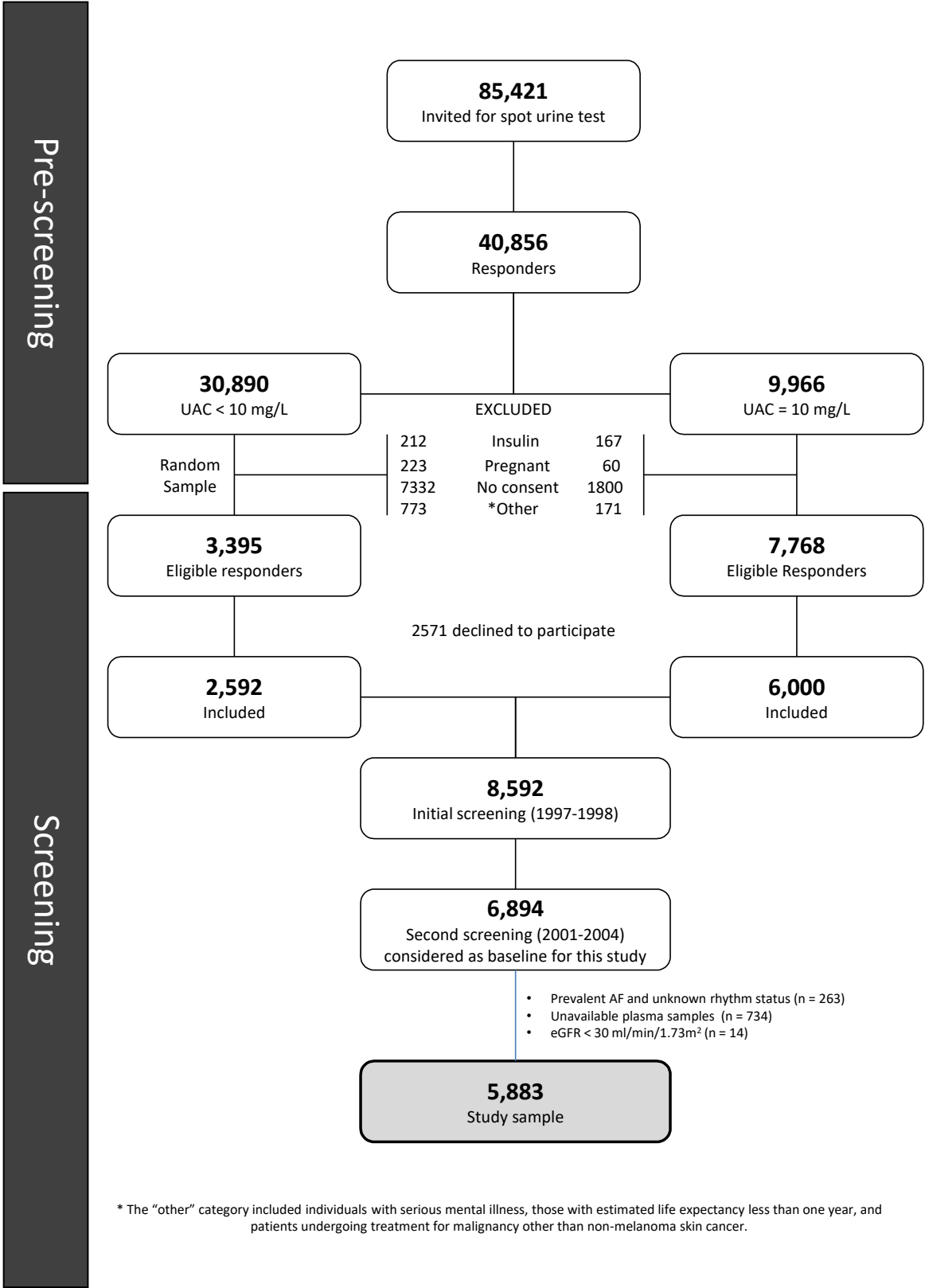


Supplementary Figure 1. PREVEND participant selection



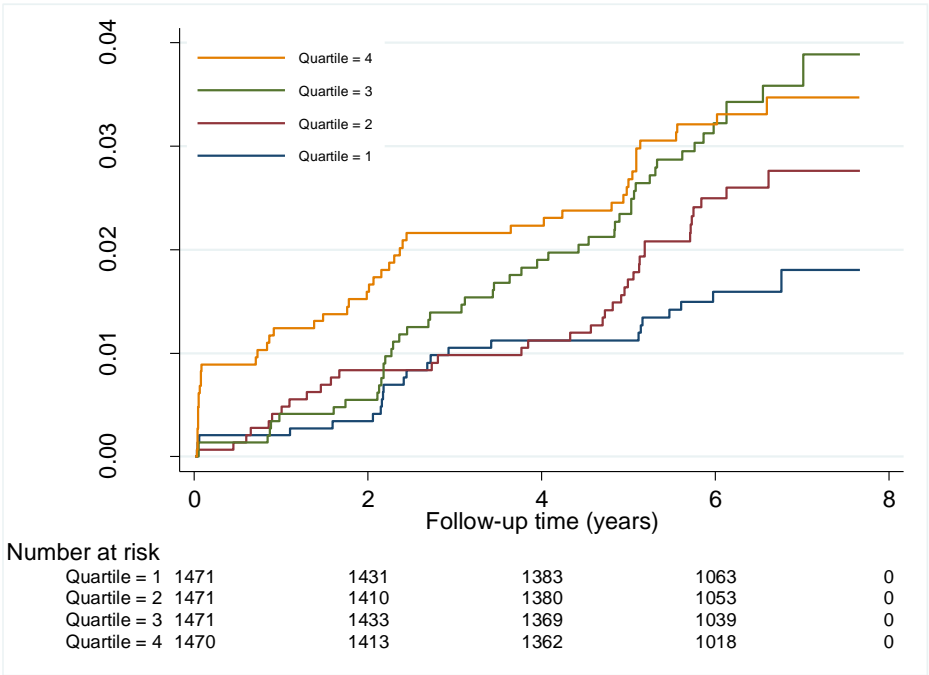
\* The “other” category included individuals with serious mental illness, those with estimated life expectancy less than one year, and patients undergoing treatment for malignancy other than non-melanoma skin cancer.

**Supplementary Figure 2.** Physiological and Pathophysiological Correlates of BMP10 versus NT-proBNP



Abbreviations: BMP10, bone morphogenetic protein 10; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RFM, relative fat mass; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; HTN, hypertension; CVD, cardiovascular disease; HF, heart failure; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate. Smoking status was classified as current smokers and non-smokers (including both never-smokers and past smokers). CVD included myocardial infarction and stroke. A value of 0 indicates lack of statistical significance. The most evident differences are highlighted in green.

**Supplementary Figure 3.** Cumulative incidence of AF across sex-pooled BMP10 quartiles



This figure illustrates the cumulative incidence of atrial fibrillation (AF) across sex-pooled quartiles of bone morphogenetic protein 10 (BMP10). The y-axis represents the cumulative incidence of AF, while the x-axis shows the time from study inclusion to AF event or censoring. The table below (number at risk) indicates the number of participants at risk at different time points for each BMP10 quartile.

