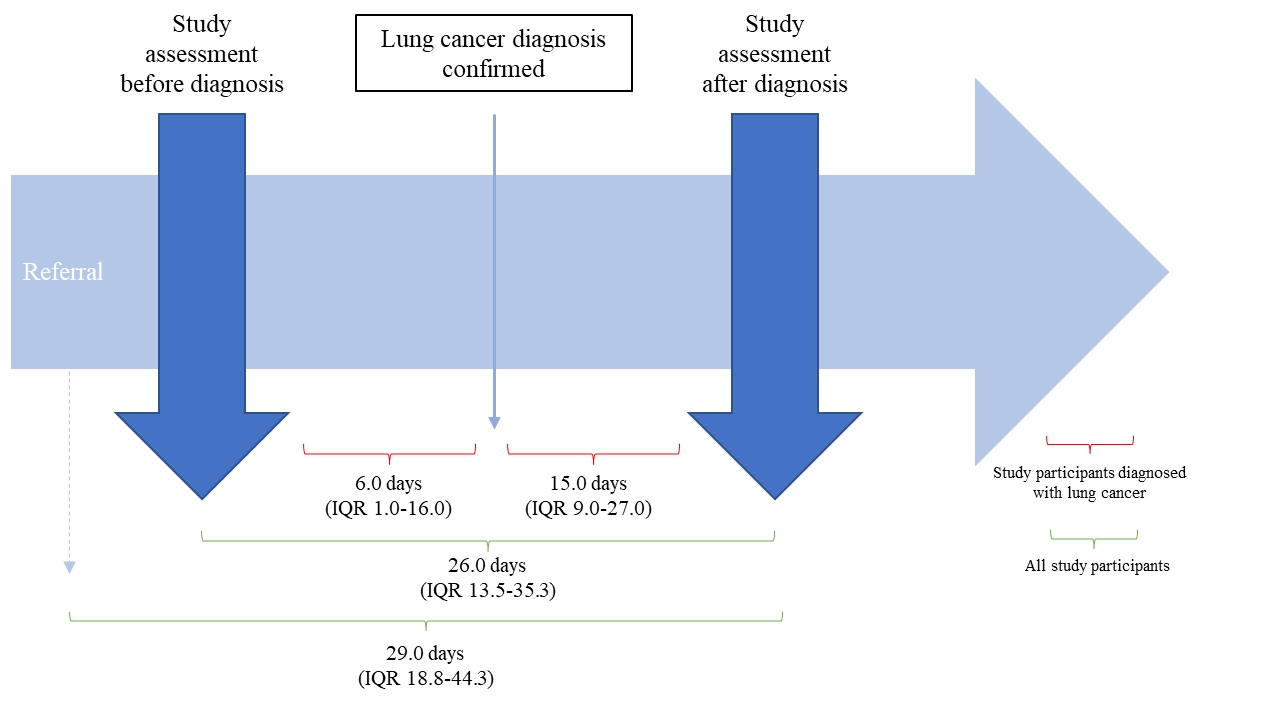
**Manuscript title:**

Psycho-biological stress response to a lung cancer diagnosis: a prospective study of patients in Iceland and Sweden.

**Supplementary material**

**Supplementary figure 1**.

Schematic diagram of the study design with time intervals for the participants in the **Distress analysis.**

