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RESEARCH ARTICLE

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Vascular endothelial growth factor is an effective biomarker for vascular dementia, not for Alzheimer's disease: A meta-analysis

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Abstract

INTRODUCTION: Vascular pathology is known to contribute to dementia and vascular endothelial growth factor (VEGF) is a well-established biomarker associated with vascular alterations. Nonetheless, research findings on VEGF in Alzheimer's disease (AD) and vascular dementia (VaD) are inconsistent across various studies.

METHODS: We conducted a meta-analysis to elucidate relationships between VEGF and AD/VaD.

RESULTS: Twenty-four studies were included. Pooled data showed that both blood and cerebrospinal fluid (CSF) VEGF levels were higher in VaD patients, whereas no significant difference was found between AD patients and healthy controls. However, the correlation between blood VEGF and AD was found among studies with AD pathology verification. And blood VEGF levels were higher in AD patients than controls in "age difference < 5 years" subgroup and CSF samples for European cohorts.

DISCUSSION: This study highlights that VEGF is more effective for the diagnosis of VaD and vascular factors are also an important contributor in AD.

KEYWORDS
Alzheimer's disease, biomarker, meta-analysis, vascular dementia, vascular endothelial growth factor

Highlights

- Vascular endothelial growth factor (VEGF) levels were higher in the vascular dementia group, but not in the overall Alzheimer's disease (AD) group.

Ling-Zhi Xu, Fang-Yu Li, and Jin Xu authors contributed equally to this work.

- Correlation between VEGF and AD was found among studies with clear AD pathological verification.
- Elevated VEGF in the cerebrospinal fluid might be a diagnostic marker for AD in European populations.

1 | INTRODUCTION

Alzheimer disease (AD) and vascular dementia (VaD) are two major types of dementia and account for most cases of dementia. AD is characterized pathologically by tau neurofibrillary tangles and amyloid beta (Aβ) plaques.[1] VaD occurs due to cerebral ischemia and is linked to multiple vascular risk factors such as arterial disease, hemodynamic changes, hemorrhage, and hematological factors.[2] AD and VaD share several risk factors, such as vascular alterations.[3] The presence of vascular pathology heightens the risk of developing dementia. Vascular risk factors not only contribute to VaD, but also play a crucial role in the development of AD.[4] Furthermore, evidence suggests that vascular changes may arise prior to the onset of amyloidosis during the preclinical phase of AD.[5]

Vascular endothelial growth factor (VEGF), a natural growth factor encoded by the *VEGFA* gene, participates in physiological processes relating to blood vessels and metabolism, including blood vessel growth, endothelial cell destruction, oxygen and glucose delivery, and blood vessel permeability.[6,7] Considering vascular factors and the role of VEGF in AD and VaD, numerous studies have evaluated the diagnostic capability of VEGF for different types of dementia in humans. Some studies have found significant differences in blood or cerebrospinal fluid (CSF) levels between AD or VaD subjects and cognitively normal (CN) subjects, suggesting the possibility of diagnosing these two forms of dementia. However, the results of the present study are less conclusive,[8] with some studies finding an increase in blood VEGF among AD patients and a decrease in other cases.[9,10] Similarly, some studies indicate no change in CSF VEGF levels among patients with VaD,[11] while others demonstrate a significant increase in CSF VEGF levels.[12] Furthermore, the sensitivity and specificity of VEGF for the two most common types of dementia are not well understood.

Therefore, this meta-analysis, combined with a network meta-analysis, investigated whether AD, VaD, and mild cognitive impairment (MCI) are associated with changes in VEGF levels in the blood and CSF, to clarify the identification and diagnostic significance of VEGF for these two major types of dementia.

2 | MATERIALS AND METHODS

2.1 | Search strategy

Two investigators independently performed a systematic review of English language literature from "PubMed", "Scopus", "Web of Science", "Embase", and "Ovid" databases. The key search terms vascular endothelial growth factor OR VEGF AND vascular dementia OR cognitive impairment OR dementia OR Alzheimer Disease were used for each database. Databases were searched until April 15, 2023. Specific search records can be found in the supporting information.

2.2 | Inclusion and exclusion criteria

The eligible studies that were included in this meta-analysis: (1) investigated the relationship between the blood or CSF VEGF levels and AD/MCI/VaD risk; (2) contained a case group of patients with AD/MCI/VaD and a group of CN; (3) contained the clinical criteria that were used to diagnose AD/MCI/VaD; (4) provided VEGF data; (5) were studies performed in humans; (6) had full text in English.

The exclusion criteria included the following: (1) no relevant data on VEGF concentrations; (2) only one group of subjects was reported; (3) the same cohort of subjects was reported repeatedly; (4) brain tissue or *post mortem* samples; (5) the study types were non-human studies, case reports, commentaries, reviews, meta-analyses, conference abstracts, or unrelated topics.

