Supplementary data

**Blood-based oxidative stress markers and cognitive performance in early old age:**

**the HAPIEE study**

Contents

[Table S1 Proportion of missing values in participant characteristics in the nested case-control sample by study centre 2](#_Toc454195073)

[Figure S1 Associations of oxidative stress markers with global cognitive score 3](#_Toc454195074)

[Table S2 Associations of d-ROMs, BAP and TTL with cognitive performance z-scores in controls 4](#_Toc454195075)

[Table S3 Associations of d-ROMs, BAP and TTL with cognitive performance z-scores excluding participants with history of diabetes and hypertension at baseline 5](#_Toc454195076)

[Table S4 Associations of d-ROMs, BAP and TTL with cognitive performance z-scores excluding participants with incident coronary or stroke events 6](#_Toc454195077)

[Table S5 Associations of d-ROMs, BAP and TTL with cognitive performance z-scores excluding participants who died within 2 years of baseline survey 7](#_Toc454195078)

# Table S1 Proportion of missing values in participant characteristics in the nested case-control sample by study centre

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Czech towns**  **(n=2,426)** | |  | **Krakow**  **(n=2,157)** | |  | **Kaunas**  **(n=1,775)** | |  | **Total**  **(n=6,358)** | |
|  | **n** | **%** |  | **n** | **%** |  | **n** | **%** |  | **n** | **%** |
| Age | 0 | 0.0 |  | 0 | 0.0 |  | 18 | 1.0 |  | 18 | 0.3 |
| Education | 24 | 1.0 |  | 2 | 0.1 |  | 23 | 1.3 |  | 49 | 0.8 |
| SES | 24 | 1.0 |  | 4 | 0.2 |  | 35 | 2.0 |  | 63 | 1.0 |
| Smoking status | 40 | 1.6 |  | 7 | 0.3 |  | 25 | 1.4 |  | 72 | 1.1 |
| Alcohol intake | 79 | 3.3 |  | 22 | 1.0 |  | 25 | 1.4 |  | 126 | 2.0 |
| Depressive symptoms | 88 | 3.6 |  | 15 | 0.7 |  | 25 | 1.4 |  | 128 | 2.0 |
| History of |  |  |  |  |  |  |  |  |  |  |  |
| MI | 102 | 4.2 |  | 17 | 0.8 |  | 25 | 1.4 |  | 144 | 2.3 |
| Stroke | 108 | 4.5 |  | 26 | 1.2 |  | 25 | 1.4 |  | 159 | 2.5 |
| Hypertension | 11 | 0.5 |  | 3 | 0.1 |  | 27 | 1.5 |  | 41 | 0.6 |
| Diabetes | 7 | 0.3 |  | 1 | 0.0 |  | 25 | 1.4 |  | 33 | 0.5 |
| TTL | 19 | 0.8 |  | 17 | 0.8 |  | 10 | 0.6 |  | 46 | 0.7 |
| d-ROMs | 19 | 0.8 |  | 10 | 0.5 |  | 5 | 0.3 |  | 34 | 0.5 |
| BAP | 19 | 0.8 |  | 17 | 0.8 |  | 6 | 0.3 |  | 42 | 0.7 |
| Immediate recall | 952 | 39.2 |  | 915 | 42.4 |  | 31 | 1.7 |  | 1898 | 29.9 |
| Delayed recall | 956 | 39.4 |  | 922 | 42.7 |  | 33 | 1.9 |  | 1911 | 30.1 |
| Verbal fluency | 949 | 39.1 |  | 915 | 42.4 |  | 27 | 1.5 |  | 1891 | 29.7 |
| Letter search | 976 | 40.2 |  | 952 | 44.1 |  | 45 | 2.5 |  | 1973 | 31.0 |
| Immediate recall (wave 2) | 803 | 33.1 |  | 740 | 34.3 |  | na |  |  |  |  |
| Delayed recall (wave 2) | 805 | 33.2 |  | 741 | 34.4 |  | na |  |  |  |  |
| Verbal fluency (wave 2) | 804 | 33.1 |  | 738 | 34.2 |  | na |  |  |  |  |
| Letter search (wave 2) | 841 | 34.7 |  | 768 | 35.6 |  | na |  |  |  |  |

**Abbreviations:** BAP, biological antioxidant potential; D-ROM, derivatives of reactive oxygen metabolites; MI, myocardial infarction; TTL, total thiol levels.



