# Heart rate variability and its relation to chronic kidney disease. Results from the PREVEND Study. Supplementary material.

**GENERAL CHARACTERISTICS pp2-6**

**Supplementary Table S1a.**  Baseline characteristics by LF, LF/HF-ratio (Q1 vs Q2-4), and Composite low HRV (yes/no) categories, total sample (N=4,605).

**Supplementary Table S1b.**  Baseline characteristics by SDNN, rMSSD, HF (Q1 vs Q2-4) categories for those without CKD at baseline (N=3,397).

**Supplementary Table S1c.**  Baseline characteristics by categories of LF, LF/HF-ratio (Q1 vs Q2-4), and Composite low HRV (yes/no), for those without CKD at baseline (N=3,397)**.**

**Supplementary Figure S1.** Overlap between SDNN, rMSSD, and HF.

**Supplementary Table S2.** Range of eGFR and UAE in those with baseline CKD and those with incident CKD during follow-up.

**ASSOCIATIONS WITH INCIDENT CKD pp7-11**

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**Supplementary Table S4a.** Association of low HRV (LF, LF/HF-ratio,; and Composite low HRV, yes vs no).with incident CKD: complete-case analysis.

**Supplementary Table S4b.** Association of low HRV (SDNN, rMSSD, HF) with incident CKD: multiple imputed datasets.

**Supplementary Table S4c.** Association of low HRV (LF, LF/HF-ratio, Composite low HRV) with incident CKD: multiple imputed datasets.

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**Supplementary Table S5b.**  Association of low HRV (SDNN, rMSSD, HF Q1 vs Q2-4) with baseline levels and slope of eGFR: multiple imputed datasets.

**Supplementary Table S5c.** Association of low HRV (LF, LF/HF-ratio, Q1 vs Q2-4) and Composite low HRV (yes vs no) with baseline levels and slope of eGFR: multiple imputed datasets.

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**Supplementary Table S6b.**  Association of low HRV (LF, LF/HF-ratio, Q1 vs Q2-4) and Composite low HRV (yes vs no) with baseline levels and slope of *ln*UAE: complete case analysis.

**Supplementary Table S6c.**  Association of low HRV (SDNN, rMSSD, HF, Q1 vs Q2-4) with baseline levels and slope of *ln*UAE: multiple imputed datasets.

**Supplementary Table S6d.**  Association of low HRV (LF, LF/HF-ratio, Q1 vs Q2-4) and Composite low HRV (yes vs no) with baseline levels and slope of *ln*UAE: multiple imputed datasets.

**ASSOCIATIONS OF CONTINUOUS HRV WITH CKD INCIDENCE AND LEVELS AND SLOPE OF eGFR pp21-24**

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**Supplementary Table S8.**  Association of continuous HRV with eGFR levels and rate of decline: complete case analysis

## GENERAL CHARACTERISTICS

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| **Supplementary Table S1a.**  Baseline characteristics by LF, LF/HF-ratio (Q1 vs Q2-4), and Composite low HRV (yes/no) categories, total sample (N=4,605). | | | | | | | | | | |
|  | **Total** | **LF** | | **p** | **LF/HF-ratio** | | **p** | **Composite low HRV *a*** | | **p** |
| **Q1**  0.16-123 m2 | **Q2-4**  >123m2 | **Q1**  0.03-0.68 | **Q2-4**  0.68-43 | **yes** | **no** |
| **N** | 4605 | 1151 | 3454 | n/a | 1149 | 3456 | n/a | 776 | 3829 | n/a |
| **Age, years** | 53 [45-63] | 63 [54-71] | 50 [43-59] | **<0.001\*** | 52 [43-64] | 53 [45-63] | 0.52 | 61 [53-70] | 52 [43-60] | **<0.001\*** |
| **Males, n** | 2270 (49%) | 528 (46%) | 1742 (50%) | **0.007\*** | 398 (35%) | 1872 (54%) | **<0.001\*** | 414 (53%) | 1856 (48%) | **0.013\*** |
| **Black race, n** | 28 (0.6%) | 8 (0.7%) | 20 (0.6%) | 0.66 | 10 (0.9%) | 18 (0.5%) | 0.19 | 7 (0.9%) | 21 (0.5%) | 0.25 |
| **Height, cm** | 173 (9.5) | 170 (9.4) | 173 (9.4) | **<0.001\*** | 171 (9.1) | 173 (9.6) | **<0.001\*** | 171 (9.5) | 173 (9.5) | **<0.001\*** |
| **BMI, kg/m2** | 27 (4.4) | 28 (4.8) | 26 (4.2) | **<0.001\*** | 27 (4.9) | 27 (4.2) | 0.30 | 28 (4.5) | 27 (4.3) | **<0.001\*** |
| **WHR** | 0.90 (0.085) | 0.92 (0.084) | 0.90 (0.084) | **<0.001\*** | 0.89 (0.087) | 0.91 (0.083) | **<0.001\*** | 0.93 (0.079) | 0.90 (0.085) | **<0.001\*** |
| **Heart rate, beats/min** | 68 (10) | 73 (11) | 67 (9.2) | **<0.001\*** | 66 (10) | 69 (9.9) | **<0.001\*** | 76 (11) | 67 (9.1) | **<0.001\*** |
| **Smoking** |  |  |  | **<0.001\*** |  |  | **<0.001\*** |  |  | 0.051 |
| **Never, n** | 1315 (29%) | 275 (24%) | 1040 (30%) |  | 295 (26%) | 1020 (30%) |  | 207 (27%) | 1108 (29%) |  |
| **Former, n** | 1934 (43%) | 497 (44%) | 1437 (42%) |  | 470 (41%) | 1464 (43%) |  | 312 (41%) | 1622 (43%) |  |
| **Current, n** | 1298 (29%) | 363 (32%) | 935 (27%) |  | 373 (33%) | 925 (27%) |  | 246 (32%) | 1052 (28%) |  |
| **SBP, mmHg** | 127 (19) | 133 (20) | 124 (18) | **<0.001\*** | 124 (20) | 127 (18) | **<0.001\*** | 134 (19) | 125 (18) | **<0.001\*** |
| **DBP, mmHg** | 74 (9.1) | 76 (9.0) | 73 (9.0) | **<0.001\*** | 72 (8.9) | 74 (9.1) | **<0.001\*** | 77 (9.0) | 73 (9.0) | **<0.001\*** |
| **Antihypertensive Rx , n** | 1019 (25%) | 412 (38%) | 607 (20%) | **<0.001\*** | 318 (31%) | 701 (23%) | **<0.001\*** | 250 (34%) | 769 (23%) | **<0.001\*** |
| **Hypertension , n** | 1578 (38%) | 608 (55%) | 970 (32%) | **<0.001\*** | 417 (40%) | 1161 (37%) | 0.11 | 398 (54%) | 1180 (35%) | **<0.001\*** |
| **Fasting glucose, mmol/L** | 4.8 [4.4-5.3] | 5.0 [4.5-5.6] | 4.7 [4.4-5.2] | **<0.001\*** | 4.8 [4.4-5.3] | 4.8 [4.4-5.3] | 0.73 | 5.0 [4.5-5.6] | 4.8 [4.4-5.3] | **<0.001\*** |
| **Antidiabetic Rx , n** | 169 (4.2%) | 89 (8.3%) | 80 (2.7%) | **<0.001\*** | 44 (4.3%) | 125 (4.1%) | 0.79 | 65 (9.0%) | 104 (3.1%) | **<0.001\*** |
| **Diabetes Mellitus , n** | 299 (7.5%) | 135 (13%) | 164 (5.6%) | **<0.001\*** | 72 (7.2%) | 227 (7.7%) | 0.61 | 96 (14%) | 203 (6.2%) | **<0.001\*** |
| **History of CVD, n** | 302 (6.8%) | 126 (11%) | 176 (5.2%) | **<0.001\*** | 97 (8.8%) | 205 (6.1%) | **0.002\*** | 66 (8.8%) | 236 (6.3%) | **0.013\*** |
| **Total cholesterol, mmol/L** | 5.5 (1.0) | 5.6 (1.0) | 5.4 (1.0) | **<0.001\*** | 5.4 (1.1) | 5.5 (1.0) | **0.022\*** | 5.7 (1.1) | 5.4 (1.0) | **<0.001\*** |
| **Lipid lowering Rx , n** | 465 (11%) | 199 (19%) | 266 (8.9%) | **<0.001\*** | 129 (13%) | 336 (11%) | 0.18 | 129 (13%) | 336 (11%) | **<0.001\*** |
| **Hypercholesterolemia, n** | 1453 (35%) | 501 (46%) | 952 (31%) | **<0.001\*** | 364 (35%) | 1089 (35%) | 0.92 | 335 (45%) | 1118 (33%) | **<0.001\*** |
| **Serum creatinine, mg/dL** | 0.82 (0.23) | 0.84 (0.32) | 0.82 (0.19) | 0.83 | 0.81 (0.26) | 0.83 (0.21) | **<0.001\*** | 0.86 (0.37) | 0.82 (0.19) | **0.006\*** |
| **Serum cystatin C, mg/L** | 0.91 (0.21) | 0.99 (0.29) | 0.88 (0.18) | **<0.001\*** | 0.92 (0.25) | 0.91 (0.20) | 0.86 | 1.0 (0.32) | 0.89 (0.18) | **<0.001\*** |
| **eGFR , ml/min/1.73m2** | 92 (17) | 84 (18) | 94 (16) | **<0.001\*** | 91 (18) | 92 (17) | 0.092 | 84 (18) | 93 (16) | **<0.001\*** |
| **UAE, mg/24h** | 8.9 [6.2-17] | 10 [6.6-24] | 8.5 [6.0-15] | **<0.001\*** | 9.0 [6.0-18] | 8.9 [6.2-16] | 0.73 | 10 [6.8-24] | 8.7 [6.1-16] | **<0.001\*** |
| **Baseline CKD** | 939 (22%) | 346 (32%) | 593 (18%) | **<0.001\*** | 253 (23%) | 686 (21%) | 0.11 | 233 (32%) | 706 (20%) | **<0.001\*** |
| **Baseline CKDeGFR<60** | 202 (4.7%) | 105 (9.7%) | 97 (3.0%) | **<0.001\*** | 67 (6.3%) | 135 (4.2%) | **0.005\*** | 76 (11%) | 126 (3.5%) | **<0.001\*** |
| **Baseline CKDUAE≥30** | 846 (18%) | 296 (26%) | 550 (16%) | **<0.001\*** | 222 (19%) | 624 (18%) | 0.34 | 198 (26%) | 648 (17%) | **<0.001\*** |
| SDNN: standard deviation of all normal-normal RR-intervals; rMSSD: root mean square of successive differences of adjacent normal-to-normal RR-intervals; HF: high frequency power spectrum; BMI: body mass index; WHR: waist/hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; CVD: cardiovascular disease; Rx: medication use; eGFR: estimated glomerular filtration rate; UAE: urinary albumin excretion; CKD: chronic kidney disease. *a* Subjects with a Q1 value in SDNN, rMSSD, and HF. \* indicates statistical significance (p < 0.05) | | | | | | | | | | |

