Original Article
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Associations between Erectile Dysfunction and Vascular Parameters: A Systematic Review and Meta-Analysis

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Purpose: Erectile dysfunction (ED) is associated with several vascular disorders, but the associations between ED and vascular parameters are still unclear.

Materials and Methods: We analyzed and synthesized a comprehensive range of studies from PubMed, Web of Science, and Scopus regarding the associations between ED and the following measures: ankle-brachial index (ABI), pulse wave velocity (PWV), intima-media thickness (IMT), nitrate-mediated dilation (NMD), flow-mediated dilation (FMD), augmentation index (AI), endothelial progenitor cells (EPCs) and other vascular parameters. Subgroup analysis was conducted according to specific types of parameters. Study quality was assessed by using the Newcastle–Ottawa Scale. Sensitivity analysis was conducted to confirm the robustness of the pooled results.

Results: Fifty-seven studies with 7,312 individuals were included. Twenty-eight studies were considered to be high-quality. ED patients had a 0.11 mm higher IMT (95% confidence interval [CI]: 0.07, 0.15), a 2.86% lower FMD (95% CI: -3.56, -2.17), a 2.34% lower NMD (95% CI: -3.37, -1.31), a 2.83% higher AI (95% CI: 0.02, 5.63), a 1.11 m/s higher PWV (95% CI: 0.01, 2.21), and a 0.72% lower percentage of EPCs (95% CI: -1.19, -0.24) compared to those without ED. However, ABI was similar between ED patients and non-ED individuals. According to sensitivity analysis, the pooled results were robust.

Conclusions: Our study confirmed the associations between ED and several vascular parameters and highlighted the importance of prevention and management of vascular and endothelial dysfunction in ED patients.

Keywords: Carotid intima-media thickness; Endothelial cells; Erectile dysfunction; Pulse wave analysis; Vascular stiffness

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INTRODUCTION

Erectile dysfunction (ED) is a common disease that primarily affects males aged 40 years or older [1]. Approximately 18.4% of men over 20 years old suffer from ED [2]. Moreover, the global incidence of ED will rise to 322 million cases by 2025 [3]. Clearly, ED is currently recognized as a significant health problem in a progressively aging population.

Although the mechanism of ED is complicated, it is usually deemed to have an intricate organic and psychogenic nature [1]. Vasculogenic ED is a common type of organic disorder [4]. Prior studies reported a higher incidence of ED in hypertension patients [5]. Inman et al [6] drew a landmark conclusion that there is an obvious elevation in the risk of subsequent cardiovascular events in young ED men compared with individuals without ED over a 10-year follow-up. ED is also recognized as a predictor of cardiovascular diseases (CVDs) in expert opinion [7]. ED and CVD share comparable risk factors, such as age, obesity, and smoking, which cause vascular and endothelial dysfunction [1].

However, the associations between ED and vascular parameters remain unclear due to inappropriate measurement methods and limited sample sizes in previous studies. Some noninvasive methods for the assessment of vascular function have been established. Pulse wave velocity (PWV) [8], a measure of arterial stiffness, is a marker of vascular function. Flow-mediated dilation (FMD), nitrate-mediated dilation (NMD) [9], endothelial progenitor cells (EPCs) and other measures [10-12] are considered markers of endothelial function. A meta-analysis by Osondu et al [13] in 2018 pointed out the potential associations between ED and subclinical CVD and several vascular parameters, such as carotid intima-media thickness (IMT) and FMD. However, due to the limited vascular parameters included in that study, the associations between ED and vascular function still need to be further investigated.

Moreover, ED can be considered a marker for vascular dysfunction, which is greatly helpful for the prevention and management of vascular-related diseases, particularly in young men [14]. This systematic review and meta-analysis aimed to examine and synthesize available evidence regarding the association between ED and vascular parameters.

MATERIALS AND METHODS

A comprehensive search of PubMed, Web of Science, and Scopus was conducted to identify studies that evaluated the association between ED and vascular parameters, which were published before 2022. Apart from ED, search terms regarding vascular parameters included 'intima-media thickness', 'flow-mediated dilatation', 'nitrate-mediated dilation', 'augmentation index', 'ankle-brachial index', 'pulse wave velocity', and 'endothelial progenitor cells' (Supplement Table 1). We excluded case reports, case series, non-English publications, and studies without available complete texts according to our predefined exclusion criteria. We also excluded single-arm studies. We collected the mean and standard deviation or median and quartiles, which were converted to the mean and standard deviation using an online calculator [15]. The search was carried out by one reviewer (HP), while eligibility assessments were conducted by the other two reviewers (HP and HZ). Only studies that met the predefined eligibility criteria and were deemed appropriate by both reviewers were included in the meta-analysis. The review was registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/, registration number CRD42023387846).

1. ED and vascular parameter assessment

The assessment of erectile function is commonly performed using the Kolner (Cologne) Evaluation of Erectile Function (KEED) or International Index of Erectile Function questionnaire (IIEF), including IIEF-15 and IIEF-5 [16,17]. The KEED questionnaire consists of six questions on a five-point Likert scale [18]. These questionnaires are widely-used, multidimensional self-report instruments for the diagnostic evaluation of ED severity. In addition, one study defined ED as a peak systolic velocity (PSV) ≤25 cm/s 15 minutes following the injection of a vasodilator.

The assessment modalities for relevant vascular parameters are described in Supplement Table 2.

2. Study quality assessment

We utilized the Newcastle–Ottawa Scale (NOS) to formally evaluate the quality of all included studies [19]. The total NOS score is up to 9 stars. The higher the score, the higher the quality of the study. All studies were assessed by two reviewers (HP and HZ) independently.

3. Statistical analysis

Statistical analyses were performed by using Review Manager software (version 5.4; The Cochrane Collaboration). Pooling was performed using inverse variance weighting to generate the mean difference (MD), and the results of the random effects model were displayed using the corresponding forest plot [20]. Additionally, we reported the heterogeneity (I^2) and between-study variance (τ^2; square) in our analysis. We also attempted to identify the source of this heterogeneity by subgroup analysis and sensitivity analysis. Sensitivity analyses were performed using the R package of meta in R software (Version 4.2.3; R Foundation for Statistical Computing). Subgroup analysis was conducted according to specific types of parameters, age groups. Funnel plots were used to evaluate the possibility of publication bias.

