Supplemental Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix.

Plasma transthyretin

In the CPGS, the 95% interval was 19.1 to 40.8 mg/dL, which agreed with the 20.0 to 40.0 mg/dL interval reported by the supplier of the transthyretin assay (Roche). Because the ELISA assay used in the Copenhagen City Heart Study was developed for research and calibrated in a lot specific manner against fresh human samples of purified transthyretin, there was no assay specific 95% reference interval. However, in-house analyses demonstrated that when calibrated against the certified reference material in human serum from IRMM (Institute for Reference Materials and Measurements) ERM-DA470k/IFCC (International Federation of Clinical Chemistry), which the Cobas® assay used in the Copenhagen General Population Study was traceable to, absolute concentrations of transthyretin, on the two different assays, agreed by a lot specific conversion factor. Of note, in the CCHS the same lot number was used for all samples. To allow for comparisons between participants in the two study cohorts, we therefore transformed the intrinsic scale of the ELISA assay to that matching the Cobas® assay.

Covariates for baseline characteristics were chosen based on current literature suggesting an association with transthyretin concentrations or risk of heart failure: age, sex, nutrition/lifestyle (body mass index, diabetes, lipid-lowering therapy, smoking, alcohol intake, physical inactivity, plasma albumin, plasma cholesterol and -triglycerides), cardiovascular disease (previous myocardial infarction and hypertension), liver synthesis capacity and liver cell damage (albumin and alanine transaminase), kidney function (creatinine), and inflammation (C-reactive protein).[1-3] Body mass index was measured weight in kilograms divided by measured height in meters squared. Hypertension was systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, and/or self-reported use of antihypertensive medication. Smoking was self-reported and converted to pack-years (1 pack-year= cumulative smoking equivalent to 20 cigarettes per day for 1 year). Alcohol consumption was self-reported and converted to average weekly units of intake (1 unit=12 grams of alcohol). Physical inactivity was self-reported weekly light physical activity in leisure time <4 hours per week. Diabetes mellitus was self-reported disease, nonfasting plasma glucose >11.0 mmol/L, medication prescribed for diabetes, and/or hospitalization due to diabetes (ICD-8 code: 249,250; ICD-10 code: E10-11, E13-14). Lipid-lowering therapy was self-reported at baseline and was>98% statins.

Information on diagnoses of ischemic heart disease (ICD-8 code: 410-414, ICD-10 code: I20-I25) before baseline examination was collected and verified from 1977 through 2017 by reviewing all hospital admissions and diagnoses entered in the Danish National Patient Registry and all causes of death entered in the national Danish Causes of Death Registry.

Statistical analyses

Baseline data were missing (primarily self-reported alcohol consumption 5%) in an arbitrary pattern and therefore imputed by the fully conditional specification method with five imputation data sets per value.[4] The most important predictors of observed plasma transthyretin were identified using ranks of standardized regression coefficients from a multivariable (adjusted by age, sex, body mass index, previous myocardial infarction, diabetes mellitus, lipid-lowering therapy, hypertension, cumulative smoking, alcohol consumption, triglycerides, creatinine, hsCRP) general linear model (GLM). A standardized regression coefficient is computed by indexing the sample standard deviation for a predictor of interest to sample standard deviation of the dependent variable. This allows for a between covariable comparisons of how much the outcome variable changes for a standardized change in each of the investigated covariables when holding the other covariables fixed. Linearity of continuous predictors in the GLM was inspected by plots of residuals using penalized log likelihood local polynomial regression (LOESS).[5] Similarly, the overall fit of the GLM was determined by a LOESS plot of observed- versus GLM predicted values of plasma transthyretin and a density plot of the corresponding residuals.

Association of age and sex with plasma transthyretin, albumin and hsCRP was investigated by natural cubic splines with interaction terms. Hazard ratios for time to event outcomes were calculated by cause-specific Cox regression which is unconfounded by the competing risk of death, because it reflects rate ratios and not absolute event probabilities.[6] To account for left truncation, a delayed entry function of age was used as the underlying timeline in the Cox model (this inherently adjusts for age).[7] Multivariable Cox regression models in both studies were adjusted for baseline covariates which were significantly different across transthyretin percentiles (age [underlying timeline], sex, body mass index, diabetes, lipid-lowering therapy, hypertension, smoking (pack-years), alcohol intake, alanine transaminase, albumin, cholesterol, triglycerides and creatinine, or all of the above including hsCRP). Because of non-proportional hazards of sex and hsCRP and an interaction between the latter and plasma transthyretin, the multivariable Cox models were stratified by sex and hsCRP levels (<1, 1-3, >3mg/L).[8] Because of possible heterogeneity by study cohort, we stratified all joint analyses on study cohort.

The association between outcome and transthyretin concentration on a continuous scale was further evaluated by natural cubic splines. To mitigate risk of overfitting we used a parsimonious model accounting for age as the underlying timeline and stratifying by sex and hsCRP. The number of knots were selected by a penalized log likelihood estimate using knots positioned in quantiles as suggested by Harrel.[9] Because plasma transthyretin is an inverse acute phase reactant, a separate sensitivity analysis was performed to investigate the attenuating influence of plasma hsCRP on the association of plasma transthyretin with outcomes. Cox proportional hazard and linear assumptions were evaluated by plots of Schoenfeld and Martingale residuals.

To maximize power for detecting possible bias and risk dependencies, all sensitivity analyses were performed on a combined dataset using participants from both the CGPS and CCHS (study cohort was used as a stratification variable to allow for between study heterogeneity). First, to determine whether the association of transthyretin and incident HF differed in individuals with high versus low hsCRP, i.e. those less likely to have subclinical organ damage and atherosclerosis, we performed a sensitivity analysis which stratified study participants by hsCRP levels ≤3mg/L versus >3 to <10 mg/L.[10] Second, to address concerns that undiagnosed prevalent HF explained the lower plasma transthyretin levels, rather than that low plasma transthyretin heralds HF, we performed an analysis which blanked all HF events that occurred within first 5 years of follow-up after blood draw. Third, because transthyretin amyloid cardiomyopathy is expected to occur primarily after 60 years of age, we tested if there was a differential impact of plasma transthyretin on incident HF as a function of age at the time of HF diagnosis or censoring. Fourth, we stratified our analyses on ischemic and non-ischemic heart failure. Fifth, we examined the association of low transthyretin concentrations with other manifestations of transthyretin-related disease: carpal tunnel syndrome, ICD10: G56.0; spinal stenosis, ICD10: M48.0; biceps tendon rupture, ICD10: S46.1 and S46.2; or with a registry diagnosis of amyloidosis, ICD10: E85.X. Finally, we examined the association of plasma transthyretin with NT-proBNP levels which were obtained on 3,891 (53%) subjects from CCHS at a repeat visit in 2001-2003.