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| **Supplementary Table S1b.**  Baseline characteristics by SDNN, rMSSD, HF (Q1 vs Q2-4) categories for those without CKD at baseline (N=3,397) | | | | | | | | | | |
|  | **Total** | **SDNN** | | **p.** | **rMSSD** | | **p** | **HF** | | **p** |
| **Q1**  4.6-24.3 ms | **Q2-4**  24.3-212 ms | **Q1**  6.4-18.0 ms | **Q2-4**  18.0-338 ms | **Q1**  3.9-107 ms2 | **Q2-4**  >107ms2 |
| **N** | 3397 | 849 | 2548 |  | 849 | 2548 |  | 849 | 2548 |  |
| **Age, years** | 51 [43-60] | 58 [51-68] | 49 [42-57] | **<0.001\*** | 57 [50-67] | 49 [42-57] | **<0.001\*** | 58 [50-67] | 49 [42-57] | **<0.001\*** |
| **Males, n** | 1559 (46%) | 394 (46%) | 1165 (46%) | 0.73 | 418 [49%) | 1141 (45%) | **0.024\*** | 419 (49%) | 1140 (45%) | **0.020\*** |
| **Black race, n** | 19 (0.6%) | 4 (0.5%) | 15 (0.6%) | 0.80 | 6 (0.7%) | 13 (0.5%) | 0.51 | 5 (0.6%) | 14 (0.5%) | 0.89 |
| **Height, cm** | 173 (9.5) | 171 (9.6) | 173 (9.4) | **<0.001\*** | 171 (9.3) | 173 (9.6) | **<0.001\*** | 171 (9.4) | 173 (9.5) | **<0.001\*** |
| **BMI, kg/m2** | 26.5 (4.2) | 27 (4.6) | 26 (4.0) | **<0.001\*** | 27 (4.4) | 26 (4.1) | **<0.001\*** | 27 (4.4) | 26 (4.1) | **<0.001\*** |
| **WHR** | 0.89 (0.082) | 0.91 (0.080) | 0.89 (0.082) | **<0.001\*** | 0.91 (0.081) | 0.89 (0.082) | **<0.001\*** | 0.91 (0.081) | 0.89 (0.084) | **<0.001\*** |
| **Heart rate, beats/min** | 68 (9.8) | 74 (10) | 66 (8.8) | **<0.001\*** | 75 (9.7) | 66 (8.6) | **<0.001\*** | 75 (9.9) | 66 (8.8) | **<0.001\*** |
| **Smoking** |  |  |  | **<0.001\*** |  |  | **0.041\*** |  |  | **0.021\*** |
| **Never, n** | 1045 (31%) | 226 (27%) | 819 (33%) |  | 243 (29%) | 802 (32%) |  | 246 (29%) | 799 (32%) |  |
| **Former, n** | 1376 (41%) | 336 (40%) | 1040 (41%) |  | 334 (40%) | 1042 (41%) |  | 328 (39%) | 1048 (42%) |  |
| **Current, n** | 934 (28%) | 277 (33%) | 657 (26%) |  | 261 (31%) | 673 (27%) |  | 265 (32%) | 669 (27%) |  |
| **SBP, mmHg** | 124 (17) | 130 (17) | 122 (17) | **<0.001\*** | 130 (18) | 122 (17) | **<0.001\*** | 130 (18) | 122 (17) | **<0.001\*** |
| **DBP, mmHg** | 73 (8.6) | 75 (8.2) | 72 (8.6) | **<0.001\*** | 76 (8.5) | 71 (8.4) | **<0.001\*** | 76 (8.4) | 72 (8.4) | **<0.001\*** |
| **Antihypertensive Rx , n** | 550 (19%) | 207 (27%) | 343 (16%) | **<0.001\*** | 178 (23%) | 372 (17%) | **<0.001\*** | 188 (24%) | 362 (17%) | **<0.001\*** |
| **Hypertension , n** | 924 (31%) | 350 (44%) | 574 (26%) | **<0.001\*** | 327 (41%) | 597 (27%) | **<0.001\*** | 337 (43%) | 587 (27%) | **<0.001\*** |
| **Fasting glucose, mmol/L** | 4.7 [4.4-5.2] | 4.8 [4.5-5.4] | 4.7 [4.4-5.2] | **<0.001\*** | 4.8 [4.5-5.4] | 4.7 [4.4-5.2] | **<0.001\*** | 4.8 [4.5-5.4] | 4.7 [4.4-5.2] | **<0.001\*** |
| **Antidiabetic Rx , n** | 68 (2.3%) | 38 (4.9%) | 30 (1.4%) | **<0.001\*** | 35 (4.5%) | 33 (1.5%) | **<0.001\*** | 34 (4.4%) | 34 (1.6%) | **<0.001\*** |
| **Diabetes Mellitus *b* , n** | 138 (4.8%) | 63 (8.3%) | 75 (3.5%) | **<0.001\*** | 59 (7.8%) | 79 (3.7%) | **<0.001\*** | 55 (7.3%) | 83 (3.9%) | **<0.001\*** |
| **History of CVD *, n*** | 150 (4.6%) | 52 (6.4%) | 98 (3.9%) | **0.004\*** | 43 (5.2%) | 107 (4.3%) | 0.28 | 48 (5.8%) | 102 (4.1%) | **0.043\*** |
| **Total cholesterol, mmol/L** | 5.4 (1.0) | 5.6 (1.0) | 5.4 (1.0) | **<0.001\*** | 5.7 (1.0) | 5.4 (1.0) | **<0.001\*** | 5.6 (0.98) | 5.4 (1.0) | **<0.001\*** |
| **Lipid lowering Rx , n** | 262 (8.9%) | 107 (14%) | 155 (7.1%) | **<0.001\*** | 95 (12%) | 167 (7.7%) | **<0.001\*** | 102 (13%) | 160 (7.4%) | **<0.001\*** |
| **Hypercholesterolemia, n** | 445 (30%) | 332 (42%) | 659 (30%) | **<0.001\*** | 322 (41%) | 669 (30%) | **<0.001\*** | 320 (41%) | 671 (30%) | **<0.001\*** |
| **Serum creatinine, mg/dL** | 0.79 [0.70-0.88] | 0.79 (0.14) | 0.80 (0.14) | **0.046\*** | 0.80 (0.14) | 0.80 (0.14) | 0.53 | 0.80 (0.15) | 0.80 (0.14) | 0.87 |
| **Serum cystatin C, mg/L** | 0.86 [0.78-0.96] | 0.92 (0.14) | 0.86 (0.13) | **<0.001\*** | 0.92 (0.14) | 0.86 (0.14) | **<0.001** | 0.92 (0.14) | 0.86 (0.13) | **<0.001\*** |
| **eGFR , ml/min/1.73m2** | 94 (14) | 89 (14) | 96 (14) | **<0.001\*** | 89 (14) | 96 (14) | **<0.001\*** | 89 (14) | 96 (14) | **<0.001\*** |
| **UAE, mg/24h** | 7.8 [5.8-11] | 8.2 [6.0-12] | 7.6 [5.7-11] | **0.008\*** | 8.1 [6.0-12] | 7.6 [5.7-11] | **0.016\*** | 8.1 [6.0-12] | 7.7 [5.7-11] | 0.098 |
| Baseline characteristics of 3397 subjects without chronic kidney disease at baseline. Data are presented as number (%), mean (sd), or median [IQR] in case of skewed distributions. SDNN: standard deviation of all normal-normal RR-intervals; rMSSD: root mean square of successive differences of adjacent normal-to-normal RR-intervals; HF: high frequency power spectrum; BMI: body mass index; WHR: waist/hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; CVD: cardiovascular disease; Rx: medication use; eGFR: estimated glomerular filtration rate; UAE: urinary albumin excretion. \* Indicates statistical significance (p < 0.05) | | | | | | | | | | |

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| **Supplementary Table S1c.**  Baseline characteristics by categories of LF, LF/HF-ratio (Q1 vs Q2-4), and Composite low HRV (yes/no), for those without CKD at baseline (N=3,397)**.** | | | | | | | | | | |
| **Variable** | **Total** | **LF** | | **p** | **LF/HF-ratio** | | **p** | **Composite low HRV *a*** | | **p** |
| **Q1**  0.16-135 ms2 | **Q2-4**  >135ms2 | **Q1**  0.04-0.68 | **Q2-4**  0.68-42.9 | **yes** | **no** |
| **N** | 3397 | 849 | 2548 |  | 847 | 2550 |  | 579 | 2818 |  |
| **Age, years** | 51 [43-60] | 59 [51-68] | 49 [42-57] | **<0.001\*** | 50 [42-60] | 52 [44-60] | **0.042\*** | 58 [51-68] | 50 [42-58] | **<0.001\*** |
| **Males, n** | 1559 (46%) | 331 (39%) | 1228 (48%) | **<0.001\*** | 591 (70%) | 1247 (49%) | **<0.001\*** | 271 (47%) | 1288 (46%) | 0.63 |
| **Black race, n** | 19 (0.6%) | 4 (0.5%) | 15 (0.6%) | 0.69 | 5 (0.6%) | 14 (0.5%) | 0.89 | 4 (0.7%) | 15 (0.5%) | 0.64 |
| **Height, cm** | 173 (9.5) | 170 (9.3) | 173 (9.5) | **<0.001\*** | 171 (9.0) | 173 (9.6) | **<0.001\*** | 171 (9.5) | 173 (9.5) | **<0.001\*** |
| **BMI, kg/m2** | 26.5 (4.2) | 27 (4.7) | 26 (4.0) | **<0.001\*** | 26 (4.7) | 26 (4.0) | 0.72 | 27 (4.6) | 26 (4.1) | **<0.001\*** |
| **WHR** | 0.89 (0.082) | 0.90 (0.083) | 0.89 (0.082) | **<0.001\*** | 0.88 (0.081) | 0.90 (0.082) | **<0.001\*** | 0.91 (0.079) | 0.89 (0.082) | **<0.001\*** |
| **Heart rate, beats/min** | 68 (9.8) | 73 (11) | 67 (9.0) | **<0.001\*** | 66 (9.4) | 69 (9.8) | **<0.001\*** | 76 (10) | 67 (8.9) | **<0.001\*** |
| **Smoking** |  |  |  | **<0.001\*** |  |  | **0.019\*** |  |  | **0.006\*** |
| **Never, n** | 1045 (31%) | 224 (27%) | 821 (33%) |  | 243 (29%) | 802 (32%) |  | 162 (28%) | 883 (32%) |  |
| **Former, n** | 1376 (41%) | 338 (40%) | 1038 (41%) |  | 332 (40%) | 1044 (42%) |  | 219 (38%) | 1157 (42%) |  |
| **Current, n** | 934 (28%) | 276 (33%) | 658 (26%) |  | 265 (32%) | 669 (27%) |  | 190 (33%) | 744 (27%) |  |
| **SBP, mmHg** | 124 (17) | 129 (18) | 122 (17) | **<0.001\*** | 121 (18) | 125 (17) | **<0.001\*** | 131 (17) | 122 (17) | **<0.001\*** |
| **DBP, mmHg** | 73 (8.6) | 74 (8.3) | 72 (8.6) | **<0.001\*** | 71 (8.4) | 73 (8.5) | **<0.001\*** | 76 (8.1) | 72 (8.5) | **<0.001\*** |
| **Antihypertensive Rx , n** | 550 (19%) | 213 (27%) | 337 (15%) | **<0.001\*** | 164 (22%) | 386 (17%) | **0.008\*** | 130 (24%) | 420 (17%) | **<0.001\*** |
| **Hypertension, n** | 924 (31%) | 349 (44%) | 575 (26%) | **<0.001\*** | 225 (30%) | 699 (31%) | 0.48 | 241 (44%) | 683 (28%) | **<0.001\*** |
| **Fasting glucose, mmol/L** | 4.7 [4.4-5.2] | 4.8 [4.5-5.4] | 4.7 [4.4-5.2] | **<0.001\*** | 4.7 [4.4-5.2] | 4.7 [4.4-5.2] | **0.017\*** | 4.8 [4.5-5.5] | 4.7 [4.4-5.2] | **<0.001\*** |
| **Antidiabetic Rx , n** | 68 (2.3%) | 32 (4.1%) | 36 (1.7%) | **<0.001\*** | 14 (1.9%) | 54 (2.5%) | 0.36 | 29 (5.5%) | 39 (1.6%) | **<0.001\*** |
| **Diabetes Mellitus, n** | 138 (4.8%) | 57 (7.5%) | 36 (1.7%) | **<0.001\*** | 28 (3.8%) | 110 (5.1%) | 0.15 | 44 (8.5%) | 94 (4.0%) | **<0.001\*** |
| **History of CVD*, n*** | 150 (4.6%) | 54 (6.7%) | 96 (3.9%) | **<0.001\*** | 43 (5.3%) | 107 (4.3%) | 0.24 | 29 (5.2%) | 121 (4.4%) | 0.43 |
| **Total cholesterol, mmol/L** | 5.4 (1.0) | 5.6 (1.0) | 5.4 (1.0) | **<0.001\*** | 5.4 (1.1) | 5.5 (1.0) | **0.040\*** | 5.7 (1.0) | 5.4 (1.0) | **<0.001\*** |
| **Lipid lowering Rx , n** | 262 (8.9%) | 109 (14%) | 153 (7.1%) | **<0.001\*** | 69 (9.2%) | 193 (8.8%) | 0.71 | 70 (13%) | 192 (7.9%) | **<0.001\*** |
| **Hypercholesterolemia, n** | 445 (30%) | 338 (42%) | 653 (29%) | **<0.001\*** | 247 (33%) | 744 (33%) | 0.84 | 230 (42%) | 761 (31%) | **<0.001\*** |
| **Serum creatinine, mg/dL** | 0.79 [0.70-0.88] | 0.78 (0.14) | 0.80 (0.14) | **<0.001\*** | 0.77 (0.14) | 0.81 (0.14) | **<0.001\*** | 0.79 (0.14) | 0.80 (0.14) | 0.10 |
| **Serum cystatin C, mg/L** | 0.86 [0.78-0.96] | 0.92 (0.14) | 0.86 (0.13) | **<0.001\*** | 0.87 (0.15) | 0.88 (0.13) | **0.019\*** | 0.92 (0.14) | 0.87 (0.13) | **<0.001\*** |
| **eGFR , ml/min/1.73m2** | 94 (14) | 88 (14) | 96 (14) | **<0.001\*** | 94 (15) | 94 (14) | 0.83 | 89 (14) | 96 (14) | **<0.001\*** |
| **UAE, mg/24h** | 7.8 [5.8-11] | 8.1 [6.0-12] | 7.6 [5.7-11] | **<0.001\*** | 7.6 [5.6-11] | 7.8 [5.8-11] | 0.16 | 8.2 [6.1-12] | 7.7 [5.7-11] | **0.029\*** |
| Baseline characteristics of 3397 subjects without chronic kidney disease at baseline. Data are presented as number (%), mean (sd), or median [IQR] in case of skewed distributions. HF: high frequency power spectrum; LF: low frequency power spectrum; BMI: body mass index; WHR: waist/hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; CVD: cardiovascular disease; Rx: medication use; eGFR: estimated glomerular filtration rate; UAE: urinary albumin excretion. *a* Subjects with a Q1 value in SDNN, rMSSD, and HF. \* indicates statistical significance (p < 0.05) | | | | | | | | | | |

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| **Supplementary Table S2.** Range of eGFR and urinary albumin excretion in those with baseline CKD and those with incident CKD during follow-up. | | |
|  | **Baseline CKD (N=939)** | **Incident CKD (N=341)** |
| **eGFR, mL/min/1.73m2** | 81 (22) | 79 [59-94] |
| **eGFR<60** | 181/889 (20%) | 111/323 (34%) |
| **UAE, mg/24h** | 43 [24-89] | 35 [17-48] |
| **UAE≥30** | 650/933 (70%) | 244/341 (72%) |
| **Both eGFR<60 and UAE≥30** | 92/901 (10%) | 14/323 (4.3%) |
| Range of eGFR and UAE in those with CKD at baseline, and in those with CKD during follow-up at the earliest moment of identification of CKD. | | |

