

Serum leptin levels may be correlated with cerebral infarction

Kun-Bin Li, Xian-Li Yao, Ping-Ge Sun, Zhi-Yuan Wu, Xiao-Xing Li, Jun-Qi Liu, Yi-Lan Li¹

Department of Neurological Rehabilitation, ¹Department of Rehabilitation Medicine, Zhengzhou Central Hospital, Zhengzhou University, Zhengzhou, People's Republic of China

Background: To investigate the relation between serum leptin levels and cerebral infarction (CI) by meta-analysis. **Materials and Methods:** Scientific literature databases were searched for studies published in Chinese and English. After retrieving relevant articles through database searches and screening using predefined selection criteria, high-quality studies related to our research topic were selected for inclusion in this meta-analysis. All statistical analyses were conducted using Comprehensive Meta-Analysis 2.0 (CMA 2.0, Biostat Inc., Englewood, New Jersey, USA). **Results:** The study results revealed that serum leptin levels were significantly higher in CI patients as compared to normal controls. The outcomes of subgroup analysis by ethnicity suggested that the serum leptin levels in CI patients were significantly higher than normal controls in both Asian and Caucasian populations. Further, subgroup analysis based on the detection method indicated that the serum leptin levels in CI patients were significantly higher compared with normal controls when measured by radioimmunoassay (RIA) but enzyme-linked immunosorbent assay (ELISA)-based measurements did not show such statistically significant differences. **Conclusion:** Our meta-analysis results suggest that serum leptin levels in CI patients may be closely correlated with CI risks.

Key words: Case-control study, cerebral infarction (CI), leptin, meta-analysis, serum levels

How to cite this article: Li KB, Yao XL, Sun PG, Wu ZY, Li XX, Liu JQ, Li YL. Serum leptin levels may be correlated with cerebral infarction. *J Res Med Sci* 2016;21:4.

INTRODUCTION

Cerebral infarction (CI) or cerebral ischemic stroke (IS) is a focal brain necrosis mainly caused by complete disruption of blood circulation to the brain region, leading to hypoxia and prolonged ischemia.^[1] CI, commonly in the older population, is the most common cause of disability as well as the second leading cause of mortality in the world.^[2,3] Apart from its complex clinical manifestations, CI is correlated with unfavorable outcomes that pose a heavy long-term burden on the society in terms of health-care costs and patient care; a previous study revealed that multiple physiopathological parameters, such as inflammation, necrosis, apoptosis, oxidative stress, hypercoagulable state, and vascular dysfunction, could be applied to evaluate CI pathogenesis.^[4] Notably, despite the

identification of some of the major risk factors for CI, including advancing age, low cerebrospinal fluid (CSF), white blood cell count, and systemic inflammation,^[5,6] effective prevention and therapeutic interventions for CI are currently not available due to the complexity of the disease and lack of reliable biomarkers for early detection. Interestingly, in this regard, a previous study has suggested that changes in the levels of certain proteins found in serum, such as serum leptin, could be associated with the pathogenesis of CI.^[7]

Leptin, a small protein of 167 amino acids, is a critical pleiotropic hormone secreted by white adipose tissue, playing an essential role in signaling to the central nervous system, as part of a feedback loop, to inhibit food intake and also activate several pathways important in the regulation of energy balance and body weight.^[8,9] Thus, the multiple effects of leptin in the human body appears to correlate with a central

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DOI:

10.4103/1735-1995.175160

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Address for correspondence: Dr. Yi-Lan Li, Department of Rehabilitation Medicine, Zhengzhou Central Hospital, Zhengzhou University, No. 61 Funiu Road, Zhengzhou - 450 007, People's Republic of China. E-mail: liyilan_0505@126.com

Received: 15-06-2015; **Revised:** 04-08-2015; **Accepted:** 28-11-2015

theme of sensing the levels of fat stores in the body and accordingly, signaling to specific brain areas to regulate food-seeking behavior, hormonal balance, and energy metabolism. In addition, leptin plays a crucial role in glucose and lipid homeostasis, immune response, fertility and reproduction, bone physiology, inflammation, and tissue remodeling.^[10,11] Although the major role of serum leptin appears to be related to obesity and insulin resistance, recent reports have suggested that leptin also plays a significant role in CI,^[12,13] and leptin might be an independent risk factor for CI, with higher serum levels of leptin reflecting increased CI risk.^[14] However, this significant correlation, potentially valuable for early detection and treatment of CI, was not found by other studies and was attributed to the comparatively small sample size in those studies.^[15,16] Considering the urgent need to identify reliable biomarkers for CI, we performed a comprehensive meta-analysis to test the association between serum leptin levels and CI.