**Supplementary table 1.** Baseline characteristics of participants in the LUCASS study who completed HADS1 questionnaire at both assessments (**Distress analysis)** and the subgroup that completed HADS questionnaire and collected urine for catecholamine measurement at both assessments (**Catecholamine analysis**) vs. non-completers.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Distress analysis** | | |  | **Catecholamine analysis** | | |
|  | **Participants**  N (%) | **Non-completers**  N (%) | **Pa** |  | **Participants** N (%) | **Non-completers**  N (%) | **Pa** |
| **Overall** (N) | 167 | 119 |  |  | 85 | 201 |  |
| **Country of participation** |  |  | 0.532 |  |  |  | 0.016 |
| Iceland | 100(59.9) | 66(55.5) |  |  | 59(69.4) | 107(53.2) |  |
| Sweden | 67(40.1) | 53(44.5) |  |  | 26(30.6) | 94(46.8) |  |
| **Age (years, mean (SD))** | 69.3(9.4) | 71.6(8.5) | 0.036 |  | 70.2(7.6) | 70.3(9.7) | 0.956 |
| **Age at diagnosis** |  |  | 0.113 |  |  |  | 0.915 |
| 65 years and under | 42(25.1) | 26(21.8) |  |  | 19(22.4) | 49(24.4) |  |
| 66-70 years | 40(24.0) | 18(15.1) |  |  | 18(21.2) | 40(19.9) |  |
| 70 years and above | 85(50.9) | 73(61.3) |  |  | 48(56.5) | 110(54.7) |  |
| NA | 0 | 2(1.7) |  |  | 0 | 2(1.0) |  |
| **Sex** |  |  | 0.904 |  |  |  | 0.566 |
| male | 86(51.5) | 63(52.9) |  |  | 47(55.3) | 102(50.7) |  |
| female | 81(48.5) | 56(47.1) |  |  | 38(44.7) | 99(49.3) |  |
| **Marital status** |  |  | 0.180 |  |  |  | 0.839 |
| single/divorced/widowed | 46(27.5) | 32(26.9) |  |  | 25(29.4) | 115(57.2) |  |
| married/partnered | 120(71.9) | 55(46.3) |  |  | 60(70.6) | 53(26.4) |  |
| NA | 1(0.6) | 32(26.9) |  |  | 0 | 33(16.4) |  |
| **Educational level** |  |  | 0.539 |  |  |  | 0.821 |
| primary | 72(43.1) | 33(27.7) |  |  | 31(36.5) | 72(35.8) |  |
| secondary | 67(40.1) | 35(29.4) |  |  | 30(35.3) | 67(33.3) |  |
| university | 26(15.6) | 18(15.1) |  |  | 23(27.1) | 28(13.9) |  |
| NA | 2(1.2) | 33(27.7) |  |  | 1(1.2) | 34(16.9) |  |
| **Occupation** |  |  | 1.000 |  |  |  | 0.503 |
| unemployed/retired | 120(71.9) | 63(52.9) |  |  | 64(75.3) | 119(59.2) |  |
| working | 47(28.1) | 24(20.2) |  |  | 21(24.7) | 50(24.8) |  |
| NA | 0 | 32(26.9) |  |  | 0 | 32(15.9) |  |
| **Financial status** |  |  | 0.250 |  |  |  | 0.451 |
| enough/bad | 79(47.3) | 48(40.3) |  |  | 46(54.1) | 81(40.3) |  |
| very good/good | 88(52.7) | 38(31.9) |  |  | 39(45.9) | 87(43.3) |  |
| NA | 0 | 33(27.7) |  |  | 0 | 33(16.4) |  |
| **Smoking status** |  |  | 0.294 |  |  |  | 0.672 |
| never | 26(15.6) | 14(11.8) |  |  | 14(16.5) | 26(12.9) |  |
| stopped | 87(52.1) | 38(31.9) |  |  | 44(51.8) | 81(40.3) |  |
| current | 54(32.3) | 37(31.1) |  |  | 27(31.8) | 64(31.8) |  |
| NA | 0 | 30(25.2) |  |  | 0 | 30(14.9) |  |
| **History of psychologic morbidity** |  |  | 0.081 |  |  |  | 0.141 |
| no | 81(48.5) | 71(59.7) |  |  | 39(45.9) | 113(56.2) |  |
| yes | 86(51.5) | 48(40.3) |  |  | 46(54.1) | 88(43,8) |  |
| **Lung Cancer** |  |  | 0.295 |  |  |  | 0.366 |
| No | 44(26.3) | 39(32.8) |  |  | 21(24.7) | 62(30.8) |  |
| Yes | 123(73.7) | 80(67.2) |  |  | 64(75.3) | 139(69.2) |  |
| **Lung Cancer type** |  |  | 0.008 |  |  |  | 0.145 |
| NSCLC | 112(91.1) | 65(81.2) |  |  | 57(89.1) | 120(86.3) |  |
| SCLC | 11(8.9) | 6(7.5) |  |  | 7(10.9) | 10(7.2) |  |
| Carcinoid | 0 | 6(7.5) |  |  | 0 | 6(4.3) |  |
| Clinical lung cancer diagnosis | 0 | 3(3.8) |  |  | 0 | 3(2.2) |  |
| **Lung cancer stage** |  |  | 0.566 |  |  |  | 0.325 |
| I-II | 53(43.1) | 30(37.5) |  |  | 30(46.9) | 53(38.2) |  |
| III-IV | 70(56.9) | 49(61.3) |  |  | 34(53.1) | 85(61.2) |  |
| NA | 0 | 1(1.2) |  |  | 0 | 1(0.7) |  |

ap-values based on Chi-square test or Fisher’s exact test when expected cell counts less than 5, excluding NA´s.

*Abbreviation:* HADS, Hospital anxiety and depression scale.

