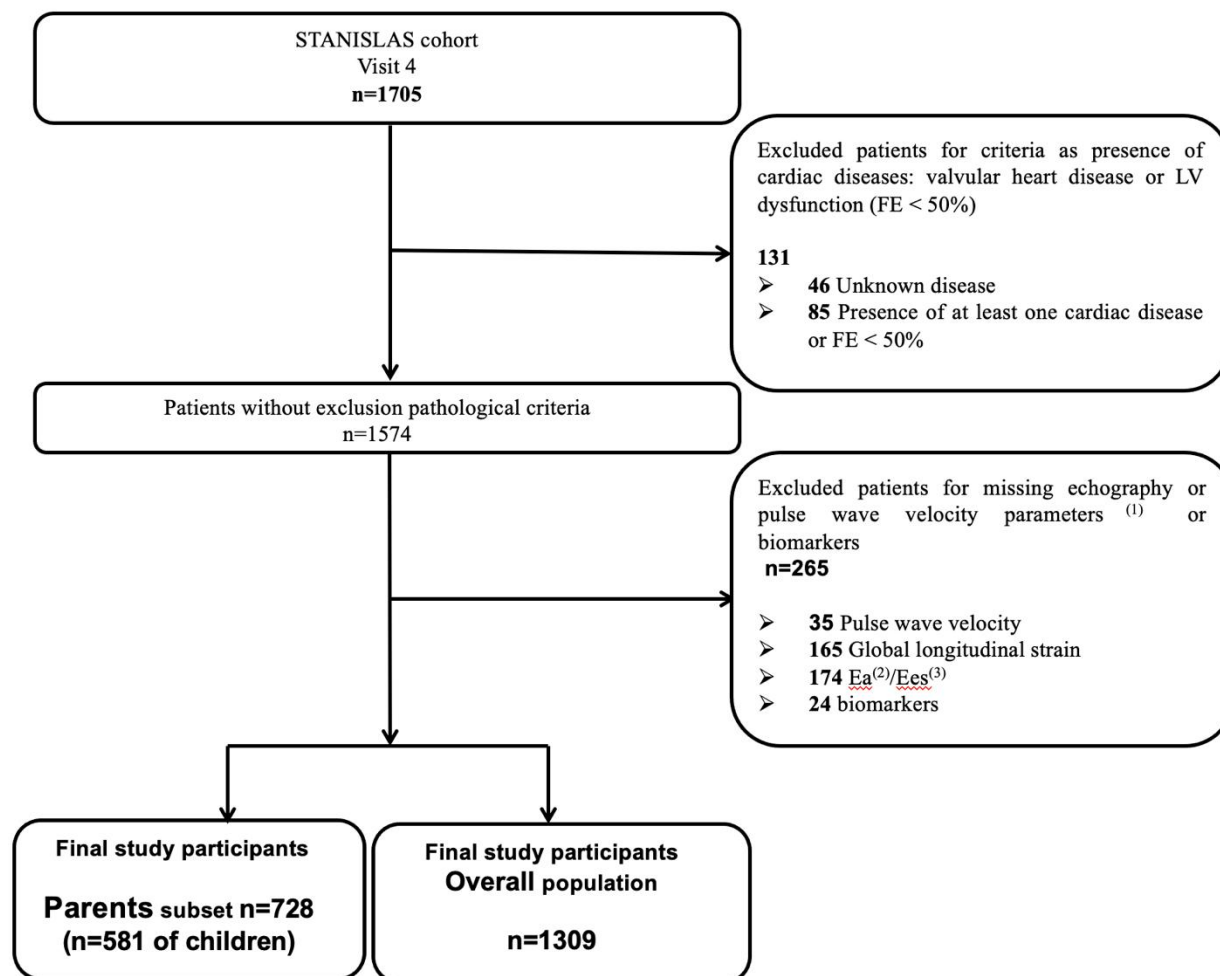
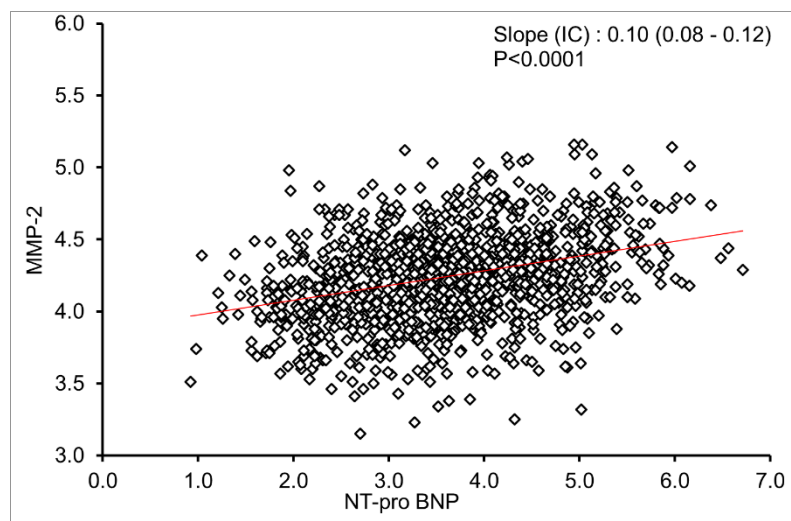


