Arterial stiffness nomogram identification by cluster analysis: A new approach of vascular phenotype modeling

Alexandre Vallée MD, PhD

Department of Epidemiology-Data-Biostatistics, Delegation of Clinical Research and Innovation (DRCI), Foch hospital, Suresnes, France

Correspondence
Alexandre Vallée MD, PhD, Department of Epidemiology-Data-Biostatistics, Delegation of Clinical Research and Innovation (DRCI), Foch hospital, Suresnes 92150, France.
Email: al.vallee@hopital-foch.com

Abstract
Arterial stiffness, measured by arterial stiffness index (ASI), can be considered as a major denominator in cardiovascular diseases. Thus, it remains essential to highlight patient phenotyping profiles with high ASI values. A nomogram of arterial stiffness was evaluated by calculation of ASI nomogram. Theoretical ASI can be performed according to age, sex, mean blood pressure, and heart rate, allowing to form an individual ASI nomogram [(measured ASI – theoretical ASI)/theoretical ASI]. An ASI nomogram > 0 defined AS. This study investigates among UK Biobank participants without cardiovascular diseases, the hypothesis that K-means cluster analysis can be used to identify homogeneous phenotyping subgroups of participants according to ASI levels and then, the phenotype differences observed between these clusters. ASI nomogram was applied on 132 851 participants. K-means clustering was implemented with 10 clusters (optimal CCC value of 105.246). One cluster showed 100% rate of AS, corresponding to 25 393 participants (41.6% of the AS participants) with ASI nomogram = .26 (.22), ASI = 11.6 (2.3)m/s. A second cluster showed a 100% of non-AS, corresponding to 27 844 participants (38.8% of the participants with no arterial stiffness) with ASI nomogram = -.22 (.13), ASI = 7.1 (1.44)m/s. Threshold values of independent factors for differencing these two clusters were total cholesterol > 5.409 mmol/L (P < .001), triglycerides > 1.286 mmol/L (P < .001), smoking pack years > 11.8 pack/years, CRP > .99 (P < .001), daily alcohol consumption > 1.794 units/days and BMI > 26.641 kg/m² (P < .001). Cluster analysis allowed to highlight homogeneous participants profile with or without AS. Determine the markers differencing these clusters participates in the management of cardiovascular preventive strategies.

KEYWORDS
alcohol, arterial stiffness, arterial stiffness nomogram, atherosclerosis, body mass index, cardiovascular disease, cluster analysis, CRP, k-means, lipids, tobacco

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2022 The Authors. The Journal of Clinical Hypertension published by Wiley Periodicals LLC.
1 | INTRODUCTION

Arterial stiffness, measured by arterial stiffness index (ASI), can be considered as a major denominator in target organ damage. Numerous noninvasive arterial parameters have been shown to be biomarkers of arterial stiffness. Arterial stiffness is the arteries capacities to expand and contracts face to the cardiac flow. Arterial stiffness can be an integrator of long-lasting arterial wall damage leading to a luminal dilation due to increase in collagen deposition. Arterial stiffness is associated with coronary atherosclerosis, cardiovascular events or inflammatory disorders. Several studies have shown that (aortic) pulse wave velocity (PWV) can be considered as the criterion standard of arterial stiffness. PWV levels are strongly correlated with time-consuming and operator dependent. Arterial stiffness, measured by arterial stiffness index (ASI), can be considered as the criterion standard of arterial stiffness. PWV measurement is time-consuming and operator dependent. Arterial stiffness, measured by arterial stiffness index (ASI), can be considered as a major denominator in target organ damage.

Moreover, several studies concluded that ASI and PWV measure methods were highly correlated. As observed with PWV, individually, simple ASI measurement does not appear relevant. However, several findings have shown that age, sex, blood pressure (BP), and heart rate (HR) are strongly related to arterial stiffness. A nomogram of arterial stiffness may be performed by the calculation of an ASI nomogram and could better represent an individual parameter of cardiovascular management. A theoretical ASI, based on these factors, was calculated to determine the individual relevance of aortic stiffness assessment. Also, an ASI nomogram was calculated as [(measured ASI/theoretical ASI)] to determine those patients with increased AS, independently of the well-known determinants such as age, sex, mean BP, and HR.

However, it remains essential to better understand the factors influencing the increase of ASI. Moreover, in the context of new challenges in personalized, predictive and preventive medicine, it is essential to understand the harmful factors which could influence cardiovascular markers, such as ASI. Correcting the potential risks of increased ASI should go through their precise targeting. Thus, creating phenotype of participants with risk of increased ASI could be off interest in this personalized medicine which is currently implemented. The creation of risk scales makes it possible to classify patients by risk profile, but to date there is no such classification for cardiovascular risk markers. Such a classification of participants showing high cardiovascular risk, that is, increased ASI nomogram levels, would allow a better understanding of the relationships between the different markers. Determining the differences between the factors of participants with or without increased ASI nomogram levels is essential to better understand the underlying pathophysiological mechanisms and thus, to be able to better manage the patients before the cardiovascular events occur.

Cluster analysis is a multivariate methodology that can be performed to identify groups of participants with similar characteristics in the context of complex mechanisms. Cluster analysis is a methodology of performing groups in which the data were not scattered evenly by n-dimensional space but instead forms clusters. This approach has been recently performed in the field of cardiology. Recently, cluster analysis based on clinical variables was observed to be mainly effective in the exploration of the characterization of phenotypes in diseases. Several findings have suggested that cluster analysis could improve the characterization of a disease phenotype. Present these clusters could make sense of this clumped data and could provide a deeper understanding of data. This novel approach has not yet been applied to ASI. In this study, our aim was to investigate the hypothesis that cluster analysis can be used to identify homogeneous phenotyping subgroups of participants according to ASI nomogram levels and then, to investigate the phenotype differences observed between these subgroups.

2 | METHODS

2.1 | UK Biobank population

The UK Biobank is a prospective cohort for the investigation, prevention, diagnosis and treatment of chronic diseases, such as cardiovascular diseases in adults. 502 478 Britons across 22 UK cities from the UK National Health Service Register were included between 2006 and 2010. The cohort was phenotyped and genotyped, by participants who responded to a questionnaire; a computer-assisted interview; physical and functional measures; and blood, urine, and saliva samples. Data included socio-economic, behavior and lifestyle, mental health battery, clinical diagnoses and therapies, genetics, imaging, and physiological biomarkers from blood and urine samples. The cohort protocol can be found in literature.

