Pulse Wave Velocity as a Measure of Arterial Stiffness in Patients with Abdominal Aortic Aneurysm: A Systematic Review and Meta-Analysis

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Abstract

Background and objective:

The relationship between pulse wave velocity (PWV) levels and abdominal aortic aneurysm (AAA) remains controversial. A meta-analysis was performed to establish whether vascular pulse wave velocity (PWV) as a measure of arterial stiffness is different in patients with abdominal aortic aneurysms and controls.

Methods

Pubmed, Embase, Cochrane and China National Knowledge Infrastructure (CNKI) were used for the meta-analysis with articles up to January 1, 2021. To compare PWV levels between AAA patients and healthy controls, pooled weighted mean difference (WMD) and its 95% confidence interval (CI) were calculated. Subgroup analysis and funnel plots are used to assess the quality of the combined results to ensure a normal distribution of data with minimal bias. Study quality for eligible studies was assessed using the Agency For Health Care Research and Quality (AHRQ) inventory tool.

Results

Nine cross-sectional studies, which included 439 abdominal aortic aneurysm cases and 382 healthy subjects, met inclusion criteria and were eligible for meta-analysis. We found that PWV levels were significantly higher [WMD(95%CI): 2.36(2.02,2.70)] in AAA patients than healthy controls. After subgroup analysis, it was found that age, sex, smoking and hypertension had significant effects on the PWV levels. The normal distribution of the Funnel plot analysis suggests a low risk for publication bias.

Conclusion

PWV levels were elevated in patients with AAA compared to healthy controls, with the effect on PWV altered by age, sex, smoking and hypertension. Our study suggests that abdominal aortic aneurysm is related to increased arterial stiffness.

Introduction

Abdominal aortic aneurysm(AAA) is defined as the localized dilatation of the aorta and is likely to rupture unexpectedly leading to serious morbidity and mortality [1, 2]. It is estimated that the incidence of AAA is about 4–8% in men and 1-1.3% in women and globally accounts for 168,200 deaths annually [3, 4, 5]. The primary mechanism by which AAA develop consists of chronic inflammation, vascular smooth muscle cell (VSMC) apoptosis, extracellular matrix (ECM) degradation, and thrombosis. [6, 7] Specifically, these factors are what contributes to atherosclerotic plaque formation, and hence atherosclerosis plays a significant role in forming AAA and plays a role in the aneurysmal wall formation.[8]

Atherosclerosis of arteries contributes to the loss of arterial elasticity, elevated arterial stiffness, and therefore increased PWV since pulse velocity travels faster in stiffed arteries. [9, 10] Arterial stiffness (AS), represented by the arterial wall rigidity, is one of the most availably detectable manifestations of adverse structural and functional alterations within the arterial vessel wall.[11] Pulse wave velocity(PWV) is the velocity of a pulse wave moving through an arterial segment and is one of the non-invasive methods of assessing AS.[12, 13] The current literature on the differences between the PWV of AAA and controls is mixed. In some studies, PWV levels were significantly lower in AAA patients than those in healthy controls. [14] Contrarily, other studies have demonstrated that PWV levels in the abdominal aorta were significantly higher in AAA patients than those in non-AAA controls.[15, 16] Additional studies have failed to confirm either association of PWV levels with AAA.[17]

Based on the mixed literature in regards to the available evidence for pulse wave velocity and AAA incidence, we hypothesized that there may be a correlation between PWV levels and AAA. Therefore, we carried out a meta-analysis using published studies on PWV levels in AAA patients.

Material And Method

Database and Search Strategies

Our meta-analysis strictly followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines[18].

We systematically searched PubMed, Embase, Cochrane Central Register of Controlled Trials, and the Chinese National Knowledge Infrastructure (CNKI database). The Medical Subject Headings (Mesh) and relevant keywords were used for literature research. The electronic literature search was complemented by a manual search of related articles. The reference lists of collected items were also manually reviewed for additional correlated articles.

