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Supplemental Tables and Figures

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Table S1 Correlation analyses

| | eGFR | Phosphate | FePi | Calcium | nox-PTH | PTH | 25-OH-vit. D ₃ | 1,25-(OH) ₂ -vit. D ₃ | CRP | FGF-23 | sKlotho |
|---|---------------------|---------------------|---------------------|-----------------|---------------------|---------------------|---------------------------|---|-------------------|-------------------|-------------------|
| eGFR | - | r = -0.27 | r = -0.43 | r = 0.03 | r = -0.29 | r = -0.36 | r=0.01 | r=0.18 | r=-0.07 | r=-0.42 | r=0.11 |
| | | p < 0.001 | p < 0.001 | p = 0.38 | p < 0.001 | p < 0.001 | p=0.66 | p<0.001 | p=0.02 | p<0.001 | p<0.001 |
| Phosphate | r = -0.27 | - | r = 0.02 | r = 0.01 | r = 0.01 | r = 0.03 | r=0.06 | r=-0.20 | r=0.02 | r=0.23 | r=-0.03 |
| | p < 0.001 | | p = 0.45 | p = 0.84 | p = 0.70 | p = 0.28 | p=0.05 | p<0.001 | p=0.50 | p<0.001 | p=0.29 |
| FePi | r = -0.43 | r = 0.02 | - | r = -0.06 | r = 0.30 | r = 0.36 | r=-0.03 | r=-0.08 | r=0.22 | r=0.28 | r=-0.04 |
| | p < 0.001 | p = 0.454 | | p = 0.07 | p < 0.001 | p < 0.001 | p=0.36 | p=0.01 | p<0.001 | p<0.001 | p=0.23 |
| Calcium | r = 0.03 | r = 0.01 | r = -0.06 | - | r = -0.06 | r = -0.07 | r=0.06 | r=-0.02 | r=0.00 | r=-0.02 | r=-0.01 |
| | p = 0.38 | p = 0.84 | p = 0.07 | | p = 0.05 | p = 0.04 | p=0.05 | p=0.58 | p=0.95 | P=0.46 | p=0.87 |
| nox-PTH | r = -0.29 | r = 0.01 | r = 0.30 | r = -0.06 | - | r = 0.55 | r=-0.10 | r=0.02 | r=0.02 | r=0.21 | r=0.01 |
| | p < 0.001 | p = 0.701 | p < 0.001 | p = 0.05 | | p < 0.001 | p=0.001 | p=0.40 | p=0.51 | p<0.001 | p=0.87 |
| PTH | r = -0.36 | r = 0.03 | r = 0.36 | r = -0.07 | r = 0.55 | - | r=-0.16 | r=0.01 | r=0.10 | r=0.30 | r=-0.00 |
| | p < 0.001 | p = 0.276 | p < 0.001 | p = 0.04 | p < 0.001 | | p<0.001 | p=0.77 | p=0.001 | p<0.001 | p=0.89 |
| 25-OH-vit. D₃ | r=0.01 | r=0.03 | r=-0.03 | r=0.06 | r=-0.10 | r=-0.16 | - | r=0.08 | r=-0.01 | r=0.04 | r=-0.06 |
| | p=0.66 | p=0.36 | p=0.36 | p=0.05 | p=0.001 | p<0.001 | | p=0.004 | p=0.79 | p=0.18 | p=0.07 |
| 1,25-(OH)₂-vit. D₃ | r=0.18 | r=-0.20 | r=-0.08 | r=-0.02 | r=0.02 | r=0.01 | r=0.08 | - | r=0.01 | r=-0.16 | r=0.06 |
| | p<0.001 | p<0.001 | p=0.01 | p=0.58 | p=0.40 | p=0.77 | p=0.004 | | p=0.82 | p<0.001 | p=0.05 |
| CRP | r=-0.07 | r=0.02 | r=0.22 | r=0.00 | r=0.02 | r=0.10 | r=-0.01 | r=0.01 | - | r=0.12 | r=-0.07 |
| | p=0.02 | p=0.50 | p<0.001 | p=0.95 | p=0.51 | p=0.001 | p=0.79 | p=0.82 | | p<0.001 | p=0.03 |
| FGF-23 | r=-0.42 | r=0.23 | r=0.28 | r=-0.02 | r=0.21 | r=0.30 | r=0.04 | r=-0.16 | r=0.12 | - | r=0.02 |
| | p<0.001 | p<0.001 | p<0.001 | P=0.46 | p<0.001 | p<0.001 | p=0.18 | p<0.001 | p<0.001 | | p=0.44 |
| sKlotho | r=0.11 | r=-0.03 | r=-0.04 | r=-0.01 | r=0.01 | r=-0.00 | r=-0.06 | r=0.06 | r=-0.07 | r=-0.08 | - |
| | p<0.001 | p=0.29 | p=0.23 | p=0.87 | p=0.87 | p=0.89 | p=0.07 | p=0.05 | p=0.03 | p=0.02 | |

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eGFR: estimated glomerular filtration rate; FePi: urinary fractional phosphate excretion; PTH: intact parathyroid hormone; nox-PTH: non-oxidized parathyroid hormone; CRP: C-reactive protein; FGF-23: fibroblast growth factor 23; sKlotho: soluble Klotho; r: correlation coefficient (Kendall-Tau).

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Table S2 Associations of parathyroid hormone / non-oxidized parathyroid hormone ratio with atherosclerotic events among 535 participants in the CARE FOR HOME study

| Variable | | Person years of FU | N events | Unadjusted analysis | | Adjustment for kidney function | | Adjustment for kidney function and classical cardiovascular risk factors | | Adjustment for kidney function, classical cardiovascular risk factors and CKD-specific risk factors | |
|--------------------------|---------------------------------------|--------------------------|-------------|---------------------|--------|-----------------------------------|------|---|------|---|------|
| | | | | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p |
| Continuous variable | | | | | | | | | | | |
| Ratio | | | | | | | | | | | |
| PTH/ nox-PTH | | 2255 | 116 | 1.07 (1.03-1.11) | <0.001 | 1.02 (0.97-1.06) | 0.50 | 1.00 (0.96-1.04) | 0.96 | 1.00 (0.96-1.05) | 0.89 |
| Categorized variable | | | | | | | | | | | |
| Ratio PTH/ nox-PTH | 1 st tertile (0.1-5.7) | 770 | 31 | Reference | | Reference | | Reference | | Reference | |
| | 2 nd tertile (5.8-7.6) | 746 | 32 | 1.09 (0.66-1.81) | 0.74 | 0.95 (0.57-1.59) | 0.85 | 0.82 (0.54-1.47) | 0.82 | 0.86 (0.50-1.47) | 0.58 |
| | 3 rd tertile (7.7-42.3) | 705 | 53 | 1.88 (1.19-2.97) | 0.007 | 1.06 (0.64-1.74) | 0.83 | 0.89 (0.54-1.47) | 0.65 | 0.90 (0.53-1.51) | 0.69 |

HR: hazard ratio; CI: confidence interval; FU: Follow-up; N: Number of patients with atherosclerotic events; PTH, nox-PTH and albuminuria have been log-transformed due to skewed distribution.

Adjustment for “kidney function” comprises eGFR and log albuminuria.

Adjustment for “kidney function and classical cardiovascular risk factors” comprises eGFR, log albuminuria, age, gender, diabetes mellitus, body mass index, LDL-cholesterol and prevalent cardiovascular disease.

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Adjustment for “kidney function, classical cardiovascular risk factors and CKD-specific risk factors” comprises eGFR, log albuminuria, age, gender, diabetes mellitus, body mass index, LDL-cholesterol, prevalent cardiovascular disease, log-CRP, plasma albumin, plasma phosphate, plasma calcium, 25-OH-vitamin D3-levels and log FGF-23.

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Table S3 Associations of parathyroid hormone / non-oxidized parathyroid hormone ratio with acute heart failure among 535 participants in the CARE FOR HOME study

| Variable | | Person years of FU | N events | Unadjusted analysis | | Adjustment for kidney function | | Adjustment for kidney function and classical cardiovascular risk factors | | Adjustment for kidney function, classical cardiovascular risk factors and CKD-specific risk factors | |
|-----------------------|---------------------------------------|--------------------------|-------------|---------------------|--------|-----------------------------------|------|---|------|---|------|
| | | | | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p |
| Continuous variable | | | | | | | | | | | |
| Ratio | | | | | | | | | | | |
| PTH/ nox-PTH | | 2405 | 58 | 1.09 (1.06-1.13) | <0.001 | 1.05 (1.01-1.10) | 0.03 | 1.02 (0.98-1.06) | 0.44 | 1.03 (0.98-1.08) | 0.23 |
| Categorized variable | | | | | | | | | | | |
| Ratio PTH/ nox-PTH | 1 st tertile (0.1-5.7) | 821 | 8 | Reference | | Reference | | Reference | | Reference | |
| | 2 nd tertile (5.8-7.6) | 792 | 18 | 2.37 (1.03-5.44) | 0.04 | 1.84 (0.80-4.28) | 0.15 | 1.42 (0.60-3.38) | 0.43 | 1.54 (0.64-3.71) | 0.33 |
| | 3 rd tertile (7.7-42.3) | 752 | 32 | 4.56 (2.10-9.89) | <0.001 | 2.46 (1.08-5.59) | 0.03 | 2.22 (0.98-5.06) | 0.06 | 1.90 (0.82-4.36) | 0.13 |

HR: hazard ratio; CI: confidence interval; FU: Follow-up; N: Number of patients with acute heart failure; PTH, nox-PTH and albuminuria have been log-transformed due to skewed distribution. Person years of follow-up are provided as median (inter-quartile range).