## ASSOCIATIONS WITH INCIDENT CKD

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| **Supplementary Table S3.** CKD incidence rates by HRV category (LF, LF/HF-ratio, Q1 vs Q2-4; and Composite low HRV, yes vs no). | | | | | | | | | | |
|  | **LF** | | **p** | **LF/HF-ratio** | | **p** |  | **Composite low HRV *a*** | | **p** |
| **Q1** | **Q2-4** | **Q1** | **Q2-4** |  | **yes** | **no** |
| **N** | 849 | 2548 | n/a | 847 | 2550 | n/a | | 579 | 2818 | n/a |
| **Person-years, [IQR]** | 5.2 [2.1-7.3] | 6.9 [3.1-7.4] | **<0.001\*** | 5.8 [2.3-7.4] | 6.8 [2.6-7.3] | **0.030\*** | | 5.5 [2.1-7.3] | 6.7 [2.7-7.4] | **<0.001\*** |
| **New-onset CKD *b* /n (%)** | 116 (14%) | 225 (8.8%) | **<0.001\*** | 99 (12%) | 242 (9.5%) | 0.065 | | 77 (13%) | 264 (9.4%) | **0.004\*** |
| **New-onset CKD /1000 py** | 29.2 | 16.7 | **<0.001\*** | 23.8 | 18.2 | **0.025\*** | | 28.0 | 17.9 | **<0.001\*** |
| Event rates by HRV category (low vs moderate-to-high HRV, Q1 vs Q2-4). LF: low frequency power spectrum; HF: high frequency power spectrum; IQR: interquartile range; CKD: chronic kidney disease; py: person-years. *a* Subjects with Q1 values in each of the main HRV parameters SDNN, rMSSD, and HF.*b* Defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m2 or urinary albumin excretion (UAE) ≥ 30 mg/24 hours. Univariable two-sided p-values were calculated using Mann-Whitney U-tests, χ2-tests, and Mantel-Cox log-rank tests where appropriate. | | | | | | | | | | |

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| **Supplementary Table S4a.** Association of low HRV (LF, LF/HF-ratio, Q1 vs Q2-4; and Composite low HRV, yes vs no).with incident CKD: complete-case analysis. | | | | | | |
| **CKD** | **LF Q1** | **p** | **LF/HF-ratio Q1** | **p** | **Composite low HRV *a*** | **p** |
| **Unadjusted HR [95%CI]** | **1.71 [1.34 ; 2.19]** | **<0.001\*** | **1.29 [1.00 ; 1.67]** | **0.047\*** | **1.52 [1.15 ; 2.01]** | **0.003\*** |
| **Adjusted HR [95%CI] 1** | 1.08 [0.83 ; 1.39] | 0.57 | **1.35 [1.05 ; 1.75]** | **0.020\*** | 0.98 [0.73 ; 1.30] | 0.86 |
| **Adjusted HR [95%CI] 2** | 1.10 [0.84 ; 1.44] | 0.49 | **1.32 [1.01 ; 1.72]** | **0.039\*** | 1.03 [0.76 ; 1.41] | 0.84 |
| **Fully adjusted HR [95%CI] 3** | 1.12 [0.86 ; 1.47] | 0.40 | **1.32 [1.01 ; 1.71]** | **0.043\*** | 1.05 [0.77 ; 1.43] | 0.75 |
| **CKDeGFR<60** |  |  |  |  |  |  |
| **Unadjusted HR [95%CI]** | **2.56 [1.72 ; 3.80]** | **<0.001\*** | 1.40 [0.91 ; 2.14] | 0.12 | **1.91 [1.22 ; 2.97]** | **0.004\*** |
| **Adjusted HR [95%CI] 1** | 1.14 [0.76 ; 1.72] | 0.52 | 1.46 [0.95 ; 2.23] | 0.08 | 0.90 [0.58 ; 1.42] | 0.66 |
| **Adjusted HR [95%CI] 2** | 0.98 [0.64 ; 1.50] | 0.93 | 1.21 [0.77 ; 1.89] | 0.41 | 0.93 [0.57 ; 1.52] | 0.78 |
| **Fully adjusted HR [95%CI] 3** | 1.03 [0.67 ; 1.58] | 0.89 | 1.24 [0.79 ; 1.94] | 0.34 | 0.96 [0.59 ; 1.56] | 0.86 |
| **CKDUAE≥30** |  |  |  |  |  |  |
| **Unadjusted HR [95%CI]** | **1.46 [1.09 ; 1.96]** | **0.011\*** | 1.25 [0.92 ; 1.68] | 0.15 | **1.45 [1.04 ; 2.01]** | **0.027\*** |
| **Adjusted HR [95%CI] 1** | 1.04 [0.77 ; 1.41] | 0.80 | 1.29 [0.96 ; 1.74] | 0.096 | 1.05 [0.75 ; 1.47] | 0.77 |
| **Adjusted HR [95%CI] 2** | 1.08 [0.78 ; 1.48] | 0.65 | 1.24 [0.90 ; 1.69] | 0.18 | 1.15 [0.79 ; 1.66] | 0.47 |
| **Fully adjusted HR [95%CI] 3** | 1.09 [0.79 ; 1.50] | 0.61 | 1.22 [0.89 ; 1.67] | 0.22 | 1.18 [0.81 ; 1.71] | 0.39 |
| Estimates of hazard ratios after multivariable Cox regression analysis. Reference group is moderate-to-high HRV (Q2-4) for LF and LF/HF-ratio. HR: hazard ratio; LF: low frequency power spectrum; rMSSD: HF: high frequency power spectrum; CI: confidence interval. ***a***Subjects with HRV-values in Q1 in each of the main HRV parameters, SDNN, rMSSD, and HF; reference group are subjects without HRV-values in Q1 in SDNN, rMSSD, or HF.  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, baseline eGFR, baseline UAE, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, and hypercholesterolemia, in addition to above. | | | | | | |

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| **Supplementary Table S4b.** Association of low HRV (SDNN, rMSSD, HF) with incident CKD: multiple imputed datasets. | | | | | | |
| **CKD** | **SDNN Q1** | **p** | **rMSSD Q1** | **p** | **HF** | **p** |
| **Unadjusted HR [95%CI]** | **1.42 [1.14 ; 1.76]** | **0.002\*** | 1.26 [1.00 ; 1.60] | 0.051 | **1.38 [1.09 ; 1.75]** | **0.008\*** |
| **Adjusted HR [95%CI] 1** | 1.01 (0.81 ; 1.26] | 0.92 | 0.95 [0.75 ; 1.21] | 0.68 | 1.02 [0.80 ; 1.30] | 0.85 |
| **Adjusted HR [95%CI] 2** | 1.00 [0.79 ; 1.26] | 1.00 | 0.95 [0.73 ; 1.24] | 0.73 | 1.03 [0.80 ; 1.34] | 0.82 |
| **Fully adjusted HR [95%CI] 3** | 1.01 [0.80 ; 1.28] | 0.91 | 0.95 [0.73 ; 1.16] | 0.73 | 1.03 [0.79 ; 1.33] | 0.85 |
| **CKDeGFR<60** |  |  |  |  |  |  |
| **Unadjusted HR [95%CI]** | **1.69 [1.28 ; 2.22]** | **<0.001\*** | 1.33 [1.00 ; 1.77] | 0.053 | **1.44 [1.08 ; 1.92]** | **0.014\*** |
| **Adjusted HR [95%CI] 1** | 0.98 [0.75 ; 1.30] | 0.91 | 0.87 [0.65 ; 1.16] | 0.33 | 0.91 [0.68 ; 1.22] | 0.54 |
| **Adjusted HR [95%CI] 2** | 0.90 [0.67 ; 1.22] | 0.51 | 0.91 [0.67 ; 1.24] | 0.56 | 0.91 [0.66 ; 1.25] | 0.57 |
| **Fully adjusted HR [95%CI] 3** | 0.91 [0.67 ; 1.24] | 0.56 | 0.92 [0.67 ; 1.26] | 0.61 | 0.93 [0.68 ; 1.28] | 0.65 |
| **CKDUAE≥30** |  |  |  |  |  |  |
| **Unadjusted HR [95%CI]** | 1.26 [0.97 ; 1.64] | 0.083 | 1.21 [0.92 ; 1.58] | 0.18 | 1.27 [0.97 ;1.66] | 0.085 |
| **Adjusted HR [95%CI] 1** | 0.99 [0.76 ; 1.30] | 0.95 | 0.98 [0.74 ; 1.29] | 0.89 | 1.02 [0.77 ; 1.34] | 0.90 |
| **Adjusted HR [95%CI] 2** | 1.03 [0.78 ; 1.35] | 0.86 | 1.02 [0.75 ; 1.39] | 0.90 | 1.08 [0.80 ; 1.44] | 0.62 |
| **Fully adjusted HR [95%CI] 3** | 1.04 [0.79 ; 1.37] | 0.76 | 1.03 [0.76 ; 1.39] | 0.87 | 1.08 [0.81 ; 1.44] | 0.61 |
| Pooled estimates from multiple imputed (MI) datasets of hazard ratios after multivariable Cox regression analysis. Reference group is moderate-to-high HRV (Q2-4). HR: hazard ratio; SDNN: standard deviation of normal-to-normal RR-intervals; rMSSD: root mean square of successive differences of adjacent normal-normal RR-intervals; HF: high frequency power spectrum; CI: confidence interval. \* indicates statistical significance (p<0.05)  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, baseline eGFR, baseline UAE, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, and hypercholesterolemia, in addition to above. | | | | | | |

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| **Supplementary Table S4c.** Association of low HRV (LF, LF/HF-ratio, Composite low HRV) with incident CKD: multiple imputed datasets. | | | | | | |
| **CKD** | **LF Q1** | **p** | **LF/HF-ratio Q1** | **p** | **Composite low HRV *a*** | **p** |
| **Unadjusted HR [95%CI]** | **1.45 [1.16 ; 1.82]** | **0.001\*** | 1.17 [0.94 ; 1.47] | 0.17 | **1.32 [1.01 ; 1.72]** | **0.041\*** |
| **Adjusted HR [95%CI] 1** | 1.04 [0.83 ; 1.30] | 0.84 | 1.20 [0.96 ; 1.49] | 0.12 | 0.97 [0.74 ; 1.26] | 0.81 |
| **Adjusted HR [95%CI] 2** | 1.04 [0.82 ; 1.31] | 0.76 | 1.21 [0.96 ; 1.52] | 0.10 | 0.98 [0.74 ; 1.29] | 0.87 |
| **Fully adjusted HR [95%CI] 3** | 1.04 [0.83 ; 1.32] | 0.71 | 1.21 [0.96 ; 1.53] | 0.10 | 0.98 [0.75 ; 1.30] | 0.91 |
| **CKDeGFR<60** |  |  |  |  |  |  |
| **Unadjusted HR [95%CI]** | **1.72 [1.31 ; 2.27]** | **<0.001\*** | 1.16 [0.86 ; 1.57] | 0.34 | **1.39 [1.01 ; 1.93]** | **0.045\*** |
| **Adjusted HR [95%CI] 1** | 0.99 [0.75 ; 1.30] | 0.94 | 1.13 [0.83 ; 1.54] | 0.42 | 0.85 [0.62 ; 1.18] | 0.34 |
| **Adjusted HR [95%CI] 2** | 0.94 [0.70 ; 1.26] | 0.68 | 1.06 [0.77 ; 1.07] | 0.70 | 0.85 [0.60 ; 1.20] | 0.35 |
| **Fully adjusted HR [95%CI] 3** | 0.95 [0.71 ; 1.28] | 0.75 | 1.08 [0.78 ; 1.48] | 0.65 | 0.86 [0.61 ; 1.22] | 0.39 |
| **CKDUAE≥30** |  |  |  |  |  |  |
| **Unadjusted HR [95%CI]** | 1.29 [0.99 ; 1.69] | 0.064 | 1.20 [0.93 ; 1.54] | 0.16 | 1.23 [0.90 ; 1.67] | 0.20 |
| **Adjusted HR [95%CI] 1** | 1.01 [0.76 ; 1.33] | 0.96 | 1.21 [0.94 ; 1.56] | 0.13 | 0.98 [0.71 ; 1.34] | 0.90 |
| **Adjusted HR [95%CI] 2** | 1.04 [0.78 ; 1.37] | 0.80 | 1.24 [0.96 ; 1.61] | 0.10 | 1.04 [0.75 ; 1.45] | 0.81 |
| **Fully adjusted HR [95%CI] 3** | 1.05 [0.80 ; 1.39] | 0.72 | 1.23 [0.95 ; 1.59] | 0.11 | 1.06 [0.76 ; 1.48] | 0.73 |
| Pooled estimates from multiple imputed datasets of hazard ratios after multivariable Cox regression analysis. Reference group is moderate-to-high HRV (Q2-4) for LF and LF/HF-ratio. HR: hazard ratio; LF: low frequency power spectrum; HF: high frequency power spectrum; CI: confidence interval. ***a***Subjects with HRV-values in Q1 in each of the main HRV parameters, SDNN, rMSSD, and HF; reference group are subjects without HRV-values in Q1 in SDNN, rMSSD, or HF.  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, baseline eGFR, baseline UAE, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, and hypercholesterolemia, in addition to above. | | | | | | |

