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Visfatin Level and The Risk of Hypertension and Cerebrovascular Accident: A Systematic Review and Meta-Analysis

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ABSTRACT

High blood pressure is related with increased cerebrovascular accident. High visfatin / NAMPT(nicotinamide phosphoribosyltransferase) plasma levels may promote vascular inflammation and atherosclerotic plaque destabilization and have been evaluated as a marker for identifying stages of essential hypertension. However, its role in the pathogenesis of hypertension and cerebrovascular accident (CVA) is still uncertain. In order to review and meta-analyze observational studies investigating visfatin concentration and the risk for hypertension or CVA, a systematic search of PubMed, ovid EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) until December 07, 2016 was performed. After data extraction and quality assessment, a meta-analysis was performed using RevMan 5.3 and STATA 14.0. A total of 1693 adults from 8 studies for hypertension (974 with hypertension) and 1696 adults from 7 CVA studies (957 with CVA) were enrolled in the current meta-analysis. Cochran's Q-statistic and I^2 test were applied to estimate the heterogeneity of the studies. The fixed-effects were used to compute the weighted mean difference in visfatin levels. Plasma visfatin concentration was much higher in hypertension and CVA patients than in healthy individuals. These evidences suggested the association of hypertension and CVA with higher plasma visfatin level.

ABBREVIATIONS

AIS	Acute ischemic Stroke
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CV	Coefficient of variation
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
NAMPT	nicotinamide phosphoribosyltransferase
PBEF	Pre-B-cell colony-enhancing factor
QC	Quality control
SMD	Standard mean difference
SD	Standard deviation
VSMC	Vascular smooth muscle cell
WMD	Weighted mean difference

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Introduction

Adipose tissue is regarded as an active endocrine organ that secretes various biomolecules, called 'adipokines'. It is proved that many adipokines play potent roles in modulating lipid and glucose, energy balance, and other physiological activities. Studies show that obesity and insulin resistance are associated with cardiovascular and cerebrovascular diseases, including coronary heart disease, cerebrovascular accident (CVA), and heart failure, often with altered levels of adipocytokines [1, 2]. Scientists thus raise a research campaign on the role of adipokines in regulating whole body physiology.

Visfatin / NAMPT, known as pre-B-cell colony-enhancing factor (PBEF) and nicotinamide phosphoribosyltransferase, is a recently identified adipocytokine [3]. Latest research studies have shown that, besides adipocytes, there are a variety of cells that secrete visfatin, such as epithelial cells, heart cells, pancreatic cells, and hepatocytes [4]. It acts as with pleiotropic effector in metabolic and stress responses, which could affect angiogenesis, cell apoptosis, and cell proliferation [5, 6]. It is highly expressed in visceral fat and circulating levels correlated with obesity; previous studies reported a positive correlation between plasma visfatin and waist-to-hip ratio (WHR), Body Mass Index and lipid profiles [7, 8]. It is considered as a key modifier of atherosclerosis, chronic kidney disease, and acute myocardial infarction [9–14]. An animal study proved that circulating visfatin levels were not statistically different in spontaneously hypertensive rats, stroke-prone spontaneously hypertensive rats, and control rats [15]. The clinic trial reported that plasma visfatin concentrations were found to be elevated in patients with stroke or blood pressure [16, 17]. Therefore, the data were underpowered to show the relationship of visfatin with hypertension and CVA. Many more clinical trials were conducted from then on, which claim more detailed analysis to obtain a more accurate conclusion. We then carried out a meta-analysis to compare the plasma visfatin levels in subjects with or without hypertension or CVA.

Materials and Methods

Standard of systematic reviews

This study is designed and performed according to the "Transparent reporting of systematic reviews and meta-analyses" (PRISMA) guidelines. All data were collected from previous published studies cited in references. All data generated or analyzed during this study were included in this published article [and its supplementary information files].