Adjustment for “kidney function” comprises eGFR and log albuminuria

Adjustment for “kidney function and classical cardiovascular risk factors” comprises eGFR, log albuminuria, age, gender, diabetes mellitus, body mass index, LDL-cholesterol and prevalent cardiovascular disease

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Adjustment for “kidney function, classical cardiovascular risk factors and CKD-specific risk factors” comprises eGFR, log albuminuria, age, gender, diabetes mellitus, body mass index, LDL-cholesterol, prevalent cardiovascular disease, log-CRP, plasma albumin, plasma phosphate, plasma calcium, 25-OH-vitamin D3-levels and log FGF-23.

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Table S4 Associations of parathyroid hormone / non-oxidized parathyroid hormone ratio with CKD-progression among 535 participants in the CARE FOR HOME study

| Variable | | Person years of FU | N events | Unadjusted analysis | | Adjustment for kidney function | | Adjustment for kidney function and classical cardiovascular risk factors | | Adjustment for kidney function, classical cardiovascular risk factors and CKD-specific risk factors | |
|----------------------|---------------------------------------|--------------------------|-------------|---------------------|--------|-----------------------------------|------|---|------|---|------|
| | | | | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p |
| Continuous variable | | | | | | | | | | | |
| Ratio | | | | | | | | | | | |
| PTH/ nox-PTH | | 2350 | 73 | 1.12 (1.08-1.15) | <0.001 | 1.02 (0.98-1.07) | 0.29 | 1.03 (0.98-1.08) | 0.28 | 1.04 (0.98-1.10) | 0.19 |
| Categorized variable | | | | | | | | | | | |
| Ratio | 1 st tertile (0.1-5.7) | 828 | 13 | Reference | | Reference | | Reference | | Reference | |
| PTH/ nox-PTH | 2 nd tertile (5.8-7.6) | 777 | 16 | 1.31 (0.63-2.71) | 0.48 | 0.92 (0.44-1.94) | 0.83 | 0.85 (0.40-1.83) | 0.69 | 0.95 (0.43-2.10) | 0.90 |
| | 3 rd tertile (7.7-42.3) | 704 | 44 | 3.82 (2.05-7.13) | <0.001 | 1.07 (0.54-2.11) | 0.85 | 0.94 (0.46-1.93) | 0.87 | 1.02 (0.49-2.13) | 0.95 |

HR: hazard ratio; CI: confidence interval; FU: Follow-up; N: Number of patients with CKD-progression; PTH, nox-PTH and albuminuria have been log-transformed due to skewed distribution. Person years of follow-up are provided as median (inter-quartile range).

Adjustment for “kidney function” comprises eGFR and log albuminuria.

Adjustment for “kidney function and classical cardiovascular risk factors” comprises eGFR, log albuminuria, age, gender, diabetes mellitus, body mass index, LDL-cholesterol and prevalent cardiovascular disease.

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Adjustment for “kidney function, classical cardiovascular risk factors and CKD-specific risk factors” comprises eGFR, log albuminuria, age, gender, diabetes mellitus, body mass index, LDL-cholesterol, prevalent cardiovascular disease, log-CRP, plasma albumin, plasma phosphate, plasma calcium, 25-OH-vitamin D3-levels and log FGF-23.

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Table S5 Associations of parathyroid hormone / non-oxidized parathyroid hormone ratio with death from any cause among 535 participants in the CARE FOR HOME study

| Variable | | Person years of FU | N events | Unadjusted analysis | | Adjustment for kidney function | | Adjustment for kidney function and classical cardiovascular risk factors | | Adjustment for kidney function, classical cardiovascular risk factors and CKD-specific risk factors | | |
|--------------------------|---------------------------------------|--------------------------|-------------|---------------------|----------------|-----------------------------------|------------------|---|------------------|---|------------------|------|
| | | | | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p | |
| Continuous variable | | | | | | | | | | | | |
| Ratio | | | | | | | | | | | | |
| PTH/ nox-PTH | | 2518 | 85 | 1.08 (1.05-1.12) | < 0.001 | 1.04 (1.00-1.08) | 0.09 | 1.02 (0.98-1.06) | 0.40 | 1.03 (0.99-1.08) | 0.16 | |
| Categorized variable | | | | | | | | | | | | |
| Ratio PTH/ nox-PTH | 1 st tertile (0.1-5.7) | 844 | 19 | Reference | | Reference | | Reference | | Reference | | |
| | 2 nd tertile (5.8-7.6) | 825 | 22 | 1.31 | 80.70-2.47) | 0.40 | 1.09 (0.58-2.07) | 0.79 | 1.10 (0.57-2.11) | 0.79 | 1.09 (0.55-2.15) | 0.81 |
| | 3 rd tertile (7.7-42.3) | 807 | 44 | 2.60 (1.48-4.58) | 0.001 | 1.51 (0.82-2.79) | 0.18 | 1.75 (0.95-3.24) | 0.07 | 1.83 (0.97-3.44) | 0.06 | |

HR: hazard ratio; CI: confidence interval; FU: Follow-up; N: Number of deceased patients; PTH, nox-PTH and albuminuria have been log-transformed due to skewed distribution. Person years of follow-up are provided as median (inter-quartile range).

Adjustment for “kidney function” comprises eGFR and log albuminuria

Adjustment for “kidney function and classical cardiovascular risk factors” comprises eGFR, log albuminuria, age, gender, diabetes mellitus, body mass index, LDL-cholesterol and prevalent cardiovascular disease

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Adjustment for “kidney function, classical cardiovascular risk factors and CKD-specific risk factors” comprises eGFR, log albuminuria, age, gender, diabetes mellitus, body mass index, LDL-cholesterol, prevalent cardiovascular disease, log-CRP, plasma albumin, plasma phosphate, plasma calcium, 25-OH-vitamin D3-levels and log FGF-23.

Figure S1: Event-free survival for atherosclerotic events. Patients were stratified into tertiles by their plasma (a) PTH- and (b) nox-PTH levels, then Kaplan-Meier analysis with log-rank testing was performed.

Figure S2: Event-free survival for CKD-progression. Patients were stratified into tertiles by their plasma (a) PTH- and (b) nox-PTH levels, then Kaplan-Meier analysis with log-rank testing was performed.

Figure S3: Event-free survival for CKD-death from any cause. Patients were stratified into tertiles by their plasma (a) PTH- and (b) nox-PTH levels, then Kaplan-Meier analysis with log-rank testing was performed.

Figure S4: Forest-plot for atherosclerotic events according to (a) PTH levels and (b) nox-PTH levels in high risk subgroups. Depicted are hazard ratios and 95% confidence intervals after full adjustment for confounders.

Figure S5: Forest-plot for acute heart failure according to (a) PTH levels and (b) nox-PTH levels in high risk subgroups. Depicted are hazard ratios and 95% confidence intervals after full adjustment for confounders.

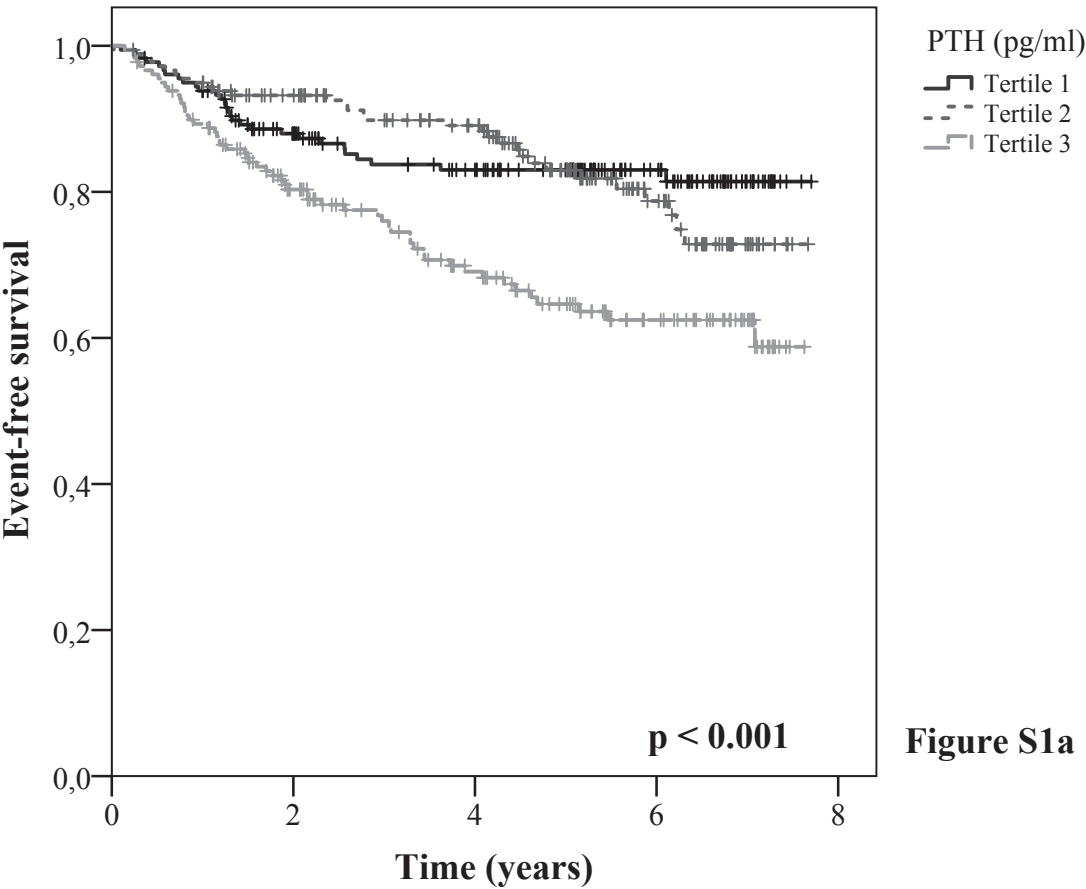
Figure S6: Forest-plot for CKD-progression according to (a) PTH levels and (b) nox-PTH levels in high risk subgroups. Depicted are hazard ratios and 95% confidence intervals after full adjustment for confounders.