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eTable 1. Risk of heart failure in individuals in the Copenhagen General Population Study and the Copenhagen City Heart Study as a function of percentile of transthyretin at baseline, excluding individuals with genetic variants in *TTR*

	≤5th percentile	**>5-95th percentile**	**>95th percentile**
Copenhagen General Population Study			
N	415	7,354	400
Incident HF, n(%)	30 (7%)	321 (4%)	16 (4%)
Covariates	**HR (95% CI)**	**—**	**HR (95% CI)**
Age and Sex[a]	1.9 (1.3-2.8)	1 [Reference]	1.2 (0.7-2.0)
Age, Sex, and hsCRP[b]	1.7 (1.2-2.5)	1 [Reference]	1.2 (0.7-2.0)
Multivariable without hsCRP[c]	1.8 (1.2-2.7)	1 [Reference]	1.0 (0.6-1.8)
Multivariable with hsCRP[d]	1.7 (1.2-2.6)	1 [Reference]	1.1 (0.6-1.9)
Copenhagen City Heart Study			
N	314	5,636	313
Incident HF, n(%)	66 (21%)	826 (15%)	42 (13%)
Covariates	**HR (95% CI)**	**—**	**HR (95% CI)**
Age and Sex[a]	1.5 (1.2-1.9)	1 [Reference]	1.1 (0.8-1.5)
Age, Sex, and hsCRP[b]	1.4 (1.1-1.8)	1 [Reference]	1.1 (0.8-1.5)
Multivariable without hsCRP[c]	1.3 (1.0-1.7)	1 [Reference]	1.1 (0.8-1.5)
Multivariable with hsCRP[d]	1.3 (1.0-1.7)	1 [Reference]	1.1 (0.8-1.6)

Number of individuals excluded due to genetic variants in *TTR*: p.T139M, n=75; p.G26S, n=2,447; p.D119N, n=5; H110N, n=6; V142I, n=1; total excluded, n=2,534.
Abbreviations: CI, confidence interval; hsCRP, high-sensitivity C-reactive protein.
[a] Adjusted by age and sex.
[b] Adjusted by age, sex and log-transformed CRP.
[c] Adjusted by age, sex, body mass index, lipid-lowering therapy, hypertension, alcohol intake, smoking (pack-years), physical inactivity, alanine transaminase, albumin, cholesterol, triglycerides and creatinine.
[d] Adjusted by all of the above covariates and log-transformed hsCRP.

eTable 2. Risk of heart failure in individuals in the Copenhagen General Population Study and the Copenhagen City Heart Study combined (n = 16 967) as a function of transthyretin percentile at baseline stratified by hsCRP ≤3 mg/L and >3 to <10 mg/L

Adjustment	**≤5th percentile (n=833)**	**>5-95th percentile (n=15,297)**	**>95th percentile (n=837)**
Endpoint			
	Hazard ratio (95% CI)		Hazard ratio (95% CI)
Age and Sex[a]			
Heart failure			
All (n=16,967)	1.5 (1.3-1.9)	1 [Reference]	1.2 (1.0-1.5)
hsCRP ≤3mg/L (n=13,236)	1.5 (1.2-1.9)	1 [Reference]	1.2 (0.9-1.6)
hsCRP >3 to <10 mg/L (n=3,731)	1.4 (1.0-1.9)	1 [Reference]	1.3 (0.8-2.0)
Multivariable[b]			
Heart failure			
All	1.4 (1.2-1.8)	1 [Reference]	1.2 (0.9-1.5)
hsCRP ≤3mg/L	1.4 (1.1-1.8)	1 [Reference]	1.3 (1.0-1.7)
hsCRP >3 to <10 mg/L	1.4 (1.0-1.9)	1 [Reference]	1.1 (0.7-1.8)

[a] Adjusted by age and sex.
[b] Adjusted by age (underlying timeline), sex, body mass index, lipid-lowering therapy, hypertension, alcohol intake, smoking (pack-years), physical inactivity, alanine transaminase, albumin, cholesterol, triglycerides and creatinine.
CI, confidence interval; hsCRP, high sensitivity C-reactive protein.

eTable 3. Hazard ratios for heart failure in individuals in the Copenhagen General Population Study and the Copenhagen City Heart Study combined (n = 16 967) as a function of transthyretin percentile at baseline with and without omission of individuals with 5 years or less of follow-up after plasma transthyretin measurement

Adjustment **Endpoint**	**≤5th percentile (n=833)**	**>5-95th percentile (n=15,297)**	**>95th percentile (n=837)**
	Hazard ratio (95% CI)		Hazard ratio (95% CI)
Age and Sex[a]			
Overall HF (events n=1,563)	1.5 (1.3-1.9)	1 [Reference]	1.2 (1.0-1.5)
HF >5 years (events n=1,200)	1.5 (1.2-1.9)	1 [Reference]	1.2 (1.0-1.6)
Age, Sex, and hsCRP[b]			
Overall HF	1.4 (1.2-1.7)	1 [Reference]	1.3 (1.0-1.6)
HF >5 years	1.4 (1.1-1.7)	1 [Reference]	1.3 (1.0-1.7)

[a] Adjusted by age and stratified by sex and study cohort.
[b] Adjusted by age (underlying timeline), log-transformed high sensitivity C-reactive protein and stratified by sex and study cohort.
CI, confidence interval; HF, heart failure; hsCRP, high sensitivity C-reactive protein.

eTable 4. Hazard ratios for any heart failure, nonischemic heart failure, and ischemic heart failure in the Copenhagen General Population Study and the Copenhagen City Heart Study combined (n = 16 967) as a function of transthyretin percentile at baseline with and without adjustment for Framingham risk factors for ischemic heart disease

Endpoint	***≤5th percentile (n=833)***	***>5-95th percentile (n=15,297)***	***>95th percentile (n=837)***
Adjustment			
	Hazard ratio (95% CI)		Hazard ratio (95% CI)
Any heart failure			
Age and Sex	1.5 (1.3-1.9)	1 [Reference]	1.2 (1.0-1.5)
Framingham[a]	1.5 (1.2-1.8)	1 [Reference]	1.2 (1.0-1.5)
Non-ischemic HF[b]			
Age and Sex	1.5 (1.2-.1.9)	1 [Reference]	1.4 (1.1-1.8)
Framingham[a]	1.4 (1.1-1.8)	1 [Reference]	1.4 (1.1-1.8)
Ischemic HF			
Age and Sex	1.7 (1.1-2.5)	1 [Reference]	0.8 (0.5-1.4)
Framingham[a]	1.6 (1.1-2.4)	1 [Reference]	0.7 (0.4-1.3)