PubMed search strategy was conducted using the following search field descriptions and tags; Title/Abstract [tiab] and MeSH Terms [MH]

#1.“pulse wave velocity [mh]” OR “PWV [tiab]” OR “aPWV [tiab]” OR “cPWV [tiab]” OR “fPWV [tiab]” OR “cfPWV [tiab]” OR “arterial distensibility [tiab]” OR “vascular distensibility [tiab]” OR “aortic distensibility [tiab]” OR “arterial stiffness [tiab]” OR “arterial stiffening [tiab]” OR “vascular stiffness [tiab]” OR “vascular stiffening [tiab]” OR “aortic stiffness [tiab]” OR “aortic stiffening [tiab]” OR “arterial compliance [tiab]” OR “vascular compliance [tiab]” OR “aortic compliance [tiab]”

#2. “abdominal aortic aneurysm [mh]” OR “Aneurysms, Abdominal aortic [tiab]” OR “Aortic Aneurysms, Abdominal [tiab]” OR “Abdominal Aortic Aneurysm [tiab]” OR “Aneurysm, Abdominal Aortic [tiab]”

Inclusion and exclusion criteria of enrolled studies

Our inclusion criteria were as follows: the study had to be observational (i.e., a case-control, cross-sectional or cohort design); the subjects enrolled had to be diagnosed by the physician as AAA; there had to be comparison of vascular PWV between patients with AAA and controls without AAA; and PWV data had to be available for all patients. Exclusion criteria included: study had undefined control groups, duplicate or overlapped populations with a previous study, or PWV values were only reported in a single group and not both AAA and control.

Data extraction

Data were independently extracted from individual studies by two reviewers. Each study’s information was obtained using standardized forms by two independent observers blinded to the authors’ names and journal titles. Discrepancies between the outputs were resolved through discussion and involvement of a third co-author. The following information was extracted from each study (Table 1): (I) trial’s name/publication year; (II)numbers of subjects enrolled; (III)country; (V)age; (VI)male; (VII)BMI; (VIII)outcome index; (IX)PWV levels; (X)device; (XI) AHRQ scores; (XII)Smoking; (XIII)Hypertension; (XV)diabetes.

Assessment of the risk for publication bias

This was conducted by two researchers independently. Because this meta-analysis included cross-sectional studies, study quality was assessed using the Agency For Health Care Research and Quality (AHRQ) inventory tool[19]. Eleven questions were answered. If the answer was “No” or “Unclear,” the rating of the item was “1”; if the answer was “Yes,” the score of the item was “1”. The quality for each study was scored as low (0-3), medium (4-7) or high (8-11). Studies graded as low quality (0-3) were excluded from the meta-analysis.

Statistical analysis

The meta-analysis was conducted using a synthesis dataset according to published eligible studies. Weighted Mean Difference (WMD) with corresponding 95% confidence interval (CI) was calculated to evaluate PWV and AAA correlations. If the I^2 value was > 50% with a p<0.1 for the test of heterogeneity, the results were considered heterogeneous.

Forest plots were used to display the results graphically. Further subgroup analysis based on anatomic location of PWV (carotid-femoral PWV and aortic PWV) was performed since some studies have argued that PWV in different locations of stiffened arteries varied unexpectedly. Additional subgroup analyses included age, sex, smoking, diabetes and hypertension. Subgroup analysis was also used to identify the factors contributing to the heterogeneity of the pooled data.

All reported P values were two-sided tests and considered statistically significant if P <0.05. Publication bias was assessed using funnel plots. All statistical analyses were performed by Stata 12.0 (Stata Corporation, College Station, TX, USA).

Results

Literature search

The literature and eligible studies are detailed in Figure 1. A preliminary electronic database search identified 244 potential records. After reviewing abstracts or full articles, 103 duplicate articles, 126 unrelated articles, 2 review articles, and 3 articles with unextractable data were excluded. In the end, nine studies qualified for the meta-analysis examining the association of PWV with AAA.

Study characteristics

The characteristics of included studies are presented in Table 1. 6 of which reported carotid-femoral PWV (cf-PWV) and 3 of which reported infrarenal arterial aortic PWV. Four studies reported data on both males and females, while 3 studies only reported data on males.

PWV measurement methods

Methods for PWV measurements varied among studies. 2 studies used a Complier SP, 2 studies used a Sphygmocor device, 2 studies used a Sonix RP system, and 3 studies used Electrocardiographically Gated 64-Detector Row CT.

Association of PWV levels with AAA

All 9 eligible studies reported on the relationship of PWV levels with AAA. As quantified using I^2 and P-value, the heterogeneity across included studies was statistically significant (P< 0.00001, I^2=98.9%). Studies were weighted based on the number of patients in each study and other factors. Meta-analysis showed that patient’s PWV values were higher in patients with AAA than those in control subjects (WMD=2.36m/s, 95% CI 2.02□2.70□P□0.001) (Figure 2A). To investigate potential publication bias, the funnel plot was created for studies included in a meta-analysis of PWV (Figure 2B), with a vertical axis for study size (standard error) and horizontal axis for the standardized difference in means which averaged overall at around 2.36. Lack of significant asymmetry in the funnel plot both on the x and Y axis in Figure 2 B suggests the low likelihood of publication bias.

