**Supplemental Data**

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Figure S1: Unadjusted mean preoperative adipokine concentrations (95% CI) according to POD status in obese (red) and non-obese (blue) patients

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Figure S2: Unadjusted mean preoperative adipokine concentrations (95% CI) according to POCD status in obese (red) and non-obese (blue) patients

Table S1: Baseline sample characteristics and surgery-related factors for full cohort and analysis sample

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristics | Full analysis sample (N=768) | Did not attend 3-month follow-up (n=242) | Attended 3-month follow-up (n=526) | p-valuea |
| Male, n (%) | 440 (57.3%) | 121 (50.0%) | 319 (60.6%) | 0.006 |
| Age, years, mean ± SD  | 72 ± 5 | 73 ± 5 | 72 ± 5 | 0.23 |
| Study center |  |  |  |  |
|  Utrecht, n (%) | 177 (23.0%) | 25 (10.3%) | 152 (28.9%) |  |
|  Berlin, n (%) | 591 (77.0%) | 217 (89.7%) | 374 (71.1%) |  |
| Surgery |  |  |  | 0.041 |
|  Intracranial, n (%) | 10 (1.3%) | 5 (2.1%) | 5 (1.0%) |  |
|  Thoracic/abdominal/pelvic, n (%) | 333 (43.4%) | 118 (48.8%) | 215 (40.9%) |  |
|  Peripheral, n (%) | 425 (55.3%) | 119 (49.2%) | 306 (58.2%) |  |
| Duration of anaesthesia (min), median (interquartile range) | 204 (121 – 311) | 220 (127 – 359) | 199 (118 – 289) | <0.001 |
| History of coronary artery disease, n (%) | 147 (19.1%) | 49 (20.2%) | 98 (18.6%) | 0.60 |
| History of stroke, n (%) | 41 (5.3%) | 16 (6.6%) | 25 (4.8%) | 0.29 |
| History of transient ischemic attack, n (%) | 28 (3.6%) | 8 (3.3%) | 20 (3.8%) | 0.73 |
| History of diabetes, n (%) | 171 (22.3%) | 70 (28.9%)  | 101 (19.2%) | 0.003 |
| History of hypertension, n (%) | 482 (62.8%) | 169 (69.8%) | 313 (59.5%) | 0.006 |
| Body mass index (kg/m2), mean ± SD | 27 ± 5 | 27 ± 5 | 27 ± 4 | 0.28 |
| Fasting, n (%) | 758 (98.7%) | 239 (98.8%) | 519 (98.7%) | 0.92 |
| MMSE, median (interquartile range) | 29 (28 – 30) | 29 (27 – 30) | 29 (28 – 30) | 0.007 |

Data shown following imputation of missing data. GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination afor difference analysis sample on POCD (n=526) versus not included in analysis sample (n=242) using Mann-Whitney, t-tests (df = 766), or chi2 tests (df = 1)

Table S2. Correlations among adipokines and of adipokines with age and body mass index

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Age | Body mass index | Total adiponectin2 | HMW adiponectin | sOB-R1 |
| Leptin | -0.03 (0.49) | 0.52 (<0.001) | -0.09 (0.01) | -0.04 (0.27) | -0.52 (<0.001) |
| sOB-R1 | 0.07 (0.08) | -0.44 (<0.001) | 0.23 (<0.001) | 0.29 (<0.001) | -- |
| HMW adiponectin | 0.10 (0.010) | -0.26 (<0.001) | 0.77 (<0.001) | -- | -- |
| Total adiponectin2 | 0.07 (0.05) | -0.26 (<0.001) | -- | -- | -- |

HMW, high molecular weight; sOB-R, soluble leptin receptor. Values are Spearman rank correlation coefficients (*P*-values). Analysis n=768, except 1n=740 and 2n=767.

Table S3. Characteristics of study participants by quartiles of leptin

|  |  |  |
| --- | --- | --- |
|  | Leptin | *P*-valuea |
|  | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |  |
| N | 191 | 192 | 194 | 191 |  |
| Leptin concentration, range, ng/mL | 0.2 – 5.7 | 5.8 – 13.4 | 13.4 – 30.6 | 30.7 – 159.9 |  |
| Age, years, mean | 73 | 72 | 73 | 72 | 0.09 |
| Male sex, % | 80.1 | 63.0 | 53.6 | 32.5 | <0.001 |
| Body mass index, kg/m2 , mean | 24 | 27 | 27 | 30 | <0.001 |
| Hypertension, % | 56.1 | 59.0 | 60.8 | 79.6 | <0.001 |
| Diabetes, % | 13.8 | 24.6 | 20.2 | 31.9 | <0.001 |
| Coronary heart disease, % | 25.3 | 21.1 | 16.0 | 16.2 | 0.07 |
| Stroke, % | 5.9 | 5.3 | 5.7 | 4.8 | 0.97 |
| Transient ischemic attack, % | 6.0 | 2.7 | 2.6 | 3.8 | 0.29 |

