Serum leptin levels may be correlated with cerebral infarction

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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

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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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/m²)		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[14]	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[15]	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[16]	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

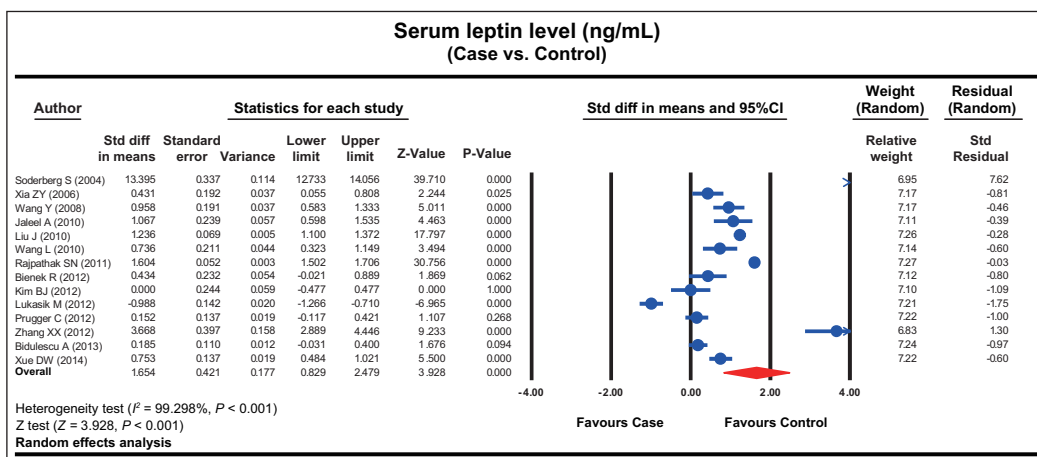CI = Confidence interval; SE = Standard error; LL = Lower limit; UL = Upper limit

Serum leptin level (ng/mL)
(Case vs. Control)

Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Std diff in means and 95%CI	Relative weight	Std Residual
Soderberg S (2004)	13.395	0.337	0.114	12733	14.056	39.710	0.000		6.95	7.62
Xia ZY (2006)	0.431	0.192	0.037	0.055	0.808	2.244	0.025		7.17	-0.81
Wang Y (2008)	0.958	0.191	0.037	0.583	1.333	5.011	0.000		7.17	-0.46
Jaleel A (2010)	1.067	0.239	0.057	0.598	1.535	4.463	0.000		7.11	-0.39
Liu J (2010)	1.236	0.069	0.005	1.100	1.372	17.797	0.000		7.26	-0.28
Wang L (2010)	0.736	0.211	0.044	0.323	1.149	3.494	0.000		7.14	-0.60
Rajpathak SN (2011)	1.604	0.052	0.003	1.502	1.706	30.756	0.000		7.27	-0.03
Bienek R (2012)	0.434	0.232	0.054	-0.021	0.889	1.869	0.062		7.12	-0.80
Kim BJ (2012)	0.000	0.244	0.059	-0.477	0.477	0.000	1.000		7.10	-1.09
Lukasik M (2012)	-0.988	0.142	0.020	-1.266	-0.710	-6.965	0.000		7.21	-1.75
Prugger C (2012)	0.152	0.137	0.019	-0.117	0.421	1.107	0.268		7.22	-1.00
Zhang XX (2012)	3.668	0.397	0.158	2.889	4.446	9.233	0.000		6.83	1.30
Bidulescu A (2013)	0.185	0.110	0.012	-0.031	0.400	1.676	0.094		7.24	-0.97
Xue DW (2014)	0.753	0.137	0.019	0.484	1.021	5.500	0.000		7.22	-0.60
Overall	1.654	0.421	0.177	0.829	2.479	3.928	0.000			

Heterogeneity test ($I^2 = 99.298\%$, $P < 0.001$)
Z test ($Z = 3.928$, $P < 0.001$)
Random effects analysis

Favours Case   Favours Control

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

A

Serum leptin level (ng/mL)
(Ethnicity: Case VS. Control)