**Supplementary text 1.**Description of the urinary catecholamine measurements.

For the Icelandic cohort, an inhouse validated LC-MS/MS method adapted from the vendor application note (Waters, MA, USA, P/N: 720005093en) was used for the quantification of urinary epinephrine and norepinephrine. The inter- and intra-assay precision were 1.1 to 3.6% for epinephrine and 2.8 to 5.2% respectively for norepinephrine and the inter- and intra-assay accuracy were -4.5 to -9.6% for epinephrine and -5.0 to 2.3% for norepinephrine. Further details in Supplementary text 2 and Supplementary table 1.

For the Swedish cohort, urinary free norepinephrine and epinephrine concentration were determined by high-performance liquid chromatography with electrochemical detection[1]. The night urinary creatinine concentrations were measured according to standard procedures and the urinary catecholamine concentrations controlled by urine creatinine secretion (nmol catecholamine/mmol creatinine)[2, 3]. Inter- and intra-assay variability (i.e., coefficient of variation) for these high-performance liquid chromatography analyses is 4–7% for epinephrine, 3–5% for norepinephrine and 2% for creatinine[2]. The method performance is monitored at both study sites by participation in an external quality scheme supplied by Birmingham Quality, an accredited proficiency testing provider (Birmingham Quality is part of the National Health Service (NHS) and University Hospitals Birmingham NHS Foundation)[4], providing a rationale for combining these measures.

**Supplementary text 2.**More detailed description of the urinary catecholamine measurement in the Icelandic study cohort within the **Catecholamine analysis.**

Sample preparation:

Inhouse validated method used, adapted from vendor application note (Waters, US, P/N: 720005093en). Calibrators, controls, and internal standard mix were purchased from Chromsystems, (P/N: 80639, 0372/0373 and 80604 respectively). Urine samples, previously acidified for preservation, were tested prior to preparation to verify pH of 3-4. 750µL 0.5 mM of ammonium acetate and 25µL of internal standard mix were added to 300µL of sample/calibrator/QC. Pre-treated samples were loaded to individual wells of an EVOLUTE® EXPRESS WCX (Biotage, Uppsala, Sweden) previously conditioned with 1 mL of MeOH and 1 mL of H2O. Samples were allowed to pass through the plate under gravity for 10 minutes, then centrifuged for 2 minutes at 200 rcf. Each well was washed with 1 mL of 20 mM ammonium acetate, followed by 1 mL of MeOH, centrifuged for 2 minutes at 200 rcf after each wash. The 96-well plate was subsequently centrifuged for one minute at 2000 rcf to remove residual methanol from the sorbent bed. The target compounds were eluted from the plate with 2 x 250 µL aliquots of 85:15 ACN: H2O containing 2% formic acid into 2 mL 96-well sample collection plate. Each elution aliquot was allowed to percolate through the well by gravity, finally centrifuged dry for one minute at 2000 rcf. 2 µL of the eluate was injected into the LC-MS/MS system.

LC-MS/MS method:

The LC-MS/MS system consisted of Aqcuity I-class system comprised of Binary Solvent Manager, Sample Manager with flow through needle, Column Heater and Auxiliary Column Heater, and XEVO TQ-S triple quadrupole mass spectrometer (Waters, MA, USA). Chromatographic method and gradient consisted of initial conditions of 0.6 mL/min 100% B (0.0-1.0 min), gradient to 90%B (1.0-2.0 min), gradient to 70%B (2.0-2.5 min) as a washing step, then back to initial conditions (2.5-2.6 min) finally equilibration (2.6-4.0 min). The mass spectrometer settings were capillary voltage 0.5kV, source temperature 150°C, desolvation temperature 550°C, cone gas flow 150 L/h, desolvation gas flow 900 L/h and running the mass spectrometer in selected reaction monitoring (SRM) mode.

**Supplementary table 2**. SRM transitions for catecholamines and metabolites.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Compound** | **Quantitative transition** | **Qualitative transition** | **IS transition** | **Cone voltage** |
| **Epinephrine** | 166.10 > 135.10 | 166.10 > 107.10 | 172.10 > 112.10 | 30 |
| **Norepinephrine** | 152.10 > 107.10 | 152.10 > 135.10 | 158.10 > 111.10 | 40 |
| **Note**. Due to detector saturation at high concentration, collision energy was used to detune the signal for individual analytes. | | | | |

*Abbreviations:* SRM, Selected reaction monitoring; IS, isotopically labeled internal standard.

**Supplementary table 3.** Study participants in multi-item measures and overview of imputed data.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Measure** | **Items in each measure** | **N**a | **Numbers of imputed values** | **Proportion of imputed responses (%)** |
| HADS-1b | 14 | 167 | 28/2171 | 1.3 |
| HADS-2c | 14 | 167 | 22/2171 | 1.1 |

aNumber of participants in each measurement.

bHospital anxiety and depression scale (14 items) before lung cancer evaluation.

cHospital anxiety and depression scale (14 items) after lung cancer evaluation.