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| **Supplementary Table S4d.** Association of low HRV with incident CKD: weighted analyses. | | | | | | |
| **CKD** | **SDNN Q1** | **rMSSD Q1** | **HF Q1** | **LF Q1** | **LF/HF Q1** | **Composite HRV*a*** |
| **Unadjusted HR [95%CI]** | **2.05 [1.48 ; 2.83]\*** | **1.76 [1.27 ; 2.44]\*** | **1.98 [1.43 ; 2.74]\*** | **2.04 [1.48 ; 2.82]\*** | 1.11 [0.79 ; 1.57] | **1.82 [1.27; 2.62]\*** |
| **Adjusted HR [95%CI] 1** | 1.23 [0.86 ; 1.75] | 1.16 [0.83 ; 1.61] | 1.27 [0.92 ; 1.75] | 1.22 [0.86 ; 1.73] | 1.20 [0.84 ; 1.70] | 1.15 [0.80 ; 1.66] |
| **Adjusted HR [95%CI] 2** | 1.10 [0.74 ; 1.64] | 1.05 [0.71 ; 1.55] | 1.14 [0.79 ; 1.63] | 1.09 [0.74 ; 1.60] | 1.17 [0.81 ; 1.70] | 0.97 [0.63 ; 1.49] |
| **Fully adjusted HR [95%CI] 3** | 1.14 [0.74 ; 1.75] | 1.07 [0.70 ; 1.64] | 1.11 [0.75 ; 1.65] | 1.18 [0.78 ; 1.76] | 1.19 [0.79 ; 1.79] | 0.97 [0.62 ; 1.54] |
| **CKDeGFR<60** |  |  |  |  |  |  |
| **Unadjusted HR [95%CI]** | **2.87 [1.75 ; 4.73]\*** | **2.39 [1.45 ; 3.94]\*** | **2.88 [1.75 ; 4.72]\*** | **3.06 [1.87 ; 5.02]\*** | 0.89 [0.51 ; 1.57] | **2.52 [1.48 ; 4.29]\*** |
| **Adjusted HR [95%CI] 1** | 1.26 [0.73 ; 2.20] | 1.23 [0.74 ; 2.03] | 1.42 [0.87 ; 2.32] | 1.36 [0.80 ; 2.31] | 0.95 [0.54 ; 1.69] | 1.23 [0.72 ; 2.11] |
| **Adjusted HR [95%CI] 2** | 1.07 [0.58 ; 1.97] | 1.20 [0.65 ; 2.21] | 1.19 [0.65 ; 2.17] | 1.15 [0.66 ; 2.01] | 0.90 [0.48 ; 1.71] | 1.10 [0.59 ; 2.04] |
| **Fully adjusted HR [95%CI] 3** | 1.09 [0.56 ; 2.10] | 1.27 [0.65 ; 2.45] | 1.27 [0.66 ; 2.47] | 1.28 [0.68 ; 2.42] | 1.02 [0.51 ; 2.05] | 1.19 [0.61 ; 2.32] |
| **CKDUAE≥30** |  |  |  |  |  |  |
| **Unadjusted HR [95%CI]** | **1.66 [1.11 ; 2.47]\*** | 1.47 [0.98 ; 2.21] | **1.52 [1.01 ; 2.28]\*** | **1.56 [1.04 ; 2.33]\*** | 1.25 [0.83 ; 1.88] | 1.52 [0.96 ; 2.38] |
| **Adjusted HR [95%CI] 1** | 1.16 [0.75 ; 1.79] | 1.07 [0.71 ; 1.63] | 1.08 [0.72 ; 1.64] | 1.08 [0.69 ; 1.68] | 1.34 [0.89 ; 2.01] | 1.08 [0.68 ; 1.71] |
| **Adjusted HR [95%CI] 2** | 1.08 [0.65 ; 1.78] | 1.12 [0.69 ; 1.83] | 1.09 [0.69 ; 1.72] | 1.02 [0.62 ; 1.68] | 1.21 [0.77 ; 1.89] | 1.00 [0.57 ; 1.75] |
| **Fully adjusted HR [95%CI] 3** | 1.12 [0.67 ; 1.88] | 1.23 [0.72 ; 2.11] | 1.12 [0.68 ; 1.84] | 1.08 [0.65 ; 1.78] | 1.17 [0.72 ; 1.91] | 1.00 [0.55 ; 1.84] |
| Estimates of hazard ratios after weighted multivariable Cox regression analysis. Reference group is moderate-to-high HRV (Q2-4). HR: hazard ratio; SDNN: standard deviation of normal-to-normal RR-intervals; rMSSD: root mean square of successive differences of adjacent normal-normal RR-intervals; HF: high frequency power spectrum; LF: low frequency power spectrum; CI: confidence interval. ***a***Subjects with HRV-values in Q1 in each of the main HRV parameters, SDNN, rMSSD, and HF; reference group are subjects without HRV-values in Q1 in SDNN, rMSSD, or HF. \* indicates statistical significance (p<0.05)  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, baseline eGFR, baseline UAE, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, and hypercholesterolemia, in addition to above. | | | | | | |

## ASSOCIATIONS WITH eGFR LEVELS AND RATE OF DECLINE

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| **Supplementary Table S5a.** Association of low HRV (LF, LF/HF-ratio, Q1 vs Q2-4) and Composite low HRV (yes vs no) with baseline levels and slope of eGFR: complete case analysis. | | | | | | | | |
|  | **LF Q1** | | | | | | | |
|  | **Total (n=4605)** | **p** |  | **No CKD (n=3397)** | **p** |  | **CKD (n=939)** | **p** |
| **Baseline eGFR-level***a* **difference (ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β [95%CI]** | **-10.5 [-11.8 ; -9.2]** | **<0.001\*** |  | **-7.68 [-8.87 ; -6.49]** | **<0.001\*** |  | **-13.5 [-17.0 ; -9.93]** | **<0.001\*** |
| **Adjusted β [95%CI]** 1 | **-1.37 [-2.41 ; -0.33]** | **0.010\*** |  | -0.98 [-1.97 ; 0.006] | 0.051 |  | **-3.07 [-5.98 ; -0.15]** | **0.039\*** |
| **Adjusted β [95%CI]** 2 | -0.97 [-2.04 ; 0.10] | 0.076 |  | -0.46 [-1.48 ; 0.56] | 0.38 |  | **-3.15 [-6.17 ; -0.14]** | **0.040\*** |
| **Fully adjusted β [95%CI]** 3 | -0.58 [-1.63 ; 0.46] | 0.27 |  | -0.41 [-1.43 ; 0.61] | 0.43 |  | -2.76 [-5.71 ; 0.19] | 0.066 |
| **eGFR-slope *b*** **difference (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope [95%CI]** | **-0.12 [-0.23 ; -0.015]** | **0.025\*** |  | -0.036 [-0.15 ; 0.076] | 0.53 |  | -0.12 [-0.42 ; 0.18] | 0.44 |
| **Adjusted βslope [95%CI]** 1 | **-0.13 [-0.23 ; -0.019]** | **0.021\*** |  | -0.049 [-0.16 ; 0.062] | 0.38 |  | -0.10 [-0.40 ; 0..19] | 0.49 |
| **Adjusted βslope [95%CI]** 2 | **-0.12 [-0.23 ; -0.015]** | **0.025\*** |  | -0.046 [-0.16 ; 0.065] | 0.41 |  | -0.11 [-0.40 ; 0.19] | 0.48 |
| **Fully adjusted βslope [95%CI]** 3 | **-0.12 [-0.23 ; -0.018]** | **0.022\*** |  | -0.047 [-0.16 ; 0.064] | 0.41 |  | -0.099 [-0.39 ; 0.20] | 0.51 |
|  | **LF/HF-ratio Q1** | | | | | | | |
|  | **Total (n=4605)** | **p** |  | **No CKD (n=3397)** | **p** |  | **CKD (n=939)** | **p** |
| **Baseline eGFR-level***a* **difference (ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β [95%CI]** | **-1.94 [-3.27 ; -0.61]** | **0.004\*** |  | -0.22 [-1.46 ; 1.01] | 0.72 |  | **-6.73 [-10.4 ; -3.03]** | **<0.001\*** |
| **Adjusted β [95%CI]** 1 | **-1.89 [-2.87 ; -0.90]** | **<0.001\*** |  | **-1.06 [-2.00; -0.11]** | **0.028\*** |  | **-3.10 [-5.92 ; -0.28]** | **0.031\*** |
| **Adjusted β [95%CI]** 2 | **-1.45 [-2.45 ; -0.45]** | **0.005\*** |  | -0.38 [-1.34 ; 0.58] | 0.44 |  | **-3.29 [-6.16 ; -0.41]** | **0.025\*** |
| **Fully adjusted β [95%CI]** 3 | **-1.15 [-2.12 ; 0.17]** | **0.022\*** |  | -0.31 [-1.26 ; 0.65] | 0.53 |  | -2.41 [-5.23 ; 0.41] | 0.094 |
| **eGFR-slope *b* difference (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope [95%CI]** | -0.90 [-0.20 ; 0.017] | 0.098 |  | -0.095 [-0.21 ; 0.016] | 0.092 |  | -0.044 [-0.34 ; 0.26] | 0.77 |
| **Adjusted βslope [95%CI]** 1 | -0.081 [-0.19 ; 0.026] | 0.14 |  | -0.091 [-0.20 ; 0.019] | 0.10 |  | -0.022 [-0.32 ; 0.27] | 0.88 |
| **Adjusted βslope [95%CI]** 2 | -0.080 [-0.19 ; 0.026] | 0.14 |  | -0.090 [-0.20 ; 0.020] | 0.11 |  | -0.026 [-0.32 ; 0.27] | 0.86 |
| **Fully adjusted βslope [95%CI]** 3 | -0.079 [-0.19 ; 0.027] | 0.14 |  | -0.090 [-0.20 ; 0.020] | 0.11 |  | -0.016 [-0.31 ; 0.28] | 0.92 |
|  | **Composite low HRV *c*** | | | | | | | |
|  | **Total (n=4605)** | **p** |  | **No CKD (n=3397)** | **P** |  | **CKD (n=939)** | **p** |
| **Baseline eGFR-level***a* **difference (ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β [95%CI]** | **-9.15 [-10.6 ; -7.65]** | **<0.001\*** |  | **-6.62 [-8.00 ; -5.23]** | **<0.001\*** |  | **-14.0 [-18.3 ; -9.75]** | **<0.001\*** |
| **Adjusted β [95%CI]** 1 | **-1.25 [-2.42 ; -0.079]** | **0.036\*** |  | -0.40 [-1.52 ; 0.71] | 0.48 |  | **-5.32 [-8.72 ; -1.92]** | **0.002\*** |
| **Adjusted β [95%CI]** 2 | **-1.36 [-2.60 ; -0.12]** | **0.032\*** |  | -0.32 [-1.51 ; 0.87] | 0.59 |  | **-6.10 [-9.67 ; -2.54]** | **<0.001\*** |
| **Fully adjusted β [95%CI]** 3 | -1.12 [-2.34 ; 0.089] | 0.069 |  | -0.33 [-1.52 ; 0.85] | 0.58 |  | **-6.31 [-9.78 ; -2.83]** | **<0.001\*** |
| **eGFR-slope *b* difference (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope [95%CI]** | -0.049 [-0.17 ; 0.077] | 0.45 |  | -0.063 [-0.19 ; 0.065] | 0.33 |  | 0.23 [-0.14 ; 0.59] | 0.23 |
| **Adjusted βslope [95%CI]** 1 | -0.051 [-0.18 ; 0.074] | 0.43 |  | -0.069 [-0.20 ; 0.058] | 0.28 |  | 0.22 [-0.14 ; 0.59] | 0.22 |
| **Adjusted βslope [95%CI]** 2 | -0.046 [-0.17 ; 0.079] | 0.47 |  | -0.066 [-0.19 ; 0.062] | 0.31 |  | 0.23 [-0.13 ; 0.59] | 0.22 |
| **Fully adjusted βslope [95%CI]** 3 | -0.049 [-0.17 ; 0.075] | 0.43 |  | -0.066 [-0.19 ; 0.061] | 0.31 |  | 0.23 [-0.13 ; 0.59] | 0.21 |
| Estimates of the association between low HRV and eGFR in the total PREVEND population, and stratified for CKD at baseline. Reference group is moderate-to-high HRV (Q2-4) for LF and LF/HF-ratio., *a* eGFR-level: difference in baseline levels of eGFR, expressed in ml/min/1.73m2, compared to reference, *b* eGFR-slope: difference in change in eGFR over time, in ml/min/1.73m2 per year, compared to reference. HRV: heart rate variability; eGFR: estimated glomerular filtration rate; LF: low frequency power spectrum; HF: high frequency power spectrum; CI: confidence interval. *c* Subjects with HRV-values in Q1 in each of the main HRV parameters, SDNN, rMSSD, and HF; reference group are subjects without HRV-values in Q1 in SDNN, rMSSD, or HF. \* indicates statistical significance (p < 0.05)  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, baseline UAE, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, hypercholesterolemia, (and baseline chronic kidney disease status in the total cohort) in addition to above. | | | | | | | | |

