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Inflammation and Aortic Stiffness: An Individual Participant Data Meta-Analysis in Patients With Inflammatory Bowel Disease

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***Background*—**The recent finding that aortic pulse wave velocity (aPWV) is increased in patients with inflammatory bowel disease may explain why the cardiovascular risk is increased despite the low prevalence of traditional cardiovascular risk factors. We aimed to test whether inflammation is associated with aortic stiffening in this setting after adjustment for major confounders and to perform subgroup analyses.

***Methods and Results*—**A systematic literature search for aPWV in inflammatory bowel disease was performed using PubMed, Scopus, Web of Science, and Google Scholar databases (last accessed May 7, 2017). Inclusion criterion was peer-reviewed publications on clinical studies reporting original data. This study followed the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data 2015 guidelines. Data were provided for 4 cohorts in 3 countries (151 participants with ulcerative colitis, 159 with Crohn's disease, and 227 control patients). Using aPWV, cohort-specific *z* scores were calculated after $\log_e$-transform and combined in meta-analysis to form pooled effects using a random-effects model. Compared with controls, aPWV was increased in patients with Crohn's disease (mean difference 0.78 *z* score; 95% confidence interval, 0.56–1.00 *z* score [$P<0.001$]) and ulcerative colitis (mean difference 0.75 *z* score; 95% confidence interval, 0.52–0.97 *z* score [$P<0.001$]). In an outlier-robust multivariate linear regression model adjusted for prespecified confounders, aPWV was associated with disease duration (years, $\beta=0.05$ *z* score; 95% confidence interval, 0.02–0.08 *z* score [$P<0.001$]) and white blood cell count (billion cells/L, $\beta=0.07$ *z* score; 95% confidence interval, 0.02–0.11 *z* score [$P=0.002$]) but not with markers of acute inflammation (C-reactive protein and erythrocyte sedimentation rate), cardiovascular risk factors, and therapy.

***Conclusions*—**The increased aPWV reported in patients with inflammatory bowel disease is associated with inflammation.

***Clinical Trial Registration*—**URL: http://www.crd.york.ac.uk. Unique identifier: PROSPERO 2016: CRD42016053070. **(*J Am Heart Assoc*. 2017;6:e007003. DOI: 10.1161/JAHA.117.007003.)**

Key Words: arterial stiffness • cardiovascular complications • Crohn's disease • inflammation • pulse wave velocity • ulcerative colitis

Aortic pulse wave velocity (aPWV) is a well-accepted vascular biomarker,[1] an independent cardiovascular risk factor,[2] and is included in the latest European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines as a marker of subclinical target organ damage.[3] Inflammation is associated with arterial stiffening in healthy individuals,[4] patients with hypertension,[5] and in patients with several chronic inflammatory diseases, including rheumatoid

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Accompanying Tables S1 through S5 and Figure S1 are available at http://jaha.ahajournals.org/content/6/10/e007003/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Aortic pulse wave velocity (aPWV) was increased in patients with inflammatory bowel disease after adjustment for major confounders.
- aPWV was associated with disease duration and white blood cell count.
- aPWV was not associated with markers of acute inflammation (C-reactive protein and erythrocyte sedimentation rate), cardiovascular risk factors, and therapy.

What Are the Clinical Implications?

- aPWV, the reference measure of aortic stiffness, is a well-accepted vascular biomarker, an independent cardiovascular risk factor, and is included in the latest European Society of Hypertension/European Society of Cardiology guidelines as a marker of subclinical target organ damage.
- The findings of this individual participant data meta-analysis indicate the potential clinical use of the measure of aPWV in patients with inflammatory bowel disease.

arthritis,[6] systemic vasculitis,[7] and systemic lupus erythematosus.[6] In several chronic inflammatory diseases, arterial stiffening may be dependent on disease duration.[6] Inflammatory bowel diseases (IBDs) such as Crohn's disease (CD) and ulcerative colitis (UC) are characterized by both chronic, systemic inflammation and episodes of acute inflammation during relapses. Although patients with IBD seem to have a low prevalence of classic cardiovascular risk factors, including obesity, dyslipidemia, and hypertension, the observed risk of coronary heart disease and cerebrovascular accident is increased.[8] We previously proposed that this apparent contradiction, reported as "inflammatory bowel disease paradox," could be at least in part explained by the chronic inflammation and consequent arterial stiffening.[9] In this regard, a significant relationship between aortic stiffness and left ventricular systolic and diastolic dysfunction in patients with IBD has recently been reported.[10] Here, we aimed to perform an individual participant data (IPD) meta-analysis to determine whether patients with IBD have an increased aPWV after adjustment for major confounders, and to test whether inflammation is associated with aortic stiffening in this setting.

Methods

Study Selection

In accordance with the PRISMA-IPD (Preferred Reporting Items for Systematic Review and Meta-Analyses of IPD) 2015 guidelines,[11] our systematic review protocol was registered with the PROSPERO (International Prospective Register of Systematic Reviews) on December 10, 2016, and it was last updated on February 2, 2017 (registration No. CRD42016053070).

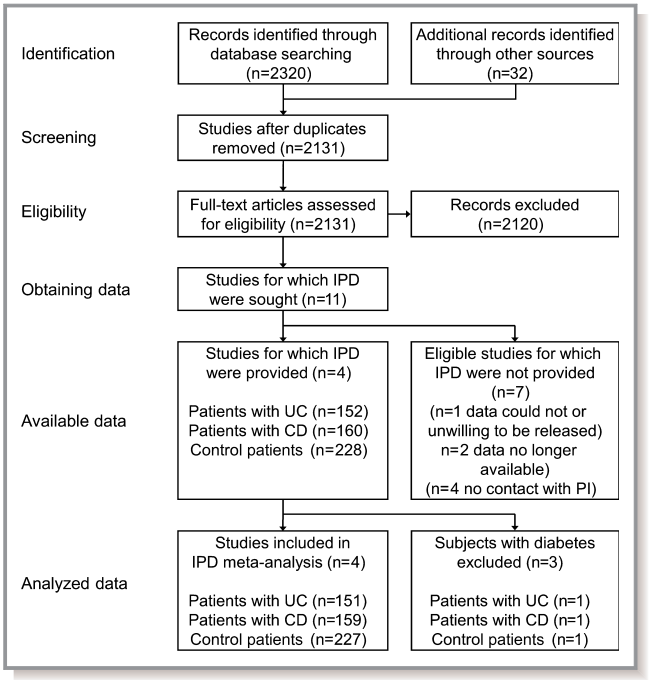

Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) of individual participant data (IPD) flow diagram illustrating the process of study identification. CD indicates Crohn's disease; PI, principal investigator; UC, ulcerative colitis.

