MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 2467-2475
DOI: 10.12659/MSM.894693

Received: 2015.05.19
Accepted: 2015.07.28
Published: 2015.08.21

Clinical Significance of Arterial Stiffness and Thickness Biomarkers in Type 2 Diabetes Mellitus: An Up-To-Date Meta-Analysis

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Data Interpretation D
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Source of support: This work was supported by China Postdoctoral Science Foundation funded project (Grant Number: 2013M531617)

Background: Type 2 Diabetes mellitus (T2DM) is associated with increased risk of cardiovascular disease (CVD). Previous studies explored the association of T2DM with arterial stiffness and thickness biomarkers including the augmentation index (AIX), aortic pulse wave velocity (aPWV), brachial-ankle PWV (baPWV), carotid intima-media wall thickness (IMT) as well as blood pressure (BP), low density lipoprotein cholesterol (LDL-C); however the conclusions are either inconsistent or incomprehensive.

Material/Methods: The average differences of each included trial were expressed as the standardized mean difference (SMD) with 95% confidence interval (CI). Analyses of carotid IMT, aPWV, baPWV and AIX Systolic BP (SBP), diastolic BP (DBP), LDL-C and HDL-C were independently performed. Furthermore, subgroup analyses by ethnicity (Caucasian or Asian) were conducted. Begg's and Egger's tests were performed for potential publication biases detection.

Results: A total of 14 case-control eligible studies with 1222 T2DM patients and 1094 control subjects were included. In the overall analysis, significant associations were observed between the carotid IMT, aPWV, baPWV, LDL-C, HDL-C, SBP, and DBP with T2DM (IMT: $p=1.1*10^{-12}$; aPWV: $p=1.1*10^{-7}$; baPWV: $p=1.8*10^{-33}$; LDL-C: $p=3.1*10^{-8}$; HDL-C: $p=6.1*10^{-18}$; SBP: $p=3.9*10^{-21}$; DBP: $p=4.8*10^{-5}$). No association was detected for AIX ($p=0.09$). Subgroup analyses indicated that aPWV, baPWV, SBP, LDL-C, and HDL-C were associated with T2DM in both white and Asian populations ($p<0.05$). The significant associations of IMT, AIX and DBP with T2DM were only observed in the Asian subgroup.

Conclusions: Carotid IMT, aPWV, baPWV, as well as LDL-C, HDL-C, SBP, and DBP but not AIX were useful noninvasive early markers for T2DM vascular dysfunction detection.

MeSH Keywords: Biological Markers • Carotid Artery Diseases • Diabetes Insipidus, Nephrogenic

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/894693

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Background

Diabetes mellitus (DM), commonly type 2 diabetes mellitus (T2DM), is one of the most serious metabolic diseases causing an increasing global health burden [1]. According to data from the International Diabetes Federation, 1 in 12 was diagnosed with diabetes among the overall population, and there were 4.9 million deaths in 2014 [2]. Accumulating studies showed that patients with T2DM were at high risk of cardiovascular diseases (CVD) such as atherosclerosis, myocardial, or infarction stroke [3–5]. Arterial stiffness and thickness are commonly regarded as the main parameters for the evaluation of CVD [6,7]. The prevention and treatment of diabetes-related disease is always one of the hot topics in clinical practice [8]. Searching for noninvasive early markers of vascular dysfunction (arterial stiffness and thickness) has great clinical importance to T2DM patients, as it will offer a target for early intervention to delay the progress of cardiovascular disease complications.

Carotid IMT, an important biomarker for arterial thickness, presents a strong relationship with cardiovascular disease risk factors and can also be used to predict cardiovascular events [9,10]. PWV and AIX are widely used biomarkers for arterial stiffness and increased arterial stiffness is associated with the incidence of coronary atherosclerosis and worse cardiovascular prognosis [11]. Additionally, accumulating researches have displayed that the BP control was beneficial for patients with DM and lower BP could reduce cardiovascular morbidity and mortality [12,13]. For example, lowing BP causes a reduction of the stroke risk by 44% in patients with hypertension and DM [13]. It was also confirmed that dyslipidemia, a common complication in patients with T2DM, is one of the key risk factors for CVD in DM [14,15]. And the levels of HDL-C for patients with T2DM are evidently reduced compared with those in the controls [14].