[a] Framingham risk score components = age (underlying timeline), sex (stratification variable), smoker, diabetes, treated hypertension, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol.
[b] This analysis included 420 less individuals who had experienced an ischemic event prior to blood draw for baseline plasma transthyretin measurement.
To account for between study heterogeneity, all analyses used study cohort as a stratification variable (allowing for separate baseline hazard functions in the two study cohorts).
CI, confidence interval; HF, heart failure; hsCRP, high sensitivity C-reactive protein.

eTable 5. Hazard ratios for spinal stenosis, carpal tunnel syndrome, biceps tendon rupture, and amyloidosis in the Copenhagen General Population Study and the Copenhagen City Heart Study combined (n = 16 967) as a function of transthyretin percentile at baseline

Endpoint	**ICD10 code**	**Total number of events**	**≤5th percentile (n=854)**	**>5th percentile (n=16,113)**
Adjustment				
			Hazard ratio (95% CI)	
Spinal stenosis	M48.0			
Age, sex and study cohort[a]		625	1.02 (0.71-1.47)	1 [Reference]
Age, sex, hsCRP and study cohort[b]		625	0.99 (0.69-1.42)	1 [Reference]
Carpal tunnel syndrome	G56.00			
Age, sex and study cohort[a]		231	1.23 (0.72-2.12)	1 [Reference]
Age, sex, hsCRP and study cohort[b]		231	1.23 (0.72-2.12)	1 [Reference]
Biceps tendon rupture	S46.1, S46.2			
Age, sex and study cohort[a]		47	NA[c]	1 [Reference]
Age, sex, hsCRP and study cohort[b]		47	NA[c]	1 [Reference]
Amyloidosis	E85.X			
Age, sex and study cohort[a]		6	4.27 (0.49-37.2)	1 [Reference]
Age, sex, hsCRP and study cohort[b]		6	3.54 (0.40-31.3)	1 [Reference]

[a] Adjusted by age and stratified by sex and study cohort.
[b] Adjusted by age (underlying timeline), log-transformed hsCRP and stratified by sex and study cohort.
[c] No events in ≤5th percentile. hsCRP, high sensitivity C-reactive protein.
NA, not applicable.

eTable 6. Baseline characteristics of individuals in the Copenhagen General Population Study as a function of *TTR* genotype

Characteristic	Other (n=3)[a]	p.G26S (n=1,378)	WT (n=8,135)	p.T139M (n=43)	*P* value
Clinical parameters					
Age, years	41 (35-78)	55 (47-65)	55 (47-65)	54 (49-70)	
Female	0.00%	53.9%	52.9%	51.1%	
Body mass index, kg/m^2	25.9 (24.7-25.9)	25.7 (23.2-28.5)	25.7 (23.3-28.5)	26.0 (22.2-28.1)	
Diabetes	0.0%	3.5%	4.1%	9.3%	
Prior myocardial infarction	0.0%	2.3%	2.1%	4.7%	
Statin	0.0%	5.5%	6.4%	2.3%	
Hypertension[b]	66.7%	56.9%	57.5%	53.5%	
Smoking, pack-years	36 (8-72)	6 (0-24)	6 (0-25)	0 (0-6)	
Alcohol, Units/week[c]	8 (8-8)	9 (4-16)	9 (4-16)	9 (4-13)	
Physical inactivity[d]	0.0%	55.4%	55.7%	55.8%	
Biomarkers					
Transthyretin, mg/dL	25.7 (23.2-30.8)	28.4 (25.0-32.3)	28.8 (24.9-33.0)	33.6 (28.7-38.7)	<.001
Alanine transaminase, U/L	25 (11-26)	21 (16-29)	21 (16-29)	21 (16-27)	
Albumin, g/L	44 (43-45)	42 (40-45)	42 (40-45)	42 (40-46)	
Cholesterol, mmol/L	5.4 (5.4-6.4)	5.7 (5.0-6.4)	5.6 (5.0-6.4)	5.7 (5.1-6.6)	
Triglycerides, mmol/L	1.8 (1.2-2.7)	1.5 (1.0-2.1)	1.5 (1.0-2.2)	1.5 (1.1-2.1)	
Creatinine, µmol/L	82 (80-129)	81 (73-89)	80 (72-88)	81 (75-96)	
hsC-reactive protein, mg/L	2.1 (0.6-3.3)	1.3 (0.6-2.8)	1.3 (0.6-2.8)	0.9 (0.7-2.4)	

[a] *TTR* p.H110N, p.D119N and p.V142I combined. For legacy names subtract 20 amino acids.

[b] Hypertension was systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or self-reported use of antihypertensive medication.
[c] 1 Unit of alcohol = 12 grams.
[d] <4 hours light leisure time physical activity per week.
Values are median (interquartile range) or percent.
P values reflect Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. Empty cells indicate *P* ≥ .001

eTable 7. Baseline characteristics of individuals in the Copenhagen City Heart Study as a function of *TTR* genotype

