Review Article

Peripheral Levels of the Brain-Derived Neurotrophic Factor in Coronary Artery Disease: A Systematic Review and Meta-Analysis

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Abstract

Background: Among its functions, brain-derived neurotrophic factor (BDNF) regulates endothelial and macrophage activation, possibly playing a role in atherosclerotic plaque pathophysiology. Given contradicting reports, this study sought to investigate whether blood levels of BDNF differed between patients with coronary heart disease (CHD) and controls.

Methods: We explored PubMed, Embase, Web of Science, and Cochrane Library for studies comparing BDNF blood levels in patients with CHD and controls. Random-effect meta-analysis was conducted to calculate the standardized mean differences (SMD) and 95% confidence intervals (CI). The Newcastle-Ottawa scale was used to evaluate the quality of included articles, and statistical analyses were conducted using R version 4.0.4.

Results: The final analysis comprised 12 investigations covering 1422 CHD cases and 929 controls with mean ages of 59.66±13.56 and 53.78±13.61 years, respectively. The initial analyses revealed a tendency toward low levels of BDNF in the CHD group compared with the control group (SMD= -0.41; 95% CI, -1.12 to 0.30; P=0.26). After the removal of outliers, the difference achieved statistical difference (SMD= -0.56; 95% CI, -0.93 to -0.19; P<0.01). Subgroup analysis demonstrated no significant difference between serum and plasma BDNF levels (P=0.54); however, subgroup analyses of studies investigating plasma BDNF showed that patients with CHD had significantly lower BDNF levels.

Conclusion: Serum and plasma BDNF concentrations were considerably lower in patients with CHD than in healthy controls. Further studies of higher quality are required on the potential role of BDNF as a biomarker of CHD pathophysiology and severity.

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Introduction

Coronary heart disease (CHD), also known as ischemic heart disease, is a leading cause of death globally. CHD is caused by a combination of mechanisms, such as endothelial dysfunction and inflammation, resulting in atherosclerotic plaques.[1] Diabetes, hypertension, smoking, and obesity all contribute to the acceleration of these events.[2] There is great interest in identifying and validating molecular diagnostic and prognostic markers for CHD, including those originating from damaged myocardial tissue, those that have increased levels in blood circulation after coronary events, and the ones with abnormal levels before coronary events.[3-5]

Brain-derived neurotrophic factor (BDNF) is a neurotrophin expressed in the central nervous system and peripheral tissues.[6, 7] Besides its role as a neurotrophic factor, BDNF is involved in the physiology of other tissues, such as the heart.[8] BDNF also plays a role in the development of the heart,[9] endothelial cells,[10] smooth muscle cells,[11] macrophages,[12] lymphocytes,[13] and atherosclerotic vessels.[11] Serum BDNF levels were shown to be low in individuals with CHD who had subsequent coronary events.[14] According to data from the Framingham Heart Study, a high BDNF concentration is related to a reduced risk of CHD and mortality.[14] Previous experimental studies have demonstrated that BDNF promotes endothelial cell survival and neoangiogenesis via the activation of nuclear factor TrκB receptors, inhibits p75-mediated apoptosis of cardiac myocytes, improves endothelial function, modulates blood flow in ischemic myocardium, and enhances left ventricular function following ischemic injury, thereby providing cardioprotective effects.[15, 16] Regardless of age, higher BDNF levels are related to higher body mass index (BMI), blood pressure, low-density lipoprotein cholesterol (LDL-C), and cholesterol.[17] On the other hand, higher levels of BDNF are statistically linked to a lower risk of cardiovascular disease and death independent of their risk factors, such as BMI or physical activity.[18]

The present systematic review and meta-analysis sought to synthesize the existing evidence on serum and plasma BDNF levels in patients with CHD compared with controls. In addition, the probable effects of sex, age, sample size, and the quality of included studies on BDNF concentrations were analyzed and discussed.

Methods

The inclusion criteria were as follows: 1) clinical studies with a control group that measured serum and/or plasma BDNF levels in control and CHD groups and 2) cross-sectional and interventional studies in which the BDNF concentration was measured before the intervention.

We excluded studies that were case reports or series, letters, reviews, conference abstracts, or pre-clinical/experimental studies.

A comprehensive search was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19] statement guidelines in international online databases, including PubMed, Embase, Web of Science, and Cochrane Library, to find studies relevant to the selection criteria in July 2022. The search terms included "BDNF" OR "brain-derived neurotrophic factor" AND "ischemic heart" OR "coronary heart disease" and other related terms. No limitations were applied in the search. The details of the searched queries are available in Supplementary Table 1.

Two reviewers (AK and AHB) independently screened all the studies with titles and abstracts for eligibility. The included studies with the full text were screened by AK and AHB separately, and disagreements were settled through discussions with the third author (PS). In addition, the references of the included studies were screened for any possible relevant study.

Two reviewers (AK and AHB) independently used the data extraction sheet designed by the third reviewer (PS) to extract data, including first author, year, and country of publication; demographic characteristics (number of participants, age, and male percentage in CHD and control groups); and plasma and serum BDNF concentrations in each group. The concentration unit was converted to picograms per milliliter (pg/mL) for all the included studies. We contacted the corresponding authors of the studies in which the absolute values of the serum BDNF level were not mentioned.

Assessment of risk of bias in the included studies was performed using the Newcastle-Ottawa Quality Assessment Scale[20] for observational studies. Two reviewers (AHB and AK) independently evaluated the quality of the included studies. Disagreements in the quality evaluation were resolved by the third investigator (PS). Selection, comparability, and outcome were the principal categories of potential bias. Scores of 9–10, 7–8, 5–6, and <5 were considered very good, good, satisfactory, and unsatisfactory studies concerning quality, respectively.