2.2 | Ethical considerations

All participants provided electronic informed consent and UK Biobank received ethical approval from the North-West Multi-center Research Ethics Committee (MREC) covering the whole of UK. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the North West – Haydock Research Ethics Committee (protocol code: 21/NW/0157, date of approval: 21 June 2021). For details:

https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics

2.3 | Study population

169 782 participants of the UK Biobank with ASI measurement were recruited. Of them, we excluded participants with previous cardiovascular events, with missing data and with extreme values of ASI
Cardiovascular diseases were defined by heart attack, angina, and stroke, as diagnosed by a doctor and reported in questionnaires. We, therefore, analyzed 132,851 participants (Figure 1).

### 2.4 Outcome

Pulse wave arterial stiffness index (ASI) was measured by non-invasive method during a volunteer’s visit to a UK Biobank Assessment Center. Pulse waveform was taken by clipping a photoplethysmography transducer (PulseTrace PCA 2, CareFusion, USA) to the rested volunteer’s finger (any finger or thumb, mainly the index finger). Volunteers were asked to breathe in and out slowly five times in a relaxed fashion and readings were taken over a 10–15 s time. ASI is performed from a single peripheral pulse waveform. The carotid-to-femoral pulse transit time was estimated from the dicrotic waveform as the time difference between a forward compound when the pressure is transmitted from the left ventricle to the finger and a reflected or backward compound as the wave is transmitted from the heart to lower body via the aorta.22 ASI was estimated in meters per second (m/s) as: \( \frac{H}{PTT} \). \( H \) is the individual’s height, and \( PTT \) is the pulse transit time or the peak-to-peak time between the systolic and diastolic wave peaks in the dicrotic waveform.22 This methodology has been validated by comparing it with carotid-femoral PWV. These studies concluded that both measure methods were highly correlated. ASI was a simple, operator independent, non-expensive and rapid method.\(^\text{10–12}\)

### 2.5 Blood pressure measurement

Systolic and diastolic blood pressure (SBD, DBP) were measured twice at the assessment center by the use of an automated BP device (Omron 705 IT electronic blood pressure monitor; OMRON Healthcare Europe B.V. Kruisweg 577 2132 NA Hoofddorp), or manually by the use of a sphygmomanometer with an inflatable cuff in association with a stethoscope if the blood pressure device failed to measure the BP or if the largest inflatable cuff of the device did not fit around the individual’s arm.\(^\text{23}\) The participant was sitting in a chair for performing all the measures. The measures were carried out by nurses trained in performing BP measures.\(^\text{24}\) Multiple available measures for one participant were averaged. The Omron 705 IT BP monitor has satisfied the Association for the Advancement of Medical Instrumentation SP10 standard and was validated by the British Hypertension Society protocol, with an overall “A” grade for both SBP and DBP.\(^\text{25}\) Nevertheless, automated devices measure higher BP in comparison to manual sphygmomanometers, thus, we adjusted both SBP and DBP which were measured using the automated device using algorithms\(^\text{26}\):

For SBP, we performed the following algorithm:

\[
SBP = 3.3171 + 0.92019 \times SBP (\text{mmHg}) + 6.02468 \times sex \\
(male = 1; female = 0)
\]

For DBP, we performed the following algorithm:

\[
DBP = 14.5647 + 0.80929 \times DBP (\text{mmHg}) + 2.01089 \times sex \\
(male = 1; female = 0)
\]

### 2.6 Covariates

Hypertension was defined as SBP at least 140 mm Hg and/or DBP at least 90 mm Hg, according to guidelines by the European Society of Cardiology, and/ or antihypertensive drug used\(^\text{27}\) or hypertension diagnosed by a doctor. Diabetes status was defined as either receiving anti-diabetic medication or diabetes diagnosed by a doctor or a fasting glucose concentration \( \geq 7 \) mmol/L. Dyslipidemia was defined as having a fasting plasma total-cholesterol or triglycerides level of \( \geq 6.61 \) mmol/L (255 mg/dl) or \( > 1.7 \) mmol/L (150 mg/dl), respectively, or taking statin medication.\(^\text{28}\) Medications were characterized by the question: “Do you regularly take any of the following medications?”.

Calculated-glomerular filtration rate (GFR) (by MDRD formula, MDRD: modification of diet in renal disease, by ml/min/1.73m\(^2\); GFR < 60 ml/min/1.73 m\(^2\) defined chronic kidney disease (CKD)). Body mass index was calculated as weight (in kg) divided by heigh\(^2\)(meter), and categorized as high (BMI > 30 kg/m\(^2\)), moderate (BMI between 25 and 30 kg/m\(^2\)) and low (less than 25 kg/m\(^2\)).
Biological parameters were detailed in the UK Biobank protocol. Current tobacco smokers were defined as participants who responded "yes, on most or all days" or "yes, only occasionally" at the question "do you smoke tobacco now". Smoking pack-years are calculated as the average number of smoking packs per day multiplied by the total number of years smoked during lifetime, for never-smokers the value was zero. Although the alcohol questionnaire has not been formally validated, several studies have shown expected associations with alcohol. Alcohol level consumption was defined as reported in the research interest (Supplemental file). A nomogram of ASI was performed to show structure in data and divide patients into groups. Principal compound analysis, mapping high-dimension data into low-dimension space, was performed to diminish the primal data into two dimensions. Here we excluded participants without missing data. The main steps in the K-means algorithm were: (1) Select initial cluster centers with the number of K, (2) Assign each point to its closest cluster center, and (3) Compute new cluster centers. In step 1, K points are defined randomly as initial cluster centers. In step 2, when we assign each point to its closest cluster center, we compute the distance, as the Euclidean distance, between points and centers. In step 3, the new cluster centers are computed as the means of all points belonging to each cluster. The optimal number of clusters showing the best fit was selected by the use of the highest cubic classification criterion (CCC), which estimates the number of clusters using Ward’s minimum variance method.

To investigate the independent factors differing clusters with ASI nomogram values strictly superior to 0 to clusters with ASI nomogram values inferior to 0, a multiple logistic regression with forward-backward stepwise model was applied based on significant covariates. A log-transformation of CRP values was applied for multiple logistic regression analysis. For each independent factor of the multiple logistic analysis, the ability of the logistic regression model to allow discrimination was quantified by the maximum Youden index, performed as:

\[ J = \max_c \left[ S_c(c) + S_y(c) - 1 \right] \]

Youden index was chosen to determine the optimal decision thresholds (c) for the discrimination. Statistics were performed using SAS software (version 9.4: SAS Institute, Carry, NC). A P value < .05 was considered statistically significant.