Group by Ethnicity	Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Std diff in means and 95%CI	Relative weight	Std Residual
Asians	Xia ZY (2006)	0.431	0.192	0.037	0.055	0.808	2.244	0.025		14.83	-0.91
Asians	Wang Y (2008)	0.958	0.191	0.037	0.583	1.333	5.011	0.000		14.84	-0.09
Asians	Jaleel A (2010)	1.067	0.239	0.057	0.598	1.535	4.463	0.000		14.24	0.07
Asians	Wang L (2010)	0.736	0.211	0.044	0.323	1.149	3.494	0.000		14.61	-0.43
Asians	Kim BJ (2012)	0.000	0.244	0.059	-0.477	0.477	0.000	1.000		14.18	-1.54
Asians	Zhang XX (2012)	3.668	0.397	0.158	2.889	4.446	9.233	0.000		11.89	3.62
Asians	Xue DW (2014)	0.753	0.137	0.019	0.484	1.021	5.500	0.000		15.41	-0.42
Asians		1.018	0.269	0.072	0.490	1.545	3.782	0.000			
Caucasians	Soderberg S (2004)	13.395	0.337	0.114	12733	14.056	39.710	0.000		13.93	6.59
Caucasians	Liu J (2010)	1.236	0.069	0.005	1.100	1.372	17.797	0.000		14.41	-0.61
Caucasians	Rajpathak SN (2011)	1.604	0.052	0.003	1.502	1.706	30.756	0.000		14.42	-0.39
Caucasians	Bienek R (2012)	0.434	0.232	0.054	-0.021	0.889	1.869	0.062		14.19	-1.08
Caucasians	Lukasik M (2012)	-0.988	0.142	0.020	-1.266	-0.710	-6.965	0.000		14.34	-1.94
Caucasians	Prugger C (2012)	0.152	0.137	0.019	-0.117	0.421	1.107	0.268		14.34	-1.26
Caucasians	Bidulescu A (2013)	0.185	0.110	0.012	-0.031	0.400	1.676	0.094		14.37	-1.24
Caucasians		2.244	0.681	0.464	0.909	3.578	3.295	0.001			

Asians: Z test ($Z = 3.782$, $P < 0.001$)
Caucasians: Z test ($Z = 3.295$, $P = 0.001$)
Random effect analysis

Favours Case   Favours Control

B

Serum leptin level (ng/mL)
(Detection Method: Case VS. Control)

Group by Detection Method	Author	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Std diff in means and 95%CI	Relative weight	Std Residual
ELISA	Xia ZY (2006)	0.431	0.192	0.037	0.055	0.808	2.244	0.025		20.03	0.45
ELISA	Jaleel A (2010)	1.067	0.239	0.057	0.598	1.535	4.463	0.000		19.38	1.34
ELISA	Kim BJ (2012)	0.000	0.244	0.059	-0.477	0.477	0.000	1.000		19.32	-0.17
ELISA	Lukasik M (2012)	-0.988	0.142	0.020	-1.266	-0.710	-6.965	0.000		20.61	-1.63
ELISA	Prugger C (2012)	0.152	0.137	0.019	-0.117	0.421	1.107	0.268		20.66	0.05
ELISA		0.121	0.347	0.120	-0.559	0.801	0.348	0.728			
RIA	Soderberg S (2004)	13.395	0.337	0.114	12733	14.056	39.710	0.000		10.85	6.91
RIA	Wang Y (2008)	0.958	0.191	0.037	0.583	1.333	5.011	0.000		11.16	-1.00
RIA	Liu J (2010)	1.236	0.069	0.005	1.100	1.372	17.797	0.000		11.29	-0.83
RIA	Wang L (2010)	0.736	0.211	0.044	0.323	1.149	3.494	0.000		11.13	-1.14
RIA	Rajpathak SN (2011)	1.604	0.052	0.003	1.502	1.706	30.756	0.000		11.30	-0.59
RIA	Bienek R (2012)	0.434	0.232	0.054	-0.021	0.889	1.869	0.062		11.09	-1.33
RIA	Zhang XX (2012)	3.668	0.397	0.158	2.889	4.446	9.233	0.000		10.68	0.73
RIA	Bidulescu A (2013)	0.185	0.110	0.012	-0.031	0.400	1.676	0.094		11.26	-1.51
RIA	Xue DW (2014)	0.753	0.137	0.019	0.484	1.021	5.500	0.000		11.23	-1.14
RIA		2.508	0.550	0.302	1.430	3.586	4.561	0.000			