Data analysis was performed using R version 4.0.4 (R Core Team [2020]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Due to different measurement

methods in the studies, the standardized mean difference (SMD) and the 95% confidence interval (CI) were used to compare CHD patients with controls. Additionally, P values <0.05 were considered the statistical significance cutoff throughout the study.

In the case of the report of the median and interquartile range or the median and range for any needed variable in an article, the mean and standard deviation were calculated based on statistical methods by Luo et al[21] and Wan et al.[22] In cases where there was a need to combine the groups' means and standard deviations, formulas suggested by Cochrane's Handbook[23] were utilized.

Statistical heterogeneity was evaluated using Higgins' I^2 test based on Cochrane's Q. The thresholds used for heterogeneity I^2 were $\leq 25\%$, 26–75%, and $\geq 75\%$ for low, moderate, and high heterogeneity, respectively. Given the high heterogeneity between the studies, the random effect model (DerSimonian and Laird) was utilized for SMD analysis. To identify the source of heterogeneity, we performed meta-regression on the mean age and the NOS score of the studies. Possible publication bias was investigated via a visual assessment of funnel plots and Egger's and Begg's tests.[24, 25] Finally, potential outliers were identified, and a sensitivity analysis was conducted to evaluate the effect of each study.

Results

The initial search yielded 1779 references: 1184 from PubMed, 390 from Embase, 47 from Cochrane Library, and 158 from Web of Science. After the exclusion of 484 duplicate studies and 1295 investigations unrelated to our topic, 73 studies examining peripheral BDNF levels in CHD were discovered and thoroughly evaluated. Subsequently, 61 studies were excluded due to various reasons described in Figure 1. Finally, 12 studies,[26-37] including 2351 participants, fulfilled all of the inclusion criteria and were included in the meta-analysis. A detailed flow chart of the search and selection process is presented in Figure 1.

The characteristics of the 12 selected studies are presented in Table 1. All the articles were published between 2005 and 2022. The included investigations yielded 2351 observations, composed of 1422 CHD cases and 929 controls. The average age of the patients and controls were 59.66±13.56 and 53.78±13.61, respectively.[26, 27, 29-37] Biological sources for BDNF analysis were the plasma[26, 29, 32, 34, 36] and the serum.[27, 28, 30, 31, 33, 35, 37] All 12 included studies assessed BDNF levels using enzyme-linked immunosorbent assay (ELISA) as the analytical procedure. All the studies were of high quality, with an average NOS score of 9.43±0.94 (Table 2).

The estimates pooled from the 12 studies showed a tendency toward lower BDNF levels in patients with CHD than in controls (SMD= -0.4089; 95% CI, -1.1168 to 0.2990;
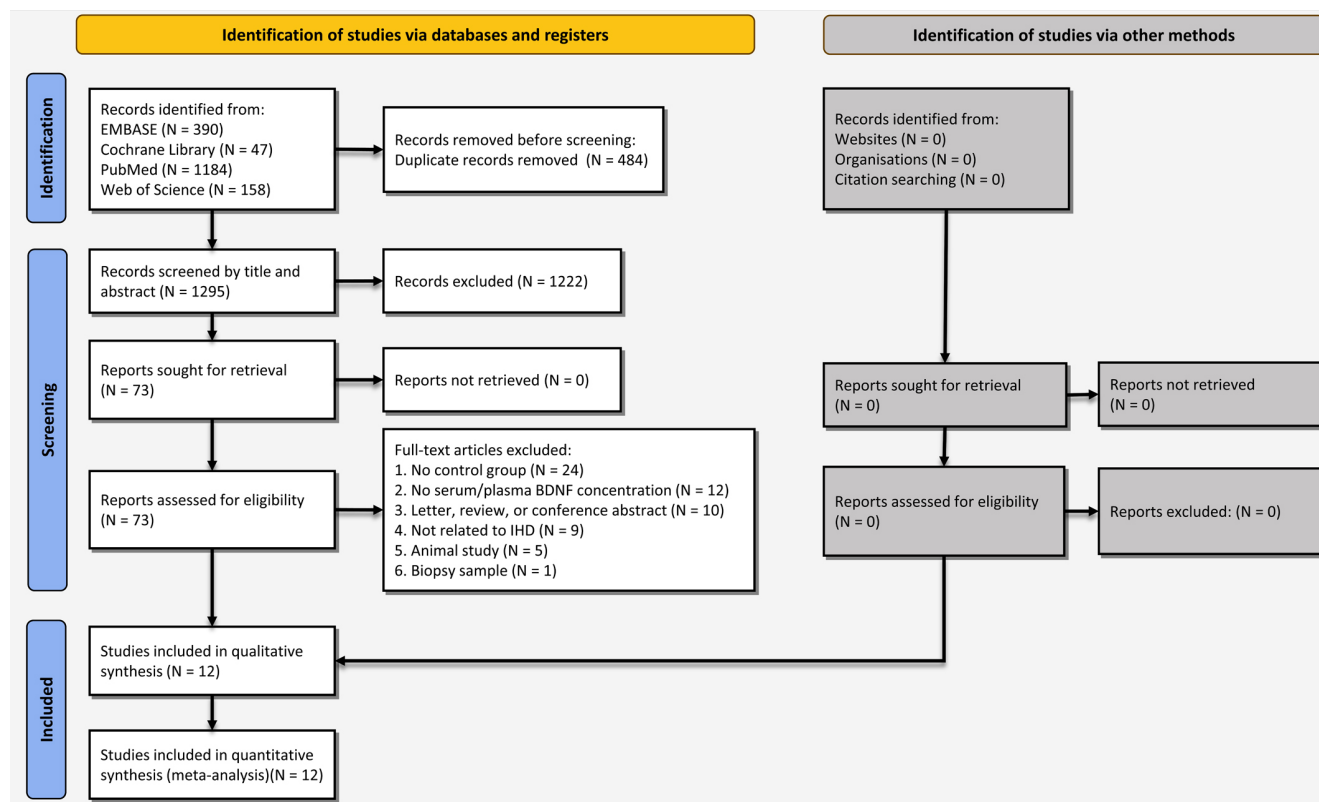

Figure 1. The flow diagram summarizes the selection of eligible studies based on the PRISMA guidelines.