### 2.9 Statistical analysis

Characteristics of the study population were described as the means with standard deviation (SD) for continuous variables. Comparisons between groups were performed using Student’s t test for continuous variables. Pearson Chi-squared test was performed for categorical variables. A cluster analysis was performed based on clinical, biological factors and behaviors consumption, that is, BMI, glycemia, HDL cholesterol, LDL cholesterol, total cholesterol, triglycerides, CRP, creatine, smoking pack years and daily alcohol consumption. K-means, a major clustering algorithm, was performed to show structure in data and divide patients into groups. Principal compound analysis, mapping high-dimension data into low-dimension space, was performed to diminish the primal data into two dimensions. Here we excluded participants without missing data. The main steps in the K-means algorithm were: (1) Select initial cluster centers with the number of K, (2) Assign each point to its closest cluster center, and (3) Compute new cluster centers. In step 1, K points are defined randomly as initial cluster centers. In step 2, when we assign each point to its closest cluster center, we compute the distance, as the Euclidean distance, between points and centers. In step 3, the new cluster centers are computed as the means of all points belonging to each cluster. The optimal number of clusters showing the best fit was selected by the use of the highest cubic classification criterion (CCC), which estimates the number of clusters using Ward’s minimum variance method.

To investigate the independent factors differing clusters with ASI nomogram values strictly superior to 0 to clusters with ASI nomogram values inferior to 0, a multiple logistic regression with forward-backward stepwise model was applied based on significant covariates. A log-transformation of CRP values was applied for multiple logistic regression analysis. For each independent factor of the multiple logistic analysis, the ability of the logistic regression model to allow discrimination was quantified by the maximum Youden index, performed as:

\[ J = \max_c \left[ S_c(c) + S_y(c) - 1 \right] \]

Youden index was chosen to determine the optimal decision thresholds (c) for the discrimination. Statistics were performed using SAS software (version 9.4: SAS Institute, Carry, NC). A P value < .05 was considered statistically significant.

### 3 RESULTS

The characteristics of the 132 851 participants were shown in Table 1. 61 084(46.0%) showed a positive ASI nomogram (with mean .26; SD=.22) for a mean ASI equal to 11.75(2.26) m/s. The remaining 71 767(54.0%) participants presented a negative ASI nomogram equal to -.22(1.14) for an ASI value equal to 7.18(1.48) m/s.

K-means clustering was implemented with 10 clusters (Table 2) proving the best fit with the optimal CCC value of 105.245 according to BMI, glycemia, HDL cholesterol, LDL cholesterol, total cholesterol,
### Table 1  Characteristics of the study population and according to the different clusters

| Study population | Clusters | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|------------------|----------|---|---|---|---|---|---|---|---|---|----|
|                  | Mean/SD%| Mean/SD%| Mean/SD%| Mean/SD%| Mean/SD%| Mean/SD%| Mean/SD%| Mean/SD%| Mean/SD%| Mean/SD%| Mean/SD% |
| Theoretical ASI  | 9.286   | 2.953 | 10.03 | 2.937 | 10.19 | 2.784 | 9.368 | 10.93 | 9.408 | 3.015 | 7.945 | 2.606 | 7.073 | 1.439 | 9.36 | 2.778 | 11.56 | 2.257 | 10.59 | 2.987 | 10.02 | 2.888 |
| ASI nomogram     |         | - | 0.667 | 0.056 | 0.821 | 0.004 | 0.314 | 0.001 | 0.306 | 0.1 | 0.285 | 0.132 | 1.00E-03 | 0.288 | 0.257 | 0.086 | 0.304 | 0.029 | 0.976 |
| Characteristics of variables for clusters construction |          |     |     |     |     |     |     |     |     |     |     |    |
| BMI              | 27.33   | 4.739 | 30.69 | 5.687 | 29.29 | 3.636 | 27.48 | 3.564 | 29.26 | 6.155 | 23.74 | 2.884 | 25.63 | 3.089 | 36.26 | 4.402 | 26.19 | 3.218 | 28.47 | 4.334 | 27.86 | 3.848 |
| Creatinine, micromol/L | 72.27 | 17.37 | 72.28 | 28.85 | 75.89 | 16.34 | 71.49 | 14.6 | 72.42 | 21.11 | 66.21 | 11.94 | 72.82 | 17.03 | 75.77 | 27.74 | 72.58 | 16.24 | 74.45 | 17.66 | 74.43 | 13.45 |
| C reactive protein (CRP), mg/L | 2.519 | 4.217 | 3.58 | 4.564 | 2.533 | 2.453 | 2.167 | 2.317 | 2.107 | 2.126 | 1.581 | 1.8 | 4.764 | 3.754 | 1.688 | 1.861 | 3.177 | 3.168 | 2.145 | 2.396 | <.001 |
| Glucose, mmol/L | 7.27   | 3.284 | 5.128 | 3.76 | 5.085 | 5.73 | 5.237 | 9.37 | 5.047 | 5.71 | 5.017 | 6.38 | 5.267 | 8.39 | 5.018 | 6.25 | 5.137 | 7.54 | 5.195 | 6.6 |
| Smoking pack years | 6.268 | 13.63 | 8.402 | 16.1 | 5.651 | 10.48 | 3.499 | 7.842 | 8.028 | 15.41 | 2.862 | 6.986 | 2.329 | 5.929 | 3.002 | 8.146 | 2.855 | 6.404 | 45.39 | 18.21 |
| Alcohol consumption (units/day) | 20.8 | 2.483 | 1.577 | 2.301 | 2.026 | 2.109 | 1.614 | 1.617 | 1.88 | 2.409 | 2.049 | 1.712 | 1.476 | 1.485 | 1.144 | 1.47 | 1.552 | 1.529 | 2.368 | 2.436 | 8.773 | 3.297 |
| HDL cholesterol, mmol/L | 1.474 | .385 | 1.215 | .343 | 1.1 | .198 | 1.505 | .273 | 1.367 | .37 | 2.068 | .307 | 1.381 | .254 | 1.232 | .262 | 1.4 | .284 | 1.324 | .316 | 1.578 | .354 |
| LDL cholesterol, mmol/L | 3.593 | .853 | 2.895 | .867 | 3.921 | .668 | 4.778 | .557 | 3.36 | .795 | 3.653 | .567 | 3.08 | .569 | 3.293 | .673 | 3.16 | .581 | 3.506 | .778 | 3.646 | .722 |
| Total cholesterol, mmol/L | 5.751 | 1.122 | 4.767 | 1.173 | 6.223 | .916 | 7.2 | .753 | 5.37 | 1.053 | 6.265 | .685 | 4.995 | .686 | 5.193 | .864 | 5.128 | .728 | 5.543 | .999 | 5.914 | .901 |
| Triglycerides, mmol/L | 1.716 | .992 | 2.334 | 1.41 | 4.09 | 1.219 | 1.929 | .663 | 1.646 | .807 | 1.059 | .368 | 1.337 | .564 | 1.856 | .695 | 1.408 | .563 | 1.935 | .88 | 1.737 | .834 |

