*Twin Research and Human Genetics*

Shared genetic factors in the co-occurrence of depression and fatigue

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Supplementary Table S1: Cross-tabulationa of depression and fatigue status within twin pairs

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Non-depressed | MiDD | MDD | Total |
| Complete twin pairs | Non-fatigued | 784 | 61 | 14.5 | 859.5 |
| Fatigued | 301.5 | 48.5 | 10.5 | 360.5 |
| Total | 1085.5 | 109.5 | 25 | 1220 |
| MZTotal | Non-fatigued | 411 | 29.5 | 5.5 | 446 |
| Fatigued | 157.5 | 31.5 | 8 | 197 |
| Total | 568.5 | 61 | 13.5 | 643 |
| MZfemale | Non-fatigued | 307.5 | 19 | 5 | 331.5 |
| Fatigued | 124 | 28.5 | 7 | 159.5 |
| Total | 431.5 | 47.5 | 12 | 491 |
| MZmale | Non-fatigued | 103.5 | 10.5 | 0.5 | 114.5 |
| Fatigued | 33.5 | 3 | 1 | 37.5 |
| Total | 137 | 13.5 | 1.5 | 152 |
| DZssTotal | Non-fatigued | 212 | 16.5 | 6 | 234.5 |
| Fatigued | 90.5 | 10.5 | 0.5 | 101.5 |
| Total | 302.5 | 27 | 6.5 | 336 |
| DZssfemale | Non-fatigued | 164.5 | 15 | 4 | 183.5 |
| Fatigued | 70 | 9 | 0.5 | 79.5 |
| Total | 234.5 | 24 | 4.5 | 263 |
| DZssmale | Non-fatigued | 47.5 | 1.5 | 2 | 51 |
| Fatigued | 20.5 | 1.5 | 0 | 22 |
| Total | 68 | 3 | 2 | 73 |
| DZosfemale-male | Non-fatigued | 163 | 11 | 5 | 179 |
| Fatigued | 54 | 7 | 1 | 62 |
| Total | 217 | 18 | 6 | 241 |
| DZosmale-female | Non-fatigued | 159 | 19 | 1 | 179 |
| Fatigued | 53 | 6 | 3 | 62 |
| Total | 212 | 25 | 4 | 241 |

aTables were made symmetrical in same-sex twin pairs by averaging over using either twin 1 or twin 2 as proband. For example, within the complete twin pairs there was 298 twin pairs where twin 1 was fatigued and twin 2 was non-depressed and 305 twin pairs where twin 2 was fatigued and twin 1 was non-depressed. Therefore, the cross-tabulation averaging over twin 1 or twin 2 as proband is (298+305)/2=301.5.

Supplementary Table S2: Relative riska of depression and fatigue in males and females.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Proband–co-twin | Depressed–non-fatigued | Depressed–fatigued | Fatigued–non-depressed | Fatigued–depressed |
| Complete cohort (n = 1220) | 0.78 (0.67-0.91) | 1.58 (1.28-1.96) | 0.92 (0.87-0.96) | 1.86 (1.36-2.56) |
| MZ total (n = 643) | 0.65 (0.51-0.83) | 1.91 (1.49-2.46) | 0.87 (0.80-0.94) | 2.56 (1.67-3.90) |
| MZ female (n = 491) | 0.57 (0.41-0.78) | 2.08 (1.61-2.68) | 0.84 (0.77-0.92) | 3.07 (1.90-4.98) |
| MZ male (n = 152) | 0.97 (0.71-1.34) | 1.09 (0.45-2.65) | 0.99 (0.87-1.12) | 1.11 (0.38-3.28) |
| DZss total (n = 336) | 0.96 (0.75-1.23) | 1.10 (0.66-1.84) | 0.99 (0.91-1.07) | 1.13 (0.57-2.23) |
| DZss female (n = 262) | 0.95 (0.72-1.25) | 1.12 (0.64-1.95) | 0.98 (0.89-1.08) | 1.15 (0.55-2.40) |
| DZss male (n = 73) | 1.00 (0.55-1.82) | 1.00 (0.25-3.98) | 1.00 (0.87-1.15) | 0.99 (0.16-6.30) |
| DZos female-male (n=241) | 0.88 (0.67-1.16) | 1.37 (0.77-2.46) | 0.96 (0.86-1.06) | 0.96 (0.86-1.08) |
| DZos male-female (n=241) | 0.92 (0.71-1.19) | 1.34 (0.73-2.47) | 1.44 (0.65-3.21) | 1.30 (0.62-2.70) |

aRelative risks were calculated with respect to non-depressed or non-fatigued status in twin 1.