**Supplementary Table 1.** Participant characteristics: baseline PREVEND sample vs study sample

Characteristics	Baseline sample	Study sample
	<b>N = 6894</b>	<b>N = 5883</b>
Age (mean, SD), years	53.9 (12.1)	53.6 (12.0)
Female sex, n (%)	3450 (50.0)	3031 (51.5)
Smoking status		
Current smokers, n (%)	1917 (27.8)	1601 (27.2)
Past smokers, n (%)	2925 (42.4)	2488 (42.3)
Height (mean, SD), cm	172.7 (9.5)	172.6 (9.5)
Weight (mean, SD), kg	79.9 (14.6)	79.5 (14.3)
Body mass index, kg/m <sup>2</sup>	26.8 (4.4)	26.7 (4.3)
Waist circumference, cm	92.3 (12.8)	92.0 (12.6)
Relative fat mass, %	31.9 (7.3)	32.0 (7.3)
Total cholesterol (mean, SD), mmol/L	5.43 (1.05)	5.43 (1.06)
HDL-C (mean, SD), mmol/L	1.25 (0.32)	1.26 (0.31)
CRP (median, P25, P75), mg/L	1.39 (0.64, 3.11)	1.35 (0.62, 3.01)
Diabetes, n (%)	483 (7.1%)	381 (6.5%)
Antidiabetic medication, n (%)	259 (3.8)	192 (3.3)
Hypertension, n (%)	2380 (34.6)	1968 (33.5)
Antihypertensive medication, n (%)	1539 (22.4)	1297 (22.1)
MI or stroke, n (%)	505 (7.3)	429 (7.3)
Heart failure, n (%)	64 (0.9)	50 (0.8)
NT-proBNP (median, P25, P75), ng/L	42.3 (21.8, 82.1)	42.3 (22.1, 80.0)
Galectin-3 (median, P25, P75), mg/L	11.5 (9.0, 14.4)	11.5 (9.0, 14.4)
UAE (median, P25, P75), mg/24h	8.8 (6.1, 16.5)	8.2 (6.0, 13.7)
eGFR (mean, SD), mL/min/1.73m <sup>2</sup>	91.8 (17.3)	92.2 (16.6)

Continuous variables are presented as mean (standard deviation) or as a median (percentile 25 – percentile 75), and categorical variables as n (%). **Abbreviations:** BMP10, bone morphogenetic protein-10; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CRP, C-reactive protein; UAE, 24h urinary albumin excretion; eGFR, estimated glomerular filtration rate.

**Supplementary Table 2.** Percentiles of BMP10 in the PREVEND cohort

	<b>Total</b>	<b>Males</b>	<b>Females</b>
<b>Percentiles</b>	<b>n = 5883</b>	<b>n = 2852</b>	<b>N = 3031</b>
1	1.32	1.30	1.44
5	1.59	1.54	1.67
10	1.70	1.65	1.80
25	1.90	1.82	2.02
<b>50</b>	<b>2.16</b>	<b>2.05</b>	<b>2.28</b>
75	2.45	2.30	2.56
90	2.76	2.57	2.87
95	2.94	2.75	3.09
99	3.42	3.13	3.58

Range of bone morphogenetic protein 10 (BMP10) in the total population was 0.06 to 4.89; in men was 0.73 to 4.52; and in women was 0.06 to 4.89. Mean (SD) BMP10 was 2.20 (0.43) in the total population; 2.08 (0.38) in men; and 2.31 (0.44) in women. Units of BMP10 are in ng/mL.

**Supplementary Table 3.** Associations of NT-proBNP with clinical risk factors and biomarkers

Characteristics	Age- and sex-adjusted		Multivariable	
	S $\beta$	P-value	S $\beta$	P-value
Age	0.39	<0.001	0.30	<0.001
Female sex	0.24	<0.001	0.43	<0.001
Smoking	0.04	0.001	0.04	0.002
Height	0.08	<0.001	0.06	<0.001
Weight	-0.06	<0.001	-	-
Body mass index	-0.09	<0.001	-	-
WC	-0.08	<0.001	-	-
Relative fat mass	-0.16	<0.001	-0.18	<0.001
Cholesterol	-0.17	<0.001	-0.16	<0.001
HDL-C	0.03	0.029	0.04	0.009
CRP	0.06	<0.001	0.13	<0.001
Diabetes	-0.01	0.231	-	-
Hypertension	0.15	<0.001	0.13	<0.001
MI or stroke	0.15	<0.001	0.08	<0.001
Heart failure	0.15	<0.001	0.10	<0.001
BMP10	0.12	<0.001	0.12	<0.001
Galectin-3	0.04	0.001	-	-
UAE	0.10	<0.001	0.05	<0.001
eGFR	-0.15	<0.001	-0.09	<0.001

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; S $\beta$ , standardized beta; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; BMP10, brain morphogenetic factor 10; CRP, C-reactive protein; UAE, 24h urinary albumin excretion; eGFR, estimated glomerular filtration rate. Although all anthropometric measures (weight, BMI, WC, and RFM) were significantly associated with BMP10 in age- and sex-adjusted models, RFM, which showed the strongest association, was retained in the multivariable model to avoid multicollinearity.