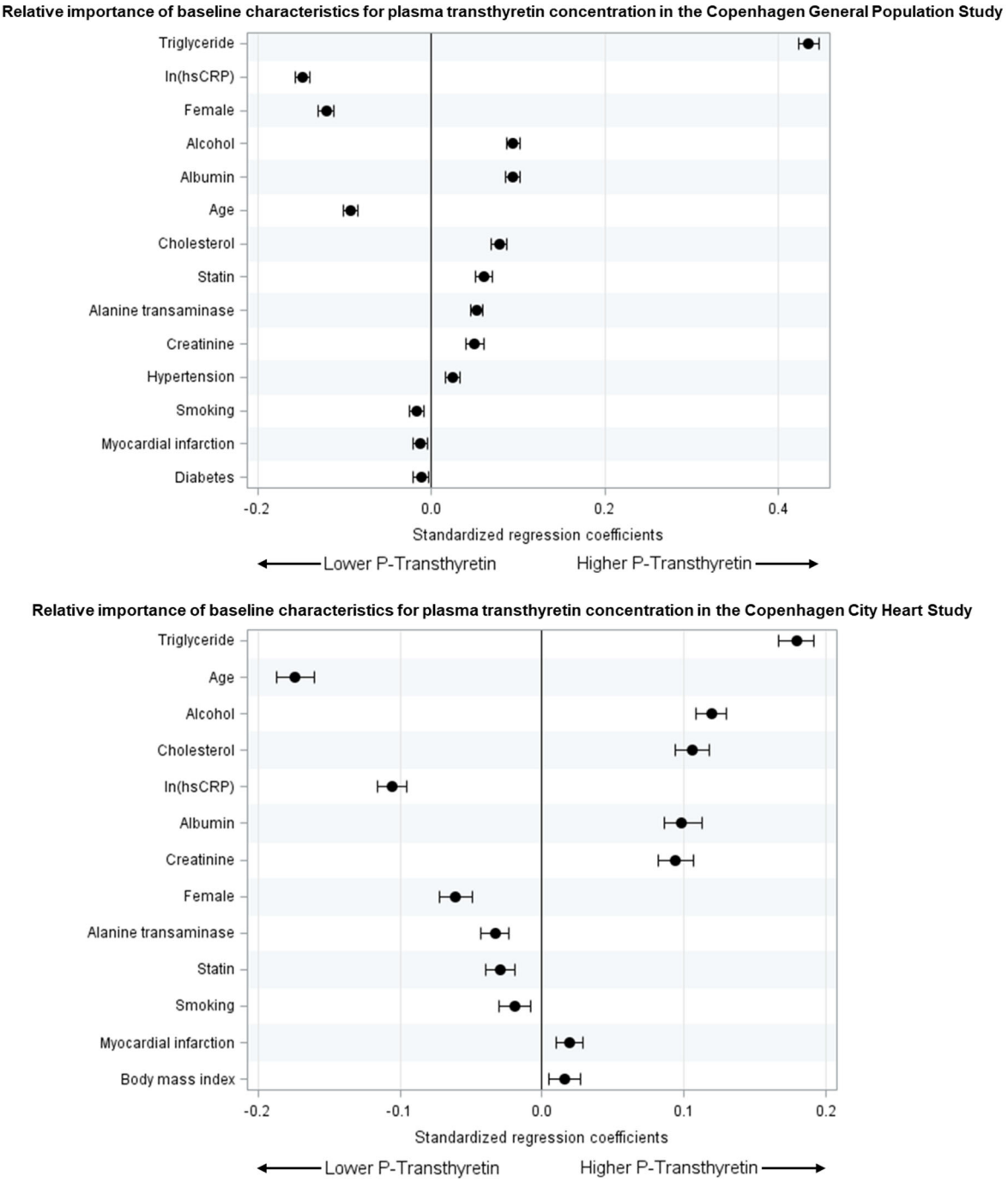
Characteristic	Other (n=9)[a]	p.G26S (n=1,069)	WT (n=5,984)	p.T139M (n=32)	*P* value
Clinical parameters					
Age, years	63 (52-72)	59 (47-69)	59 (46-69)	62 (47-71)	
Female	33.3%	60.0%	59.7%	71.9%	
Body mass index, kg/m^2	22.6 (20.6-23.6)	24.9 (22.3-28.1)	24.9 (22.5-27.9)	24.9 (22.6-27.7)	
Diabetes	11.1%	2.4%	3.9%	6.3%	
Prior myocardial infarction	22.2%	2.4%	2.2%	6.3%	<.001
Statin	0.0%	0.8%	0.9%	0.0%	
Hypertension[b]	33.3%	54.2%	53.1%	56.3%	
Smoking, pack-years	29 (3-38)	14 (0-31)	12 (0-30)	2 (0-23)	
Alcohol, Units/week[c]	5 (2-10)	6 (2-13)	6 (2-13)	4 (1-6)	
Physical inactivity[d]	44.4%	64.3%	65.1%	65.6%	
Biomarkers					
Transthyretin, mg/dL	19.8 (17.1-22.8)	22.8 (19.2-27.6)	23.2 (19.2-28.4)	30.5 (23.4-36.9)	<.001
Alanine transaminase, U/L	14 (9-19)	12 (9-18)	13 (9-18)	12 (9-16)	
Albumin, g/L	32 (32-35)	32 (31-33)	32 (31-33)	31 (30-33)	
Cholesterol, mmol/L	6.3 (5.5-7.0)	6.1 (5.3-6.9)	6.1 (5.2-7.0)	5.8 (5.2-6.5)	
Triglycerides, mmol/L	1.3 (0.9-1.4)	1.6 (1.1-2.2)	1.5 (1.1-2.2)	1.4 (1.0-2.2)	
Creatinine, µmol/L	85 (82-89)	85 (78-95)	86 (78-94)	85 (74-95)	
hsC-reactive protein, mg/L	1.3 (1.3-1.5)	1.7 (1.2-2.8)	1.6 (1.2-2.6)	1.6 (1.3-2.2)	

[a] *TTR* p.H110N, p.D119N and p.V142I combined. For legacy names subtract 20 amino acids.
[b] Hypertension was systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or self-reported use of antihypertensive medication.
[c] 1 Unit of alcohol = 12 grams.
[d] <4 hours light leisure time physical activity per week.
Values are median (interquartile range) or percent.
P values reflect Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. Empty cells indicate *P* ≥ .001.

eTable 8. Hazard ratios for heart failure in individuals in the Copenhagen General Population Study and the Copenhagen City Heart Study combined (n = 16 672) as a function of transthyretin concentration at baseline (adjusted for *TTR* genotype) and *TTR* genotype (adjusted for transthyretin)

Multivariable adjustment[a]	**Hazard ratio (95% CI) for heart failure (n=1,504 events)**
Plasma transthyretin	
>5-100th percentile (n=15,843)	1 [Reference]
≤5th percentile (n=829)	1.4 (1.1-1.7)
TTR genotype	
p.T139M (n=75)	1 [Reference]
WT (n=14,118)	1.0 (0.5-2.3)
p.G26S (n=2,467)	1.2 (0.5-2.6)
Other variants (n=12)	2.1 (0.5-8.4)