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| **Supplementary Table S5b.**  Association of low HRV (SDNN, rMSSD, HF Q1 vs Q2-4) with baseline levels and slope of eGFR: multiple imputed datasets. | | | | | | | | |
|  | **SDNN Q1** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| **Baseline eGFR-level difference***a* **(ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β(se)** | **-6.25 (0.59)** | **<0.001\*** |  | **-4.67 (0.53)** | **<0.001\*** |  | **-8.28 (1.62)** | **<0.001\*** |
| **Adjusted β (se)** 1 | -0.37 (0.45) | 0.41 |  | -0.19 (0.44) | 0.67 |  | -1.77 (1.26) | 0.16 |
| **Adjusted β (se)** 2 | -0.25 (0.47) | 0.60 |  | -0.046 (0.46) | 0.92 |  | -1.77 (1.31) | 0.18 |
| **Fully adjusted β (se)** 3 | -0.14 (0.46) | 0.77 |  | -0.036 (0.47) | 0.94 |  | -1.70 (1.29) | 0.19 |
| **eGFR-slope difference *b* (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope (se)** | -0.052 (0.052) | 0.32 |  | -0.052 (0.052) | 0.32 |  | 0.079 (0.15) | 0.60 |
| **Adjusted βslope (se)** 1 | -0.058 (0.052) | 0.27 |  | -0.061 (0.052) | 0.24 |  | 0.065 (0.15) | 0.67 |
| **Adjusted βslope (se)** 2 | -0.056 (0.051) | 0.28 |  | -0.060 (0.052) | 0.25 |  | 0.066 (0.15) | 0.66 |
| **Fully adjusted βslope (se)** 3 | -0.059 (0.051) | 0.25 |  | -0.060 (0.052) | 0.24 |  | 0.068 (0.15) | 0.65 |
|  | **rMSSD Q1** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| **Baseline eGFR-level difference***a* **(ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β(se)** | **-5.49 (0.57)** | **<0.001\*** |  | **-4.16 (0.52)** | **<0.001\*** |  | **-4.67 (1.60)** | **0.004\*** |
| **Adjusted β (se)** 1 | -0.32 (0.45) | 0.47 |  | -0.26 (0.42) | 0.55 |  | -0.32 (1.24) | 0.79 |
| **Adjusted β (se)** 2 | -0.48 (0.48) | 0.32 |  | -0.40 (0.45) | 0.38 |  | -0.34 (1.32) | 0.80 |
| **Fully adjusted β (se)** 3 | -0.31 (0.46) | 0.51 |  | -0.40 (0.45) | 0.38 |  | -0.40 (1.29) | 0.75 |
| **eGFR-slope difference *b* (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope (se)** | -0.048 (0.050) | 0.34 |  | -0.051 (0.052) | 0.33 |  | 0.18 (0.14) | 0.20 |
| **Adjusted βslope (se)** 1 | -0.050 (0.050) | 0.32 |  | 0.056 (0.052) | 0.28 |  | 0.17 (0.14) | 0.22 |
| **Adjusted βslope (se)** 2 | -0.046 (0.050) | 0.36 |  | -0.054 (0.052) | 0.29 |  | 0.17 (0.14) | 0.21 |
| **Fully adjusted βslope (se)** 3 | -0.047 (0.050) | 0.35 |  | -0.055 (0.052) | 0.29 |  | 0.17 (0.14) | 0.21 |
|  | **HF Q1** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| **Baseline eGFR-level difference***a* **(ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β(se)** | **-5.84 (0.60)** | **<0.001\*** |  | **-4.50 (0.58)** | **<0.001\*** |  | **-6.87 (1.56)** | **<0.001\*** |
| **Adjusted β (se)** 1 | -0.32 (0.45) | 0.48 |  | -0.21 (0.44) | 0.63 |  | -1.39 (1.21) | 0.25 |
| **Adjusted β (se)** 2 | -0.43 (0.47) | 0.36 |  | -0.29 (0.46) | 0.53 |  | -1.50 (1.27) | 0.24 |
| **Fully adjusted β (se)** 3 | -0.24 (0.46) | 0.61 |  | -0.27 (0.46) | 0.56 |  | -1.45 (1.24) | 0.24 |
| **eGFR-slope difference *b* (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope (se)** | -0.069 (0.054) | 0.20 |  | -0.064 (0.053) | 0.23 |  | 0.15 (0.15) | 0.31 |
| **Adjusted βslope (se)** 1 | -0.071 (0.053) | 0.19 |  | -0.071 (0.052) | 0.17 |  | 0.14 (0.15) | 0.33 |
| **Adjusted βslope (se)** 2 | -0.066 (0.053) | 0.21 |  | -0.070 (0.052) | 0.18 |  | 0.15 (0.15) | 0.31 |
| **Fully adjusted βslope (se)** 3 | -0.069 (0.053) | 0.20 |  | -0.071 (0.052) | 0.18 |  | 0.15 (0.15) | 0.31 |
| Pooled estimates (and their standard errors, se) from multiple imputed datasets of the association between low HRV and eGFR in the total PREVEND population, and stratified for CKD at baseline. Reference group is moderate-to-high HRV (Q2-4), *a* eGFR-level: difference in baseline levels of eGFR, expressed in ml/min/1.73m2, compared to reference, *b* eGFR-slope: difference in change in eGFR over time, in ml/min/1.73m2 per year, compared to reference. HRV: heart rate variability; eGFR: estimated glomerular filtration rate; SDNN: standard deviation of normal-to-normalRR-intervals; rMSSD: root mean square of successive differences of adjacent normal-normal RR-intervals; HF: high frequency power spectrum; CI: confidence interval.  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, baseline UAE, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, hypercholesterolemia, (and baseline chronic kidney disease status in the total cohort) in addition to above.  \* indicates statistical significance (p < 0.05) | | | | | | | | |

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| **Supplementary Table S5c.** Association of low HRV (LF, LF/HF-ratio, Q1 vs Q2-4) and Composite low HRV (yes vs no) with baseline levels and slope of eGFR: multiple imputed datasets. | | | | | | | | |
|  | **LF Q1** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| **Baseline eGFR-level difference***a* **(ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β(se)** | **-7.11 (0.56)** | **<0.001\*** |  | **-5.12 (0.51)** | **<0.001\*** |  | **-9.55 (1.51)** | **<0.001\*** |
| **Adjusted β (se)** 1 | -0.46 (0.44) | 0.30 |  | -0.37 (0.43) | 0.39 |  | -1.82 (1.21) | 0.13 |
| **Adjusted β (se)** 2 | -0.19 (0.45) | 0.68 |  | -0.051 (0.44) | 0.91 |  | -1.62 (1.23) | 0.19 |
| **Fully adjusted β (se)** 3 | 0.022 (0.44) | 0.96 |  | -0.017 (0.44) | 0.97 |  | -1.39 (1.22) | 0.25 |
| **eGFR-slope difference *b* (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope (se)** | -0.093 (0.051) | 0.072 |  | -0.050 (0.052) | 0.34 |  | -0.017 (0.15) | 0.91 |
| **Adjusted βslope (se)** 1 | -0.095 (0.052) | 0.067 |  | -0.057 (0.052) | 0.28 |  | -0.018 (0.15) | 0.91 |
| **Adjusted βslope (se)** 2 | -0.093 (0.051) | 0.072 |  | -0.056 (0.052) | 0.29 |  | -0.020 (0.15) | 0.90 |
| **Fully adjusted βslope (se)** 3 | -0.094 (0.051) | 0.067 |  | -0.056 (0.052) | 0.28 |  | -0.017 (0.15) | 0.91 |
|  | **LF/HF-ratio Q1** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| **Baseline eGFR-level difference***a* **(ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β(se)** | -0.77 (0.58) | 0.18 |  | 0.14 (0.56) | 0.81 |  | **-3.33 (1.61)** | **0.039\*** |
| **Adjusted β (se)** 1 | -0.79 (0.44) | 0.069 |  | -0.26 (0.43) | 0.61 |  | -2.04 (1.22) | 0.094 |
| **Adjusted β (se)** 2 | -0.48 (0.44) | 0.27 |  | 0.13 (0.43) | 0.76 |  | -1.99 (1.22) | 0.10 |
| **Fully adjusted β (se)** 3 | -0.34 (0.37) | 0.35 |  | 0.17 (0.43) | 0.69 |  | -1.73 (1.22) | 0.16 |
| **eGFR-slope difference *b* (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope (se)** | -0.066 (0.048) | 0.17 |  | -0.060 (0.049) | 0.23 |  | -0.051 (0.15) | 0.73 |
| **Adjusted βslope (se)** 1 | -0.059 (0.048) | 0.22 |  | -0.056 (0.049) | 0.25 |  | -0.042 (0.15) | 0.78 |
| **Adjusted βslope (se)** 2 | -0.058 (0.048) | 0.22 |  | -0.055 (0.049) | 0.26 |  | -0.040 (0.15) | 0.78 |
| **Fully adjusted βslope (se)** 3 | -0.078 (0.041) | 0.060 |  | -0.055 (0.049) | 0.26 |  | -0.037 (0.15) | 0.80 |
|  | **Composite low HRV *c*** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| **Baseline eGFR-level difference***a* **(ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β(se)** | **-6.24 (0.66)** | **<0.001\*** |  | **-4.60 (0.64)** | **<0.001\*** |  | **-9.93 (1.86)** | **<0.001\*** |
| **Adjusted β (se)** 1 | -0.77 (0.50) | 0.13 |  | -0.37 (0.51) | 0.73 |  | **-3.29 (1.46)** | **0.024\*** |
| **Adjusted β (se)** 2 | -0.86 (0.52) | 0.10 |  | -0.40 (0.53) | 0.46 |  | **-3.47 (1.50)** | **0.021\*** |
| **Fully adjusted β (se)** 3 | -0.74 (0.51) | 0.15 |  | -0.39 (0.53) | 0.46 |  | **-3.70 (1.47)** | **0.012\*** |
| **eGFR-slope difference *b* (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope (se)** | -0.049 (0.061) | 0.42 |  | -0.064 (0.059) | 0.28 |  | 0.17 (0.18) | 0.33 |
| **Adjusted βslope (se)** 1 | -0.050 (0.061) | 0.42 |  | -0.070 (0.059) | 0.24 |  | 0.16 (0.18) | 0.37 |
| **Adjusted βslope (se)** 2 | -0.047 (0.061) | 0.44 |  | -0.068 (0.059) | 0.25 |  | 0.16 (0.17) | 0.36 |
| **Fully adjusted βslope (se)** 3 | -0.049 (0.061) | 0.42 |  | -0.068 (0.059) | 0.25 |  | 0.16 (0.17) | 0.36 |
| Pooled estimates (se) from multiple imputed (MI) datasets of the association between low HRV and eGFR in the total PREVEND population, and stratified for CKD at baseline. Reference group is moderate-to-high HRV (Q2-4), *a* eGFR-level: difference in baseline levels of eGFR, expressed in ml/min/1.73m2, compared to reference, *b* eGFR-slope: difference in change in eGFR over time, in ml/min/1.73m2 per year, compared to reference. HRV: heart rate variability; eGFR: estimated glomerular filtration rate; of normal-to-normal RR-intervals; HF: high frequency power spectrum; LF: low frequency power spectrum, CI: confidence interval. *c*Subjects with HRV-values in Q1 in each of the main HRV parameters, SDNN, rMSSD, and HF; reference group are subjects without HRV-values in Q1 in SDNN, rMSSD, or HF.  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, baseline UAE, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, hypercholesterolemia, (and baseline chronic kidney disease status in the total cohort) in addition to above.\* indicates statistical significance (p < 0.05) | | | | | | | | |