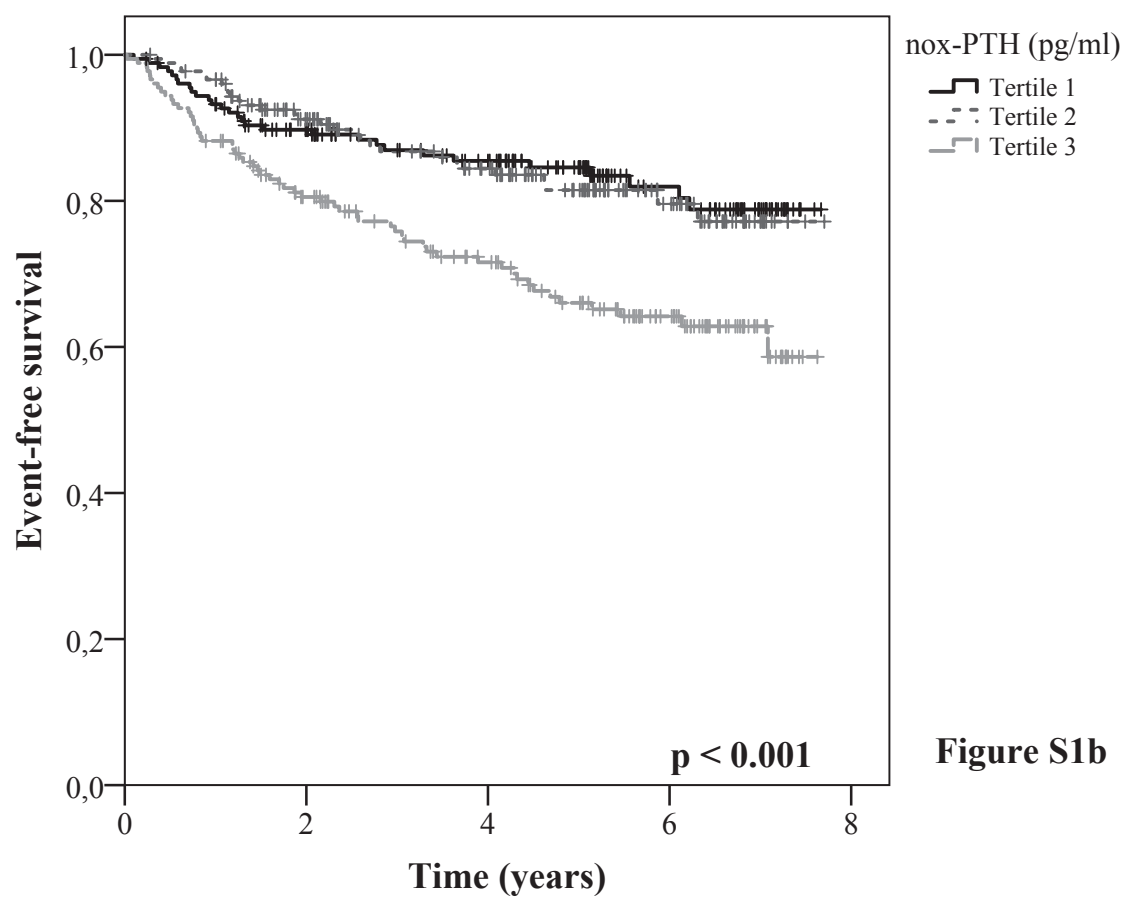
Figure S7: Forest-plot for all-cause death according to (a) PTH levels and (b) nox-PTH levels in high risk subgroups. Depicted are hazard ratios and 95% confidence intervals after full adjustment for confounders.

Figure S8: Receiver operating curves (ROC) comparing the discriminative power of plasma PTH and nox-PTH within the first 4 years of follow-up for CKD-progression. Correlated ROC curves were compared by the Delong's test for significance.

Figure S9: Receiver operating curves (ROC) comparing the discriminative power of plasma PTH and nox-PTH within the first 4 years of follow-up for all-cause death. Correlated ROC curves were compared by the Delong's test for significance.

Figure S10: Receiver operating curves (ROC) comparing the discriminative power of plasma PTH and nox-PTH within the first 4 years of follow-up for atherosclerotic events. Correlated ROC curves were compared by the Delong's test for significance.





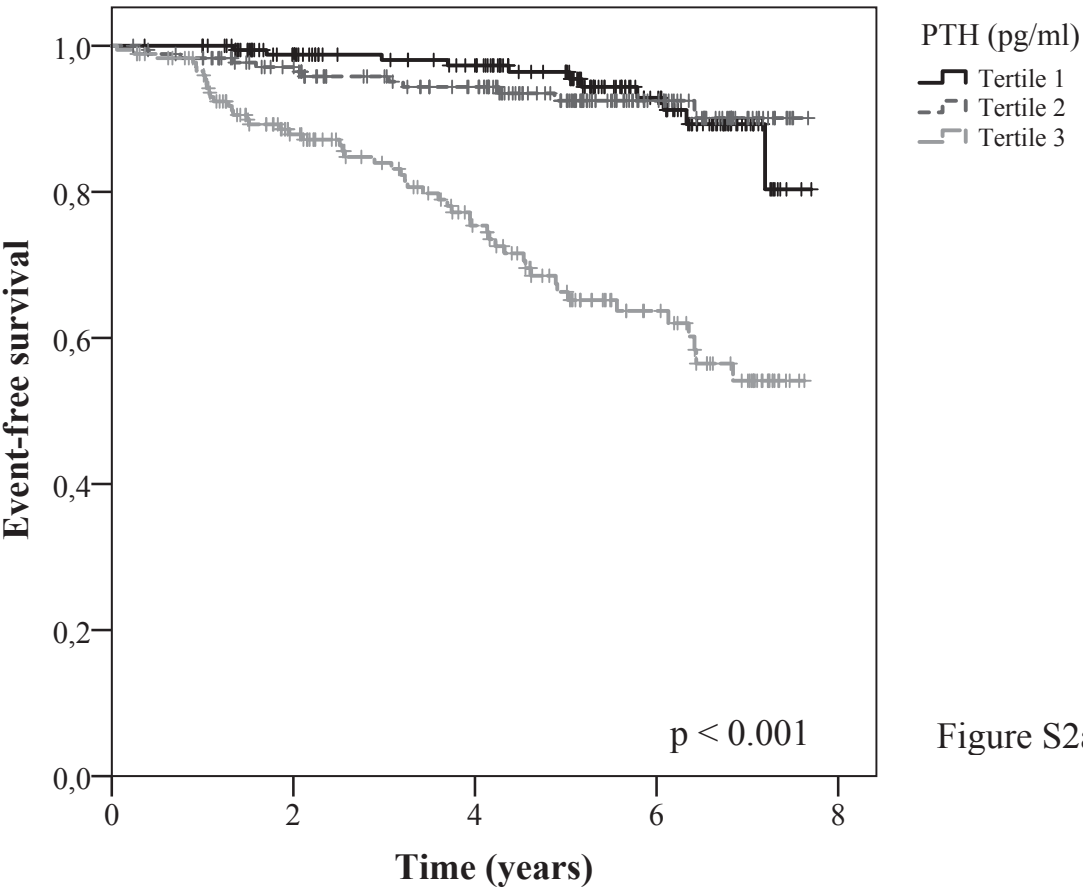
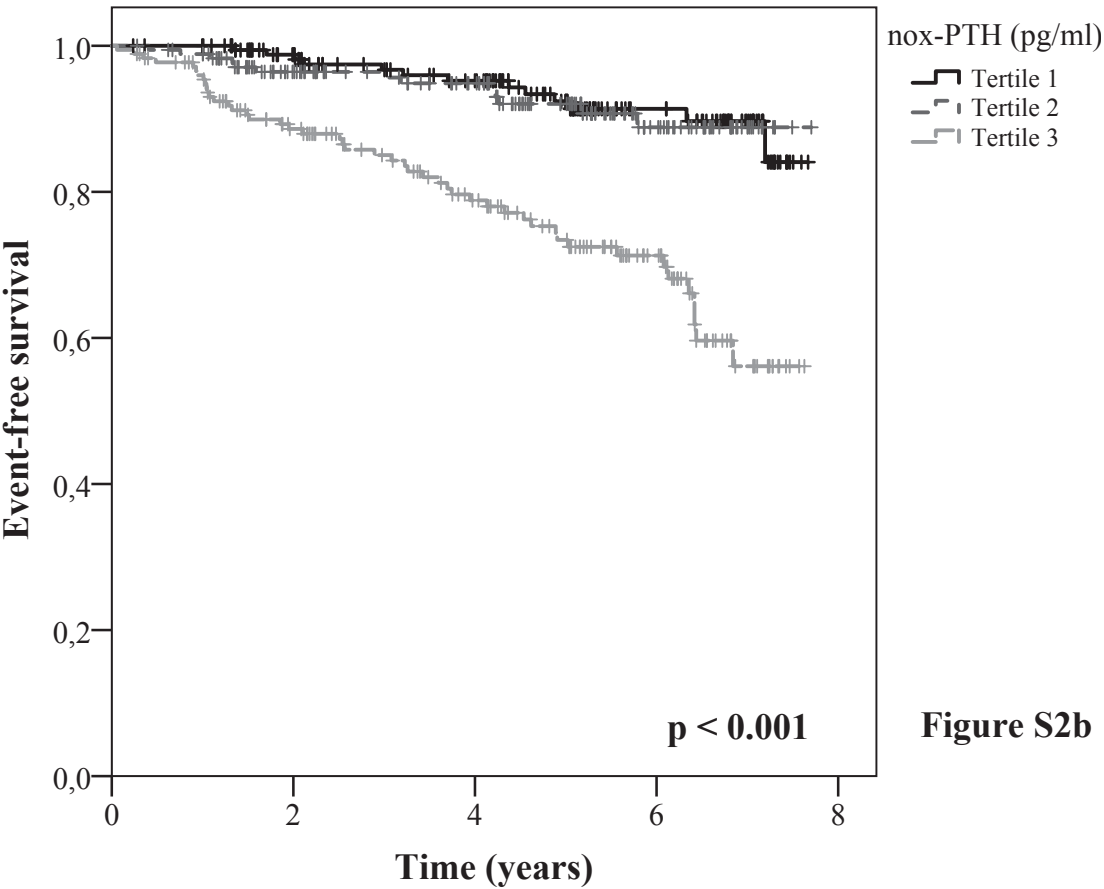