Although some studies have been conducted to detect the associations between the main biomarkers of arterial stiffness and thickness in T2DM [3,4,11,16–26], the results are often inconsistent and incomprehensive. Herein, we performed a meta-analysis to investigate whether patients with T2DM were associated with LDL-C, HDL-C, SBP, DBP and the main biomarkers related to arterial stiffness and thickness, including carotid IMT, PWV and AIX.

Material and Methods

We performed a meta-analysis with most up-to-date published case-control studies to assess the associations between the main arterial stiffness and thickness biomarkers (including carotid IMT, aPWV, baPWV and AIX), LDL-C, HDL-C, SBP and DBP

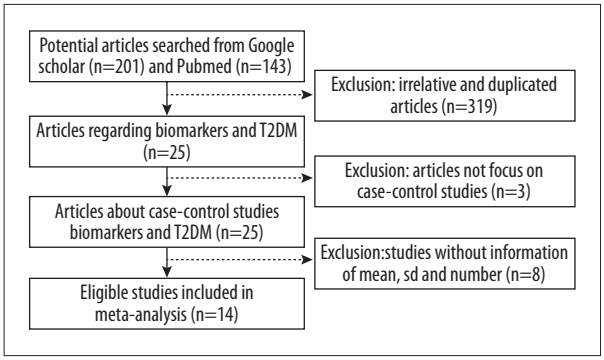

Figure 1. Flow chart of procedures for eligible studies collection and identification.

with T2DM. All qualified studies were retrieved from PubMed database and Google Scholar. The analyses were conducted for the entire population, as well as different subgroups according to the ethnicity. STATA software (release 12; College Station, TX) was employed for assisting all statistical analyses.

Data collection

With the advancing on medical technology, the difference of measurement accuracy for some biomarkers may cause heterogeneity in our study. We try to use latest studies to lower the possible uncertainty in the subsequent statistical tests. All studies on the association between the arterial stiffness and thickness in T2DM published from 2000 to 2014 were identified by comprehensive searches of PubMed and Google Scholar. The following key words, "arterial stiffness", "arterial thickness", "type 2 diabetes mellitus", "pulse wave velocity", "intima-media wall thickness" and "augmentation index" were used for the searching. A total of 344 publications (143 from PubMed and 201 from Google Scholar) were obtained. The inclusion criteria for qualified studies for this meta-analysis were as following: (i) relative articles, non-duplicated articles; (ii) case-control studies published in peer-reviewed journals; (iii) studies focusing on the relationship between carotid IMT, PWV and AIX with T2DM; (iv) with detailed information about means, standard deviation and total number of cases and controls. For each qualified study, the following data were extracted: first author's last name, year of publication, country of origin, ethnicity, age, body mass index (BMI), information of carotid IMT, PWV, AIX, LDL-C, HDL-C, BP and the total number of cases and controls. The procedure of article collection is shown in Figure 1.

Statistical methods

In this study, STATA was used for all meta-analyses. The associations between arterial stiffness and thickness, LDL-C, HDL-C, SBP and DBP in T2DM patients were assessed using all databases. The average differences of each included trial were

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Table 1. Characteristics of literatures included in the meta-analysis.