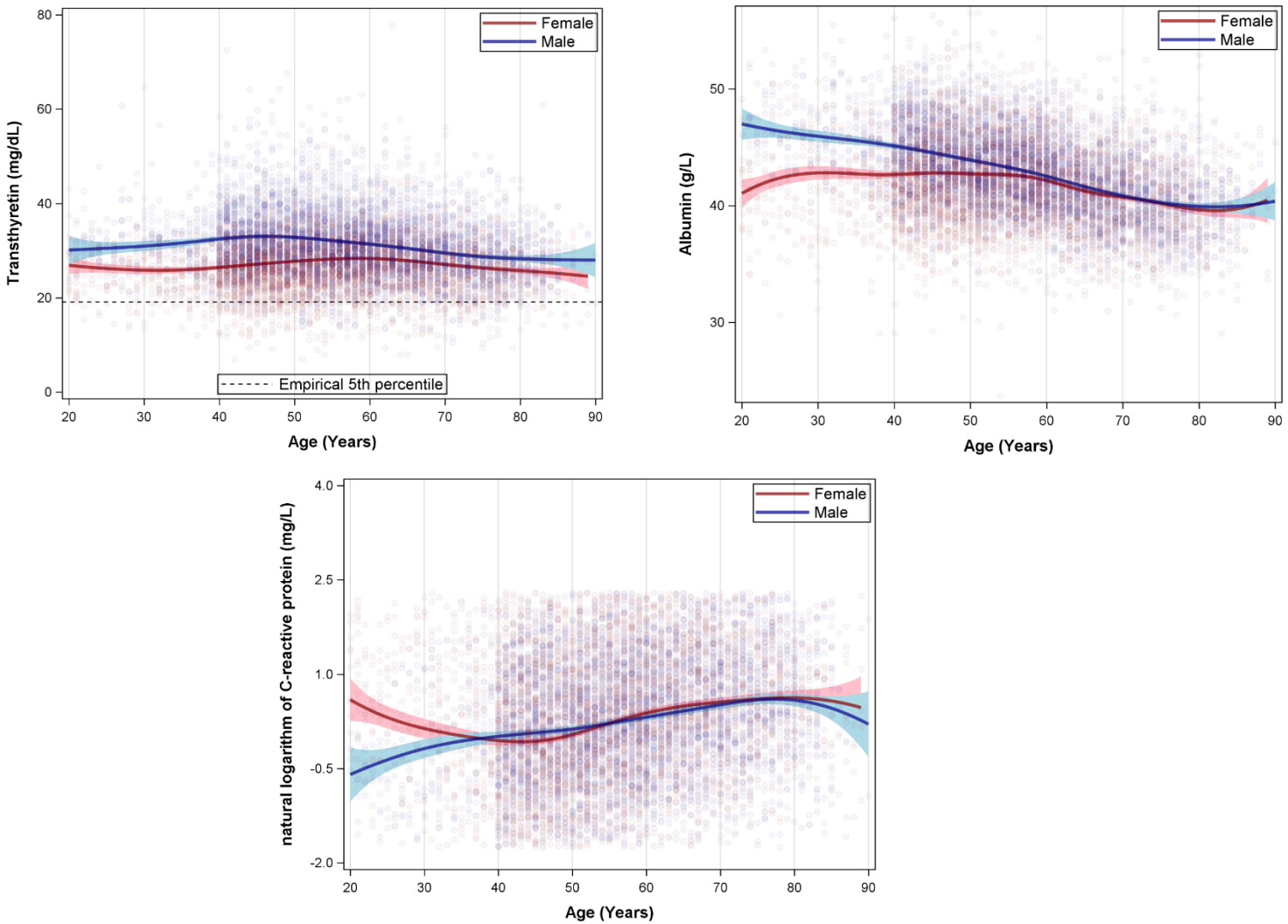
[a]Adjusted by age (underlying timeline), sex, body mass index, lipid-lowering therapy, hypertension, alcohol intake, smoking (pack-years), physical inactivity, alanine transaminase, albumin, cholesterol, triglycerides, log-transformed hsCRP, creatinine and *TTR* genotype (plasma transthyretin, top) or plasma transthyretin (*TTR* genotypes, bottom). Stratified by sex and study cohort.
CI, confidence interval; hsCRP, high sensitivity C-reactive protein.



eFigure 1. Forest plot depicting the relative importance (cross-sectional) of baseline characteristics for plasma transthyretin concentrations in the Copenhagen General Population Study (top panel) and the Copenhagen City Heart Study (bottom panel)

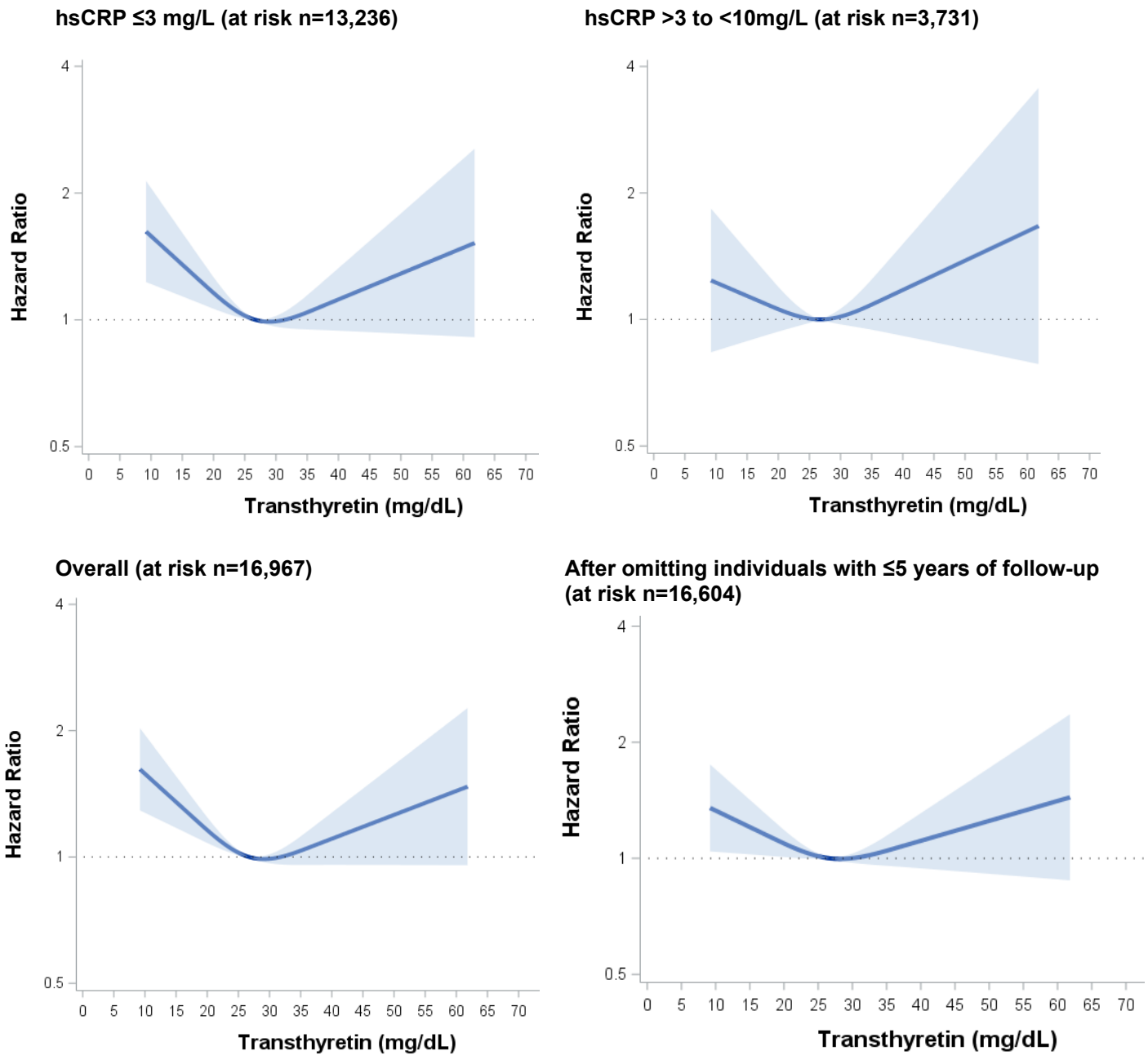
Baseline characteristics (y-axis) are ranked by descending importance, i.e. standardized regression coefficients (x-axis). A standardized regression coefficient is an estimate of the magnitude of change in the outcome variable (plasma transthyretin) for a standardized change in each of the investigated variables when holding all other covariables fixed. The solid vertical line indicates no effect; a negative value of the