Figure S2a



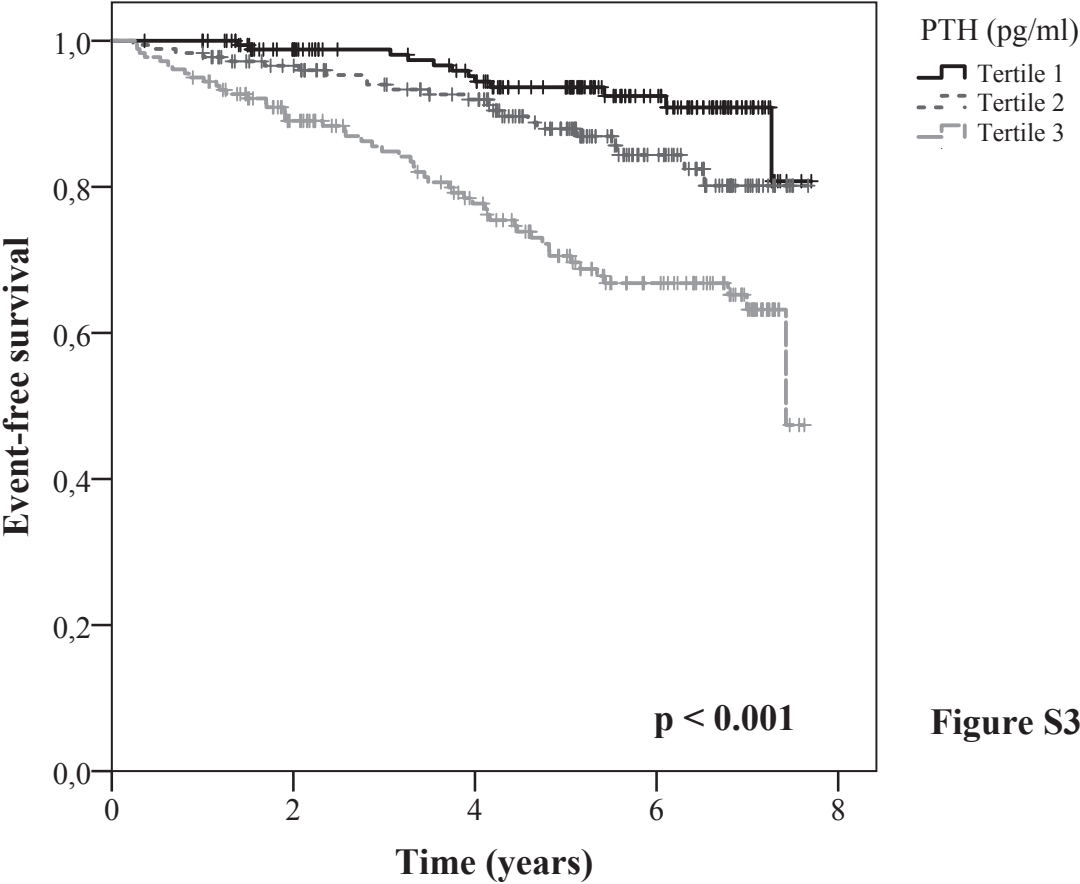
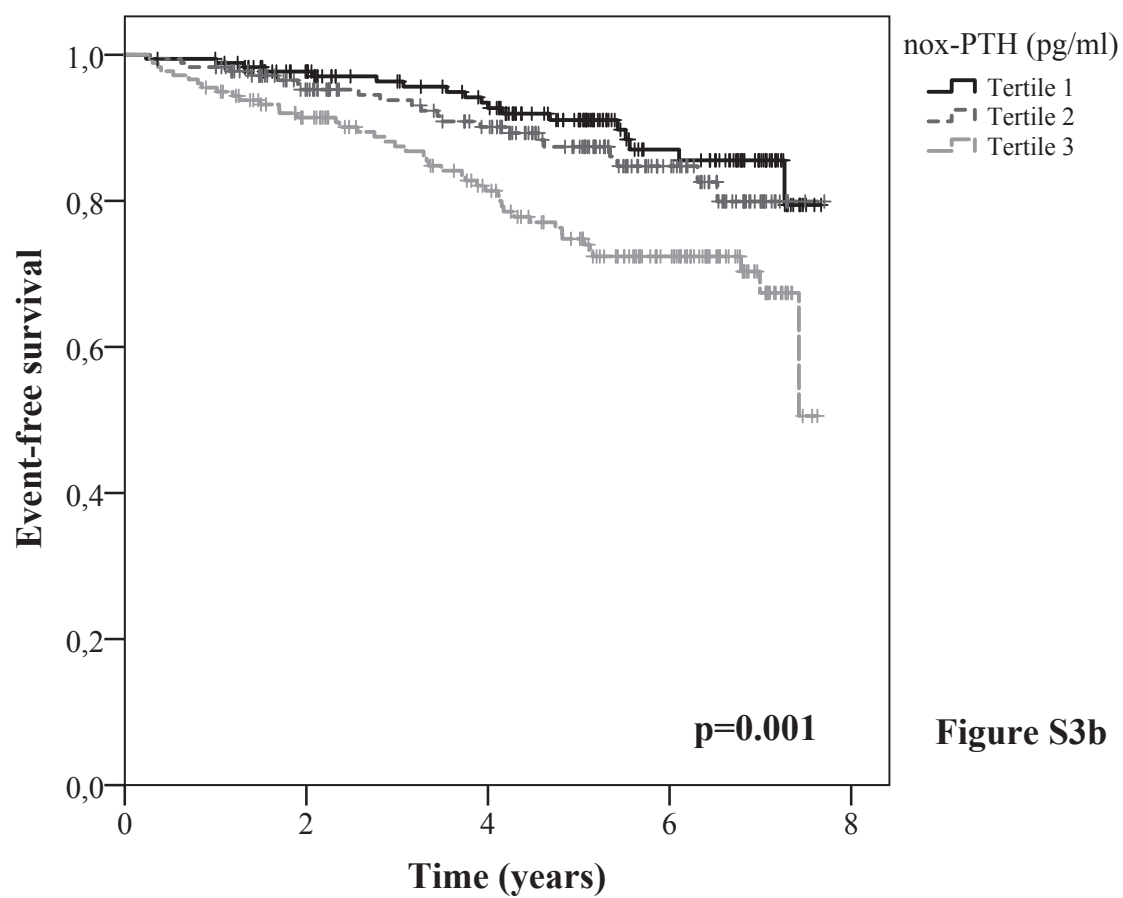