Subgroup analysis

Subgroup meta-analysis results are summarized in Table 2. High levels of pulse wave velocity were associated with AAA as defined by cf-PWV (WMD=0.63m/s,95% CI 0.26-1.00, P<0.00001) and infrarenal PWV (WMD=12.65m/s,95% CI11.75-13.54, P=0.004) (Figure 3B).

Subgroup analysis was also performed if it was possible to match risk factors such as age (9/9 studies), sex (7/9 studies), smoking(6/9 studies), diabetes(5/9 studies) and hypertension(5/9 studies) (Table 2).

The PWV levels were significantly lower in AAA patients than those in the control group if there was significant inter-group difference in age between AAA and control (WMD:-0.48; 95%CI:-0.94,-0.01, I^2=77%, P=0.005), however, PWV levels were significantly higher in AAA patients than those in the control group if there was not significant inter-group difference in age between AAA and control (WMD:5.59; 95%CI:5.09,6.09, I^2=99%, P<0.000)(Figure 3B).

The PWV levels were significantly lower in AAA patients than those in the control group if there was significant inter-group difference in hypertension between AAA and control(WMD:-0.52;95%CI:-0.99,-0.06, I^2=88.8%, P=0.003), however, PWV levels were significantly higher in AAA patients than those in the control group if there was not significant inter-group difference in hypertension between AAA and control (WMD:2.05; 95%CI:1.23,2.87, I^2=96.7%, P<0.000)(Figure 4A).

The PWV levels were significantly lower in AAA patients than those in the control group if there was significant inter-group difference in diabetes between AAA and control(WMD:-2.10; 95%CI:-3.23,-0.97), however, PWV levels were significantly higher in AAA patients than those in the control group if there was not significant inter-group difference in diabetes between AAA and control (WMD:0.52;95%CI:0.11,0.93, I^2=95.2%, P<0.000)(Figure 4B).

The PWV levels were not significantly different in AAA patients than those in the control group if there was significant inter-group difference in sex between AAA and control(WMD:-0.20; 95%CI:-0.71,0.31), however, PWV levels were significantly higher in AAA patients than those in the control group if there was not significant inter-group difference in sex between AAA and control (WMD:4.35;95%CI:3.89, 4.80, I^2=99.1%, P<0.000)(Figure 5A).

The PWV levels were significantly higher in AAA patients than those in the control group if there was significant inter-group difference in smoking between AAA and control(WMD:1.12; 95%CI:0.44,1.81), PWV levels were also significantly higher in AAA patients than those in the control group if there was not significant inter-group difference in smoking between AAA and control (WMD: 0.43 ;95%CI: -0.00, 0.87, I^2=95.2%, P<0.000)(Figure 5B).

Discussion

This meta-analysis investigated whether vascular PWV levels as a measure of arterial stiffness is different in patients with abdominal aortic aneurysms compared to controls. A total of 9 cross-sectional studies met inclusion criteria for our analysis. Our results demonstrated that PWV levels in patients with AAA were significantly higher than those in controls, indicating the relationship between the abdominal aortic aneurysm and increased arterial stiffness.

There are several mechanisms by which atherosclerosis of arteries contributes to abdominal aortic aneurysms. Both conditions are multifactorial diseases with known risk factors that contribute toward disease development. Carotid atherosclerosis is positively correlated to the growth of aortic diameter and aneurysmal formation.[20] Pulse wave velocity (PWV) is assumed to be the velocity of a pulse wave moving through an arterial segment. This meta-analysis shows that the PWV levels of AAA patients are higher than those of the control group, indicating that abdominal aortic aneurysm is related to increased arterial stiffness. Vascular PWV as a measure of arterial stiffness is changed in patients with AAA. Aortic stiffness, the manifestation of pulse wave velocity, is associated with the change in the structural protein of the medial extracellular matrix, such as elastin and collagen.[21, 22] Elevated blood pressure and repetitive cyclic stress leads to the wearing out of the elastic components of the aortic walls[23], which leads to the stiffening and dilation of the aortic wall. Furthermore, the inflammatory process within the arterial wall, accompanied by invasion of monocytes and macrophages and increased levels of IL-6, can accelerate the formation and development of AAA.[24] A series of published literature support the association of inflammatory markers with arterial stiffness in patients with cardiovascular diseases.[25] Finally, calcium deposition in the AAA wall results in increased arterial stiffness in AAA.[26]