The prespecified inclusion criterion included peer-reviewed publications reporting original data in humans. The PRISMA-IPD 2015 flow diagram illustrating the process of study identification is shown in Figure 1. Two independent reviewers (L.Z. and P.L.) undertook a systematic search in MEDLINE, Web of Science, and Google Scholar databases without restrictions on the year of publication from December 2016 to May 2017. The search terms used were "arterial stiffness," "vascular stiffness," or "pulse wave velocity" in combination with "inflammatory bowel disease," "inflammatory bowel diseases," "Crohn's disease," or "ulcerative colitis." The reference lists of the analyzed articles were also searched. These articles were subjected to the same selection procedures. In cases of doubt on the inclusion of an article, a decision was achieved by consensus. A total of 2131 articles were assessed for eligibility. Most of them (n=2120) were excluded because aPWV values were unavailable in patients with IBD. Corresponding authors of 11 eligible cohorts[12–22] were invited by email, mail, and phone, and during participation at international meetings to provide anonymized individual-level patient data (Table S1), including aPWV and a range of covariates (age, sex, blood pressure, heart rate, body mass index, smoking status, lipids, comorbidities, markers of inflammation, and therapy). Seven of 11 cross-sectional studies potentially eligible for inclusion in this IPD

meta-analysis were excluded (n=1, data could not or were unable to be released[18]; n=2, data were no longer available[16,17]; n=4, no response from the principal investigator[19–22]). The remaining 4 articles[12–15] were included in this IPD meta-analysis. IPD data were checked, including range and consistency checks, to ensure the accuracy and completeness of data. To evaluate the risk of bias, we compiled a checklist of items relevant to our IPD review question (Table S2). Two independent aggregate meta-analyses were also performed using respective data of the 4 articles with available IPD[12–15] and of the 7 articles that were excluded because the IPD were unavailable.[16–22] The ethics committee of the University of Catania approved the study protocol.

Definitions of Cardiovascular Risk Factors

Cardiovascular risk factors were defined according to the ESH/ESC guidelines for the management of arterial hypertension.[3] Dyslipidemia was defined as total cholesterol >4.9 mmol/L (190 mg/dL), and/or low-density lipoprotein cholesterol >3.0 mmol/L (115 mg/dL), and/or high-density lipoprotein cholesterol (men <1.0 mmol/L [40 mg/dL], women <1.2 mmol/L [46 mg/dL]), and/or triglycerides >1.7 mmol/L (150 mg/dL), and/or use of lipid-lowering agents. Hypertension was defined as systolic/diastolic blood pressure ≥140/90 mm Hg and/or use of antihypertensive drugs. Obesity was defined as body mass index ≥30 kg/m^2 (height^2), and older age was defined as 55 years or older in men and 65 years and older in women.

Statistical Analysis

The main data were summarized and reported as mean (SD) and number (percentage) for continuous and categorical variables, respectively. Positively skewed continuous variables were reported as median and interquartile range, and after $\log_e$-transformed, data were reported as mean (SD). aPWV measurement is influenced by the method used to measure the transit distance and software algorithm. According to the latest guidelines,[3,23] the transit distance measurement was standardized using direct distance and a scaling factor of 0.8 to obtain the actual aPWV. The Arteriograph pulse wave velocity ($PWV_{Arteriograph}$) was converted in SphygmoCor aPWV calculated using the direct distance scaled for 0.8 ($aPWV_{SphygmoCor}$) according to the relationship previously found by Ring et al[24]:

$$PWV_{Arteriograph}(m/s) = 3.2846 + 0.6152 \times aPWV_{SphygmoCor}(m/s)$$

However, because our main goal was to examine the relative value of the aPWV within a study and then pool these estimates, we used the cohort-specific *z* score of $\log_e$-transformed aPWV in the analyses, as aPWV values were positively skewed. Thus, effect estimates for each study reflect the change for a 1-SD increase in $\log_e$ aPWV. A cohort-specific *z* score was calculated as previously reported,[2] according to the following formula: *z* score=((individual value−population mean)/population SD), where the mean values and SD were calculated in the controls of each cohort. Clinical and hemodynamic variables were compared using Kruskal-Wallis Test for continuous variables with Dunn test for multiple comparison and chi-square tests for categorical variables at univariate analyses. To study the determinants of the aPWV, we performed an outlier-robust multivariate linear regression analysis.

In sensitivity analyses, we fitted all models using the untransformed data but still assessed by using *z* scores within studies (Figure S1). The sensitivity of results to missing covariate data was examined by performing an outlier-robust multivariate linear regression analysis in all patients and in those with available heart rate and white blood cells (Table 1). The generalizability of results was tested performing an aggregate meta-analysis using data of the 4 studies included in this individual participant data meta-analysis[12–15] and another aggregate meta-analysis using data of the remaining 7 eligible studies[16–22] excluded from this individual participant data meta-analysis (Figure 2).

The prespecified outcome addressed was the aPWV, a reference measure of aortic stiffness. Cohort-specific *z* scores of $\log_e$-transformed aPWV were combined in meta-analysis to form pooled effects using a fixed-effect model. Results of a random-effects model were also reported in Figure 3A through 3D.

The following protocol prespecified potential effect modifiers were tested: sex, known cardiovascular risk factors, IBD, therapy (anti–tumor necrosis factor, salicylates, and other therapies), and active disease. For each potential effect modifier considered, we estimated the strata-specific effect of the aPWV in each study separately. These estimates were pooled across studies, which were then tested to determine whether the aPWV differed between strata.

The following potential confounding factors were prespecified: age, sex, mean blood pressure, known cardiovascular risk factors, and study of origin. Consequently, we performed linear regression analyses adjusted for these confounding factors using the $\log_e$-transformed aPWV as a dependent variable, and UC and CD as independent variables. In patients with UC and in those with CD, we also tested the hypothesis that the aPWV would increase according to disease duration, a marker of chronic inflammation. Heterogeneity was tested using I^2 according to the following formula:

$$I^2 = 100\% \times (Q - df)/Q$$

where Q is Cochran heterogeneity statistic and df is the degrees of freedom. A value of 0% indicates no observed

Table 1. Outlier-Robust Multivariate Linear Regression Analyses for aPWV

Determinants of aPWV, *z* Score $\log_e$(m/s)	Units	R^2 Increment	ß Coefficients (95% CI)	*P* Value
Analysis performed in all patients*				
Inflammatory bowel disease		0.09		
Ulcerative colitis	Yes		0.64 (0.46–0.81)	<0.001
Crohn's disease	Yes		0.76 (0.59–0.93)	<0.001
Analysis performed in 449 patients with available heart rate and white blood cells†				
Inflammatory bowel disease		0.09		
Ulcerative colitis	Yes		0.65 (0.46–0.84)	<0.001
Crohn's disease	Yes		0.74 (0.55–0.93)	<0.001

aPWV indicates aortic pulse wave velocity; CI, confidence interval.
*Adjusted for age, sex, mean blood pressure, dyslipidemia, obesity, older age, smoking, and the study of origin.
†Adjusted for age, sex, mean blood pressure, heart rate, dyslipidemia, obesity, older age, smoking and the study of origin.

heterogeneity, and larger values show increasing heterogeneity.[25] The significance level was set at a 2-sided *P* value <0.05.