Precise range is not shown due to rounding. N=768. afrom analyses of variance (ANOVA, df = 3) or chi2 tests (df = 3)

Table S4. Characteristics of study participants by quartiles of total adiponectin

|  |  |  |
| --- | --- | --- |
|  | Total adiponectin | *P*-valuea |
|  | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |  |
| N | 193 | 190 | 193 | 191 |  |
| Adiponectin concentration, range, ng/µL | 2.7 – 9.1 | 9.2 – 12.8 | 12.9 – 18.0 | 18.1 – 61.1 |  |
| Age, years, mean | 72 | 73 | 72 | 73 | 0.07 |
| Male sex, % | 68.9 | 62.6 | 53.4 | 44.0 | <0.001 |
| Body mass index, kg/m2 , mean | 28 | 28 | 27 | 25 | <0.001 |
| Hypertension, % | 71.1 | 66.8 | 63.1 | 54.2 | 0.005 |
| Diabetes, % | 30.7 | 31.0 | 16.5 | 12.6 | <0.001 |
| Coronary heart disease, % | 26.5 | 14.4 | 19.3 | 17.9 | 0.028 |
| Stroke, % | 4.2 | 5.9 | 4.8 | 6.9 | 0.68 |
| Transient ischemic attack, % | 4.3 | 1.6 | 4.9 | 4.2 | 0.35 |

Precise range is not shown due to rounding. N=767. afrom analyses of variance (ANOVA, df = 3) or chi2 tests (df = 3)

Table S5. Characteristics of study participants by quartiles of soluble leptin receptor

|  |  |  |
| --- | --- | --- |
|  | sOB-R | *P*-valuea |
|  | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |  |
| N | 180 | 187 | 185 | 188 |  |
| sOB-R concentration, range, ng/mL | 2.6 – 15.1 | 15.1 – 19.6 | 19.6 – 25.0 | 25.1 – 83.9 |  |
| Age, years, mean | 71 | 73 | 73 | 72 | <0.001 |
| Male sex, % | 46.7 | 61.5 | 64.9 | 56.9 | 0.003 |
| Body mass index, kg/m2 , mean | 30 | 28 | 27 | 24 | <0.001 |
| Hypertension, % | 71.3 | 64.1 | 65.6 | 54.6 | 0.010 |
| Diabetes, % | 27.9 | 22.7 | 22.5 | 19.9 | 0.33 |
| Coronary heart disease, % | 20.9 | 17.8 | 20.4 | 19.6 | 0.89 |
| Stroke, % | 3.4 | 7.2 | 6.1 | 6.0 | 0.45 |
| Transient ischemic attack, % | 5.1 | 4.4 | 2.8 | 3.3 | 0.67 |

Precise range is not shown due to rounding. sOB-R, leptin receptor. N=740. afrom analyses of variance (ANOVA, df = 3) or chi2 tests (df = 3)

Table S6. Characteristics of study participants by quartiles of high-molecular weight adiponectin

|  |  |  |
| --- | --- | --- |
|  | HMW adiponectin | *P*-valuea |
|  | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |  |
| N | 195 | 192 | 188 | 193 |  |
| HMW adiponectin concentration, range, ng/µL | 0.0 – 1.0 | 1.0 – 1.7 | 1.7 – 2.5 | 2.5 – 8.4 |  |
| Age, years, mean | 72 | 72 | 72 | 73 | 0.07 |
| Male sex, % | 74.4 | 64.1 | 54.3 | 36.3 | <0.001 |
| Body mass index, kg/m2 , mean | 28 | 28 | 27 | 25 | <0.001 |
| Hypertension, % | 67.0 | 65.8 | 64.9 | 57.7 | 0.23 |
| Diabetes, % | 34.7 | 27.7 | 14.6 | 13.2 | <0.001 |
| Coronary heart disease, % | 30.5 | 17.6 | 13.6 | 16.4 | <0.001 |
| Stroke, % | 4.1 | 7.0 | 4.3 | 6.4 | 0.53 |
| Transient ischemic attack, % | 2.6 | 5.9 | 2.7 | 3.7 | 0.31 |

Precise range is not shown due to rounding. HMW, high molecular weight. N=768. afrom analyses of variance (ANOVA, df = 3) or chi2 tests (df = 3)

