Original Article

Clustering of major cardiovascular risk factors is associated with arterial stiffness in adults

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Abstract

Objective: Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide. Previous studies have indicated that clustering of major CVD risk factors is common. We aimed to explore the association of clustering of CVD risk factors with arterial stiffness in adults.

Methods: A total of 9984 adults were enrolled. We investigated clustering of four major CVD risk factors (defined as two or more of the following: hypertension, diabetes, dyslipidemia, and high body mass index) and their association with arterial stiffness. Arterial stiffness was evaluated using the carotid-femoral pulse wave velocity (cfPWV).

Results: In the study group (52.2% men, the mean age was 55.4 ± 10.5 years; only 11.9% of participants were free of any pre-defined CVD risk factors and 61.8% of participants had clustering of CVD risk factors. The cfPWV was significantly higher in the clustered risk factors group than in the no risk factor or the single risk factor groups (16.1 ± 3.1, 13.4 ± 2.2, and 14.3 ± 2.6 m/s, respectively; $P < 0.001$). Multiple linear regression analysis revealed that age, gender, clustering of CVD risk factors, serum uric acid, and decreased renal function positively correlated with cfPWV. For a categorical outcome, the highest cfPWV quartile (cfPWV ≥ 16.9 m/s) was compared with the lower three quartiles. After adjusting for potential confounders, clustering of CVD risk factors significantly correlated with increased cfPWV compared with that in the no risk factor group, with an odds ratio of 5.76 (95% confidence interval: 4.46–7.44).

Conclusions: Clustering of CVD risk factors significantly correlated with arterial stiffness; this confirms the importance of lifestyle modification to reduce the burden of CVD.

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Keywords: Cardiovascular disease; Cluster; Arterial stiffness; Pulse wave velocity

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Introduction

Cardiovascular disease (CVD) is the main cause of mortality and morbidity worldwide.[1,2] Hence, it is important to launch programs aimed at reducing the burden of CVD. Screening for risk of CVD is one fundamental strategy for primary prevention of CVD, but high-risk patients should be identified to maximize the benefit/cost ratio of treatments. Hypertension, diabetes, dyslipidemia and excess weight are four major CVD risk factors.[3−5] Previous studies indicate that CVD risk factors tend to be clustered in certain individuals.[6−8] A recent study in Chinese adult population demonstrated that the prevalence of clustering of major CVD risk factors was 36.2%, only 31.1% were free of any pre-defined CVD risk factors.[9]

Arterial stiffness predicts cardiovascular events; however as per our knowledge, little is known about a direct association between clustering of CVD risk factors with arterial stiffness. Hence, we performed this cross-sectional study in a large population to describe the relationship between clustering of CVD risk factors and arterial stiffness evaluated using carotid-femoral pulse wave velocity (cfPWV).

Methods

Study population

Adults who visited the Health Checkup Clinic at the Qianfoshan Hospital affiliated with the Shandong University were enrolled in the study. The participants needed to fulfil the following criteria: (a) age $\geq$ 18 years; (b) no malignant disease, heart failure, severe liver disease or infection; (c) not pregnant. Altogether, 9984 participants were included in the final analysis. The investigation was conducted from July 2012 to December 2013. The ethics committee of Qianfoshan Hospital approved the study (2016s001). All participants provided written informed consent for participation in the study.

Blood biochemistry measurements and biometric parameters

Blood was collected by means of vein puncture, after an overnight fast of at least 10 hours. Fasting blood glucose, serum creatinine, serum uric acid, serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) levels were measured by the automatic biochemistry analyzer in the central laboratory of Qianfoshan Hospital. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on creatinine levels.[10,11] Decreased eGFR (DeGFR) was defined as an eGFR < 60 ml·min^{-1}·1.73 m^{-2}.

Sociodemographic characteristics, health history (eg., hypertension, diabetes), and lifestyle behavior (eg, smoking) were recorded using questionnaires. The body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured using a sphygmomanometer, with three measurements taken using the right arm at 5 minute intervals, with the participant seated. When the mean of the three readings was greater than 10 mmHg, the mean of the two closest readings was used.

All study investigators and staff members completed a training program to learn the methodology and procedures used in the study.

Determination of arterial stiffness

The cfPWV was assessed using the SphygmoCor device (AtCor Medical Ltd., Sydney, Australia) as previously described.[12] A measuring tape was used to measure the distance between the carotid and femoral artery recording sites. The cfPWV was calculated automatically by dividing this distance by the time interval between the rapid upstroke in the pulse wave at the carotid and femoral arteries, using the peak of the R-wave on electrocardiography as a reference point. The upper quartile of the cfPWV was used as a categorical dependent variable for analyses, in comparison with the lower three quartiles. In the absence of evidence about whether a logarithmically or otherwise transformed cfPWV measurement was a valid indicator of risk, we adopted the categorical approach. We chose to separate the highest quartile because the cfPWV measurements in this quartile were substantially higher than in the lower three quartiles. The highest cfPWV quartile ($\geq$16.9 m/s) was termed 'increased cfPWV'. The cfPWV measurement in the lower three quartiles, in contrast, were tightly bunched over a limited range, and these quartiles were combined for analysis.