Meta-analysis showed that patients' PWV values were higher in patients with AAA than those in control subjects (WMD = 2.36m/s, 95% CI 2.02–2.70,P<0.001). The subgroup meta-analyses of smoking and detection location supported the result that the PWV levels were significantly higher in AAA patients. However, there were unexpected findings in the subgroup meta-analyses of age, diabetes, hypertensive and sex. These may possibly due to the heterogeneity among the studies. Subgroup analysis found that several factors influenced the effect sizes in PWV between AAA and control subjects (Table 2). Age, smoking and hypertension promote atherosclerosis, vascular wall medial degeneration and ultimately alter PWV [27]. It has been shown that elevated blood pressure worsens arterial stiffness indirectly. [28, 29] Arterial stiffness (change of PWV) also triggers loop feedback on systolic blood pressure (afterload) by accelerating wave reflection. [30.31.32] For example, the rate of increase in cf-PWV with pre-hypertension (systolic BP 120–139 mmHg) or hypertension(systolic BP ≥ 140mmHg) is steeper compared with men with normal systolic BP (systolic BP < 120mmHg). [33] In contrast, advancing age is predominantly associated with reduced arterial distensibility and thus aortic compliance. Cf-PWV increased monotonically before age 50–60 years and then exponentially thereafter. [34] Additionally, smoking was also an independent predictor of adult PWV and biomarkers of endothelial function[35], all critically affecting PWV as well as AAA.

There are several limitations of our meta-analysis. First, only 9 cohort studies of PWV about abdominal aortic aneurysms were enrolled for the final analysis due to inclusion criterias. Because some included studies were cross-sectional, we cannot rule out the possibility of selection bias. Second, the different PWV location detection methods renders our study a certain degree of lack of reliability. Current arterial stiffness methods include the local measurement of arterial stiffness using ultrasonography and magnetic resonance imaging and regional measurement by tonometer and Doppler probes.[36] Due to the limited number of studies, we included all the studies with different PWV measurement methods. Therefore, variation inevitably exists and cannot be avoided, and we should also keep in mind the variability of measuring each individual patient. Third, the presence of other risk factors and publication bias suggests that the analysis results may not be entirely accurate. These limitations may potentially influence the reliability and accuracy of our results.

In conclusion, our meta-analysis showed that PWV levels in AAA patients were significantly higher than those in control subjects. PWV value as a measure of arterial stiffness is changed in patients with abdominal aortic aneurysm and may be used to monitor disease progression. Our analysis warrants further investigation into the the association of PWV levels with AAA disease in a more well-designed prospective cohort study.

Declarations

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

HLZ, YYS, TTC contribute to the conception and design of the study, HLZ, YYS,TTC, YZ , JTW, YKW, WJZ, GC, DLL, XXF, CX, BHX, JJJ and XFC contribute to analysis and interpretation of data, HLZ and XFC contribute to drafting the article, All of authors revise it critically for important intellectual content, and final approval of the version to be published.

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Authors' information

Not applicable

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Tables

Table 1: Baseline characteristics

Author/Year	n	Country	Age(year)	Male	BMI(kg/m^2)	Case/control	Outcome index	PWV(m/s)	device
Abbas, A.et Al2015[17]	88	UK	AAA:73.1±5.7 Control:66.3±1	46(100%) 42(100%)	27.1±4.2 25.9±3.2	46/42	cf-PWV	10.8±2.2 12.9±3.1	Sphygmocor device
Durmus, I.2014[15]	38	Turkey	AAA:69±4 Control:66±6	11(61%) 13(65%)	26.7±4.4 29.5±4.4	18/20	cf-PWV	14.8±4.9 10±1.7	Sphygmocor device
Bailey,M.A.2014[16]	309	UK	AAA:73±7.5 Control:69.7±7.8	120(74.5%) 128(86.4%)	28±4.6 28±4.5	148/161	cf-PWV	9.55±2.3 9.75±2.3	Vicoder device
Li, R. X.2013[24]	20	USA	NA	NA	NA	5/15	Aortic PWV	10.54±6.52 6.03±1.68	A Sonix RP system
Lee, C. W.2013[20]	102	TaiWan	AAA:75.2±11.6 Control:74.3±12.5	47(92.2%) 46(90.2%)	23.8±4.2 24.9±3.4	51/51	cf-PWV	12.1±2.7 13.6±3.5	Colin VP-200
Kadoglou, N. P. E.2012[21]	149	Greece	AAA:72±4 Control:69±8	108(100%) 41(100%)	28.98±4.23 29.36±5.79	108/41	cf-PWV	12.99±3.75 10.03±1.57	Complior SP, Alam Medical,France
Kadoglou, N. P. 2 E.2012[22]	79	Greece	AAA:71±4 Control:69±4	48(100%) 31(100%)	28.6±4.2 27.9±3.5	48/31	cf-PWV	13.11±3.57 7.97±2.17	Complior SP, Alam Medical,France
Li, R. X.2011[23]	10	USA	NA	NA	NA	2/8	Aortic PWV	10.54±6.52 6.03±1.68	A Sonix RP system
Li L2016[14]	26	China	NA	10(76.9%) 10(76.9%)	NA	13/13	Aortic PWV	18.63±1.3 5.7±1.06	Electrocardiographi Gated 64-Detector c CT

