**SUPPLEMENT**

**Heritability of ALS and association of ALS with psychiatric and cardiovascular disorders estimated from the Danish Registries**

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**table e-1. ICD codes of diseases studied**

|  |  |  |  |
| --- | --- | --- | --- |
| Defined Group | Diagnosis | ICD10 | ICD8 |
| ALSa | Amyotrophic lateral sclerosis or Motor Neuron Disease | G122  | 3480  |
| SCZb | Schizophrenia | F20 | 295.x9 (excluding 295.79) |
| Other psychotic disordersb | Schizophrenia and related disorders | F20-F29 | 295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.83 |
| BPDb | Bipolar disorders | F30-F31 | 296.19, 296.39, 298.19 |
| All mental disorderscAnorexiac | Mood disorders  | F30-F39 | 296.x9 (excluding 296.89), 298.09, 298.19, 300.49, 301.19 |
| All mental disordersc | F00-F99 | 290-315 |
| Anorexiac | F50.0 | 306.50 |
| CVD | A broad definition of heart disease  | I00-I25, I27, I30-I52 | 390-429 |
| MI | A narrow definition, MI only | I21  | 410 |

####  ALS = Amyotrophic lateral sclerosis, SCZ= Schizophrenia, BPD= Bipolar disorders, CVD= Cardiovascular Disease, MI = myocardial infarction. a: age at diagnosis > 16 years. b: age at diagnosis > 10 years. c: age at diagnosis > 1 years.

#### Table e-2. Sex-age matching of controls

| **Days +/- from birth date of case** | **Frequency** | **Percent** | **CumulativeFrequency** | **CumulativePercent** |
| --- | --- | --- | --- | --- |
| 0 | 537 | 9.25 | 537 | 9.3 |
| 1 | 4316 | 74.31 | 4853 | 83.6 |
| 2 | 632 | 10.88 | 5485 | 94.4 |
| 3 | 182 | 3.13 | 5667 | 97.6 |
| 4 | 65 | 1.12 | 5732 | 98.7 |
| 5 | 25 | 0.43 | 5757 | 99.1 |
| 6 | 20 | 0.34 | 5777 | 99.5 |
| 7 | 6 | 0.10 | 5783 | 99.6 |
| 8 | 5 | 0.09 | 5788 | 99.7 |
| 9+a | 20 | 0.34 | 5808 | 100.0 |

#### a: maximum of 47 days

#### table e-3. Year of birth of cases and controls

| **FrequencyColumn %**  | **ALS**  |
| --- | --- |
| **Birth year** | **Control** | **Case** | **Total** |
| 1886-1900 | 5,3000.9 | 530.9 | 5,353 |
| 1901-1920 | 116,81020.1 | 1,16820.1 | 117,978 |
| 1921-1940 | 249,32742.9 | 2,49342.9 | 251,820 |
| 1941-1960 | 176,76330.4 | 1,76830.4 | 178,531 |
| 1961-1980 | 28,8005.0 | 2885.0 | 29,088 |
| 1981-2000 | 3,8000.7 | 380.7 | 3,838 |
| **Total** | **580,800** | **5,808** | **586,608** |

| FrequencyRow % | **Link to mother** | **Link to father** | **Link to both parents** |
| --- | --- | --- | --- |
|  | **Missing** | **Non-missing** | **Missing** | **Non-missing** | **Missing**a | **Non-missing** |
| **control** | 485,43283.6 | 95,36816.4 | 490,40784.4 | 90,39315.6 | 492,89584.9 | 87,90515.1 |
| **case** | 4,90584.4 | 90315.6 | 4,95485.3 | 85414.7 | 4,97285.6 | 83614.4 |
| **Total** | **490,337** | **96,271** | **495,361** | **91,247** | **497,867** | **88,741** |

#### table e-4. Missing/non-missing rates of mother/father identities for ALS cases/controls

a: Missing being missing link to one or both parents

#### table e-5. Numbers of full-siblings identified for cases/controls

| **FrequencyColumn %**  |  |
| --- | --- |
| **Number of siblings**  | **Control** | **Case** | **Total** |
| NA | 492,89584.86 | 4,97285.61 | 497,867 |
| 0 | 25,8784.46 | 2414.15 | 26,119 |
| 1 | 31,4015.41 | 3005.17 | 31,701 |
| 2 | 19,1533.30 | 1853.19 | 19,338 |
| 3 | 7,5401.30 | 631.08 | 7,603 |
| 4 | 2,4760.43 | 290.50 | 2,505 |
| 5 | 8640.15 | 130.22 | 877 |
| 6+ | 5930.10 | 50.09 | 598 |
| **Total** | **580,800** | **5,808** | **586,608** |