## ASSOCIATIONS WITH *ln*UAE LEVELS AND RATE OF INCREASE

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| **Supplementary Table S6a.**  Association of low HRV (SDNN, rMSSD, HF, Q1 vs Q2-4) with baseline levels and slope of *ln*UAE: complete case analysis. | | | | | | | | |
|  | **SDNN Q1** | | | | | | | |
|  | **Total (n=4605)** | **p** |  | **No CKD (n=3397)** | **p** |  | **CKD (n=939)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** | | | | | | | | |
| **Unadjusted β(se)** | **0.26 (0.037)** | **<0.001\*** |  | **0.086 (0.022)** | **<0.001\*** |  | 0.067 (0.10) | 0.51 |
| **Adjusted β (se)** 1 | **0.087 (0.038)** | **0.022\*** |  | 0.038 (0.023) | 0.10 |  | 0.089 (0.11) | 0.40 |
| **Adjusted β (se)** 2 | 0.049 (0.040) | 0.21 |  | 0.021 (0.024) | 0.39 |  | 0.0098 (0.11) | 0.93 |
| **Fully adjusted β (se)** 3 | 0.013 (0.031) | 0.68 |  | 0.017 (0.024) | 0.47 |  | 0.010 (0.11) | 0.93 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** |  |  |  |  |  |  |  |  |
| **Unadjusted βslope (se)** | 0.0024 (0.0043) | 0.58 |  | 0.0056 (0.0038) | 0.14 |  | 0.00070 (0.016) | 0.97 |
| **Adjusted βslope (se)** 1 | 0.0028 (0.0043) | 0.52 |  | 0.006 (0.0038) | 0.12 |  | 0.00070 (0.016) | 0.97 |
| **Adjusted βslope (se)** 2 | 0.0024 (0.0043) | 0.57 |  | 0.006 (0.0038) | 0.12 |  | 0.00056 (0.016) | 0.97 |
| **Fully adjusted βslope (se)** 3 | 0.0030 (0.0043) | 0.49 |  | 0.006 (0.0038) | 0.11 |  | 0.00052 (0.016) | 0.97 |
|  | **rMSSD Q1** | | | | | | | |
|  | **Total (n=4605)** | **p** |  | **No CKD (n=3397)** | **p** |  | **CKD (n=939)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** | | | | | | | | |
| **Unadjusted β(se)** | **0.28 (0.037)** | **<0.001\*** |  | **0.078 (0.022)** | **<0.001\*** |  | 0.045 (0.10) | 0.66 |
| **Adjusted β (se)** 1 | **0.13 (0.038)** | **<0.001\*** |  | 0.038 (0.023) | 0.10 |  | 0.062 (0.11) | 0.56 |
| **Adjusted β (se)** 2 | **0.11 (0.041)** | **0.005\*** |  | 0.026 (0.025) | 0.30 |  | -0.054 (0.11) | 0.63 |
| **Fully adjusted β (se)** 3 | 0.032 (0.032) | 0.32 |  | 0.027 (0.025) | 0.28 |  | -0.070 (0.11) | 0.53 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** | | | | | | | | |
| **Unadjusted βslope (se)** | -0.0027 (0.0043) | 0.54 |  | 0.0041 (0.0037) | 0.28 |  | **-0.037 (0.016)** | **0.022\*** |
| **Adjusted βslope (se)** 1 | -0.0024 (0.0043) | 0.58 |  | 0.0042 (0.0037) | 0.26 |  | **-0.037 (0.016)** | **0.022\*** |
| **Adjusted βslope (se)** 2 | -0.0026 (0.0043) | 0.54 |  | 0.0043 (0.0037) | 0.25 |  | **-0.037 (0.016)** | **0.022\*** |
| **Fully adjusted βslope (se)** 3 | -0.0022 (0.0043) | 0.61 |  | 0.0044 (0.0037) | 0.24 |  | **-0.036 (0.016)** | **0.022\*** |
|  | **HF** | | | | | | | |
|  | **Total (n=4605)** | **p** |  | **No CKD (n=3397)** | **P** |  | **CKD (n=939)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** | | | | | | | | |
| **Unadjusted β(se)** | **0.28 (0.037)** | **<0.001\*** |  | **0.072 (0.022)** | **0.001\*** |  | 0.074 (0.10) | 0.47 |
| **Adjusted β (se)** 1 | **0.12 (0.038)** | **0.002\*** |  | 0.026 (0.23) | 0.26 |  | 0.095 (0.11) | 0.37 |
| **Adjusted β (se)** 2 | **0.091 (0.040)** | **0.024\*** |  | 0.0090 (0.025) | 0.71 |  | -0.026 (0.11) | 0.82 |
| **Fully adjusted β (se)** 3 | 0.012 (0.031) | 0.71 |  | 0.0072 (0.024) | 0.77 |  | -0.023 (0.11) | 0.83 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** | | | | | | | | |
| **Unadjusted βslope (se)** | -0.0026 (0.0044) | 0.54 |  | 0.0040 (0.0038) | 0.28 |  | -0.028 (0.016) | 0.086 |
| **Adjusted βslope (se)** 1 | -0.0024 (0.0044) | 0.58 |  | 0.0042 (0.0038) | 0.26 |  | -0.028 (0.016) | 0.087 |
| **Adjusted βslope (se)** 2 | -0.0027 (0.0043) | 0.53 |  | 0.0043 (0.0038) | 0.25 |  | -0.029 (0.016) | 0.073 |
| **Fully adjusted βslope (se)** 3 | -0.0018 (0.0044) | 0.67 |  | 0.0044 (0.0038) | 0.24 |  | -0.029 (0.016) | 0.073 |
| Estimates (and their standard errors, se) of the association between low HRV and lnUAE in the total PREVEND population, and stratified for CKD at baseline. Reference group is moderate-to-high HRV (Q2-4), *a ln*UAE-level: difference in baseline levels of the natural logarithm (ln) of UAE, compared to reference, *b ln*UAE-slope: difference in change in the natural logarithm of UAE over time, compared to reference. HRV: heart rate variability; UAE: Urinary albumin excretion; SDNN: standard deviation of normal-to-normal RR-intervals; rMSSD: root mean square of successive differences; HF: high frequency power spectrum.  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, eGFR, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, hypercholesterolemia, (and baseline chronic kidney disease status in the total cohort) in addition to above.  \* indicates statistical significance (p < 0.05) | | | | | | | | |

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| **Supplementary Table S6b.**  Association of low HRV (LF, LF/HF-ratio, Q1 vs Q2-4) and Composite low HRV (yes vs no) with baseline levels and slope of *ln*UAE: complete case analysis. | | | | | | | | |
|  | **LF Q1** | | | | | | | |
|  | **Total (n=4605)** | **p** |  | **No CKD (n=3397)** | **p** |  | **CKD (n=939)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** | | | | | | | | |
| **Unadjusted β(se)** | **0.28 (0.037)** | **<0.001\*** |  | **0.087 (0.022)** | **<0.001\*** |  | 0.048 (0.10) | 0.64 |
| **Adjusted β (se)** 1 | **0.087 (0.039)** | **0.024** |  | 0.039 (0.023) | 0.091 |  | 0.074 (0.11) | 0.49 |
| **Adjusted β (se)** 2 | **0.085 (0.039)** | **0.029** |  | 0.038 (0.024) | 0.11 |  | 0.038 (0.11) | 0.73 |
| **Fully adjusted β (se)** 3 | 0.0077 (0.018) | 0.68 |  | 0.034 (0.023) | 0.14 |  | 0.044 (0.11) | 0.68 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** | | | | | | | | |
| **Unadjusted βslope (se)** | 0.0026 (0.0043) | 0.55 |  | 0.0056 (0.0038) | 0.13 |  | -0.0014 (0.016) | 0.93 |
| **Adjusted βslope (se)** 1 | 0.0031 (0.0043) | 0.48 |  | 0.0059 (0.0038) | 0.12 |  | -0.0014 (0.016) | 0.93 |
| **Adjusted βslope (se)** 2 | 0.0025 (0.0043) | 0.57 |  | 0.0058 (0.0038) | 0.12 |  | -0.0014 (0.016) | 0.93 |
| **Fully adjusted βslope (se)** 3 | -0.0025 (0.0060) | 0.67 |  | 0.0059 (0.0038) | 0.12 |  | -0.0019 (0.016) | 0.91 |
|  | **LF/HF-ratio Q1** | | | | | | | |
|  | **Total (n=4605)** | **p** |  | **No CKD (n=3397)** | **p** |  | **CKD (n=939)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** | | | | | | | | |
| **Unadjusted β(se)** | 0.022 (0.038) | 0.56 |  | -0.010 (0.022) | 0.66 |  | 0.033 (0.10) | 0.75 |
| **Adjusted β (se)** 1 | 0.021 (0.037) | 0.56 |  | -0.036 (0.022) | 0.87 |  | 0.039 (0.11) | 0.71 |
| **Adjusted β (se)** 2 | **0.073 (0.036)** | **0.046\*** |  | 0.018 (0.022) | 0.41 |  | 0.10 (0.10) | 0.34 |
| **Fully adjusted β (se)** 3 | 0.043 (0.028) | 0.13 |  | 0.016 (0.022) | 0.48 |  | 0.094 (0.10) | 0.36 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** | | | | | | | | |
| **Unadjusted βslope (se)** | 0.0042 (0.0043) | 0.33 |  | 0.0028 (0.0037) | 0.46 |  | 0.019 (0.016) | 0.24 |
| **Adjusted βslope (se)** 1 | 0.0042 (0.0043) | 0.33 |  | 0.0028 (0.0037) | 0.46 |  | 0.019 (0.016) | 0.24 |
| **Adjusted βslope (se)** 2 | 0.0040 (0.0043) | 0.35 |  | 0.0028 (0.0037) | 0.45 |  | 0.019 (0.016) | 0.23 |
| **Fully adjusted βslope (se)** 3 | 0.0046 (0.0043) | 0.28 |  | 0.0029 (0.0037) | 0.45 |  | 0.019 (0.016) | 0.24 |
|  | **Composite low HRV *c*** | | | | | | | |
|  | **Total (n=4605)** | **p** |  | **No CKD (n=3397)** | **P** |  | **CKD (n=939)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** | | | | | | | | |
| **Unadjusted β(se)** | **0.26 (0.043)** | **<0.001\*** |  | **0.091 (0.025)** | **<0.001\*** |  | 0.074 (0.12) | 0.55 |
| **Adjusted β (se)** 1 | **0.094 (0.044)** | **0.030\*** |  | 0.047 (0.026) | 0.074 |  | 0.097 (0.13) | 0.45 |
| **Adjusted β (se)** 2 | 0.063 (0.045) | 0.16 |  | 0.034 (0.027) | 0.22 |  | -0.026 (0.13) | 0.84 |
| **Fully adjusted β (se)** 3 | 0.039 (0.044) | 0.38 |  | 0.033 (0.027) | 0.22 |  | -0.023 (0.13) | 0.86 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** | | | | | | | | |
| **Unadjusted βslope (se)** | -0.0041 (0.0050) | 0.42 |  | 0.0051 (0.0043) | 0.23 |  | -0.023 (0.020) | 0.25 |
| **Adjusted βslope (se)** 1 | -0.0038 (0.0050) | 0.45 |  | 0.0053 (0.0043) | 0.22 |  | -0.023 (0.020) | 0.25 |
| **Adjusted βslope (se)** 2 | -0.0042 (0.0050) | 0.40 |  | 0.0054 (0.0043) | 0.21 |  | -0.024 (0.020) | 0.23 |
| **Fully adjusted βslope (se)** 3 | -0.0039 (0.0050) | 0.44 |  | 0.0056 (0.0043) | 0.20 |  | -0.024 (0.020) | 0.23 |
| Estimates (and their standard errors, se) of the association between low HRV and lnUAE in the total PREVEND population, and stratified for CKD at baseline. Reference group is moderate-to-high HRV (Q2-4), *a ln*UAE-level: difference in baseline levels of the natural logarithm (ln) of UAE, compared to reference, *b ln*UAE-slope: difference in change in the natural logarithm of UAE over time, compared to reference. HRV: heart rate variability; UAE: Urinary albumin excretion; LF: low frequency power spectrum; HF: high frequency power spectrum. *c*Subjects with HRV-values in Q1 in each of the main HRV parameters, SDNN, rMSSD, and HF; reference group are subjects without HRV-values in Q1 in SDNN, rMSSD, or HF.  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, eGFR, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, hypercholesterolemia, (and baseline chronic kidney disease status in the total cohort) in addition to above.  \* indicates statistical significance (p < 0.05) | | | | | | | | |