standardized regression coefficient signifies an inverse correlation between the investigated variable and transthyretin concentration, while a positive value signifies a direct correlation between the investigated variable and plasma transthyretin.
ln(hsCRP), natural logarithm of high-sensitivity C reactive protein



eFigure 2. Heat maps of plasma transthyretin (top left panel), plasma albumin (top right panel), and natural log–transformed plasma high-sensitivity C-reactive protein by sex and age in the Copenhagen General Population Study

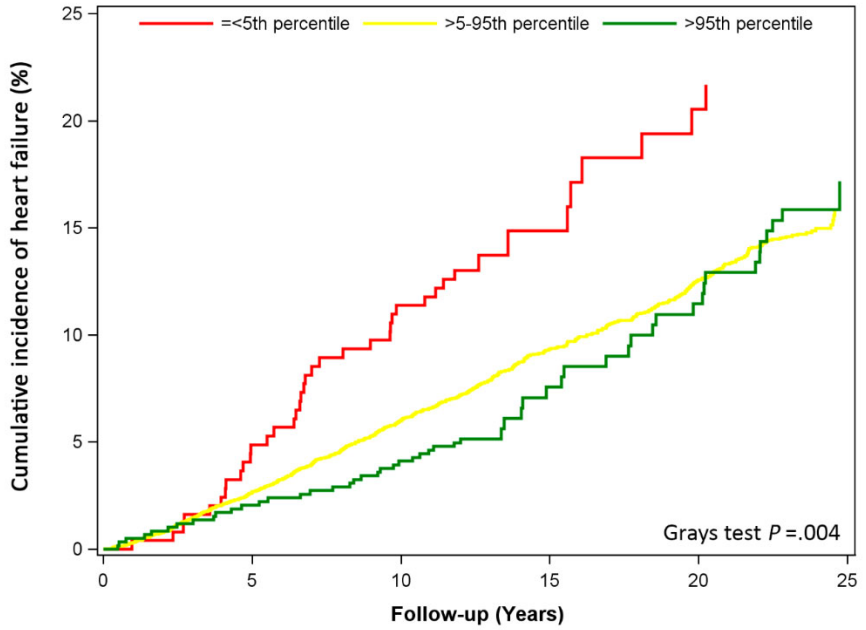
Regression lines indicate natural cubic splines for the association of age with plasma transthyretin, plasma albumin, and plasma hsCRP, respectively. Shaded areas correspond to 95% confidence limits for the regression line.



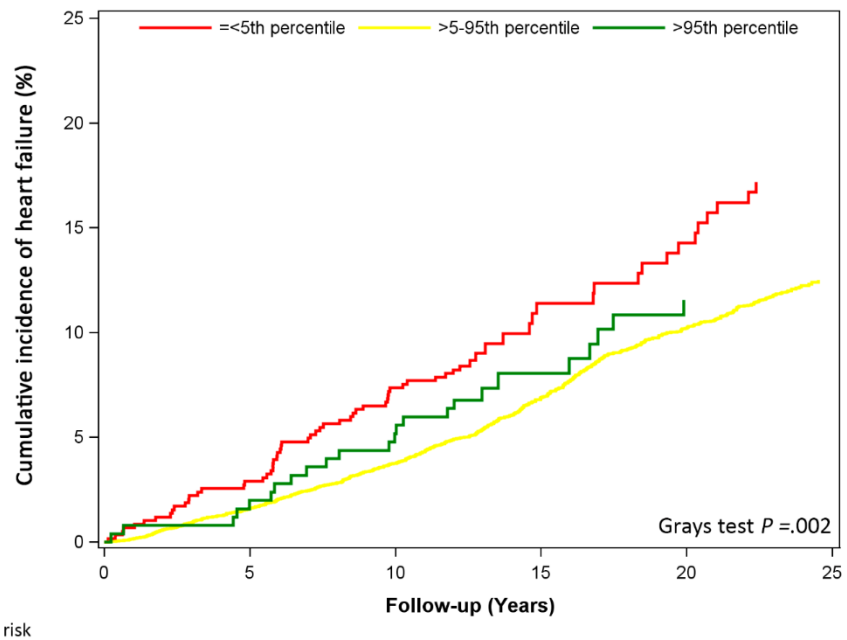
eFigure 3. Hazard ratios for incident heart failure according to cubic spline regression of plasma transthyretin in the Copenhagen General Population Study and the Copenhagen City Heart Study combined (n = 16 967; top left panel), after omitting individuals with 5 years or less of follow-up (n = 19 604; top right panel), and stratified by high-sensitivity C-reactive protein levels (bottom left and right panels)

Hazard ratios reflect adjustment by age and stratification by sex and study cohort. Top left and top right panel reflect stratification according to baseline high-sensitivity C-reactive protein ≤3mg/L and >3 to <10 mg/L, respectively. *P*=0.03 for test of interaction between plasma transthyretin and baseline high-sensitivity C-reactive protein level (≤3 mg/L) on risk of incident heart failure. Bottom right panel: 363 heart

failure events had occurred within the first 5 years of follow-up and 1,200 events occurred after the first 5 years (only 1 event was tallied per subject).
hsCRP, high-sensitivity C-reactive protein.