NA: not available

*PWV(Pulse wave velocity)

*AAA(abdominal aortic aneurysm)

*cf-PWV carotid-femoral PWV,cfPWV)

*Aortic PWV(the infrarenal PWV)

Table 2: Subgroup analysis of PWV in AAA group and control group

Subgroup	N	WMD(95%CI)	Test of SMD=0		Heterogeneity	
			Z	P For Z	I^2(%)	P for I^2
All studies	9	2.23(2.02,2.70)			98.9	0.000
Age between AAA and control						
Significance difference	4	-0.48(-0.94,-0.01)	2.01	0.044	77.0	0.005
Not significance difference	5	5.59(5.09,6.09)	22.04	0.000	99.0	0.000
Diabete between AAA and control						
Significance difference	1	-2.10(-3.23,-0.97)	3.63	0.000	/	/
Not significance difference	4	0.52(0.11,0.93)	2.49	0.013	95.2	0.000
Hypertensive between AAA and control						
Significance difference	2	-0.52(-0.99,-0.06)	2.20	0.028	88.8	0.003
Not significance difference	3	2.05(1.23,2.87)	4.89	0.000	96.7	0.000
Sex between AAA and control						
Significance difference	1	-0.2(-0.71,0.31)	0.76	0.445	/	/
Not significance difference	6	4.35(3.89.4.80)	18.73	0.000	99.1	0.000
Smoking between AAA and control						
Significance difference	2	1.12(0.44,1.81)	3.23	0.001	98.0	0.000
Not significance difference	4	0.43(-0.00,0.87)	1.94	0.052	96.3	0.000
Detection location						
cf-PWV	6	0.63(0.26,1.00)	3.37	0.001	96.2	0.000
Aortic PWV	3	2.36(2.02,2.70)	27.65	0.000	81.9	0.004

*AAA(abdominal aortic aneurysm)