# Figure S1 Associations of oxidative stress markers with global cognitive score

Data shown are unstandardized regression coefficients (diamonds) with 95% CIs (solid lines). Model 1 is adjusted for age group, sex, centre and case-control status. Model 2 is additionally adjusted for education, SES, smoking, alcohol, depression, history of MI and stroke. Model 3 is additionally adjusted for history of diabetes and hypertension. Prospective models are additionally adjusted for cognitive test vs. re-test status. Biomarker units: d-ROMs, U.CARR; BAP, meq/L; and TTL, umol/L.

# Table S2 Associations of d-ROMs, BAP and TTL with cognitive performance z-scores in controls

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Immediate recall**  **z-score** | | **Delayed recall**  **z-score** | | **Verbal fluency**  **z-score** | | **Letter search**  **z-score** | | **Global**  **cognition** | |
|  | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** |
| **Cross-sectional (n=3,066)** | |  |  |  |  |  |  |  |  |  |
| **d-ROMs (U.CARR )** |  |  |  |  |  |  |  |  |  |  |
| ≤340 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 341-400 | 0.00 | [-0.07,0.07] | -0.02 | [-0.10,0.05] | -0.08\* | [-0.16,-0.00] | -0.04 | [-0.12,0.04] | -0.04 | [-0.09,0.02] |
| ≥401 | -0.07 | [-0.15,0.02] | -0.03 | [-0.11,0.06] | -0.11\* | [-0.20,-0.02] | -0.06 | [-0.15,0.04] | -0.06\* | [-0.13,-0.00] |
| P for trend |  | 0.128 |  | 0.559 |  | 0.015 |  | 0.242 |  | 0.041 |
|  |  |  |  |  |  |  |  |  |  |  |
| **BAP (meq/L)** |  |  |  |  |  |  |  |  |  |  |
| >2200 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 2000-2200 | 0.03 | [-0.05,0.11] | 0.03 | [-0.05,0.11] | 0.00 | [-0.08,0.08] | -0.03 | [-0.12,0.06] | 0.01 | [-0.05,0.07] |
| <2000 | 0.03 | [-0.06,0.13] | -0.02 | [-0.12,0.08] | 0.03 | [-0.07,0.13] | -0.05 | [-0.16,0.06] | -0.00 | [-0.07,0.07] |
| P for trend |  | 0.496 |  | 0.737 |  | 0.550 |  | 0.358 |  | 0.977 |
|  |  |  |  |  |  |  |  |  |  |  |
| **TTL (umol/L)** |  |  |  |  |  |  |  |  |  |  |
| 4th Q | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 3rd Q | -0.05 | [-0.14,0.04] | -0.01 | [-0.11,0.08] | -0.05 | [-0.15,0.04] | 0.03 | [-0.07,0.13] | -0.02 | [-0.09,0.05] |
| 2nd Q | -0.03 | [-0.12,0.05] | -0.03 | [-0.12,0.06] | -0.09 | [-0.18,0.00] | 0.06 | [-0.04,0.16] | -0.02 | [-0.09,0.04] |
| 1st Q | -0.09\* | [-0.18,-0.00] | -0.06 | [-0.15,0.03] | -0.00 | [-0.10,0.09] | 0.06 | [-0.04,0.16] | -0.02 | [-0.09,0.04] |
| P for trend |  | 0.077 |  | 0.178 |  | 0.851 |  | 0.197 |  | 0.519 |
|  |  |  |  |  |  |  |  |  |  |  |
| **Prospective (n=2,371)** |  |  |  |  |  |  |  |  |  |  |
| **d-ROMs (U.CARR )** |  |  |  |  |  |  |  |  |  |  |
| ≤340 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 341-400 | 0.01 | [-0.08,0.10] | 0.02 | [-0.07,0.11] | -0.00 | [-0.09,0.09] | 0.03 | [-0.06,0.12] | 0.01 | [-0.05,0.08] |
| ≥401 | -0.08 | [-0.18,0.02] | -0.05 | [-0.15,0.06] | -0.09 | [-0.19,0.02] | -0.04 | [-0.14,0.06] | -0.06 | [-0.14,0.01] |
| P for trend |  | 0.149 |  | 0.421 |  | 0.118 |  | 0.475 |  | 0.116 |
|  |  |  |  |  |  |  |  |  |  |  |
| **BAP (meq/L)** |  |  |  |  |  |  |  |  |  |  |
| >2200 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 2000-2200 | -0.00 | [-0.08,0.08] | -0.02 | [-0.10,0.07] | -0.01 | [-0.09,0.08] | -0.01 | [-0.09,0.08] | -0.01 | [-0.07,0.05] |
| <2000 | 0.07 | [-0.04,0.19] | -0.02 | [-0.14,0.10] | -0.02 | [-0.14,0.10] | -0.05 | [-0.17,0.07] | -0.01 | [-0.09,0.08] |
| P for trend |  | 0.329 |  | 0.666 |  | 0.701 |  | 0.482 |  | 0.843 |
|  |  |  |  |  |  |  |  |  |  |  |
| **TTL (umol/L)** |  |  |  |  |  |  |  |  |  |  |
| 4th Q | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 3rd Q | 0.00 | [-0.10,0.10] | -0.00 | [-0.11,0.10] | 0.04 | [-0.07,0.14] | 0.00 | [-0.10,0.10] | 0.01 | [-0.07,0.08] |
| 2nd Q | 0.11 | [0.00,0.21] | 0.03 | [-0.08,0.13] | 0.06 | [-0.05,0.16] | 0.00 | [-0.10,0.11] | 0.05 | [-0.03,0.12] |
| 1st Q | 0.11\* | [0.00,0.22] | 0.06 | [-0.05,0.17] | 0.05 | [-0.06,0.16] | -0.02 | [-0.13,0.09] | 0.05 | [-0.03,0.13] |
| P for trend |  | 0.011 |  | 0.239 |  | 0.364 |  | 0.796 |  | 0.133 |