Assessment criteria

We investigated the clustering of four major CVD risk factors, which was defined as two or more of the following: hypertension, diabetes, dyslipidemia and high BMI. Hypertension was defined using three consecutive findings of mean systolic blood pressure

>140 mmHg or mean diastolic blood pressure >90 mmHg, or both obtained two weeks apart at the clinic or patients already having been prescribed antihypertensive medication. Diabetes was defined as fasting blood glucose ≥7.0 mmol/L, use of hypoglycemic agents, or self-reported history of diabetes. Dyslipidemia was defined as presence of at least one of the following: serum TC level ≥5.2 mmol/L, TG level ≥1.7 mmol/L, LDL-C level ≥3.4 mmol/L, and HDL-C level <1.0 mmol/L.[13] High BMI was defined as either overweight ($24 \leq BMI < 28$ kg/m^2) or obesity (BMI $\geq$ 28 kg/m^2).[14]

Statistical analysis

Data were presented as proportions for categorical variables and mean ± SD or median [interquartile range (IQR)] for continuous variables. The significance of differences in continuous variables between groups was tested using one-way analysis of variables or Kruskal–Wallis *H* test, as appropriate. The difference in the distribution of categorical variables was evaluated using the Chi-square test. Multiple linear regression analysis was performed to assess the combined effect of clinical variables on the cfPWV. The association between clustering of CVD risk factors and increased cfPWV was analyzed using Logistic regression models. Age- and sex-adjusted odds ratios (*OR*s) with 95% confidence interval (*CI*) were reported. We then used forward selection method to build a parsimonious model to adjust for other confounders.

Covariates under consideration included age (continuous), sex (female *vs.* male), clustering of CVD risk factors (yes/no), decreased renal function (yes/no), serum uric acid (continuous). We included age and gender into the model. Covariates that could not enter the model were added individually. If the *OR* of clustering of CVD risk factors changed by > 20%, we retained them in the final model.

All analyses were performed by SPSS statistical package, version 16.0 (SPSS, Inc., Chicago, IL). A *P* value < 0.05 is considered statistically significant.

Results

Characteristics of the participants based on CVD risk factors are presented in Table 1. Out of the 9984 individuals in the study, only 11.9% were free of any pre-defined CVD risk factors and 61.8% had clustering of CVD risk factors. Compared with the group of participants without any defined CVD risk factors or the group of participants with a single major CVD risk factor group, the group of participants with clustering of CVD risk factors had more participants who were male and those who had hypertension, diabetes, overweight, dyslipidemia and DeGFR (*P* < 0.05). The cfPWV was significantly higher in the clustered risk factors group than in the no risk factor or single risk factor groups (16.1 ± 3.1, 13.4 ± 2.2, and 14.3 ± 2.6 m/s, respectively; *P* < 0.001) (Table 1).

In the multiple linear regression analysis, age, sex, clustering of CVD risk factors, serum uric acid and

Table 1
Characteristics of the participants according to CVD risk factors.

Characteristics	Total	None	Single	Cluster	*P* value
Prevalence, *n* (%)	9984 (100.0)	1191 (11.9)	2618 (26.3)	6175 (61.8)	NA
Age, years, mean ± SD	55.4 ± 10.5	50.5 ± 11.4	53.8 ± 10.2	57.0 ± 10.0	<0.001
< 65, *n* (%)	8170 (60.0)	1050 (12.9)	2249 (27.5)	4871 (59.6)	NA
≥ 65, *n* (%)	1814 (40.0)	141 (7.8)	369 (20.3)	1304 (71.9)	NA
Male, *n* (%)	7566 (75.8)	689 (57.9)	1876 (71.7)	5001 (81.0)	<0.001
SBP, mmHg, mean ± SD	138.5 ± 19.4	120.5 ± 11.5	128.9 ± 14.9	146.1 ± 18.2	<0.001
DBP, mmHg, mean ± SD	78.9 ± 11.6	69.8 ± 8.8	74.2 ± 9.6	82.6 ± 11.3	<0.001
BMI, kg/m^2, mean ± SD	25.6 ± 3.3	21.7 ± 1.6	24.4 ± 3.0	26.9 ± 2.9	<0.001
Hypertension, *n* (%)	4360 (43.7)	0	364 (13.9)	3996 (64.7)	<0.001
Diabetes, *n* (%)	1245 (12.5)	0	58 (2.2)	1187 (19.2)	<0.001
Overweight, *n* (%)	6824 (68.3)	0	1300 (49.7)	5524 (89.5)	<0.001
Dyslipidemia, *n* (%)	5763 (57.7)	0	896 (34.2)	4867 (78.8)	<0.001
Serum uric acid, μmol/L, mean ± SD	310.2 ± 91.0	263.5 ± 79.4	298.6 ± 84.1	324.1 ± 92.3	<0.001
eGFR, ml/min/1.73 m^2, mean ± SD	92.8 ± 12.2	95.6 ± 11.6	93.6 ± 11.7	91.9 ± 12.4	<0.001
Decreased renal function, *n* (%)	85 (0.85)	6 (0.5)	13 (0.5)	66 (1.1)	0.011
cfPWV, m/s, mean ± SD	15.3 ± 3.1	13.4 ± 2.2	14.3 ± 2.6	16.1 ± 3.1	<0.001
Increased cfPWV, *n* (%)	2490 (24.9)	83 (7.0)	334 (12.8)	2073 (33.6)	<0.001