RESULTS

The flow diagram of the article search is shown in Fig. 1. Fifty-seven studies met the inclusion criteria. Overall, 24 studies examined IMT outcomes [21-44], 4 studies measured AI [27,41,45,46], 5 studies measured ABI [32,47-50], 6 studies measured PWV [31,41,48,51-53], 25 studies assessed FMD [24,29-31,37,41-43,54-70], and 9 studies measured NMD [30,31,37,41,56,64,67,69,70]. Moreover, 11 studies measured several types of EPC [40,59,60,67,71-77]. The baseline characteristics of the included studies are provided in Supplement Table 3. A summary of the quality assessment is provided in Supplement Table 4. Twenty-eight studies were considered high-quality (7–9 stars), while twenty-nine studies were medium-quality (4–6 stars) [78].

1. ED and vascular structure

1) ED and IMT

In all, 24 studies with 2,758 participants assessed the association between ED and IMT (Fig. 2), including 20 studies of carotid IMT (cIMT) [21-24,27-38,41-44], 5 studies of cavernous IMT [25,26,35,39,40], 2 studies of bran-

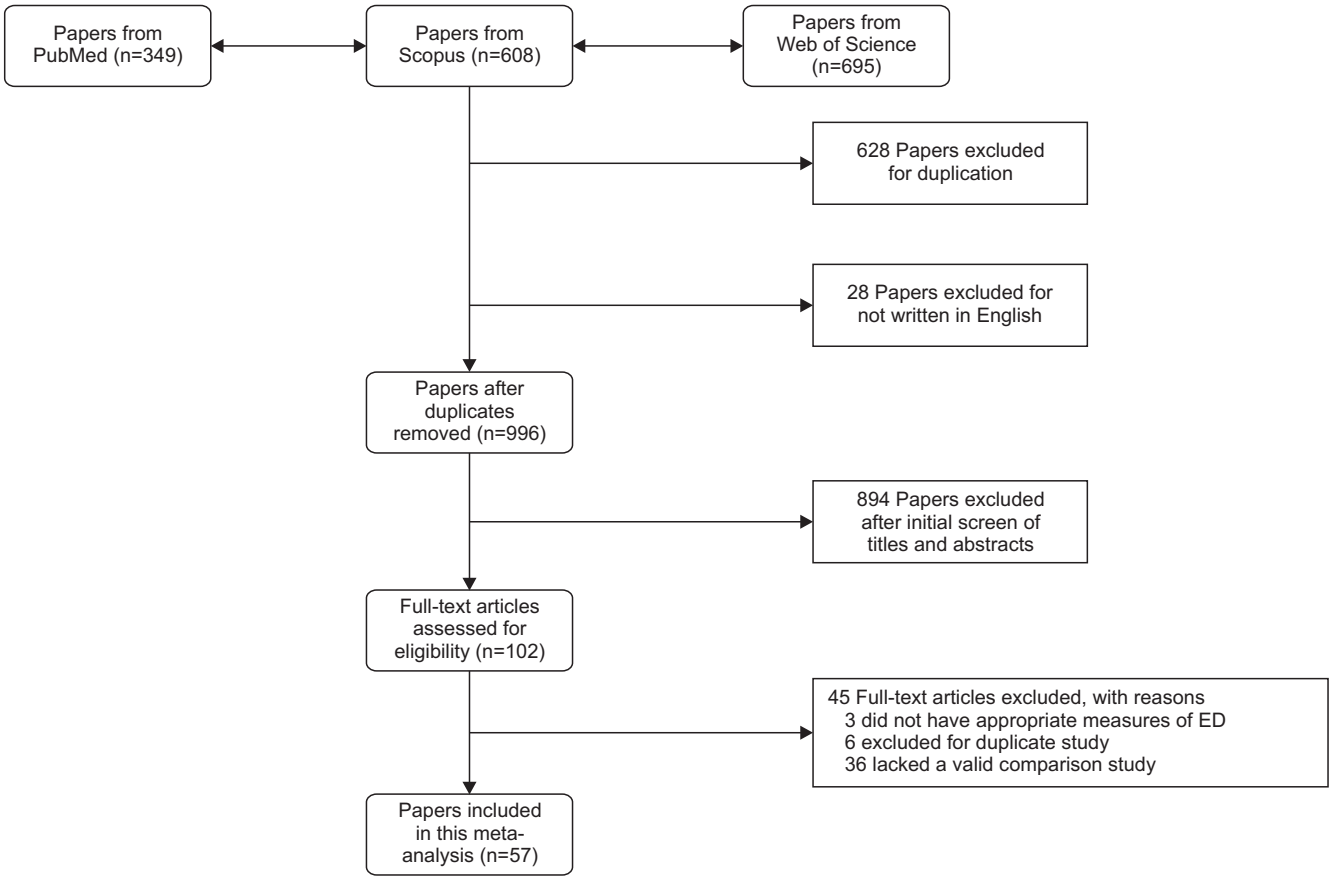


Fig. 1. Systematic review search results. ED: erectile dysfunction.