Characteristics of the clusters

| Characteristic | Mean/SD% | Mean/SD% | Mean/SD% | Mean/SD% | Mean/SD% | Mean/SD% | Mean/SD% | Mean/SD% | Mean/SD% | Mean/SD% | Mean/SD% |
|----------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| BMI level |          |          |          |          |          |          |          |          |          |          |          |
| High | 31.500 | 23.79% | 780 | 49.87% | 3473 | 38.78% | 4956 | 22.29% | 727 | 35.76% | 507 | 2.79% | 2481 | 8.91% | 10758 | 97.77% | 3354 | 13.21% | 2605 | 32.39% | 1958 | 25.79% |
| Moderate | 56.345 | 42.41% | 539 | 34.46% | 4595 | 51.31% | 11599 | 52.16% | 801 | 39.40% | 4915 | 27.02% | 13269 | 47.65% | 244 | 2.22% | 12654 | 49.83% | 3801 | 47.26% | 3928 | 51.73% |
| Low | 44.907 | 33.80% | 245 | 15.66% | 888 | 9.92% | 5683 | 25.56% | 505 | 24.84% | 12763 | 70.18% | 12094 | 43.43% | 1 | 0.1% | 9385 | 36.96% | 1636 | 20.34% | 1707 | 22.48% |
| Diabetes | 8313 | 6.26% | 1564 | 100.00% | 537 | 6.00% | 358 | 1.61% | 159 | 7.82% | 321 | 1.77% | 1396 | 5.01% | 1610 | 14.63% | 1342 | 5.28% | 714 | 8.88% | 312 | 4.11% |
| Antidiabetic therapy | 4406 | 3.32% | 1074 | 68.67% | 205 | 2.29% | 49 | .22% | 81 | 3.98% | 69 | .38% | 760 | 2.73% | 908 | 8.25% | 744 | 2.93% | 390 | 4.85% | 126 | 1.66% | <.001 |

(Continues)
| Clusters | Study population | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|----------|-----------------|---|---|---|---|---|---|---|---|---|----|
|         | Mean/SD | Mean/SD | Mean/SD | Mean/SD | Mean/SD | Mean/SD | Mean/SD | Mean/SD | Mean/SD | Mean/SD | P value* | P value** |
| Dyslipidemia | 74123 | 5.57% | 1354 | 86.57% | 100.00% | 1997 | 89.92% | 9492 | 34.09% | 9734 | 38.33% | 5467 | 67.98% | 59.14% | <.001 | <.001 |
| Statin therapy | 19862 | 15.05% | 972 | 62.83% | 1360 | 15.33% | 759 | 3.43% | 282 | 14.02% | 997 | 5.50% | 4511 | 59.41% | <.001 | <.001 |
| Hypertension | 61653 | 46.41% | 1144 | 73.15% | 5008 | 55.95% | 10399 | 46.76% | 1097 | 53.96% | 6076 | 33.41% | 10768 | 38.67% | <.001 | <.001 |
| Antihypertensive therapy | 24807 | 18.80% | 778 | 50.29% | 1773 | 19.98% | 2664 | 12.05% | 504 | 25.06% | 1746 | 9.64% | 4786 | 17.29% | <.001 | <.001 |
| CKD | 784 | 2.10% | 69 | 4.41% | 179 | 2.00% | 437 | 1.71% | 90 | 4.43% | 458 | 1.64% | 612 | 1.69% | <.001 | <.001 |
| GFR | 91.9 | 17.21 | 100.03 | 24.89 | 94.33 | 18.55 | 89.76 | 15.73 | 16.79 | 17.48 | 17.00 | 17.48 | <.001 | <.001 |
| Tobacco | 13215 | 9.95% | 164 | 10.49% | 1181 | 13.19% | 1680 | 7.55% | 248 | 12.20% | 1768 | 6.35% | 681 | 6.19% | 2122 | 8.36% | 2920 | 36.31% | 1451 | 19.11% | <.001 | <.001 |

Characteristics of variables for nomogram calculation

| Age (years) | 56.48 | 5.81 | 58.01 | 7.52 | 56.51 | 8.158 | 57.86 | 7.405 | 57.42 | 8.11 | 57.13 | 7.583 | 54.46 | 8.996 | 56.44 | 8.102 | 54.46 | 8.996 | <.001 | <.001 |
| Sex | men | 60113 | 42.25% | 978 | 62.53% | 6377 | 71.20% | 8154 | 36.67% | 889 | 43.73% | 2830 | 15.56% | 13712 | 49.25% | 4265 | 38.76% | 12046 | 47.44% | 4994 | 38.76% | 12046 | 47.44% | <.001 | <.001 |
| women | 72738 | 54.75% | 586 | 37.47% | 2579 | 28.80% | 14084 | 63.33% | 1144 | 56.27% | 15355 | 50.75% | 6738 | 61.24% | 13347 | 52.56% | 3048 | 37.90% | 1725 | 22.72% | <.001 | <.001 |
| Systolic BP mmHg | 132.8 | 17.73 | 138.1 | 16.16 | 137.3 | 15.19 | 1348 | 17.31 | 129 | 14.02 | 1299 | 17.88 | 136 | 16.74 | 130.3 | 17.12 | 136.6 | 17.49 | 140 | 17 | <.001 | <.001 |
| Diastolic BP mmHg | 82.06 | 8.34 | 82.73 | 8.154 | 84.93 | 8.741 | 83.14 | 8.049 | 82.57 | 8.43 | 79.35 | 8.89 | 80.37 | 8.127 | 85.13 | 7.89 | 81.15 | 8.35 | 82.72 | 8.091 | 85.77 | 8.04 | <.001 | <.001 |
| Mean BP mmHg | 98.97 | 10.682 | 101.2 | 9.602 | 102.4 | 9.733 | 100.4 | 10.27 | 99.61 | 10.45 | 95.88 | 10.62 | 96.87 | 10.62 | 99.61 | 10.45 | 95.88 | 10.62 | 96.87 | 10.62 | 99.61 | 10.45 | <.001 | <.001 |
| HR bpm | 68.69 | 10.87 | 77.42 | 12.26 | 72.05 | 11.4 | 68.91 | 10.42 | 74.38 | 12.03 | 66.89 | 10.01 | 67.14 | 10.79 | 72.42 | 11.57 | 67.72 | 9.853 | 70.09 | 11.03 | 68.9 | 11.28 | <.001 | <.001 |