CVD: cardiovascular disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; eGFR: estimated glomerular filtration rate; ABI: ankle-brachial index; cfPWV: carotid-femoral pulse wave velocity; SD: standard deviation; NA: no applicable.

Table 2
Multiple linear regression analysis of the association of cfPWV (m/s) with different variables.

Variables[a]	Unstandardized Coefficients (95% CI)	S.E.	Standardized Coefficients	P value
Constant	5.36 (4.93−5.78)	0.22	NA	<0.01
Age, year	0.17 (0.16−0.17)	<0.01	0.57	<0.01
Sex (1 = male, 2 = female)	−0.37 (−0.50−0.24)	0.07	−0.05	<0.01
Smoking (yes vs. no)	−0.09 (−0.20−0.02)	0.06	−0.01	0.09
Clustering of CVD risk factors (yes vs. no)	1.31 (1.21−1.41)	0.05	0.20	<0.01
Serum uric acid (per 1 mg/dl increase)	0.07 (0.03−0.10)	0.02	0.03	<0.01
DeGFR (yes vs. no)	1.06 (0.52−1.61)	0.28	0.03	<0.01

cfPWV: carotid-femoral pulse wave velocity; CVD: cardiovascular disease; DeGFR: decreased estimated glomerular filtration rate; CI: confidence interval; S.E.: standard error; NA: no applicable.
[a] The variables in the fully adjusted models included age, sex, smoking, clustering of CVD risk factors, serum uric acid, decreased renal function.

DeGFR positively correlated with cfPWV ($P < 0.01$), but smoking was not associated with cfPWV ($P = 0.09$) (Table 2).

As a categorical outcome, prevalence of the highest cfPWV quartile (increased PWV $\geq$ 16.9 m/s) was compared with that of the lower three quartiles. Compared with that in the no-risk factor group in the age and sex adjusting analysis, clustering of CVD risk factors significantly correlated with increased cfPWV, with an *OR* of 5.87 (95% *CI*: 4.55−7.57). After adjusting for potential confounders including age, gender, smoking, serum uric acid, DeGFR, clustering of CVD risk factors also significantly correlated with increased cfPWV compared with the no-risk factor group, with an *OR* of 5.76 (95% *CI*: 4.46−7.44, Table 3). To further explore the association of increased cfPWV with different variables according to gender, after adjusting for potential confounders, clustering of CVD risk factors were associated with increased cfPWV in both males (*OR* = 5.16, 95% *CI*: 3.89−6.84) and females (*OR* = 8.12, 95% *CI*: 4.23−15.59, Table 4).

Discussion

Our study revealed higher prevalence of increased arterial stiffness in adult population with clustering of CVD risk factors. After adjusting for potential confounders including age, gender, smoking, serum uric acid and DeGFR, clustering of CVD risk factors was still positively associated with arterial stiffness. Increased vascular stiffness is an independent predictor of CVD outcome.[15−17] The epidemiological features of CVD risk factor clustering are valuable for designing targeted intervention strategies. Preventive and interventional strategies should be initiated since a younger age to reduce the burden of CVD.

In our study, the prevalence of clustering of major CVD risk factors was 61.8%, and only 11.9% of participants were free of any pre-defined CVD risk factors. Epidemiological studies have demonstrated that CVD risk factors could cluster in twins and among family members prone to CVD,[18,19] suggesting that genetic factors might play an important role in development of CVD risk factors. Other studies suggest that,

Table 3
Multivariate Logistic regression analysis of the association of increased cfPWV with different variables.