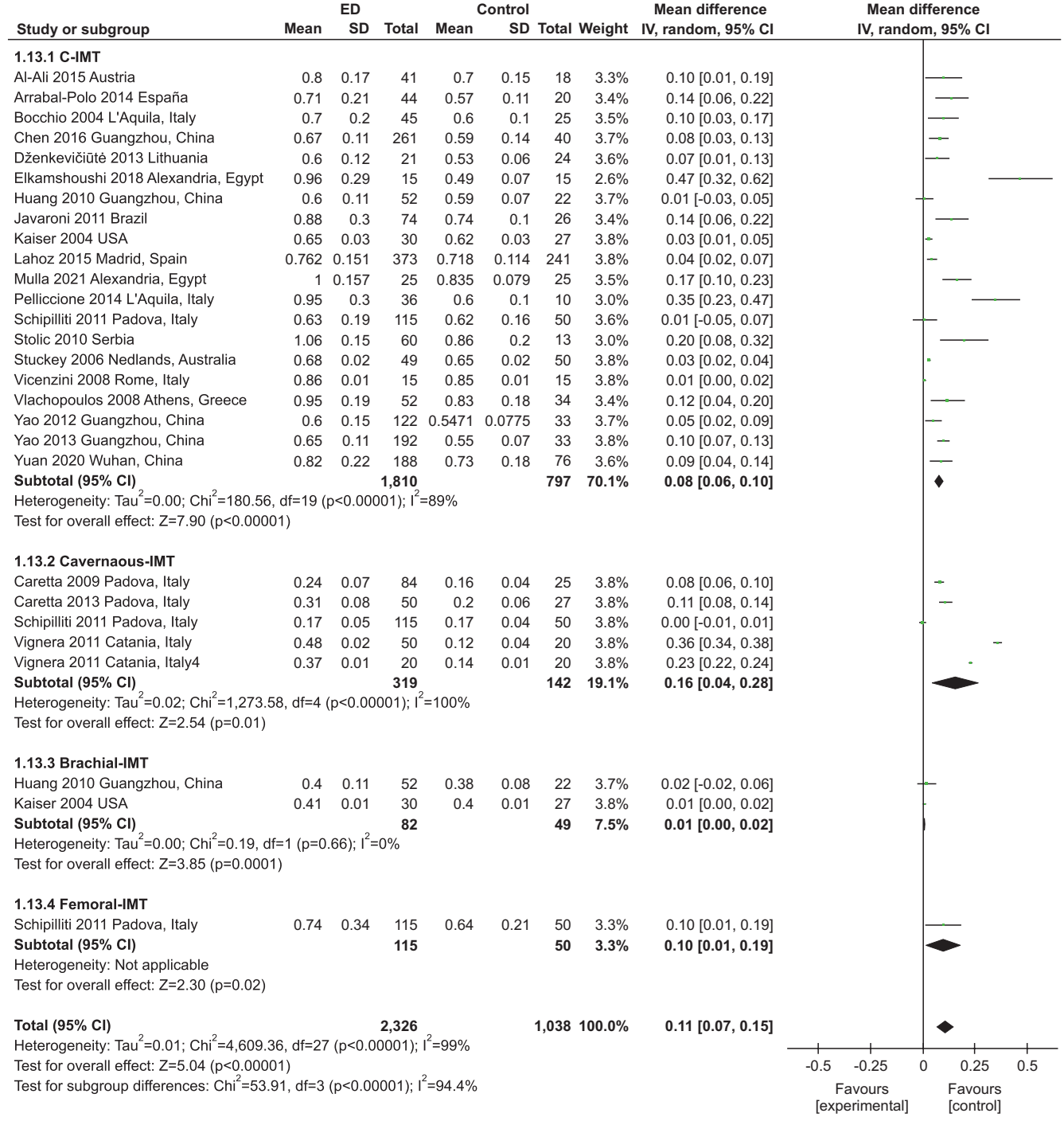


Fig. 2. Meta-analysis of studies on the relationship between erectile dysfunction (ED) and intima-media thickness (IMT). The results are shown as differences in percentage change between the ED and non-ED groups and their pooled mean difference (MD). SD: standard deviation, CI: confidence interval.

chial IMT [29,31], and one study of femoral IMT [35]. We found that ED patients had significantly higher IMT than individuals without ED (MD: 0.11 mm; 95% CI: 0.07 mm, 0.15 mm). Significant heterogeneity among enrolled studies was found (I^2=99%).

In the subgroup analysis, ED patients had significantly higher cIMT (MD: 0.08 mm; 95% CI: 0.06 mm, 0.10 mm), higher cavernous IMT (MD: 0.16 mm; 95% CI: 0.04 mm, 0.28 mm) and higher branchial IMT (MD: 0.01 mm; 95% CI: 0.00 mm, 0.02 mm) than individuals without ED.

2. ED and vascular stiffness

1) ED and PWV

Seven studies involving 1,439 participants investigated the correlation between ED and PWV, including brachial-ankle (baPWV) [48,52,53], carotid-femoral (cfPWV) [41,51], aortic (aoPWV) [31], and femoral-ankle (faPWV) [53]. Patients with ED had higher PWV than individuals without ED (MD: 1.11; 95% CI: 0.01, 2.21). Significant heterogeneity among the enrolled studies was found (I^2=99%) (Fig. 3).

2) ED and ABI

A total of 5 studies with 1,250 participants were included in the analysis of ABI [32,47-50]. Only one study assessed ED by using the IIEF-15, while others used the IIEF-5. No significant association was found between ED and ABI (MD: 0.00; 95% CI: -0.02, 0.02) (Fig. 4A). Significant heterogeneity among enrolled studies was found (I^2=58%).

3) ED and AI

Four studies with 526 participants examined the association between ED and AI (Fig. 4B) [27,41,45,46]. Three of them assessed ED by using the IIEF-5. ED patients had a higher AI than those without ED (MD: 2.83; 95% CI: 0.02, 5.63). Significant heterogeneity among enrolled studies was found (I^2=70%).

3. ED and endothelial function

1) ED and FMD

Twenty-five studies including 3,089 participants evaluated the association between ED and FMD [24,29-31,37,41-43,54-70]. Only one study measured penis FMD and cuff inflation to not less than 10 mmHg above systolic blood pressure (BP) [68], while other studies measured brachial FMD. Moreover, the concrete operation of brachial FMD assessment was not universal among the studies. Out of the 25 studies, at least seven involved placing the cuff on the forearm, including one study that used the wrist [31,56,60,62,64,66,67],