\* P < 0.05, \*\* P ≤ 0.01, \*\*\*P ≤ 0.001

Models are adjusted for age group, sex, study centre, education, SES, smoking, alcohol, depression, history of MI, history of stroke and case-control status. Prospective models are additionally adjusted for cognitive test vs. re-test status.

# Table S3 Associations of d-ROMs, BAP and TTL with cognitive performance z-scores excluding participants with history of diabetes and hypertension at baseline

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Immediate recall**  **z-score** | | **Delayed recall**  **z-score** | | **Verbal fluency**  **z-score** | | **Letter search**  **z-score** | | **Global**  **cognition** | |
|  | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** |
| **Cross-sectional (n=1,548)** | |  |  |  |  |  |  |  |  |  |
| **d-ROMs (U.CARR )** |  |  |  |  |  |  |  |  |  |  |
| ≤340 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 341-400 | 0.07 | [-0.04,0.18] | 0.02 | [-0.09,0.13] | -0.02 | [-0.13,0.10] | 0.04 | [-0.08,0.15] | 0.03 | [-0.05,0.11] |
| ≥401 | -0.03 | [-0.16,0.09] | -0.06 | [-0.19,0.07] | -0.14\* | [-0.27,-0.01] | 0.01 | [-0.13,0.14] | -0.06 | [-0.15,0.03] |
| P for trend |  | 0.688 |  | 0.413 |  | 0.040 |  | 0.905 |  | 0.262 |
|  |  |  |  |  |  |  |  |  |  |  |
| **BAP (meq/L)** |  |  |  |  |  |  |  |  |  |  |
| >2200 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 2000-2200 | 0.05 | [-0.07,0.16] | 0.03 | [-0.09,0.15] | -0.03 | [-0.15,0.09] | 0.04 | [-0.09,0.16] | 0.02 | [-0.06,0.11] |
| <2000 | 0.03 | [-0.10,0.17] | 0.01 | [-0.13,0.14] | 0.02 | [-0.12,0.17] | 0.08 | [-0.06,0.23] | 0.04 | [-0.06,0.13] |
| P for trend |  | 0.641 |  | 0.949 |  | 0.729 |  | 0.257 |  | 0.466 |
|  |  |  |  |  |  |  |  |  |  |  |
| **TTL (umol/L)** |  |  |  |  |  |  |  |  |  |  |
| 4th Q | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 3rd Q | -0.05 | [-0.17,0.08] | -0.02 | [-0.15,0.11] | 0.04 | [-0.10,0.17] | 0.11 | [-0.02,0.25] | 0.02 | [-0.07,0.11] |
| 2nd Q | -0.04 | [-0.17,0.08] | -0.06 | [-0.19,0.07] | -0.02 | [-0.15,0.11] | 0.10 | [-0.04,0.24] | -0.01 | [-0.10,0.09] |