Variables	Age- and Sex-adjusted OR[a] (95% CI)	P value	Multivariable adjusted OR[b] (95% CI)	P value
Age	1.15 (1.15−1.16)	<0.01	1.15 (1.15−1.16)	<0.01
Sex	0.80 (0.70−0.91)	<0.01	0.88 (0.76−1.04)	0.13
Smoking	0.98 (0.86−1.11)	0.72	1.01 (0.89−1.14)	0.92
Clustering of CVD risk factors				
None	Ref	−	Ref	−
Single	1.86 (1.41−2.45)	<0.01	1.84 (1.39−2.43)	<0.01
Cluster	5.87 (4.55−7.57)	<0.01	5.76 (4.46−7.44)	<0.01
Serum uric acid	1.09 (1.05−1.14)	<0.01	1.03 (0.99−1.07)	0.13
DeGFR	1.84 (1.03−3.28)	0.04	1.63 (0.90−2.93)	0.10

cfPWV: carotid-femoral pulse wave velocity; CVD: cardiovascular disease; DeGFR: decreased estimated glomerular filtration rate; OR: odds ratio; CI: confidence interval; Ref: reference.
[a] Except for *OR* of age and sex, all *OR*s were age and sex adjusted; Ref.: reference.
[b] Model was adjusted for age, sex, smoking, clustering of CVD risk factors, serum uric acid, DeGFR.

Table 4
Multivariate Logistic regression analysis of the association of increased cfPWV with different variables according to sex.

Variables	Male		Female	
	Crude *OR* (95% *CI*)	Multivariable adjusted *OR*[a] (95% *CI*)	Crude *OR* (95% *CI*)	Multivariable adjusted *OR*[a] (95% *CI*)
Age	1.14 (1.14–1.15)	1.15 (1.14–1.16)	1.20 (1.18–1.21)	1.18 (1.16–1.20)
Smoking	0.71 (0.64–0.79)	0.99 (0.88–1.13)	3.09 (0.98–9.77)	0.59 (0.13–2.74)
Clustering of CVD risk factors				
None	Ref.	Ref.	Ref.	Ref.
Single	1.38 (1.06–1.80)	1.17 (1.23–2.26)	4.44 (2.39–8.25)	2.67 (1.34–5.33)
Cluster	4.03 (3.17–5.13)	5.16 (3.89–6.84)	23.77 (13.25–42.62)	8.12 (4.23–15.59)
Serum uric acid	0.91 (0.87–0.94)	1.02 (0.97–1.06)	1.31 (1.21–1.43)	1.08 (0.98–1.20)
DeGFR	4.44 (2.66–7.39)	1.85 (1.01–3.43)	8.71 (2.61–29.05)	0.55 (0.10–2.92)

cfPWV: carotid-femoral pulse wave velocity; CVD: cardiovascular disease; DeGFR: decreased estimated glomerular filtration rate; *OR*: odds ratio; *CI*: confidence interval; Ref.: reference.
  [a] *OR* was adjusted for age, smoking, clustering of CVD risk factors, serum uric acid, DeGFR.

of these CVD risk factors, hypertension and diabetes mellitus are multifactorial diseases under the influence of both genetic and environmental factors.[20] Multiple modifiable lifestyle-related risk factors are associated with clustering of CVD risk factors, such as habitual drinking, physical inactivity, and chronic use of nonsteroidal antiinflammatory drugs.[9] In addition, lifestyle interventions (eg. physical exercise and consuming a low-fat diet) could effectively prevent development of type 2 diabetes, hypertension and dyslipidemia in high-risk subjects.[21–24] Therefore, comprehensive lifestyle interventions may be an effective strategy for controlling CVD risk factors in order to reduce the burden of CVD.

Possible mechanisms for relationship between clustering of CVD risk factors and arterial stiffness remain unclear. The key mechanism may be vascular endothelial damage.[25,26] Endothelial dysfunction alters endothelial properties and exerts structural and functional effects on target vessels, and may therefore enhance inward remodeling.[27,28] Thus, vascular endothelial damage may cause atherosclerosis.

Our study has a few limitations that must be mentioned. First, this study used a convenience sample which was not based on community-based screening and could introduce bias. Second, we could not collect detailed data of medication that the participants received; medications may affect arterial stiffness. Third, nontraditional risk factors of increased cfPWV, such as inflammatory factors and renin-angiotensin system, were not explored in the present study. Finally, our data were cross-sectional and did not provide an insight into the mechanisms that are responsible for the observed association.

Conclusions

Our study indicates that clustering of CVD risk factors is common in adult population, and is positively associated with arterial stiffness. Therefore, comprehensive interventions to address multiple lifestyle risk factors might be feasible and cost-effective for controlling the burden of CVD.

Conflicts of interest

The authors declare that they have no competing interests.

Acknowledgements

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