ELISA: Z test ($Z = 0.348$, $P = 0.728$)
RIA: Z test ($Z = 4.561$, $P < 0.001$)
Random effect analysis
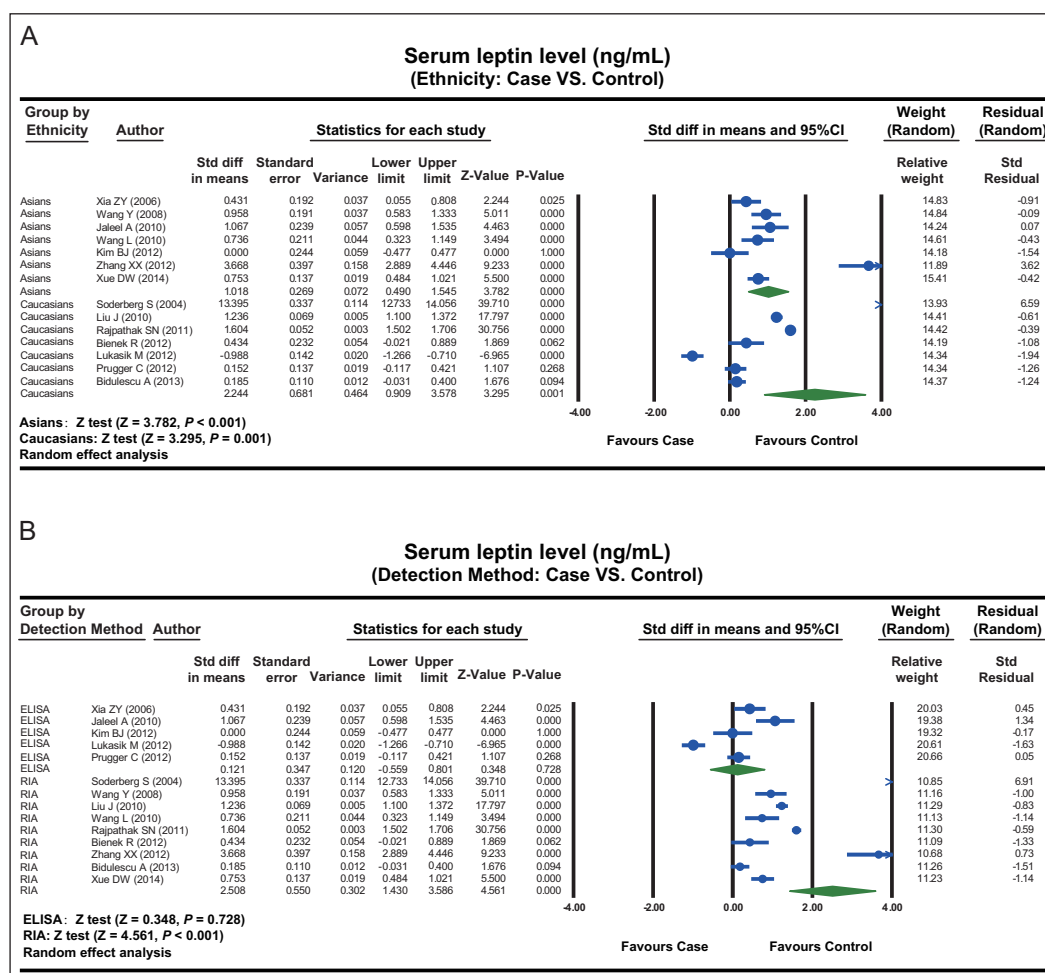
Favours Case   Favours Control