Supplementary material

Supplementary figure 1. Population flowchart



Supplementary figure 2. Correlation between MMP-2 and NT-proBNP



Supplementary table 1. VAC variables and their association with MMP-2 and NT ProBNP

		Whole cohort				
		Model 1		Model 2		Model 3
Dependent variable	Biomarker	Beta (95% CI)	P-value	Beta (95% CI)	P-value	Beta (95% CI)
			FDR		FDR	
E _a	Matrix metalloproteinase-2 (MMP-2)	-0.02 (-0.04; 0.00)	0.11	-0.03 (-0.05; -0.004)*	0.023	-0.02 (-0.04; 0.01)
	N-terminal prohormone brain natriuretic peptide (NT-pro BNP)	-0.023 (-0.05; 0.00)	0.071	-0.03 (-0.05; -0.00)	0.024	-0.01 (-0.03; 0.03)
E _{es}	Matrix metalloproteinase-2 (MMP-2)	0.001 (-0.02; 0.03)	0.92	-0.01 (-0.03; 0.02)	0.54	0.00 (-0.02; 0.04)
	N-terminal prohormone brain natriuretic peptide (NT-pro BNP)	0.007 (-0.02; 0.03)	0.61	0.001 (-0.03; 0.03)	0.96	0.02 (-0.02; 0.06)
		Exp (Beta) (95% CI)	P-value	Exp (Beta) (95% CI)	P-value	Exp (Beta) (95% CI)
PWV (log transformed)	Matrix metalloproteinase-2 (MMP-2)	0.99 (0.99 ; 1.01)	0.84	0.99 (0.99 ; 1.00)	0.3	0.99 (0.98 ; 1.00)
	N-terminal prohormone brain natriuretic peptide (NT-pro BNP)	1.00 (0.99 ; 1.01)	0.96	0.99 (0.99 ; 1.01)	0.55	1.00 (0.99 ; 1.02)
		Beta (95% CI)	P-value	Beta (95% CI)	P-value	Beta (95% CI)
GLS	Matrix metalloproteinase-2 (MMP-2)	0.39 (0.22 ; 0.55)	<.0001	0.31 (0.15 ; 0.47)	0.0002	0.39 (0.22 ; 0.55)
	N-terminal prohormone brain natriuretic peptide (NT-pro BNP)	0.43 (0.24 ; 0.61)	<.0001	0.40 (0.22 ; 0.57)	<.0001	0.43 (0.24 ; 0.61)
		Exp (Beta) (95% CI)	P-value	Exp (Beta) (95% CI)	P-value	Exp (Beta) (95% CI)
1/GLS (log transformed)	Matrix metalloproteinase-2 (MMP-2)	0.98 (0.97 ; 0.99)	<.0001	0.98 (0.98 ; 0.99)	0.0002	0.98 (0.97 ; 0.99)
	N-terminal prohormone brain natriuretic peptide (NT-pro BNP)	0.98 (0.97 ; 0.99)	<.0001	0.98 (0.97 ; 0.99)	<.0001	0.98 (0.97 ; 0.99)

Supplementary table 2. Linear relationships between PWV/GLS with circulating biomarkers in the whole population and those with prevalent valvular heart disease or left ventricular ejection fraction below 50%.