Categorical values: n and %, continuous values: mean and SD (standard deviation).
Abbreviations: BP, blood pressure; BMI, body mass index; CKD, chronic kidney disease; GFR, Glomerular filtration rate, ml/min/1.73 m².
*P value for difference between all the clusters.
**P value for difference between cluster 6 and cluster 8.
**TABLE 2** K-means clusters

| Cluster | N     | ASI nomogram > 0 proportion |
|---------|-------|-----------------------------|
| 1       | 1564  | 48.7%                        |
| 2       | 8956  | 56.0%                        |
| 3       | 22238 | 46.6%                        |
| 4       | 2033  | 44.4%                        |
| 5       | 18185 | 26.9%                        |
| 6       | 27844 | 0%                           |
| 7       | 11003 | 44.4%                        |
| 8       | 25393 | 100%                         |
| 9       | 8042  | 61.4%                        |
| 10      | 7593  | 52.1%                        |

**TABLE 3** Number of K means clusters analyses, and optimal cubic classification criterion (CCC)

| Method       | N cluster | CCC     | Best       |
|--------------|-----------|---------|------------|
| K means cluster | 3        | -178.11 |            |
| K means cluster | 4        | -126.78 |            |
| K means cluster | 5        | -92.288 |            |
| K means cluster | 6        | -47.685 |            |
| K means cluster | 7        | -21.24  |            |
| K means cluster | 8        | 11.6806 |            |
| K means cluster | 9        | 66.3024 | Optimal CCC |
| K means cluster | 10       | 105.246 |            |
| K means cluster | 11       | 85.1972 |            |
| K means cluster | 12       | 92.6492 |            |
| K means cluster | 13       | 93.7034 |            |
| K means cluster | 14       | 85.3906 |            |

The remaining eight clusters showed rate of ASI nomogram > 0 ranged 26.9% to 61.4% (Table 2).

Parallel coordinate plots for the display of the structure of the observations in each cluster showing how the clusters differ. This figure presents the different cluster hierarchies (Figure 3).

Clusters 6 and 8 with 100% of classified rates represented 53 2387 participants for 40.0% of the population.

Cluster 6 and 8 were significantly different for all the parameters (Table 1). After applying a multiple regression logistic with forward-backward stepwise model, the independent factors determining participants from cluster 8 to the cluster 6 according to ASI nomogram values were total cholesterol, triglycerides, smoking pack years, alcohol consumption, BMI levels, and CRP (Table 4). Threshold values for different clustering 8 to cluster 6 corresponded to total cholesterol superior to 5.409 mmol/L (P < .001), triglycerides superior to 1.286 mmol/L (P < .001), smoking pack years superior to 11.8 pack/years, CRP superior to .99 (P < .001), daily alcohol consumption superior to 1.794 units/days and BMI superior to 26.641 kg/m² (P < .001) (Table 4).

**4 DISCUSSION**

The K-means cluster analysis presented 10 interested clusters for different profiles of participants. The K-means clustering allowed us to discriminate two different profiles of homogeneous participants for ASI values independently of age, sex, HR and mean BP. In one cluster, the participants presented no arterial stiffness, and represented 27 844 participants and 38.8% of all participants with ASI nomogram > 0. Another cluster, with only participants with ASI nomogram > 0 represented 25 393 participants and 41.6% of participants with arterial stiffness. Between these two clusters of ASI nomogram, smoking pack years, alcohol consumption, BMI, CRP and lipid profiles were the independent determinants.

The calculation of ASI nomogram was based on age, sex, mean BP and HR. Advancing age could be one of the major potent independent factor of future cardiovascular events. After adjusted on age, ASI nomogram appears to be associated with cardiovascular risk factors, such as BMI, tobacco use, alcohol consumption, dyslipidemia and CRP. However, the association between time exposure and cardiovascular events occurring is not completely explained by time-related changes in cardiovascular risk factors. The biological age of vessels could be different, even if chronological age is associated with cardiovascular risk. Thus, repeated exposure to possible cardiovascular risk factors could enhanced differences in vascular function and structure and leads to a possible dissociation between chronological and biological age. The differences observed could be associated with inter-individual differences in vascular health. The definition of an integrative measure of vascular structure adjusted on age could provide better prediction of the real age of arteries. Thus, the calculation of ASI nomogram may appear as an integrative risk factor associated with time exposure of cardiovascular risk factors and regardless sex specificities, blood pressure and heart rate levels.
The study of biological heterogeneity requires the identification of subgroups of population with specific combinations of patterns. This approach identifies phenotypes of the subgroups, describes the patterns of diseases within each one, and facilitates the initiation of development of more targeted patient management. Non-hierarchical cluster analysis, as K-means methodology, yielded an informative categorization of patients generating reasonable patterns from clinical and biological information, and identified phenotypes for subgroups of patients. The results of this work identified two specific subgroups of patients with 100% ASI nomogram superior or inferior to 0, corresponding to 40% of the study population. These results can be translated into clinical practice. Clinical practice guidelines could oriented their recommendations toward these two phenotypes subgroups of patients. Thus, face to medically complex patients population, we can categorized these into two distinct patient profiles that are amenable to varying strategies for resource allocation and coordinated care interventions. This methodology provides empirical data which could inform conceptual models of complexity in general middle-aged population and further support the diversity of patients. By identifying the key variables which define the specific different patient profiles between these two clusters, this study offers data to guide efforts for operationalizing patient identification and to outline the types of different information that could be required for complex care prevention management.