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
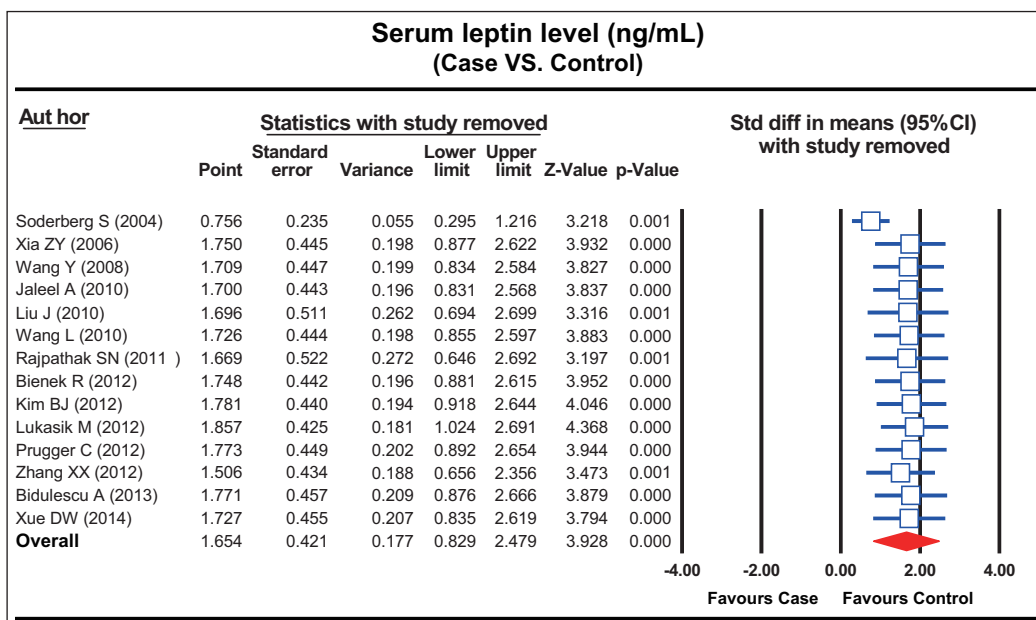
Serum leptin level (ng/mL)
(Case VS. Control)

Aut hor	Statistics with study removed							Std diff in means (95% CI) with study removed
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Soderberg S (2004)	0.756	0.235	0.055	0.295	1.216	3.218	0.001	
Xia ZY (2006)	1.750	0.445	0.198	0.877	2.622	3.932	0.000	
Wang Y (2008)	1.709	0.447	0.199	0.834	2.584	3.827	0.000	
Jaleel A (2010)	1.700	0.443	0.196	0.831	2.568	3.837	0.000	
Liu J (2010)	1.696	0.511	0.262	0.694	2.699	3.316	0.001	
Wang L (2010)	1.726	0.444	0.198	0.855	2.597	3.883	0.000	
Rajpathak SN (2011)	1.669	0.522	0.272	0.646	2.692	3.197	0.001	
Bienek R (2012)	1.748	0.442	0.196	0.881	2.615	3.952	0.000	
Kim BJ (2012)	1.781	0.440	0.194	0.918	2.644	4.046	0.000	
Lukasik M (2012)	1.857	0.425	0.181	1.024	2.691	4.368	0.000	
Prugger C (2012)	1.773	0.449	0.202	0.892	2.654	3.944	0.000	
Zhang XX (2012)	1.506	0.434	0.188	0.656	2.356	3.473	0.001	
Bidulescu A (2013)	1.771	0.457	0.209	0.876	2.666	3.879	0.000	
Xue DW (2014)	1.727	0.455	0.207	0.835	2.619	3.794	0.000	
Overall	1.654	0.421	0.177	0.829	2.479	3.928	0.000	

-4.00   -2.00   0.00   2.00   4.00

Favours Case   Favours Control

Figure 3: Sensitivity analysis for the differences of serum leptin levels between cerebral infarction patients and healthy controls in the present study
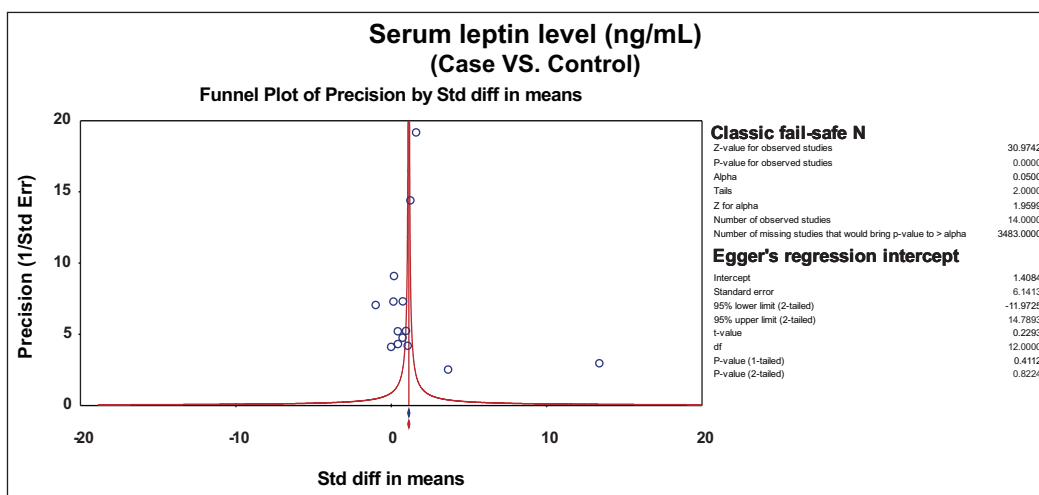
Figure 4: Funnel plots, classic fail-safe N test and Egger's test for assessing the publication bias of included studies by comparing the serum leptin levels between cerebral infarction patients and healthy controls