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Systematic search and study selection

We searched PubMed, ovid EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL), until January 13, 2019 without language restrictions. As no human subjects or medical records were reviewed in this study, institutional review board approval was not required. For the PubMed search, the following terms were used: (((blood pressure) OR hypertension) OR ((stroke OR ((cerebrovascular OR cerebral) AND (event OR accident OR stroke OR disease)) OR ((ischaemic OR ischemic OR hemorrhagic) AND stroke) OR brain infarction OR cerebrovascular accident OR CVA))) AND (((nampt) OR visfatin)) to identify observational studies that reported the relation of plasma visfatin levels with hypertension or CVA in general adult population. Similar search terms were used for the EMBASE and Cochrane search. All searches were conducted without restrictions.

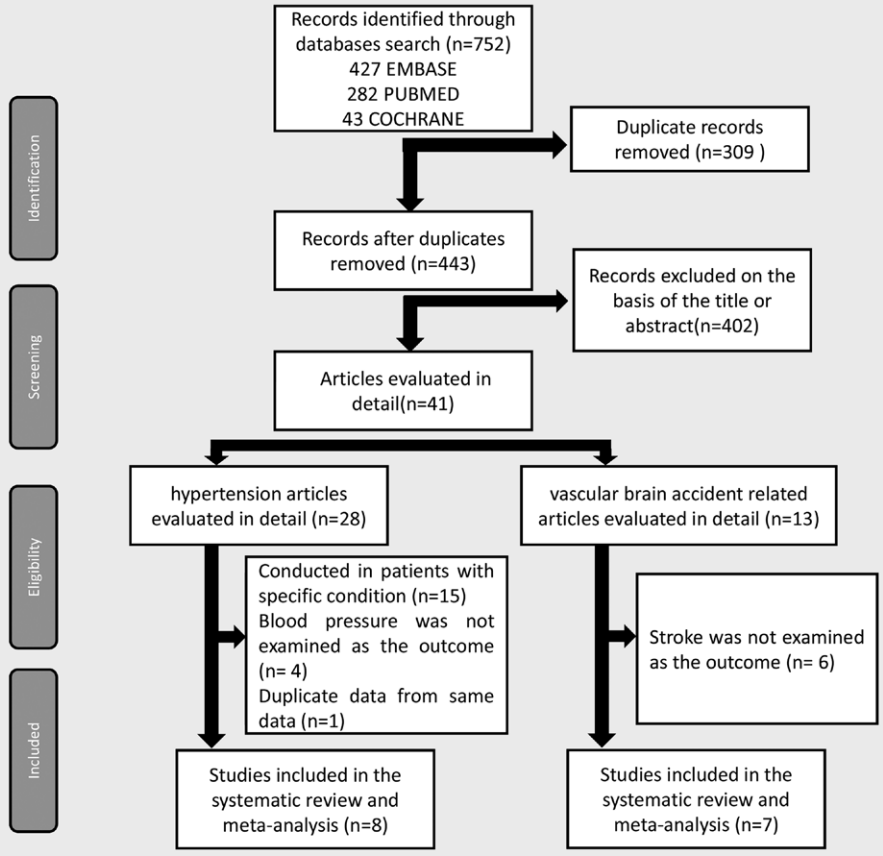
Only studies reporting on the association between human plasma visfatin concentration and hypertension or CVA were considered eligible. For hypertension and CVA, a full endpoint-criterion description had to be presented, or referred to in previously published articles. Studies were excluded if: 1) studies on animals or cell lines and studies of genetic variation in visfatin-related genes; 2) they were commentaries, or reviews; 3) hypertension or CVA was not an outcome; and 4) they were conducted in children, adolescents, or pregnant women. Besides, we also excluded patients with specific conditions (diabetes mellitus, coronary heart disease, and metabolic syndrome) in whom the relationship between visfatin and hypertension might differ (see ▶ **Fig. 1**). Research results were independently screened by two reviewers (F-X.Z. and P-L.Y) using a structured literature tool (Endnote X7, Thomson Reuters, USA). Any disagreements were resolved through consensus reached by discussion with a third researcher (C.W.).

Data extraction and quality assessment

Investigators (F-X.Z. and P-L.Y) used a standardized form to extract the following relevant data and another investigator (C.W.) independently confirmed their accuracy: study design, sample size, source population, mean age, definition of hypertension, mean and standard deviation (SD) of visfatin level, number of outcome events, and adjusted confounders. Disagreement was resolved by discussion with the third person (P-L.Y.). We assessed how visfatin levels were measured: assay method; timing of sample collection in relation to hypertension diagnosis; collection, process, and storage of sample; blinding of laboratory personnel; use of quality control (QC) sample; coefficient of variation (CV). The study quality was assessed using a previously proposed scale [3, 18]. We assessed each item individually.