Author	Year	Country	Case			Control			Ethnicity	Parameter type
			Age*	BMI*	No.	Age*	BMI*	No.		
Zhang	2014	China	53.6/9.3	25.5/5.8	50	53.1/12.0	24.7/2.0	41	Asian	LDL-C; HDL-C; sBP; dBP; aPWV; IMT.
Li	2014	China	56.8/6.0	25.4/3.0	382	56.2/6.0	25.1/3.0	323	Asian	LDL-C; sBP; dBP; baPWV.
Lenkey	2014	Hungary	61.0/9.0	30.0/4.5	152	61.0/9.0	27.6/4.1	186	Caucasian	LDL-C; HDL-C; sBP; dBP; aPWV; AIx.
Yiu	2013	China	62.0/10.0	25.5/4.2	100	60.0/9.0	23.5/3.4	150	Asian	LDL-C; HDL-C; sBP; dBP; baPWV; IMT.
Bagherzadeh	2013	Iran	52.1/8.5	27.9/4.5	64	48.7/6.2	29.1/5.1	57	Caucasian	sBP; dBP; aPWV.
Yoo (a)	2011	Korea	53.1/6.8	23.9/2.3	30	54.1/8.1	24.0/2.9	30	Asian	LDL-C; HDL-C; sBP; dBP; baPWV; IMT.
Yoo (b)	2011	Korea	56.5/6.0	24.2/2.1	30	54.1/8.1	24.0/2.9	30	Asian	LDL-C; HDL-C; sBP; dBP; baPWV; IMT.
Zhang	2011	China	60.2/9.6	24.7/2.6	79	60.1/9.5	24.4/2.6	79	Asian	LDL-C; HDL-C; sBP; dBP; AIx.
Bruno	2011	Italy	55.3/9.6	31.0/6.7	32	51.0/7.1	26.1/4.1	27	Caucasian	LDL-C; HDL-C; sBP; dBP; aPWV; AIx.
Phillips	2010	Australia	56.3/9.5	26.8/na	10	46.4/10.7	23/na	8	Caucasian	AIx.
Charvat	2010	Czech	61.1/6.3	31.0/3.7	82	61.2/4.7	28.7/4.6	41	Caucasian	LDL-C; HDL-C; sBP; dBP.
Suzuki	2009	Japan	59.7/6.5	23.0/4.6	45	59.4/6.4	22.7/1.7	38	Asian	HDL-C; sBP; dBP; baPWV.
Loimaala	2005	Finland	52.3/5.6	29.1/3.7	49	48.3/7.4	25.2/2.4	15	Caucasian	sBP; dBP; baPWV.
Yoshida	2004	Japan	58.9/12.3	23.7/3.9	98	60.1/9.8	23.4/3.8	61	Asian	baPWV; IMT.
Hope	2004	Australia	66.0/11.0	28.4/5.3	19	65.0/10.0	27.9/4.0	38	Caucasian	sBP; dBP; AIx.

* Data are formatted as mean/SD.

expressed as the standardized mean difference (SMD) with 95% confidence interval. Analyses of the main biomarkers of arterial stiffness and thickness including carotid IMT, aPWV, baPWV and AIX were independently performed. The evaluation of LDL-C, HDL-C, SBP and DBP in T2DM were assessed as supplementary analyses. Subgroup analyses by ethnicity were performed for Caucasian and Asian population. Heterogeneity among trials was assessed by I^2 index. Higher I^2 index represents more significant heterogeneity. When $I^2 \leq 25\%$, we assume that there is no significant heterogeneity between pooled data; Mantel-Haenszel (M-H) fixed-effect model set should be applied to analyze the datasets. When $I^2 > 75\%$, there is high heterogeneity and DerSimonian and Laird (D-L) random-effect model should be applied. If I^2 index is between 25% and 75%, which is considered as median heterogeneity, either fixed-effect model or random-effect model can be applied for analysis. SMDs were calculated within each model with 95% confidence intervals. Forest plots were generated to summarize the results. Potential publication bias was assessed by the Begg's funnel plots and the Egger's test. All reported p values were 2-sided.

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Table 2. Information of carotid IMT, PWV, AIX, LDL-C, HDL-C, SBP and DBP in included studies.