Table 1. Characteristics of the included studies

Author	Year	Design	Country	Analytical Technology	Source	Population	Control	n total	n CHD	Age	% Male
Amadio et al	2021	Cross-Sectional	Italy	ELISA	Plasma	>50% stenosis by visual estimate at angiography	No history of CAD, no MI symptoms, no CV therapy	76	55	61.89±11.62	86.84
Aslan et al	2020	Cross-Sectional	Turkey	ELISA	Serum	Presence of typical exertional angina, positive stress test or reversible myocardial perfusion defects during stress imaging, and angiographically normal coronary arteries (MVA)	Normal coronary arteries, inconclusive findings in stress tests or functional imaging, and no CAD in angiography	152	91	57.28±29.11	44.74
Bai et al	2019	Cross-Sectional	China	ELISA	Serum	Chronic CHD according to the clinical guidelines by the ACC/AHA	NR	211	108	NR	NR
Ejiri et al	2005	Cross-Sectional	Japan	Sandwich ELISA	Plasma (Peripheral Vein)	>75% stenotic lesions in the LCA determined by myocardial perfusion scintigraphy to be the culprit lesion (UA or SA)	No significant coronary artery stenosis >25% luminal diameter	107	83	64.46±25.86	65.42
Esmaeili et al	2021	Cross-Sectional	Iran	ELISA	Serum	At least one major coronary artery with > 50% stenosis confirmed by angiography (CAD)	Normal angiogram and no coronary stenosis	146	84	53.50±9.41	60.96
Forent et al	2022	Cross-Sectional	Canada	ELISA	Plasma	Documented CHD	Without cardiac disease and aortic stenosis symptoms	59	39	64.92±8.07	71.19
Han et al	2019	Cross-Sectional	China	DAS-ELISA	Serum	At least one of the three major coronary arteries or major branches significant coronary artery stenosis ≥50%	Normal clinical, physical, radiographic, and ECG examinations	257	156	59.58±9.83	58.37
Jin et al	2018	Cross-Sectional	China	ELISA	Plasma	>50% stenosis of the primary coronary artery or its major branches	<20% stenosis	234	143	65.92±10.54	65.38
Monisha et al	2020	Cross-Sectional	India	ELISA	Serum	Lesion >30% in the primary coronary artery or its major branches	Lesion ≤30%	221	116	55.94±10.97	NR
Sustar et al	2019	Cross-Sectional	Croatia	ELISA	Plasma	>50% stenotic lesions in at least one major coronary vessel, MI, coronary stent implantation, and coronary artery bypass surgery. (CHD=SA/UA)	Screened during routine physical check-ups in the same hospital	364	208	50.72±11.14	53.30
Wu et al	2022	Cross-Sectional	China	ELISA	Serum	Criteria of coronary heart disease in "Diagnostic Criteria for Coronary Atherosclerotic Heart Disease", and coronary angiography shows that the inner diameter of any one of the left main trunks, left circumflex artery, left anterior descending artery, and right coronary artery stenosis degree ≥50% or left main stem stenosis >30%	NR	277	132	51.35±10.23	42.60
Xia et al	2022	Cross-Sectional	China	ELISA	Serum	Diagnosed as CHD by coronary angiography	Non-CHD by coronary angiography	247	207	NR	NR

SA, Stable angina; UA, Unstable angina; MI, Myocardial infarction; CAD, Coronary artery disease; CHD, Coronary heart disease; ACS, Acute coronary syndrome; CV, Cardiovascular; MVA, Microvascular Angina; LCA, Left coronary artery; ECG, Electrocardiogram; ACC, American College of Cardiology; AHA, American Heart Association; NR, Not reported

Table 2. Quality assessment of the included studies based on the Newcastle-Ottawa scale (NOS)