		Whole cohort				
		Model 1		Model 2		Model 3
Biomarker		Exp (Beta)*	FDR adjusted p-value	Exp (Beta)	FDR adjusted p-value	Exp (Beta)
Fatty acid-binding protein adipocyte (FABP4)		1.02 (1.01 ; 1.04)	0.009	1.01 (0.99 ; 1.02)	0.63	1.03 (1.01 ; 1.05)
Receptor for advanced glycosylation end products (RAGE)		0.99 (0.97 ; 1.00)	0.08	0.99 (0.98 ; 1.01)	0.56	0.98 (0.96 ; 1.00)
Interleukin-6 (IL-6)		1.03 (1.01 ; 1.04)	0.001	1.01 (1.00 ; 1.02)	0.25	1.03 (1.01 ; 1.05)
Interleukin-8 (IL-8)		1.00 (0.98 ; 1.01)	0.55	0.99 (0.98 ; 1.01)	0.56	1.00 (0.98 ; 1.02)

Interleukin-1 receptor-like 2 (IL1RL2)	0.99 (0.97 ; 1.00)	0.11	0.99 (0.98 ; 1.00)	0.42	0.99 (0.97 ; 1.00)
Osteopontin (OPN)	0.99 (0.98 ; 1.00)	0.32	1.00 (0.99 ; 1.01)	0.91	0.99 (0.97 ; 1.00)
Tumor necrosis factor receptor 1 (TNF-R1)	1.01 (1.00 ; 1.02)	0.29	1.00 (0.99 ; 1.01)	0.97	1.01 (1.00 ; 1.02)
Transforming growth factor beta receptor type 3 (TGFB3)	0.98 (0.97 ; 0.99)	0.009	0.98 (0.97 ; 0.99)	0.069	0.98 (0.97 ; 0.99)
Vascular cell adhesion protein 1 (VCAM1)	0.99 (0.98 ; 1.00)	0.32	0.99 (0.98 ; 1.00)	0.50	0.99 (0.98 ; 1.00)
Intercellular adhesion molecule 1 (ICAM1)	1.01 (1.00 ; 1.02)	0.25	1.00 (0.99 ; 1.01)	0.91	1.01 (0.99 ; 1.02)
Monocyte chemotactic protein 1 (MCP-1)	1.00 (0.98 ; 1.01)	0.78	1.00 (0.99 ; 1.01)	0.9	0.99 (0.98 ; 1.00)
Growth/differentiation factor 15 (GDF-15)	1.04 (1.02 ; 1.05)	<.0001	1.02 (1.00 ; 1.03)	0.092	1.05 (1.03 ; 1.07)
Galectin-3 (Gal-3) -	1.01 (0.99 ; 1.02)	0.48	1.00 (0.99 ; 1.01)	0.96	1.01 (0.99 ; 1.02)
Matrix metalloproteinase-1 (MMP-1)	1.02 (1.00 ; 1.03)	0.029	1.01 (1.00 ; 1.02)	0.2	1.02 (1.01 ; 1.03)
Matrix metalloproteinase-2 (MMP-2)	0.98 (0.97 ; 0.99)	0.011	0.98 (0.97 ; 0.99)	0.058	0.98 (0.97 ; 0.99)
Matrix metalloproteinase-9 (MMP-9)	1.02 (1.00 ; 1.03)	0.029	1.01 (1.00 ; 1.02)	0.37	1.02 (1.01 ; 1.03)
Matrix metalloproteinase-12 (MMP-12)	1.02 (1.00 ; 1.03)	0.029	1.01 (1.00 ; 1.02)	0.23	1.02 (1.00 ; 1.03)
C-Termina of type 1 collagen propeptide (C1CP)	1.00 (0.98 ; 1.01)	0.55	1.00 (0.99 ; 1.01)	0.71	0.99 (0.98 ; 1.00)
N-terminal propeptide of type III procollagen (P3NP)	1.00 (0.99 ; 1.01)	0.99	1.00 (0.99 ; 1.01)	0.91	1.00 (0.99 ; 1.01)
ST2 protein (ST2)	1.01 (1.00 ; 1.03)	0.21	1.01 (0.99 ; 1.02)	0.65	1.02 (1.00 ; 1.03)
N-terminal prohormone brain natriuretic peptide (NT-pro BNP)	0.98 (0.97 ; 1.00)	0.042	0.98 (0.97 ; 1.00)	0.15	0.99 (0.97 ; 1.00)
Natriuretic peptides B (BNP) -	0.99 (0.98 ; 1.00)	0.29	0.99 (0.98 ; 1.00)	0.42	0.99 (0.98 ; 1.00)
Troponin I cardiac muscle (TNNI3)	1.01 (0.99 ; 1.02)	0.55	1.00 (0.99 ; 1.01)	0.97	1.01 (0.99 ; 1.02)
C-type natriuretic peptide (NPPC)	1.01 (0.99 ; 1.02)	0.55	1.00 (0.99 ; 1.02)	0.69	1.01 (0.99 ; 1.02)
Metalloproteinase inhibitor 1 (TIMP1)	1.00 (0.98 ; 1.01)	0.55	0.99 (0.98 ; 1.00)	0.44	1.00 (0.98 ; 1.01)
Metalloproteinase inhibitor 4 (TIMP4)	1.00 (0.99 ; 1.01)	0.79	0.99 (0.98 ; 1.00)	0.37	1.00 (0.99 ; 1.01)
Adrenomedullin (ADM)	1.02 (1.01 ; 1.04)	0.009	1.01 (0.99 ; 1.02)	0.5	1.03 (1.01 ; 1.05)
Angiogenin (ANG)	1.00 (0.99 ; 1.01)	0.79	1.00 (0.99 ; 1.01)	0.92	1.00 (0.99 ; 1.01)
Vascular endothelial growth factor A (VEGF-A)	1.01 (1.00 ; 1.02)	0.15	1.01 (0.99 ; 1.02)	0.63	1.01 (1.00 ; 1.02)