**table e-6. Number of children identified for cases/controls**

| **FrequencyColumn %** | **ALS case** |
| --- | --- |
| **Number of children** | **Control** | **Case** | **Total** |
| 0 | 166,23328.6 | 1,74330.0 | 167,976 |
| 1 | 108,32518.7 | 1,10919.1 | 109,434 |
| 2 | 181,22331.2 | 1,77230.5 | 182,995 |
| 3 | 88,35215.2 | 83714.4 | 89,189 |
| 4 | 26,9884.7 | 2604.5 | 27,248 |
| 5 | 6,7951.2 | 711.2 | 6,866 |
| 6+ | 2,8840.5 | 160.3 | 2,900 |
| **Total** | **580,800** | **5,808** | **586,608** |

**table e-7. Number of first-degree relatives identified for cases/controls**

| **FrequencyColumn%**  |  |
| --- | --- |
| **Number of first-degree relatives** | **Control** | **Case** | **Total** |
| 0 | 148,61825.59 | 1,51826.14 | 150,136 |
| 1 | 99,21017.08 | 1,05018.08 | 100,260 |
| 2 | 155,91726.85 | 1,56226.89 | 157,479 |
| 3 | 92,24415.88 | 89215.36 | 93,136 |
| 4 | 45,0397.75 | 4427.61 | 45,481 |
| 5 | 22,0133.79 | 2053.53 | 22,218 |
| 6 | 10,2721.77 | 751.29 | 10,347 |
| 7 | 4,3670.75 | 370.64 | 4,404 |
| 8 | 1,7710.30 | 120.21 | 1,783 |
| 9 | 7850.14 | 80.14 | 793 |
| 10+ | 5640.10 | 70.12 | 571 |
| **Total** | **580,800** | **5,808** | **586,608** |

**table e-8A-D. Disease/disorder counts in each relative type of ALS cases and controls, and risk ratios for ALS cases compared to ALS controls**

**table e-8A (Mothers)**

| **Count** | **No record of given disorder in mothers** | **Mother is recorded as having given disorder** |  |
| --- | --- | --- | --- |
| **% of ALS Control or Case Count** | **Control** | **Case** | **Total** | **Control** | **Case** | **Total** | **Risk ratio** |
| **ALS** | 95,22499.84 | 89599.11 | 96,119 | 1440.15 | 80.89 | 152 | **5.87****2.89-11.9** |
| **All mental disorders** | 81,35285.3 | 76784.9 | 82,119 | 14,01614.7 | 13615.1 | 14,152 | 1.020.88-1.20 |
| **Schizophrenia** | 95,03399.64 | 89699.22 | 95,929 | 3350.35 | 70.78 | 342 | **2.21****1.05-4.65** |
| **Other psychotic disorders** | 94,04298.6 | 89799.34 | 94,939 | 1,3261.4 | 60.66 | 1,332 | 0.480.21-1.06 |
| **Bipolar Disorder** | 94,61299.2 | 89799.34 | 95,509 | 7560.79 | 60.66 | 762 | 0.840.37-1.88 |
| **Other affective disorders** | 90,31494.7 | 86095.2 | 91,174 | 5,0545.3 | 434.8 | 5,097 | 0.900.67-1.20 |
| **Anorexia** | 95,35299.98 | 90399.94 | 96,255 | 160.02 | 00.06 | 16 | 3.300.20-55.0 |
| **Heart disease** | 50,55653.0 | 48253.9 | 51,038 | 44,81247.0 | 41246.1 | 45,233 | 0.980.91-1.05 |
| **Myocardial infarction** | 86,62990.8 | 82190.9 | 87,450 | 8,7399.2 | 829.1 | 8,821 | 0.990.81-1.22 |

NB 0.5 was added to the case count for anorexia to enable estimation of the risk ratio