2.3 | Data extraction

Information regarding the first author, year of publication, study location (country), study design, number of patients and controls, diagnostic criteria, average age of each group, sex distribution of each group, sampling type (blood serum, blood plasma, or CSF), patient medication and measurement method (enzyme-linked immunosorbent assay [ELISA]; others), apolipoprotein E (*APOE*) $\varepsilon 4$ carriers frequency, AD pathology verification (yes or no), VEGF concentrations including the mean and standard deviation (SD) or median and interquartile range (IQR) or median and the minimum and maximum were extracted from the included studies. If the case or control groups were further divided into subgroups, the data from the subgroups were merged as $n = n_1 + n_2$, $\bar{x} = \frac{n_1\bar{x}_1+n_1\bar{x}_2}{n_1+n_2}$, and $SD = \sqrt{\frac{(n_1-1)SD_1^2+(n_2-1)SD_2^2+\frac{n_1n_2}{n_1+n_2}(\bar{x}_1^2+\bar{x}_2^2-2\bar{x}_1\bar{x}_2)}{n_1+n_2-1}}$. When a study provided medians and IQRs (instead of means and SDs), without the minimum or maximum values, we treated the medians as the means and calculated the SDs as SD = IQR/1.35.[13] If the study provided the minimum and maximum, we imputed the means and SDs as described by Hozo et al.[14] For studies which only showed mean (μ) and variance (σ^2) of log data,

we converted to the original mean and variance referring to formula of $\exp(\mu + \frac{\sigma^2}{2})$ and $[\exp(\sigma^2) - 1]\exp(2\mu + \sigma^2)$.[15,16]

The data extraction was performed by two investigators independently in the case of incorrect or missing data. Any disputes were resolved by discussion with a third author during data extraction.

2.4 | Quality evaluation

The quality of included studies was evaluated based on the Newcastle–Ottawa Scale (NOS) recommended by the Agency for Healthcare Research and Quality (AHQR) of the United States. Comparability of the cases and controls based on the design or analysis was evaluated based on whether the age and sex matched. The methodological quality of the cross-sectional studies included was assessed using an 11-item checklist recommended by the AHRQ. The studies with NOS scores < 5, or AHRQ scores < 4 were recognized to be of inferior quality and therefore excluded (see Tables S1, S2 in supporting information).

2.5 | Statistical analysis

The VEGF levels were compared between AD/MCI/VaD and CN by calculating the pooled standardized mean difference (SMD). SMD and two-sided 95% confidence intervals (CIs) were used as the summary statistics for the meta-analysis. SMD is the mean difference in the outcome between cases and controls divided by the pooled SD, which gives the result of a unit free effect size. The significance of the pooled SMD was determined using a *Z* test, and the level was set at $P < 0.05$. Heterogeneity across the studies was assessed using the *Q* test and the I^2 statistic. Random-effect models were chosen for the meta-analysis.

Network meta-analysis is a generalization of pairwise meta-analysis that compares all pairs of different classifications within a number of diseases for the same condition.[17] To discriminate AD, MCI, and VaD, we assessed the comparative value of VEGF in these dementia diseases using network meta-analysis. Between-studies heterogeneity was tested using the "network sidesplit" command. Direct and indirect comparison effects were jointly estimated using the node-splitting method. The output reports the estimated direct and indirect comparisons and their difference; the *P* value for the difference is a test of consistency (Table S3 in supporting information).

To analyze the potential influences of age difference, sex difference, sampling type, and study location, we performed a subgroup analysis. Subgroup analyses based on age difference (< 5 years or ≥ 5 years), sampling type (blood or CSF), study location (European, East Asia, etc.), and measurement method (ELISA or other) were performed. A meta-regression with restricted maximum likelihood estimation (REML) was performed to assess the potentially important covariate exerting substantial impact on the between-study heterogeneity. The age difference (< 5 years or ≥ 5 years), sampling type (blood or CSF), study location (European, East Asia, etc.), and measurement method (ELISA or others) were included in the meta-regression analysis. For the literature that provided the frequency of *APOE* ε4 alleles, we also analyzed the relationship between *APOE* ε4 carriers frequency and SMD in the AD group using meta-regression.

A funnel plot asymmetry was assessed using an Egger linear regression test, with $P < 0.05$ representing significant publication bias. The sensitivity analysis was performed by sequentially excluding the individual studies to assess the stability of the results. All the analyses were performed using STATA 12.0 software (Stata Corporation). The significance level for all statistical tests was set at a two-sided *P* value of < 0.05.

RESEARCH IN CONTEXT

1. **Systematic review**: Vascular pathology is an important contributor to dementia. Vascular endothelial growth factor (VEGF) is a well-established biomarker associated with vascular alterations. However, the findings regarding the relationship between VEGF and dementia remain inconclusive. We reviewed the literatureliters on VEGF in Alzheimer's disease (AD), mild cognitive impairment, and vascular dementia.
2. **Interpretation**: Our findings suggest that VEGF is effective for the diagnosis of vascular dementia, and vascular factors cannot be ignored in dementia, including AD.
3. **Future directions**: The failure to find significant changes in VEGF in AD similar to vascular dementia is mainly because AD is a more complex neurodegenerative disease and the results are influenced by many factors. The presence or absence of definite AD pathology strongly influences results of VEGF in AD, so future studies should consider AD pathology verification. Improved age matching could also reduce the heterogeneity of AD biomarker research and strengthen the reliability of findings.

