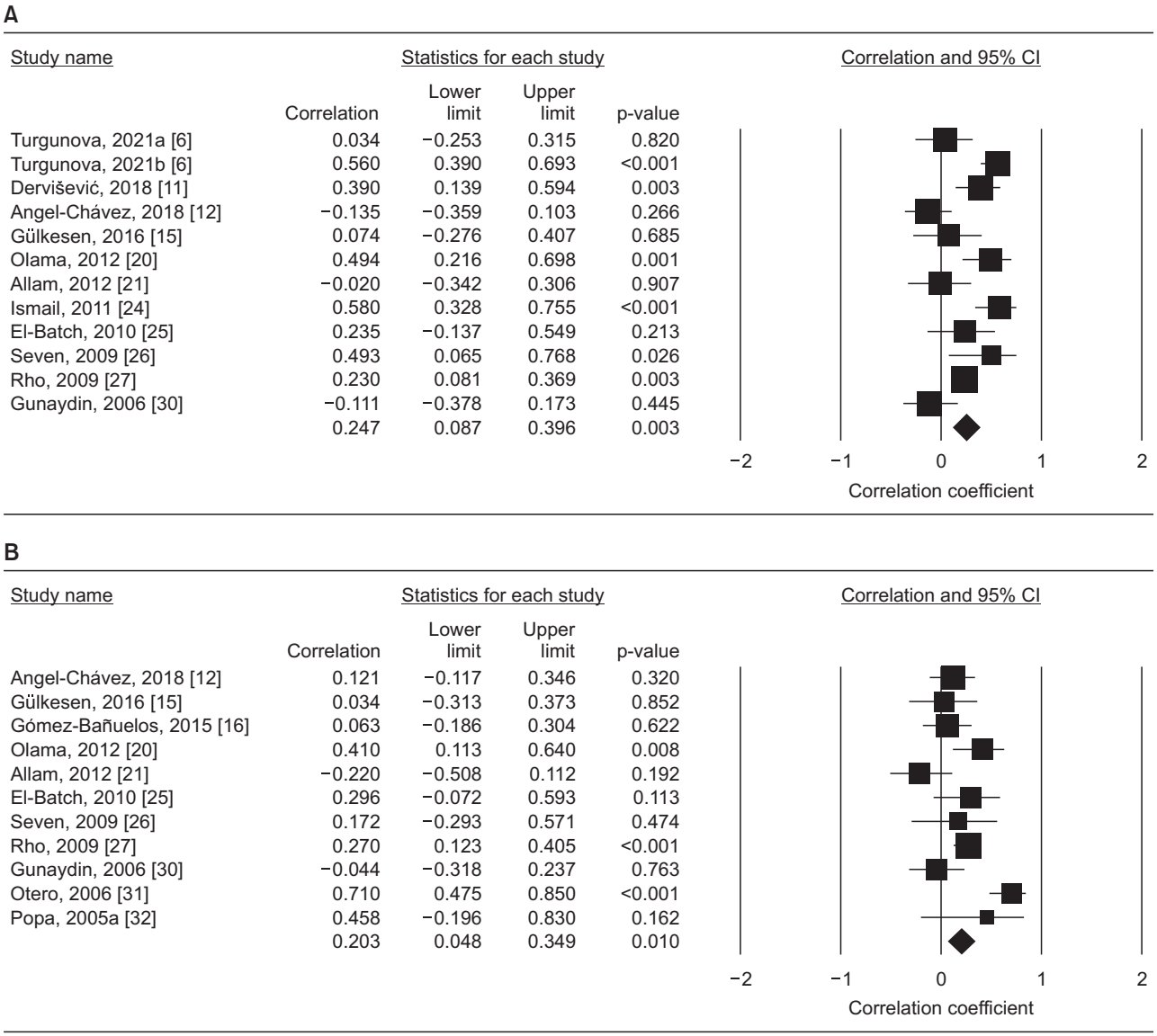

Figure 3. Meta-analysis of the relationship between leptin and the DAS28-ESR (A) as well as CRP (B). CI: confidence interval, DAS28-ESR: Disease Activity Score 28-erythrocyte sedimentation rate, CRP: C-reactive protein.