**table e-8B (Fathers)**

| **Count** | **No record of given disorder in fathers** | **Father is recorded as having given disorder** |  |
| --- | --- | --- | --- |
| **% of ALS Control or Case Count** | **Control** | **Case** | **Total** | **Control** | **Case** | **Total** | **Risk ratio** |
| **ALS** | 90,21699.8 | 84799.2 | 91,063 | 1770.2 | 70.8 | 184 | **4.19****1.97-8.88** |
| **All mental disorders** | 81,35090.0 | 74487.1 | 82,094 | 9,04310.0 | 11012.9 | 9,153 | **1.29****1.08-1.53** |
| **Schizophrenia** | NA | NA | 91,095 | NA | NA | 152 | NA |
| **Other psychotic disorders** | 89,82099.36 | 84498.8 | 90,664 | 5730.63 | 101.2 | 583 | 1.850.99-3.44 |
| **Bipolar Disorder** | 89,96199.52 | 84799.18 | 90,808 | 4320.48 | 70.82 | 439 | 1.720.82-3.61 |
| **Other affective disorders** | 87,85197.2 | 82196.1 | 88,672 | 2,5422.8 | 333.9 | 2,575 | 1.370.98-1.92 |
| **Anorexia** | 90,393100 | 854100 | 91,247 | 00 | 00 | 0 | \_ |
| **Heart disease** | 45,80650.7 | 44950.6 | 46,255 | 44,58749.3 | 40547.4 | 44,992 | 0.960.90-1.03 |
| **Myocardial infarction** | 75,29083.3 | 71283.4 | 76,002 | 15,10316.7 | 14216.2 | 15,245 | 1.000.86-1.16 |

NA: when the count is fewer than 4 actual numbers cannot be displayed.

NB The risk ratio for anorexia was not calculated since neither cases nor controls had a father recorded as having anorexia.

**table e-8C (Full-siblings)**

| **Count** | **No record of given disorder in full-siblings** | **One or more full-siblings recorded as having given disorder** |  |
| --- | --- | --- | --- |
| **% of ALS Control or Case Count** | **Control** | **Case** | **Total** | **Control** | **Case** | **Total** | **Risk ratio** |
| **ALS** | 61,96299.9 | 58798.7 | 62,549 | 650.1 | 81.3 | 73 | **12.8****6.2-26.6** |
| **All mental disorders** | 543,83398.0 | 5,46198.1 | 549,294 | 11,0892.0 | 1061.9 | 11,195 | 0.950.79-1.15 |
| **Schizophrenia** | 553,91499.81 | 5,55999.86 | 559,473 | 1,0080.18 | 80.14 | 1,016 | 0.790.39-1.59 |
| **Other psychotic disorders** | 553,93199.82 | 5,55299.73 | 559,483 | 9910.18 | 150.27 | 1,006 | 1.510.91-2.51 |
| **Bipolar Disorder** | 554,13299.86 | 5,56199.89 | 559,693 | 7900.14 | 60.11 | 796 | 0.760.34-1.69 |
| **Other affective disorders** | 551,13599.31 | 5,52499.22 | 556,659 | 3,7870.68 | 430.77 | 3,830 | 1.130.84-1.53 |
| **Anorexia** | NA | NA | 560,401 | NA | NA | 88 | NA |
| **Heart disease** | 539,13497.2 | 5,41497.3 | 544,548 | 15,7882.8 | 1532.7 | 15,941 | 0.970.83-1.13 |
| **Myocardial infarction** | 552,61699.58 | 5,54999.68 | 558,165 | 2,3060.42 | 180.32 | 2,324 | 0.780.49-1.24 |

NA: when the count is fewer than 4 actual numbers cannot be displayed.