Statistical analysis

We performed analyses to evaluate the relation between visfatin levels and the risk of hypertension or CVA. Cochran's Q-statistic and I^2 test were applied to estimate the heterogeneity of the studies firstly: if $I^2 > 50\,\%$ and $p < 0.05$, heterogeneity was considered to be significant; otherwise, not significant. Publication bias was investigated by Egger test and by visual inspection of the funnel plot. We pooled the weighted standard mean difference (SMD) between control and patient groups (hypertension or CVA), using the DerSimonian-Laird fixed-effects method to incorporate between-study heterogeneity. In addition, the single factor and multi-factor meta-regression analysis was utilized to assess the potential sources of heterogeneity.



▶ **Fig. 1** Process of literature search and study selection.

Statistical software

Review Manager 5.3 (Cochrane Editorial Unit, London, UK) software and STATA 14.0 (Stata Corporation, College Station, TX, USA) software were used to analyze the included studies. A 2-sided $p < 0.05$ was considered statistically significant.

Results

Search results and characteristics of included studies

From the initial search, 752 articles and abstracts (including 309 duplicates) were extracted. The evaluation excluded 402 of these, with 41 selected for full screening. Among these articles, 28 hypertension articles and 13 CVA related articles were assessed in detail. After final assessment, 8 hypertension articles and 6 CVA related articles were used for meta-analyses as shown in ▶ **Fig. 1**.

Our systematic search identified 8 studies that included 1693 adults (974 with hypertension) in Asia (3 studies), Europe (4 studies), and United States (1 study) (▶ **Table 1**) [19–26]. Most studies included middle-age adults, with 5 studies with a mean age ≥ 50 years. Eight studies examined incident hypertension and 6 studies diagnosed hypertension based on measurements over ≥ 2 separate visits. All studies are case-control studies, 5 of them applied matching criteria and the ratios of cases to controls were 1:1 in 1 study.

Our systematic search identified 6 CVA related studies that included 1522 adults (859 with CVA) in Asia (5 studies in China), and Europe (1 study) (▶ **Table 1**) [16, 27–31]. Most studies included middle-age adults, with 5 studies with a mean age ≥ 60 years. Three studies examined ischemic CVA and three studies diagnosed hemorrhagic incidents. All studies are case-control studies, 3 of them applied matching criteria and the ratios of cases to controls were 1:1 in 3 studies.

Quality of reporting on visfatin assay

The collection, process, and storage of sample are described in sufficient details in include studies (**Table 1S**). No studies collected blood samples before the diagnosis. Blinding of laboratory personnel was barely reported, and the use of QC sample was frequently reported. In all 14 studies, the intra-assay and inter-assay CVs were good to excellent (< 10 %), and the CVs of studies were not mentioned in others studies. Antihypertensive drugs were allowed at the time of sampling in 5 studies. We also presented the study quality in (**Table 2S**). Two of CVA studies were considered to be relatively 'high quality' (score 5), while other studies were not (score 2–4).

Visfatin levels between hypertensive and normotensive adults

Of 8 included studies, 6 studies reported that visfatin levels were significantly higher in hypertensive adults than in normotensive

▶ **Table 1** Characteristics of included studies.