MATERIALS AND METHODS

Search strategy

Published studies were retrieved using a systematic search of the following English and Chinese databases from inception to October 2014: PubMed, EBSCO, Ovid, Springerlink, Wiley, Web of Science, Wanfang, China National Knowledge Infrastructure (CNKI), and VIP database, with these search terms: cerebral infarction or CI, ischemia stroke, stroke, intracranial embolism, brain infarction, leptin, obesity hormone, recombination leptin, and antiobesity factor. The database search was conducted independently by two coauthors.

Selection criteria

Two authors independently reviewed each clinical trial and determined the eligibility for selection of the studies for this meta-analysis on the basis of the following inclusion criteria:

1. Research topic: The association of serum leptin levels with CI;
2. Study design;
3. Study subjects: Patients with a clinical diagnosis of CI and further proved by computed tomography (CT);
4. End outcomes: Serum leptin levels of the case group and control group.

The exclusion criteria were:

1. Reviews and editorials;
2. Animal studies;
3. Duplicated articles;
4. Data unavailable for meta-analysis;
5. For overlapping articles, only the most complete or recent study was incorporated.

Statistical analyses

To assess the relation of serum leptin levels to CI, standard mean difference (SMD) at 95% confidence interval (CI) was calculated using a fixed effects model or random effects model. The significance of overall effect size was performed using Z-test.^[17] Homogeneity across studies was assessed by the Q statistic with significance set at $P_h < 0.05$.^[18] The I^2 test was employed as a second measure of heterogeneity at 0-100% range, with 0% suggesting no existence of heterogeneity and greater than 50% showing high heterogeneity.^[19] A random effects model was used when significant heterogeneity was found ($P_h < 0.05$ or $I^2 > 50%$); otherwise, the fixed effects model was applied.^[19] Univariate and multifactor meta-regression analyses were performed to test the source of heterogeneity, and further examined by the Monte Carlo method.^[18,20,21] To measure the effect of a single study on the overall results, sensitivity analysis was applied in the present meta-analysis. Publication bias and reliability of studies were examined by funnel plots, classic fail-safe N test, and Egger's test.^[22-24] All data analyses were performed using the Comprehensive Meta-Analysis (CMA) 2.0 (Biostat Inc., Englewood, New Jersey, USA) software and all tests were two-sided ($P < 0.05$ represents statistical significance).

RESULTS

Baseline characteristics

We initially retrieved 302 articles from our database search and subsequently, rejected 2 duplicate studies, 9 reviews or letters, 85 animal studies, and 79 studies that were not relevant to our topic of interest. The remaining 127 studies were screened using our stringent inclusion criteria and studies that were noncohort/case-control studies ($n = 37$), had low relevance to our topic ($n = 75$), or contained incomplete data ($n = 1$)^[25] were further excluded. Finally, a total of 14 case-control studies published between 2004 and 2014 were selected for this meta-analysis based on their high quality.^[14-16,26-36] The selected studies included a combined total of 2,372 patients with CI and 11,208 healthy controls, with 7 studies performed among Caucasians and 7 in the Asian population. Among five trials, the detection method was used applying enzyme-linked immunosorbent assay (ELISA), and radioimmunoassay (RIA) was used in another 9 trials. Baseline characteristics of the included studies are shown in Table 1.

The correlation of serum leptin levels and cerebral infarction

In the present study, significant heterogeneity was detected and accordingly, a random effects model was employed ($I^2 = 99.298%$, $P_h < 0.001$). The results of this analysis revealed that serum leptin levels in CI patients were significantly higher compared to normal controls (SMD = 1.654, 95%