| 1st Q | -0.06 | [-0.19,0.07] | -0.04 | [-0.18,0.09] | -0.05 | [-0.18,0.09] | 0.16\* | [0.02,0.30] | 0.00 | [-0.09,0.10] |
| P for trend |  | 0.441 |  | 0.421 |  | 0.362 |  | 0.047 |  | 0.893 |
|  |  |  |  |  |  |  |  |  |  |  |
| **Prospective (n=1,198)** |  |  |  |  |  |  |  |  |  |  |
| **d-ROMs (U.CARR )** |  |  |  |  |  |  |  |  |  |  |
| ≤340 |  |  |  |  |  |  |  |  |  |  |
| 341-400 | -0.01 | [-0.14,0.11] | -0.01 | [-0.14,0.12] | 0.02 | [-0.11,0.15] | 0.00 | [-0.13,0.13] | -0.00 | [-0.09,0.09] |
| ≥401 | -0.05 | [-0.20,0.09] | -0.07 | [-0.22,0.07] | -0.10 | [-0.25,0.05] | -0.01 | [-0.15,0.14] | -0.06 | [-0.16,0.05] |
| P for trend |  | 0.492 |  | 0.340 |  | 0.211 |  | 0.925 |  | 0.292 |
|  |  |  |  |  |  |  |  |  |  |  |
| **BAP (meq/L)** |  |  |  |  |  |  |  |  |  |  |
| >2200 |  |  |  |  |  |  |  |  |  |  |
| 2000-2200 | 0.04 | [-0.07,0.16] | 0.01 | [-0.11,0.12] | 0.05 | [-0.07,0.17] | 0.02 | [-0.10,0.13] | 0.03 | [-0.06,0.11] |
| <2000 | 0.15 | [-0.01,0.31] | 0.03 | [-0.13,0.19] | 0.01 | [-0.15,0.17] | 0.06 | [-0.10,0.22] | 0.06 | [-0.05,0.18] |
| P for trend |  | 0.088 |  | 0.751 |  | 0.738 |  | 0.497 |  | 0.287 |
|  |  |  |  |  |  |  |  |  |  |  |
| **TTL (umol/L)** |  |  |  |  |  |  |  |  |  |  |
| 4th Q |  |  |  |  |  |  |  |  |  |  |
| 3rd Q | 0.06 | [-0.09,0.20] | -0.01 | [-0.16,0.13] | 0.08 | [-0.07,0.22] | 0.03 | [-0.11,0.17] | 0.04 | [-0.06,0.14] |
| 2nd Q | 0.15\* | [0.01,0.30] | 0.07 | [-0.08,0.21] | 0.11 | [-0.04,0.26] | 0.01 | [-0.14,0.15] | 0.08 | [-0.02,0.19] |
| 1st Q | 0.23\*\* | [0.08,0.39] | 0.12 | [-0.04,0.27] | 0.05 | [-0.11,0.20] | 0.06 | [-0.09,0.21] | 0.11\* | [0.00,0.22] |
| P for trend |  | 0.001 |  | 0.083 |  | 0.448 |  | 0.543 |  | 0.027 |

\* P < 0.05, \*\* P ≤ 0.01, \*\*\*P ≤ 0.001

Models are adjusted for age group, sex, study centre, education, SES, smoking, alcohol, depression, history of MI, history of stroke and case-control status. Prospective models are additionally adjusted for cognitive test vs. re-test status.