Figure S3a



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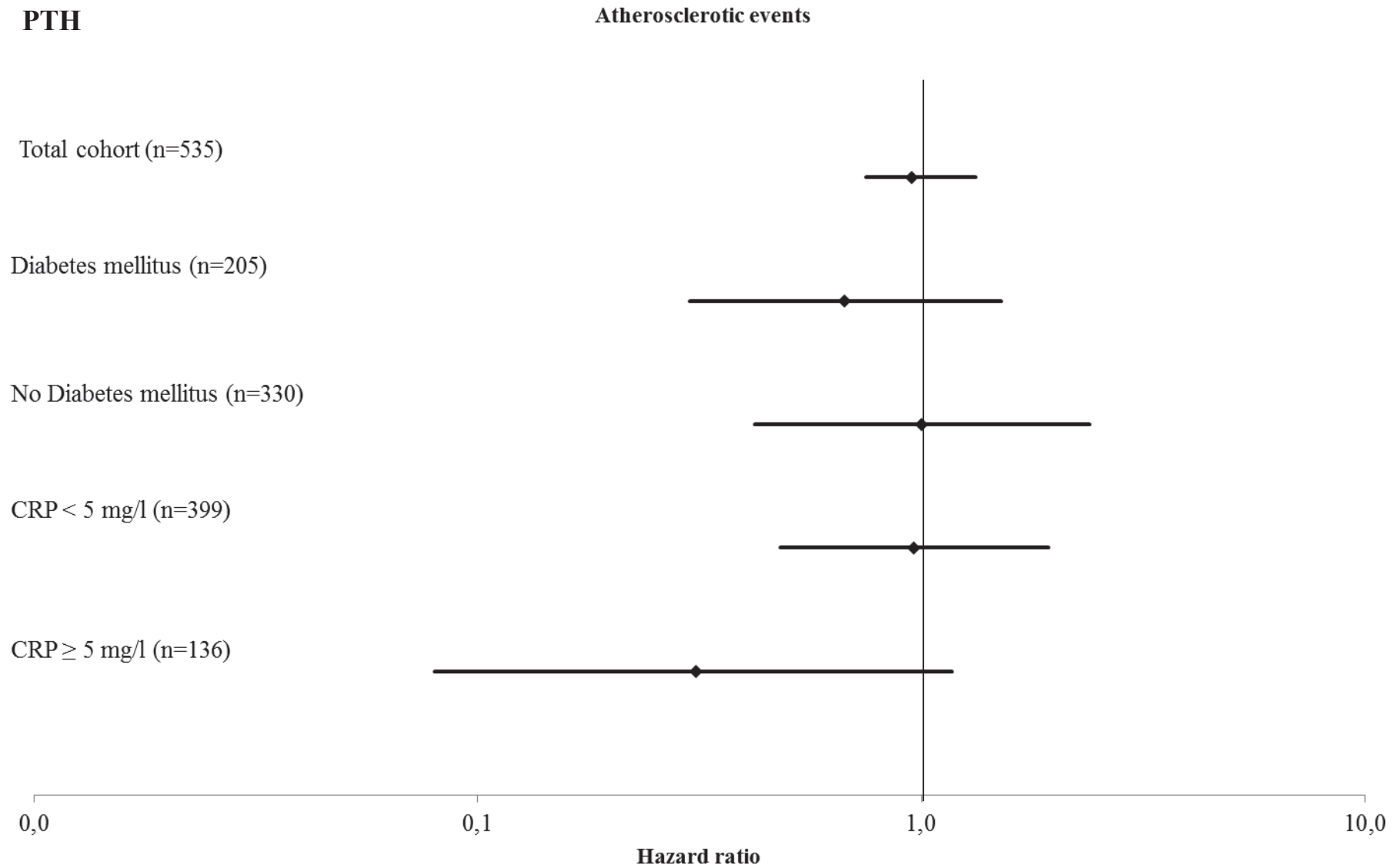


Figure S4a

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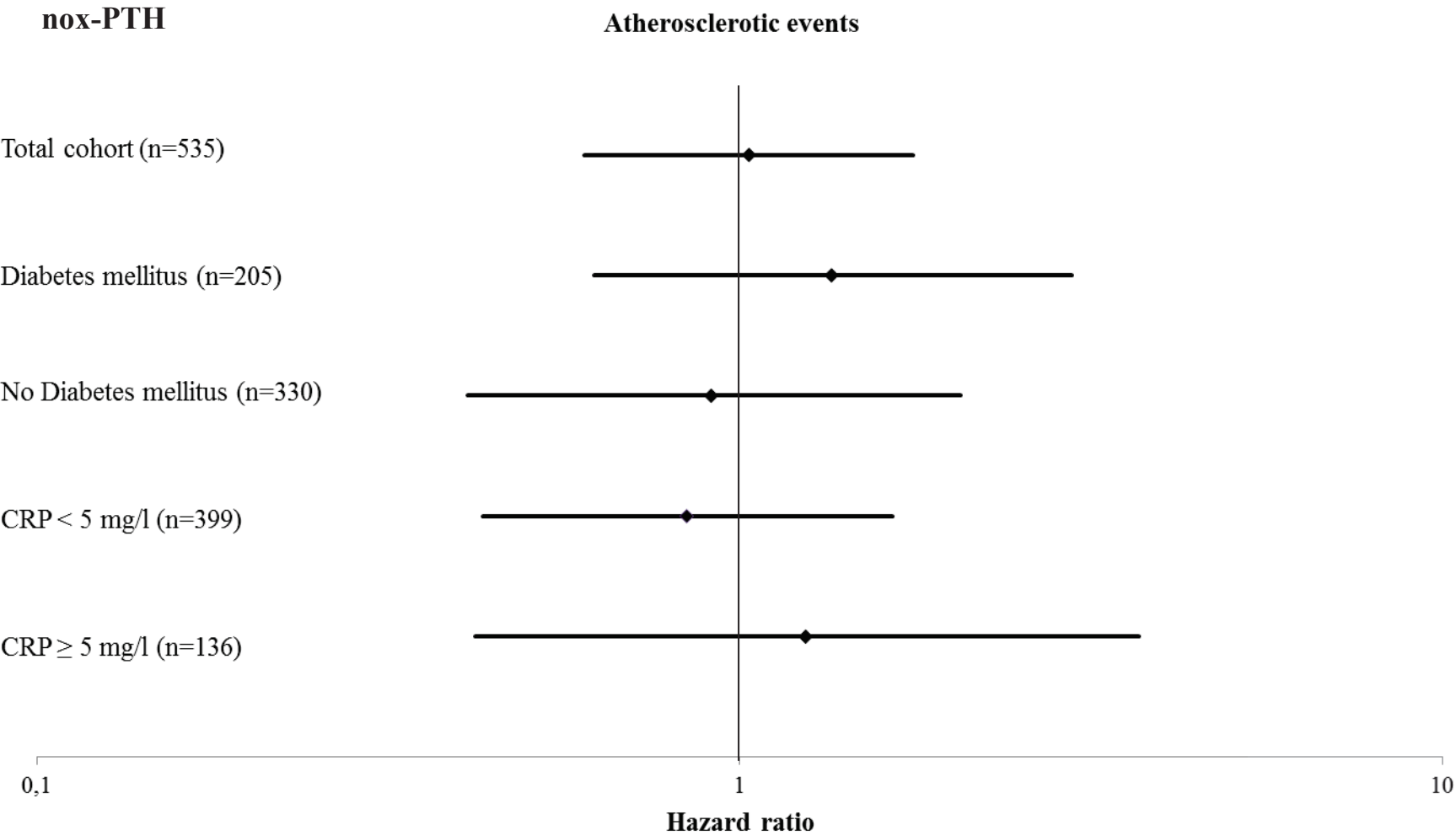


Figure S4b

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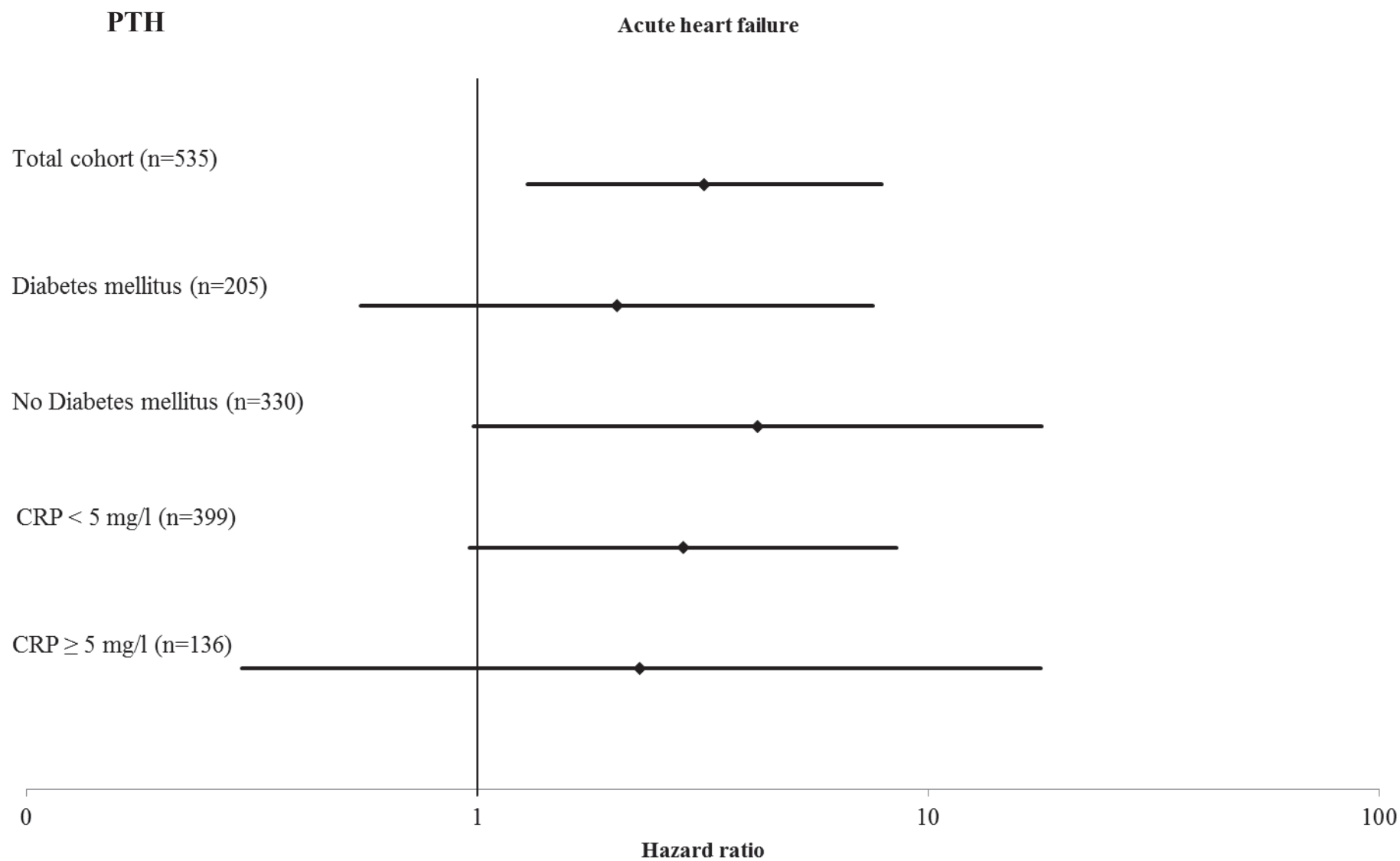