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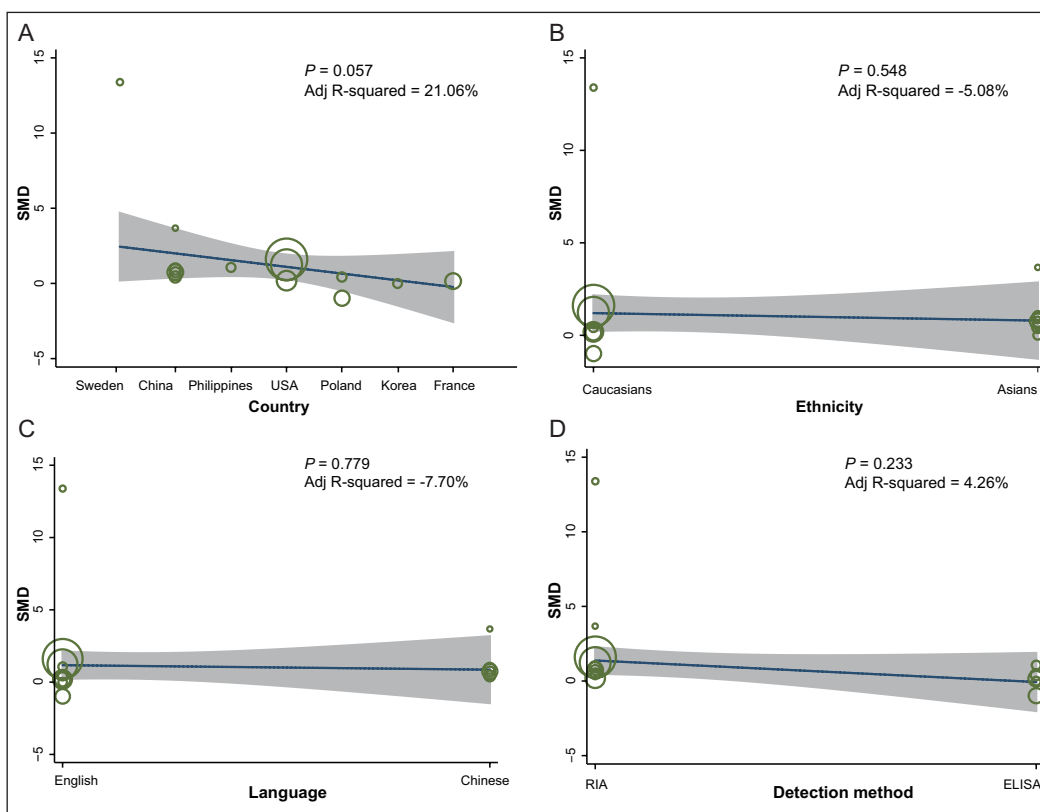
Figure 5: Univariate and multifactor meta-regression analyses to explore the source of heterogeneity (a) univariate and multifactor meta-regression analyses on country (b) univariate and multifactor meta-regression analyses on ethnicity (c) univariate and multifactor meta-regression analyses on language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

measurement. Generally, the detection of leptin 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.

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.