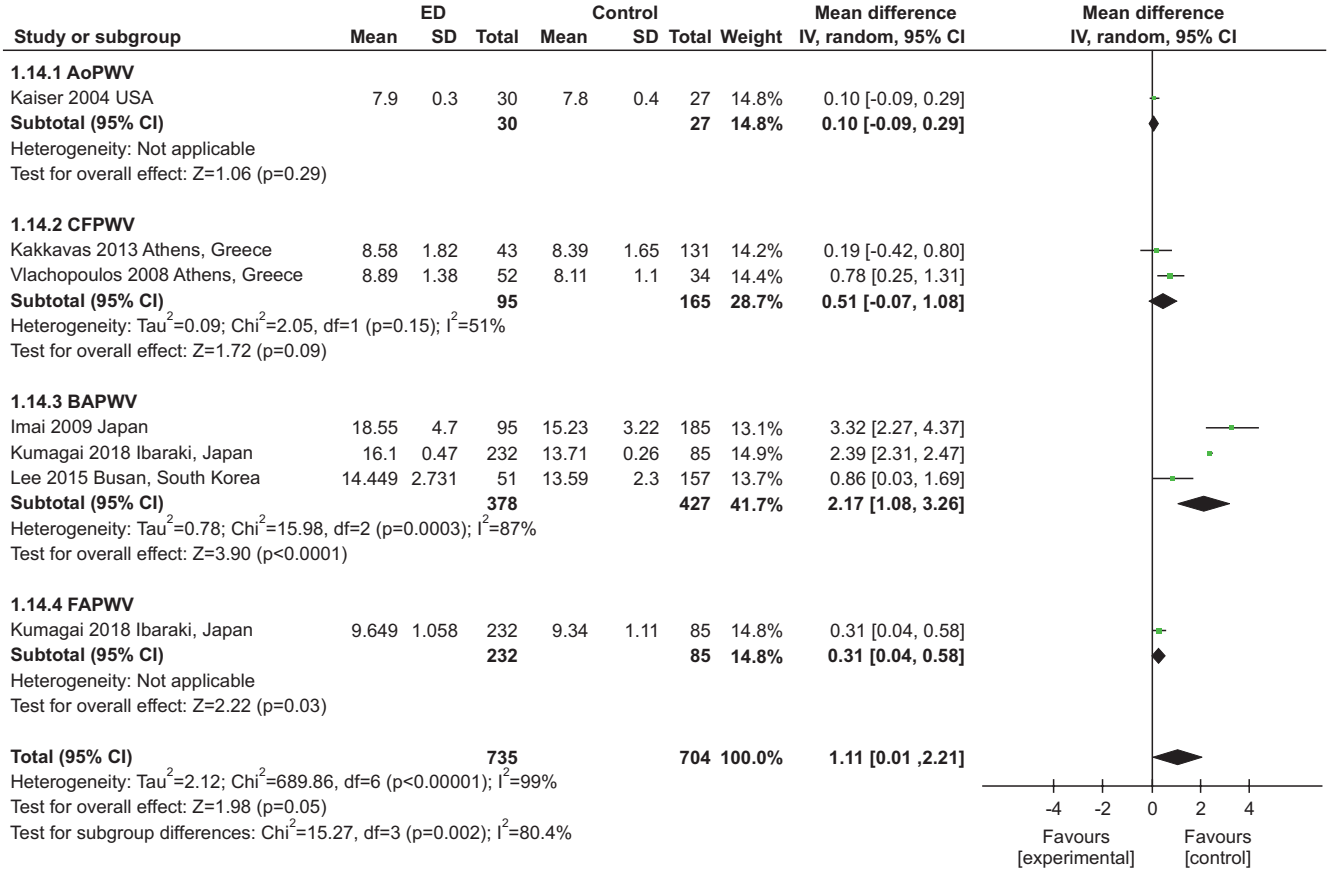
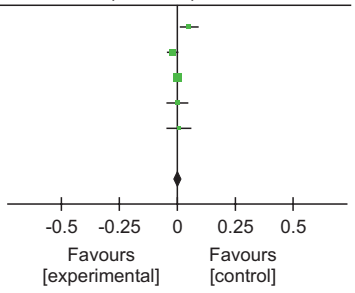


Fig. 3. Meta-analysis of studies on the relationship between erectile dysfunction (ED) and pulse wave velocity (PWV). AoPWV: aortic PWV, CFPWV: carotid-femoral PWV, BAPWV: brachial-ankle PWV, FAPWV: femoral-ankle PWV, SD: standard deviation, CI: confidence interval.

A

Study or subgroup	ED Mean	ED SD	ED Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, random, 95% CI
Bulbul 2022 Trabzon, Turkey	1.11	0.14	74	1.06	0.1	86	14.8%	0.05 [0.01, 0.09]
Lahoz 2015 Madrid, Spain	1.16	0.14	373	1.18	0.14	241	25.1%	-0.02 [-0.04, 0.00]
Lee 2015 Madrid, South Korea	1.21	0.02	51	1.21	0.01	157	38.5%	0.00 [-0.01, 0.01]
Malpartida 2011 Valencia, Spain	1.08	0.16	105	1.08	0.12	49	11.8%	0.00 [-0.05, 0.05]
Severo 2014 Porto Alegre, Brazil	1.1089	0.1509	82	1.1029	0.1152	32	9.8%	0.01 [-0.05, 0.06]
Total (95% CI)			**685**			**565**	**100.0%**	**0.00 [-0.02, 0.02]**

Heterogeneity: Tau^2=0.00; Chi^2=9.60, df=4 (p=0.05); I^2=58%
Test for overall effect: Z=0.32 (p=0.75)



B

Study or subgroup	ED Mean	ED SD	ED Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, random, 95% CI
Dženkevičiūtė 2013 Lithuania	28.58	4.31	21	28.4	7.98	24	22.7%	0.18 [-3.51, 3.87]
Kovac 2014 USA	4.19	1.6	111	1.24	2.86	31	35.6%	2.95 [1.90, 4.00]
Kumagai 2020 Chiba, Japan	32	12	185	24	15	68	21.4%	8.00 [4.04, 11.96]
Vlachopoulos 2008 Athens, Greece	27.1	11.3	52	27	8.7	34	20.2%	0.10 [-4.14, 4.34]
Total (95% CI)			**369**			**157**	**100.0%**	**2.83 [0.02, 5.63]**

Heterogeneity: Tau^2=5.46; Chi^2=10.14, df=3 (p=0.02); I^2=70%
Test for overall effect: Z=1.98 (p=0.05)

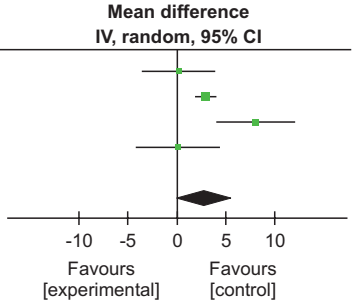


Fig. 4. (A) Meta-analysis of studies on the relationship between erectile dysfunction (ED) and ankle-brachial index. The results are shown as differences in percentage change between the ED and non-ED groups and their pooled mean difference. (B) Meta-analysis of studies on the relationship between ED and augmentation index. SD: standard deviation, CI: confidence interval.