3 | RESULTS

3.1 | Study selection and characteristics

The initial search generated 702 records from PubMed, 959 from Web of Science, 2495 from Embase, 406 from Scopus, and 3905 from Ovid. After the removal of duplicates and screening of titles and abstracts, 138 relevant articles were selected for full-text evaluation. Of these, 111 records were excluded due to: not blood or CSF sample ($n = 18$), no detailed data available ($n = 14$), only one group or no detailed group ($n = 27$), reviews or meta-analyses ($n = 3$), not written in English ($n = 1$), no VEGF level and AD/MCI/VaD ($n = 28$), abstract ($n = 19$), and duplicate sample ($n = 1$). There were four studies from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset,[18–21] and we retained one of the latest studies and excluded the others.[20] Finally, we

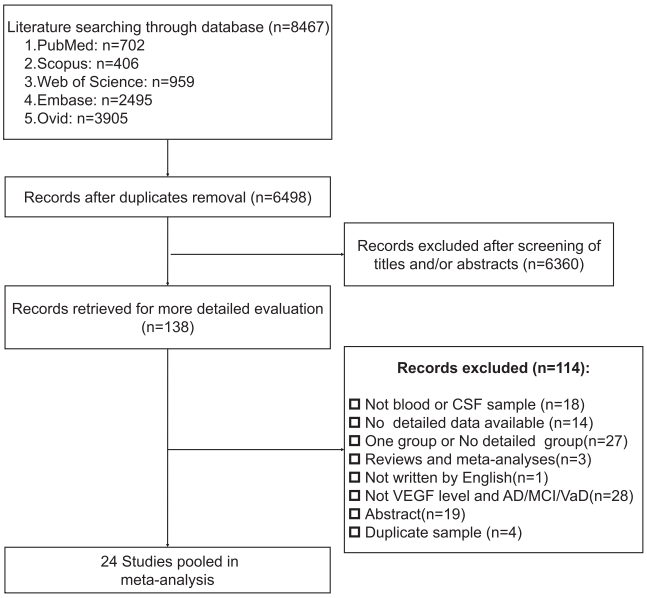

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the study-selection process. AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; VaD, vascular dementia; VEGF, vascular endothelial growth factor.

identified 24 studies using our inclusion and exclusion criteria. A flow diagram of the study selection is displayed in Figure 1.

Data from the 24 studies included in this meta-analysis were collected from either the publication or through direct communication with the authors as required. Study characteristics were described in Table 1 and Table S4 in supporting information. Among these, 22 studies researched the association between VEGF levels and AD. The total sample sizes were 3484 including 1341 cases and 2143 controls. The average ages of each study ranged from 63 to 81.9 years for AD patients and 64.5 to 79.8 years for CN. Twenty-one studies documented the sex information of the two groups. Males ranged from 20% to70% for AD patients and 23.81% to 66.67% for CN. Seventeen (77.27%) studies reported blood VEGF levels and only 5 (22.73%) studies reported CSF VEGF levels. Furthermore, there were 10 and 4 studies reporting the VEGF levels data of MCI and VaD, respectively.

3.2 | Association between the VEGF levels and AD/MCI/VaD in all eligible comparisons

Meta-analyses were performed to detect the association between the VEGF levels and AD/MCI/VaD risk. The total results showed VEGF level was not associated with AD risk. The pooled SMD using a random-effects model was 0.01 (95% CI: −0.38 to 0.39, $P = 0.967$; $I^2 = 94.6\%$; Figure 2). We also found no correlation between VEGF levels and MCI patients in 10 studies (SMD = 0.05, 95% CI [−0.61, 0.70], $P = 0.892$; $I^2 = 96.8\%$; Figure 2). The meta-analysis of four studies which provided comparisons between VaD and controls showed that a higher VEGF level was associated with increased VaD risk (SMD = 0.45, 95% CI [0.13, 0.76], $P = 0.005$; $I^2 = 58.0\%$; Figure 2).

3.3 | Comparative value of VEGF in different neurodegenerative dementia patients

To discriminate among AD, MCI, and VaD, we assessed the value of VEGF in these dementia diseases using network meta-analysis (Figures S1, S2 in supporting information). The comparative value of VEGF is shown in Figure S3 in supporting information. Among the AD, MCI, and VaD cases, compared to controls, all of the included dementia diseases were not associated with significant increases in VEGF expression levels (AD: SMD = 0.14, 95% CI [−0.43, 0.71]; MCI: SMD = −0.04, 95% CI [−0.79, 0.72]; VaD: SMD = −0.17, 95% CI [−1.34, 1.01]). Comparing AD and other dementia diseases, no significant difference was observed in MCI (SMD = −0.18, 95% CI [−0.97, 0.62]) and VaD (SMD = −0.31, 95% CI [−1.48,0.87]). There was no significant difference in VEGF levels comparing MCI and VaD.

3.4 | Subgroup analysis for AD

Subgroup analysis of the 22 AD comparisons according to whether the study diagnostic criteria contained AD pathology was conducted. Seven studies had further confirmation of AD pathology and 15 had no information about further pathology verification. The subgroup analysis of "with pathology verification" showed a higher VEGF in AD patients and there was little heterogeneity among the studies (with verification: SMD = 0.33, 95% CI [0.13, 0.53], $P = 0.001$; $I^2 = 18.0\%$; Figure 3A). VEGF levels were not associated with AD in the "no relative pathology information" subgroup analysis (SMD = −0.17, 95% CI [−0.72, 0.37], $P = 0.532$; $I^2 = 96.3\%$). When distinguishing the subgroups by sex difference, VEGF levels were associated with AD in "sex difference < 5%" subgroup (SMD = −0.80, 95% CI [−1.59, −0.01], $P = 0.048$; $I^2 = 96.4\%$), and were not associated with AD in the "sex difference > 5%" subgroup (SMD = 0.36, 95% CI [−0.14, 0.86], $P = 0.156$; $I^2 = 93.9\%$; Figure 3B).