**Supplementary Table 4:** PREVEND participant characteristics according to incident AF status

Characteristics	No incident AF	Incident AF	P-value
	<b>N = 5729</b>	<b>N = 154</b>	
BMP10 (mean, SD), ng/mL	2.2 (0.43)	2.3 (0.42)	0.059
Age (mean, SD), years	53.3 (12.0)	65.4 (8.4)	<0.001
Female sex, n (%)	2988 (52.2)	43 (27.9)	<0.001
Smoking status			<0.001
Current smokers, n (%)	1562 (27.3)	39 (25.3)	
Past smokers, n (%)	2401 (41.9)	87 (56.4)	
Height (mean, SD), cm	172.5 (9.5)	175.2 (9.4)	<0.001
Weight (mean, SD), kg	79.2 (14.3)	87.9 (14.6)	<0.001
Body mass index, kg/m <sup>2</sup>	26.6 (4.3)	28.6 (4.4)	<0.001
Waist circumference, cm	91.7 (12.5)	101.8 (12.4)	<0.001
Relative fat mass, %	32.0 (7.3)	32.4 (6.9)	0.52
Cholesterol (mean, SD), mmol/L	5.44 (1.06)	5.28 (6.9)	0.075
HDL-C (mean, SD), mmol/L	1.26 (0.31)	1.16 (0.33)	<0.001
CRP (median, P25, P75), mg/L	1.32 (0.62, 2.96)	2.00 (0.95, 4.30)	<0.001
Diabetes, n (%)	359 (6.3)	22 (14.4)	<0.001
Antidiabetic medication, n (%)	182 (3.2)	10 (6.5)	0.023
Hypertension, n (%)	1857 (32.5)	111 (72.1)	<0.001
Antihypertensive medication, n (%)	1208 (21.1)	89 (57.8)	<0.001
MI or stroke, n (%)	384 (6.7)	45 (29.2)	<0.001
Heart failure, n (%)	36 (0.6)	14 (9.1)	<0.001
NT-proBNP (median, P25, P75), ng/L	41.3 (21.8, 77.6)	149.9 (72.0, 306.7)	<0.001
Galectin-3 (median, P25, P75), mg/L	11.5 (9.0, 14.3)	12.8 (9.8, 16.3)	0.004
UAE (median, P25, P75), mg/24h	8.1 (5.9, 13.5)	12.2 (7.5, 37.7)	<0.001
eGFR (mean, SD), mL/min/1.73m <sup>2</sup>	92.5 (16.4)	79.4 (18.2)	<0.001

Abbreviations: AF, atrial fibrillation; BMP10, brain morphogenetic factor 10; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CRP, C-reactive protein; UAE, 24h urinary albumin excretion; eGFR, estimated glomerular filtration rate. Continuous variables are presented as mean (standard deviation) or as a median (percentile 25 – percentile 75), and categorical variables as n (%).

**Supplementary Table 5.** Associations of BMP10 with incident atrial fibrillation: Sensitivity Analyses

	<b>Hazard Ratio (95% CI)</b>	<b>P-value</b>
Clinical model + eGFR	1.49 (1.14-1.96)	0.004
Clinical model + CRP	1.54 (1.18-2.00)	0.001
Clinical model + NT-proBNP	1.39 (1.08-1.79)	0.011

Abbreviations: AF, atrial fibrillation; BMP10, bone morphogenetic protein 10; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; NT-proBNP, N-terminal pro-B-type-natriuretic peptide. The clinical model included age, sex, components of the CHARGE-AF model: height, smoking, weight, history of type-2 diabetes, history of hypertension, history of myocardial infarction or stroke, and history of heart failure. BMP10 and sex were treated as time-varying covariates in these analyses. Hazard ratios are presented per 1SD increase in BMP10.