Table 1: Baseline characteristics of 14 included studies

First author	Year	Country	Ethnicity	Detection Method	Number		BMI (kg/m ²)		Gender (M/F)		Age (years)	
					Case	Control	Case	Control	Case	Control	Case	Control
Soderberg ^[26]	2004	Sweden	Caucasians	RIA	276	552	27.0 (26.5-27.5)	25.9 (25.6-26.2)	157/119	314/238	54.9 (53.9-55.9)	54.9 (54.2-55.6)
Xia ^[27]	2006	China	Asians	ELISA	54	57	≤27	≤27	NR	NR	NR	NR
Wang ^[28]	2008	China	Asians	RIA	62	60	NR	NR	34/28	32/28	62.2±7.5	61.2±5.5
Jaleel ^[29]	2010	Philippines	Asians	ELISA	40	40	NR	NR	NR	NR	58.2 ± 0.9	58.0 ± 0.9
Liu ^[30]	2010	USA	Caucasians	RIA	225	4571	31.0±6.5	31.5±7.0	93/132	1643/2928	NR	NR
Wang ^[31]	2010	China	Asians	RIA	60	40	NR	NR	37/23	21/19	60.6±5.7	57.2±8.1
Rajpathak ^[32]	2011	USA	Caucasians	RIA	972	972	27.7±5.9	27.0±5.3	0/972	0/972	68.7±6.4	68.7±6.4
Bienek ^[33]	2012	Poland	Caucasians	RIA	69	26	27.3±4.38	26.01±3.18	32/37	12/14	70.2±13.0	65.1±13.8
Kim ^[34]	2012	Korea	Asians	ELISA	26	48	24.4±3.0	24.1±3.1	22/4	29/19	64.0±12.1	61.9±10.4
Lukasik ^[34]	2012	Poland	Caucasians	ELISA	184	78	28.2±4.8	28.6±5.3	89/95	38/40	61.5±8.5	63.0±12.0
Prugger ^[35]	2012	France	Caucasians	ELISA	80	160	NR	NR	NR	NR	55.5±2.9	55.4±2.7
Zhang ^[35]	2012	China	Asians	RIA	33	35	NR	NR	30/3	NR	71-79	80-89
Bidulescu ^[36]	2013	USA	Caucasians	RIA	87	4491	31.2±5.85	31.35±6.95	31/56	1602/2889	NR	NR
Xue ^[36]	2014	China	Asians	RIA	204	78	NR	NR	NR	NR	52-79	53-82

BMI = Body mass index; M = Male; F = Female; NR = Not reported; ELISA = Enzyme-linked immunosorbent assay; RIA = Radioimmunoassay

CI = 0.829~2.479, $P < 0.001$) [See Figure 1]. The results of subgroup analysis by ethnicity also showed that serum leptin levels were significantly higher in CI patients than normal controls in both the Asian and Caucasian populations (Asians: SMD = 1.018, 95% CI = 0.490~1.545, $P < 0.001$; Caucasians: SMD = 2.244, 95% CI = 0.909~3.578, $P = 0.001$) [Figure 2a]. Interestingly, additional subgroup analysis based on the detection method revealed that when the serum leptin levels were measured by RIA, CI patients exhibited significantly higher leptin levels compared to normal controls (SMD = 2.508, 95% CI = 1.430 ~ 3.586, $P < 0.001$); for serum leptin levels detected by ELISA, no significant difference was found (SMD = 0.121, 95%CI = -0.559 ~ 0.801, $P = 0.728$) [Figure 2b].

Source of heterogeneity

The sensitivity analysis results demonstrated that all included studies had no apparent influence on pooled SMD [as shown in Figure 3]. The funnel plot was symmetrical suggesting no obvious publication bias, and was further confirmed by applying classic fail-safe N test and Egger’s test (all $P > 0.05$) [shown in Figure 4]. Univariate and multifactor meta-regression analyses showed that country, ethnicity, language, and detection method were not the source of heterogeneity or the key factors influencing the overall effect size ($P > 0.05$) [See Figure 5 and Table 2].

DISCUSSION

The major purpose of this meta-analysis was to determine the correlation between serum leptin level and CI risk. Additionally, we were interested in the specific methods employed in the selected studies as potential influencing factors in obtaining disease correlations between serum leptin and CI. The overall results demonstrated that serum leptin levels in CI patients were significantly higher compared to normal individuals. Thus, based on our results, leptin serum levels are closely correlated with CI risk and leptin may be a useful biomarker for the early diagnosis of CI.