Results

The flow chart of the selection of papers in the systematic review is shown in Figure 1. Inclusion and exclusion criteria, main data of eligible studies, and algorithms and devices used to measure the aPWV are presented in Tables S3 and S4. The 4 studies included in this IPD meta-analysis included 228 control patients, 152 patients with UC, and 160 patients with CD. No significant issue was identified in checking IPD. The risk of bias was judged low since all of the studies included in this IPD meta-analysis reached a score ≥75% (higher values indicates no risk of bias). Among the 4 cohorts with available IPD, only 3 individuals with diabetes mellitus were reported, and all of them were enrolled in a single study.[14] To reduce heterogeneity between studies, we excluded these 3 individuals with diabetes mellitus from analyses. Consequently, 227 control patients, 151 patients with UC, and 159 patients with CD were finally included in this IPD meta-analysis. Repeating the analyses with the individuals with diabetes mellitus did not substantially change the results. Moreover, because participants enrolled in the 4 studies with available IPD presented with cardiovascular risk factors, we performed a subgroup analysis of a reference population of patients without known cardiovascular risk factors (70 patients with CD, 64 patients with UC, and 109 control patients). All studies had information on all principal variables, except for heart rate, which was available in 3 studies,[12–14] and white blood cell count, which was available in patients with IBD enrolled in 3 studies.[12–14] We did not identify any significant issues after assessing the individual participant data. Detailed data of individuals enrolled in this IPD meta-analysis are shown in Table S5.

aPWV is Increased in Patients With UC and CD

Compared with controls, the aPWV was higher in patients with UC (I^2=73.0%; mean difference 0.75 *z* score; 95% confidence interval [CI], 0.52–0.97 *z* score [*P*<0.001]) (Figure 3A) and in those with CD (I^2=40.1%; mean difference 0.78 *z* score; 95% CI, 0.56–1.00 *z* score [*P*<0.001]) (Figure 3B). After excluding individuals with known cardiovascular risk factors, the mean difference of the aPWV increased in patients with UC (I^2=0.0%; mean difference 0.82 *z* score; 95% CI, 0.51–1.12 *z* score [*P*<0.001]). The increased aPWV in patients with IBD was also confirmed in an outlier-robust multivariate linear regression analysis adjusted for major confounders (Table 1). The results of subgroup analyses are presented in Figure 3E and 3F.

aPWV was significantly associated with heart rate in all groups (UC: ß 0.27 heart rate [10 beats/min]; 95% CI, 0.14–0.40 heart rate [*P*<0.001]; CD: ß 0.31 heart rate [10 beats/min]; 95% CI, 0.16–0.45 heart rate [*P*<0.001]; control patients: ß 0.18 heart rate; 95% CI, 0.07–0.28 heart rate [*P*=0.001]) (Figure 4A).The association between aPWV and age is reported in Figure 4B.

aPWV and Markers of Inflammation

In the linear regression model, disease duration and total white blood cell count were positively associated with the aPWV (Figure 4C and 4D). These results were confirmed in a robust multivariate linear regression analysis adjusted for the prespecified confounding factors, performed in a group of 266 patients with IBD without missing data (Table 2). A positive interaction between age and the disease duration was also reported (ß age×disease duration [100 years^2]: 0.26 m/s; 95% CI, 0.03–0.48 m/s [*P*=0.03]). C-reactive protein level and erythrocyte sedimentation rate were not associated with aPWV.