Study or subgroup	ED Mean	ED SD	ED Total	Control Mean	Control SD	Control Total	Weight	Mean difference IV, random, 95% CI
Averbeck 2012 Porto Alegre, Brazil	4.24	7.06	34	11.33	6.08	18	2.0%	-7.09 [-10.77, -3.41]
Bhatia 2013 Lucknow, India	6.4	4.6	163	9.1	4.87	62	3.9%	-2.70 [-4.10, -1.30]
Chen 2016 Guangzhou, China	9.44	2.7	261	13	2.89	40	4.3%	-3.56 [-4.51, -2.61]
Chiurlia 2005 Modena, Italy	2.36	1.75	70	3.92	2.2	73	4.5%	-1.56 [-2.21, -0.91]
Esposito 2007 Naples, Italy	5.5426	5.4489	30	10.664	2.952	20	3.1%	-5.12 [-7.46, -2.78]
Esposito 2008 Naples, Italy	5.8	4.1	30	10.5	2.55	20	3.5%	-4.70 [-6.54, -2.86]
Esposito 2009 Naples, Italy	5.9	0.6	30	10.5	0.9	30	4.6%	-4.60 [-4.99, -4.21]
Foresta 2006 Padova, Italy	9.2	3.2	26	12.7	2.7	23	3.7%	-3.50 [-5.15, -1.85]
Gerber 2015 Massachusetts, England	7.2	0.24	277	6.6	0.33	112	4.7%	0.60 [0.53, 0.67]
Guaraldi 2012 Modena, Italy	7.14	4.89	79	7.27	4	54	3.8%	-0.13 [-1.65, 1.39]
Huang 2010 Guangzhou, China	8.72	2.67	52	14.24	2.13	22	4.1%	-5.52 [-6.67, -4.37]
Ioakeimidis 2016 Athens, Greece	7.6	2	180	5.7	1.9	50	4.5%	1.90 [1.30, 2.50]
Javaroni 2011 Brazil	7.1	3.3	74	10.5	4.5	26	3.5%	-3.40 [-5.29, -1.51]
Kaiser 2004 USA	1.3	0.3	30	2.4	0.3	27	4.6%	-1.10 [-1.26, -0.94]
Kaya 2006 Istanbul, Turkey	6.01	2.9	32	12.3	3.5	25	3.6%	-6.29 [-7.99, -4.59]
Lojanapiwat 2009 Chiang Mai, Thailand	8.7	1	41	5.1	0.6	30	4.6%	3.60 [3.23, 3.97]
Mazo 2006 Moscow, Russia	5	2.8	38	14.7	3	15	3.6%	-9.70 [-11.46, -7.94]
Murata 2012 Saitama, Japan	2.84	0.34	42	3.82	0.39	58	4.6%	-0.98 [-1.12, -0.84]
Simsek 2014 Istanbul, Turkey	7.1	4.07	150	10.9	3.6	50	4.1%	-3.80 [-4.99, -2.61]
Stuckey 2006 Nedlands, Australia	3.69	0.44	49	4.47	0.48	50	4.6%	-0.78 [-0.96, -0.60]
Uslu 2005 Istanbul, Turkey	4.1	3.1	30	9.7	3.5	25	3.6%	-5.60 [-7.36, -3.84]
Vlachopoulos 2008 Athens, Greece	2.96	1.64	52	4.07	1.68	34	4.4%	-1.11 [-1.83, -0.39]
Yao 2012 Guangzhou, China	7.81	2.44	122	13.28	3.29	33	4.1%	-5.47 [-6.67, -4.27]
Yao 2013 Guangzhou, China	8.16	2.43	192	13.3	3.25	33	4.1%	-5.14 [-6.30, -3.98]
Yavuzgil 2005 Izmir, Turkey	3.2	3	36	6	4	39	3.7%	-2.80 [-4.39, -1.21]
Total (95% CI)			**2,120**			**969**	**100.0%**	**-2.86 [-3.56, -2.17]**

Heterogeneity: Tau^2=2.73; Chi^2=2,366.16, df=24 (p<0.00001); I^2=99%
Test for overall effect: Z=8.04 (p<0.00001)

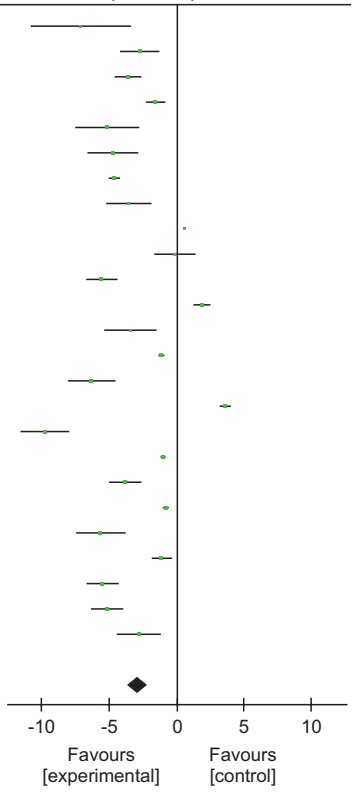


Fig. 5. Meta-analysis of studies on the association between erectile dysfunction (ED) and flow-mediated dilatation. SD: standard deviation, CI: confidence interval.

while the remaining studies involved inflating the cuff over the arm [24,29,42,43,54,55,57-59,65,69,70] or did not specify [30,37,41,61,63]. Moreover, the inflating pressures used in the studies were inconsistent, with reported pressures ranging from 250 mmHg to 300 mmHg [24,29,31,42,43,64-66,69,70], while others used cuff pressures that were 50 mmHg above the systolic BP [30,37,41,54-56,67]. The cuff pressure used in one study was at least 100 mmHg above the systolic BP [62]. One study had cuff pressures approximately 20 mm Hg above the systolic BP [60]. However, some studies have not specified the value above systolic pressure [57-59,63]. In the majority of studies, cuff occlusion lasted for 4–5 minutes, and the brachial artery diameter was measured at baseline and 30–90 seconds after cuff occlusion. Patients with ED had lower FMD than those without ED (MD: -2.86; 95% CI: -3.56, -2.17). Significant heterogeneity among enrolled studies was found (I^2=99%). In subgroup meta-analyses, the MD was significantly varied among different age groups (Fig. 5, Supplement Fig. 1).

2) ED and NMD

The correlation between ED and NMD was evaluated in 9 studies involving 772 participants. [30,31,37,41,56,64,67,69,70]. ED patients had less FMD than those without ED (MD: -2.34; 95% CI: -3.37, -1.31) (Fig. 6).