Figures

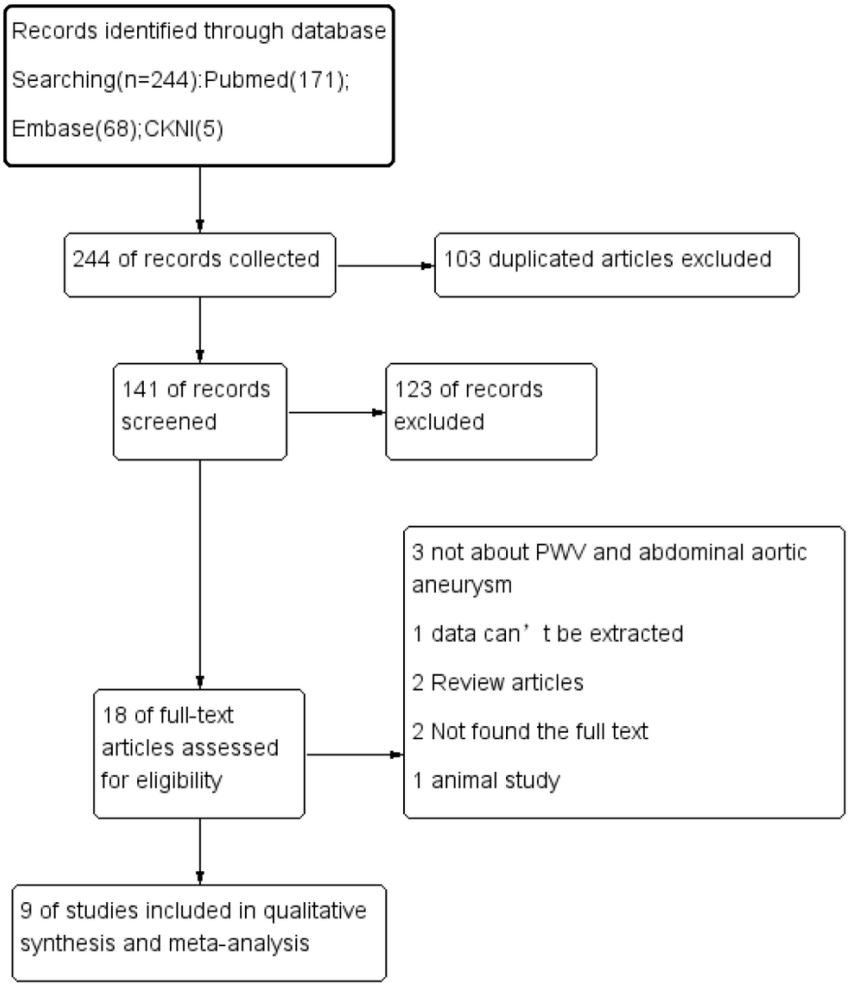

Figure 1

Flow diagram of the literature.

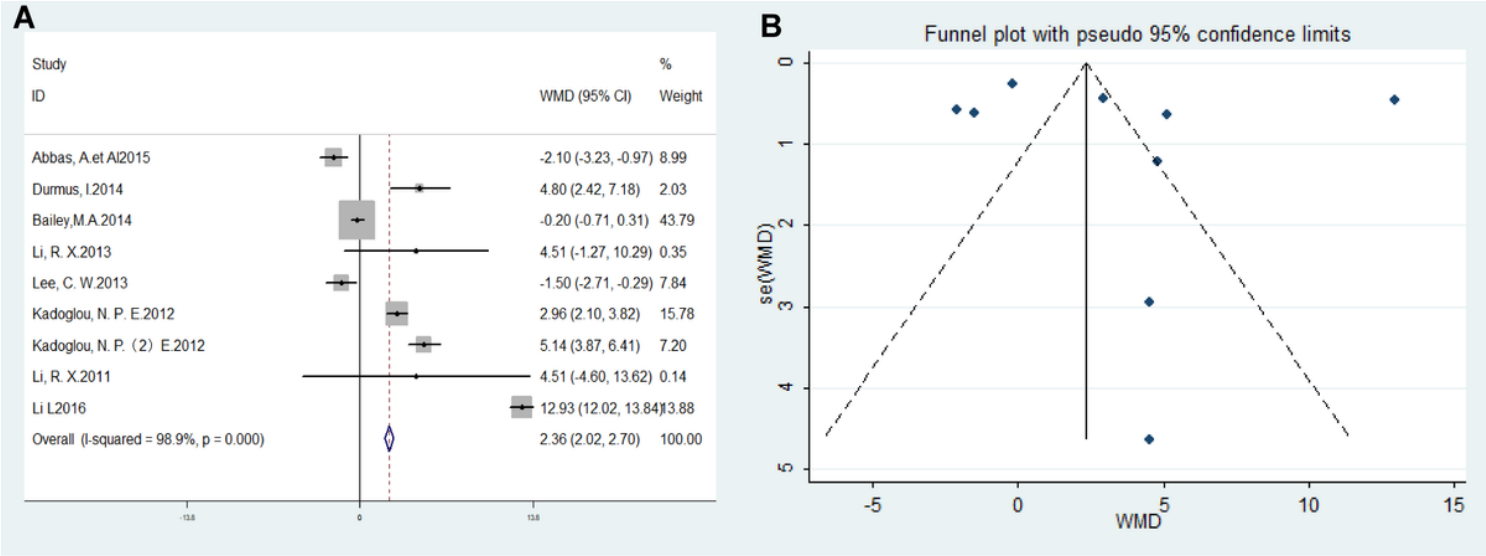

Figure 2

(A) Forest plot comparing PWV levels between AAA patients and non-AAA control. (B) Funnel plot of the association between PWV and AAA.