REFERENCES

1. Zhang B, Wu T, Song C, Chen M, Li H, Guo R. Association of CD40 — 1C/T polymorphism with cerebral infarction susceptibility and its effect on sCD40L in Chinese population. Int Immunopharmacol 2013;16:461-5.
2. Park JH, Lee HS, Kim JH, Lee JH, Kim J, Choi SW. Reverse dipper and high night-time heart rate in acute stage of cerebral infarction are associated with increased mortality. J Stroke Cerebrovasc Dis 2014;23:1171-6.
3. Chen CH, Chang YJ, Sy HN, Chen WL, Yen HC. Risk assessment of the outcome for cerebral infarction in tuberculous meningitis. Rev Neurol (Paris) 2014;170:512-9.
4. Schut ES, Lucas MJ, Brouwer MC, Vergouwen MD, van der Ende A, van de Beek D. Cerebral infarction in adults with bacterial meningitis. Neurocrit Care 2012;16:421-7.
5. Katchanov J, Heuschmann PU, Endres M, Weber JR. Cerebral infarction in bacterial meningitis: Predictive factors and outcome. J Neurol 2010;257:716-20.
6. Ye H, Wang L, Yang XK, Fan LP, Wang YG, Guo L. Serum S100B levels may be associated with cerebral infarction: A meta-analysis. J Neurol Sci 2015;348:81-8.
7. Camerlingo M, Valente L, Tognozzi M, Beretta GL, Moschini L, Cesana BM. C-reactive protein levels in the first three hours after acute cerebral infarction. Int J Neurosci 2011;121:65-8.
8. Farr OM, Tsoukas MA, Mantzoros CS. Leptin and the brain: Influences on brain development, cognitive functioning and psychiatric disorders. Metabolism 2015;64:114-30.
9. Paz-Filho G, Mastronardi CA, Licinio J. Leptin treatment: Facts and expectations. Metabolism 2015;64:146-56.
10. Mantzoros CS, Magkos F, Brinkoetter M, Sienkiewicz E, Dardeno TA, Kim SY, *et al*. Leptin in human physiology and pathophysiology. Am J Physiol Endocrinol Metab 2011;301:E567-84.
11. Scotece M, Conde J, Lopez V, Lago F, Pino J, Gomez-Reino JJ, *et al*. Leptin in joint and bone diseases: New insights. Curr Med Chem 2013;20:3416-25.
12. Valerio A, Dossena M, Bertolotti P, Boroni F, Sarnico I, Faraco G, *et al*. Leptin is induced in the ischemic cerebral cortex and exerts neuroprotection through NF-kappaB/c-Rel-dependent transcription. Stroke 2009;40:610-7.
13. Amantea D, Tassorelli C, Russo R, Petrelli F, Morrone LA, Bagetta G, *et al*. Neuroprotection by leptin in a rat model of permanent cerebral ischemia: Effects on STAT3 phosphorylation in discrete cells of the brain. Cell Death Dis 2011;2:e238.
14. Kim BJ, Lee SH, Ryu WS, Kim CK, Yoon BW. Adipocytokines and ischemic stroke: Differential associations between stroke subtypes. J Neurol Sci 2012;312:117-22.
15. Prugger C, Luc G, Haas B, Arveiler D, Machez E, Ferrieres J, *et al*. Adipocytokines and the risk of ischemic stroke: The PRIME Study. Ann Neurol 2012;71:478-86.
16. Bidulescu A, Liu J, Chen Z, Hickson DA, Musani SK, Samdarshi TE, *et al*. Associations of adiponectin and leptin with incident coronary heart disease and ischemic stroke in African Americans: The Jackson Heart Study. Front Public Health 2013;1:16.
17. Chen H, Manning AK, Dupuis J. A method of moments estimator for random effect multivariate meta-analysis. Biometrics 2012;68:1278-84.
18. Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med 2012;31:3805-20.
19. Zintzaras E, Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. Genet Epidemiol 2005;28:123-37.
20. Huizenga HM, Visser I, Dolan CV. Testing overall and moderator effects in random effects meta-regression. Br J Math Stat Psychol 2011;64:1-19.
21. Ferrenberg AM, Swendsen RH. New Monte Carlo technique for studying phase transitions. Phys Rev Lett 1988;61:2635-8.
22. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. J Clin Epidemiol 2001;54:1046-55.
23. Wikstrom EA, Naik S, Lodha N, Cauraugh JH. Balance capabilities after lateral ankle trauma and intervention: A meta-analysis. Med Sci Sports Exerc 2009;41:1287-95.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
25. Jimenez I, Sobrino T, Rodríguez-Yáñez M, Pouso M, Cristobo I, Sabucedo M, *et al*. High serum levels of leptin are associated with post-stroke depression. Psychol Med 2009;39:1201-9.
26. Soderberg S, Stegmayr B, Stenlund H, Sjöström LG, Agren A, Johansson L, *et al*. Leptin, but not adiponectin, predicts stroke in males. J Intern Med 2004;256:128-36.
27. Xia ZY, Yang H, Cui KM, Gong DR. Study of plasma resistin and leptin levels and their correlation in patients with stroke. Chinese Journal of Geriatric Heart Brain and Vessel Diseases 2006;329-32.
28. Wang Y, Li QR, Li SY. Study of the correlation between leptin and acute stroke. Med J Qilu 2008;502-3+6.
29. Jaleel A, Aqil S, Jaleel S, Jaleel F. Adipocytokines in subjects with and without ischemic cerebrovascular disease. Acta Neurol Belg 2010;110:234-8.
30. Liu J, Butler KR, Buxbaum SG, Sung JH, Campbell BW, Taylor HA. Leptinemia and its association with stroke and coronary heart disease in the Jackson Heart Study. Clin Endocrinol (Oxf) 2010;72:32-7.
31. Wang L, Liu RZ. Changes and clinical significance of serum leptin and IL-6 levels in patients with acute cerebral infarction. Chinese Journal of Integrative Medicine on Cardio/Cerebrovascular Disease 2010;8:939-40.
32. Rajpathak SN, Kaplan RC, Wassertheil-Smoller S, Cushman M, Rohan TE, McGinn AP, *et al*. Resistin, but not adiponectin and leptin, is associated with the risk of ischemic stroke among postmenopausal women: Results from the Women's Health Initiative. Stroke 2011;42:1813-20.
33. Bienek R, Marek B, Kajdaniuk D, Borgiel-Marek H, Piecha T, Nowak M, *et al*. Adiponectin, leptin, resistin and insulin blood concentrations in patients with ischaemic cerebral stroke. Endokrynol Pol 2012;63:338-45.
34. Lukasik M, Michalak S, Dworacki G, Siewiera K, Kaczmarek M, Watala C, *et al*. Reactive leptin resistance and the profile of platelet activation in acute ischaemic stroke patients. Thromb Haemost 2012;108:107-18.