Source (Published Year)	Country	Study design For Visfatin	Study Population	Sample Size *	Mean Age year	Patient Male %	Patient BMI kg/m^2	Inclusion criteria	Matching criteria
Hypertension studies (n = 8)									
Dogru [19] (2007)	Turkey	Case-control	Case: newly diagnosed and previously untreated hypertension Control: Normotensive adults	33 / 33	22.1 ± 2.5	100	24.0 ± 1.8	Patients were considered hypertensive if their BPs on three separate occasions exceeded 140 / 90 mmHg.	NR
Xia [20] (2015)	China	Case-control	Case: obesity and hypertension Control: BMI-matched, normal blood pressure	48 / 54	NA	0	22.2 ± 1.7	BP ≥ 140 / 90 mmHg or BP medication on two measurements	Age matched
Horbal [21] (2016)	USA	Case-control	The MH-GRID study	134 / 116	48.6 ± 6.0	33.3	33.9 ± 7.8	BP ≥ 140 / 90 mmHg	NR
Kocelak [22] (2015)	Poland	Case-control	The PolSenior study	591 / 2198	78 ± 8	52 %	NA	Average systolic BP values were at least 140 mmHg and / or average diastolic BP values were at least 90 mmHg based on two readings of BP measurements	NR
Gunes [23] (2012)	Turkey	Case-control	Case: newly diagnosed hypertensive patients Control: healthy participants	30 / 46	52.6±10.6	30.4 %	31.3 ± 4.4	Blood pressure was measured by the same investigator at each visit	Age -matched
Liakos [24] (2015)	Greece	Case-control	Case: high normal BP Control: normal or optimal BP	25 / 35	57 ± 4	25 %	24.0 ± 1.7	High normal BP was defined as SBP 130–139 and / or DBP 85–89 mmHg	matched for age, gender, smoking and body mass index (BMI)
Rotkegel [25] (2013)	Poland	Case-control	Case: hypertensive patients with visceral obesity Control: normotensive subjects with visceral obesity	12 / 11	42 ± 10	50 %	30.5 ± 2	Hypertension was defined according WHO criteria (RR ≥ 140 / 90 mm Hg or using hypertensive drugs).	matched for gender
Andreeva [26] (2013)	Ukraine	Case-control	Case: hypertension Control: normal blood pressure	28 / 19	59.3 ± 5.4	NR	NR	NR	Matched for age, gender
Vascular brain accident (n = 6)									
Gu [27] (2013)	China	Case-control	Case: intracerebral hemorrhage patients Control: age and sex matched individuals	85 / 85	65.9 ± 9.5	55.3 %	25.8 ± 2.2	Presented with acute spontaneous basal ganglia hemorrhage for the first time and were assessed within 6 h after the incident	Age- and sex-matched
Huang [28] (2013)	China	Case-control	Case: acute spontaneous basal ganglia hemorrhage patients Control: healthy individuals	128 / 128	63.6 ± 9.2	63.3 %	24.8 ± 2.3	Patients with acute basal ganglia hemorrhage	NR

▶ **Table 1** Continued.

Source (Published Year)	Country	Study design For Visfatin	Study Population	Sample Size *	Mean Age year	Patient Male %	Patient BMI kg/m²	Inclusion criteria	Matching criteria
Wang [29] (2013)	China	Case-control	Case: aneurysmal subarachnoid hemorrhage patients Control: age-matched healthy subjects	172 / 172	45.3 ± 12.1	76.7%	NR	Subarachnoid hemorrhage secondary to cerebral aneurysm rupture, which was confirmed by computerized tomography (CT) angiography with or without digital subtraction angiography of the four vessel	Sex and age-matched
Kadoglou [30] (2014)	Greece	Case-control	Case: acute ischemic stroke patients Control: stroke-free, age and sex matched individuals	168 / 58	70 ± 9	47.6%	29.09 ± 5.01	AIS was defined as a sudden focal neurologic defect lasting for more than 24 h and diagnosed on the basis of clinical history, neurologic examination, and brain imaging study by computed tomography or magnetic resonance imaging	Age-and sex-matched
Lu [16] (2009)	China	Case-control	Case: ischemic stroke patients Control: stroke-free, age and sex matched individuals	12 / 120	71.4 ± 11.7	53.3%	25.6 ± 10.6	Stroke was defined as an acute or sudden focal neurologic defect lasting or more than 24 h and diagnosed on the basis of clinical history, neurologic examinations, and brain imaging studies by computed tomography, magnetic resonance imaging, or magnetic resonance angiography.	NR
Yin [31] (2013)	China	Case-control	Case: ischemic stroke patients Control: Healthy individuals	186 / 100	65.2 ± 8.4	54.8%	25.2 ± 2.2	Patients be admitted for the treatment of first-ever ischemic stroke confirmed by brain magnetic resonance imaging, and be diagnosed at the emergency room	NR

BMI: Body mass index; BP: Blood pressure; CVD: Cardiovascular disease; NA: Not applicable; NR: Not reported; * Sample size for case-control and nested case-control studies are presented in number of cases / number of controls.