We also conducted subgroup analysis on additional factors that could affect AD. For other subgroup analyses based on age difference (< 5 years or ≥ 5 years), sampling type (blood or CSF), study location (European, East Asia, etc.), and measurement method (ELISA or others), the heterogeneity within each subgroup remained high, and the results showed VEGF levels were not associated with AD (Figures S4-S7 in supporting information).

3.5 | Subgroup analysis for AD in the European population

Most AD enrollment studies (n = 11) are from European population cohorts. Although there was no evidence of an association between VEGF and AD in the overall European cohort, we used subgroup

TABLE 1 The detailed characteristics of all the eligible studies for the association with the VEGF levels and AD/MCI/VaD.

Study		Sample size				Mean age				Sex (male/female)				Mean VEGF (SD) concentrations				
First author	Year	AD	MCI	VaD	CN	AD	MCI	VaD	CN	AD	MCI	VaD	CN	AD	MCI	VaD	CN	Unit
Huang et al.	2013	31	28		29	71.7	71.1		73.3	13/18	12/16		12/17	205.03 (11.05)	281.42 (20.02)		387.89 (33.95)	pg/mL
Huang et al.	2020	65	143		83	75.4	74.7		75.7	28/37	47/96		43/40	14.67 (1.62)	15.16 (1.98)		15.41 (1.54)	pg/mL
Janelidze et al.	2017	75	61	28	65	76	69	75	75	24/51	27/34	13/15	23/42	73.2 (27.7)	65.0 (32.0)	80.8 (33.5)	58.0 (19.1)	pg/mL
Jung et al.	2015	49			26	76.94			74.08	9/40			11/15	307.70 (228.33)			252.40 (117.43)	pg/mL
Kim et al.	2012	20			18	74.8			74.8	14/6			12/6	0.9 (0.6)			0.46 (0.3)	ng/mL
Koca et al.	2022	25			25	73.2			65.8	14/11			14/11	89 (51.77)			197.1 (174.6)	pg/mL
Liang et al.	2021	28	51		12	78.3	75.6		66.3	7/21	11/40		3/9	33.3 (15.85)	29.1 (15.70)		25.4 (14.22)	pg/mL
Lourenco et al.	2021	14	14		25	74.2	71.6		67.8	4/10	8/6		10/15	7.6 (3.5)	5.3 (2.7)		6.6 (3.1)	pg/mL
Mateo et al.	2007	51			66	73.4			79.8	15/36			20/46	215.9 (101.5)			308.6 (223.9)	pg/mL
Menne et al.	2022	52			63	74.88			67.68	25/27			15/48	332.74 (242.20)			317.38 (211.80)	pg/mL
Alvareza et al.	2018	245	48		60	74.99	73.46		68.44	52/193	13/35		17/43	367.67 (397.58)	284.65 (344.62)		240.86 (220.42)	pg/mL
Callahan et al.	2020	12	17		20	71.37	76.35		70.73	4/8	9/8		8/12	53.76 (47.57)	84.38 (52.35)		43.38 (25.24)	pg/mL

(Continues)

TABLE 1 (Continued)

Study		Sample size				Mean age				Sex (male/female)				Mean VEGF (SD) concentrations				
First author	Year	AD	MCI	VaD	CN	AD	MCI	VaD	CN	AD	MCI	VaD	CN	AD	MCI	VaD	CN	Unit
Chakraborty et al.	2018	50		21	21	67.4		68.6	65.9	21/29		15/7	11/10	2.75 (0.97)		3.1 (1.3)	2.7 (1.1)	pg/mL
Chen et al.	2021	60			30	72.16			72.13	28/32			14/16	141.20 (35.97)			203.12 (33.15)	ng/l
Chiappelli et al.	2006	72			10									230 (247)			42 (15)	pg/mL
Cho et al.	2017	76	75		120	75.1	73.01		71.9	18/ 58	29/46		50/70	167 (11.8)	185 (21)		142 (7.4)	pg/mL
Corsi et al.	2011	70			6	75.6			73.4	28/44			2/4	211 (190)			43 (19)	pg/mL
Gertje et al.	2023		247		495		70.89		72.02		151/96		201/294		5.1 (2.42)		4.81 (1.51)	pg/mL
Tarkowski et al.	2002	20		26	27	63		71		8/12		19/7		0.50 (0.85)		0.13 (0.16)	0.13 (0.03)	ng/mL
Yu et al.	2016	50			40	76.42			77	30/20			13/7	93.15 (267.5)			35.04 (48.46)	pg/mL
Schipke et al.	2019	81			79	81.9			64.5	27/54			51/28	465.7 (581.1)			409.6 (225.1)	pg/mL
Shen et al.	2019		57		57		68.77		67.77		39/18		39/18		41.55 (24.43)		56.49 (37.95)	pg/mL
Silva et al.	2023	32			40	77			73.5	12/20			11/29	57.54 (38.72)			85.83 (60.15)	pg/mL
Trares et al.	2022	163		195	1278					74/89			575/703	12.36 (0.66)		12.48 (0.8)	12.17 (0.70)	—
Zorkina et al.	2023		142		75		72.5		68.9		0/142		0/75		33 (28.29)		102 (131.11)	

Abbreviations: AD, Alzheimer's disease; CN, cognitively normal; MCI, mild cognitive impairment; SD, standard deviation; VaD, vascular dementia; VEGF, vascular endothelial growth factor.