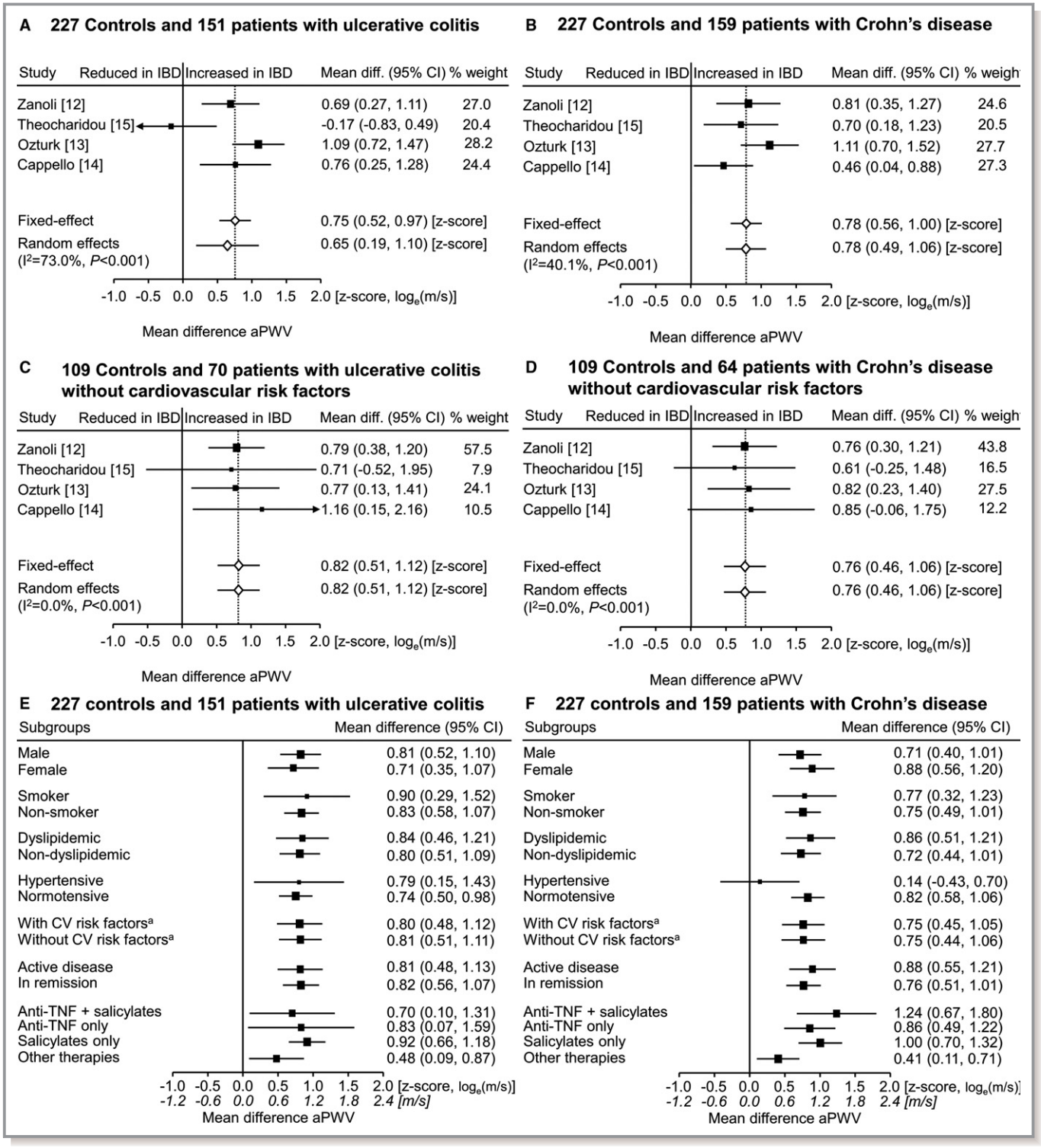

Figure 2. Forest plot for aortic pulse wave velocity (aPWV) in patients with ulcerative colitis and in those with Crohn's disease compared with controls sorted by year of publication. A and B, Whole patients; (C and D) individuals without obesity, older age, dyslipidemia, hypertension, and smoking; (E and F) prespecified subgroups analyses. *Dyslipidemia, hypertension, obesity, age (men ≥55 years, women ≥65 years), and smoking. Anti-TNF indicates anti–tumor necrosis factor; CI, confidence interval; CV, cardiovascular; IBD, inflammatory bowel disease. Weights are from random-effects analysis.

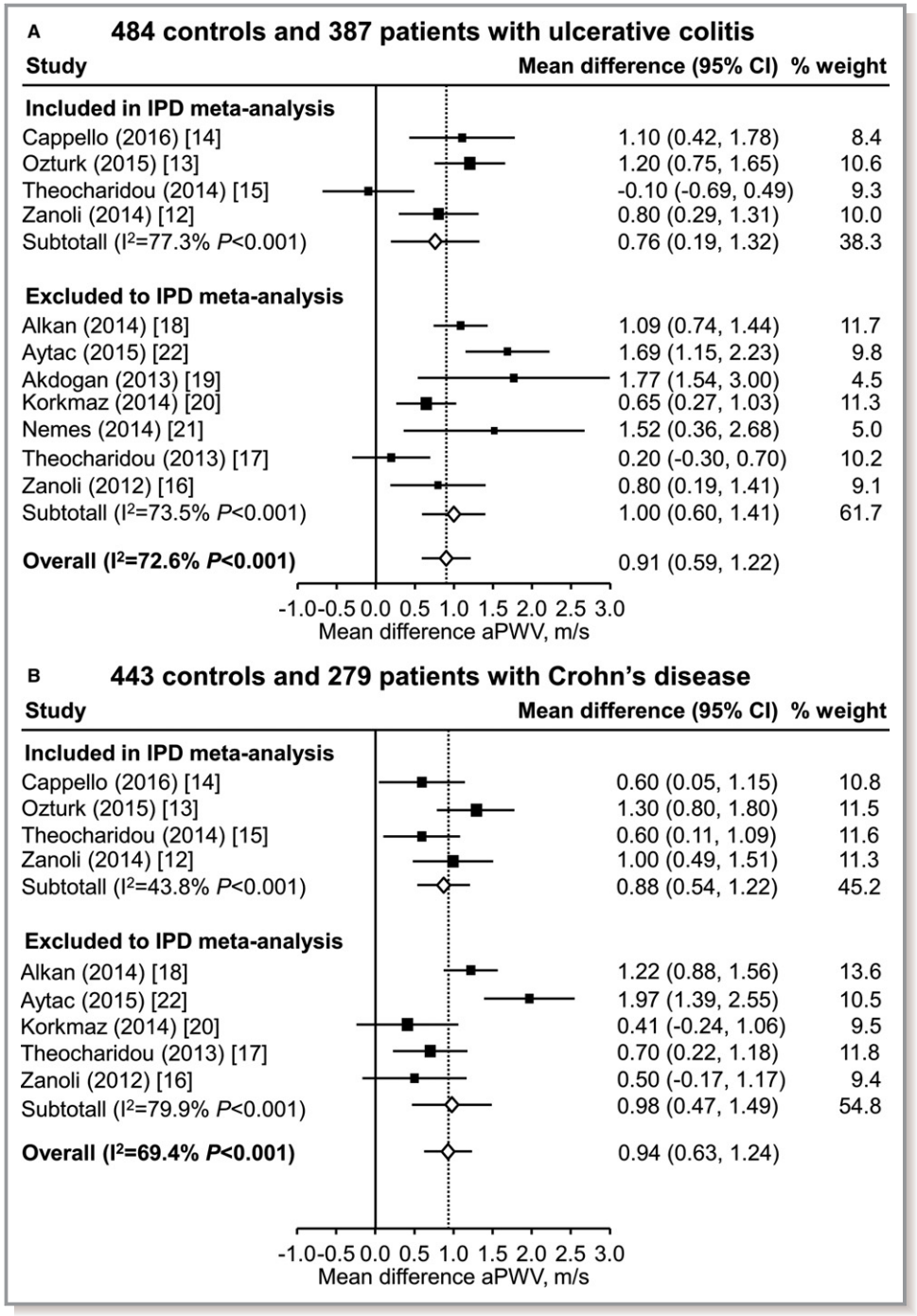

Figure 3. Forest plot of the 11 eligible studies. A, Patients with ulcerative colitis. B, Patients with Crohn's disease. CI indicates confidence interval; IPD, individual participant data.

aPWV and Therapy

The association between aPWV and therapy is shown in Figure 3. In an outlier-robust multivariate linear regression model adjusted for the prespecified confounding factors (Table 2), therapy was weakly associated with aPWV. This association was lost in a model adjusted for both prespecified confounding factors and markers of inflammation (fully adjusted model of Table 2).

Discussion

The main finding of this IPD meta-analysis is that aortic stiffness, assessed by the measurement of aPWV, was increased in patients with UC and in those with CD and dependent on disease duration and white blood cell count but not on known cardiovascular risk factors and therapy.