4. ED and serum biomarkers

1) ED and EPCs

Eleven studies with 859 participants and 8 types of EPCs were included in this meta-statistic [40,59,60,67,71-77]. Nine studies [40,59,60,67,71,72,74,76,77] assessed ED by the IIEF-5, while only one study [73] assessed ED by the IIEF-15. In addition, one study [75] used KEED. All studies detected EPCs by flow cytometry. However, the counting mode of EPCs was varied. In studies, EPCs were evaluated by the percentage of total events [40,76,77], while the counts of EPCs were determined in 10^6 events in studies [59,74]. Four studies [60,71-73] counted EPCs per ml of peripheral blood. One study [67] counted EPCs per 100 ml of peripheral blood. In addition, one study analyzed the levels of EPCs as variables after log-transformation (log base 10) to normalize distribution [75]. As shown in Fig. 7, there was a 0.72% decrease in EPCs in ED patients compared to non-ED persons (MD: -0. 72; 95% CI: -1.19, -0.24). In the subgroup analysis, CD34+/CD133+, CD133+/KDR+, and CD34+/CD133+/KDR+ were less abundant in the ED group, while the other types of EPCs were not significantly different.

5. Assessment of publication bias and sensitivity analysis

According to funnel plots, in meta-analysis regarding NMD, AI, ABI, and EPC, no obvious publication biases were found. However, the funnel plots regarding the meta-analysis on IMT, PWV and FMD were asymmetric, indicating a high risk of bias (Supplement Fig. 2). Except for NMD, other results of the sensitivity analysis confirmed the robustness of the pooled results (Supplement Fig. 3–5). In studies of NMD, the study conducted by Kaiser et al [31] appears to be the primary cause of the heterogeneity observed in this meta-

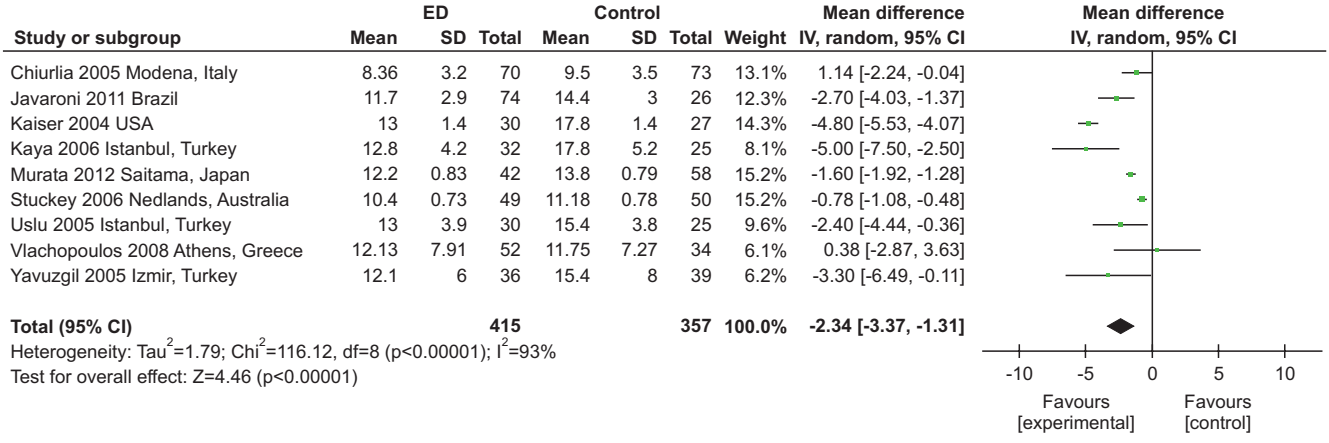


Fig. 6. Meta-analysis of studies on the association between erectile dysfunction (ED) and nitrate-mediated dilatation. SD: standard deviation, CI: confidence interval.