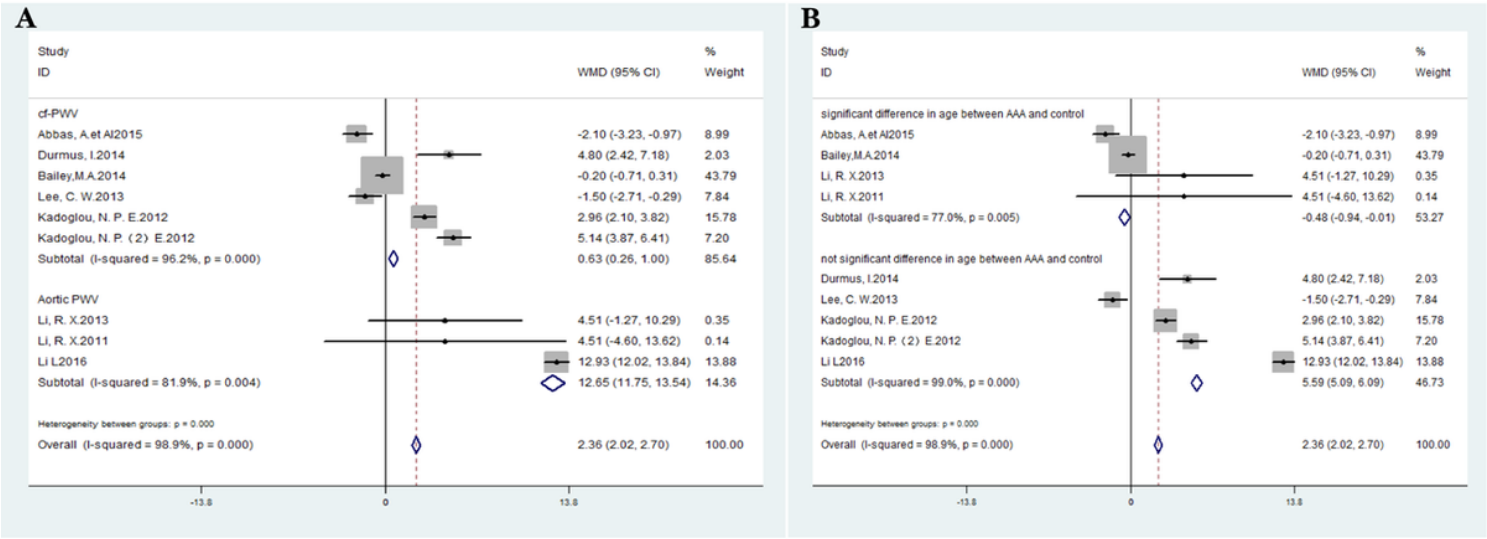

Figure 3

Forest plots of meta-analysis data (A) subgroup analysis according to significant difference or not significant difference in age between AAA and control group; (B) subgroup analysis according to PWV measurement location (carotid-femoral PWV and aortic PWV).