The restricted energy supply to the brain is the underlying cause and is a hallmark of CI because of the disrupted delivery of oxygen and glucose, which slows or stops

Table 2: Meta-regression analysis of potential source of heterogeneity

Heterogeneity factors	Coefficient	SE	t	P (adjusted)	95% CI	
					LL	UL
Country	-1.965	0.625	-3.15	0.062	-3.379	-0.552
Ethnicity	-1.478	2.574	-0.57	0.876	-7.301	4.346
Language	-3.974	2.791	-1.42	0.426	-10.288	2.340
Detection method	0.215	2.042	0.11	1.000	-4.404	4.833

CI = Confidence interval; SE = Standard error; LL = Lower limit; UL = Upper limit

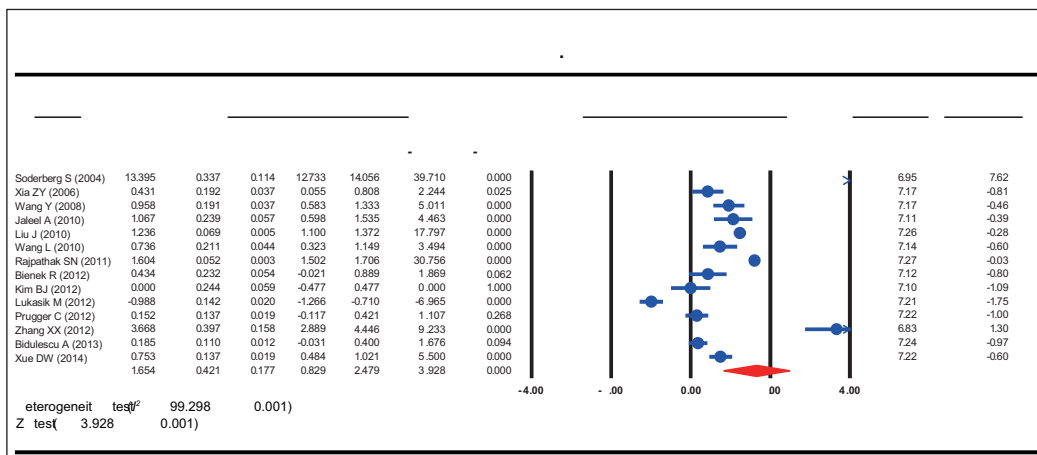


Figure 1: Forest plot for differences in serum leptin levels between cerebral infarction patients and healthy controls