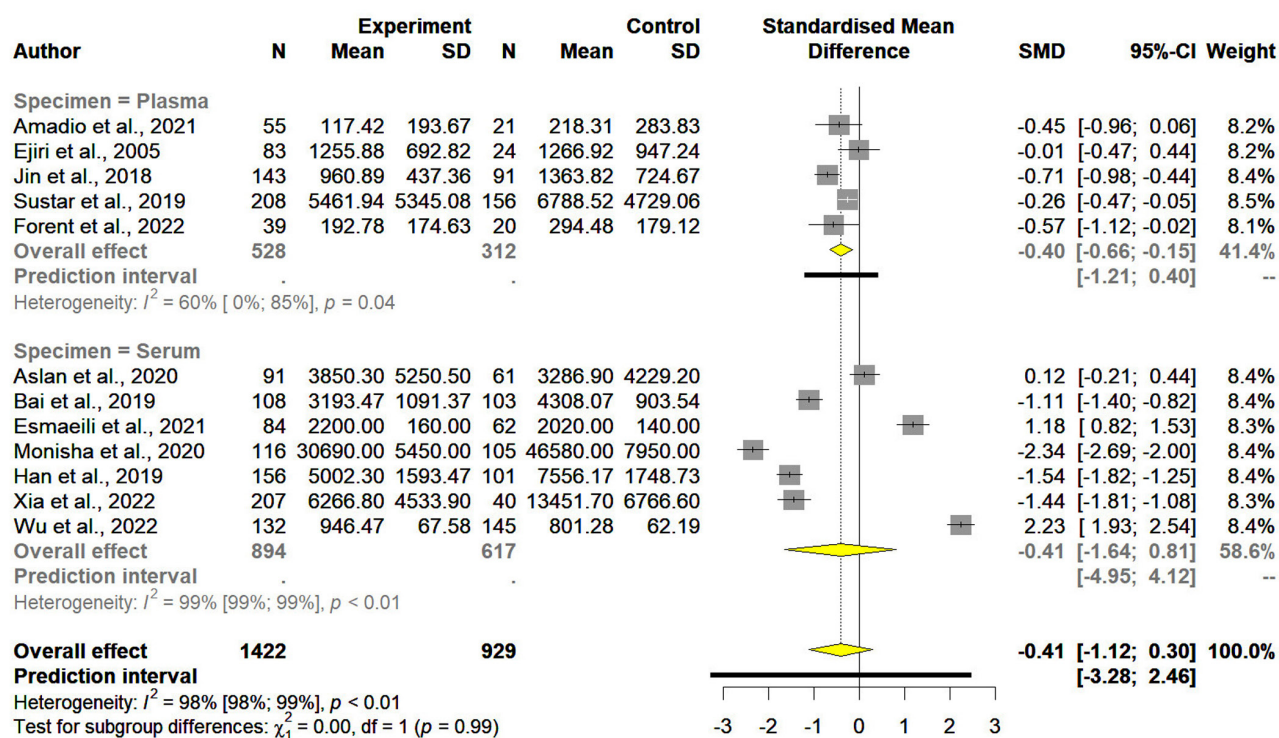| Study	Selection				Comparability	Outcome		Overall Score
	Representation	Sample Size	Non-Respondents	Exposure		Outcome	Statistical Test	
Amadio et al	*	*	*	**	**	**	*	10
Aslan et al	*	*	*	**	0	**	*	8
Bai et al	*	*	*	**	**	**	*	10
Ejiri et al	*	*	*	**	0	**	*	8
Esmaeili et al	*	*	*	**	**	**	*	10
Forent et al	*	*	*	**	**	**	*	10
Han et al	*	*	*	**	**	**	*	10
Jin et al	*	*	*	**	**	**	*	10
Monisha et al	*	*	*	**	0	**	*	8
Sustar et al	*	*	*	**	**	**	*	10
Wu et al	*	*	*	**	**	**	*	10
Xia et al	*	*	*	**	0	**	*	8

Figure 2. The image illustrates the forest plot of the subgroup meta-analysis of BDNF levels in the CHD group compared with the control group.
BDNF, Brain-derived neurotrophic factor; CHD, Coronary heart disease

$P=0.2576$) (Figure 2). However, there was significant statistical heterogeneity across the studies (I^2, 98.2%; $P<0.0001$).

In the I^2 studies included in this meta-analysis, BDNF levels were investigated in the serum by 7 and in the plasma by 5. Lower BDNF levels were found in CHD compared with controls in both subgroups of studies. The pooled SMD was -0.4148 (95% CI, -1.6426 to 0.8130; $P=0.51$) for BDNF levels assessed in the serum and -0.4042 (95% CI, -0.6589 to -0.1494; $P<0.01$) for BDNF levels assessed in the plasma (Figure 2). Subgroup comparisons found no

significant difference between BDNF concentration SMD reported in the serum and plasma between CHD and controls ($P=0.9867$).

The funnel plot was symmetric (Figure 3). Moreover, Begg's and Egger's tests did not reveal significant evidence of publication bias among the included studies (Begg's test: $P=1.00$; Egger's test: $P=0.98$).

Meta-regression analyses were applied to investigate heterogeneity sources between the studies and the influence of modifiers. Univariable meta-regression models showed no relationships between sample size, age, NOS score,

sex, and BDNF levels (Table 3 & Figure 4). Moreover, age accounted for 17.83%, and male sex accounted for 11.18% of observed heterogeneity, while the others could not justify the heterogeneity.

A)