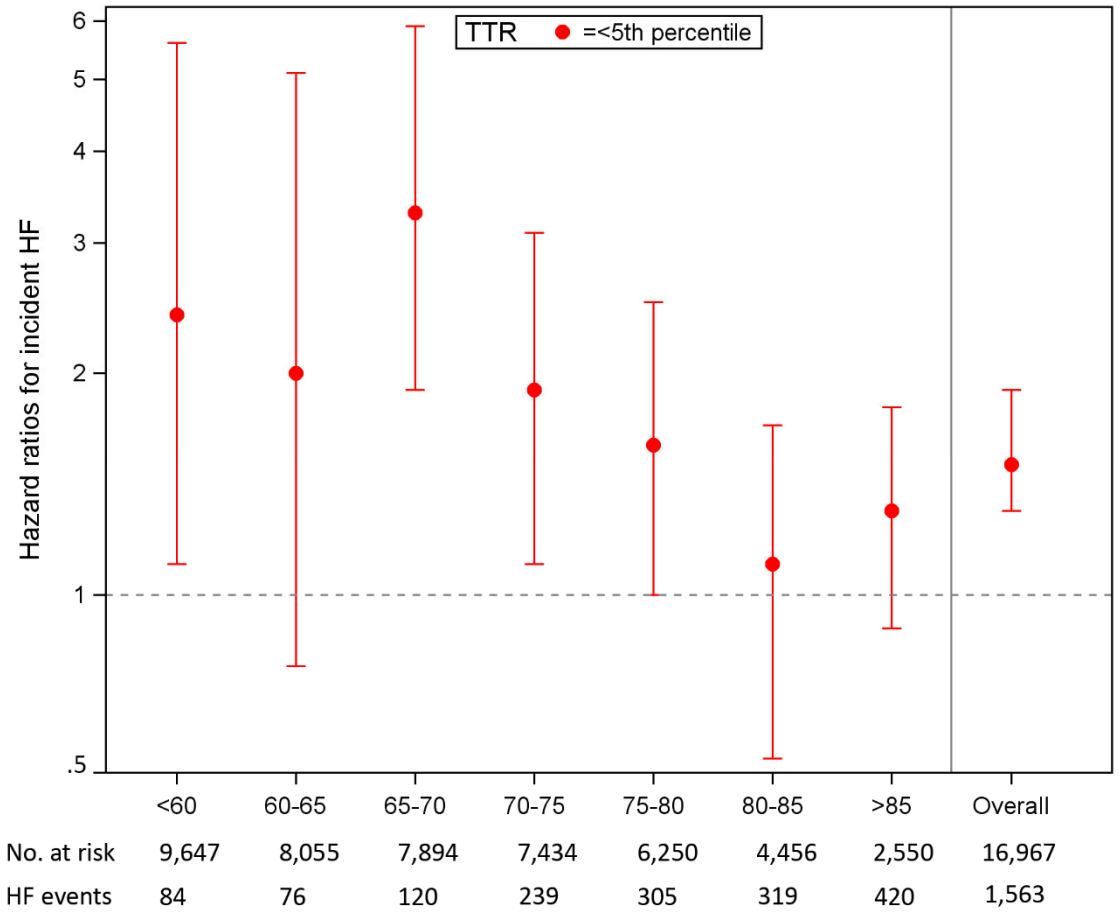
No. at risk						
≤5th percentile	247	194	150	40	26	0
5-95th percentile	6,606	6,007	5,218	1,577	1,279	63
>95th percentile	585	549	500	156	129	23



No. at risk						
≤5th percentile	586	525	447	131	98	0
5-95th percentile	8,691	8,192	7,417	2,654	2,127	100
>95th percentile	252	237	215	109	89	25

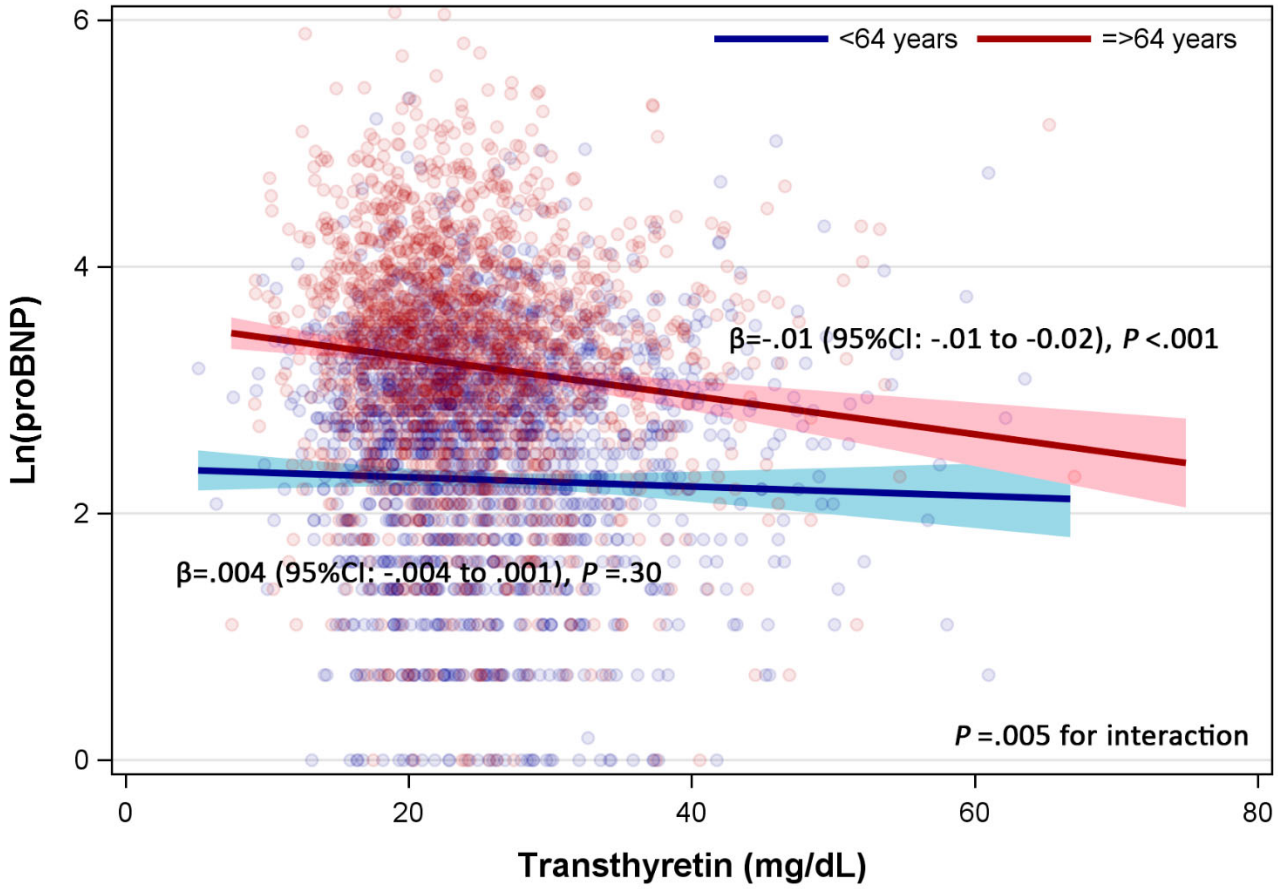
eFigure 4. Cumulative incidence of heart failure in men (left panel; n = 7438) and women (right panel; n = 9529) as a function of years since blood testing (baseline) and transthyretin percentile groups in the Copenhagen General Population Study and the Copenhagen City Heart Study