▶ **Table 2** Summary of main findings in included studies.

Source (Published Year)	Visfatin level mean ± SD or median (IQR)	
Hypertension studies (n = 8)		
Dogru [19] (2007)	HTN: no HTN:	30.6 ± 5.6 ng/ml 27.7 ± 6.6 ng/ml
Xia [20] (2015)	HTN: no HTN:	Nonobse: 3.75 (1.63, 6.67) ng/l Obse: 3.84 (3.4, 5.35) ng/l Nonobse: 3.23 (1.92, 4.64) ng/l Obse: 3.19 (0.69, 9.45) ng/l
Horbal [21] (2016)	HTN: no HTN: (Severe resistant hypertension)	1.6 ± 0.9 pg/ml 1.0 ± 0.8 pg/ml
Kocelak [22] (2015)	HTN: no HTN:	1.005 ± 0.65 ng/ml 1.03 ± 0.07 ng/ml
Gunes [23] (2012)	HTN: no HTN:	55.2 ± 29.6 ng/dl 26.9 ± 16.2 ng/dl
Liakos [24] (2015)	HNBP: no HNBP:	11.0 ± 2.0 ng/ml 7.2 ± 0.9 ng/ml
Rotkegel [25] (2013)	HTN: no HTN:	11 ± 2.5 ng/ml 6.8 ± 0.8 ng/ml
Andreeva [26] (2013)	HTN: no HTN:	166.4 ± 2.9 MM PT.CT 124.3 ± 3.8 MM PT.CT
Vascular brain accident (n = 6)		
Gu [27] (2013)	Patient: Control:	86.2 ± 30.5 ng/ml 12.7 ± 5.0 ng/ml
Huang [28] (2013)	Patient: Control:	94.9 ± 31.6 ng/ml 12.5 ± 5.4 ng/ml
Wang [29] (2013)	Patient: Control:	92.1 ± 20.5 ng/ml 12.4 ± 3.2 ng/ml
Kadoglou [30] (2014)	Patient: Control:	86.2 ± 30.5 ng/ml 12.7 ± 5.0 ng/ml
Lu [16] (2009)	Patient: Control:	86.2 ± 30.5 ng/ml 12.7 ± 5.0 ng/ml
Yin [31] (2013)	Patient: Control:	86.2 ± 30.5 ng/ml 12.7 ± 5.0 ng/ml

HTN: Hypertension; HNBP: High normal BP.

adults, whereas 2 studies found no significant difference between adults with or without hypertension (▶ **Table 2**).

To avoid heterogeneity, we sub-grouped the studies on the basis of lab kit types. Within both two subgroups, the pooled Weighted Mean Difference (WMD) was consistently positive. Among 8 studies, visfatin level was lower in normotensive adults than in hypertensive adults (95 % confidence interval (CI): −0.61 to −0.40; $I^2 = 94\,\%$, $p < 0.00001$) (▶ **Fig. 2**). The weighted SMD was −0.51. According to the detection method and kit used for visfatin testing (**Table 1S**), we sub-grouped these studies to 4 subgroups, the pooled WMD of the groups except group 3 was consistently positive (▶ **Fig. 2**).

Furthermore, the meta-regression analysis presented in (**Table 3S**) indicated that neither mean age of all subjects nor publication year was the potential sources of heterogeneity.

Relationship between visfatin levels and CVA

Of 6 included studies, all studies reported that visfatin levels were significantly higher in patients than healthy individuals (▶ **Table 2**). The fixed-effects model was used. Among 6 studies, visfatin level was much higher in CVA adults than in healthy adults (95 % CI: −2.23 to −1.93; $I^2 = 99.7\,\%$, $p < 0.00001$) (▶ **Fig. 3a**). The weighted SMD was −2.08. Besides, the adjusted visfatin level was available in Lu' study (adjustments for age, sex, BMI, waist circumference, and smoking status). The adjusted visfatin level was even much higher in CVA adults than in healthy adults (95 % CI: −3.22 to −2.85; $I^2 = 99.5\,\%$, $p < 0.00001$) (▶ **Fig. 3b**). The weighted SMD was −3.04