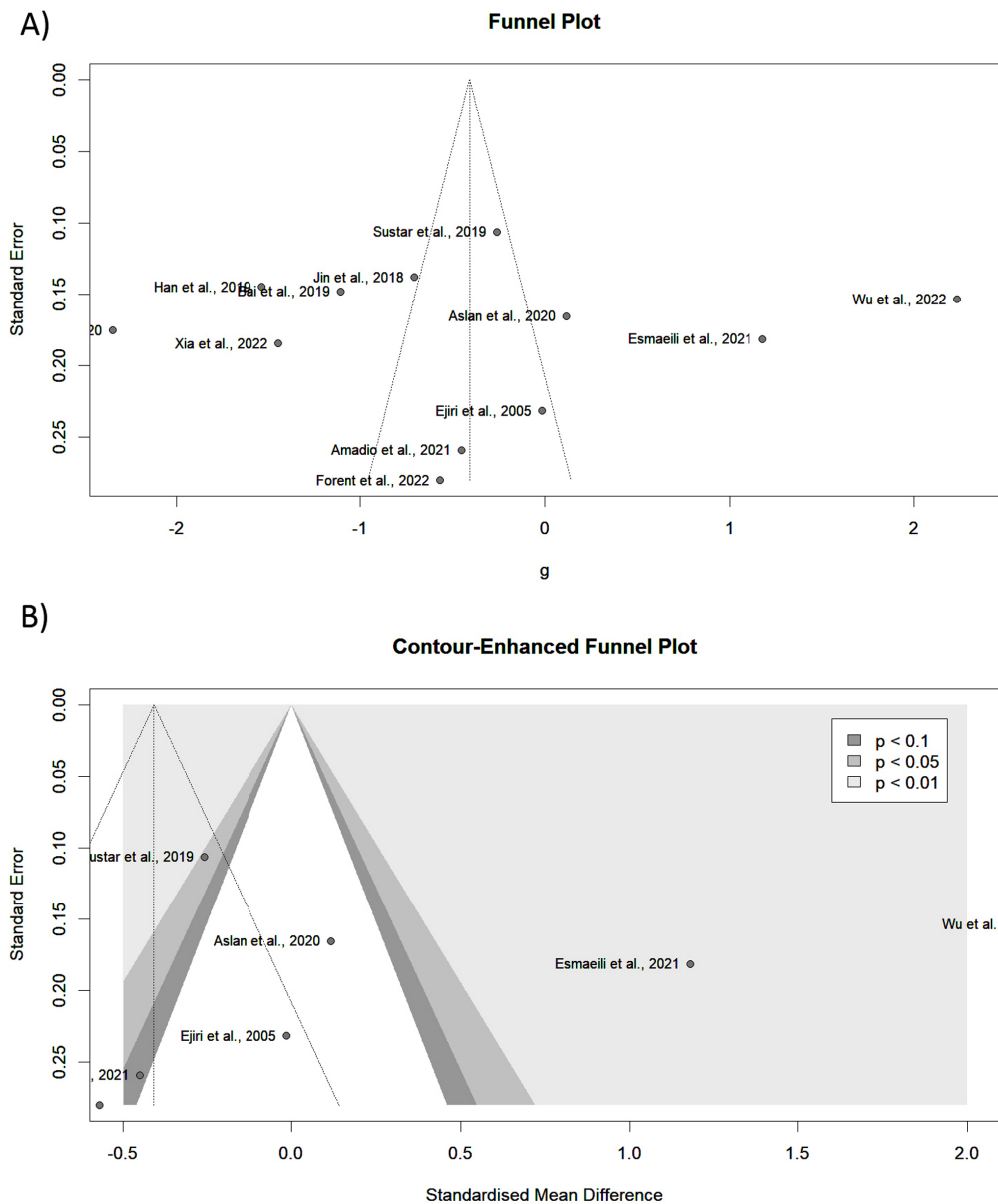**Funnel Plot**

B)

Contour-Enhanced Funnel Plot

Figure 3. A) The funnel plot shows no evidence of publication bias, statistically supported by Egger's regression test. B) The image presents the counter-enhanced funnel plot.

Table 3. Meta-regression of BDNF levels in patients with CHD and healthy controls

Moderator	No. of comparisons	No. of Subjects		Meta-Regression			P	R^2 Analog (proportion of the variance explained)
		CHD	HC	Slope	Lower 95% CI	Upper 95% CI		
Sample Size	12	1422	929	-0.005	-0.019	0.010	0.527	0%
Age (mean, y)	11	1314	826	-0.118	-0.258	0.021	0.096	17.8%
NOS score	12	1422	929	0.387	-0.367	1.141	0.315	0%
Sex (male, %)	10	1198	721	-0.034	-0.082	0.014	0.161	11.2%

NOS, Newcastle-Ottawa scale; CHD, Coronary heart disease; HC, Healthy control; CI, Confidence interval

Studies by Han et al,[30] Monisha et al,[31] and Esmaeili et al[33] were identified as outliers. Accordingly, we repeated the meta-analysis of the remaining 6 studies. The results showed an SMD of -0.5595 (95% CI, -0.9293 to -0.1896; *P*=0.0030) (Figure 5), indicating statistically significantly lower BDNF levels in CHD participants than in controls. (The *P* value dropped from 0.2576 to 0.003.) However, considerable statistical heterogeneity remained across the
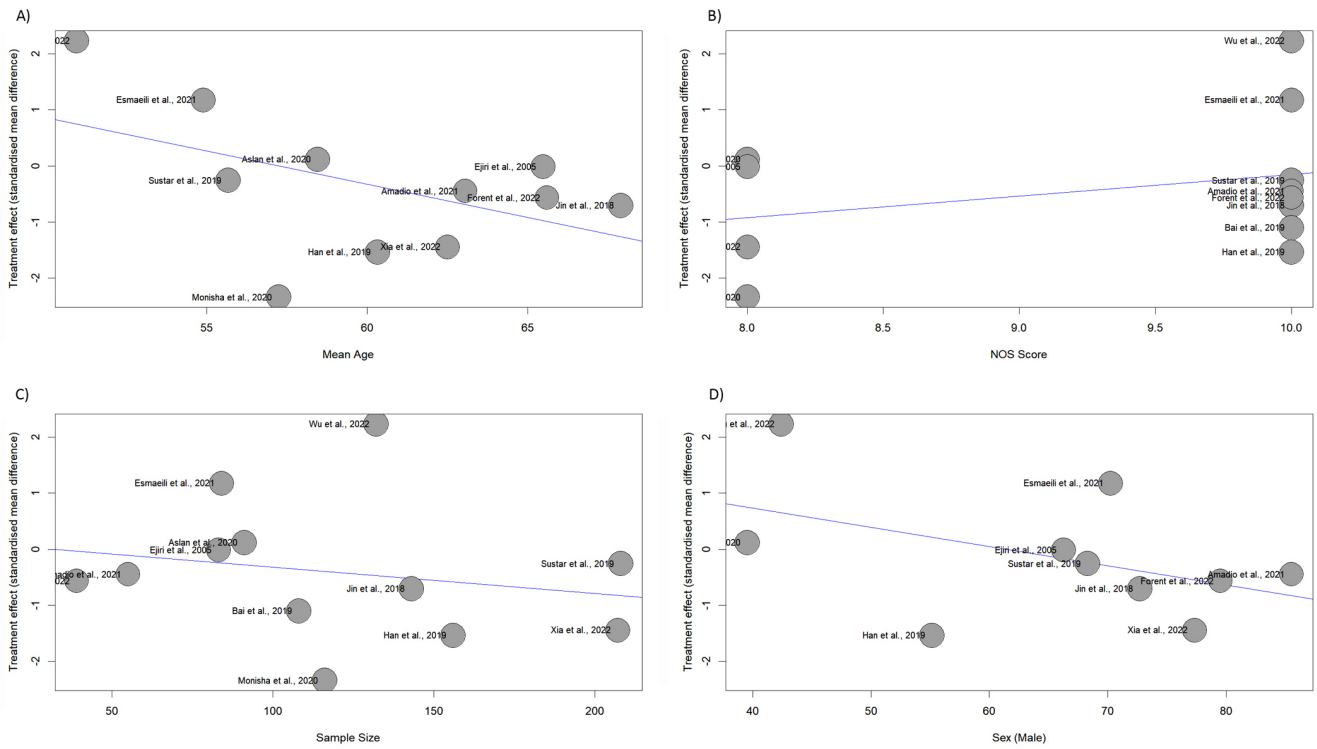

Figure 4. The images present the bubble plots of the meta-regression.