Author	Group	LDL-cholesterol (mmol/l)*	HDL-cholesterol (mmol/l)*	sBP (mmHg)*	dBP (mmHg)*	IMT (cm)*	PWV (m/sec)*	AIx (%)*
Zhang	Case	3.1/0.1	1.6/0.2	134.9/18.8	86.5/12.1	063/0.17	8.40/3.30	
	Control	2.9/0.2	1.6/0.1	116.1/12.2	79.8/9.2	0.57/0.12	7.27/1.33	
Li	Case	2.7/0.7		135.7/13.0	82.2/6.7		15.7/1.05	
	Control	2.4/0.7		132.1/10.4	79.5/7.8		14.3/1.03	
Lenkey	Case	3.6/0.8	1.3/0.3	136.8/17.4	81.4/11.5		9.70/1.70	29.3/13.0
	Control	3.3/0.4	1.5/0.3	136.7/17.0	81.3/10.1		9.30/1.50	31.9/12.8
Yiu	Case	2.8/0.7	1.4/0.4	138.0/19.0	77/9.0	0.96/0.20	17.98/3.91	
	Control	3.0/0.7	1.5/0.4	121.0/19.0	74/9.0	0.86/0.14	15.70/2.96	
Bagherzadeh	Case			131.0/17.3	76.0/8.7		10.11/2.45	
	Control			123.5/14.0	77.5/10.1		8.00/1.61	
Yoo (a)	Case	2.3/0.6	1.2/0.3	119.0/10.5	74.5/8.6	0.86/0.12	14.29/2.57	
Yoo (b)	Case	2.3/0.5	1.3/0.3	129.8/17.9	77.7/9.9	0.98/0.16	16.22/3.07	
	Control	2.6/0.8	1.4/0.4	119.7/12.7	77.7/10.1	0.84/0.11	13.26/1.77	
Zhang	Case	3.1/0.7	1.3/0.4	123.1/11.0	72.9/8.4			24.2/9.8
	Control	2.6/0.5	1.5/0.3	119.3/11.0	72.2/8.1			28.1/10.3
Bruno	Case	3.4/1.5	1.2/0.3	137.5/12.6	78.0/8.3		8.60/1.80	24.6/14.1
	Control	3.6/0.6	1.5/0.5	130.3/8.0	78.5/6.1		7.50/1.10	21.1/12.5
Phillips	Case							24.4/6.8
	Control							22.3/12.7
Charvat	Case	2.8/0.9	1.2/0.3	126.0/4.0	77.0/3.0			
	Control	3.0/0.9	1.5/0.4	123.0/4.0	76.0/2.0			
Suzuki	Case		1.3/0.4	132.0/17.0	72.0/10.0		16.90/3.17	
	Control		1.4/0.4	122.0/7.0	76.0/7.0		13.00/1.12	
Loimaala	Case			144.0/16	87.0/8.0		10.00/1.70	
	Control			122.0/6.0	81.0/8.0		14.20/2.70	
Yoshida	Case					0.75/0.24	17.60/4.10	
	Control					0.59/0.11	12.90/1.50	
Hope	Case			133.0/22.0	68.0/11.0			18.0/10.2
	Control			134.0/23.0	70.0/10.0			13.1/9.8

* Data are formatted as mean/SD.

Results

In the current study, a total of 14 case-control eligible studies with 1222 T2DM patients and 1094 health control subjects were included in our meta-analysis [3,4,11,16–26]. The main characteristics of these studies were shown in Table 1. Among all the 14 eligible studies, there were 5 studies for the IMT, 4 studies for the aPWV, 7 studies for the baPWV, 5 studies for the AIX, 9 studies for

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Table 3. Meta-analysis of entire database for carotid IMT, aPWV, baPWV AIX, LDL-C, HDL-C, SBP and DBP.

Parameter	Analysis method	Heterogeneity		OR				Publication Bias	
		I^2 (%)	p-value	Overall	Lower	Upper	p-value	Begg	Egger
aPWV	Random	76.1	0.006	0.462	0.299	0.624	$1.1*10^{-7}$	0.734	0.188
baPWV	Random	94.8	$8.8*10^{-20}$	1.077	0.961	1.194	$1.8*10^{-33}$	0.707	0.576
IMT	Fixed	44.9	0.123	0.612	0.448	0.776	$1.1*10^{-12}$	0.806	0.572
AIx	Fixed	62.0	0.032	–0.137	–0.295	0.021	0.090	0.462	0.174
sBP	Random	81.3	$1.8*10^{-9}$	0.426	0.339	0.513	$3.9*10^{-21}$	0.640	0.242
dBP	Fixed	68.4	$5.8*10^{-5}$	0.186	0.100	0.272	$4.8*10^{-5}$	0.428	0.185
LDL-C	Random	88.3	$5.6*10^{-12}$	0.272	0.179	0.366	$3.1*10^{-8}$	0.602	0.286
HDL-C	Fixed	45.7	0.064	–0.522	–0.637	–0.406	$6.1*10^{-18}$	0.917	0.925

the LDL-C, 9 studies for the HDL-C, 13 studies for the SBP, and 13 studies for the DBP. For ethnicity subgroup analysis, there were 7 studies of Asian and 7 studies of Caucasian (Table 1). The information of country, ethnicity, total patient number, means and standard deviation of age and BMI was collected for both cases and controls, as shown in Table 1. The information of IMT, PWV, AIX, LDL-C, HDL-C, SBP and DBP was shown in Table 2.