The clinically and biologically complex patient phenotypes identified in this study have been described in different and previous studies. This study suggests that BMI, smoke pack years, alcohol consumption, dyslipidemia and CRP are the determinants differencing the two specific clusters of ASI nomogram participants.

BMI and arterial stiffness are closely associated. We observed that a BMI > 26.64 kg/m² (ie, overweight body) is mainly associated with increased arterial stiffness. Increase in BMI can be a factor for arterial remodeling leading to a modification in hemodynamic and arterial changes detrimental to vascular function and vascular endothelial wall.

Tobacco use, expressed by smoking pack years appeared as an independent factor of increased arterial stiffness, with a threshold over 11.8 pack/years. Numerous studies have explained the possible link between tobacco use and arterial stiffness. Active tobacco smoking is associated with increased arterial wall thickness and arterial stiffness, suggesting that active tobacco smoking accelerates atherosclerosis, reduces endothelium-dependent arterial dilatation and increases the stiffness of muscular arteries. As we observed a significant role of alcohol consumption in our study, future investigations should be focused on the double-consumption of both alcohol and tobacco as synergistic effect on arterial stiffness.

Indeed, the association between alcohol consumption and increased arterial stiffness remains unclear, with no association, J-shaped association or significant increased association or binge pattern of drinking. In our study we found a significant relationship between alcohol consumption and increased arterial stiffness, with a threshold over 1.794 units/days. A recent study has shown that energy from alcohol (in calories) could be considered as a significant predictor of increased PWV. Longitudinal studies showed a
FIGURE 3  K-Means clustering method. Parallel coordinate plots for the display of the structure of the observations in each cluster showing how the clusters differ

Strong association between alcohol consumption and future arterial stiffness.\textsuperscript{44} This relationship remains unclear, complex and related to the methodological assessment of alcohol consumption. The definitions of alcohol consumption were different among studies and challenge the formulation of consumption thresholds. Nevertheless, two studies showed a dose-response relationship between alcohol consumption and arterial stiffness in men.\textsuperscript{45,46} A possible mechanism could be the effects of alcohol on lipids but this link remains unknown.\textsuperscript{42} Alcohol can also induce changes in the arterial wall by degrading the eslatin induced by matrix metalloproteinase and enhancement of oxidative stress leading to vascular damages.\textsuperscript{47}

Moreover, high alcohol consumption level is mainly associated with arterial calcification,\textsuperscript{48} inflammation\textsuperscript{49} and then with alcohol-induced arterial stiffness.\textsuperscript{50}

Several findings have shown that inflammation and dyslipidemia are correlated with increased arterial stiffness.\textsuperscript{51–53} Dyslipidemia is closely associated to inflammation. Patients with dyslipidemia presented higher levels of inflammatory factors in comparison to normal participants.\textsuperscript{55} Moreover, dyslipidemia was associated with dietary cholesterol intake among participants without cardiovascular diseases,\textsuperscript{55} and the level of CRP was modulated by dietary fatty acid intake.\textsuperscript{56} Several processes could explained the relationship between
inflammation and dyslipidemia and then in atherosclerosis mechanisms. LDL cholesterol participates in the vascular intimal layer and then in the modulation of proinflammatory factors via lectin-like oxidized LDL cholesterol receptor-1 (LOX-1).57 This link enhances the expression of vascular cell adhesion molecules (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and macrophage colony-stimulating factors (M-CSF) from endothelial cells and vascular smooth muscle cells.57 The inflammation role in the process of atherosclerosis is well-known.58 Furthermore, the implication of inflammatory factors in arterial stiffness has been observed in several studies.35,59 The mechanisms of inflammation lead to arterial stiffness through modifying the structure of arterial walls. In arterial wall, CRP can induce leukocytes to release matrix metalloproteinases to destroy the elastin fibers.60 CRP overexpression increases in vascular smooth muscle cells the production of bioapatite leading to promote arterial wall calcification.51 The effects of dyslipidemia towards arterial stiffness is mediated by inflammation, but this hypothesis remained unclear. A recent study has found that the cholesterol year score (CYS) was a significant factor of CRP.61 Indeed, CYS levels was depended by the duration and severity of dyslipidemia. Both CYS and CRP were independent factors of increased PWV. A synergistic effect of dyslipidemia and inflammation was observed for increased arterial stiffness.61 Increased inflammation was defined as CRP > 1 mg/dl, and in our study we observed that the threshold of .99 mg/dl was significant to determine increased arterial stiffness. Thus, we can suggest that CRP measurement could be beneficial for the management of arterial stiffness.

4.1 Strengths and limitations

The main strength of this study is the very large sample size of the cohort. The cross-sectional observational design limits the relationship of causality. Reverse causation cannot be ruled out. A potential limitation could stem from the utilization of the Pulse Trace device to measure arterial stiffness on account of greater variability in ASI values relative to other available devices.62 The UK Biobank study showed a low response rate of 5.5% and possible volunteer bias may be involved. Nevertheless, given the large sample size and high internal validity, these are unlikely to affect the reported associations.53,64 In addition, the study cohort consisted of middle-aged European participants, so our findings cannot be generalized to other age groups and ethnic populations. Nevertheless, the UK Biobank used standardized protocols to collect anthropometric data; this ensures replication of data collection for all volunteers regardless of when, where and by whom they are performed and adds validity to our results.65 Our study presents some limitations. Calculation of an ASI nomogram is dependent on the theoretical determination, which is expected to be different in another population study and potentially depends on the method used to measure ASI. Medical history and comorbidities were collected by self-reporting and physician assertion during medical examinations in health centers. The cross-sectional design of the study could represent a limitation since reverse causation cannot be excluded.

5 CONCLUSIONS

Ten clusters were identified with two specific clusters based on ASI nomogram determination. Independent factors differing these two clusters of participants with and without arterial stiffness were lipids (total cholesterol and triglycerides), smoking pack years, daily alcohol consumption, CRP and BMI. Cluster analysis allowed to highlight homogeneous participants profile with or without increased arterial stiffness. Determine the markers differing these clusters participates in the management of cardiovascular preventive strategies. Future clinical trials may involve these parameters to better understand their associations with arterial stiffness and their role in the increase of vascular stiffening in patients. These phenotyping could optimize the clinical trial designs.

ACKNOWLEDGMENT

This research received no external funding.