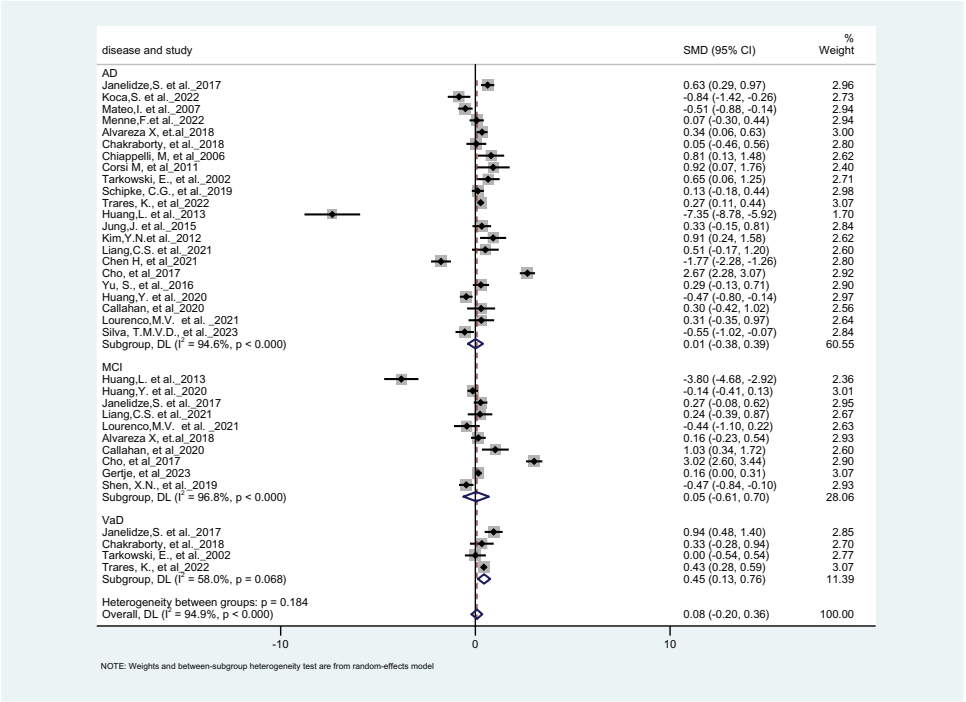

FIGURE 2 Meta-analysis using a random-effects model between AD/MCI/VaD group and control group. AD, Alzheimer's disease; CI, confidence interval; MCI, mild cognitive impairment; SMD, standardized mean difference; VaD, vascular dementia.

analysis to minimize the heterogeneity of the studies and identify meaningful, high-quality studies. There were 10 studies that provided mean age information of the two groups, and five had an age difference > 5 years, and five had an age difference < 5 years. When distinguishing the subgroups by age difference, VEGF levels were higher in AD than in controls in the "age difference < 5 years" subgroup (SMD = 0.56, 95% CI [0.28, 0.84], $P < 0.001$; $I^2 = 24.7\%$), and were not associated with AD in the "age difference > 5 years" subgroup (SMD = −0.12, 95% CI [−0.50, 0.26], $P = 0.535$; $I^2 = 81.6\%$; Figure 4A). We further divided the studies into blood and CSF based on the sampling source type, and results showed "CSF" subgroup with higher VEGF levels in AD (SMD = 0.46, 95% CI [0.08, 0.84], $P = 0.016$; $I^2 = 47.6\%$). There was no association in "blood" subgroup (SMD = 0.11, 95% CI [−0.18, 0.39], $P = 0.470$; $I^2 = 79.6\%$; Figure 4B). Four studies had further confirmation of AD pathology and seven had no information about further verification in the 11 European AD comparisons. The results also showed a higher VEGF level in AD than controls in "with pathology verification" subgroup for European population (SMD = 0.34, 95% CI [0.01, 0.68], $P = 0.047$; $I^2 = 58.5\%$) but not in the "no relative pathology information" subgroup (SMD = 0.11, 95% CI [−0.22, 0.44], $P = 0.499$; $I^2 = 82.4\%$; Figure 4C). Subgroup analysis of the 11 comparisons was carried out according to the measurement method. The results suggested that the measurement methods might not impact the results of the difference in the VEGF levels between the patients with AD and controls (Figure S8 in supporting information).

3.6 | Meta-regression analyses

Meta-regression analysis was performed to explore the influence of sampling source type, age difference, measurement method, AD pathology verification, and study location on the study effect size. The result revealed that these five covariates were not the potential factors exerting substantial impact on the between-study heterogeneity for AD (all $P > 0.05$, Table S5 in supporting information).

There were seven studies showing *APOE* ε4 carriers frequency; we did meta-regression analyses between SMD and *APOE* ε4+ frequency in the AD group, and found that *APOE* ε4 carriers frequency could explain 50.31% of the between-study variance (coefficient = −0.06, standard error [SE] = 0.022, $t = -2.54$, and $P = 0.05$; Table S6 in supporting information).

For European AD patients, results of meta-regression analysis between SMD and age difference showed that age difference could explain 45.95% of the between-study variance (coefficient = −0.69, [SE] = 0.27, $t = -2.57$, and $P = 0.033$, Table S7 in supporting information).