Supplementary table 3. Linear relationships between E_a/E_{es} with circulating biomarkers in the whole population and parents – all patients without excluding those with **prevalent valvular heart disease or left ventricular ejection fraction below 50%**.

Biomarker	Whole cohort				Parents			
	Model 1		Model 2		Model 1		Model 2	
	Beta	FDR adjusted p-value	Beta	FDR adjusted p-value	Beta	FDR adjusted p-value	Beta	FDR adjusted p-value
Fatty acid-binding protein adipocyte (FABP4)	0.003 (-0.010; 0.015)	0.97	-0.004 (-0.019; 0.011)	0.85	-0.004 (-0.021; 0.012)	0.92	-0.008 (-0.028; 0.012)	0.82
Receptor for advanced glycosylation end products (RAGE)	-0.011 (-0.022; 0.000)	0.3	-0.010 (-0.022; 0.001)	0.35	-0.015 (-0.029; 0.000)	0.8	-0.014 (-0.030; 0.001)	0.8
Interleukin-6 (IL-6)	0.001 (-0.010; 0.012)	0.97	-0.004 (-0.016; 0.008)	0.78	-0.006 (-0.019; 0.008)	0.8	-0.008 (-0.022; 0.006)	0.8
Interleukin-8 (IL-8)	-0.000 (-0.011; 0.011)	1.00	-0.002 (-0.013; 0.010)	0.89	0.001 (-0.013; 0.015)	0.95	0.001 (-0.013; 0.015)	0.94
Interleukin-1 receptor-like 2 (IL1RL2)	0.004 (-0.007; 0.016)	0.97	0.005 (-0.006; 0.017)	0.74	-0.010 (-0.026; 0.007)	0.8	-0.009 (-0.026; 0.008)	0.81
Osteopontin (OPN)	0.002 (-0.010; 0.013)	0.97	0.002 (-0.009; 0.014)	0.85	-0.006 (-0.021; 0.009)	0.8	-0.005 (-0.020; 0.010)	0.82
Tumor necrosis factor receptor 1 (TNF-R1)	-0.002 (-0.014; 0.009)	0.97	-0.006 (-0.018; 0.006)	0.68	-0.007 (-0.021; 0.007)	0.8	-0.009 (-0.024; 0.006)	0.8
Transforming growth factor beta receptor type 3 (TGFB3)	-0.013 (-0.023; 0.002)	0.3	-0.012 (-0.023; 0.001)	0.23	-0.010 (-0.025; 0.004)	0.8	-0.010 (-0.024; 0.004)	0.8
Vascular cell adhesion protein 1 (VCAM1)	-0.002 (-0.012; 0.009)	0.97	0.000 (-0.011; 0.011)	0.98	0.000 (-0.014; 0.015)	0.96	0.001 (-0.014; 0.015)	0.94
Intercellular adhesion molecule 1 (ICAM1)	-0.001 (-0.012; 0.010)	0.97	-0.004 (-0.015; 0.007)	0.78	-0.001 (-0.016; 0.013)	0.95	-0.002 (-0.017; 0.013)	0.92