Subgroup analysis was performed to assess diagnostic abilities of visfatin. Within both two subgroups (ischemic and hemorrhagic CVA), the pooled WMD was consistently positive. Among 6 studies, three studies were ischemic CVA, while 3 studies were hemorrhagic incidents. Visfatin level was much higher in ischemic CVA adults than in healthy adults (95 % CI: −1.44 to −1.09; $I^2 = 98\,\%$, $p < 0.00001$), the weighted SMD was −1.26 (▶ **Fig. 3a**). The Lu' study belong to the ischemic sub-group, and the weighted SMD of adjusted vsifatin level was −2.14 (▶ **Fig. 3b**). Visfatin level was also much higher in hemorrhagic CVA adults than in healthy adults (95 % CI: −4.28 to −4.64; $I^2 = 99\,\%$, $p < 0.00001$) (▶ **Fig. 3a**).

Next we performed meta-regression to evaluate the effect of some factors on the estimate of SMD. In meta-regression, mean age of all subjects, publication year and proportion of male were proved to be significant contributing factors (**Table 4S**).

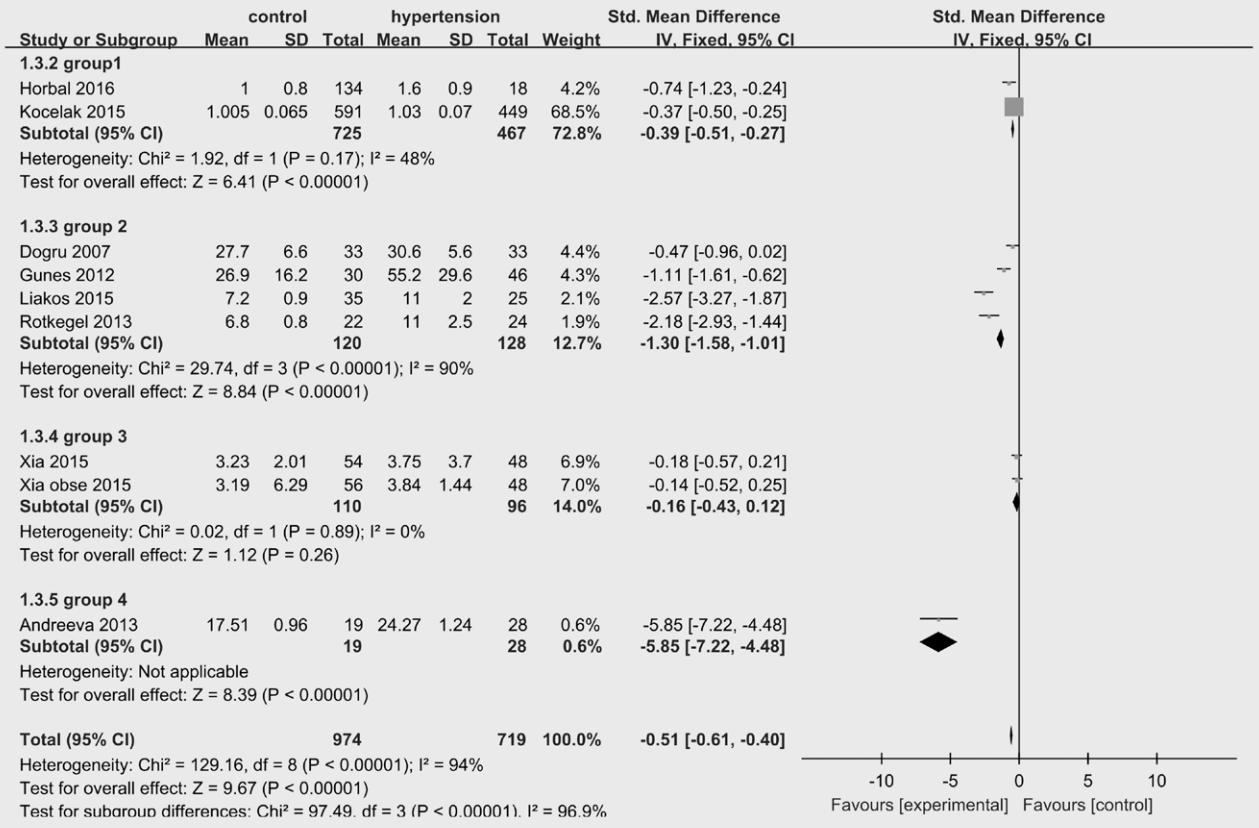
Sensitivity analysis and publication bias