Table S7. Adjusted odds and 95% CI of POD stratified by obesity status, and interaction terms (model 2)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Obese subgroup (BMI≥30kg/m2) | Non-obese subgroup (BMI<30kg/m2) | Interaction terms adipokine x BMI |
|  | OR (95% CI) per 1 SD increment | *P*-value | OR (95% CI) per 1 SD increment | *P*-value | OR (95% CI) | *P*interaction |
| Leptin | 0.81 (0.55, 1.19) | 0.28 | 1.19 (0.82, 1.72) | 0.37 | 0.90 (0.97, 1.04)  | 0.80 |
| sOB-R1 | 0.75 (0.43, 1.28) | 0.29 | 1.06 (0.87, 1.31) | 0.56 | **0.95 (0.92, 0.99)** | **0.010** |
| Totaladiponectin2 | 0.51 (0.25, 1.02) | 0.06 | 1.09 (0.89, 1.33) | 0.43 | **0.94 (0.90, 0.98)** | **0.006** |
| HMW adiponectin | 0.67 (0.37, 1.20) | 0.18 | 1.02 (0.83, 1.26) | 0.85 | 0.98 (0.94, 1.01) | 0.20 |
| FLI1 | 1.04 (0.79, 1.38) | 0.77 | 1.08 (0.76, 1.54) | 0.67 | 1.00 (0.98, 1.04) | 0.79 |
| LAR2 | 0.91 (0.64, 1.30) | 0.60 | 1.15 (0.82, 1.60) | 0.41 | 1.00 (0.97, 1.03) | 0.91 |

BMI, body mass index; CI, confidence interval; FLI, free leptin index; HMW, high molecular weight; LAR, leptin/adiponectin ratio; sOB-R, leptin receptor

Analysis n=768. Of these, n=174 (22.7%) in the ‘obese’ group and n=594 (77.3%) in the ‘non-obese’ group.

1Analysis n=740. Of these, n=169 (22.8%) in the ‘obese’ group and n=571 (77.2%) in the ‘non-obese’ group.

2Analysis n=767. Of these, 174 (22.7%) in the ‘obese’ group and n=593 (77.3%) in the ‘non-obese’ group.

 Logistic regression analyses based on Wald chi2 statistic (df = 1).

All analyses adjusted for age, sex, fasting, surgery type, body mass index (and for leptin, sOB-R, FLI, LAR additionally for analysis lab)

Adipokines were standardized, so that OR estimates show the change in odds of cognitive impairment for each SD increment in adipokine.

Interaction terms from analysis of (adipokine x body mass index) in separate logistic regression models of each adipokine and POD in total sample. Results unchanged after excluding underweight patients from “non-obese” subgroup.

Table S8. Adjusted odds and 95% CI of POD stratified by obesity status, and interaction terms (model 4)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Obese subgroup (BMI≥30kg/m2) | Non-obese subgroup (BMI<30kg/m2) | Interaction terms adipokine x BMI |
|  | OR (95% CI) per 1 SD increment | *P*-value | OR (95% CI) per 1 SD increment | *P*-value | OR (95% CI) | *P*interaction |
| Leptin | 0.83 (0.56, 1.23) | 0.35 | 1.19 (0.82, 1.73) | 0.37 | 1.00 (0.97, 1.04) | 0.84 |
| sOB-R1 | 0.74 (0.46, 1.21) | 0.23 | 1.11 (0.89, 1.28) | 0.35 | **0.95 (0.91, 0.98)** | **0.004** |
| Totaladiponectin2 | 0.48 (0.23, 1.03) | 0.06 | 0.99 (0.79, 1.24) | 0.96 | **0.95 (0.90, 0.99)** | **0.020** |
| HMW adiponectin | 0.66 (0.35, 1.23) | 0.19 | 1.06 (0.85, 1.31) | 0.62 | 0.98 (0.94, 1.02) | 0.26 |
| FLI1 | 1.04 (0.78, 1.38) | 0.81 | 1.06 (0.71, 1.54) | 0.78 | 1.01 (0.98, 1.04) | 0.75 |
| LAR2 | 0.95 (0.65, 1.40) | 0.80 | 1.14 (0.82, 1.60) | 0.43 | 1.00 (0.97, 1.03) | 0.90 |

BMI, body mass index; CI, confidence interval; FLI, free leptin index; HMW, high molecular weight; LAR, leptin/adiponectin ratio; sOB-R, leptin receptor

Analysis n=768. Of these, n=174 (22.7%) in the ‘obese’ group and n=594 (77.3%) in the ‘non-obese’ group.

1Analysis n=740. Of these, n=169 (22.8%) in the ‘obese’ group and n=571 (77.2%) in the ‘non-obese’ group.

2Analysis n=767. Of these, 174 (22.7%) in the ‘obese’ group and n=593 (77.3%) in the ‘non-obese’ group.

Logistic regression analyses based on Wald chi2 statistic (df = 1).

All analyses adjusted for age, sex, fasting, surgery type, (and for leptin, sOB-R, FLI, LAR additionally for analysis lab), body mass index, diabetes, hypertension, stroke, transient ischemic attack, coronary heart disease, anesthesia duration

Adipokines were standardized, so that OR estimates show the change in odds of cognitive impairment for each SD increment in adipokine.