A) mean age, B) NOS score, C) sample size, and D) sex (male)

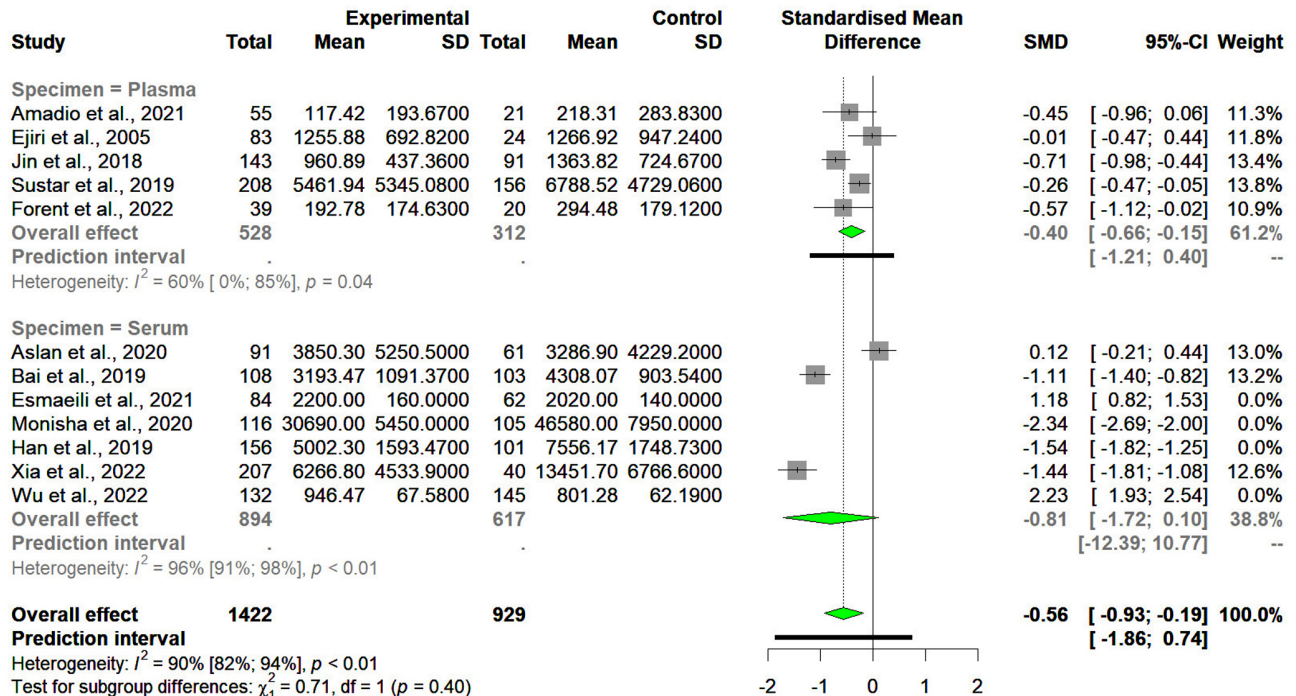| Study	Total	Experimental Mean	SD	Total	Control Mean	SD	Standardised Mean Difference	SMD	95%-CI	Weight
Specimen = Plasma										
Amadio et al., 2021	55	117.42	193.6700	21	218.31	283.8300		-0.45	[-0.96; 0.06]	11.3%
Ejiri et al., 2005	83	1255.88	692.8200	24	1266.92	947.2400		-0.01	[-0.47; 0.44]	11.8%
Jin et al., 2018	143	960.89	437.3600	91	1363.82	724.6700		-0.71	[-0.98; -0.44]	13.4%
Sustar et al., 2019	208	5461.94	5345.0800	156	6788.52	4729.0600		-0.26	[-0.47; -0.05]	13.8%
Forent et al., 2022	39	192.78	174.6300	20	294.48	179.1200		-0.57	[-1.12; -0.02]	10.9%
Overall effect	**528**			**312**				**-0.40**	**[-0.66; -0.15]**	**61.2%**
Prediction interval	.			.					[-1.21; 0.40]	--
Heterogeneity: $I^2 = 60\%$ [0%; 85%], $p = 0.04$										
Specimen = Serum										
Aslan et al., 2020	91	3850.30	5250.5000	61	3286.90	4229.2000		0.12	[-0.21; 0.44]	13.0%
Bai et al., 2019	108	3193.47	1091.3700	103	4308.07	903.5400		-1.11	[-1.40; -0.82]	13.2%
Esmaeili et al., 2021	84	2200.00	160.0000	62	2020.00	140.0000		1.18	[0.82; 1.53]	0.0%
Monisha et al., 2020	116	30690.00	5450.0000	105	46580.00	7950.0000		-2.34	[-2.69; -2.00]	0.0%
Han et al., 2019	156	5002.30	1593.4700	101	7556.17	1748.7300		-1.54	[-1.82; -1.25]	0.0%
Xia et al., 2022	207	6266.80	4533.9000	40	13451.70	6766.6000		-1.44	[-1.81; -1.08]	12.6%
Wu et al., 2022	132	946.47	67.5800	145	801.28	62.1900		2.23	[1.93; 2.54]	0.0%
Overall effect	**894**			**617**				**-0.81**	**[-1.72; 0.10]**	**38.8%**
Prediction interval	.			.					[-12.39; 10.77]	--
Heterogeneity: $I^2 = 96\%$ [91%; 98%], $p < 0.01$										
Overall effect	**1422**			**929**				**-0.56**	**[-0.93; -0.19]**	**100.0%**
Prediction interval									**[-1.86; 0.74]**	
Heterogeneity: $I^2 = 90\%$ [82%; 94%], $p < 0.01$										
Test for subgroup differences: $\chi^2_1 = 0.71$, df = 1 ($p = 0.40$)										

Figure 5. The forest plot of the meta-analysis of BDNF levels in patients with CHD after the removal of outliers is presented herein.