3.7 | Sensitivity analysis

In the sensitivity analysis, one eligible study was excluded at a time to assess the influence of each dataset on the pooled SMD. We observed no changes in the corresponding pooled SMD or in the significance of

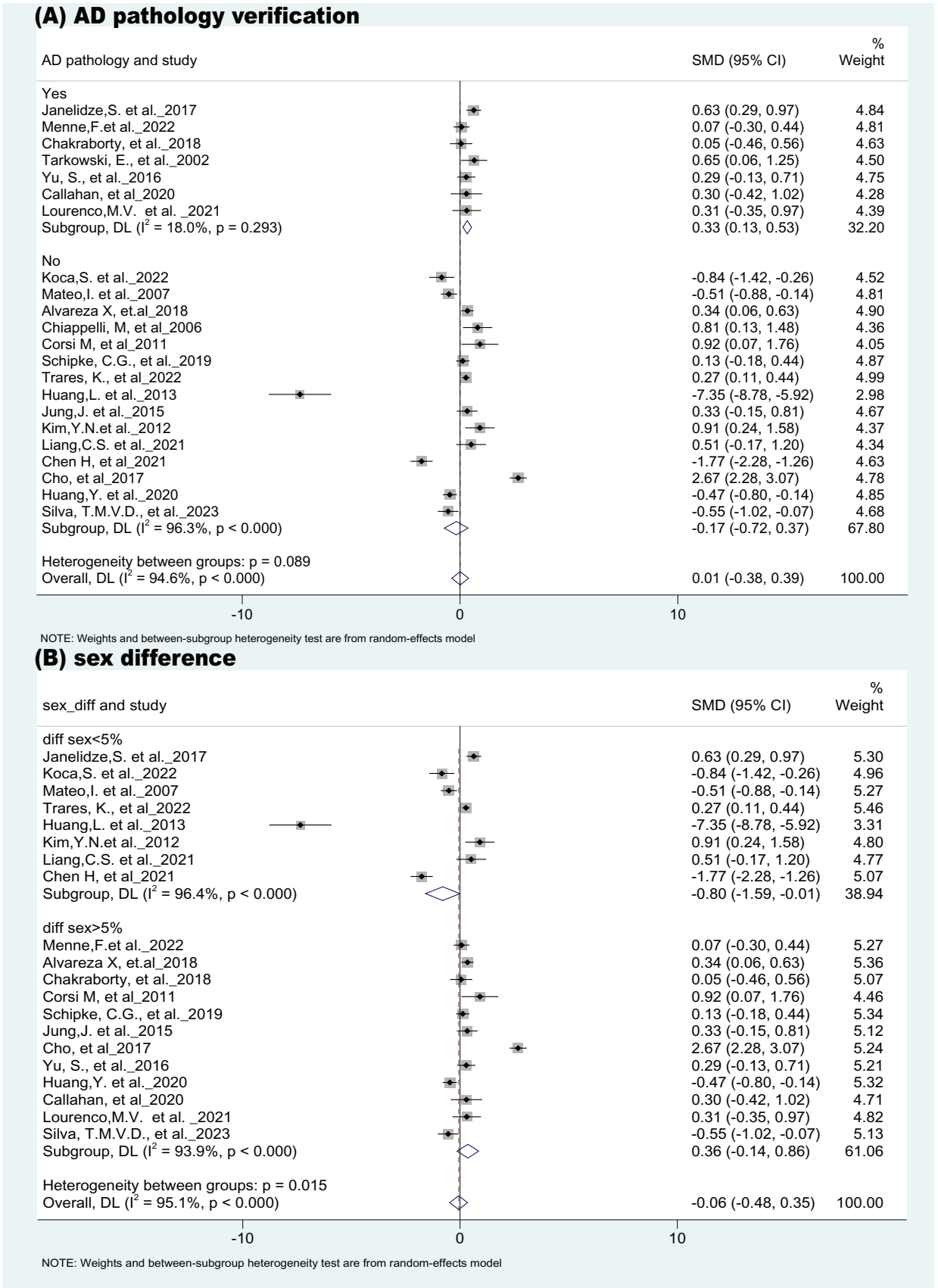

FIGURE 3 AD pathology verification (A) and sex difference (B) subgroups analysis using a random-effects model between AD group and control group. AD, Alzheimer's disease; CI, confidence interval; SMD, standardized mean difference.