**Supplementary table 4.** Baseline characteristics of study participants stratified by country of participation.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Distress analysis** | | | |  | **Catecholamine analysis** | | | |
|  | **All**  N (%) | **Iceland**  N (%) | **Sweden**  N (%) | **P**a |  | **All**  N (%) | **Iceland**  N (%) | **Sweden**  N (%) | **P**a |
| **Overall,** N | 167 | 100(59,9) | 67(40.1) |  |  | 85 | 59(69.4) | 26(30.6) |  |
| **Age (years, mean (SD))** | 69.3(9.4) | 67.8(7.3) | 71.5(11.6) | 0.013 |  | 70.2(7.6) | 69.2(6.7) | 72.4(8.9) | 0.072 |
| **Age at diagnosis** |  |  |  | 0.003 |  |  | 15(25.4) | 4(15.4) | 0.117 |
| 65 years and under | 42(25.1) | 30(30.0) | 12(17.9) |  |  | 19(22.4) | 15(25.4) | 3(11.5) |  |
| 66-70 years | 40(24.0) | 30(30.0) | 10(14.9) |  |  | 18(21.2) | 29(49.2) | 19(73.1) |  |
| 70 years and above | 85(50.9) | 40(40.0) | 45(67.2) |  |  | 48(56.5) |  |  |  |
| **Sex** |  |  |  | 0.343 |  |  |  |  | 0.173 |
| male | 86(51.5) | 55(55.0) | 31(46.3) |  |  | 47(55.3) | 36(61.0) | 11(42.3) |  |
| female | 81(48.5) | 45(45.0) | 36(53.7) |  |  | 38(44.7) | 23(39.0) | 15(57.7) |  |
| **Marital status** |  |  |  | 0.465 |  |  |  |  | 1.000 |
| single/divorced/widowed | 46(27.5) | 30(30.0) | 16(23.9) |  |  | 25(29.4) | 17(28.8) | 8(30.8) |  |
| married/partnered | 120(71.9) | 69(69.0) | 51(76.1) |  |  | 60(70.6) | 42(71.2) | 18(69.2) |  |
| NA | 1(0.6) | 1(1.0) | 0 |  |  | 0 | 0 | 0 |  |
| **Educational level** |  |  |  | 0.451 |  |  |  |  | 0.312 |
| primary | 72(43.1) | 46(46.0) | 26(38.8) |  |  | 31(36.5) | 23(39.0) | 8(30.8) |  |
| secondary | 67(40.1) | 39(39.0) | 28(41.8) |  |  | 30(35.3) | 22(37.3) | 8(30.8) |  |
| university | 26(15.6) | 13(13.0) | 13(19.4) |  |  | 23(27.1) | 13(22.0) | 10(38.5) |  |
| NA | 2(1.2) | 2(2.0) | 0 |  |  | 1(1.2) | 1(1.7) | 0 |  |
| **Occupation** |  |  |  | 0.010 |  |  |  |  | 0.111 |
| unemployed/retired | 120(71.9) | 64(64.0) | 56(83.6) |  |  | 64(75.3) | 41(30.5) | 23(88.5) |  |
| working | 47(28.1) | 36(36.0) | 11(16.4) |  |  | 21(24.7) | 18(69.5) | 3(11.5) |  |
| **Financial status** |  |  |  | <0.001 |  |  |  |  | 0.002 |
| enough/bad | 79(47.3) | 64(64.0) | 15(22.4) |  |  | 46(54.1) | 39(66.1) | 7(26.9) |  |
| very good/good | 88(52.7) | 36(36.0) | 52(77.6) |  |  | 39(45.9) | 20(33.9) | 19(73.1) |  |
| **Smoking status** |  |  |  | <0.001 |  |  |  |  | 0.001 |
| never | 26(15.6) | 10(10.0) | 16(23.9) |  |  | 14(16.5) | 5(8.5) | 9(34.6) |  |
| stopped | 87(52.1) | 44(44.0) | 43(64.2) |  |  | 44(51.8) | 29(49.2) | 15(57.7) |  |
| current | 54(32.3) | 46(46.0) | 8(11.9) |  |  | 27(31.8) | 25(42.4) | 2(7.7) |  |
| **History of psychologic morbidity** |  |  |  | 0.206 |  |  |  |  | 0.788 |
| no | 81(48.5) | 44(44.0) | 37(55.2) |  |  | 39(45.9) | 26(44.1) | 13(50.0) |  |
| yes | 86(51.5) | 56(56.0) | 30(44.8) |  |  | 46(54.1) | 33(55.9) | 13(50.0) |  |
| **Lung Cancer diagnosis** | 123(73.7) | 76(76.0) | 47(70.1) | 0.508 |  | 64(75.3) | 45(76.3) | 19(73.1) |  |
| **Lung Cancer type** |  |  |  | 0.441 |  |  |  |  | 0.612 |
| NSCLC | 112(91.1) | 69(90.8) | 43(91,5) |  |  | 57(89.0) | 39(86.7) | 18(94.7) |  |
| SCLC | 11(9.0) | 7(9.2) | 4(8.5) |  |  | 7(11.0) | 6(13.3) | 1(5.3) |  |
| **Lung Cancer stage**b |  |  |  | 0.400 |  |  |  |  | 0.049 |
| I-II | 53(43.1) | 30(39.5) | 23(48.9) |  |  | 30(46.9) | 17(37.8) | 13(68.4) |  |
| III-IV | 70(56.9) | 46(60.5) | 24(51.1) |  |  | 34(53.1) | 28(62.2) | 6(31.6) |  |