AUTHOR CONTRIBUTIONS

Conceptualization, Alexandre Vallée; methodology, Alexandre Vallée; formal analysis, Alexandre Vallée; writing—original draft preparation, Alexandre Vallée; The author has read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ORCID

Alexandre Vallée MD, PhD https://orcid.org/0000-0001-9158-4467

REFERENCES

1. Leoncini G, Ratto E, Viazzi F, et al. Increased ambulatory arterial stiffness index is associated with target organ damage in primary hypertension. Hypertension. 2006; 48:397-403. 
2. Ben-Shlomo Y, Spears M, Boustrud C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol. 2014; 63: 636-646. 
3. Said MA, Eppinga RN, Lipsic E, et al. Relationship of arterial stiffness index and pulse pressure with cardiovascular disease and mortality. J Am Heart Assoc. 2018;7:e007621.
4. Duprez DA, Cohn JN. Arterial stiffness as a risk factor for coronary atherosclerosis. Curr Atheroscler Rep.2007;9:139-144. 
5. Gao L, Lu D, Xia G, et al. The relationship between arterial stiffness index and coronary heart disease and its severity. BMC Cardiovasc Disord.2021:21:527.
6. Dregan A. Arterial stiffness association with chronic inflammatory disorders in the UK Biobank study. Heart Br Card Soc.2018;104:1257-1262.
7. Fernandes VRS, Polak JF, Cheng S, et al. Arterial stiffness is associated with regional ventricular systolic and diastolic dysfunction: the multi-ethnic study of atherosclerosis. Arterioscler Thromb Vasc Biol. 2008; 28: 194-201.
8. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006; 27: 2588-2605.
9. Vallée A, Cinaud A, Protogerou A, et al. Arterial stiffness and coronary ischemia: new aspects and paradigms. *Curr Hypertens Rep*. 2020; 22: 5.

10. Alty SB, Angarita-Jaimes N, Millasseau SC, et al. Predicting arterial stiffness from the digital volume pulse waveform. *IEEE Trans Biomed Eng*. 2007; 54: 2268-2275.

11. Sollinger D, Mohaupt MG, Wilhelm A, et al. Arterial stiffness assessed by digital volume pulse correlates with comorbidity in patients with ESRD. *Am J Kidney Dis*. 2006; 48: 456-463.

12. Millasseau SC, Kelly RP, Ritter JM, et al. Determination of age-related increases in large artery stiffness by digital pulse contour analysis. *Circulation*. 1979; 103: 371-377.

13. Vallée A, Safar ME, Blacher J. Application of a decision tree to establish factors associated with a nomogram of aortic stiffness. *J Clin Hypertension*. 2019; 21: 1484-1492.

14. Nichols W, O’Rourke M. *McDonald’s Blood Flow in Arteries Theoretical* and *Experimental and Clinical Principles*. 4th ed. Edward Arnold; 2006.

15. Vallée A. Arterial stiffness determinants for primary cardiovascular prevention among healthy participants. *J Clin Med*. 2022; 11: 2512.

16. Horiuchi Y, Tanimoto S, Latif AHMM, et al. Identifying novel phenotypes of acute heart failure using cluster analysis of clinical variables. *Int J Cardiol*. 2018; 262: 57-63.

17. Weatherall M, Shirtcliffe P, Travers J, et al. Use of cluster analysis to define COPD phenotypes. *Eur Respir J*. 2010; 36: 472-474.

18. Ahmad T, Pencina MJ, Schulte PJ, et al. Clinical implications of chronic heart failure phenotypes defined by cluster analysis. *J Am Coll Cardiol*. 2014; 64: 1765-1774.

19. Soudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015; 12: e1001779.

20. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018; 562: 203-209.

21. Berger A, Kiefer M. Comparison of different response time outlier exclusion methods: a simulation study. *Front Psychol*. 2021; 12: 675558.

22. Woodman RJ, Kingwell BA, Beilin LJ, et al. Assessment of central and peripheral arterial stiffness: studies indicating the need to use a combination of techniques. *Am J Hypertens*. 2005; 18: 249-260.

23. UK Biobank. *Arterial Pulse-Wave Velocity*. Accessed March, 2022. https://biobank.ndph.ox.ac.uk/ukb/docs/Pulsewave.pdf

24. UK Biobank. *Arterial Pulse-Wave Velocity*. Accessed March, 2022. https://biobank.ctsu.ox.ac.uk/crystal/docs/Bloodpressure.pdf

25. Coleman A, Freeman P, Steel S, et al. Validation of the Omron 705IT (HEM-759-E) oscillometric blood pressure monitoring device according to the British Hypertension Society protocol. *Blood Press Monit*. 2006; 11: 27-32.

26. Stang A, Moebus S, Mohlenkamp S, et al. Algorithms for converting random-zero to automated oscillometric blood pressure values, and vice versa. *Am J Epidemiol*. 2006; 164: 85-94.

27. Williams B, Mancia G, Spiering W, et al. Practice guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC task force for the management of arterial hypertension. *J Hypertens*. 2018; 36: 2284-2309.

28. Cherfan M, Vallée A, Kab S, et al. Unhealthy behavior and risk of hyper tension: the CONANCES population-based cohort. *J Hypertens*. 2019; 37: 2180-2189.

29. UK Biobank. Biomarker assay quality procedures: approaches used to minimise systematic and random errors (and the wider epidemiological implications). https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/biomarker_issues.pdf2019

30. Jani BD, McQueenie R, Nicholl BI, et al. Association between patterns of alcohol consumption (beverage type, frequency and consumption with food) and risk of adverse health outcomes: a prospective cohort study. *BMC Med*. 2021; 19: 8.

31. Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet Lond Engl*. 2018; 391: 1513-1523.

32. Daviet R, Aydogan G, Jagannathan K, et al. Associations between alcohol consumption and gray and white matter volumes in the UK Biobank. *Nat Commun*. 2022; 13: 1175.

33. Guo Q, Lu X, Gao Y, et al. Cluster analysis: a new approach for identification of underlying risk factors for coronary artery disease in essential hypertensive patients. *Sci Rep*. 2017; 7: 43965.

34. Thijsse M, Carter SE, Green DJ. Arterial structure and function in vascular ageing: are you as old as your arteries? *J Physiol*. 2016; 594: 2275-2284.

35. Jain S, Khera R, Corrales-Medina VF, Townsend RR, Chirinos JA. Inflammation and arterial stiffness in humans. *Atherosclerosis*. 2013; 237: 381-390.

