**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** | **Cumulative Frequency** | **Cumulative Percent** |
| --- | --- | --- | --- | --- |
| 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

| **Frequency Column %** | **ALS** | | |
| --- | --- | --- | --- |
| **Birth year** | **Control** | **Case** | **Total** |
| 1886-1900 | 5,300 0.9 | 53 0.9 | 5,353 |
| 1901-1920 | 116,810 20.1 | 1,168 20.1 | 117,978 |
| 1921-1940 | 249,327 42.9 | 2,493 42.9 | 251,820 |
| 1941-1960 | 176,763 30.4 | 1,768 30.4 | 178,531 |
| 1961-1980 | 28,800 5.0 | 288 5.0 | 29,088 |
| 1981-2000 | 3,800 0.7 | 38 0.7 | 3,838 |
| **Total** | **580,800** | **5,808** | **586,608** |

| Frequency  Row % | **Link to mother** | | **Link to father** | | **Link to both parents** | |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Missing** | **Non-missing** | **Missing** | **Non-missing** | **Missing**a | **Non-missing** |
| **control** | 485,432 83.6 | 95,368 16.4 | 490,407 84.4 | 90,393 15.6 | 492,895  84.9 | 87,905  15.1 |
| **case** | 4,905 84.4 | 903 15.6 | 4,954 85.3 | 854 14.7 | 4,972  85.6 | 836  14.4 |
| **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

| **Frequency Column %** | |  | |
| --- | --- | --- | --- |
| **Number of siblings** | **Control** | **Case** | **Total** |
| NA | 492,895 84.86 | 4,972 85.61 | 497,867 |
| 0 | 25,878 4.46 | 241 4.15 | 26,119 |
| 1 | 31,401 5.41 | 300 5.17 | 31,701 |
| 2 | 19,153 3.30 | 185 3.19 | 19,338 |
| 3 | 7,540 1.30 | 63 1.08 | 7,603 |
| 4 | 2,476 0.43 | 29 0.50 | 2,505 |
| 5 | 864 0.15 | 13 0.22 | 877 |
| 6+ | 593 0.10 | 5 0.09 | 598 |
| **Total** | **580,800** | **5,808** | **586,608** |

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

| **Frequency Column %** | | **ALS case** | |
| --- | --- | --- | --- |
| **Number of children** | **Control** | **Case** | **Total** |
| 0 | 166,233 28.6 | 1,743 30.0 | 167,976 |
| 1 | 108,325 18.7 | 1,109 19.1 | 109,434 |
| 2 | 181,223 31.2 | 1,772 30.5 | 182,995 |
| 3 | 88,352 15.2 | 837 14.4 | 89,189 |
| 4 | 26,988 4.7 | 260 4.5 | 27,248 |
| 5 | 6,795 1.2 | 71 1.2 | 6,866 |
| 6+ | 2,884 0.5 | 16 0.3 | 2,900 |
| **Total** | **580,800** | **5,808** | **586,608** |

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

| **Frequency Column%** |  | | |
| --- | --- | --- | --- |
| **Number of first-degree relatives** | **Control** | **Case** | **Total** |
| 0 | 148,618 25.59 | 1,518 26.14 | 150,136 |
| 1 | 99,210 17.08 | 1,050 18.08 | 100,260 |
| 2 | 155,917 26.85 | 1,562 26.89 | 157,479 |
| 3 | 92,244 15.88 | 892 15.36 | 93,136 |
| 4 | 45,039 7.75 | 442 7.61 | 45,481 |
| 5 | 22,013 3.79 | 205 3.53 | 22,218 |
| 6 | 10,272 1.77 | 75 1.29 | 10,347 |
| 7 | 4,367 0.75 | 37 0.64 | 4,404 |
| 8 | 1,771 0.30 | 12 0.21 | 1,783 |
| 9 | 785 0.14 | 8 0.14 | 793 |
| 10+ | 564 0.10 | 7 0.12 | 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** | 95,224  99.84 | 895  99.11 | 96,119 | 144  0.15 | | 8  0.89 | 152 | **5.87**  **2.89-11.9** |
| **All mental disorders** | 81,352  85.3 | 767  84.9 | 82,119 | 14,016  14.7 | | 136  15.1 | 14,152 | 1.02  0.88-1.20 |
| **Schizophrenia** | 95,033  99.64 | 896  99.22 | 95,929 | 335  0.35 | | 7  0.78 | 342 | **2.21**  **1.05-4.65** |
| **Other psychotic disorders** | 94,042  98.6 | 897  99.34 | 94,939 | 1,326  1.4 | | 6  0.66 | 1,332 | 0.48  0.21-1.06 |
| **Bipolar Disorder** | 94,612  99.2 | 897  99.34 | 95,509 | 756  0.79 | | 6  0.66 | 762 | 0.84  0.37-1.88 |
| **Other affective disorders** | 90,314  94.7 | 860  95.2 | 91,174 | 5,054  5.3 | | 43  4.8 | 5,097 | 0.90  0.67-1.20 |
| **Anorexia** | 95,352  99.98 | 903  99.94 | 96,255 | 16  0.02 | | 0  0.06 | 16 | 3.30  0.20-55.0 |
| **Heart disease** | 50,556  53.0 | 482  53.9 | 51,038 | 44,812  47.0 | | 412  46.1 | 45,233 | 0.98  0.91-1.05 |
| **Myocardial infarction** | 86,629  90.8 | 821  90.9 | 87,450 | 8,739  9.2 | | 82  9.1 | 8,821 | 0.99  0.81-1.22 |