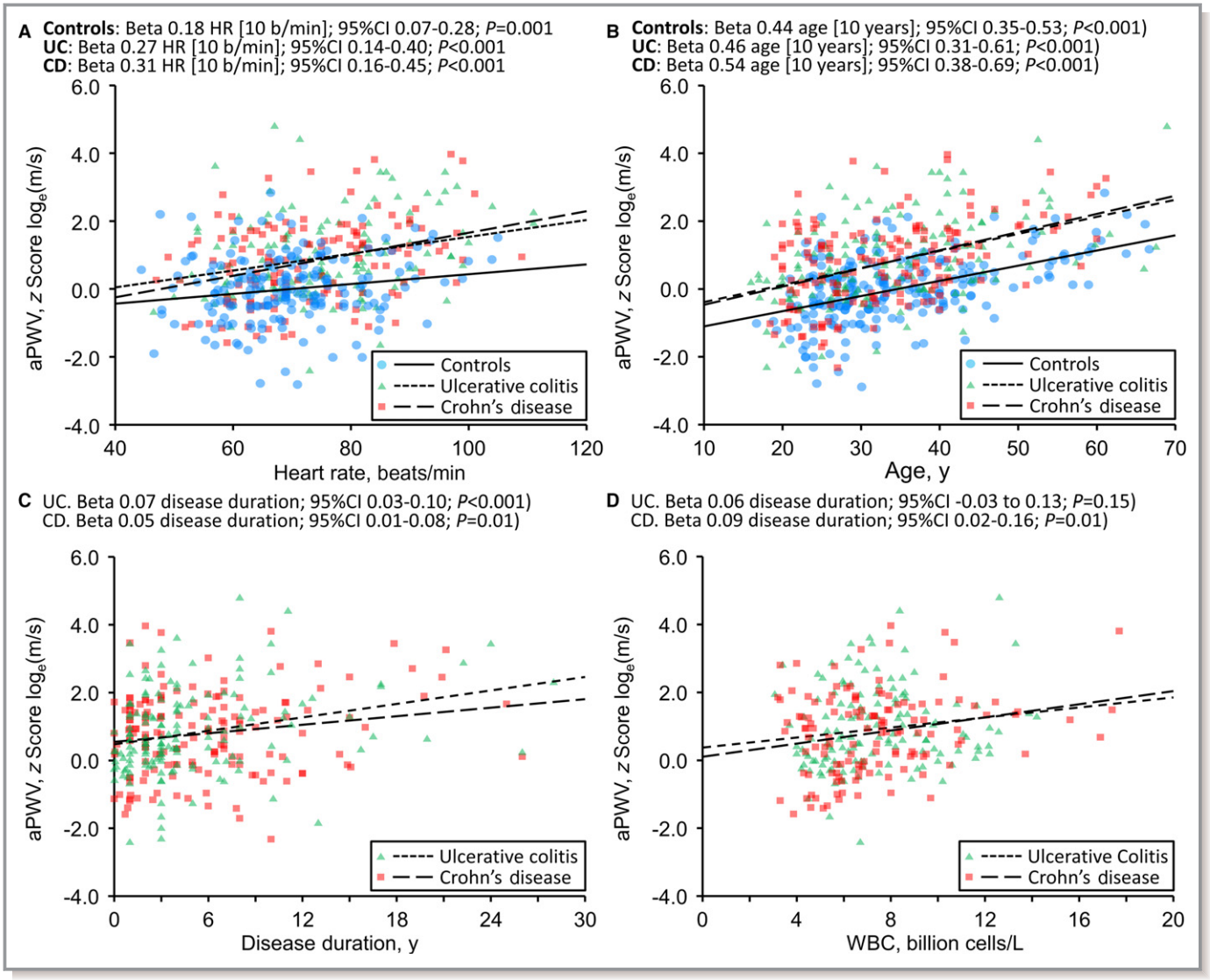

Figure 4. Association between aortic pulse wave velocity (aPWV) and heart rate (A), age (B), disease duration (C), and white blood cells (WBCs) (D). b/min indicates beats per minute; CD, Crohn's disease; CI, confidence interval; HR, heart rate; UC, ulcerative colitis.

Our results extend the findings of 2 aggregate meta-analyses,[26,27] which showed that the aPWV is increased in patients with IBD, by adding new data, calculating the mean difference of the aPWV between patients with IBD and control patients in several subgroups, and testing the factors associated with the aPWV, including several markers of inflammation, after adjusting for prespecified confounding factors (age, sex, mean blood pressure, known cardiovascular risk factors, and study of origin). Interestingly, our results show that the apparent absence of an increase of aPWV in patients with UC enrolled in the study by Theocharidou et al[15] could be explained by the confounding effect of known cardiovascular risk factors since, after excluding patients with known cardiovascular risk factors, the aPWV was confirmed to also be higher in patients with UC in the cohort of Theocharidou et al.

Moreover, we tested the association between aPWV and several markers of inflammation and reported that the aPWV was associated with disease duration, a surrogate marker of chronic inflammatory burden, and white blood cell count, a surrogate marker of inflammation associated with active infection, but not with known cardiovascular risk factors (Table 2, model D). These results would suggest that inflammation has a pivotal role in aortic stiffening in patients with IBD, more important than that of known cardiovascular risk factors. However, since patients effectively treated have better nutrition and are more likely to be exposed to cardiovascular risk factors, in addition to inflammation, it would not be surprising that in the near future, with the improvement of therapy, the prevalence and role of classic cardiovascular risk factors will increase in patients with IBD.

Table 2. Robust Multivariate Linear Regression Analyses for aPWV Performed in 266 Patients With IBD With Available Heart Rate and White Blood Cells

Determinants of aPWV, *z* Score $\log_e$(m/s)	Units	R^2 Increment	ß Coefficients (95% CI)	*P* Value
Univariate analyses				
Disease duration	Years	0.09	0.07 (0.05–0.10)	<0.001
White blood cells	Billion cells/L	0.03	0.07 (0.02–0.12)	0.005
C-reactive protein	$\log_e$(billion nmol/L)	…	…	0.69
Erythrocyte sedimentation rate	$\log_e$(mm/h)	…	…	0.74
Therapy		0.06		
Other	Yes		0.00	
Salicylates	Yes		0.59 (0.26–0.92)	<0.001
Anti-TNF	Yes		0.52 (0.01–1.03)	<0.05
Anti-TNF+salicylates	Yes		1.09 (0.47–1.71)	<0.001
Multivariate analyses adjusted for prespecified confounding factors[†]				
Disease duration	Years	0.03	0.05 (0.02–0.07)	<0.001
White blood cells	Billion cells/L	0.02	0.07 (0.03–0.11)	0.001
Therapy		0.02		
Other	Yes		0.00	
Salicylates	Yes		0.13 (−0.28 to 0.53)	0.55
Anti-TNF	Yes		0.41 (0.001–0.812)	0.049
Anti-TNF+salicylates	Yes		0.57 (−0.001 to 1.14)	0.05
Full model also adjusted for prespecified confounding factors[†]				
Disease duration	Years	0.03	0.05 (0.02–0.08)	<0.001
White blood cells	Billion cells/L	0.02	0.07 (0.02–0.11)	0.002
Therapy		0.01		
Other	Yes		0.00	
Salicylates	Yes		0.11 (−0.29 to 0.51)	0.59
Anti-TNF	Yes		0.21 (−0.19 to 0.62)	0.30
Anti-TNF+salicylates	Yes		0.46 (−0.10 to 1.02)	0.11