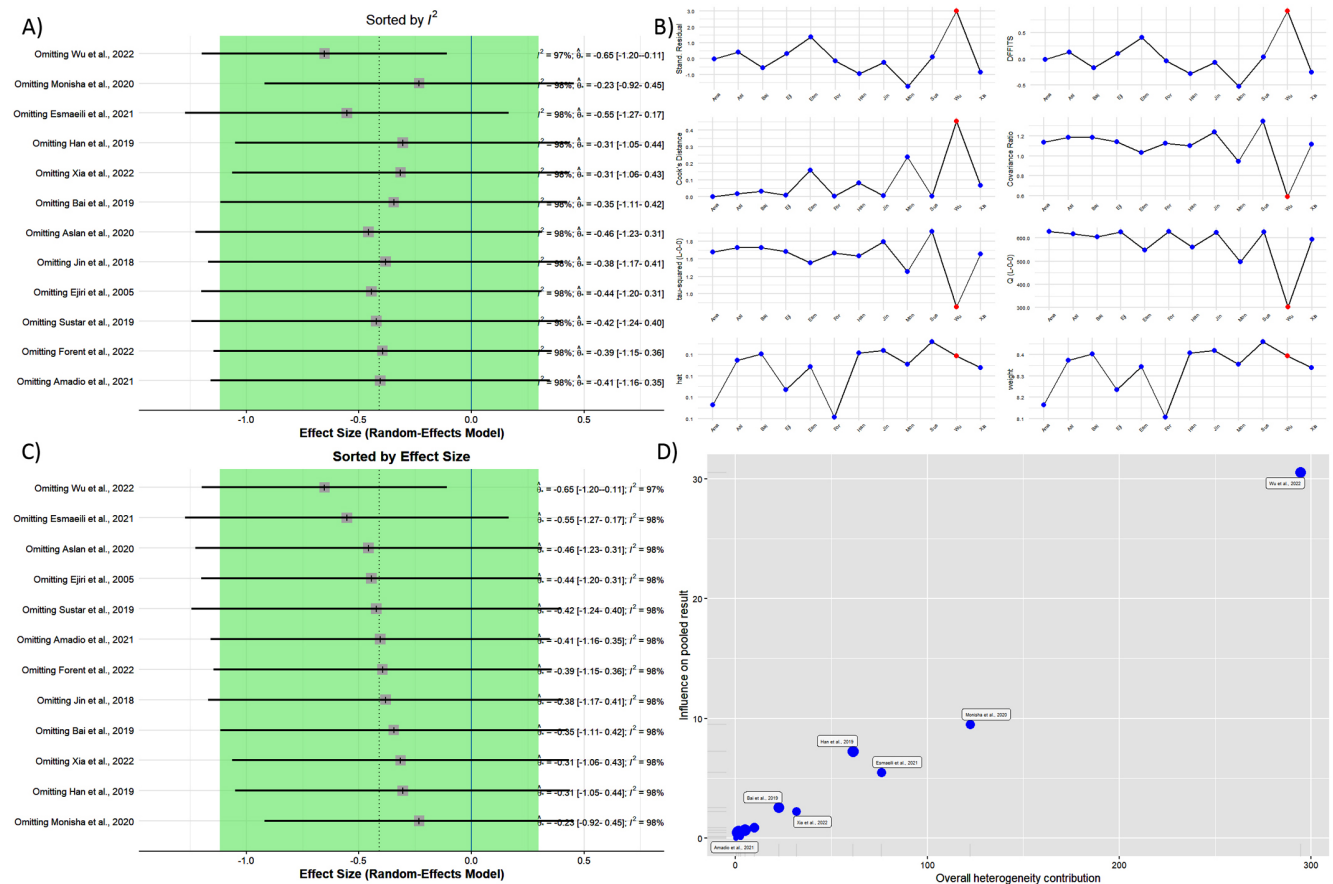BDNF, Brain-derived neurotrophic factor; CHD, Coronary heart disease

Figure 6. The images present the results of the sensitivity analyses (leave-one-out analysis) of the meta-analysis.

A) Sorted by I^2.

B) The influence analysis plot shows influence diagnostics, including externally standardized residuals, the DFFITS value, Cook's distance, covariance ratio, leave-one-out τ^2, Q value, hat value, and study Weight.

C) Sorted by effect size

D) Baujat's plot is illustrated herein.

DFFITS, Difference in fits

studies (I^2, 89.7%; *P*<0.0001).

The impact of each study on the overall estimate was determined by systematically omitting studies and comparing the pooled estimate from the remaining 11 studies to the pooled estimate from all 12 studies. The results indicated that patients with CHD had lower peripheral BDNF levels than controls in all the studies except for that by Wu et al,[37] which changed the results statistically significantly after being removed (SMD= -0.65; 95% CI, -1.20 to -0.111) (Figure 6).

Discussion

To our knowledge, this is the first meta-analysis of studies to compare BDNF peripheral levels between patients with chronic CHD and healthy controls. CHD was associated with significantly lower levels of BDNF. Moreover, subgroup analysis revealed statistically significantly lower plasma BDNF levels in patients with CHD and not serum levels.