The result of sensitivity analysis showed that all enrolled studies had no significant effect on the pooled SMDs on correlations between serum visfatin levels and hypertension or CVA. For risk assessment, the asymmetric funnel plots, suggested that there was publication bias in the enrolled studies (**Fig. 1S**, **2S**) and the Egger linear regression analysis further confirmed the publication bias ($p = 0.028$ for hypertension studies, $p = 0.008$ for CVA studies) (**Table 5S**, **6S**). The result of publication bias was mainly due to the limited number of included studies.

Discussion

Our systematic review demonstrated that hypertension and CVA adults had higher mean visfatin levels than healthy adults. These findings suggested that visfatin is possible biomarker of hypertension and CVA.

Visfatin was initially identified as an adipocytokine exhibiting insulin mimetic properties [32]. It is highly expressed in visceral fat and circulating levels correlate with obesity, previous studies reported a positive correlation between plasma visfatin and waist-to-hip ratio (WHR), body mass index and lipid profiles [7, 8]. However, the relationship of visfatin with hypertension and CVA remains conflicting. An animal study proved that circulating visfatin levels were not statistically different in spontaneously hypertensive rats, stroke-prone spontaneously hypertensive rats and control rats [15].



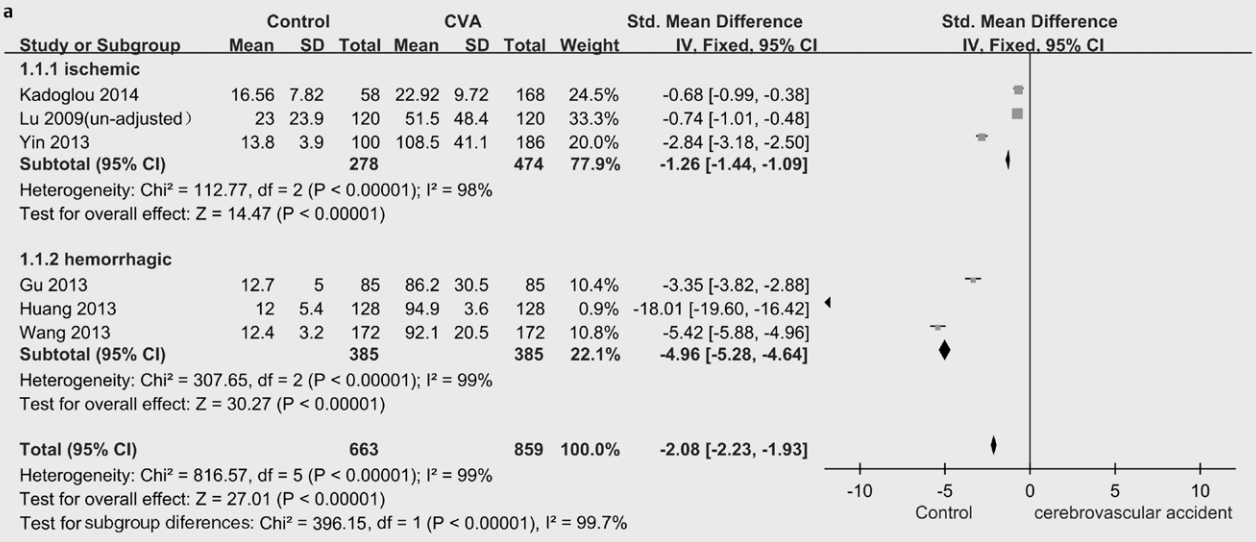
▶ **Fig. 2** SMD of visfatin level by hypertension status.

However, clinic trials reported that plasma visfatin concentrations were found to be elevated in patients with stroke or blood pressure [16].

