

SUPPLEMENTAL MATERIALS

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Table S1. Baseline characteristics by CF-PWV tertile among participants of the FHS without DM

	Lowest PWV Tertile	Middle PWV Tertile	Highest PWV Tertile
N	1,920	1,905	1,851
PWV, m/s	6.0 (5.6-6.3)	7.3 (7.0-7.7)	9.5 (8.7-11.2)
Age, years	37 (31-43)	45 (39-52)	58 (51-67)
Male sex, n (%)	614 (32%)	975 (51%)	1,026 (55%)
Current smoker, n (%)	310 (16%)	300 (16%)	236 (13%)
Family history of diabetes mellitus, n (%)	80 (4%)	133 (7%)	212 (11%)
BMI, kg/m ²	24 (22-27)	26 (23-29)	28 (25-31)
Waist circumference, in	34 (31-37)	37 (34-40)	39 (26-43)
Fasting blood glucose, mg/dl	90 (85-94)	94 (89-100)	97 (92-104)
Total cholesterol, mg/dl	178 (157-201)	194 (173-218)	201 (177-225)
Calculated LDL, mg/dl	102 (83-123)	117 (97-137)	120 (99-143)
HDL, mg/dl	56 (46-66)	52 (42-65)	51 (41-64)
Triglycerides, mg/dl	77 (57-108)	98 (72-141)	118 (83-168)
eGFR, ml/min/1.73m ²	108 (97-116)	101 (90-108)	88 (77-99)
High-sensitivity c-reactive protein, mg/L	0.8 (0.4-2.2)	1.2 (0.5-2.8)	2.0 (0.9-4.4)
SBP, mmHg	109 (102-116)	117 (109-126)	129 (120-141)
DBP, mmHg	70 (65-76)	76 (70-82)	78 (71-85)
MAP, mmHg	83 (78-89)	90 (84-96)	95 (88-102)
Brachial PP, mmHg	38 (33-44)	41 (36-47)	51 (42-62)
Central PP, mmHg	46 (40-53)	47 (40-55)	53 (43-64)
Treated hypertension, n (%)	80 (4%)	241 (13%)	502 (27%)
Number of antihypertensive medications, n (%)			
1	68 (4%)	178 (9%)	340 (18%)
2	12 (<1%)	50 (3%)	126 (7%)
3	0 (0%)	9 (<1%)	29 (2%)
≥4	0 (0%)	4 (<1%)	7 (<1%)
Antihypertensive class			
Renin-angiotensin system blocker, n (%)	29 (2%)	103 (5%)	195 (11%)

Thiazide diuretic, n (%)	6 (<1%)	41 (2%)	99 (5%)
Calcium channel blocker, n (%)	5 (<1%)	44 (2%)	129 (7%)
Beta-blocker, n (%)	38 (2%)	91 (5%)	186 (10%)
Flow velocity, cm/s	57 (46-68)	53 (42-65)	40 (26-56)
Third generation, n (%)	1,771 (92%)	1,388 (73%)	594 (32%)

Continuous variables are reported as median (IQR)

Abbreviations: BMI = body mass index; CF-PWV = carotid-femoral pulse wave velocity; DBP = diastolic blood pressure; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation); FHS = Framingham Heart Study; HDL = high density lipoprotein; LDL = low density lipoprotein; MAP = mean arterial pressure; PP = pulse pressure; SBP = systolic blood pressure.

Table S2. Baseline characteristics of FHS participants without baseline DM who underwent CF-PWV compared with those who did not.

	FHS CF-PWV sub-cohort	FHS participants without CF-PWV
N	5,676	2,916
Age, years	46 (37-55)	56 (45-66)
Male sex, n (%)	2,615 (46%)	1,389 (48%)
Current smoker, n (%)	846 (15%)	193 (7%)
Family history of DM, n (%)	425 (7%)	196 (7%)
BMI, kg/m ²	26 (23-29)	28 (25-32)
Waist circumference, in	37 (33-40)	39 (35-44)
Fasting blood glucose, mg/dl	94 (88-100)	96 (89-103)
Total cholesterol, mg/dl	190 (168-215)	195 (170-219)
Calculated LDL, mg/dl	113 (92-135)	117 (94-139)
HDL, mg/dl	53 (43-65)	51 (40-62)
Triglycerides, mg/dl	109 (77-158)	119 (84-167)
eGFR, ml/min/1.73m ²	99 (87-109)	93 (81-104)
High-sensitivity c-reactive protein, mg/L	1.3 (0.6-3.2)	2.5 (1.2-5.5)
SBP, mmHg	117 (108-128)	122 (112-135)
DBP, mmHg	75 (68-81)	75 (69-81)
MAP, mmHg	89 (82-96)	91 (84-98)
Brachial PP, mmHg	42 (36-50)	46 (39-57)
Central PP, mmHg	48 (41-57)	51 (42-60)
Treated hypertension, n (%)	823 (15%)	357 (12%)
Number of antihypertensive medications, n (%)		
1	586 (10%)	194 (7%)
2	188 (3%)	115 (4%)
3	38 (1%)	38 (1%)
≥4	11 (<1%)	10 (<1%)