Supplementary Table S3: Relative riska of depression and fatigue within monozygotic (MZ), same-sex dizygotic (DZss), and opposite-sex dizygotic (DZos) twin pairs.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Proband–co-twin | MZ (n = 643) | DZss (n = 336) | DZos (n = 241)(Female-Male) | DZos (n = 241)(Male-Female) |
| MiDD–non-fatigued | 0.67 (0.52-0.87) | 0.87 (0.64-1.18) | 1.01 (0.80-1.28) | 0.81 (0.56-1.19) |
| MiDD–fatigued | 1.86 (1.41-2.45) | 1.31 (0.79-2.16) | 0.96 (0.46-2.00) | 1.56 (0.84-2.92) |
| MDD–non-fatigued | 0.56 (0.30-1.07) | 1.22 (0.89-1.66) | 0.33 (0.06-1.82) | 1.11 (0.77-1.60) |
| MDD–fatigued | 2.14 (1.35-3.39) | 0.48 (0.08-2.98) | 3.00 (1.63-5.53) | 0.67 (0.11-4.07) |
| Fatigued–MiDD | 2.41 (1.51-3.86) | 1.48 (0.71-3.09) | 1.84 (0.75-4.53) | 0.91 (0.38-2.18) |
| Fatigued–MDD | 3.29 (1.12-9.61) | 0.39 (0.05-3.17) | 0.58 (0.07-4.85) | 8.66 (0.92-81.74) |

aRelative risks were calculated with respect to non-depressed or non-fatigued status in twin 1.

Supplementary Table S4: Polychoric correlations with their 95% confidence intervals for fatigue and depression in twin pairs according to zygosity.

|  |
| --- |
| Minor depression (non-depressed, MiDD) |
|  | Twin 1 | Twin 2 |
| MiDD | Fatigue | MiDD | Fatigue |
| Monozygotic twin pairs (n = 643 pairs) |
| Twin 1 | MiDD | 1.00 |  |  |  |
| Fatigue | 0.49 (0.35-0.64)a | 1.00 |  |  |
| Twin 2 | MiDD | 0.37 (0.17-0.56)b | 0.32 (0.16-0.47)c | 1.00 |  |
| Fatigue | 0.32 (0.16-0.49)c | 0.43 (0.31-0.54)b | 0.42 (0.28-0.57)a | 1.00 |
| Dizygotic twin pairs (n = 577 pairs) |
| Twin 1 | MiDD | 1.00 |  |  |  |
| Fatigue | 0.49 (0.34-0.64)a | 1.00 |  |  |
| Twin 2 | MiDD | 0.21 (-0.04-0.45)b | 0.18 (-0.01-0.37)c | 1.00 |  |
| Fatigue | 0.03 (-0.17-0.22)c | 0.14 (0.001-0.28)b | 0.54 (0.40-0.69)a | 1.00 |
| **Major depression (non-depressed, MDD)** |
|  | Twin 1 | Twin 2 |
| MDD | Fatigue | MDD | Fatigue |
| Monozygotic twin pairs (n = 643 pairs) |
| Twin 1 | MDD | 1.00 |  |  |  |
| Fatigue | 0.36 (0.12-0.59)a | 1.00 |  |  |
| Twin 2 | MDD | 0.46 (-0.01-0.93)b | 0.43 (0.15-0.70)c | 1.00 |  |
| Fatigue | 0.28 (0.03-0.52)c | 0.43 (0.31-0.54)b | -a | 1.00 |
| Dizygotic twin pairs (n = 577 pairs) |
| Twin 1 | MDD | 1.00 |  |  |  |
| Fatigue | 0.47 (0.20-0.74)a | 1.00 |  |  |
| Twin 2 | MDD | -b | -0.32 (-0.67-0.02)c | 1.00 |  |
| Fatigue | 0.14 (-0.18-0.46)c | 0.14 (0.001-0.28)b | 0.56 (0.33-0.79)a | 1.00 |
| **Three-category depression (non-depressed, MiDD, MDD)** |
|  | Twin 1 | Twin 2 |
| Depression | Fatigue | Depression | Fatigue |
| Monozygotic twin pairs (n = 643 pairs) |
| Twin 1 | Depression | 1.00 |  |  |  |
| Fatigue | 0.46 (0.33-0.59)a | 1.00 |  |  |
| Twin 2 | Depression | 0.48 (0.33-0.62)b | 0.36 (0.22-0.50)c | 1.00 |  |
| Fatigue | 0.32 (0.18-0.47)c | 0.43 (0.31-0.54)b | 0.51 (0.39-0.64)a | 1.00 |
| Dizygotic twin pairs (n = 577 pairs) |
| Twin 1 | Depression | 1.00 |  |  |  |
| Fatigue | 0.50 (0.36-0.64)a | 1.00 |  |  |
| Twin 2 | Depression | 0.24 (0.04-0.43)b | 0.05 (-0.13-0.23)c | 1.00 |  |
| Fatigue | 0.06 (-0.12-0.24)c | 0.14 (0.001-0.28)b | 0.57 (0.45-0.70)a | 1.00 |