Interaction terms from analysis of (adipokine x body mass index) in separate logistic regression models of each adipokine and POD in total sample. Results unchanged after excluding underweight patients from “non-obese” subgroup.

Table S9. Adjusted odds and 95% CI of POCD stratified by obesity status, and interaction terms (model 2)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Obese subgroup (BMI≥30kg/m2) | Non-obese subgroup (BMI<30kg/m2) | Interaction term adipokine x BMI |
|  | OR (95% CI) per 1 SD increment | *P*-value | OR (95% CI) per 1 SD increment | *P*-value | OR (95% CI) | *P*interaction |
| Leptin | 0.61 (0.36, 1.05) | 0.08 | 1.09 (0.61, 1.94) | 0.78 | 1.03 (0.97, 1.09) | 0.33 |
| sOB-R1 | **4.00 (1.01, 15.86)** | **0.049** | 0.82 (0.52, 1.29) | 0.39 | 1.05 (0.97, 1.13) | 0.21 |
| Totaladiponectin2 | 1.18 (0.62, 2.28) | 0.61 | 0.84 (0.55, 1.26) | 0.39 | 1.04 (0.96, 1.12) | 0.33 |
| HMW adiponectin | 0.94 (0.44, 2.01) | 0.87 | 0.83 (0.57, 1.20) | 0.31 | 1.01 (0.94, 1.08) | 0.75 |
| FLI1 | 0.58 (0.30, 1.10) | 0.09 | 0.94 (0.44, 2.00) | 0.88 | 1.05 (0.96, 1.14) | 0.28 |
| LAR2 | 0.60 (0.34, 1.07) | 0.08 | 1.00 (0.54, 1.86) | 0.99 | 1.04 (0.97, 1.10) | 0.28 |

BMI, body mass index; CI, confidence interval; FLI, free leptin index; HMW, high molecular weight; LAR, leptin/adiponectin ratio; sOB-R, leptin receptor

Analysis n=526. Of these, n=114 (21.7%) in the ‘obese’ group and n=412 (78.3%) in the ‘non-obese’ group.

1Analysis n=503. Of these, n=110 (21.9%) in the ‘obese’ group and n=397 (78.1%) in the ‘non-obese’ group.

2Analysis n=525. Of these, 114 (21.7%) in the ‘obese’ group and n=411 (78.3%) in the ‘non-obese’ group.

Logistic regression analyses based on Wald chi2 statistic (df = 1).

All analyses adjusted for age, sex, fasting, surgery type, body mass index, (and for leptin, sOB-R, FLI, LAR additionally for analysis lab)

Adipokines were standardized, so that OR estimates show the change in odds of cognitive impairment for each SD increment in adipokine.

Interaction terms from analysis of (adipokine x body mass index) in separate logistic regression models of each adipokine and POCD in total sample. Results unchanged after excluding underweight patients from “non-obese” subgroup.

Table S10. Adjusted odds and 95% CI of POCD stratified by obesity status, and interaction terms (model 4)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Obese subgroup (BMI≥30kg/m2) | Non-obese subgroup (BMI<30kg/m2) | Interaction terms adipokine x BMI |  |
|  | OR (95% CI) per 1 SD increment | *P*-value | OR (95% CI) per 1 SD increment | *P*-value | OR (95% CI) | *P*interaction |
| Leptin | 0.66 (0.36, 1.20) | 0.17 | 1.06 (0.59, 1.91) | 0.84 | 1.03 (0.97, 1.09) | 0.33 |
| sOB-R1 | **4.99 (1.09, 22.77)** | **0.038** | 0.80 (0.49, 1.31) | 0.38 | 1.05 (0.98, 1.13) | 0.20 |
| Totaladiponectin2 | 1.12 (0.56, 2.24) | 0.74 | 0.87 (0.56, 1.34) | 0.52 | 1.04 (0.96, 1.12) | 0.36 |
| HMW adiponectin | 0.91 (0.39, 2.10) | 0.82 | 0.81 (0.55, 1.19) | 0.28 | 1.01 (0.94, 1.08) | 0.80 |
| FLI1 | 0.62 (0.31, 1.27) | 0.19 | 0.91 (0.43, 1.93) | 0.80 | 1.05 (0.96, 1.15) | 0.22 |
| LAR2 | 0.63 (0.34, 1.17) | 0.15 | 0.98 (0.52, 1.90) | 0.96 | 1.04 (0.97, 1.10) | 0.22 |

BMI, body mass index; CI, confidence interval; FLI, free leptin index; HMW, high molecular weight; LAR, leptin/adiponectin ratio; sOB-R, leptin receptor

Analysis n=526. Of these, n=114 (21.7%) in the ‘obese’ group and n=412 (78.3%) in the ‘non-obese’ group.

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