Previous studies have suggested a significant role for BDNF in cardiovascular development, functions, risk factors, and disorders.[38-41] In mice, BDNF perfusion increased cardiac contraction force and systolic pressure but decreased diastolic pressure, not affecting coronary blood flow.[42] In a prospective cohort, a lower plasma level of BDNF was associated with a higher risk of major coronary events in angina pectoris patients with a median follow-up of 48 months.[43] There is also an inverse relation between BDNF and atherogenic index (total cholesterol/HDL-C), high-sensitivity C-reactive protein, and oxidized LDL.[44] The higher levels of BDNF in multiple sclerosis patients with higher activities may be attributable to the normal population and can be another possible mechanism indirectly affecting CHD.[45] Conversely, higher BDNF levels were related to higher BMI, blood pressure, LDL-C, and cholesterol[17] (ie, risk factors for CHD). In this scenario,

BDNF might increase as a response to risk factors of disease progression (eg, high cholesterol), exerting protective roles.

Several studies have suggested the pathophysiology of the association between cardiovascular disease and circulating BDNF. BDNF is expressed in vascular endothelial cells, the smooth muscle of atherosclerotic coronary arteries, and macrophages, in addition to the neural system.[29, 46] Thus, a study suggested that BDNF might affect plaque stability, although the clinical relevance of this hypothesis is still uncertain.[47] In contrast with this local effect, the effect of BDNF on the integrity and maintenance of cardiac vasculature may be more critical. In an in vivo study, low BDNF levels in mice resulted in less survival of the endothelial cells in myocardial arteries and, finally, postnatal death.[48]

As serum and plasma BDNF levels have a strong positive correlation,[49] we used both sources of BDNF (plasma and serum) in this meta-analysis as subgroup analysis. The average serum BDNF level is higher (100-fold in a study by Radka et al[49] and 14-fold in a study by Yoshimura et al[50]) than plasma levels. As human platelets contain large amounts of BDNF, this difference is due to the clotting process in which platelets degranulate.[51, 52] Serum BDNF levels, in contrast with plasma levels, are primarily dependent on clotting time, which varies between studies.[53] These disparities in serum levels may be why our results in the plasma subgroup were statistically significant. We found no relevant study that evaluated both serum and plasma levels of BDNF in patients with CHD and controls. Further research may help investigate the difference we mentioned in terms of meaningfulness.

The results of the present study suggest the possibility of the diagnostic value of BDNF for CHD, but more importantly, it highlights the possible pathophysiological pathway from BDNF to CHD, which can assist in designing and using novel therapies for CHD. Until now, the most therapeutic applications of BDNF have been in neurological diseases, with an oral BDNF agonist from the plant flavonoids showing effectiveness on stroke and Parkinson's disease in mice.[54] Further trials and studies are needed to investigate such effects for the prevention of cardiovascular disease.

While being the first meta-analysis to investigate blood BDNF levels in CHD, this study had some limitations. Firstly, the lack of proper matching for confounders in the studies could influence their results and, therefore, our analysis. We only included cross-sectional, case-control, or cohort studies that had both CHD and control groups. The low number of included studies and the low number of studies in our subgroup analysis were also considerable limitations. We excluded studies that mentioned the BDNF levels only graphically and/or did not mention the quantitative data. The authors did not respond to our email requests for their data, and we had to exclude the studies due to not having the required data for meta-analysis. Finally, the statistical methods used for converting the median and the interquartile range to the mean and standard deviation, as suggested by Luo et al[21] and Wan et al,[22] although they are used in many meta-analysis studies, may affect the results due to the possible skewness of a variable distribution. Future studies with larger sample sizes investigating the association between the severity of chronic CHD and BDNF levels might help identify the pathophysiology of our findings.

Conclusion

To summarize, peripheral concentrations of BDNF were significantly lower in patients with CHD than in healthy controls, principally because of studies that measured plasma BDNF.

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Supplementary Material

Table 1. Search queries used for each database and the search results

	Query	Results (No.)
	PubMed	
#1	"Brain-Derived Neurotrophic Factor"[Mesh] OR "BDNF" OR "brain-derived neurotrophic factor"	29,312
#2	"Myocardial Ischemia"[Mesh] OR "Myocardial ischemia" OR "Coronary Artery Disease"[Mesh] OR "Coronary Atherosclerosis" OR "Coronary Disease"[Mesh] OR "Coronary Heart Disease*" OR "ischemic heart" OR "ischemia"	707,485
#3	#1 AND #2	1,184
	Embase	
#1	'brain derived neurotrophic factor'/exp OR 'bdnf' OR 'brain derived neurotrophic factor' OR 'brain-derived neurotrophic factor'	50,031
#2	('ischemic heart disease'/exp OR 'coronary heart disease' OR 'ischemia heart disease' OR 'ischemic cardiac disease' OR 'ischemic cardiopathy' OR 'ischemic heart disease')	807,302
#3	#1 AND #2	390
	Web of Science	
#1	TS="brain-derived neurotrophic factor" OR TS="BDNF" OR TS="brain derived neurotrophic factor"	33,432
#2	TS="myocardial ischemia" OR TS="coronary artery disease" OR TS="coronary atherosclerosis" OR TS="coronary diseases" OR (TS="heart disease" AND TS="coronary") OR (TS="heart disease" AND TS="ischemic") OR TS="ischemic cardiac disease"	307,020
#3	#1 AND #2	158
	Cochrane Library	
#1	"BDNF" OR "brain-derived neurotrophic factor"	1,802
#2	"Myocardial Ischemia" OR "Coronary Artery Disease" OR "ischemia" OR "ischemic heart" OR "heart disease, coronary" OR "ischemic cardiac disease"	44,993
#3	#1 AND #2	47