aPhenotypic correlation between depression and fatigue. bTwin correlation. cCross-twin cross-trait correlation

Supplementary Table S5: Bivariate heritability model fits

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Model | Minus 2 log likelihood | χ2 | Δ df | P-value | AIC |
| MiDD |
| ACE | 4228.32 |  |  |  | -5401.68 |
| **AE** | **4228.71** | **0.39** | **3** | **0.94** | **-5407.29** |
| CE | 4239.54 | 11.21 | 3 | 0.01 | -5396.46 |
| E | 4295.28 | 66.96 | 6 | 1.71 × 10-12 | -5346.72 |
| ADE | 4227.72 | -0.61 | 0 | 1.00 | -5402.28 |
| MDD |
| ACE | 3330.32 |  |  |  | -5961.68 |
| **AE** | **3330.62** | **0.30** | **3** | **0.96** | **-5967.38** |
| CE | 3342.63 | 12.32 | 3 | 0.01 | -5955.37 |
| E | 3381.46 | 51.14 | 6 | 2.78 × 10-9 | -5922.50 |
| ADE | 3327.68 | -2.64 | 0 | 1.00 | -5964.33 |
| Three-category depression |
| ACE | 4647.74 |  |  |  | -5080.26 |
| **AE** | **4649.28** | **1.54** | **3** | **0.67** | **-5084.72** |
| CE | 4661.68 | 13.94 | 3 | 3.00 × 10-3 | -5072.32 |
| E | 4724.88 | 77.14 | 6 | 1.39 × 10-14 | -5015.12 |
| ADE | 4647.42 | -0.32 | 0 | 1.00 | -5080.58 |

Note: Fit statistics are compared to ACE model and best fitting models are indicated in bold.

χ2: likelihood-ratio chi-squared test; Δ df: difference in degrees of freedom.

Supplementary Table S6: co-twin control of minor depression and fatigue [na].

|  |  |  |
| --- | --- | --- |
| Sample | Risk factor: MiDDOutcome: fatigue | Risk factor: fatigueOutcome: MiDD |
| General Population | 7.39 (4.33-12.61) [1,247] | 7.39 (4.33-12.61) [1,247] |
| Discordant DZ | 5.75 (2.89-11.48) [78] | 5.47 (2.58-11.59) [201] |
| Discordant MZ | 1.77 (0.96-3.25) [85] | 1.83 (0.97-3.46) [192] |

MiDD: Minor depressive disorder. aWithin the General Population sample n is is the number of individuals, while within the Discordant MZ and DZ samples n is the number of discordant twin pairs.

Supplementary Table S7: Cross-tabulationa of depression and fatigue status within twin pairs independent of overlapping symptoms

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Non-depressed | MiDD | MDD | Total |
| MZTotal | Non-fatigued | 264.5 | 4.5 | 0 | 269 |
| Fatigued | 34 | 2 | 0 | 36 |
| Total | 298.5 | 6.5 | 0 | 305 |
| DZssTotal | Non-fatigued | 126.5 | 2.5 | 0 | 129 |
| Fatigued | 24 | 1 | 0 | 25 |
| Total | 150.5 | 3.5 | 0 | 154 |
| DZosfemale-male | Non-fatigued | 90 | 2 | 0 | 92 |
| Fatigued | 10 | 1 | 0 | 11 |
| Total | 100 | 3 | 0 | 103 |
| DZosmale-female | Non-fatigued | 84 | 4 | 0 | 88 |
| Fatigued | 15 | 0 | 0 | 15 |
| Total | 99 | 4 | 0 | 103 |

aTables were made symmetrical in same-sex twin pairs by averaging over using either twin 1 or twin 2 as proband.