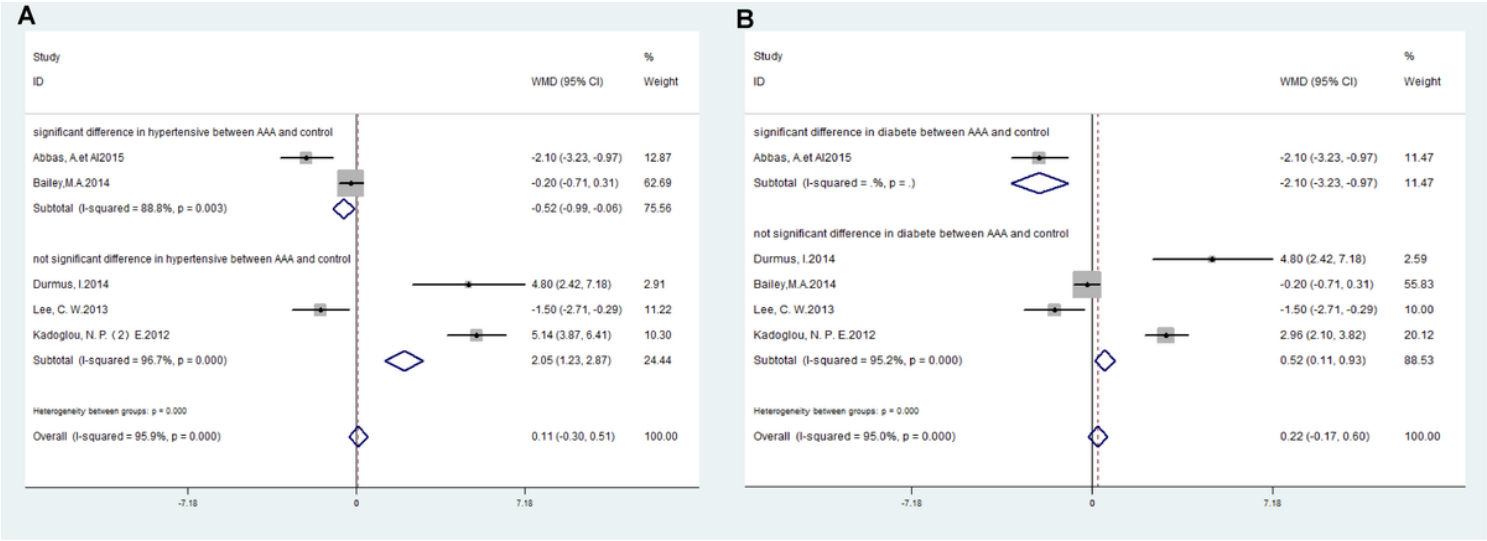

Figure 4

Forest plots of meta-analysis data (A) subgroup analysis according to significant difference or not significant difference in hypertensive between AAA and control group; (B) subgroup analysis according to significant difference or not significant difference in diabete between AAA and control group.

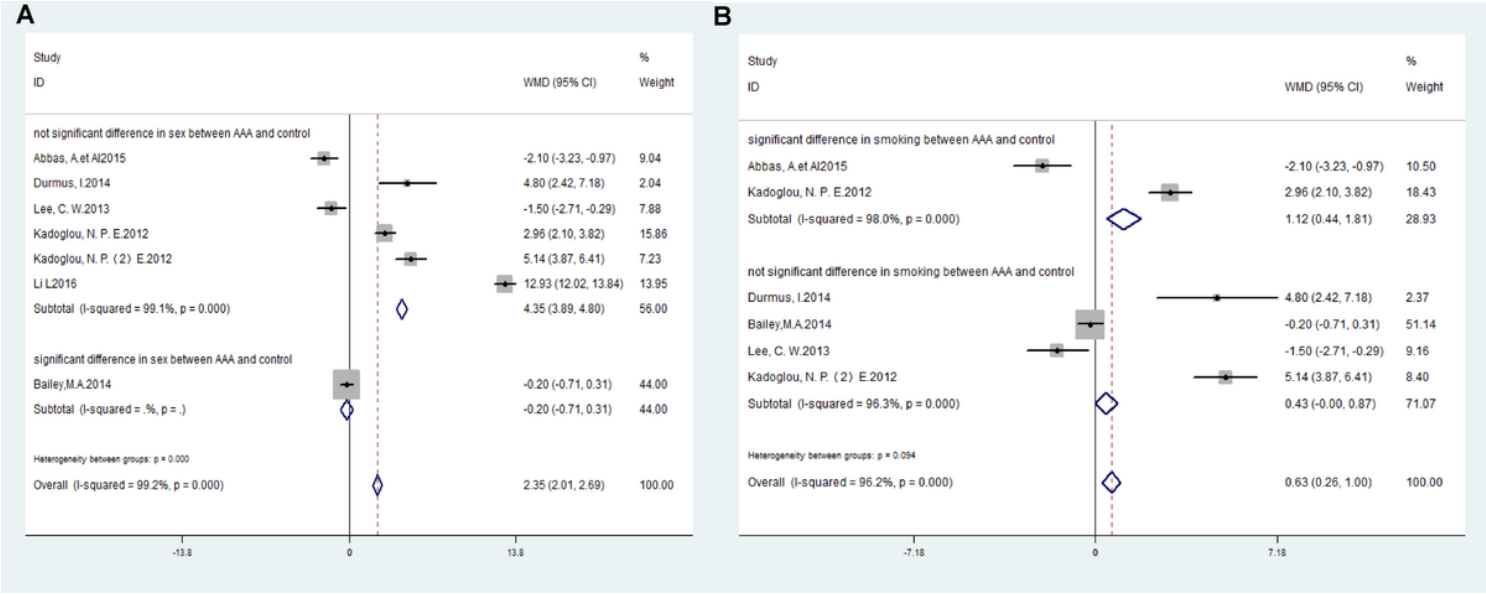

Figure 5

Forest plots of meta-analysis data (A) subgroup analysis according to significant difference or not significant difference in sex between AAA and control group; (B) subgroup analysis according to significant difference or not significant difference in smoking between AAA and control group.