Event rates reflect heart failure probabilities in percent when using death as a competing event.



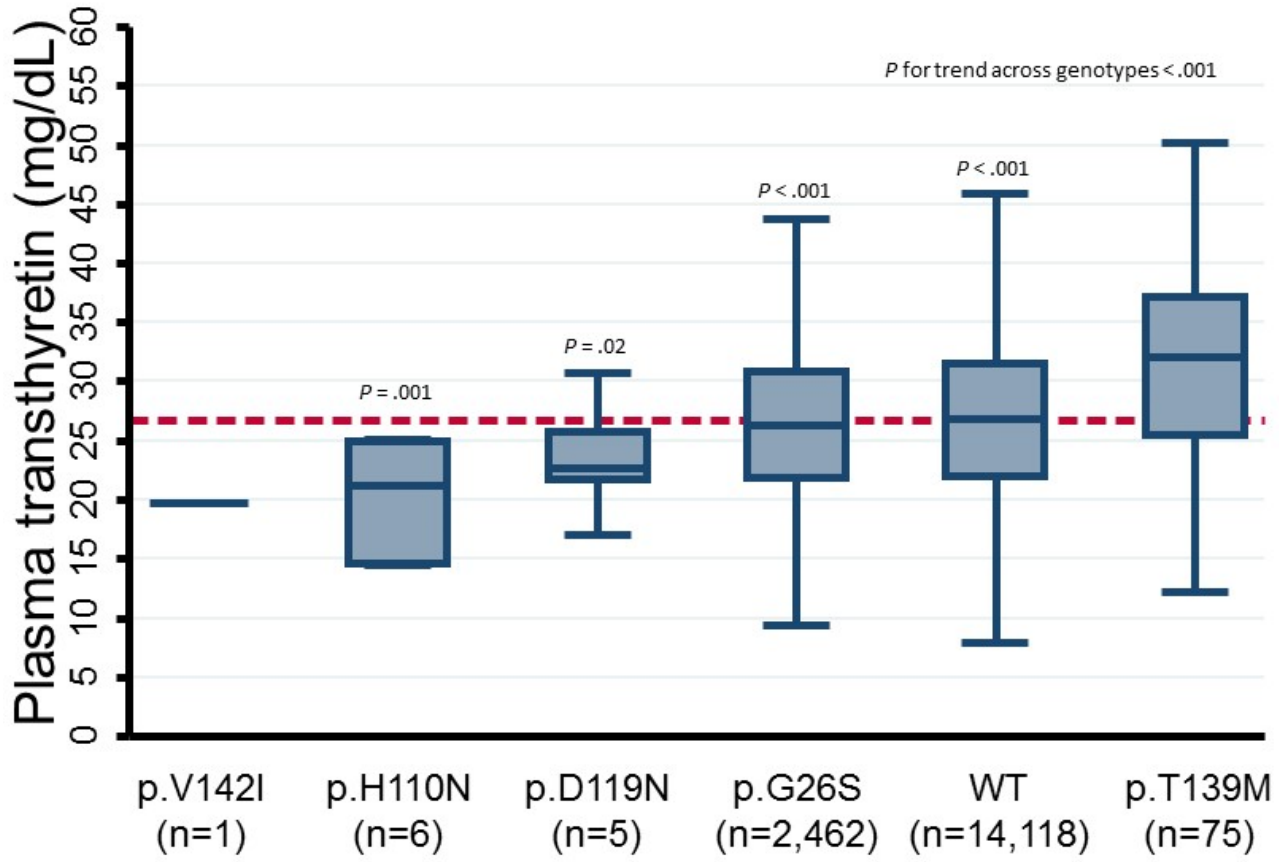
eFigure 5. Hazard ratios and 95% CIs for incident heart failure as a function of age at time of heart failure diagnosis or censoring for those with plasma transthyretin concentration at or below the 5th percentile at baseline (using 5th to 95th percentile as reference)

Hazard ratios reflect adjustment by age and stratification by study cohort, sex and high-sensitivity C-reactive protein. The number of individuals at risk do not sum up to 16,967, because each participant could be at risk in multiple age-categories provided he/she was observed but did not develop heart failure (sigma algebra). HF, heart failure.



eFigure 6. NT-proBNP as a function of plasma transthyretin concentration stratified by age in 3891 individuals from the 2001-2003 examination of the Copenhagen City Heart Study

Blue reflects age below (min-max 31-64 years) and red above (min-max 64-97 years) the study median. NT-proBNP, N-terminal pro-brain natriuretic peptide. Of note, these data should be interpreted with caution, because the approximate 10-year gap between these data (2001-2003) and the measurement of plasma transthyretin concentration (in 1991-1994) introduces possible immortal time bias, i.e. those who died between 1991-1994 and 2001-2003 were ineligible (likely the most ill).



eFigure 7. Plasma transthyretin concentration as a function of *TTR* genotypes in the Copenhagen City Heart Study and the Copenhagen General Population Study combined

P values are by Mann-Whitney U test with *TTR* T139M heterozygotes, the most stable genotype, as the reference. Values are median and interquartile range.