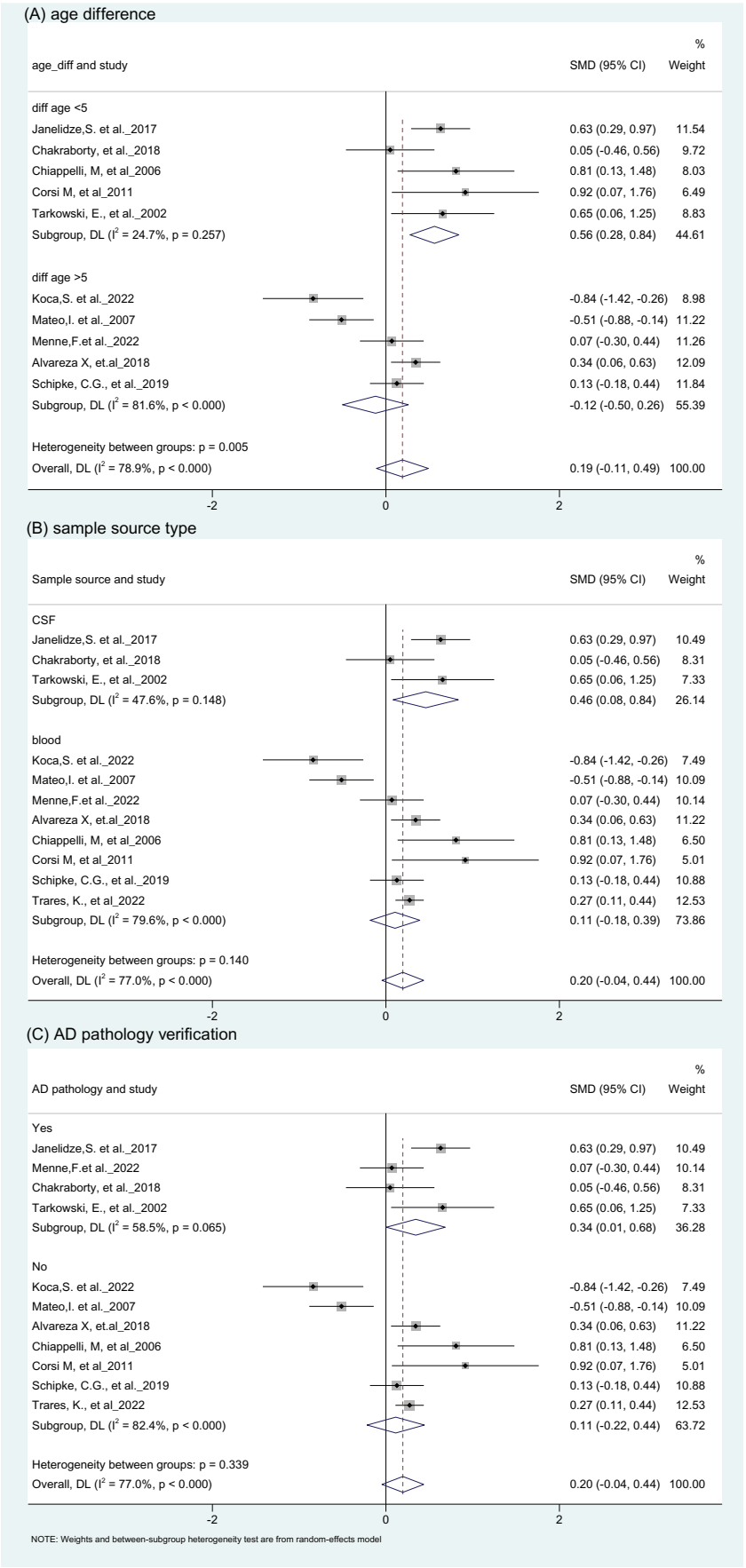

FIGURE 4 Age difference (A), sample source type (B), and AD pathology verification (C) subgroups analysis using a random-effects model between AD group and control group in European population. AD, Alzheimer's disease; CI, confidence interval; SMD, standardized mean difference.

the results (Figure S9 in supporting information), which indicated that our results were significantly stable to the study-selection process.

3.8 | Publication bias

The Egger and Begg tests did not indicate evidence of publication bias ($P = 0.978$, $P = 0.209$, respectively). The funnel plot for the overall results also did not show any significant bias (Figure S10 in supporting information).

4 | DISCUSSION

Twenty-four studies were included in this meta-analysis, with 22 examining AD and CN, 10 examining MCI and CN, and 4 examining VaD and CN. We found that the included studies did not hypothesize a direction of action, nor did they suggest that VEGF may be high or low in AD and VaD. VEGF level differences were not found among AD, MCI, and VaD through network meta-analysis. The VEGF level was higher in the VaD group compared to the CN group. However, no difference was found between the AD and CN groups, nor between the MCI and CN groups. This implies that both blood and CSF VEGF may have greater significance in diagnosing and predicting VaD. The correlation between VEGF and AD was stronger when the intergroup was sex matched. Interestingly, VEGF levels were higher in AD than in controls in the "age difference < 5 years" subgroup and CSF samples for European cohorts. In addition, the variation of VEGF between AD and CN groups was impacted by the degree of sex matching used in the study. Studies with better sex matching displayed a strong association between VEGF levels and AD, consistently indicating reduced VEGF in AD groups. Conversely, studies with poorer sex matching showed no discernible differences in VEGF between AD and CN groups. *APOE* is the primary susceptibility gene for AD; our findings demonstrate that it considerably influences the heterogeneity of VEGF levels in AD.

VaD is a cognitive impairment syndrome resulting from ischemic stroke, hemorrhagic stroke, and cerebral vascular disease, and is associated with dysfunction of the vascular endothelium.[22] Therefore, vascular alterations and related factors exert a substantial impact on VaD. While Aβ and tau are the hallmark indicators of AD, vascular modifications are also significant contributors to AD pathology. These changes can lead to impaired energy and cerebral blood flow, and blood–brain barrier degradation, and can facilitate AD-associated neurodegeneration.[23] Vascular pathology may also worsen other AD characteristics such as plaque accumulation, neuron loss, and behavioral alterations.[24] Some studies propose that there may be vascular changes that precede the onset of amyloidosis in the preclinical phase of AD.[5,25] VEGF, a significant factor in vascular permeability, plays a vital role in neurogenesis, angiogenesis, and functional recuperation after hypoxia.[26] Numerous studies have documented alterations in VEGF among patients with AD and VaD. Nevertheless, these findings lack consistency, and it remains uncertain how sensitive and specific VEGF is for distinguishing between the two types of dementia. It is worth noting that four studies included both the VaD and AD groups and compared them.[11,12,27,28] The VEGF level in the VaD group was marginally higher than in the AD group and there was no significant difference in the AD group, indicating that VEGF could be a diagnostic marker for VaD but not for AD. Conceivably, this could arise due to AD being a more intricate neurodegenerative disorder involving more complex pathological factors. Furthermore, AD research displays more heterogeneity than VaD, so VEGF should be used with more caution in the diagnosis of AD. When damage to vascular and endothelial cells occurs in the brain, increased VEGF levels may act as a compensatory protective effect. It is considered an important factor for vasculogenic and angiogenic remodeling.[29] Although Chakraborty et al. did not observe a difference between VaD and control groups,[27] this observation might be due to the age and sex differences between the two groups in the study cohort. Nevertheless, VEGF still holds some diagnostic significance for VaD, and further validation of results can be achieved by enhancing the quality of the research cohort.