Figure S5a

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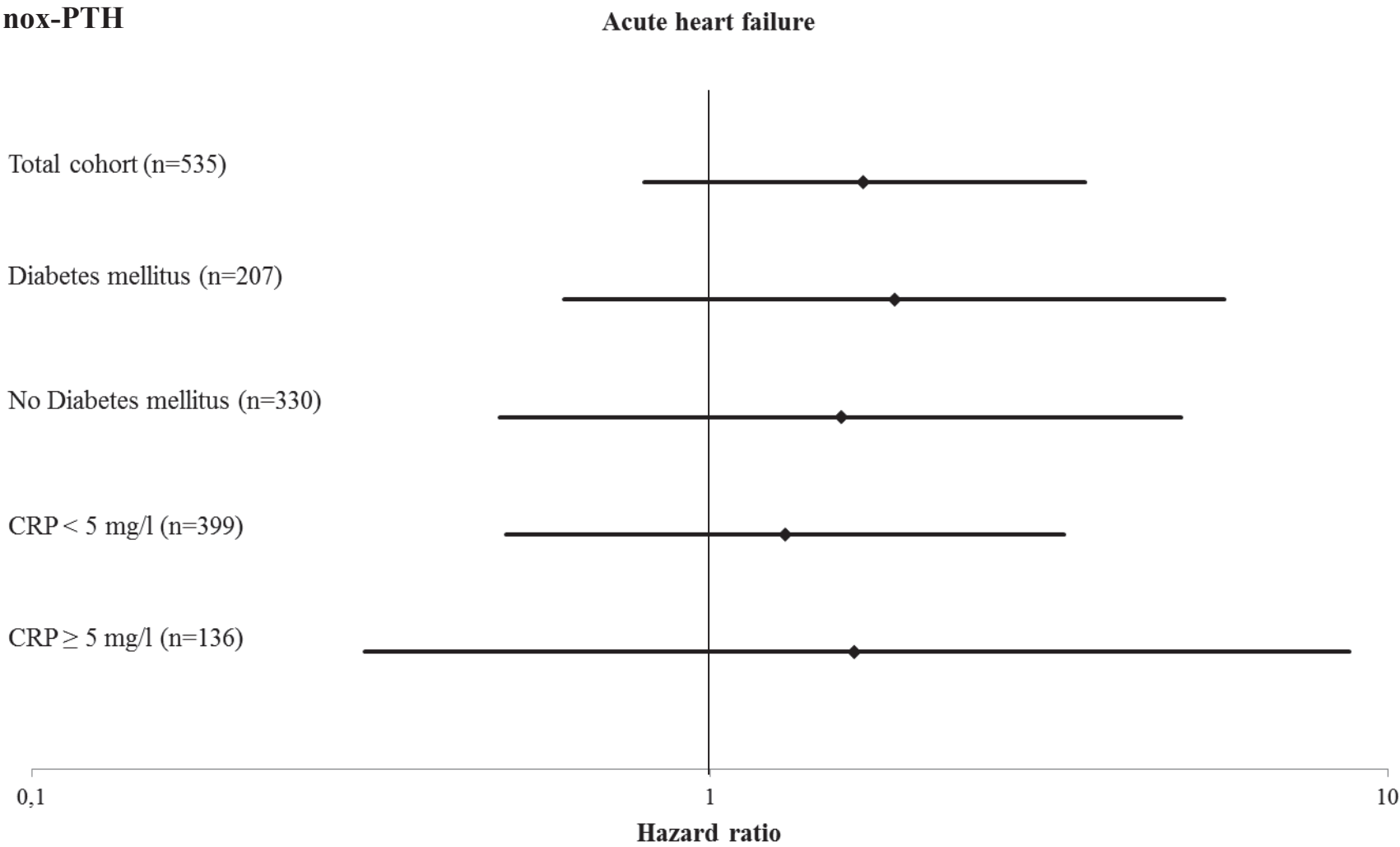


Figure S5b

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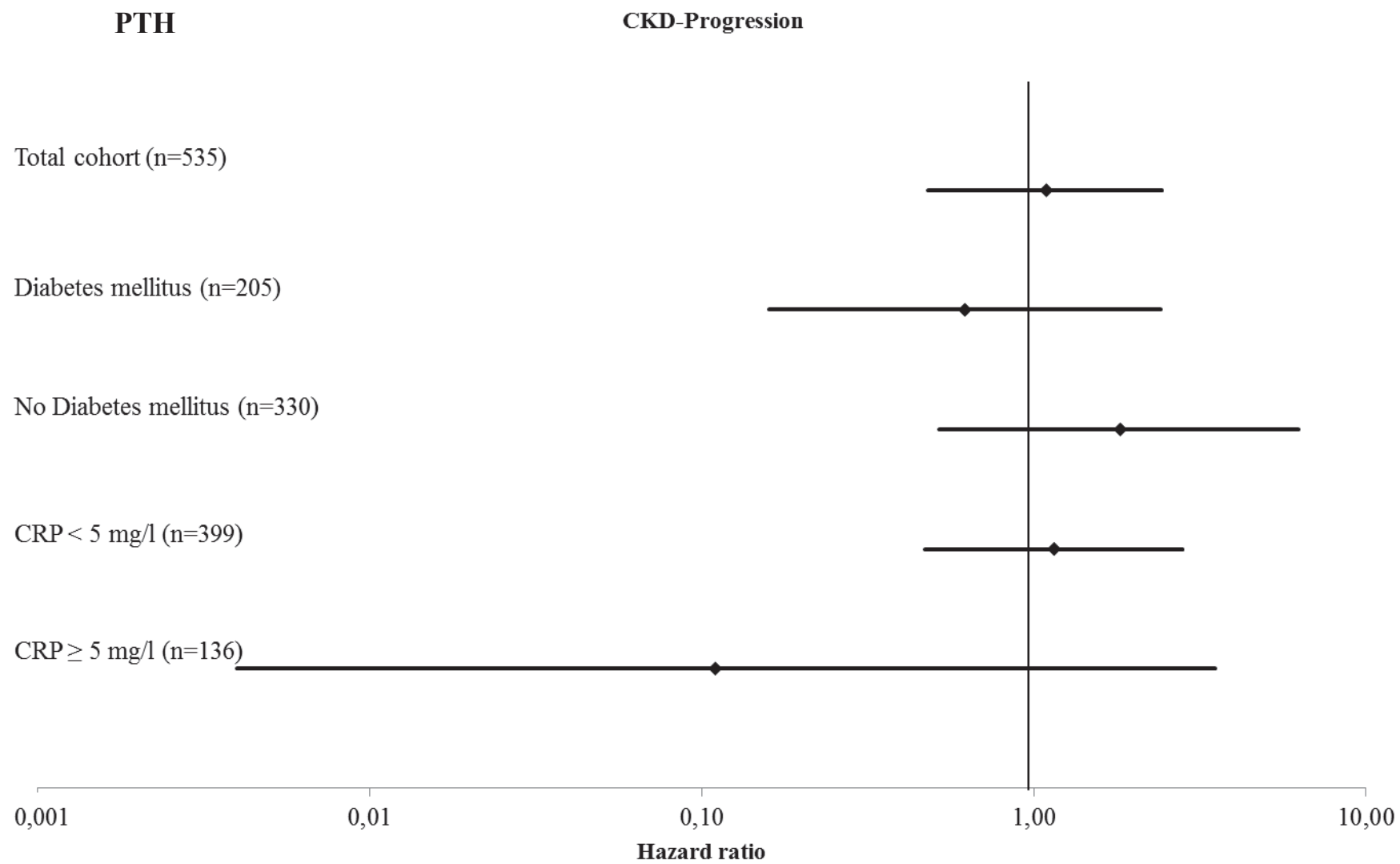