Anti-TNF indicates anti–tumor necrosis factor; aPWV, aortic pulse wave velocity; IBD, inflammatory bowel disease.
[†]Adjusted for age, sex, mean blood pressure, obesity, older age, dyslipidemia, smoking, and study of origin.

Interestingly, in a fully adjusted model that included the therapy, the associations between markers of inflammation and aPWV remained almost the same (Table 2, model E). This finding is potentially clinically relevant, and it could suggest that therapy has a weak effect on the association between inflammation and arterial stiffness in patients with IBD or that the effect of therapy on arterial stiffness is mediated by the reduction of inflammation. However, longitudinal studies are required to answer this question.

Another important finding of this study was that chronic inflammation increased aortic stiffness at any given age. This suggests that arterial stiffening provided by IBD could be additive to that of normal aging.

Finally, we did not find any association between aPWV and C-reactive protein level and erythrocyte sedimentation rate, 2 markers of active inflammation. These results were confirmed even in subgroup analyses performed separately in patients with UC and in those with CD. As IBD are characterized by chronic inflammation and episodes of reactivation of the disease, our lack of a finding could suggest that a single measurement of markers of active inflammation may not be sufficient to provide information on the amount of chronic inflammation over time. However, longitudinal studies are needed to confirm this hypothesis.

Study Strengths and Limitations

The present study has several strengths. First, as a result of the study design, we performed a meta-analysis after excluding known cardiovascular risk factors. Our results suggest that the

comparable aPWV between controls and patients with UC reported by Theacharidou et al[15] was attributable to the confounding effect of the cardiovascular risk factors that could mask the effects of inflammation on aPWV. In this regard, after excluding individuals with cardiovascular risk factors, we found that the aPWV was also increased in patients with UC in the study by Theacharidou et al.[15] Second, to evaluate the risk of bias, we performed an aggregate meta-analysis using data of the 4 studies included in this individual participant data meta-analysis and another aggregate meta-analysis using data of the remaining 7 eligible studies excluded from this individual participant data meta-analysis (Figure 2). Results of these two aggregate meta-analyses were similar both in patients with UC and in those with CD. Third, we tested several markers of acute and chronic inflammation, and we found that the disease duration and total white blood cell count were associated with increased aPWV. This finding is clinically relevant and confirms the role of inflammation on arterial stiffening in patients with IBD. Finally, the number of patients included in this IPD meta-analysis enabled us to perform subgroup analyses and to adjust for major confounders.

This study also has some limitations. First, we reported only data of cross-sectional studies. Therefore, since causation cannot be determined for any of the observed relationships, including the effect of therapy on the aPWV and whether anti–tumor necrosis factor therapy is effective for reducing arterial stiffness in patients with IBD remain unknown, longitudinal studies are required to answer this question. Second, all of the studies included in this IPD meta-analysis included patients from southern Europe, which reflects the geographical distribution of the studies published on the date of publication of this meta-analysis. Third, among the 4 studies included in this study, the aPWV values were measured with different devices. Fourth, in this meta-analysis, only 21 patients with CD had hypertension. This would reasonably explain why patients with hypertension with CD did not have a significantly higher aPWV than controls. Finally, the small number of patients on treatment with antihypertensive drugs (n=6) and lipid-lowering agents (n=4) was not sufficient to perform subgroup analyses.

Perspectives

There are important clinical and research implications to the findings of this study. First, the cardiovascular risk of patients with UC and CD has been considered low for decades. Therefore, the role of nontraditional cardiovascular risk factors has probably been overlooked in these diseases. During the past decade, the growing evidence of the increased risk of ischemic heart disease and cerebrovascular accidents raises the interest of the role of nontraditional cardiovascular risk factors in patients with IBD.[8] In this regard, the results of this IPD meta-analysis open a new area of cardiovascular research in patients with IBD. Although there is evidence that aortic stiffness is increased in patients with IBD and associated with markers of inflammation, the mechanisms at the basis of arterial stiffening in this model of inflammation has been only hypothesized.[28] The finding that endothelial function is impaired in patients with IBD suggests that functional arterial stiffening could be involved.[27,28] Whether structural arterial stiffening is involved in these patients remains unknown. Finally, since increased aortic stiffness is associated with cardiovascular events in the general population and in patients with chronic inflammation, the findings of this IPD meta-analysis indicate the potential clinical use of the measure of aPWV in patients with IBD.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Individual participant data requested.

- anonymous patient code	- central systolic blood pressure [mmHg]
- date of examination	- central diastolic blood pressure [mmHg]
- group [controls/CD/UC]	- central mean blood pressure [mmHg]
- date of birth or age [years]	- active disease [yes/no]
- sex [male/female]	- any score of activity used
- height [m]	- anti-tumor necrosis factor therapy [yes/no]
- weight [kg]	- salicylates therapy [yes/no]
- Smoking [yes/no]	- disease duration [years]
- Total cholesterol [mg/dl]	- any marker of inflammation available (C-reactive protein, erythrocyte sedimentation rate, white blood cells, neutrophils, lymphocytes, monocytes)
- HDL cholesterol [mg/dl]	
- LDL cholesterol [mg/dl]	- carotid-femoral PWV [m/s]
- triglycerides [mg/dl]	- augmentation index
- brachial systolic blood pressure [mmHg]	- hypertension [yes/no]
- brachial diastolic blood pressure [mmHg]	- hyperlipidaemia [yes/no]
- heart rate [b/min]	- diabetes [yes/no]

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis

Table S2. Quality assessment (risk of bias).