Among overall enrolled AD studies, no significant differences in VEGF levels were observed between AD patients and controls, primarily because of the extensive heterogeneity of the studies. To clarify the relationship between VEGF and AD more clearly, we performed a subgroup analysis of the included studies. As known, it is crucial to have pathological verification of AD to reveal any alterations in VEGF. Our findings show that seven studies were validated by AD pathology, while the remaining studies lacked such verification. Those studies verified by AD pathology have demonstrated low heterogeneity and revealed an elevation of VEGF in AD. In contrast, studies without pathological verification have shown no significant difference. Based on the findings of the AD group with rigorous diagnosis and pathological confirmation, VEGF was found to be elevated in AD. This similarity in elevation is consistent with the results of four studies that enrolled and compared VaD and AD. However, the increase in VEGF was more significant in the VaD group than in the AD group, indicating that VEGF may be more effective in diagnosing VaD to some extent. Furthermore, this implies that rigorous diagnostic and pathological verification is crucial for the quality and reliability of AD biomarker research.

Most research on VEGF focuses on European populations,[11,12,27,28,30–36] with comparatively few studies on East Asian,[10,37–42] North American,[18–21,43] and South American[44,45] populations. Therefore, we focused on these European populations in the hope of reaching meaningful conclusions. Age, AD pathology verification, detection methods, and sample sources all significantly influence AD biomarkers. To further lower the heterogeneity of European population studies, we performed subgroup analyses based on the above subgroups. Studies with better age matching and studies with clear pathological confirmation of AD have lower heterogeneity and the stronger the correlation between VEGF and AD, showing changes consistent with the results of the VaD group. Conversely, no correlation was observed between VEGF and AD in subgroups with poor age matching and lack of definite pathological verification of AD. This proposes that the study cohort quality substantially impacts the results. Some studies have demonstrated that VEGF decreases with aging and is affected by age,[27,46] and age is also a major factor affecting

the heterogeneity of VEGF studies in a European AD cohort. And, the availability or lack of clear AD pathological verification will also be an important factor that cannot be ignored in influencing the results of AD biomarkers. Furthermore, studies on CSF VEGF exhibited less heterogeneity than those on blood VEGF levels. Additionally, CSF VEGF levels were elevated in the AD group and showed association with AD. These findings indicate that CSF VEGF may be a more valuable diagnostic indicator of AD than blood VEGF. We observed no differences with various detection methods, indicating that these methods do not have a significant impact on changes in VEGF in AD.

APOE is the most significant genetic risk factor. In meta-regression analysis, we observed a considerable impact of the proportion of *APOE* ε4 carriers in both overall and European AD groups on the findings of VEGF research. Recent research has indicated that there is a correlation between *APOE* ε4 and *VEGF* gene expressions in the brain, which affects cognitive functioning.[47] The *VEGFA* AA genotype also presents an increased cognitive decline in *APOE* ε4+ patients suffering from AD.[31,48] Alvarez et al. have discovered that elevated serum VEGF levels were associated with enhanced memory and language abilities in individuals with moderately severe AD who carry the *APOE* ε4 gene variant.[30]

There are limitations to our study. Primarily, the limited number of studies requires further research to substantiate our findings. Especially for CSF samples, only five items were included and more data need be included in future studies. Additionally, significant heterogeneity was observed among trials, cautioning against definitive conclusions. Finally, minor unpublished studies could have been missed as conference proceedings were not incorporated. At the same time, our study will indicate which factors ought to be taken into account for future VEGF research on dementia disease for better consistency and significance.

5 | CONCLUSION

Our research mainly indicated that VEGF is more predictive for the diagnosis of VaD. However, it also holds reference value in diagnosing AD in European populations, particularly in CSF. And, age matching and pathological verification are crucial in improving the quality and reliability of studies on the association between VEGF and AD. Moreover, *APOE* ε4 carriers remains a vital influencing factor in AD. Our research demonstrates that VEGF has higher effectiveness for identifying and diagnosing VaD, and more evidence is needed for VEGF to diagnose AD.

AUTHOR CONTRIBUTIONS

Ling-Zhi Xu contributed to drafting/revision of the manuscript, study concept and design, and interpretation of data; Fang-Yu Li contributed to drafting/revision of the manuscript for content, study concept or design, analysis or interpretation of data; Jin Xu contributed to search strategy, acquisition of data, and drafting of the manuscript; Bing-Qiu Li contributed to the acquisition of data and study design; Ying Li contributed to the acquisition of data; Jian-Ping Jia contributed to medical writing for content and the supervision of the study work.

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CONFLICT OF INTEREST STATEMENT

On behalf of all authors, the corresponding author states that there are no conflicts of interest. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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