The meta-analysis results for the association between the main arterial stiffness and thickness biomarkers (carotid IMT, aPWV, baPWV and AIX) with T2DM incidence were summarized in Table 3. All the I^2 indexes for the biomarkers were larger than 25%. In this research, the fixed-effect model was chosen for analysis when I^2 indexes for the biomarkers were larger than 25% and lower than 75%. Forest plots were shown in Figure 2. Significant associations with T2DM were observed between the carotid IMT, aPWV and baPWV respectively for overall population (aPWV: SMD=0.462, 95% CI (0.299–0.624), $p=1.1*10^{-7}$, Figure 2A; baPWV: SMD=1.077, 95% CI (0.961–1.194), $p=1.8*10^{-33}$, Figure 2B; IMT: SMD=0.612, 95% CI (0.448–0.776), $p=1.1*10^{-12}$, Figure 2C), while no significant association was detected for AIX (SMD=–0.137, 95% CI (–0.295–0.021), p=0.090, Figure 2D). These results suggested that in the overall dataset analysis, arterial stiffness and thickness evaluation biomarkers IMT, aPWV and baPWV but not AIX might have clinical significance for T2DM incidence.

For the supplementary analyses, as showed in Table 3, significant associations were observed between LDL-C, HDL-C, SBP and DBP in T2DM patient for overall population (SBP: SMD=0.426, 95% CI (0.339–0.513), $p=3.9*10^{-21}$, Figure 2E; DBP: SMD=0.186, 95% CI (0.100–0.272), $p=4.8*10^{-5}$, Figure 2F; LDL-C: SMD=0.272, 95% CI (0.179–0.366), $p=3.1*10^{-8}$, Figure 2G; HDL-C: SMD=–0.522, 95% CI (–0.637– –0.406), $p=6.1*10^{-18}$, Figure 2H), indicating that in the overall dataset analysis, all the additional parameters including LDL-C, HDL-C, SBP and DBP were associated with T2DM.

Subgroup meta-analyses based on ethnics were performed for Caucasian and Asian population. For the main arterial stiffness and thickness biomarkers, as showed in Table 4, the I^2 indexes for IMT in Asian and AIX in Caucasian were ranged from 25% to 75%, implying statistically median heterogeneity in those groups and the fixed-effect model was applied for assessing the statistical association in these groups. The results showed that aPWV and baPWV were significantly associated with T2DM in both Caucasian (aPWV: SMD=0.467, 95% CI (0.291–0.643), $p=5.4*10^{-7}$; baPWV: SMD=–2.131, 95% CI (–2.821– –1.442), $p=4.2*10^{-9}$) and Asian population (aPWV: SMD=0.434, 95% CI (0.016–0.851), p=0.042; baPWV: SMD=1.172, 95% CI (1.054–1.291), $p=1.6*10^{-22}$). While statistically significant associations of IMT and AIX with T2DM incidence were only observed in Asian subgroup (IMT: SMD=0.612, 95% CI (0.448–0.776), $p=1.1*10^{-12}$; AIX: SMD=–0.388, 95% CI (–0.703– –0.073), p=0.016).

The same analyses were conducted in the supplementary parameters (LDL-C, HDL-C, SBP and DBP). As showed in Table4, SBP, LDL-C and HDL-C were significantly associated withT2DM in both Caucasian (SBP: SMD=0.325, 95% CI (0.177–0.474), $p=3.9*10^{-6}$; LDL-C: SMD=0.254, 95% CI (0.077–0.431), p=0.005; HDL-C: SMD=–0.751, 95% CI (–0.9322– –0.570), $p=2.3*10^{-1}$) and Asian population (SBP: SMD=0.478, 95% CI (0.371–0.585), $p=9.5*10^{-18}$; LDL-C: SMD=0.280, 95% CI (0.170–0.390), $p=1.6*10^{-6}$; HDL-C: SMD=–0.363, 95% CI (–0.514– –0.213), $p=6.4*10^{-6}$). While statistically significant association of DBP with T2DM incidence was only observed in Asian subgroup (DBP: SMD=0.253, 95% CI (0.147–0.359), $p=7.3*10^{-6}$).

No statistically significant publication bias was observed for both Begg's and Egger's test for the overall dataset. The funnel plots of each group are shown in Figure 3. Due to limited sample size, publication bias detection was not carried out for subgroup dataset.