36. Tang B, Luo F, Zhao J, et al. Relationship between body mass index and arterial stiffness in a health assessment Chinese population. *Medicine (Baltimore)*. 2020; 99: e18793.

37. Kappus RM, Fahs CA, Smith D, et al. Obesity and overweight associated with increased carotid diameter and decreased arterial function in young otherwise healthy men. *Am J Hypertens*. 2014; 27: 628-634.

38. Fahs CA, Smith DL, Horn GP, et al. Impact of excess body weight on arterial structure, function, and blood pressure in firefighters. *Am J Cardiol*. 2009; 104: 1441-1445.

39. Mack WJ, Islam T, Lee Z, et al. Environmental tobacco smoke and carotid arterial stiffness. *Prev Med*. 2003; 37: 148-154.

40. Celermajer DS, Sorensen KE, Georgakopoulos D, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation*. 1993; 88: 2149-2155.

41. Podzolkov VI, Bragina AE, Druzhinina NA, et al. Relation between tobacco smoking/electronic smoking and albuminuria/vascular stiffness in young people without cardiovascular diseases. *Kidney Blood Press Res*. 2020; 45: 467-476.

42. Hwang C-L, Muchira J, Hibner BA, et al. Alcohol consumption: a new risk factor for arterial stiffness? *Cardiovasc Toxicol*. 2022; 22: 236-245.

43. Tisdell DM, Gadberry JJ, Burke SL, et al. Dietary fat and alcohol in the prediction of indices of vascular health among young adults. *Nutr Burbank Los Angeles Cty Calif*. 2021; 84: 111120.

44. O’Neill D, Britton A, Brunner EJ, et al. Twenty-five-year alcohol consumption trajectories and their association with arterial aging: a prospective cohort study. *J Am Heart Assoc*. 2017; 6: e005288.

45. Nakanishi N, Kawashimo H, Nakamura K, et al. Association of alcohol consumption with increase in aortic stiffness: a 9-year longitudinal study in middle-aged Japanese men. *Ind Health*. 2001; 39: 24-28.

46. Kim MK, Shin J, Kweon S-S, et al. Harmful and beneficial relationships between alcohol consumption and subclinical atherosclerosis. *Nutr Metab Cardiovasc Dis*. 2014; 24: 767-776.

47. Phillips SA, Osborn K, Hwang C-L, et al. Ethanol induced oxidative stress in the vascularule: friend or foe? *Curr Hypertens Rep*. 2020; 16: 181-191.

48. Fletcher MJ, Varosy P, Kiefe CI, et al. Alcohol consumption, binge drinking, and early coronary calcification: findings from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Epidemiol*. 2005; 161: 423-433.

49. González-Reimers E, Santolaria-Fernández F, Martín-González MC, et al. Alcoholism: a systemic proinflammatory condition. *Circulation*. 2014; 20: 14660-14671.

50. Costantino S, Paneni F, Cosentino F. Ageing, metabolism and cardiovascular disease. *J Physiol*. 2016; 594: 2061-2073.

51. Aminuddin A, Lazim MRMLM, Hamid AA, et al. The association between inflammation and pulse wave velocity in dyslipidemia: an evidence-based review. *Mediators Inflamm*. 2020; 2020: 4732987.
52. Vallée A. Association between lipids and arterial stiffness for primary cardiovascular prevention in a general middle-aged European population. Front Cardiovasc Med. 2022; 9: 899841.

53. Vallée A, Lelong H, Lopez-Sublet M, et al. Association between different lipid parameters and aortic stiffness: clinical and therapeutic implication perspectives. J Hypertens. 2019; 37: 2240-2246.

54. Holven KB, Narverud I, Lindvig HW, et al. Subjects with familial hypercholesterolemia are characterized by an inflammatory phenotype despite long-term intensive cholesterol lowering treatment. Atherosclerosis. 2014; 233: 561-567.

55. Mazidi M, Heidari-Bakavoli A, Khayyatzadeh SS, et al. Serum hs-CRP varies with dietary cholesterol, but not dietary fatty acid intake in individuals free of any history of cardiovascular disease. Eur J Clin Nutr. 2016; 70: 1454-1457.

56. Mazidi M, Gao H-K, Vatanparast H, et al. Impact of the dietary fatty acid intake on C-reactive protein levels in US adults. Medicine (Baltimore). 2017; 96: e5736.

57. Barale C, Frascaroli C, Senkeev R, et al. Simvastatin effects on inflammation and platelet activation markers in hypercholesterolemia. BioMed Res Int. 2018; 2018: 6508709.

58. Raggi P, Genest J, Giles JT, et al. Role of inflammation in the pathogenesis of atherosclerosis and therapeutic interventions. Atherosclerosis. 2018; 276: 98-108.

59. Vallée A, Yannoutsos A, Temmar M, et al. Determinants of the aortic pulse wave velocity index in hypertensive and diabetic patients: predictive and therapeutic implications. J Hypertens. 2018; 36: 2324-2332.

60. Montero I, Orbe J, Varo N, et al. C-reactive protein induces matrix metalloproteinase-1 and -10 in human endothelial cells: implications for clinical and subclinical atherosclerosis. J Am Coll Cardiol. 2006; 47: 1369-1378.

61. Cheng HM, Ye ZX, Chiou KR, et al. Vascular stiffness in familial hypercholesterolaemia is associated with C-reactive protein and cholesterol burden. Eur J Clin Invest. 2007; 37: 197-206.

62. DeLoach SS, Townsend RR. Vascular stiffness: its measurement and significance for epidemiologic and outcome studies. Clin J Am Soc. 2008; 3: 184-192.

63. Richiardi L, Pizzi C, Pearce N. Commentary: representativeness is usually not necessary and often should be avoided. Int J Epidemiol. 2013; 42; 1018-1022.

64. Rothman KJ, Gallacher JE, Hatch EE. Why representativeness should be avoided. Int J Epidemiol. 2013; 42: 1012-1014.

65. Vallée A. Association between serum uric acid and arterial stiffness in a large-aged 40–70 years old population. J Clin Hypertens. 2022; 24: 885-897. https://doi.org/10.1111/jch.14527

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Vallée A. Arterial stiffness nomogram identification by cluster analysis: A new approach of vascular phenotype modeling. J Clin Hypertens. 2022;24:1415–1426. https://doi.org/10.1111/jch.14571