Selection of patients	Was the selection of patients conducted in such a way to avoid bias?	Yes: patients with inflammatory bowel disease and control subjects were matched for known cardiovascular risk factors No: patients with inflammatory bowel disease and control subjects were matched for known cardiovascular risk factors Unclear: no information about the manner in which patients were recruited is given
Study sample-size	Has the study sample-size been explained in detail?	Yes: a sample-size calculation is available No: a sample-size calculation is unavailable
Pulse wave velocity measurement	Has the device and method used to measure carotid-femoral pulse wave velocity been reported in detail?	Yes: the device and method used is available No: the device and method used is unavailable
Cardiovascular risk factors	Have patients with known cardiovascular risk factors been identified or excluded from the study?	Yes: data of all pre-specified cardiovascular risk factors (smoking, dyslipidemia, hypertension, obesity, smoking) are available No: data of all pre-specified cardiovascular risk factors (smoking, dyslipidemia, hypertension, obesity, smoking) are unavailable

Score: Yes=1; No/Unclear=0. All the study included in this individual participant data meta-analysis reach a score ≥3.

Table S3. Studies reporting aortic pulse wave velocity in subjects with inflammatory bowel disease sorted by year of publication.

Authors (year of publication)	Body mass index, Kg/m^2		Systolic/diastolic blood pressure, mm Hg		Age, years				Aortic pulse wave velocity, m/s			
	IBD	Controls	IBD	Controls	IBD			Controls	IBD			Controls
					CD	UC	All		CD	UC	All	
Studies included in the individual participant data meta-analysis												
Zanoli L (2014) [1]	24.2±4.8	24.7±4.3	118±12/70±11	115±12/70±9	36±14	38±14	37±14	38±13	8.0±1.6	7.8±1.7	7.9±1.7	7.0±1.1
Theocharidou E. (2014) [2]	23.7 (16.5-37.4)	24.3 (18.0-36.3)	115±14/71±12	117±16/72±11	38±10	32±11	36±10	37±11	7.0±1.2	6.3±1.2	6.8±1.2	6.4±0.9
Ozturk K. (2015) [3]	23.7±3.7	23.6±2.8	119±15/72±8	117±12/70±8	30±9	33±8	32±9	31±7	8.2±1.7	8.1±1.6	8.1±1.6	6.9±1.0
Cappello M. (2016) [4]	22.3±3.6	24.0±4.4	118±19/75±14	118±13/76±11	32±7	31±10	32±8	30±6	8.6±1.3	9.1±1.4	8.7±1.3	8.0±1.2
Studies excluded to the individual participant data meta-analysis												
Zanoli L. (2012) [5]	23.5±3.6	24.3±2.8	115±10/66±10	113±11/68±8	29±9	31±8	30±9	31±7	6.5±1.5	6.8±1.3	6.6±1.4	6.0±0.8
Theocharidou E. (2013) [6]	23.7 (16.5-37.2)	24.3 (18.3-34.2)	86 (62-107)	86 (41-113)	38±10	35±12	38 (18-60)	38 (22-60)	6.8±1.3	6.3±1.1	6.6±1.3	6.1±0.9
Akdogan RA (2013) [7]	27.0±4.4	27.5±4.1	n.a.	n.a.	n.a.	48±15	48±15	45±8	n.a.	8.9±3.0	8.9±3.0	7.2±1.7
Korkmaz H. (2014) [8]*	26.6±2.6	26.8±3.1	105±9/74±8	104±10/72±9	n.a.	n.a.	43±13	45±11	n.a.	n.a.	6.4±1.3	6.0±1.3
Korkmaz H. (2014) [8]†	25.3±3.5	26.8±3.1	107±6/75±7	104±10/72±9	n.a.	n.a.	45±10	45±11	n.a.	n.a.	6.6±1.0	6.0±1.3
Alkan E. (2014) [9]	23.7±1.9	23.7±1.6	118±10/74±8	117±10/71±7	n.a.	n.a.	38±7	38±6	7.2±0.7	7.1±0.8	7.2±0.9	6.0±0.5
Nemes A (2014) [10]	27.4±4.1	26.4±5.2	124±18	123±9	n.a.	39±12	39±12	39±11	n.a.	9.2±1.6	9.2±1.6	7.7±1.4
Aytaç E (2015) [11]	24.0	25.4±1.9	121/75	108±10/59±7	39±10	45±12	n.a.	42±7	9.6±1.4	9.3±1.3	n.a.	7.6±0.3

Data are presented as percentages (%), counts, mean ± standard deviation or median (range). n.a., not available; CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease. *in remission; †active disease.

Table S4. Algorithms and devices used to measure aortic pulse wave velocity.

Authors (ranked by year of publication)	**Year of publication**	**Subjects, n**			**Algorithm**	**Pathway measurement**	**Device**
		CD	**UC**	**Controls**			
Zanoli L [1]	2014	34	40	80	Intersecting tangent	Direct x 0.8	SphygmoCor system
Theocharidou E. [2]	2014	29	15	44	Intersecting tangent	Direct x 0.8	SphygmoCor system
Ozturk K. [3]	2015	52	74	66		Direct	Arteriograph
Cappello M. [4]	2016	44	22	37	Max upstroke	Direct	SphygmoCor system
Subjects included in IPD meta-analysis, n		**159**	**151**	**227**			
Zanoli L. et al. [5]	2012	16	16	32	Intersecting tangent	Subtracted	SphygmoCor system
Theocharidou E [6]	2013	43	23	44	Intersecting tangent	Direct	SphygmoCor system
Akdogan RA [7]	2013	0	37	30	Intersecting tangent	Subtracted	SphygmoCor system
Korkmaz H. et al. [8]	2014	18	84	74		Direct	Mobil-O-Graph
Alkan E. et al. [9]	2014	17	23	40	Intersecting tangent	Subtracted	SphygmoCor system
Nemes A [10]	2014	0	11	22		Direct	Arteriograph
Aytaç E [11]	2015	25	30	25	Max upstroke	Direct	Complior
Subjects excluded to IPD meta-analysis, n		**119**	**224**	**267**			

CD, Crohn's disease; IBD, inflammatory bowel disease; PWV, pulse wave velocity; UC, ulcerative colitis.

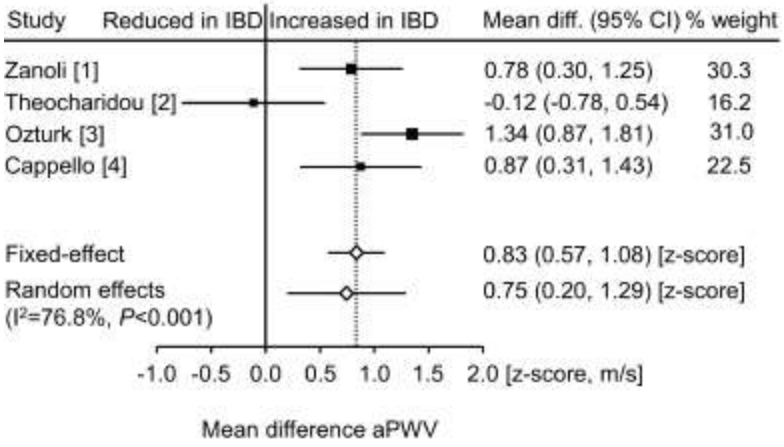
Table S5. Participant characteristics.