Increasing evidences identify visfatin as a biomarker or even a predictor in the cardiovascular diseases. Visfatin is considered harmful to blood vessel, such as stimulating vascular smooth muscle cell (VSMC) cell proliferation, monocyte / macrophage activation and recruitment [33, 34]. Andreeva et al. showed that antihypertensive therapy reducing the level of visfatin in hypertensive patients with abdominal obesity, which implied high blood pressure may be associated with progressive increase in the level of visfatin [26]. Besides, antihypertensive drugs treatment decreased the visfatin in combination with abdominal obesity, not in simple hypertension individuals [26]. Then we speculated that visfatin concentration may be affected by other factors in hypertension, not blood pressure.

As a leading risk factor for vascular cognitive impairment, hypertension is the major risk factor for CVA [35]. It is proved that visfatin had a neuroprotective effect in CVA through its enzymatic activity for nicotinamide adenine dinucleotide production [36, 37]. In the above CVA studies, plasma visfatin concentration is used for identifying the clinical outcome of CVA patients. Moreover, in the studies of Kadoglou et al. [30] and Lu et al. [16], stroke-patients appeared with elevated levels of blood pressure (BP) ($p < 0.01$). While Kadoglou et al. also performed logistic multiple regression analysis to estimate the association of acute ischemic Stroke (AIS) with clinical and biochemical variables. After adjustment for conventional stroke risk factors including hypertension, the circulating levels of visfatin was identified as an independent risk factor of AIS. These indicated that the visfatin levels is correlated with the severity of CVA, and may be even higher in the group of subjects having both hypertension and cerebrovascular accident.

It was proved that visfatin is negatively associated with vascular endothelial function [38]. As a pro-inflammatory molecule, visfatin increases inflammatory and adhesion molecule expression, such as IL-6, MMP-3, CAMs, ICAM-1 and VCAM-1, and positive correlation was established between the level of visfatin and IL-4 or hs-CRP in serum [16, 26, 39, 40]. Study also showed that, in human vascular smooth muscle cells, administration of visfatin promotes the expression of iNOS [41, 42]. Increased visfatin promotes the proliferation of vascular smooth muscle cells and of fibroblasts, and plays a part in myocardial fibrosis and cardiac remodeling, which is an important process of hypertension [43]. Kong et al. proved that increased serum visfatin levels were associated with the occurrence of atherosclerosis in patients with ischemic cerebral infarction [44]. These funding might suggest a potential role of this adipokine in vascular function. Andreeva et al. did not mention the exact measurement of BP, but proved that antihypertensive therapy reduces the level of visfatin in hypertensive patients with abdominal obesity, Ozal et al. also proved visfatin levels are higher in patients with resistant hypertension than controlled hypertension [17, 26]. These implied that high blood pressure may be associated with progressive increase in the level of visfatin.



▶ **Fig. 3** **a** SMD of un-adjusted visfatin level by CVA diseases. **b** SMD of adjusted visfatin level by CVA diseases.

There are some limitations to our study. First, because of high heterogeneity and variable methodological quality of included studies, our meta-analysis should be interpreted with caution. Second, sample size was the relatively small, the statistical power might not enough for confirming the role of the plasma visfatin level in the two disease (the dose-response data for hypertension were available in only 2 of 8 studies). Third, geographical limitation exists (most of CVA studies in china, patients' background having selection bias). However, we believe that our results still provide helpful information in the study of adipocytokines regardless of these limitations.

Conclusion

In conclusion, this meta-analysis showed a significant increase in plasma visfatin levels in hypertension and CVA patients. Plasma visfatin level is positively correlated with blood pressure, and may act as a biomarker in patients with CVA. Therefore, visfatin measurement might have potential benefits in the detection of hypertension or CVA.

Author Contributions

One investigator (F-X.Z.) used a standardized form to extract the following relevant data and another investigator (C.W.) independently confirmed their accuracy: study design, sample size, source population, mean age, definition of hypertension, mean and standard deviation (SD) of visfatin level, number of outcome events, and adjusted confounders. Disagreement was resolved by discussion with the third person (P-L.Y.). Wei Li (W.L.) analyzed the data. F-X.Z. and P-L.Y. designed the experiment and wrote the manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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