							0.012)	
Monocyte chemotactic protein 1 (MCP-1)	-0.004 (-0.015; 0.007)	0.97	-0.006 (-0.018; 0.005)	0.68	-0.006 (-0.021; 0.008)	0.8	-0.006 (-0.021; 0.008)	0.82
Growth/differentiation factor 15 (GDF-15)	-0.002 (-0.015; 0.011)	0.97	-0.008 (-0.022; 0.006)	0.68	0.002 (-0.015; 0.018)	0.95	-0.002 (-0.020; 0.016)	0.94
Galectin-3 (Gal-3) -	-0.001 (-0.012; 0.011)	0.97	-0.003 (-0.014; 0.009)	0.85	0.003 (-0.012; 0.018)	0.95	0.001 (-0.014; 0.016)	0.94
Matrix metalloproteinase-1 (MMP-1)	-0.002 (-0.013; 0.008)	0.97	-0.004 (-0.015; 0.007)	0.78	0.005 (-0.008; 0.018)	0.81	0.004 (-0.009; 0.018)	0.82
Matrix metalloproteinase-2 (MMP-2)	-0.011 (-0.022; -0.000)	0.3	-0.011 (-0.022; 0.001)	0.35	-0.013 (-0.028; 0.001)	0.8	-0.011 (-0.028; 0.001)	0.8
Matrix metalloproteinase-9 (MMP-9)	-0.006 (-0.016; 0.005)	0.84	-0.010 (-0.021; 0.001)	0.35	-0.009 (-0.024; 0.005)	0.8	-0.009 (-0.026; 0.004)	0.8
Matrix metalloproteinase-12 (MMP-12)	0.007 (-0.004; 0.019)	0.69	0.004 (-0.008; 0.016)	0.78	-0.001 (-0.015; 0.013)	0.95	-0.001 (-0.017; 0.012)	0.92
C-Termina of type 1 collagen propeptide (C1CP)	-0.001 (-0.011; 0.010)	0.97	0.000 (-0.010; 0.011)	0.98	-0.006 (-0.020; 0.008)	0.8	-0.006 (-0.020; 0.009)	0.82
N-terminal propeptide of type III procollagen (P3NP)	-0.001 (-0.011; 0.009)	0.97	-0.001 (-0.012; 0.009)	0.89	0.001 (-0.013; 0.014)	0.95	0.002 (-0.012; 0.016)	0.92
ST2 protein (ST2)	-0.000 (-0.012; 0.012)	1.00	0.000 (-0.012; 0.013)	0.98	-0.007 (-0.023; 0.009)	0.8	-0.007 (-0.026; 0.007)	0.8
N-terminal prohormone brain natriuretic peptide (NT-pro BNP)	-0.015 (-0.028; -0.003)	0.3	-0.015 (-0.027; -0.003)	0.18	-0.011 (-0.027; 0.004)	0.8	-0.011 (-0.027; 0.004)	0.8
Natriuretic peptides B (BNP) -	-0.009 (-0.021; 0.002)	0.48	-0.009 (-0.021; 0.002)	0.4	-0.006 (-0.019; 0.007)	0.8	-0.006 (-0.019; 0.008)	0.82