Figure S6a

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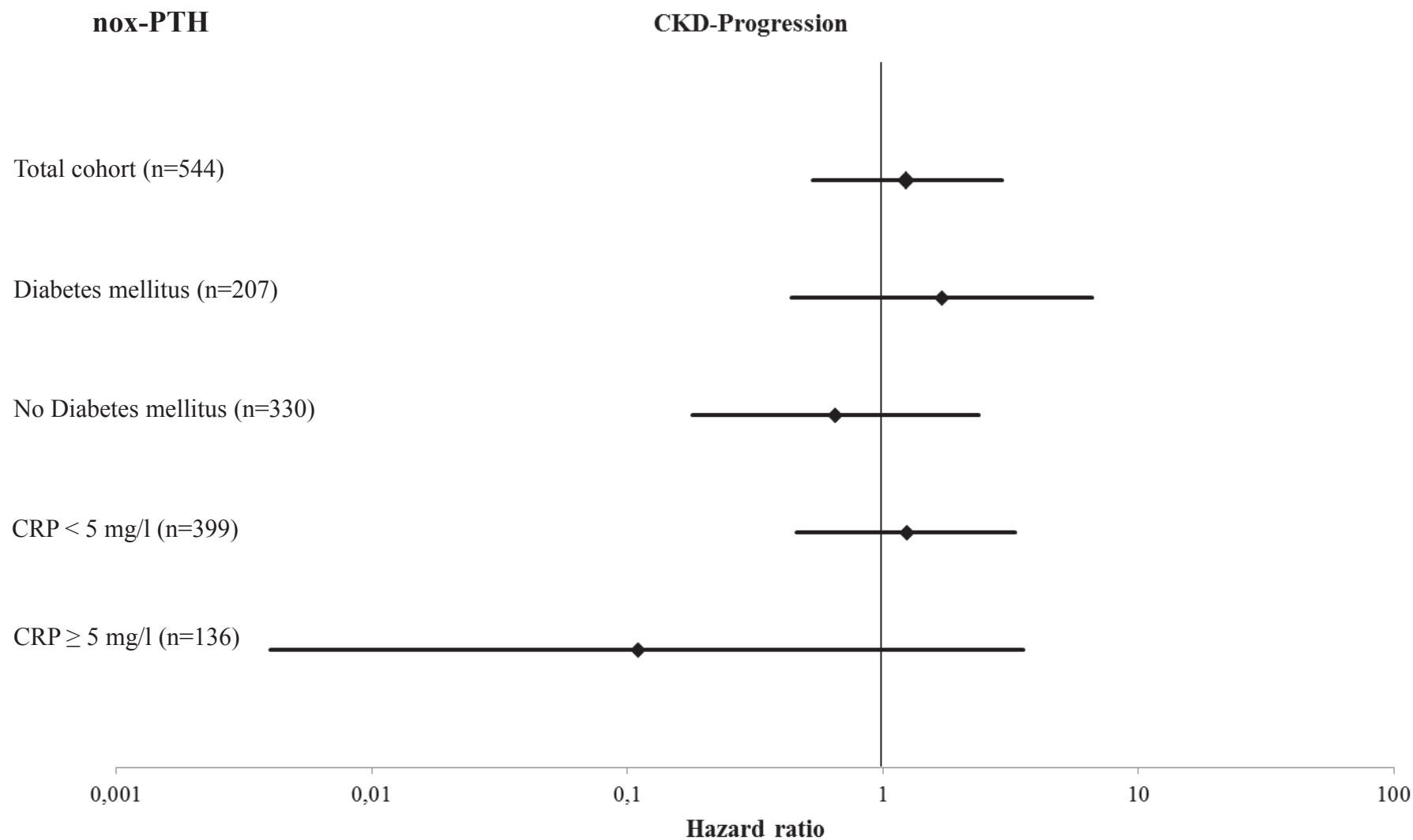