ap-values based on Chi-square test or Fisher’s exact test when expected cell counts less than 5, excluding NA´s.

bOnly for the Lung Cancer group

**Supplementary table 5.** Distress before and after diagnostic work-up for lung cancer **(Distress analysis).**

HADS (Hospital Anxiety and Depression Scale), mean scores (SD) and proportions of scores with potential clinical significance (HADS-Total, HADS-Depression and HADS-Anxiety before and after final diagnosis of lung changes.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| HADS variable | Lung cancer diagnosis | Before lung cancer assessment | | After lung cancer assessment | | Change between assessments | . |
|  |  |  | p-value\* |  | p-value\* | p-value\* | p-value\*\* |
| HADS-T |  |  |  |  |  |  |  |
| mean (SD) | No | 9.0(6.5) | 0.430 | 7.4(5.8) | 0.002 | 0.070 | 0.004 |
| Yes | 10.2(7.0) | 11.6(8.0) | 0.010 |
| HADS-T > 13 |  |  |  |  |  |  |  |
| N (%) | No | 10/22.7 | 0.388 | 7/15.9 | 0.002 | 0.164 | 0.007 |
| N (%) | Yes | 37/30.1 | 53/43.1 | 0.003 |
| HADS-D |  |  |  |  |  |  |  |
| mean (SD) | No | 3.9(3.7) | 0.241 | 3.1(3.0) | 0.0004 | 0.126 | 0.006 |
| Yes | 4.8(3.8) | 5.7(4.1) | 0.005 |
| HADS-D > 5 |  |  |  |  |  |  |  |
| N (%) | No | 16/36.4 | 0.319 | 11/25.0 | 0.001 | 0.117 | 0.038 |
| N (%) | Yes | 59/48.0 | 68/55.3 | 0.150 |
| HADS-A |  |  |  |  |  |  |  |
| mean (SD) | No | 5.1(3.8) | 0.774 | 4.3(3.5) | 0.031 | 0.103 | 0.023 |
| Yes | 5.4(4.0) | 5.9(4.5) | 0.090 |
| HADS-A > 7 |  |  |  |  |  |  |  |
| N (%) | No | 15/34.1 | 0.660 | 10/22.7 | 0.030 | 0.052 | 0.042 |
| N (%) | Yes | 46/37.4 | 50/40.7 | 0.464 |

\* p-values corrected for age, sex, and country of participation. \*\* p-values of test for interaction between lung cancer diagnosis and change in HADS measure between assessments.

*Abbreviations:* HADS, Hospital anxiety and depression scale; HADS-T, Hospital anxiety and depression scale – total score.

HADS-D, Hospital anxiety and depression scale – depression score; HADS-A, Hospital anxiety and depression scale –anxiety score.

HADS cutoff scores: HADS-T > 13, HADS-D > 5, HADS-A > 7.

**Supplementary table 6*.*** HADS (Hospital Anxiety and Depression Scale), cutoff scores (HADS-Depression >7, HADS-Anxiety >9) according to Annunxiata et al[5].

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| HADS variable | Lung cancer diagnosis | Before lung cancer assessment | | After lung cancer assessment | | Change between assessments |  |
|  |  |  | p-value\* |  | p-value\* | p-value\* | p-value\*\* |
| HADS-D > 7 |  |  |  |  |  |  |  |
| N (%) | No | 8/18.2 | 0.290 | 4/9.1 | 0.0003 | 0.041 | 0.0007 |
| N (%) | Yes | 34/27.6 | 54/43.9 | 0.001 |
| HADS-A > 9 |  |  |  |  |  |  |  |
| N (%) | Yes | 6/13.6 | 0.351 | 5/11.4 | 0.095 | 0.656 | 0.385 |
| N (%) | No | 25/20.3 | 30/24.4 | 0.274 |

\* p-values corrected for age, sex, and country of participation, \*\* p-values of test for interaction between lung cancer diagnosis and change in HADS measure between assessments.