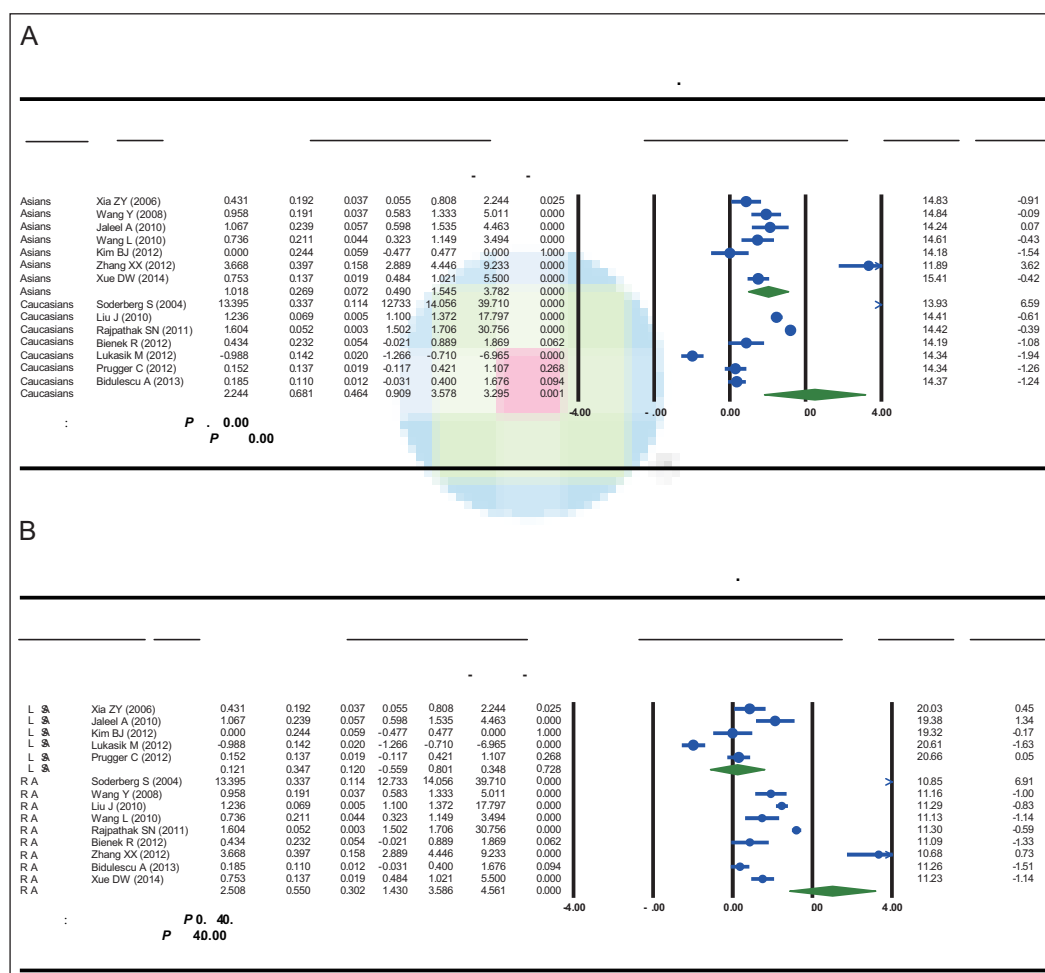


Figure 2: Subgroup analyses for sources of heterogeneity in the associations of serum leptin levels and cerebral infarction patients (a) Subgroup analyses based on ethnicity (b) Subgroup analyses based on the detection method

ATP synthesis required to maintain membrane potential differences and ionic gradients.^[37,38] Previous studies have shown links between obesity and increased CI risk. In this respect, studies observed that leptin secretion from fatty tissue is increased in the obese condition and promptly decreases upon weight reduction.^[33,39] Leptin is closely

related to mechanisms that regulate fat stores in the body and to the body mass through its influence on hunger and satiety centers in the brain, and also boosts energy expenditure as an anorexigenic factor.^[40] Leptin has a remarkable impact on inflammatory pathways and the pituitary hormonal axes, indirectly affecting the secretion

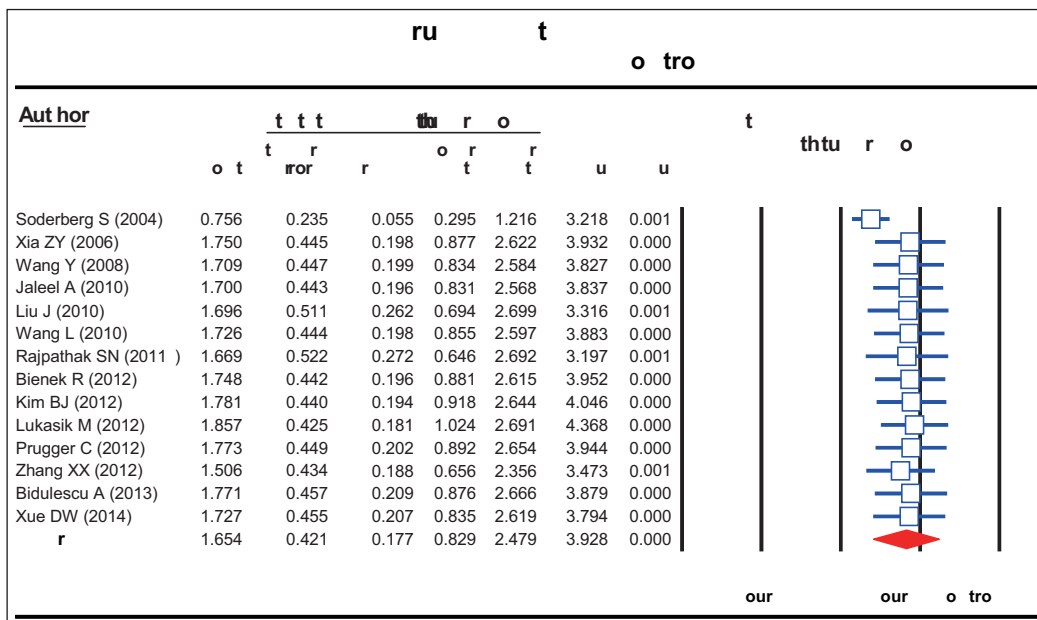


Figure 3: Sensitivity analysis for the differences of serum leptin levels between cerebral infarction patients and healthy controls in the present study