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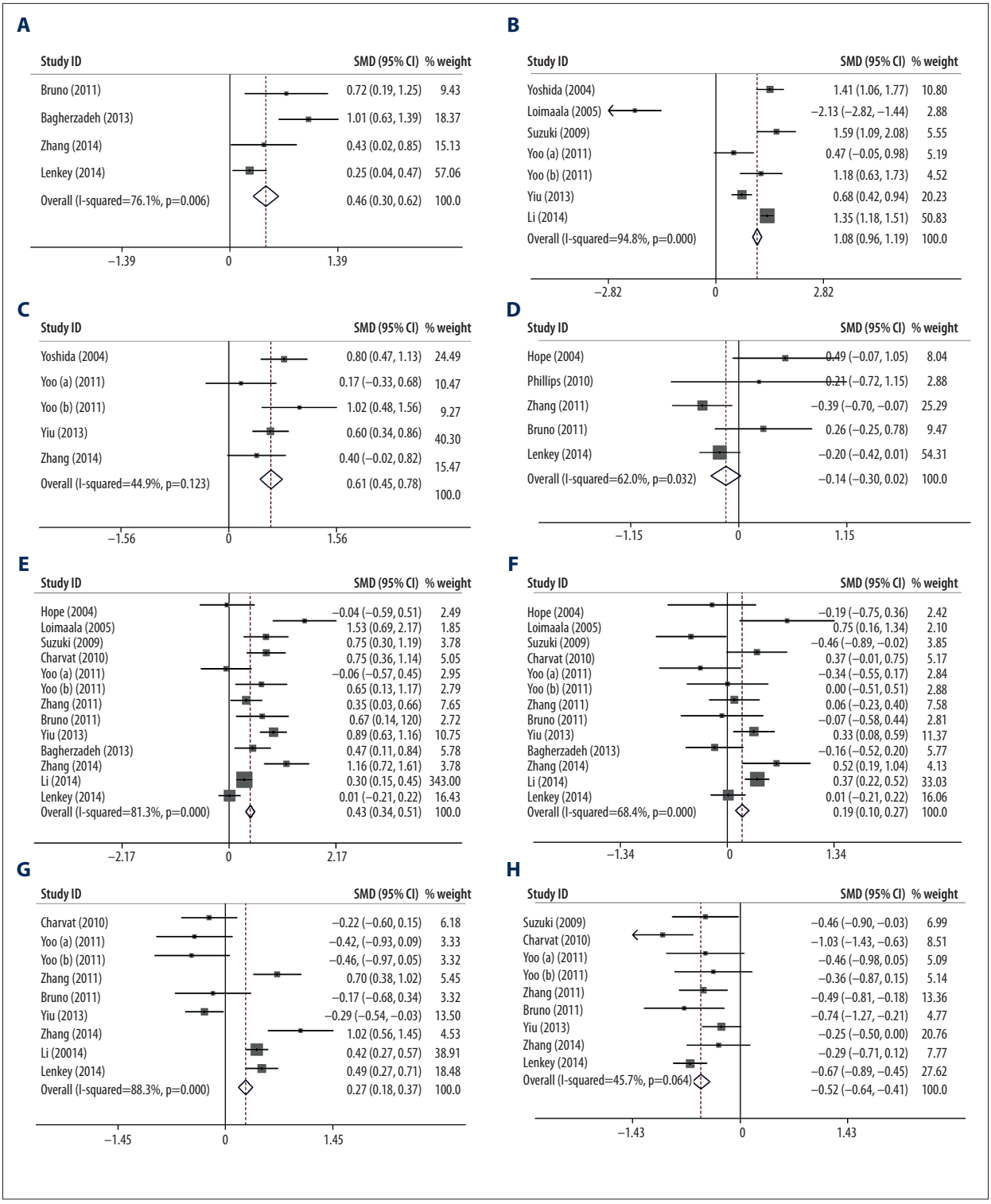

Figure 2. Forest plots of overall population for (**A**) aPWV, (**B**) baPWV, (**C**) carotid IMT, (**D**) AIX, (**E**) SBP, (F) DBP, (**G**) LDL-C and (**H**) HDL-C.

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Table 4. Subgroup meta-analysis of the association between carotid IMT, aPWV, baPWV AIX, LDL-C, HDL-C, SBP, DBP and T2DM.