Study or subgroup	ED Mean	ED SD	ED Total	Control Mean	Control SD	Control Total	Weight	Std. Mean difference IV, random, 95% CI
1.15.1 CD34+/CD133+								
Esposito 2009 Naples, Italy	157.4	16.2	30	145.8	13.9	25	4.0%	0.75 [0.20, 1.30]
Foresta 2005 Padova, Italy	862.4	345.1	28	1,903.5	558.6	22	3.8%	-2.27 [-3.00, -1.55]
Foresta 2006 Padova, Italy	1,309.9	440.9	26	1,867.7	373.3	23	3.9%	-1.34 [-1.96, -0.71]
Foresta 2006 Padua, Italy	1,546.6	563.7	68	1,945.3	470.3	25	4.1%	-0.73 [-1.20, -0.26]
Foresta 2009 Padova, Italy	1,159	302	20	1,747	211	15	3.7%	-2.15 [-3.01, -1.29]
Maiorino 2015 Naples, Italy	149.3	74.7	38	145.6	82.3	80	4.1%	0.05 [-0.34, 0.43]
Murata 2012 Saitama, Japan	49	6	58	72	12	42	4.0%	-2.53 [-3.07, -2.00]
Subtotal (95% CI)			**268**			**232**	**27.7%**	**-1.15 [-2.08, -0.22]**
Heterogeneity: Tau^2=1.48; Chi^2=117.41, df=6 (p<0.00001); I^2=95%								
Test for overall effect: Z=2.43 (p=0.01)								
1.15.2 CD34+/KDR+								
Baumhäkel 2006 Homburg/Saar, Germany	1.85	0.25	71	1.83	0.25	48	4.1%	0.08 [-0.29, 0.45]
Esposito 2009 Naples, Italy	63.1	4	30	92.4	6	25	3.3%	-5.77 [-7.01, -4.53]
Maiorino 2015 Naples, Italy	30.35	8.47	38	31.76	20.38	80	4.1%	-0.08 [-0.47, 0.31]
Subtotal (95% CI)			**139**			**153**	**11.5%**	**-1.76 [-3.62, 0.10]**
Heterogeneity: Tau^2=2.55; Chi^2=80.15, df=2 (p<0.00001); I^2=98%								
Test for overall effect: Z=1.86 (p=0.06)								
1.15.3 CD133+/KDR+								
Esposito 2009 Naples, Italy	20.1	1.8	30	22.4	1.8	25	4.0%	-1.26 [-1.84, -0.68]
Maiorino 2015 Naples, Italy	17.35	5.39	38	27.94	15.85	80	4.1%	-0.78 [-1.18, -0.38]
Subtotal (95% CI)			**68**			**105**	**8.1%**	**-0.97 [-1.43, -0.52]**
Heterogeneity: Tau^2=0.05; Chi^2=1.74, df=1 (p=0.19); I^2=42%								
Test for overall effect: Z=4.17 (p<0.0001)								
1.15.4 CD34+								
Esposito 2009 Naples, Italy	453.7	37	30	446.8	32.4	25	4.0%	0.19 [-0.34, 0.73]
Foresta 2009 Padova, Italy	2,948	612	20	3,313	581	15	3.9%	-0.60 [-1.28, 0.09]
Maiorino 2015 Naples, Italy	246.91	94.76	38	274.41	157.03	80	4.1%	-0.19 [-0.58, 0.19]
Subtotal (95% CI)			**88**			**120**	**12.0%**	**-0.16 [-0.54, 0.22]**
Heterogeneity: Tau^2=0.05; Chi^2=3.28, df=2 (p=0.19); I^2=39%								
Test for overall effect: Z=0.83 (p=0.41)								
1.15.5 CD133+								
Baumhäkel 2006 Homburg/Saar, Germany	2.47	0.31	71	2.59	0.21	48	4.1%	-0.43 [-0.81, -0.06]
Esposito 2009 Naples, Italy	222.2	20.8	30	219.9	19.5	25	4.0%	0.11 [-0.42, 0.64]
Maiorino 2015 Naples, Italy	169.86	86.29	38	196.34	116.26	80	4.1%	-0.24 [-0.63, 0.14]
Subtotal (95% CI)			**139**			**153**	**12.3%**	**-0.24 [-0.52, 0.05]**
Heterogeneity: Tau^2=0.02; Chi^2=2.74, df=2 (p=0.25); I^2=27%								
Test for overall effect: Z=1.64 (p=0.10)								
1.15.6 KDR+								
Esposito 2009 Naples, Italy	338	25.4	30	361.1	30.1	25	4.0%	-0.82 [-1.38, -0.27]
Maiorino 2015 Naples, Italy	78.94	29.27	38	87.59	33.22	80	4.1%	-0.27 [-0.66, 0.12]
Subtotal (95% CI)			**68**			**105**	**8.1%**	**-0.51 [-1.05, 0.03]**
Heterogeneity: Tau^2=0.09; Chi^2=2.59, df=1 (p=0.11); I^2=61%								
Test for overall effect: Z=1.85 (p=0.06)								
1.15.7 CD34+/CD133+/KDR+								
Esposito 2009 Naples, Italy	9.6	0.9	30	13	0.9	25	3.7%	-3.72 [-4.62, -2.83]
Foresta 2009 Padova, Italy	29	7	20	57	3	15	3.1%	-4.83 [-6.21, -3.46]
Maiorino 2015 Naples, Italy	11.29	7.7	38	17.65	6.79	80	4.1%	-0.89 [-1.29, -0.49]
Subtotal (95% CI)			**88**			**120**	**10.9%**	**-3.09 [-5.61, -0.58]**
Heterogeneity: Tau^2=4.70; Chi^2=54.68, df=2 (p<0.00001); I^2=96%								
Test for overall effect: Z=2.41 (p=0.02)								

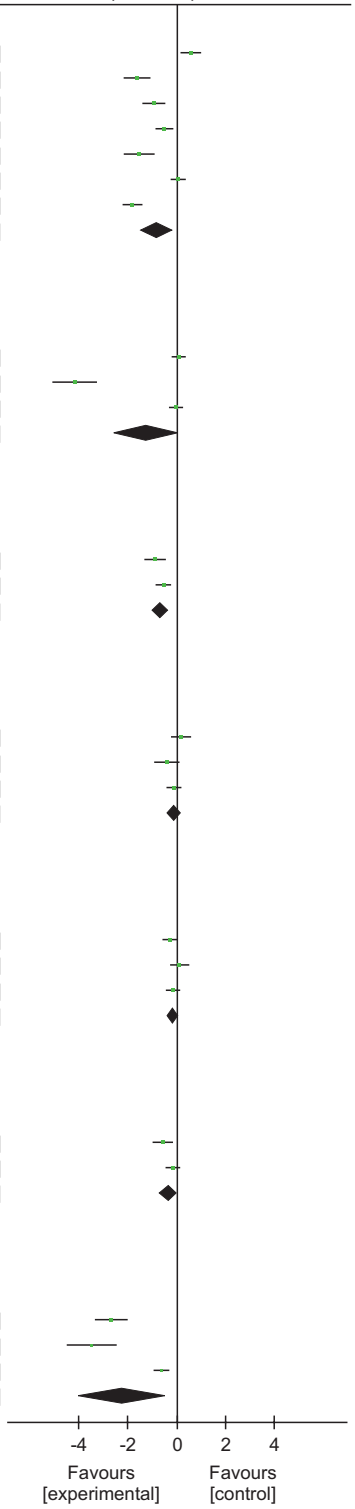


Fig. 7. Meta-analysis of studies on the association between erectile dysfunction (ED) and endothelial progenitor cells. SD: standard deviation, CI: confidence interval.

analysis, as removing this study resulted in a reduction of over 16% in I^2 (93% to 77%) (Supplement Fig. 6). After removing this study and reperforming the meta-analysis, individuals with ED still had less NMD than those without ED (MD: -1.72; 95% CI: -2.41, -1.04).

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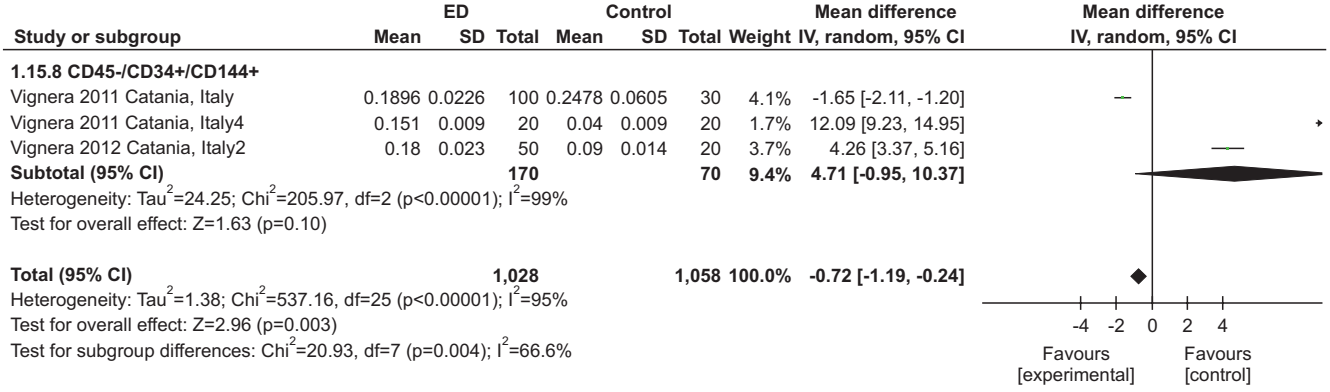

Fig. 7. Continued.