35. Zhang XX, Gu SM, Li SH. Clinical significance of the detection of plasma leptin, serum Hcy, hs-CRP, IL-6 in elderly ACI patients before and after treatment. J Radioimmunology 2012;25:414-6.
36. Xue DW, Yuan P, lI F. Studies on serum leptin and adiponectin levels in patients with acute cerebral infarction. Chinese Journal of Practical Internal Medicine 2014;34:91-3.
37. Zhang J, Deng Z, Liao J, Song C, Liang C, Xue H, *et al*. Leptin attenuates cerebral ischemia injury through the promotion of energy metabolism via the PI3K/Akt pathway. J Cereb Blood Flow Metab 2013;33:567-74.
38. Sims NR, Muyderman H. Mitochondria, oxidative metabolism and cell death in stroke. Biochim Biophys Acta 2010;1802:80-91.
39. Cho ER, Kim H, Seo HS, Suh S, Lee SK, Shin C. Obstructive sleep apnea as a risk factor for silent cerebral infarction. J Sleep Res 2013;22:452-8.
40. Kominiarek MA, Zhang J, Vanveldhuisen P, Troendle J, Beaver J, Hibbard JU. Contemporary labor patterns: The impact of maternal body mass index. Am J Obstet Gynecol 2011;205:244.e1-8.
41. Carlton ED, Demas GE, French SS. Leptin, a neuroendocrine mediator of immune responses, inflammation, and sickness behaviors. Horm Behav 2012;62:272-9.
42. Neidert S, Katan M, Schuetz P, Fluri F, Ernst A, Bingisser R, *et al*. Anterior pituitary axis hormones and outcome in acute ischaemic stroke. J Intern Med 2011;269:420-32.
43. Beltowski J. Leptin and atherosclerosis. Atherosclerosis 2006;189:47-60.
44. Avraham Y, Davidi N, Lassri V, Vorobiev L, Kabesa M, Dayan M, *et al*. Leptin induces neuroprotection neurogenesis and angiogenesis after stroke. Curr Neurovasc Res 2011;8:313-22.
45. Zhang JY, Yan GT, Liao J, Deng ZH, Xue H, Wang LH, *et al*. Leptin attenuates cerebral ischemia/reperfusion injury partially by CGRP expression. Eur J Pharmacol 2011;671:61-9.
46. Kuhre RE, Wewer Albrechtsen NJ, Hartmann B, Deacon CF, Holst JJ. Measurement of the incretin hormones: Glucagon-like peptide-1 and glucose-dependent insulinotropic peptide. J Diabetes Complications 2015;29:445-50.