Parameter	Caucasian				Asian			
	I^2 (%)	ph#	OR (95%CI)	pOR##	I^2 (%)	ph#	OR (95%CI)	pOR##
aPWV	84.0	0.002	0.467(0.291–0.643)	5.4*10–7	–	–	0.434(0.016–0.851)	0.042
baPWV	–	–	–2.131 (–2.821– –1.442)	4.2*10–9	83.3	$6.9*10^{-6}$	1.172 (1.054–1.291)	$1.6*10^{-22}$
IMT	–	–	–	–	44.9	0.123	0.612(0.448–0.776)	$1.1*10^{-12}$
AIx	58.7	0.064	–0.052 (–0.235–0.131)	0.577	–	–	–0.388(–0.703—0.073)	0.016
sBP	83.8	$4.4*10^{-6}$	0.325 (0.177–0.474)	$3.9*10^{-6}$	80.4	$1.3*10^{-5}$	0.478(0.371–0.585)	$9.5*10^{-18}$
dBP	52.3	0.063	0.060 (–0.087–0.206)	0.425	74.0	0.001	0.253(0.147–0.359)	$7.3*10^{-6}$
LDL-C	84.9	0.001	0.254 (0.077–0.431)	0.005	90.9	$6.2*10^{-11}$	0.280(0.170–0.390)	$1.6*10^{-6}$
HDL-C	18.2	0.294	–0.751 (–0.9322–0.570)	$2.3*10^{-15}$	0.0	0.866	–0.363(–0.514—0.213)	6.4*10–6

P-value from heterogeneity test; ## P-value from OR test.

Discussion

Numerous attentions have been attracted for noninvasive methods in detecting arterial stiffness and thickness changes in Diabetes mellitus patients [27,28], which are considered as risk factors for cardiovascular events. In the current study, we presented an up-to-date meta-analysis including 1222 T2DM patients and 1094 health controls to evaluate the clinical significance of the main arterial stiffness and thickness biomarkers carotid IMT, aPWV, baPWV and AIX in T2DM patients. In addition, supplementary parameters including LDL-C, HDL-C, SBP and DBP were also explored.

The results from our current study showed that the main arterial thickness and stiffness biomarkers carotid IMT, aPWV and baPWV were statistically associated with T2DM in overall population analysis. However, studies from Yuan et al. and Bagherzadeh et al. found no statistical significant association of IMT with T2DM [6,11], possibly due to the small sample size in their survey. Our results are consistent with previous studies which patients with T2DM have higher carotid IMT (an important marker for early atherosclerosis) than healthy control people [28,29]. PWV is an automated non-invasive method monitoring arterial stiffness changes and is considered as a sign of elevated cardiovascular risk. Studies from Yuan et al. and Bagherzadeh et al. did not find out the association of this biomarker with T2DM [6,11]. Strong associations of aPWV and baPWV with T2DM were identified in current and previous studies [30,31], indicating its high risk of heart disease.

Augmentation index is increasingly employed for estimating arterial thickness and CVD risk in patients with verified coronary artery disease [32]. Different from the conclusion in Philips's study [19], no statistically significant association was detected for the AIX in T2DM in current meta-analysis. Some studies showed that other factors may alter the AIX in T2DM patients. For instance, study showed that the increased sympathetic activity caused by hyper-insulinemia in some T2DM patients lowers the AIX [24]. Moreover, the participants' age, gender and height can also affect AIX [26]. Thus, our results suggested that aPWV and baPWV, but not AIX are among the main contributors to the association between arterial stiffness and T2DM. AIX is not a suitable biomarker for detecting arterial stiffness in patients with T2DM.

LDL-C, HDL-C, SBP and DBP, the common managing indexes clinically for patients with CVD, were found had significant associations with T2DM in our study, which confirmed the importance of these parameters for predicting vascular dysfunction in T2DM. There is mounting evidence that low level of LDL-C and high level of HDL-C causes the reduction in CV risk during the statins treatment [33]. Studies also showed that the lower BP plays an important role in the prevention of cardiovascular and renal events in patients with T2DM and hypertention [34].

Thus, our study highlighted the clinical significance of multiple arterial stiffness and thickness biomarkers including aPWV, baPWV and carotid IMT, LDL-C, HDL-C and BP in T2DM. AIX is not an appropriate biomarker for T2DM patients in arterial stiffness detection.

It is interesting that aPWV, baPWV, carotid IMT, LDL-C, HDL-C, SBP and DBP showed significant associations for both Caucasian and Asian ethnics in the subgroup analysis. While in Asian populations, significance was only observed for carotid IMT, AIX and DBP. The reasons for the clinical significance differences of these biomarkers in Caucasian and Asian groups are still unknown, probably due to the limited sample size or different ethnic background. Thus caution should be used when trying to identify ethnic specific markers in T2DM patients.