# Table S4 Associations of d-ROMs, BAP and TTL with cognitive performance z-scores excluding participants with incident coronary or stroke events

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Immediate recall**  **z-score** | | **Delayed recall**  **z-score** | | **Verbal fluency**  **z-score** | | **Letter search**  **z-score** | | **Global**  **cognition** | |
|  | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** |
| **Cross-sectional (n=3,761)** |  |  |  |  |  |  |  |  |  |  |
| **d-ROMs (U.CARR )** |  |  |  |  |  |  |  |  |  |  |
| ≤340 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 341-400 | 0.00 | [-0.06,0.07] | -0.02 | [-0.09,0.05] | -0.08\* | [-0.16,-0.01] | -0.04 | [-0.12,0.04] | -0.03 | [-0.09,0.02] |
| ≥401 | -0.06 | [-0.14,0.02] | -0.03 | [-0.11,0.05] | -0.11\*\* | [-0.19,-0.03] | -0.06 | [-0.15,0.03] | -0.07\* | [-0.12,-0.01] |
| P for trend |  | 0.141 |  | 0.392 |  | 0.007 |  | 0.165 |  | 0.023 |
|  |  |  |  |  |  |  |  |  |  |  |
| **BAP (meq/L)** |  |  |  |  |  |  |  |  |  |  |
| >2200 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 2000-2200 | 0.01 | [-0.06,0.09] | 0.03 | [-0.05,0.10] | 0.01 | [-0.06,0.09] | -0.01 | [-0.09,0.07] | 0.01 | [-0.04,0.06] |
| <2000 | 0.01 | [-0.07,0.10] | 0.00 | [-0.09,0.09] | 0.07 | [-0.02,0.16] | 0.00 | [-0.10,0.10] | 0.02 | [-0.04,0.08] |
| P for trend |  | 0.779 |  | 0.929 |  | 0.152 |  | 0.993 |  | 0.524 |
|  |  |  |  |  |  |  |  |  |  |  |
| **TTL (umol/L)** |  |  |  |  |  |  |  |  |  |  |
| 4th Q | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 3rd Q | -0.03 | [-0.11,0.06] | -0.01 | [-0.09,0.08] | -0.04 | [-0.12,0.05] | 0.05 | [-0.04,0.14] | -0.01 | [-0.07,0.05] |
| 2nd Q | -0.07 | [-0.15,0.02] | -0.03 | [-0.12,0.05] | -0.07 | [-0.16,0.01] | 0.07 | [-0.02,0.16] | -0.02 | [-0.08,0.04] |
| 1st Q | -0.10\* | [-0.18,-0.02] | -0.07 | [-0.15,0.02] | -0.03 | [-0.12,0.05] | 0.03 | [-0.06,0.13] | -0.04 | [-0.10,0.02] |
| P for trend |  | 0.009 |  | 0.086 |  | 0.375 |  | 0.419 |  | 0.137 |
|  |  |  |  |  |  |  |  |  |  |  |
| **Prospective (n=2,578)** |  |  |  |  |  |  |  |  |  |  |
| **d-ROMs (U.CARR )** |  |  |  |  |  |  |  |  |  |  |
| ≤340 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 341-400 | -0.01 | [-0.09,0.08] | -0.00 | [-0.09,0.08] | -0.01 | [-0.09,0.08] | 0.03 | [-0.06,0.11] | 0.00 | [-0.06,0.07] |
| ≥401 | -0.11 | [-0.20,-0.01] | -0.08 | [-0.18,0.02] | -0.10\* | [-0.20,-0.01] | -0.05 | [-0.15,0.04] | -0.09\* | [-0.16,-0.02] |
| P for trend |  | 0.032 |  | 0.117 |  | 0.046 |  | 0.320 |  | 0.020 |
|  |  |  |  |  |  |  |  |  |  |  |
| **BAP (meq/L)** |  |  |  |  |  |  |  |  |  |  |
| >2200 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 2000-2200 | -0.01 | [-0.08,0.07] | -0.01 | [-0.09,0.07] | -0.02 | [-0.10,0.07] | -0.02 | [-0.10,0.06] | -0.01 | [-0.07,0.05] |
| <2000 | 0.10 | [-0.01,0.21] | 0.00 | [-0.11,0.11] | -0.01 | [-0.12,0.11] | -0.03 | [-0.14,0.09] | 0.02 | [-0.07,0.10] |
| P for trend |  | 0.190 |  | 0.957 |  | 0.791 |  | 0.597 |  | 0.882 |
|  |  |  |  |  |  |  |  |  |  |  |
| **TTL (umol/L)** |  |  |  |  |  |  |  |  |  |  |
| 4th Q | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 3rd Q | -0.01 | [-0.11,0.09] | -0.04 | [-0.14,0.06] | 0.03 | [-0.07,0.13] | -0.03 | [-0.13,0.07] | -0.01 | [-0.09,0.06] |
| 2nd Q | 0.10 | [-0.00,0.19] | 0.01 | [-0.09,0.12] | 0.04 | [-0.06,0.14] | -0.03 | [-0.13,0.07] | 0.03 | [-0.04,0.10] |
| 1st Q | 0.08 | [-0.02,0.18] | 0.03 | [-0.08,0.14] | 0.04 | [-0.07,0.14] | -0.04 | [-0.14,0.07] | 0.03 | [-0.05,0.10] |
| P for trend |  | 0.032 |  | 0.397 |  | 0.485 |  | 0.497 |  | 0.302 |