**table e-8D (Children)**

| **Count** | **No record of given disorder in children** | **Children recorded as having given disorder** |  |
| --- | --- | --- | --- |
| **% of ALS Control or Case Count** | **Control** | **Case** | **Total** | **Control** | **Case** | **Total** | **Risk ratio****95% CI** |
| **ALS** | 414,29099.93 | 4,05099.63 | 418,340 | 2770.07 | 150.37 | 292 | **5.52****3.29-9.28** |
| **All mental disorders** | 326,72878.8 | 3,19078.5 | 329,918 | 87,83921.2 | 87521.5 | 88,714 | 1.020.96-1.08 |
| **Schizophrenia** | 406,95898.2 | 3,97797.8 | 410,935 | 7,6091.8 | 882.2 | 7,697 | 1.180.96-1.45 |
| **Other psychotic disorders** | 407,33298.3 | 3,99498.3 | 411,326 | 7,2351.7 | 711.7 | 7,306 | 1.000.79-1.26 |
| **Bipolar Disorder** | 408,94998.6 | 4,00998.6 | 412,958 | 5,6181.4 | 561.4 | 5,674 | 1.020.78-1.32 |
| **Other affective disorders** | 385,62793.0 | 3,80193.5 | 389,428 | 28,9407.0 | 2646.5 | 29,204 | 0.930.83-1.05 |
| **Anorexia** | 413,14899.7 | 4,05399.7 | 417,201 | 1,4190.34 | 120.30 | 1,431 | 0.860.49-1.52 |
| **Heart disease** | 326,41578.7 | 3,22579.3 | 329,640 | 88,15221.3 | 84020.7 | 88,992 | 0.970.91-1.03 |
| **Myocardial infarction** | 403,95397.4 | 3,97197.7 | 407,924 | 10,6142.6 | 942.3 | 10,708 | 0.900.74-1.10 |

**table e-9. Estimates of heritability of ALS based on relative risk of ALS for different type of relatives, including sensitivity analyses**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Mothers** | **Fathers** | **Siblings** | **Children** | **1st degree** | **Sensitivity**a |
| Risk for relatives of controls (%) | 0.15 | 0.20 | 0.10 | 0.07 | 0.15 | 0.15 |
| Risk for relatives of cases (%) | 0.89 | 0.82 | 1.34 | 0.37 | 0.88 | 0.70 |
| Increased risk of ALS in relatives of those with ALS | 5.87 | 4.19 | 12.83 | 5.52 | 5.78 | 4.57 |
| s.e. of estimate | 0.36 | 0.39 | 0.38 | 0.27 | 0.17 | 0.19 |
| 95% Confidence Interval | 2.89-11.9 | 1.97-8.88 | 6.18-26.6 | 3.29-9.28 | 4.17-8.00 | 3.17-6.58 |
| Estimate of heritability, assuming lifetime risk 0.25% | 0.44 | 0.34 | 0.68 | 0.42 | 0.43 | 0.36 |
| s.e. of estimate | 0.11 | 0.10 | 0.13 | 0.08 | 0.05 | 0.05 |
| 95% Confidence Interval | 0.24-0.66 | 0.15-0.56 | 0.45-0.95 | 0.28-0.58 | 0.34-0.53 | 0.27-0.47 |
| Estimate of heritability, assuming lifetime risk 0.20% | 0.42 | 0.33 | 0.65 | 0.40 | 0.41 | 0.36 |
| s.e. of estimate | 0.1 | 0.1 | 0.12 | 0.07 | 0.05 | 0.05 |
| 95% Confidence Interval | 0.23-0.62 | 0.14-0.53 | 0.43-0.90 | 0.26-0.55 | 0.32-0.50 | 0.26-0.45 |
| Estimate of heritability, assuming lifetime risk 0.30% | 0.45 | 0.35 | 0.71 | 0.44 | 0.45 | 0.38 |
| s.e. of estimate | 0.11 | 0.11 | 0.13 | 0.08 | 0.05 | 0.05 |
| 95% Confidence Interval | 0.25-0.69 | 0.16-0.59 | 0.47-0.99 | 0.29-0.60 | 0.35-0.55 | 0.28-0.49 |

**figure e-1. Distribution of year of first ALS diagnosis**



NB. At the time of establishment of the registry some ALS cases may have been prevalent rather than incident.

We found that annual incidence was higher in later years consistent with the previously reported increase in age-adjusted incidence of 1.6% annually after 1982(1). This increase in reported cases approximately coincides with the addition of outpatient records in 1994.

**figure e-2. Distribution of Age at time of first ALS diagnosis**



NB. At the time of establishment of the registry some ALS cases may have been prevalent rather than incident. Median 67.1 years, interquartile range 58.4 to 72 years.

1. Seals RM, Hansen J, Gredal O, Weisskopf MG**.** Age-period-cohort analysis of trends in amyotrophic lateral sclerosis in Denmark, 1970-2009. Am J Epidemiol. 2013;178(8):1265-71.