Figure S6b

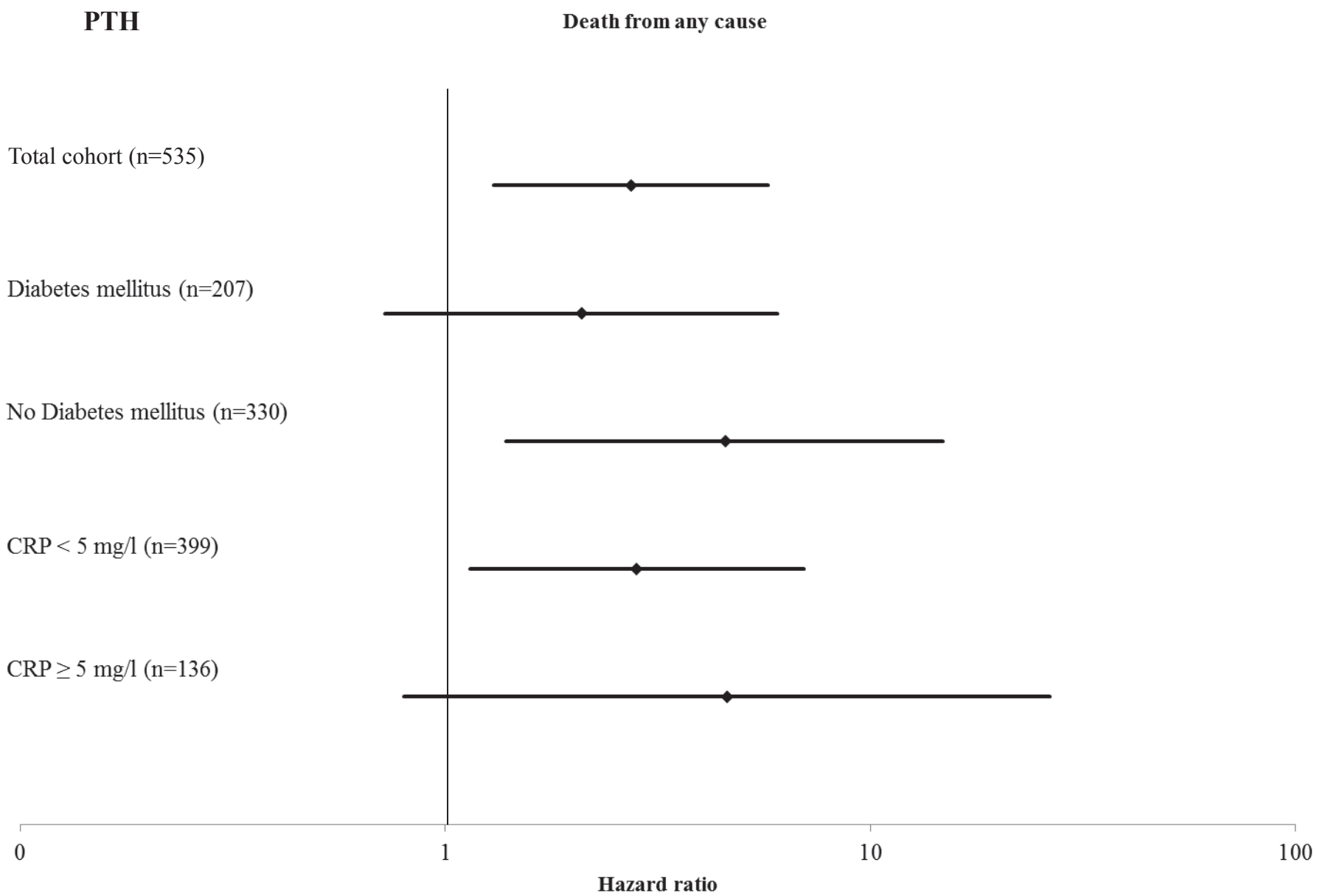


Figure S7a

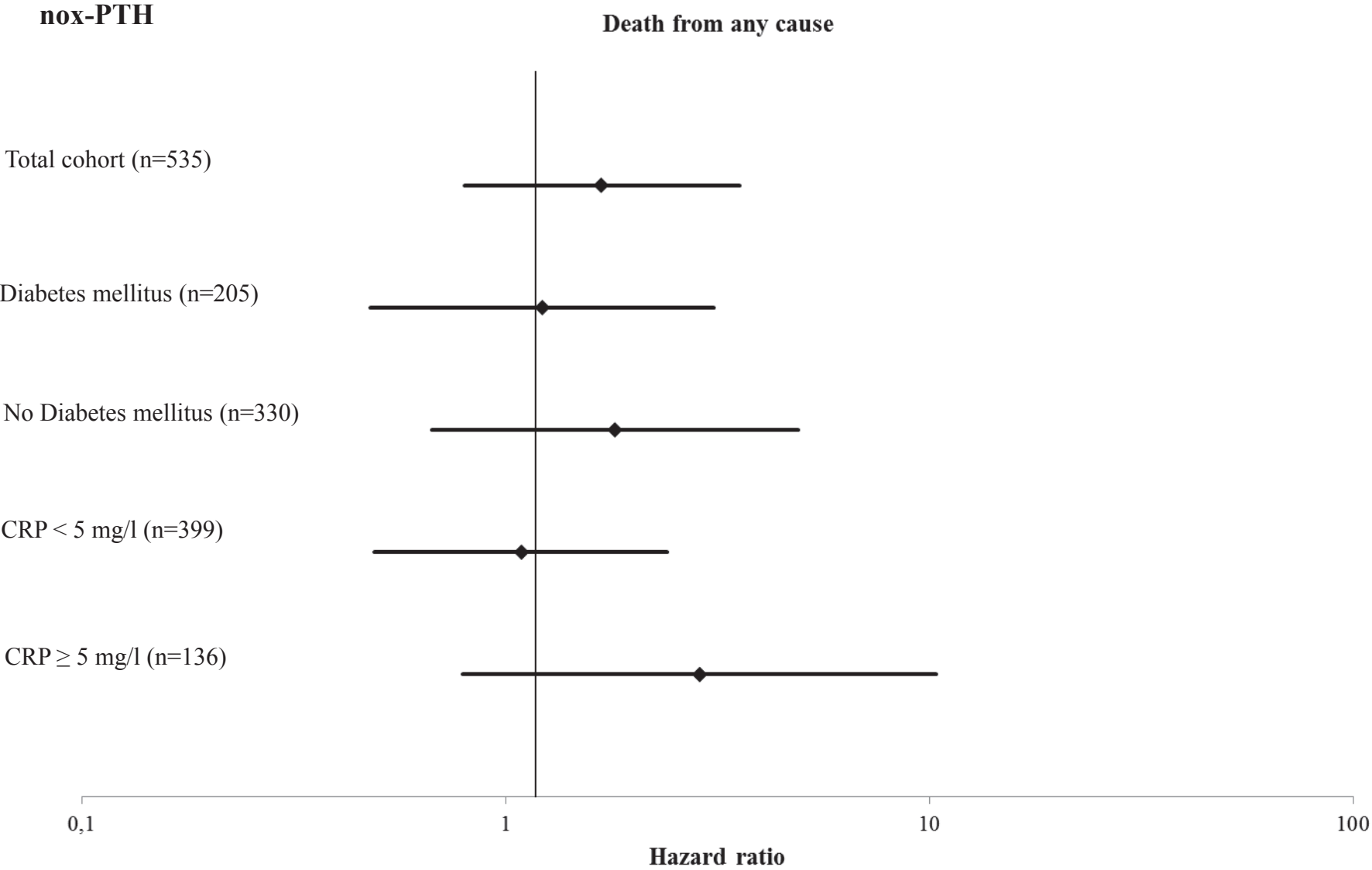
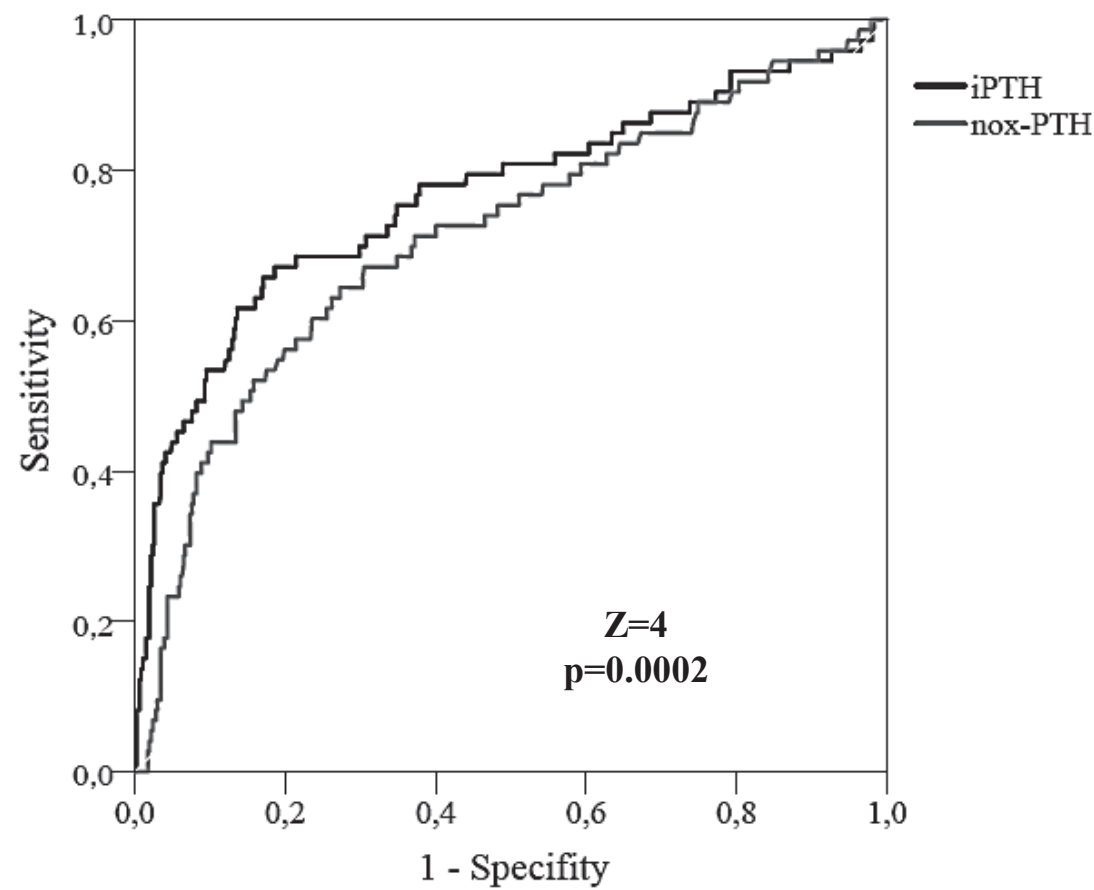


Figure S7b

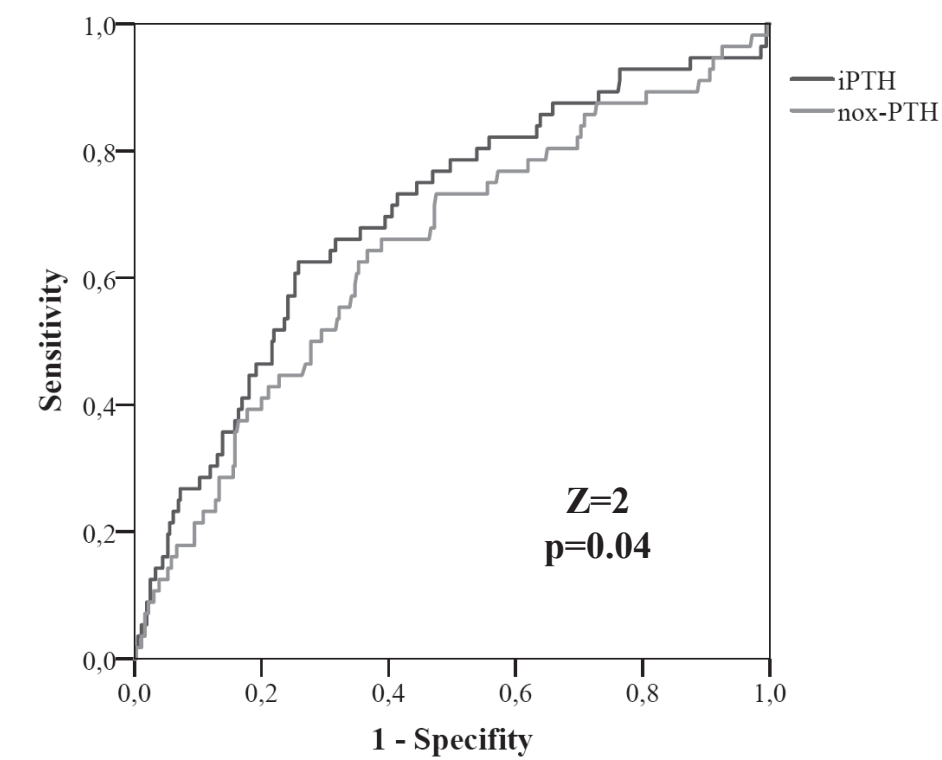
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| CKD-MBD parameter | AUC | SE | 95 % CI | p |
|----------------------|-------|-------|-------------|--------|
| PTH | 0.815 | 0.040 | 0.738-0.894 | <0.001 |
| nox-PTH | 0.735 | 0.044 | 0.649-0.820 | <0.001 |

Figure S8

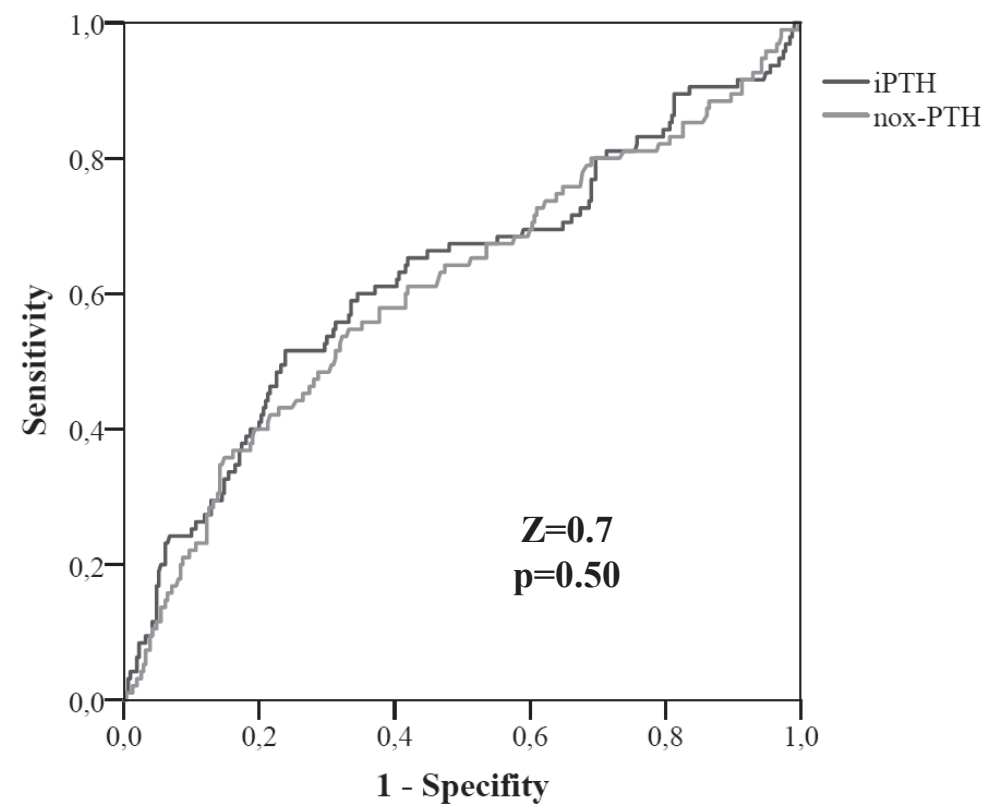
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| CKD-MBD parameter | AUC | SE | 95 % CI | p |
|----------------------|-------|-------|-------------|--------|
| PTH | 0.695 | 0.039 | 0.617-0.772 | <0.001 |
| nox-PTH | 0.642 | 0.041 | 0.561-0.723 | 0.001 |

Figure S9

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| CKD-MBD parameter | AUC | SE | 95 % CI | p |
|-------------------|-------|-------|-------------|--------|
| PTH | 0.625 | 0.035 | 0.556-0.695 | <0.001 |
| nox-PTH | 0.607 | 0.035 | 0.538-0.676 | 0.002 |

Figure S10