*Abbreviations:* HADS, Hospital anxiety and depression scale

HADS-D, Hospital anxiety and depression scale – depression score; HADS-A, Hospital anxiety and depression scale –anxiety score.

HADS cutoff scores: HADS-T > 13, HADS-D > 5, HADS-A > 7.

**Supplementary table 7*.*** Distress before and after lung cancer diagnosis stratified by tumor stage.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **cTNM stage I-II**  N (%) |  | **cTNM stage III-IV**  N (%) |  | **P\*** |
| **Overall,** N | 53 |  | 70 |  |  |
| **HADS score**before diagnosis |  |  |  |  |  |
| HADS-T (mean (SD)) | 10.3(6.4) |  | 10.2(7.5) |  | 0.976 |
| HADS-D(mean (SD)) | 5.0(3.5) |  | 4.7(4.0) |  | 0.669 |
| HADS-A(mean (SD)) | 5.3(3.7) |  | 5.5(4.3) |  | 0.635 |
| **HADS score**after  diagnosis |  |  |  |  |  |
| HADS-T (mean (SD)) | 11.6(8.3) |  | 11.6(7.8) |  | 0.871 |
| HADS-D(mean (SD)) | 5.6(4.1) |  | 5.7(4.1) |  | 0.884 |
| HADS-A(mean (SD)) | 5.9(4.7) |  | 5.9(4.3) |  | 0.873 |

\*p-values based on Chi-square test or Fisher’s exact test when expected cell counts less than 5, adjusted for age, sex and country of participation.

*Abbreviations:c*TNM stage (Tumor, Node and Metastasis) clinical staging according to the International Staging System, 7th edition.

HADS, Hospital anxiety and depression scale; HADS-T, Hospital anxiety and depression scale – total score.

HADS-D, Hospital anxiety and depression scale – depression score; HADS-A, Hospital anxiety and depression scale –anxiety score.

**Supplementary table 8*.*** Comparison of distress before and after diagnostic work-up for lung cancer in both study groups.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Participants only in the Distress analysis**  N (%) |  | **Participants in the Catecholamine analysis**  N (%) |  | **P**\* |
| **Overall,** N | 82 |  | 85 |  |  |
| **Lung Cancer diagnosis** | 59(72.0) |  | 64(75.3) |  | 0.753 |
| **HADS score**before diagnosis |  |  |  |  |  |
| HADS-T (mean (SD)) | 10.4(7.7) |  | 9.4(6.0) |  | 0.605 |
| HADS-D(mean (SD)) | 4.9(4.2) |  | 4.3(3.2) |  | 0.369 |
| HADS-A(mean (SD)) | 5.6(4.2) |  | 5.1(3.7) |  | 0.975 |
| **HADS score**after  diagnosis |  |  |  |  |  |
| HADS-T (mean (SD)) | 9.7(8.0) |  | 11.3(7.3) |  | 0.166 |
| HADS-D(mean (SD)) | 4.7(4.3) |  | 5.3(3.7) |  | 0.409 |
| HADS-A(mean (SD)) | 5.0(4.3) |  | 6.0(4.2) |  | 0.084 |

\*p-values based on Chi-square test or Fisher’s exact test when expected cell counts less than 5, adjusted for age sex and country of participation.

*Abbreviations:* HADS, Hospital anxiety and depression scale; HADS-T, Hospital anxiety and depression scale – total score.

HADS-D, Hospital anxiety and depression scale – depression score; HADS-A, Hospital anxiety and depression scale –anxiety score.