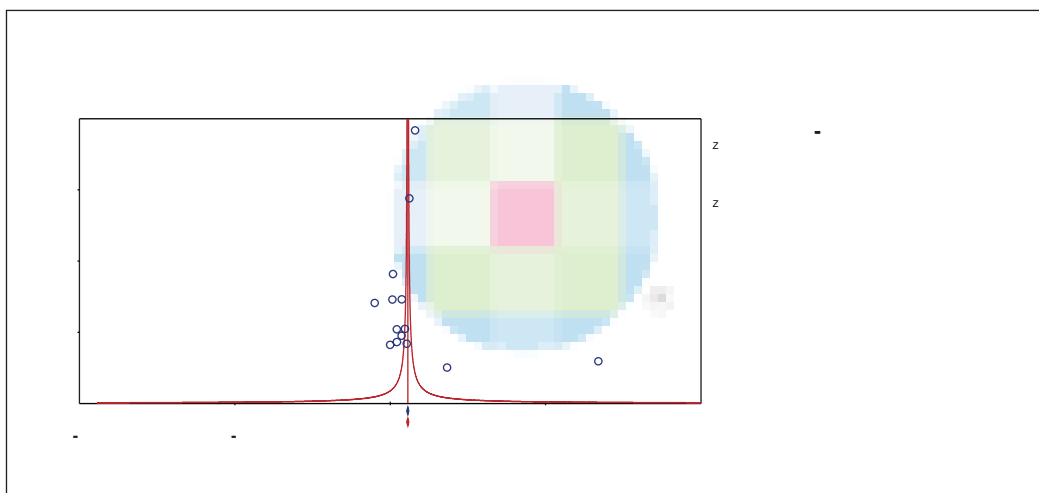


Figure 4: Funnel plots, classic fail-safe N test and Egger's test for assessing the publication bias of included studies by comparing the serum leptin levels between cerebral infarction patients and healthy controls

of thyroid hormones, glucocorticoids, catecholamines, and androgens.^[41,42] Significantly, leptin could mediate cardiovascular disease outcomes via its involvement in the neuroendocrine and metabolic pathways related to blood pressure, with direct effects on the vascular wall, thrombocytes, and endothelium.^[33,43] Moreover, leptin could induce neuroprotection neurogenesis and angiogenesis after stroke as well as cause increase of leptin receptor and potent AMP kinase concentrations.^[44] Previous studies have suggested that leptin might be a vital risk factor for CI, with higher serum levels of leptin reflecting increased CI risk, and it is in accordance with our results where the serum levels of leptin in CI patients were remarkably higher than normal individuals, suggesting that leptin might be strongly linked to CI risk.^[12,14] In study

of Avraham *et al.*, the outcomes suggested that PI3K/Akt pathway might be the critical pathway for the mediation of leptin-induced CI.^[37] Furthermore, results of Zhang *et al.* suggested that the neuroprotective effects of leptin against CI might be closely related with the upregulation of CGRP levels.^[45]

The subgroup analysis based on ethnicity indicated that serum leptin levels in CI patients were higher, compared to normal individuals among both Asians and Caucasians. Additional subgroup analysis based on the detection method revealed that the serum leptin levels in CI patients were significantly higher compared to healthy controls when RIA was the method used but no such difference was found when ELISA was the method used for leptin