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| **Supplementary Table S6c.**  Association of low HRV (SDNN, rMSSD, HF, Q1 vs Q2-4) with baseline levels and slope of *ln*UAE: multiple imputed datasets. | | | | | | | | |
|  | **SDNN Q1** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** | | | | | | | | |
| **Unadjusted β(se)** | **0.17 (0.032)** | **<0.001\*** |  | **0.039 (0.019)** | **0.042\*** |  | 0.046 (0.093) | 0.63 |
| **Adjusted β (se)** 1 | 0.033 (0.032) | 0.31 |  | 0.0042 (0.020) | 0.83 |  | 0.042 (0.096) | 0.66 |
| **Adjusted β (se)** 2 | 0.0072 (0.033) | 0.83 |  | -0.0080 (0.020) | 0.69 |  | 0.019 (0.095) | 0.84 |
| **Fully adjusted β (se)** 3 | -0.0077 (0.024) | 0.75 |  | -0.010 (0.020) | 0.61 |  | 0.011 (0.095) | 0.91 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** | | | | | | | | |
| **Unadjusted βslope (se)** | 0.0014 (0.0037) | 0.70 |  | 0.0033 (0.0032) | 0.29 |  | 0.0031 (0.014) | 0.83 |
| **Adjusted βslope (se)** 1 | 0.0017 (0.0037) | 0.64 |  | 0.0035 (0.0032) | 0.27 |  | 0.0031 (0.014) | 0.83 |
| **Adjusted βslope (se)** 2 | 0.0015 (0.0037) | 0.69 |  | 0.0036 (0.0032) | 0.26 |  | 0.0028 (0.0014) | 0.85 |
| **Fully adjusted βslope (se)** 3 | 0.0020 (0.0037) | 0.59 |  | 0.0036 (0.0032) | 0.25 |  | 0.0027 (0.0014) | 0.85 |
|  | **rMSSD Q1** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** | | | | | | | | |
| **Unadjusted β(se)** | **0.18 (0.036)** | **<0.001\*** |  | 0.035 (0.019) | 0.073 |  | 0.077 (0.095) | 0.42 |
| **Adjusted β (se)** 1 | 0.064 (0.035) | 0.064 |  | 0.0040 (0.019) | 0.84 |  | 0.074 (0.096) | 0.44 |
| **Adjusted β (se)** 2 | 0.051 (0.037) | 0.17 |  | -0.0056 (0.020) | 0.78 |  | 0.039 (0.10) | 0.70 |
| **Fully adjusted β (se)** 3 | 0.0083 (0.026) | 0.76 |  | -0.0063 (0.020) | 0.75 |  | 0.028 (0.10) | 0.78 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** | | | | | | | | |
| **Unadjusted βslope (se)** | -0.0028 (0.0038) | 0.45 |  | 0.00024 (0.0033) | 0.94 |  | -0.015 (0.015) | 0.30 |
| **Adjusted βslope (se)** 1 | -0.0026 (0.0038) | 0.49 |  | 0.00035 (0.0033) | 0.92 |  | -0.015 (0.015) | 0.30 |
| **Adjusted βslope (se)** 2 | -0.0028 (0.0038) | 0.46 |  | 0.00045 (0.0033) | 0.89 |  | -0.015 (0.015) | 0.30 |
| **Fully adjusted βslope (se)** 3 | -0.0025 (0.0038) | 0.51 |  | 0.00047 (0.0033) | 0.89 |  | -0.016 (0.015) | 0.29 |
|  | **HF** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** | | | | | | | | |
| **Unadjusted β(se)** | **0.19 (0.035)** | **<0.001\*** |  | 0.033 (0.019) | 0.094 |  | 0.12 (0.098) | 0.23 |
| **Adjusted β (se)** 1 | 0.059 (0.035) | 0.089 |  | 0.0014 (0.020) | 0.94 |  | 0.12 (0.099) | 0.25 |
| **Adjusted β (se)** 2 | 0.038 (0.036) | 0.29 |  | -0.013 (0.020) | 0.53 |  | 0.070 (0.099) | 0.48 |
| **Fully adjusted β (se)** 3 | -0.0027 (0.027) | 0.92 |  | -0.014 (0.020) | 0.47 |  | 0.060 (0.098) | 0.54 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** | | | | | | | | |
| **Unadjusted βslope (se)** | -0.0022 (0.0039) | 0.58 |  | 0.00093 (0.0033) | 0.78 |  | -0.011 (0.015) | 0.44 |
| **Adjusted βslope (se)** 1 | -0.0019 (0.0039) | 0.63 |  | 0.0011 (0.0033) | 0.75 |  | -0.011 (0.015) | 0.44 |
| **Adjusted βslope (se)** 2 | -0.0022 (0.0039) | 0.58 |  | 0.0012 (0.0033) | 0.72 |  | -0.012 (0.015) | 0.40 |
| **Fully adjusted βslope (se)** 3 | -0.0016 (0.0039) | 0.68 |  | 0.0012 (0.0033) | 0.71 |  | -0.013 (0.015) | 0.40 |
| Pooled estimates (and their standard errors, se) from multiple imputed (MI) datasets of the association between low HRV with lnUAE in the total PREVEND population, and stratified for CKD at baseline. Reference group is moderate-to-high HRV (Q2-4), *a ln*UAE-level: difference in baseline levels of the natural logarithm (ln) of UAE, compared to reference, *b ln*UAE-slope: difference in change in the natural logarithm of UAE over time, compared to reference. HRV: heart rate variability; UAE: Urinary albumin excretion; LF: low frequency power spectrum; HF: high frequency power spectrum. *c*Subjects with HRV-values in Q1 in each of the main HRV parameters, SDNN, rMSSD, and HF; reference group are subjects without HRV-values in Q1 in SDNN, rMSSD, or HF.  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, eGFR, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, hypercholesterolemia, (and baseline chronic kidney disease status in the total cohort) in addition to above.  \* indicates statistical significance (p < 0.05) | | | | | | | | |

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| **Supplementary Table S6d.**  Association of low HRV (LF, LF/HF-ratio, Q1 vs Q2-4) and Composite low HRV (yes vs no) with baseline levels and slope of *ln*UAE: multiple imputed datasets. | | | | | | | | |
|  | **LF Q1** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** |  |  |  |  |  |  |  |  |
| **Unadjusted β(se)** | **0.19 (0.032)** | **<0.001\*** |  | **0.042 (0.019)** | **0.030\*** |  | 0.078 (0.094) | 0.41 |
| **Adjusted β (se)** 1 | 0.033 (0.032) | 0.30 |  | 0.0048 (0.020) | 0.81 |  | 0.075 (0.098) | 0.44 |
| **Adjusted β (se)** 2 | 0.033 (0.032) | 0.31 |  | 0.0048 (0.020) | 0.81 |  | 0.084 (0.094) | 0.37 |
| **Fully adjusted β (se)** 3 | 0.0015 (0.025) | 0.95 |  | 0.0027 (0.020) | 0.89 |  | 0.079 (0.093) | 0.40 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** |  |  |  |  |  |  |  |  |
| **Unadjusted βslope (se)** | 0.0019 (0.0039) | 0.63 |  | 0.0036 (0.0034) | 0.28 |  | -0.0041 (0.016) | 0.80 |
| **Adjusted βslope (se)** 1 | 0.0022 (0.0039) | 0.57 |  | 0.0038 (0.0034) | 0.26 |  | -0.0040 (0.016) | 0.80 |
| **Adjusted βslope (se)** 2 | 0.0018 (0.0039) | 0.65 |  | 0.0038 (0.0034) | 0.26 |  | -0.0039 (0.016) | 0.80 |
| **Fully adjusted βslope (se)** 3 | 0.0024 (0.0038) | 0.53 |  | 0.0038 (0.0034) | 0.25 |  | -0.0042 (0.016) | 0.79 |
|  | **LF/HF-ratio Q1** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** |  |  |  |  |  |  |  |  |
| **Unadjusted β(se)** | 0.0076 (0.034) | 0.82 |  | -0.0080 (0.019) | 0.68 |  | -0.056 (0.089) | 0.53 |
| **Adjusted β (se)** 1 | 0.0080 (0.032) | 0.80 |  | -0.0049 (0.019) | 0.80 |  | -0.057 (0.089) | 0.52 |
| **Adjusted β (se)** 2 | 0.041 (0.031) | 0.19 |  | 0.012 (0.019) | 0.54 |  | -0.021 (0.087) | 0.81 |
| **Fully adjusted β (se)** 3 | 0.0090 (0.024) | 0.71 |  | 0.0098 (0.019) | 0.60 |  | -0.027 (0.087) | 0.75 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** |  |  |  |  |  |  |  |  |
| **Unadjusted βslope (se)** | 0.0044 (0.0039) | 0.26 |  | 0.0025 (0.0034) | 0.46 |  | 0.017 (0.015) | 0.27 |
| **Adjusted βslope (se)** 1 | 0.0044 (0.0039) | 0.26 |  | 0.0024 (0.0034) | 0.47 |  | 0.017 (0.015) | 0.27 |
| **Adjusted βslope (se)** 2 | 0.0042 (0.0039) | 0.28 |  | 0.0025 (0.0034) | 0.46 |  | 0.017 (0.015) | 0.25 |
| **Fully adjusted βslope (se)** 3 | 0.0047 (0.0039) | 0.23 |  | 0.0025 (0.0034) | 0.45 |  | 0.017 (0.015) | 0.26 |
|  | **Composite low HRV *c*** | | | | | | | |
|  | **Total (N=6894)** | **p** |  | **No CKD (N=5081)** | **p** |  | **CKD (N=1391)** | **p** |
| ***ln*UAE-level***a* **difference (ln (mg/24h))** |  |  |  |  |  |  |  |  |
| **Unadjusted β(se)** | **0.17 (0.039)** | **<0.001\*** |  | 0.029 (0.022) | 0.19 |  | 0.089 (0.12) | 0.44 |
| **Adjusted β (se)** 1 | 0.040 (0.038) | 0.29 |  | -0.0044 (0.022) | 0.84 |  | 0.086 (0.12) | 0.47 |
| **Adjusted β (se)** 2 | 0.018 (0.038) | 0.64 |  | -0.014 (0.022) | 0.54 |  | 0.043 (0.12) | 0.71 |
| **Fully adjusted β (se)** 3 | -0.010 (0.029) | 0.73 |  | -0.016 (0.022) | 0.48 |  | 0.041 (0.12) | 0.72 |
| ***ln*UAE-slope *b*** **difference (ln (mg/24h per year))** |  |  |  |  |  |  |  |  |
| **Unadjusted βslope (se)** | -0.0017 (0.0045) | 0.71 |  | 0.0016 (0.0038) | 0.67 |  | -0.0037 (0.017) | 0.83 |
| **Adjusted βslope (se)** 1 | -0.0015 (0.0046) | 0.75 |  | 0.0017 (0.0038) | 0.65 |  | -0.0037 (0.017) | 0.83 |
| **Adjusted βslope (se)** 2 | -0.0018 (0.0046) | 0.70 |  | 0.0019 (0.0038) | 0.63 |  | -0.0043 (0.017) | 0.80 |
| **Fully adjusted βslope (se)** 3 | -0.00092 (0.0045) | 0.84 |  | 0.0019 (0.0038) | 0.62 |  | -0.0043 (0.017) | 0.80 |
| Pooled estimates (and their standard errors, se) from multiple imputed (MI) datasets of the association between low HRV with lnUAE in the total PREVEND population, and stratified for CKD at baseline. Reference group is moderate-to-high HRV (Q2-4), *a ln*UAE-level: difference in baseline levels of the natural logarithm (ln) of UAE, compared to reference, *b ln*UAE-slope: difference in change in the natural logarithm of UAE over time, compared to reference. HRV: heart rate variability; UAE: Urinary albumin excretion; LF: low frequency power spectrum; HF: high frequency power spectrum. *c*Subjects with HRV-values in Q1 in each of the main HRV parameters, SDNN, rMSSD, and HF; reference group are subjects without HRV-values in Q1 in SDNN, rMSSD, or HF.  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, eGFR, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, hypercholesterolemia, (and baseline chronic kidney disease status in the total cohort) in addition to above.  \* indicates statistical significance (p < 0.05) | | | | | | | | |

## ASSOCIATIONS OF CONTINUOUS HRV WITH CKD INCIDENCE AND LEVELS AND DECLINE OF eGFR

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| **Supplementary Table S7.** Association of continuous HRV with CKD incidence: complete case analysis. | | | | | | | | | | |
| **CKD** | **lnSDNN** | **p** | **lnrMSSD** | **p** | **lnHF** | **p** | **lnLF** | **p** | **lnLF/HF ratio** | **p** |
| **Unadjusted HR [95%CI]** | **0.59 [0.45 ; 0.76]** | **<0.001\*** | **0.70 [0.55 ; 0.89]** | **0.003\*** | **0.83 [0.74 ; 0.92]** | **<0.001\*** | **0.75 [0.68 ; 0.83]** | **<0.001\*** | 0.88 [0.76 ; 1.02] | 0.097 |
| **Adjusted HR [95%CI] 1** | 1.02 [0.78 ; 1.32] | 0.90 | 1.08 [0.86 ; 1.35] | 0.52 | 1.03 [0.92 ; 1.14] | 0.64 | 0.95 [0.85 ; 1.07] | 0.41 | 0.88 [0.76 ; 1.02] | 0.085 |
| **Adjusted HR [95%CI] 2** | 0.93 [0.69 ; 1.27] | 0.67 | 0.99 [0.75 ; 1.30] | 0.93 | 1.00 [0.88 ; 1.13] | 0.96 | 0.92 [0.81 ; 1.05] | 0.23 | 0.89 [0.76 ; 1.04] | 0.16 |
| **Fully adjusted HR [95%CI] 3** | 0.92 [0.68 ; 1.26] | 0.61 | 0.98 [0.74 ; 1.28] | 0.87 | 1.00 [0.88 ; 1.13 | 0.96 | 0.92 [0.81 ; 1.05] | 0.23 | 0.89 [0.76 ; 1.05] | 0.16 |
| **CKDeGFR<60** |  |  |  |  |  |  |  |  |  |  |
| **Unadjusted HR [95%CI]** | **0.39 [0.28 ; 0.55]** | **<0.001\*** | **0.58 [0.42 ; 0.80]** | **<0.001\*** | **0.74 [0.65 ; 0.86]** | **<0.001\*** | **0.65 [0.57 ; 0.73]** | **<0.001\*** | **0.78 [0.64 ; 0.95]** | **0.015\*** |
| **Adjusted HR [95%CI] 1** | 1.01 [0.72 ; 1.42] | 0.95 | 1.15 [0.87 ; 1.52] | 0.31 | 1.07 [0.94 ; 1.23] | 0.29 | 0.97 [0.83 ; 1.12] | 0.66 | **0.82 [0.68 ; 0.99]** | **0.041\*** |
| **Adjusted HR [95%CI] 2** | 0.90 [0.63 ; 1.28] | 0.57 | 0.89 [0.65 ; 1.22] | 0.46 | 0.95 [0.82 ; 1.10] | 0.49 | 0.94 [0.80 ; 1.11] | 0.49 | 1.01 [0.83 ; 1.23] | 0.92 |
| **Fully adjusted HR [95%CI] 3** | 0.90 [0.64 ; 1.27] | 0.55 | 0.86 [0.63 ; 1.17] | 0.34 | 0.94 [0.82 ; 1.09] | 0.43 | 0.97 [0.83 ; 1.14] | 0.70 | 1.06 [0.88 ; 1.29] | 0.54 |
| **CKDUAE≥30** |  |  |  |  |  |  |  |  |  |  |
| **Unadjusted HR [95%CI]** | **0.66 [0.49 ; 0.89]** | **0.006\*** | **0.74 [0.56 ; 0.96]** | **0.025\*** | **0.84 [0.75 ; 0.95]** | **0.005\*** | **0.78 [0.69 ; 0.88]** | **<0.001\*** | 0.91 [0.77 ; 1.07] | 0.25 |
| **Adjusted HR [95%CI] 1** | 1.01 [0.75 ; 1.37] | 0.93 | 1.03 [0.79 ; 1.34] | 0.81 | 1.00 [0.88 ; 1.13] | 0.97 | 0.94 [0.82 ; 1.07] | 0.33 | 0.91 [0.77 ; 1.07] | 0.24 |
| **Adjusted HR [95%CI] 2** | 0.89 [0.62 ; 1.27] | 0.52 | 0.93 [0.67 ; 1.30] | 0.68 | 0.97 [0.83 ; 1.12] | 0.67 | 0.89 [0.77 ; 1.03] | 0.13 | 0.88 [0.74 ; 1.06] | 0.17 |
| **Fully adjusted HR [95%CI] 3** | 0.88 [0.62 ; 1.26] | 0.50 | 0.92 [0.66 ; 1.29] | 0.64 | 0.97 [0.84 ; 1.12] | 0.67 | 0.90 [0.77 ; 1.04] | 0.14 | 0.89 [0.74 ; 1.06] | 0.20 |
| Estimates of hazard ratios after multivariable Cox regression analysis. HRV was natural log-transformed, hence estimates are per 2.72-fold increase in HRV measure. HR: hazard ratio; SDNN: standard deviation of normal-to-normal RR-intervals; rMSSD: root mean square of successive differences of adjacent normal-normal RR-intervals; HF: high frequency power spectrum; LF: low frequency power spectrum; CI: confidence interval. \* indicates statistical significance (p<0.05)  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, baseline eGFR, baseline UAE, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, and hypercholesterolemia, in addition to above. | | | | | | | | | | |