**Supplementary table 9.** The estimateda association between psychological distress (HADS) and the urinary levels of catecholamines before and after lung cancer diagnosis (**Catecholamine analysis**) with extended correlational model.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **HADS-total** |  | **HADS-depression** |  | **HADS-anxiety** |
|  | **Lung cancer diagnosis** | *Beta (CI),*  *p-valueb* |  | *Beta (CI),*  *p-valueb* |  | *Beta (CI),*  *p-valueb* |
| **Before diagnosis** |  |  |  |  |  |  |
| epinephrine |  |  |  |  |  |  |
|  | No | 0.069(-0.002-0.140)  0.086 |  | 0.069(-0.061-0.199)  0.324 |  | 0.10712(-0.004-0.218)  0.088 |
|  | Yes | 0.006(-0.013-0.026)  0.517 |  | 0.018(-0.019-0.055)  0.339 |  | 0.004(-0.029-0.037)  0.815 |
| norepinephrine |  |  |  |  |  |  |
|  | No | -0.006(-0.051-0.039)  0.803 |  | -0.019(-0.093-0.055)  0.629 |  | 0.002(-0.068-0.073)  0.947 |
|  | Yes | -0.001(-0.020-0.018)  0.917 |  | 0.004(-0.031-0.039)  0.824 |  | -0.006(-0.038-0.026)  0.705 |
| **After diagnosis** |  |  |  |  |  |  |
| epinephrine |  |  |  |  |  |  |
|  | No | -0.026(-0.078-0.026)  0.345 |  | -0.081(-0.182-0.020)  0.147 |  | -0.018(-0.102-0.066)  0.680 |
|  | Yes | 0.004(-0.014-0.023)  0.647 |  | -0.007(-0.045-0.031)  0.722 |  | 0.018(-0.014-0.051)  0.269 |
| norepinephrine |  |  |  |  |  |  |
|  | No | -0.013(-0.068-0.042)  0.659 |  | 0.002(-0.135-0.096)  0.745 |  | -0.020(-0.106-0.066)  0.657 |
|  | Yes | -0.007(-0.028-0.013)  0.472 |  | -0.011(-0.052-0.029)  0.578 |  | -0.014(-0.049-0.021)  0.444 |

aEstimated effect size (β- value) of baseline characteristics, with p-test for test of correlation and 95% confidence interval, from multivariate regression analysis.

bAdjusted for age, sex, education, occupation, smoking and country.

*Abbreviations:* HADS-total, Hospital anxiety and depression scale –total score; HADS-depression, Hospital anxiety and depression scale –depression score;

HADS-anxiety, Hospital anxiety and depression scale –anxiety score; CI, 95% confidence interval.

**Supplementary table 10*.*** The estimateda association between the change of psychological distress (HADS) and the change of urinary levels of catecholamines before and after lung cancer diagnosis (**Catecholamine analysis**) with extended correlational model.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Change in**  **u-catecholamines** | **Lung cancer diagnosis** | Change in **HADS-total**  *Beta (CI),*  *p-valueb* | |  | | Change in **HADS-depression**  *Beta (CI),*  *p-valueb* |  | Change in **HADS-anxiety**  *Beta (CI),*  *p-valueb* |
| epinephrine |  |  |  | |  | |  |  |
|  | No | 0.04(-0.281-0.358)  0.816 |  | | 0.002(-0.385-0.389)  0.993 | |  | 0.21(-0.533-0.950)  0.594 |
|  | Yes | -0.04(-0.106-0.029)  0.272 |  | | 0.02(-0.084-0.117)  0.755 | |  | -0.16(-0.282- -0.040)  0.012\* |
| norepinephrine |  |  |  | |  | |  |  |
|  | No | 0.61(-0.808-2.020)  0.421 |  | | 0.36(-1.395-2.109)  0.698 | |  | 2.00(-1.214-5.200)  0.251 |
|  | Yes | 0.18(-0.484-0.850)  0.593 |  | | 1.05(0.102-1.989)  0.034\* | |  | -1.05(-2.275-0.168)  0.097 |

aEstimated effect size (β- value) of baseline characteristics, with p-test for test of correlation and 95% confidence interval, from multivariate regression analysis.

bAdjusted for, age, sex, education, occupation, smoking, and country of participation.

\*p values that reach statistical significance.

*Abbreviations:* HADS-total, Hospital anxiety and depression scale –total score; HADS-depression, Hospital anxiety and depression scale –depression score;

HADS-anxiety, Hospital anxiety and depression scale –anxiety score; CI, 95% confidence interval.

.

**Supplementary figure 2.** Overnight urinary catecholamine levels before and after diagnostic work-up for lung cancer, with 95% CI, p-values corrected for age, sex, and country of participation (**Catecholamine analysis + 3 with extremely high catecholamine measurements** (n=88)).

1. Overnight urinary epinephrine levels
2. Overnight urinary norepinephrine levels

\*Test for interaction between lung cancer diagnosis and change in urinary levels of catecholamines between assessments.

A diagram of a patient's lung cancer

Description automatically generatedA diagram of a patient's lung cancer

Description automatically generateda. b.