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** | 90,216  99.8 | 847  99.2 | 91,063 | 177  0.2 | | 7  0.8 | 184 | **4.19**  **1.97-8.88** |
| **All mental disorders** | 81,350  90.0 | 744  87.1 | 82,094 | 9,043  10.0 | | 110  12.9 | 9,153 | **1.29**  **1.08-1.53** |
| **Schizophrenia** | NA | NA | 91,095 | NA | | NA | 152 | NA |
| **Other psychotic disorders** | 89,820  99.36 | 844  98.8 | 90,664 | 573  0.63 | | 10  1.2 | 583 | 1.85  0.99-3.44 |
| **Bipolar Disorder** | 89,961  99.52 | 847  99.18 | 90,808 | 432  0.48 | | 7  0.82 | 439 | 1.72  0.82-3.61 |
| **Other affective disorders** | 87,851  97.2 | 821  96.1 | 88,672 | 2,542  2.8 | | 33  3.9 | 2,575 | 1.37  0.98-1.92 |
| **Anorexia** | 90,393  100 | 854  100 | 91,247 | 0  0 | | 0  0 | 0 | \_ |
| **Heart disease** | 45,806  50.7 | 449  50.6 | 46,255 | 44,587  49.3 | | 405  47.4 | 44,992 | 0.96  0.90-1.03 |
| **Myocardial infarction** | 75,290  83.3 | 712  83.4 | 76,002 | 15,103  16.7 | | 142  16.2 | 15,245 | 1.00  0.86-1.16 |

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** | 61,962  99.9 | 587  98.7 | 62,549 | 65  0.1 | | 8  1.3 | 73 | **12.8**  **6.2-26.6** |
| **All mental disorders** | 543,833  98.0 | 5,461  98.1 | 549,294 | 11,089  2.0 | | 106  1.9 | 11,195 | 0.95  0.79-1.15 |
| **Schizophrenia** | 553,914  99.81 | 5,559  99.86 | 559,473 | 1,008  0.18 | | 8  0.14 | 1,016 | 0.79  0.39-1.59 |
| **Other psychotic disorders** | 553,931  99.82 | 5,552  99.73 | 559,483 | 991  0.18 | | 15  0.27 | 1,006 | 1.51  0.91-2.51 |
| **Bipolar Disorder** | 554,132  99.86 | 5,561  99.89 | 559,693 | 790  0.14 | | 6  0.11 | 796 | 0.76  0.34-1.69 |
| **Other affective disorders** | 551,135  99.31 | 5,524  99.22 | 556,659 | 3,787  0.68 | | 43  0.77 | 3,830 | 1.13  0.84-1.53 |
| **Anorexia** | NA | NA | 560,401 | NA | | NA | 88 | NA |
| **Heart disease** | 539,134  97.2 | 5,414  97.3 | 544,548 | 15,788  2.8 | | 153  2.7 | 15,941 | 0.97  0.83-1.13 |
| **Myocardial infarction** | 552,616  99.58 | 5,549  99.68 | 558,165 | 2,306  0.42 | | 18  0.32 | 2,324 | 0.78  0.49-1.24 |

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** | 414,290 99.93 | 4,050  99.63 | 418,340 | | 277  0.07 | 15  0.37 | 292 | **5.52**  **3.29-9.28** |
| **All mental disorders** | 326,728 78.8 | 3,190 78.5 | 329,918 | | 87,839  21.2 | 875  21.5 | 88,714 | 1.02  0.96-1.08 |
| **Schizophrenia** | 406,958 98.2 | 3,977  97.8 | 410,935 | | 7,609  1.8 | 88  2.2 | 7,697 | 1.18  0.96-1.45 |
| **Other psychotic disorders** | 407,332 98.3 | 3,994  98.3 | 411,326 | | 7,235  1.7 | 71  1.7 | 7,306 | 1.00  0.79-1.26 |
| **Bipolar Disorder** | 408,949  98.6 | 4,009  98.6 | 412,958 | | 5,618  1.4 | 56  1.4 | 5,674 | 1.02  0.78-1.32 |
| **Other affective disorders** | 385,627  93.0 | 3,801  93.5 | 389,428 | | 28,940  7.0 | 264  6.5 | 29,204 | 0.93  0.83-1.05 |
| **Anorexia** | 413,148  99.7 | 4,053  99.7 | 417,201 | | 1,419  0.34 | 12  0.30 | 1,431 | 0.86  0.49-1.52 |
| **Heart disease** | 326,415  78.7 | 3,225  79.3 | 329,640 | | 88,152  21.3 | 840  20.7 | 88,992 | 0.97  0.91-1.03 |
| **Myocardial infarction** | 403,953 97.4 | 3,971  97.7 | 407,924 | | 10,614  2.6 | 94  2.3 | 10,708 | 0.90  0.74-1.10 |

**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.