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| **Supplementary Table S8.**  Association of continuous HRV with eGFR levels and rate of decline : complete case analysis | | | | | | | | |
|  | **lnSDNN** | | | | | | | |
|  | **Total** | **p** |  | **No CKD** | **p** |  | **CKD** | **p** |
| **Baseline eGFR-level** *a* **(ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β [95%CI]** | **10.1 [8.90 ; 11.2]** | **<0.001\*** |  | **8.04 [6.90 ; 9.18]** | **<0.001\*** |  | **10.1 [7.00 ; 13.2]** | **<0.001\*** |
| **Adjusted β [95%CI]** 1 | 0.77 [-0.22 ; 1.76] | 0.13 |  | 0.53 [-0.46 ; 1.53] | 0.29 |  | 1.21 [-1.37 ; 3.80] | 0.36 |
| **Adjusted β [95%CI]** 2 | 0.72 [-0.41 ; 1.83] | 0.21 |  | 0.23 [-0.90 ; 1.37] | 0.68 |  | 1.42 [-1.43 ; 4.28] | 0.33 |
| **Fully adjusted β [95%CI]** 3 | 0.52 [-0.60 ; 1.63] | 0.36 |  | 0.19 [-0.94 ; 1.32] | 0.74 |  | 1.28 [-1.52 ; 4.08] | 0.37 |
| **eGFR-slope *b* (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope [95%CI]** | 0.082 [-0.02 ; 0.18] | 0.11 |  | 0.070 [-0.04 ; 0.18] | 0.20 |  | -0.10 [-0.37 ; 0.18] | 0.49 |
| **Adjusted βslope [95%CI]** 1 | 0.084 [-0.02 ; 0.18] | 0.099 |  | 0.082 [-0.02 ; 0.19] | 0.13 |  | -0.10 [-0.37 ; 0.17] | 0.47 |
| **Adjusted βslope [95%CI]** 2 | 0.075 [-0.02 ; 0.17] | 0.14 |  | 0.080 [-0.03 ; 0.19] | 0.14 |  | -0.11 [-0.38 ; 0.16] | 0.42 |
| **Fully adjusted βslope [95%CI]** 3 | 0.076 [-0.02 ; 0.17] | 0.14 |  | 0.080 [-0.03 ; 0.19] | 0.14 |  | -0.11 [-0.38 ; 1.52] | 0.40 |
|  | **lnrMSSD** | | | | | | | |
|  | **Total** | **p** |  | **No CKD** | **p** |  | **CKD** | **p** |
| **Baseline eGFR-level** *a* **(ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β [95%CI]** | **7.15 [6.12 ; 8.18]** | **<0.001\*** |  | **5.99 [4.99 ; 6.99]** | **<0.001\*** |  | **5.91 [3.15-8.68]** | **<0.001\*** |
| **Adjusted β [95%CI]** 1 | -0.04 [-0.90 ; 0.81] | 0.92 |  | 0.04 [-0.82 ; 0.89] | 0.93 |  | 0.12 [-2.11 ; 2.36] | 0.91 |
| **Adjusted β [95%CI]** 2 | 0.18 [-0.84 ; 1.20] | 0.73 |  | 0.32 [-0.72 ; 1.35] | 0.55 |  | 0.18 [-2.37 ; 2.72] | 0.89 |
| **Fully adjusted β [95%CI]** 3 | 0.21 [-0.80 ; 1.22] | 0.69 |  | 0.36 [0.67 ; 1.39] | 0.50 |  | 0.30 [-2.20 ; 2.79] | 0.82 |
| **eGFR-slope *b* (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope [95%CI]** | 0.05 [-0.04 ; 0.14] | 0.26 |  | 0.05 [-0.04 ; 0.15] | 0.25 |  | -0.13 [-0.36 ; 0.11] | 0.28 |
| **Adjusted βslope [95%CI]** 1 | 0.05 [-0.03 ; 0.14] | 0.23 |  | 0.06 [-0.03 ; 0.16] | 0.18 |  | -0.13 [-0.36 ; 0.10] | 0.27 |
| **Adjusted βslope [95%CI]** 2 | 0.05 [-0.04 ; 0.13] | 0.30 |  | 0.06 [-0.03 ; 0.16] | 0.19 |  | -0.14 [-0.37 ; 0.09] | 0.23 |
| **Fully adjusted βslope [95%CI]** 3 | 0.05 [-0.04 ; 0.13] | 0.29 |  | 0.06 [-0.03 ; 0.16] | 0.19 |  | -0.14 [-0.37 ; 0.09] | 0.24 |
|  | **lnHF** | | | | | | | |
|  | **Total** | **p** |  | **No CKD** | **p** |  | **CKD** | **p** |
| **Baseline eGFR-level** *a* **(ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β [95%CI]** | **3.70 [3.23 ; 4.16]** | **<0.001\*** |  | **2.97 [2.52 ; 3.43]** | **<0.001\*** |  | **3.43 [2.16 ; 4.69]** | **<0.001\*** |
| **Adjusted β [95%CI]** 1 | 0.05 [-0.34 ; 0.45] | 0.78 |  | -0.01 [-0.40 ; 0.39] | 0.97 |  | 0.32 [-0.72 ; 1.36] | 0.55 |
| **Adjusted β [95%CI]** 2 | 0.16 [-0.30 ; 0.61] | 0.50 |  | 0.10 [-0.36 ; 0.55] | 0.68 |  | 0.40 [-0.78 ; 1.57] | 0.51 |
| **Fully adjusted β [95%CI]** 3 | 0.13 [-0.32 ; 0.58] | 0.58 |  | 0.10 [-0.36 ; 0.56] | 0.66 |  | 0.37 [-0.78 ; 1.52] | 0.52 |
| **eGFR-slope *b* (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope [95%CI]** | 0.03 [-0.01 ; 0.07] | 0.11 |  | 0.03 [-0.01 ; 0.08] | 0.13 |  | -0.06 [-0.17 ; 0.05] | 0.27 |
| **Adjusted βslope [95%CI]** 1 | 0.03 [-0.01 ; 0.07] | 0.09 |  | 0.04 [-0.01 ; 0.08] | 0.09 |  | -0.06 [-0.17 ; 0.05] | 0.27 |
| **Adjusted βslope [95%CI]** 2 | 0.03 [-0.01 ; 0.07] | 0.13 |  | 0.04 [-0.01 ; 0.08] | 0.09 |  | -0.07 [-0.18 ; 0.04] | 0.23 |
| **Fully adjusted βslope [95%CI]** 3 | 0.03 [-0.01 ; 0.07] | 0.12 |  | 0.04 [-0.01 ; 0.08] | 0.09 |  | -0.07 [-0.18 ; 0.04] | 0.23 |
|  | **lnLF** | | | | | | | |
|  | **Total** | **p** |  | **No CKD** | **p** |  | **CKD** | **p** |
| **Baseline eGFR-level** *a* **(ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β [95%CI]** | **4.94 [4.44 ; 5.43]** | **<0.001\*** |  | **3.84 [3.35 ; 4.33]** | **<0.001\*** |  | **5.46 [4.13 ; 6.79]** | **<0.001\*** |
| **Adjusted β [95%CI]** 1 | **0.65 [0.21 ; 1.08]** | **0.004\*** |  | 0.40 [-0.03 ; 0.84] | 0.069 |  | 1.09 [-0.06 ; 2.24] | 0.064 |
| **Adjusted β [95%CI]** 2 | **0.54 [0.07 ; 1.01** | **0.025\*** |  | 0.13 [-0.34 ; 0.61] | 0.58 |  | 1.19 [-0.04 ; 2.43] | 0.057 |
| **Fully adjusted β [95%CI]** 3 | 0.38 [-0.09 ; 0.86] | 0.11 |  | 0.09 [-0.39 ; 0.57] | 0.71 |  | 0.85 [-0.37 ; 2.06] | 0.17 |
| **eGFR-slope *b* (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope [95%CI]** | **0.05 [0.003 ; 0.09]** | **0.038\*** |  | 0.03 [-0.01 ; 0.08] | 0.15 |  | -0.03 [-0.15 ; 0.09] | 0.64 |
| **Adjusted βslope [95%CI]** 1 | **0.05 [0.003 ; 0.09]** | **0.037\*** |  | 0.04 [-0.01 ; 0.09] | 0.092 |  | -0.03 [-0.15 ; 0.09] | 0.61 |
| **Adjusted βslope [95%CI]** 2 | 0.04 [-0.000 ; 0.09] | 0.052 |  | 0.04 [-0.01 ; 0.09] | 0.099 |  | -0.03 [-0.15 ; 0.08] | 0.57 |
| **Fully adjusted βslope [95%CI]** 3 | 0.04 [-0.000 ; 0.09] | 0.052 |  | 0.04 [-0.01 ; 0.09] | 0.097 |  | -0.04 [-0.16 ; 0.08] | 0.53 |
|  | **lnLF/HF-ratio** | | | | | | | |
|  | **Total** | **p** |  | **No CKD** | **p** |  | **CKD** | **p** |
| **Baseline eGFR-level***a* **(ml/min/1.73m2)** | | | | | | | | |
| **Unadjusted β [95%CI]** | **0.95 [0.25 ; 1.65]** | **0.008\*** |  | 0.38 [-0.29 ; 1.04] | 0.27 |  | **2.93 [1.00 ; 4.86]** | **0.003\*** |
| **Adjusted β [95%CI]** 1 | **0.85 [0.32 ; 1.38]** | **0.002\*** |  | **0.59 [0.07 ; 1.11]** | **0.027\*** |  | 1.20 [-0.32 ; 2.71] | 0.12 |
| **Adjusted β [95%CI]** 2 | 0.52 [-0.04 ; 1.08] | 0.069 |  | 0.05 [-0.50 ; 0.61] | 0.85 |  | 1.21 [-0.39 ; 2.80] | 0.14 |
| **Fully adjusted β [95%CI]** 3 | 0.35 [-0.21 ; 0.91] | 0.22 |  | -0.01 [-0.56 0.54] | 0.97 |  | 0.68 [-0.89 ; 2.25] | 0.40 |
| **eGFR-slope *b* (ml/min/1.73m2 per year)** | | | | | | | | |
| **Unadjusted βslope [95%CI]** | 0.01 [-0.05 ; 0.07] | 0.69 |  | -0.01 [-0.07 ; 0.05] | 0.80 |  | 0.08 [-0.08 ; 0.23] | 0.34 |
| **Adjusted βslope [95%CI]** 1 | 0.01 [-0.05 ; 0.07] | 0.76 |  | -0.01 [-0.07 ; 0.05] | 0.79 |  | 0.07 [-0.09 ; 0.23] | 0.39 |
| **Adjusted βslope [95%CI]** 2 | 0.01 [-0.05 ; 0.07] | 0.74 |  | -0.01 [-0.07 ; 0.05] | 0.80 |  | 0.07 [-0.08 ; 0.23] | 0.35 |
| **Fully adjusted βslope [95%CI]** 3 | 0.01 [-0.05 ; 0.07] | 0.74 |  | -0.01 [-0.07 ; 0.05] | 0.80 |  | 0.07 [-0.09 ; 0.22] | 0.39 |
| Estimates of the association between HRV and eGFR in the total PREVEND population, and stratified for CKD at baseline. HRV was natural log-transformed, hence estimates are per e (2.72)-fold increase in HRV measure.  a eGFR, expressed in ml/min/1.73m2,  *b* eGFR-slope: change in eGFR over time, in ml/min/1.73m2 per year; negative values correspond to faster rate of decline,  HRV: heart rate variability; eGFR: estimated glomerular filtration rate; SDNN: standard deviation of normal-to-normal RR-intervals; rMSSD: root mean square of successive differences of adjacent normal-normal RR-intervals; HF: high frequency power spectrum; LF: low frequency power spectrum; CI: confidence interval.  1 Adjusted for age  2 Adjusted for sex, BMI, WHR, mean IBI, smoking status, baseline UAE, in addition to above  3 Adjusted for history of cardiovascular disease, diabetes, hypertension, hypercholesterolemia in addition to above.  \* indicates statistical significance (p<0.05) | | | | | | | | |