**Supplementary Table 6.** Exploratory subgroup / interaction analyses

	No	Yes	
	HR (95% CI)	HR (95% CI)	P-interaction
Older age*	1.28 (0.79, 2.09)	1.66 (1.23, 2.56)	0.802
Female sex	1.60 (1.21, 2.12)	1.25 (0.69, 2.25)	0.599
Obesity (BMI)*	1.64 (1.22, 2.21)	1.43 (0.90, 2.26)	0.184
Obesity (RFM)*	1.60 (1.16, 2.24)	1.43 (0.96, 2.11)	0.477
Proinflammatory status*	1.02 (0.65, 1.58)	1.87 (1.36, 2.59)	<b>0.002</b>
Prevalent CVD*	1.51 (1.10, 2.09)	1.45 (1.00, 2.12)	0.892
Renal dysfunction*	1.78 (1.12, 2.83)	1.28 (0.93, 1.77)	0.222

The stratified models were adjusted for age and sex. While examining associations of sex with incident AF, models were adjusted only for age. Hazard ratios are given per 20 µg/L increase in IGFBP7 levels.

Abbreviations: BMI, body mass index; RFM, relative fat mass; HF, heart failure; CVD, cardiovascular disease; CKD, chronic kidney; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

\* Older age was defined as age ≥ 65 years; BMI-based obesity was defined as BMI ≥ 30 kg/m<sup>2</sup>; RFM-based obesity was defined as RFM ≥ 30 in men and RFM ≥ 40 in women; proinflammatory status was defined as CRP ≥ 2mg/L; CVD was defined as myocardial infarction or stroke or heart failure; renal dysfunction was defined as estimated glomerular filtration rate ≤ 60 mL/min/1.63m<sup>2</sup>.

**Supplementary Table 7.** Predictive performance of BMP10 and NT-proBNP relative to clinical model

	AUC	$\Delta$ AUC	AIC	$\Delta$ AIC
Clinical model	0.84	-	2367	
Clinical model + BMP10	0.84	0.00	2359	-8
Clinical model + NT-proBNP	0.88	0.04	2269	-90

Abbreviations: BMP10, bone morphogenetic protein 10; NT-proBNP, N-terminal pro-B-type natriuretic peptide; AUC, area under the ROC curve; AIC, Akaike information criterion. Clinical model includes age, sex, smoking, height, weight, history of diabetes, history of hypertension, history of myocardial infarction or stroke, and history of heart failure.  $\Delta$ AIC values are calculated relative to the clinical model ( $\Delta$ AIC = AIC<sub>candidate</sub> - AIC<sub>clinical</sub>); negative values indicate improved model fit compared with the clinical model. Following conventional interpretation, a reduction in AIC of <2 suggests no meaningful improvement, a reduction of 4–7 indicates modest improvement, and a reduction >10 indicates strong improvement in model fit.

**Supplementary Table 8.** Predictive performance of BMP10 relative to a clinical model and NT-proBNP

	AUC	$\Delta$ AUC	AIC	$\Delta$ AIC
Clinical model + NT-proBNP	0.88	0.04	2269	0
Clinical model + NT-proBNP + BMP10	0.87	-0.01	2267	-2

Abbreviations: BMP10, bone morphogenetic protein 10; NT-proBNP, N-terminal pro-B-type natriuretic peptide; AUC, area under the ROC curve; AIC, Akaike information criterion. Clinical model includes age, sex, smoking, height, weight, history of diabetes, history of hypertension, history of myocardial infarction or stroke, and history of heart failure.  $\Delta$ AIC values are calculated relative to the clinical + NT-proBNP model. Negative values indicate improved fit, although a reduction <2 indicates negligible improvement.