**Supplementary table 11**. The estimateda association between the change of psychological distress (HADS) before and after lung cancer diagnosis and of urinary levels of catecholamines after lung cancer diagnosis (**Catecholamine analysis + 3 with extremely high catecholamine measurements** (n=88)).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Change in  **HADS-total** | Change in  **HADS-depression** | Change in  **HADS-anxiety** |
| **u-catecholamines after diagnosis** | **Lung cancer diagnosis** | *Beta (CI),*  *p-value*b | *Beta (CI),*  *p-value*b | *Beta (CI),*  *p-value*b |
| epinephrine |  |  |  |  |
|  | No | 0.01(-0.067-0.091)  0.776 | 0.02(-0.091-0.130)  0.736 | 0.005(-0.131-0.141)  0.939 |
|  | Yes | 0.005(-0.034-0.024)  0.730 | -0.03(-0.070-0.018)  0.248 | 0.02(-0.033-0.073)  0.462 |
| norepinephrine |  |  |  |  |
|  | No | 0.05(-0.031-0.121)  0.260 | 0.02(-0.089-0.131)  0.711 | 0.10(-0.025-0.227)  0.136 |
|  | Yes | 0.005(-0.025-0.036)  0.729 | 0.02(-0.033-0.063)  0.535 | -0.003(-0.060-0.055)  0.923 |

aEstimated effect size (β- value) of baseline characteristics, with p-test for test of correlation and 95% confidence interval, from multivariate regression analysis.

bAdjusted for, age, sex, and country of participation.

*Abbreviations:* HADS-total, Hospital anxiety and depression scale –total score; HADS-depression, Hospital anxiety and depression scale –depression score; HADS-anxiety, Hospital anxiety and depression scale –anxiety score; CI, 95% confidence interval.

**Table 12**. The estimateda association between the change of psychological distress (HADS) and the change of urinary levels of catecholamines before and after lung cancer diagnosis (**Catecholamine analysis + 3 with extremely high catecholamine measurements** (n=88)).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | Change in  **HADS-total** |  | Change in  **HADS-depression** |  | Change in  **HADS-anxiety** |
| **Change in**  **u-catecholamines** | **Lung cancer diagnosis** | *Beta (CI),*  *p-value*b |  | *Beta (CI),*  *p-value*b |  | *Beta (CI),*  *p-value*b |
| epinephrine |  |  |  |  |  |  |
|  | No | -0.04(-0.275-0.197)  0.749 |  | -0.02(-0.356-0.307)  0.887 |  | -0.08(-0.483-0.325)  0.708 |
|  | Yes | -0.08(-0.172-0.009)  0.082 |  | -0.045(-0.188-0.098)  0.540 |  | -0.21(-0.380- -0.053)  0.012\* |
| norepinephrine |  |  |  |  |  |  |
|  | No | 0.09(-1.108-1.293)  0.882 |  | -0.13(-1.810-1.558)  0.885 |  | 0.46(-1.587-2.509)  0.665 |
|  | Yes | 0.16(-0.902-0.582)  0.647 |  | -0,57(0.579-1.712)  0,336 |  | -1,36(-2.704-0.025)  0.050\* |

aEstimated effect size (β- value) of baseline characteristics, with p-test for test of correlation.and 95% confidence interval, from multivariate regression analysis.

bAdjusted for, age, sex, and country of participation.

\*p values that reach statistical significance.

*Abbreviations:* HADS total, Hospital anxiety and depression scale –total score; HADS depression, Hospital anxiety and depression scale –depression score; HADS anxiety: Hospital anxiety and depression scale –anxiety score; CI, 95% confidence interval.

**Supplementary figure 3.** Overnight urinary catecholamine levels before and after diagnostic work-up for lung cancer, with 95% CI, p-values corrected for age, sex, and country of participation. (**Catecholamine analysis** without 6 participants where lung cancer diagnosis was confirmed after surgery and therefore the second urinary collection took place after treatment initiation (n=78)).

1. Overnight urinary epinephrine levels
2. Overnight urinary norepinephrine levels

\*Test for interaction between lung cancer diagnosis and change in urinary levels of catecholamines between assessments.

A diagram of a patient's lung cancer

Description automatically generatedA diagram of a patient's lung cancer

Description automatically generateda. b.

References

1. Macdonald, I.A. and D.M. Lake, *An improved technique for extracting catecholamines from body fluids.* J Neurosci Methods, 1985. **13**(3-4): p. 239-48

2. Masi, C.M., et al., *Gender and ethnic differences in urinary stress hormones: the population-based Chicago Health, Aging, and Social Relations Study.* J Appl Physiol (1985), 2004. **97**(3): p. 941-7 DOI: 10.1152/japplphysiol.00256.2004.

3. Darr, R., et al., *Dipping in Ambulatory Blood Pressure Monitoring Correlates With Overnight Urinary Excretion of Catecholamines and Sodium.* J Clin Hypertens (Greenwich), 2016. **18**(9): p. 921-6 DOI: 10.1111/jch.12791.

4. *Birmingham Quality*. June, 2022]; Available from: <https://birminghamquality.org.uk/>.

5. Annunziata, M.A., et al., *Hospital Anxiety and Depression Scale (HADS) accuracy in cancer patients.* Support Care Cancer, 2020. **28**(8): p. 3921-3926 DOI: 10.1007/s00520-019-05244-8.