Antihypertensive class		
Renin-angiotensin system blocker, n (%)	327 (6%)	121 (4%)
Thiazide diuretic, n (%)	146 (3%)	89 (3%)
Calcium channel blocker, n (%)	178 (3%)	132 (5%)
Beta blocker, n (%)	315 (6%)	144 (5%)

Continuous variables are reported as median (IQR)

Abbreviations: BMI = body mass index; CF-PWV = carotid-femoral pulse wave velocity; DBP = diastolic blood pressure; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation); FHS = Framingham Heart Study; HDL = high density lipoprotein; LDL = low density lipoprotein; MAP = mean arterial pressure; PP = pulse pressure; SBP = systolic blood pressure.

Table S3. Mediation analyses evaluating the relationship between CF-PWV, flow-mediated dilation, and incident DM in FHS

	sHR (95% CI)	% Mediation
FHS		
CF-PWV (not adjusted for flow mediated dilation)	1.36 (1.03-1.76)	
CF-PWV (adjusted for flow mediated dilation)	1.26 (0.95-1.69)	
Flow mediated dilation (adjusted for CF-PWV)	0.92 (0.78-1.08)	9% (7%-11%)
CF-PWV (not adjusted for fasting glucose)	1.36 (1.03-1.76)	
CF-PWV (adjusted for fasting glucose)	1.10 (0.83-1.45)	
Fasting blood glucose (adjusted for CF-PWV)	3.03 (2.56-3.59)	55% (45%-68%)

Abbreviations: CF-PWV = carotid-femoral pulse wave velocity; CI = confidence interval; DM = diabetes mellitus; FHS = Framingham Heart Study; sHR = standardized hazard ratios

All models are adjusted for age, sex, BMI, MAP, HR, eGFR, smoking, total cholesterol, high density lipoprotein, thiazide diuretic use, beta-blocker use, total number of antihypertensive medications, c-reactive protein, and family history of diabetes

Table S4. Odds of new onset diabetes by CF-PWV in the FHS using generalized estimating equations

	Unadjusted	Model 1*	Model 2 [†]	Model 3 [‡]	Model 4 [§]
	sOR (95% CI)	sOR (95% CI)	sOR (95% CI)	sOR (95% CI)	sOR (95% CI)
CF-PWV	2.07 (1.83-2.34)	1.87 (1.53-2.30)	1.56 (1.22-1.98)	1.52 (1.19-1.94)	1.41 (1.10-1.81)
Brachial pulse pressure	1.36 (1.28-1.46)	1.29 (1.14-1.47)	1.20 (1.05-1.38)	1.18 (1.03-1.36)	1.20 (1.04-1.39)
Central pulse pressure	1.51 (1.37-1.66)	1.36 (1.20-1.55)	1.26 (1.08-1.47)	1.24 (1.06-1.45)	1.29 (1.10-1.52)

Abbreviations: CF-PWV = carotid-femoral pulse wave velocity; CI = confidence interval; FHS = Framingham Heart Study; FMD = flow mediated dilation (calculated as the difference in baseline mean flow and mean flow deflation); sOR = standardized odds ratio (calculated using generalized estimating equations accounting for clustering by family across cohorts, determined for each standard deviation increase in PWV)

* Model 1: Adjusted for age, sex, and BMI

† Model 2: Adjusted for Model 1 + MAP and HR

‡ Model 3: Adjusted for Model 2 + eGFR

§ Model 4: Adjusted for Model 3 + smoking + total cholesterol + high density lipoprotein + thiazide diuretic + beta-blocker + total antihypertensive medications + family history of diabetes

Table S5. Sensitivity analyses using robust Mendelian randomization methods.*

	Mean arterial pressure	Brachial pulse pressure
	sOR (95% CI)	sOR (95% CI)
Univariable Mendelian Randomization		
IVW	1.11 (1.03-1.21)	1.19 (1.07-1.32)
Weighted median	1.08 (1.04-1.12)	1.05 (1.00-1.11)
MR-PRESSO	1.08 (1.05-1.12)	1.11 (1.05-1.16)
MR-LASSO	1.08 (1.06-1.11)	1.08 (1.04-1.11)
Multivariable Mendelian Randomization		
IVW	1.03 (0.92-1.15)	1.16 (1.00-1.35)
Weighted median	1.07 (1.04-1.11)	1.02 (0.97-1.07)
MR-PRESSO	1.05 (0.99-1.10)	1.06 (0.99-1.14)
MR-LASSO	1.07 (1.02-1.13)	1.01 (0.96-1.07)

Abbreviations: CI = confidence interval; IVW = inverse variance weighting; MR-LASSO = Mendelian randomization least absolute shrinkage and selection operator; MR-PRESSO = Mendelian randomization pleiotropy residual sum and outlier; sOR = standardized odds ratio

*Estimates represent odds ratios for type 2 diabetes standardized per 5 mmHg higher genetically-predicted levels of the blood pressure parameter