	Controls	Ulcerative colitis	Crohn's disease	*P*-value
	n=227	n=151	n=159	
Age, median (range), years	32 (17-67)	32 (16-69)	33 (18-61)	0.54
Age, mean (SD), years	35 (11)	34 (11)	33 (10)	0.54
Male sex, No. (%)	124 (54.6)	97 (64.2)	92 (57.9)	0.18
BMI, median (range), Kg/m^2	24.2 (17.3-40.0)	23.7 (15.1-42.2)	23.0 (13.9-43.3)	0.01
Cholesterol				
Total[*], mean (SD), mmol/L	4.7 (0.9)	4.4 (0.9)	4.1 (0.9)	<0.001
HDL[†], mean (SD), mmol/L	1.3 (0.4)	1.3 (0.4)	1.2 (0.3)	0.03
LDL[†], mean (SD), mmol/L	2.9 (0.9)	2.6 (0.9)	2.4 (0.8)	<0.001
Triglycerides[†], median (range), mmol/L	1.0 (0.4-5.8)	1.1 (0.4-3.0)	1.1 (0.4-2.4)	0.15
Cardiovascular risk factors, No. (%)	118 (52.0)	81 (53.6)	95 (59.7)	0.30
Dyslipidemia, No. (%)	90 (39.6)	57 (37.7)	70 (44.0)	0.51
Hypertension, No. (%)	14 (6.2)	20 (13.2)	21 (13.2)	0.03
Obesity, No. (%)	17 (7.5)	11 (7.3)	7 (4.4)	0.43
Age[‡], No. (%)	10 (4.4)	4 (2.6)	4 (2.5)	0.51
Current smoking, No. (%)	43 (18.9)	18 (11.9)	48 (30.2)	<0.001
SBP, mean (SD), mmHg	117 (13)	120 (12)	117 (17)	0.09
DBP, mean (SD), mmHg	71 (10)	73 (11)	71 (11)	0.31
PP, mean (SD), mmHg	45 (10)	47 (10)	46 (14)	0.43
MBP, mean (SD), mmHg	86 (11)	88 (10)	87 (11)	0.08
Heart rate, median (range), b/min[§]	69 (45-105)	74 (47-157)	72 (47-159)	<0.001
Heart rate, mean (SD), b/min[§]	70 (12)	75 (13)	73 (13)	<0.001
aPWV, median (range), m/s	6.5 (3.3-10.6)	7.0 (4.1-14.2)	7.2 (4.6-11.6)	<0.001
aPWV, mean (SD), m/s	6.4 (1.3)	7.6 (2.2)	7.5 (2.0)	<0.001
aPWV, mean (SD), z-score $\log_e$(m/s)	0.00 (1.00)	0.81 (1.25)	0.79 (1.21)	<0.001
AIx, mean (SD), %	14.0 (15.3)	12.7 (14.0)	13.3 (14.0)	0.72
Active disease, No. (%)	---	49 (32.5)	46 (28.9)	0.50
Disease duration, median (range), years	---	3 (0-28)	5 (0-26)	0.17
Disease duration, mean (SD), years	---	5 (5)	6 (5)	0.17
White blood cells, median (range), billion cells/L[§]	5.9 (3.5-13.0)	6.8 (3.1-14.2)	6.8 (3.2-17.7)	0.89
White blood cells, mean (SD), billion cells/L [§]	6.2 (1.5)	7.4 (2.4)	7.3 (2.9)	0.89
C-reactive protein, median (range), nmol/L[‖]	30 (3-189)	29 (0-882)	30 (0-1524)	0.01
C-reactive protein, $\log_e$(nmol/L) [‖]	86 (76)	95 (143)	95 (171)	0.69
ESR, median (range), mm/h[#]	9 (1-58)	14 (1-111)	13 (1-117)	<0.001
ESR mean (SD), $\log_e$(mm/h) [#]	2.15 (0.79)	2.63 (1.03)	2.48 (1.08)	0.004
Therapy				
Anti-tumor necrosis factor and salicylates, No. (%)	---	11 (7.3)	14 (8.8)	0.62
Anti-tumor necrosis factor only, No. (%)	---	7 (4.6)	33 (20.8)	<0.001
Salicylates only, No. (%)	---	104 (68.9)	58 (36.5)	<0.001
Other, No. (%)	---	29 (19.2)	54 (34.0)	0.003

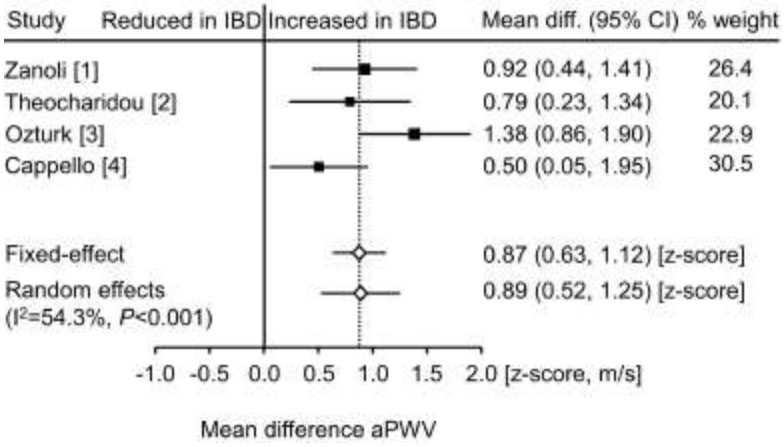
[*]available in 482 participants; [†]available in 383 participants; [‡]men ≥55 years, women ≥65 years; [§]available in 449 participants; [‖]available in 349 participants; [#]available in 336 participants.
Abbreviations: AIx, augmentation index; aPWV, aortic pulse wave velocity; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; MBP, mean blood pressure; No., number; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation.

Figure S1. Forest Plot for aortic pulse wave velocity (aPWV) in 227 Controls and 151 patients with ulcerative colitis (**A**) and in 227 Controls and 159 patients with Crohn's disease (**B**) included in this individual participant data meta-analysis. Works are sorted by year of publication.

A



B



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