Troponin I cardiac muscle (TNNI3)	-0.001 (-0.012; 0.011)	0.97	-0.002 (-0.014; 0.009)	0.85	-0.001 (-0.017; 0.014)	0.95	-0.004 (-0.019; 0.012)	0.9
C-type natriuretic peptide (NPPC)	-0.006 (-0.018; 0.006)	0.84	-0.005 (-0.017; 0.007)	0.78	-0.001 (-0.015; 0.013)	0.95	-0.001 (-0.016; 0.013)	0.94
Metalloproteinase inhibitor 1 (TIMP1)	-0.012 (-0.023; -0.001)	0.3	-0.013 (-0.025; -0.002)	0.18	-0.008 (-0.022; 0.006)	0.8	-0.010 (-0.024; 0.005)	0.8
Metalloproteinase inhibitor 4 (TIMP4)	-0.007 (-0.019; 0.004)	0.69	-0.009 (-0.021; 0.002)	0.4	-0.005 (-0.020; 0.010)	0.82	-0.007 (-0.022; 0.009)	0.82
Adrenomedullin (ADM)	0.003 (-0.009; 0.015)	0.97	-0.004 (-0.017; 0.009)	0.78	-0.002 (-0.018; 0.014)	0.95	-0.005 (-0.023; 0.013)	0.82
Angiogenin (ANG)	-0.006 (-0.016; 0.005)	0.84	-0.007 (-0.018; 0.004)	0.62	-0.004 (-0.018; 0.009)	0.9	-0.005 (-0.019; 0.010)	0.82
Vascular endothelial growth factor A (VEGF-A)	-0.010 (-0.021; 0.001)	0.3	-0.014 (-0.025; -0.003)	0.18	-0.008 (-0.022; 0.006)	0.8	-0.009 (-0.023; 0.005)	0.8

Supplementary table 4. Medications for hypertension, dyslipidemia, or diabetes in the whole population (n=1309) and parent generation (n=728)

		Overall (n=1309)	Parents only (n=728)
Antihypertensive treatment	1309	216 (16.5%)	202 (27.8%)
ACE Inhibitors	1309	43 (3.3%)	41 (5.6 %)
ARBs	1309	107 (8.2%)	101 (13.9 %)
Beta-Blockers	1309	84 (6.4%)	75 (10.3 %)
Calcium Channel Blockers	1309	63 (4.8%)	62 (8.5 %)
Central Antihypertensive Drugs	1309	67 (5.1%)	60 (8.2 %)
Diuretics	1309	80 (6.1%)	75 (10.3 %)
Lipid lowering therapy	1309	177 (13.5%)	176 (24.2%)
Statins	1309	144 (11.0 %)	144 (19.8 %)
Cholesterol Absorption Inhibitors	1309	14 (1.1 %)	13 (1.8 %)
Fibrates	1309	25 (1.9 %)	25 (3.4 %)
Omega-3 Ethyl Esters	1309	1 (0.1 %)	1 (0.1 %)
Other Lipid-Lowering Therapy	1309	5 (0.4%)	5 (0.7 %)
Diabetes Treatment	1309	39 (3.0%)	35 (4.8%)
DPP-4 Inhibitors	1309	16 (1.2 %)	15 (2.1 %)
GLP-1 Agonists	1309	1 (0.1 %)	1 (0.1 %)
Insulin	1309	5 (0.4 %)	2 (0.3 %)
Metformin	1309	29 (2.2 %)	29 (4.0 %)
Repaglinide	1309	2 (0.2 %)	2 (0.3 %)
Sulfonylureas	1309	20 (1.5 %)	20 (2.7 %)

ACE, Angiotensin converting enzyme; ARBs, Angiotensin receptor blockers; DPP-4, Dipeptidyl peptidase 4; GLP-1, Glucagon-like peptide