\* P ≤ 0.05, \*\* P ≤ 0.01, \*\*\*P ≤ 0.001

Models are adjusted for age group, sex, study centre, education, SES, smoking, alcohol, depression, history of MI, history of stroke and case-control status. Prospective models are additionally adjusted for cognitive test vs. re-test status.

# Table S5 Associations of d-ROMs, BAP and TTL with cognitive performance z-scores excluding participants who died within 2 years of baseline survey

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Immediate recall**  **z-score** | | **Delayed recall**  **z-score** | | **Verbal fluency**  **z-score** | | **Letter search**  **z-score** | | **Global**  **cognition** | |
|  | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** | **β** | **[95% CI]** |
| **Cross-sectional (n=4,064)** | |  |  |  |  |  |  |  |  |  |
| **d-ROMs (U.CARR )** |  |  |  |  |  |  |  |  |  |  |
| ≤340 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 341-400 | -0.00 | [-0.07,0.06] | -0.01 | [-0.08,0.06] | -0.08\* | [-0.15,-0.01] | -0.06 | [-0.14,0.01] | -0.04 | [-0.09,0.01] |
| ≥401 | -0.06 | [-0.13,0.01] | -0.04 | [-0.12,0.03] | -0.11\*\* | [-0.18,-0.03] | -0.05 | [-0.13,0.04] | -0.06 | [-0.12,-0.01] |
| P for trend |  | 0.128 |  | 0.261 |  | 0.006 |  | 0.244 |  | 0.021 |
|  |  |  |  |  |  |  |  |  |  |  |
| **BAP (meq/L)** |  |  |  |  |  |  |  |  |  |  |
| >2200 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 2000-2200 | 0.00 | [-0.06,0.07] | 0.02 | [-0.05,0.09] | 0.01 | [-0.06,0.09] | -0.01 | [-0.09,0.07] | 0.01 | [-0.04,0.06] |
| <2000 | -0.01 | [-0.09,0.07] | -0.01 | [-0.10,0.07] | 0.06 | [-0.03,0.15] | -0.01 | [-0.11,0.08] | 0.01 | [-0.05,0.07] |
| P for trend |  | 0.857 |  | 0.783 |  | 0.171 |  | 0.810 |  | 0.816 |
|  |  |  |  |  |  |  |  |  |  |  |
| **TTL (umol/L)** |  |  |  |  |  |  |  |  |  |  |
| 4th Q | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 3rd Q | -0.03 | [-0.11,0.04] | -0.02 | [-0.10,0.07] | -0.03 | [-0.11,0.06] | 0.05 | [-0.04,0.14] | -0.01 | [-0.07,0.05] |
| 2nd Q | -0.07 | [-0.15,0.01] | -0.05 | [-0.13,0.03] | -0.07 | [-0.15,0.02] | 0.05 | [-0.04,0.14] | -0.03 | [-0.09,0.02] |