Table 3. Meta-analysis of the correlation between leptin levels and RA activity (DAS28, CRP)

Comparison	No. of studies	Test of association			Test of heterogeneity		
		Correlation coefficient	95% CI	p-value	Model	p-value	I^2
DAS28-ESR	12	0.247	0.087~0.396	0.003	R	<0.001	75.8
CRP	11	0.203	0.048~0.349	0.010	R	0.010	64.9

RA: rheumatoid arthritis, CI: confidence interval, R: random effects model, DAS28-ESR: Disease Activity Score 28-erythrocyte sedimentation rate, CRP: C-reactive protein.

ables, the heterogeneity within the RA group, and the diversity of ethnic backgrounds among the participants. Furthermore, genetic and environmental factors may also have contributed to the observed levels of leptin.

However, several issues were identified in this meta-analysis that need to be addressed. Firstly, there is a lack of large-scale

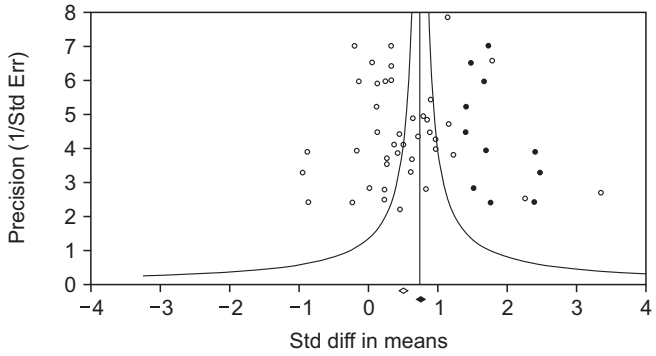

Figure 4. The funnel plot displaying the results of the studies that investigated the connection between RA and leptin levels. The filled circles indicate the studies that demonstrate publication bias. The diamonds at the bottom of the graph represent the summary estimates of the impact, both before and after accounting for publication bias. RA: rheumatoid arthritis.

studies examining the relationship between leptin levels and RA activity. Secondly, the variety of publications evaluated might have influenced the results, and factors such as body mass index (BMI), sex, and a lack of clinical data were not specifically assessed. It has been found that circulating leptin levels were highly correlated with BMI, with the exception of the BMI range near the bottom of the U shape [40]. Despite conducting a sensitivity test and meta-regression analysis, there was not enough data to draw definitive conclusions. Thirdly, while we did ethnicity-based analyses to investigate possible variations in the association between leptin levels and RA activity across various ethnic groups, we acknowledge that a specific area does not necessarily reflect a particular ethnicity. Despite these limitations, the meta-analysis provides the most comprehensive data to date on leptin status in RA patients, and the results suggest that leptin may play a role in the development and progression of RA.

CONCLUSION

In conclusion, this comprehensive meta-analysis, which incorporates data from 37 separate studies and a total of 2,350 RA patients and 1,815 controls demonstrates that the circulating leptin levels of RA patients are elevated, and provides compelling evidence of the significant relationship between leptin levels and the activity of RA. The findings of this research suggesting that leptin plays a significant role in the pathophysiology of this disease. Further large-scale studies are needed to establish the exact role of leptin in RA and to determine if targeting leptin levels can be a potential therapeutic strategy for the treatment of RA.

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CONFLICT OF INTEREST

Y.H.L. has been an editorial board member since March 2003, but has no role in the decision to publish this article. G.G.S. has no conflict of interest.

AUTHOR CONTRIBUTIONS

Y.H.L. was involved in conception and design of study, acquisition of data, analysis and/or interpretation of data, drafting the manuscript, revising the manuscript critically for important intellectual content. G.G.S. was involved in conception and design of study, analysis and interpretation of data, drafting the manuscript.

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