DISCUSSION

In this systematic review and meta-analysis, we demonstrated that ED was associated with several vascular parameters. CIMT is an intermediate phenotype for early atherosclerosis and is also a predictive marker for the development of atherosclerosis. A previous meta-analysis demonstrated that increased cIMT is a significant predictor of future CVD events [79]. The association between cIMT and CVD events, such as angina pectoris, myocardial infarction, and coronary intervention, as well as cerebrovascular events, has been investigated in various longitudinal studies [80-90]. These studies demonstrated that cIMT can be used as an important risk predictor of CVD. In addition to cIMT, carotid plaque and carotid stenosis can also be detected by carotid ultrasonography. Some researchers believe carotid plaques are better than cIMT for predicting future CVD events [91,92]. In our meta-analysis, ED patients were found to have higher cIMT than non-ED individuals.

PWV is considered the most commonly used measure of arterial stiffness, with baPWV and cfPWV being the most commonly used measures in clinical and research settings. Numerous studies have demonstrated the correlation between PWV and coronary atherosclerosis [93]. In addition, certain studies have demonstrated a positive association between PWV and the risk and severity of CAD [94-98]. In a 2.7-year follow-up study [99], coronary artery calcification progression was positively correlated with baseline baPWV. Except for CVD, recent studies found an association between cerebral small vessel disease and PWV in the overall population or cardiovascular or cerebrovascular disease patients [93]. Several studies have also demonstrated that PWV is associated with cognitive decline in elderly individuals [100,101]. Additionally, previous studies reported associations between various types of PWV and cIMT or carotid plaque [93]. The findings of these studies suggest that PWV may serve as a strong predictive marker of CVD.

In our meta-analysis, the associations between ABI and ED were not significant. Paradoxically, some studies have used ABI <0.9 as a cutoff and found that the proportion of ABI <0.9 in ED is much higher than that in individuals without ED [32,102-104]. ABI <0.9 is defined as a symbol of peripheral arterial disease. A previous meta-analysis concluded that smoking, diabetes, hypertension and hypercholesterolemia are major risk factors for peripheral arterial disease [105], which are also risk factors for ED [106]. This suggests that ED may not directly cause decreased ABI but acts as an intermediary for risk factors such as smoking, diabetes, hypertension and hypercholesterolemia to increase the proportion of ABI <0.9 in the population. Additionally, differences in studies and sample sizes may also lead to such intriguing diverse results. More research should be conducted to further confirm the association between ED and ABI.

The relationship between ED and CVD has been well established. Some subclinical CVDs (such as subclinical atherosclerosis) occur earlier than vascular ED, while CVD occurs after vascular ED. The fundamental reason is that they share common mechanisms of vascular and endothelial dysfunction [107,108]. A meta-analysis regarding FMD reported that a 1% FMD elevation is associated with a 13% lower risk of CVD events [109]. Some meta-analysis studies demonstrate that improved FMD is also an important predictor of CVD events after optimized therapy [110-112]. In addition, a meta-

analysis reported the association between FMD and neurocognition, indicating its potential as an indicator in neuroimaging measures of cerebral blood flow [113]. However, the criteria for FMD assessment are still subjective, which may cause significant bias in clinical practice.

EPCs are popular noninvasive detection methods for endothelial function. EPCs play a part in the regulation of tissue homeostasis, which means that they can work as biomarkers of endothelial dysfunction. Several studies have emphasized the relationship between CVD and EPCs [114-116]. These studies confirmed the relationship between ED and endothelial dysfunction, which is helpful for preventing and detecting diseases related to endothelial dysfunction in ED patients.

ED and vascular and endothelial dysfunction are considered to share the same risk factors and common mechanisms. This also means that vascular and endothelial dysfunction are potential therapeutic targets for ED. PDE5 inhibitors treat ED by promoting vasodilation through increasing intracellular cyclic adenosine monophosphate levels in vascular smooth muscle cells [117]. In addition, researchers have recently tried to treat patients unresponsive to PDE5 inhibitors through methods such as stem cell transplantation, endothelial nitric oxide synthase or intracavernosal vascular endothelial growth factor gene therapy [118]. These studies have brought new hope for ED patients. However, longitudinal relationships should be assessed to further assess the relationship between ED and vascular and endothelial dysfunction.

1. Limitations

All of the included studies were cross-sectional or case–control studies, which indicated the lack of longitudinal studies to investigate the temporal association between ED and vascular and endothelial dysfunction. Additionally, most included articles did not make a clear differential diagnosis of organic ED or psychogenic ED, and some studies made diagnosis of ED according to PSV, not IIEF-5, which may introduce bias. The definition and measurement modality of some vascular parameters varied among different studies, leading to potential bias. Significant heterogeneity within studies in the meta-analysis should also be noted. Although we conducted subgroup analysis and sensitivity analysis, we were unable to fully identify the cause of this heterogeneity. In addition, the presence of funnel plot asymmetry in the studies analyzing IMT, FMD and PWV suggested a higher likelihood of publication bias.

CONCLUSIONS

Our study demonstrates associations between ED and vascular and endothelial function, suggesting the significance of ED management in individuals with vascular and endothelial dysfunction. In the future, research should prioritize investigating the longitudinal associations between ED and vascular or endothelial function, utilizing larger sample sizes to enhance the validity of the findings.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: HL. Data curation: HL. Formal analysis: XL. Investigation: TW. Methodology: JL. Project administration: YZ. Resources: SX. Supervision: WS, YZ. Visualization: HP. Writing – original draft: HP, HZ. Writing – review & editing: WS, YZ.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.5534/wjmh.230192.

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