| 1st Q | -0.08\* | [-0.16,-0.00] | -0.06 | [-0.14,0.02] | -0.00 | [-0.09,0.08] | 0.04 | [-0.05,0.13] | -0.03 | [-0.09,0.03] |
| P for trend |  | 0.027 |  | 0.088 |  | 0.730 |  | 0.484 |  | 0.237 |
|  |  |  |  |  |  |  |  |  |  |  |
| **Prospective (n=2,882)** | |  |  |  |  |  |  |  |  |  |
| **d-ROMs (U.CARR )** |  |  |  |  |  |  |  |  |  |  |
| ≤340 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 341-400 | -0.01 | [-0.09,0.07] | -0.02 | [-0.10,0.07] | -0.02 | [-0.10,0.07] | 0.02 | [-0.06,0.10] | -0.01 | [-0.07,0.05] |
| ≥401 | -0.12\* | [-0.21,-0.03] | -0.11\* | [-0.21,-0.02] | -0.12\*\* | [-0.22,-0.03] | -0.05 | [-0.14,0.05] | -0.10\*\* | [-0.17,-0.03] |
| P for trend |  | 0.012 |  | 0.018 |  | 0.011 |  | 0.360 |  | 0.004 |
|  |  |  |  |  |  |  |  |  |  |  |
| **BAP (meq/L)** |  |  |  |  |  |  |  |  |  |  |
| >2200 | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 2000-2200 | 0.01 | [-0.06,0.09] | 0.03 | [-0.04,0.11] | 0.00 | [-0.08,0.08] | -0.00 | [-0.08,0.07] | 0.01 | [-0.04,0.07] |
| <2000 | 0.08 | [-0.03,0.18] | 0.02 | [-0.09,0.13] | -0.00 | [-0.11,0.11] | -0.02 | [-0.13,0.08] | 0.02 | [-0.06,0.10] |
| P for trend |  | 0.188 |  | 0.550 |  | 0.973 |  | 0.730 |  | 0.602 |
|  |  |  |  |  |  |  |  |  |  |  |
| **TTL (umol/L)** |  |  |  |  |  |  |  |  |  |  |
| 4th Q | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  | 0.00 |  |
| 3rd Q | -0.03 | [-0.12,0.06] | -0.05 | [-0.15,0.04] | 0.00 | [-0.09,0.10] | -0.04 | [-0.14,0.05] | -0.03 | [-0.10,0.04] |
| 2nd Q | 0.09 | [-0.00,0.19] | 0.01 | [-0.09,0.10] | 0.02 | [-0.08,0.12] | -0.04 | [-0.13,0.06] | 0.02 | [-0.05,0.09] |
| 1st Q | 0.09 | [-0.01,0.19] | 0.03 | [-0.07,0.13] | 0.01 | [-0.09,0.11] | -0.04 | [-0.14,0.06] | 0.02 | [-0.05,0.10] |
| P for trend |  | 0.009 |  | 0.305 |  | 0.761 |  | 0.456 |  | 0.278 |

\* P ≤ 0.05, \*\* P ≤ 0.01, \*\*\*P ≤ 0.001

Models are adjusted for age group, sex, study centre, education, SES, smoking, alcohol, depression, history of MI, history of stroke and case-control status. Prospective models are additionally adjusted for cognitive test vs. re-test status.