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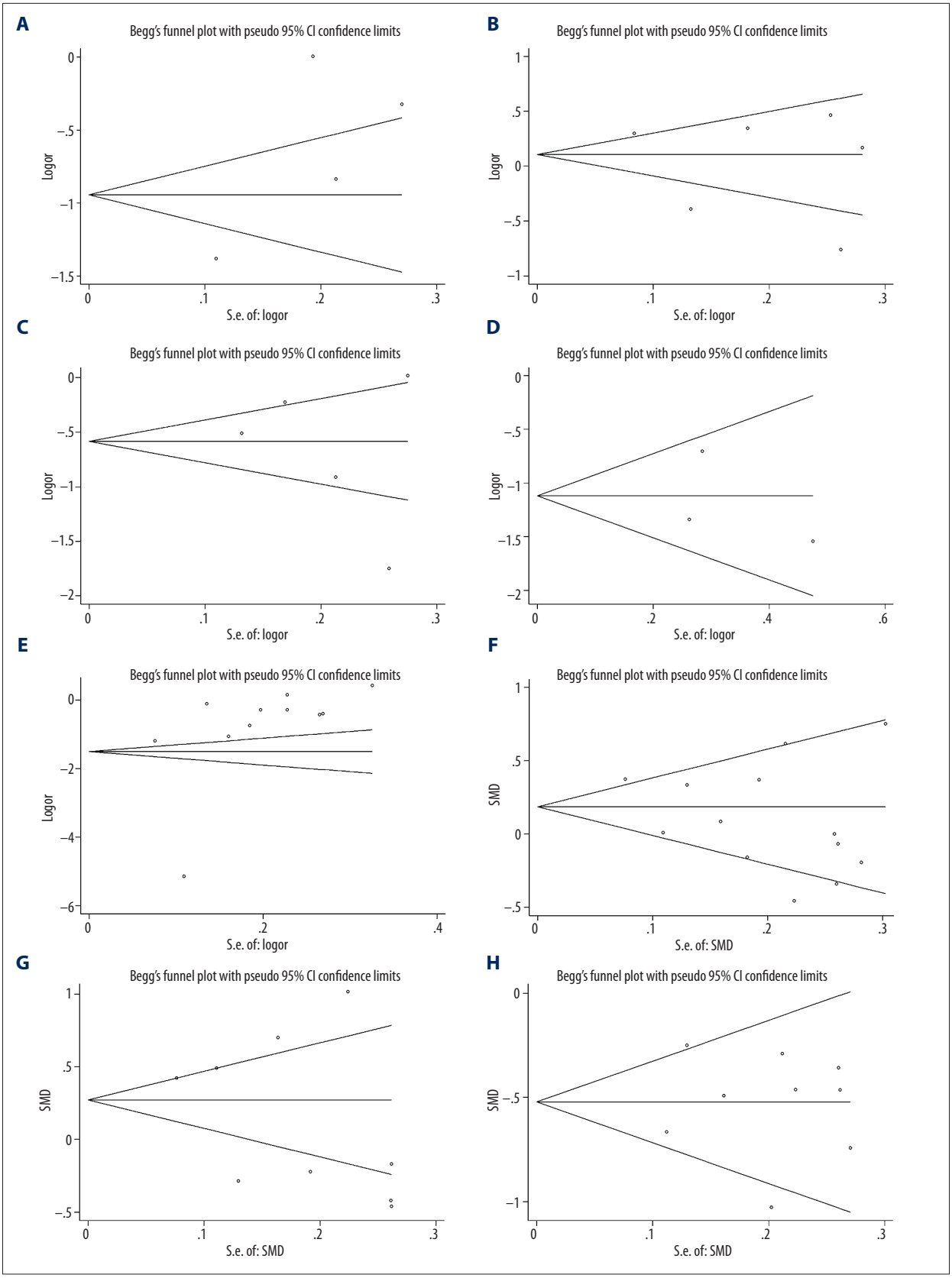

Figure 3. Funnel plots of overall population for (**A**) aPWV, (**B**) baPWV, (**C**) carotid IMT, (**D**) AIX, (**E**) SBP, (**F**) DBP, (**G**) LDL-C, and (**H**) HDL-C.

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Conclusions

Our study clarifies the inconsistent conclusions from previous studies, and provides a precise estimation for the clinical significance of the main arterial stiffness and thickness biomarkers in T2DM. The main biomarkers of arterial stiffness and thickness, including carotid IMT, aPWV, and baPWV but not AIX, are of great clinical significance for T2DM patients in early cardiovascular disease detection and intervention. We believe our study results will benefit future diabetes studies.

Acknowledgments

The authors are grateful to all study participants.

Declaration of interest

The authors declare that they have no competing interests.

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