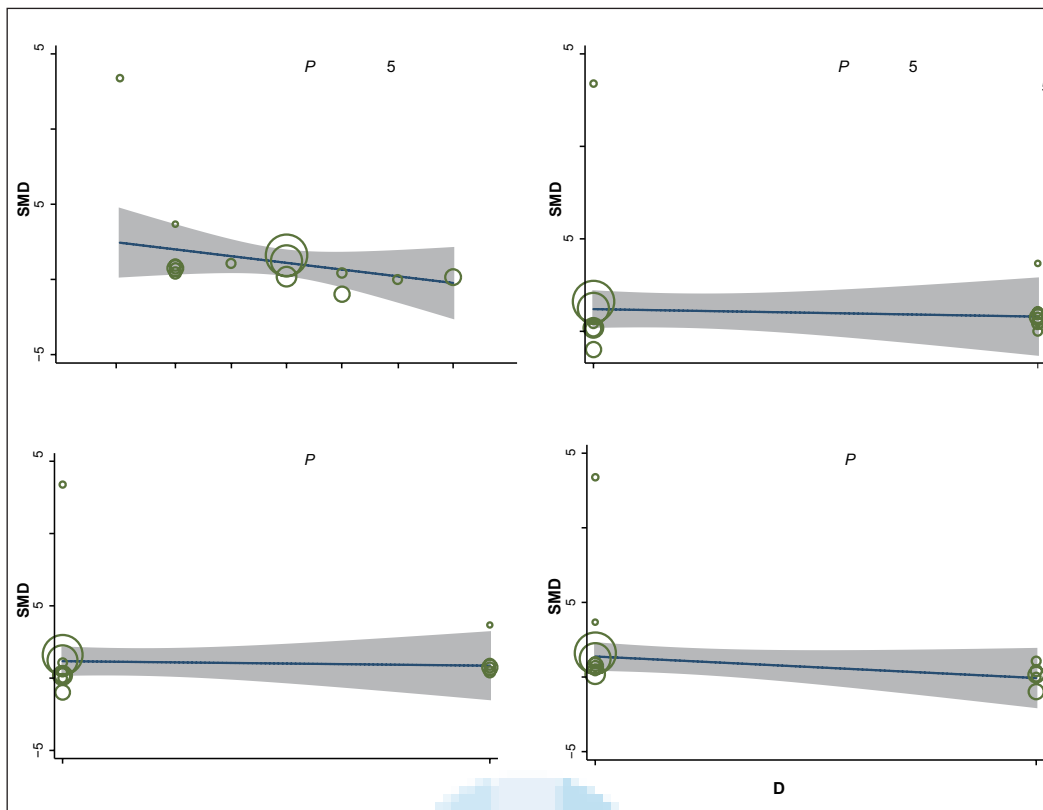


Figure 5: Univariate and multifactor meta-regression analyses to explore the source of heterogeneity (a) univariate and multifactor meta-regression analyses on country (b) univariate and multifactor meta-regression analyses on ethnicity (c) univariate and multifactor meta-regression analyses on language (d) univariate and multifactor meta-regression analyses on the detection method

measurement. Generally, the detection of leptin using RIA was done as follows: dilutions, buffer solution, samples, marked leptin, and antibody were added into each tube in proper order at 4°C for 24 h. Immune separation agent was used; the liquid was shaking for 3 min, and was separated for 15min (3,500 r/min). Supernatant fluid was absorbed and discarded. A small portion of each solution was calculated to determine total radioactivity. The detection of leptin by ELISA was conducted as follows: veinal blood 4.5 mL was obtained from each object of study after 1h; blood was separated using centrifugation and divided into equal parts stored at -80°C, and blood serum was estimated with kits supplied by Linco Research, St. Charles, MO, USA. RIA is a sensitive detection method and its very high signal-to-noise ratio is a significant advantage over ELISA-based methods, when high sensitivity is a crucial factor in diagnosis.^[46] Therefore, we believe that the results of subgroup analysis based on detection methods is likely related to the much higher sensitivity of RIA compared to ELISA. As such, future studies and clinical applications should consider our results as a guideline for selecting the appropriate method, at least for serum leptin measurements in CI patients.

Some limitations of the present study should be acknowledged. Although we made significant efforts to limit the inclusion of studies to only those that contained

sufficient data, a few selected articles still had incomplete information in the present meta-analysis, which might have influenced our results. The data about other biomarkers of CI including adiponectin, IL-6 provided by included studies were insufficient and accordingly we only analyzed the correlation of serum leptin levels with CI. Furthermore, we could not conduct subgroup analysis on CI owing to insufficient data. Thus, the novelty of our results may be low, and further studies considering other biomarkers and subgroup analysis on CI should be conducted.

CONCLUSION

In conclusion, our meta-analysis results indicated that leptin serum levels closely correlate with CI risks. Additionally, our study revealed differences between the methods used for measurement of serum leptin levels, and may be used as a cautionary note for future studies when choosing between RIA and ELISA.

Acknowledgments

We would like to acknowledge the helpful comments on this paper received from our reviewers.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

KBL designed the study, conceived and supervised the study, performed the examination and the analysis and drafted the paper. XLY conceived and supervised the study, performed the statistical analysis, and interpreted the results. PGS and ZYW performed the statistical analysis, interpreted the results, and drafted the paper. XXL, JQL and YLL performed the examination and the analysis, performed the statistical analysis, and interpreted the results.

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