Supplementary Table S8: Relative riska of depression and fatigue estimated independently of overlapping symptoms within monozygotic (MZ), same-sex dizygotic (DZss), and opposite-sex dizygotic (DZos) twin pairs.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Proband - co-twin | MZ (n = 319) | DZss (n = 160) | DZos (n = 119)(Female-Male) | DZos (n = 119)(Male-Female) |
| Depressed -non-fatigued | 0.78 (0.47-1.31) | 0.85 (0.44-1.65) | 1.18 (1.08-1.28) | 0.74 (0.33-1.65) |
| Depressed - fatigued | 2.70 (0.82-8.93) | 1.79 (0.33-9.77) | 0 | 3.33 (0.61-18.34) |
| Fatigued - non-depressed | 0.96 (0.89-1.04) | 0.98 (0.90-1.06) | 0.93 (0.41-42.45) | 1.05 (1.00-1.10) |
| Fatigued - depressed | 3.32 (0.65-16.93) | 2.06 (0.21-20.16) | 4.18 (0.41-42.45) | 0 |

aRelative risks were calculated with respect to non-depressed or non-fatigued status in twin 1.

Supplementary Table S9: Polychoric correlations with their 95% confidence intervals for fatigue and depression independent of overlapping symptoms in twin pairs according to zygosity.

|  |  |  |
| --- | --- | --- |
|  | Twin 1 | Twin 2 |
| MiDD | Fatigue | MiDD | Fatigue |
| Monozygotic twin pairs (n = 643 pairs) |
| Twin 1 | MiDD | 1.00 |  |  |  |
| Fatigue | 0.38 (0.01-0.74)a | 1.00 |  |  |
| Twin 2 | MiDD | -b | 0.37 (-0.05-0.80)c | 1.00 |  |
| Fatigue | 0.23 (-0.18-0.65)c | 0.20 (-0.07-0.48)b | -0.77 (-1.00-1.00)a | 1.00 |
| Dizygotic twin pairs (n = 577 pairs) |
| Twin 1 | MiDD | 1.00 |  |  |  |
| Fatigue | 0.50 (0.19-0.80)a | 1.00 |  |  |
| Twin 2 | MiDD | -b | 0.16 (-0.38-0.71)c | 1.00 |  |
| Fatigue | 0.08 (-0.33-0.49)c | 0.10 (-0.18-0.38)b | 0.40 (-0.04-0.85)a | 1.00 |

aPhenotypic correlation between depression and fatigue. bTwin correlation. cCross-twin cross-trait correlation.



Figure S1: Path diagram of the bivariate Cholesky model variance estimates (with their 95% confidence intervals) for minor depressive disorder (MiDD) and fatigue. The observed traits are shown in the rectangles. Similarly, the latent variables (additive genetic factors: A, and unique environmental factors: E) are depicted by circles. The arrows depict the relationship between the variables. The genetic and environmental correlations between MiDD and fatigue were 0.76 (0.52-1.00) and 0.29 (0.11-0.46), respectively.



Figure S2: Path diagram of the bivariate Cholesky model variance estimates (with their 95% confidence intervals) for major depressive disorder (MDD) and fatigue. The observed traits are shown in the rectangles. Similarly, the latent variables (additive genetic factors: A, and unique environmental factors: E) are depicted by circles. The arrows depict the relationship between the variables. The genetic and environmental correlations between MDD and fatigue were 0.57 (0.21-1.00) and 0.46 (0.09-0.52), respectively.



Figure S3: Path diagram of the bivariate Cholesky model variance estimates (with their 95% confidence intervals) for three-category depression (non-depressed, MiDD, MDD) and fatigue. The observed traits are shown in the rectangles. Similarly, the latent variables (additive genetic factors: A, and unique environmental factors: E) are depicted by circles. The arrows depict the relationship between the variables. The genetic and environmental correlations between MiDD and fatigue were 0.71 (0.51-0.93) and 0.35 (0.18-0.51), respectively.



Figure S4: Path diagram of the bivariate Cholesky model variance estimates (with their 95% confidence intervals) for depression and fatigue independent of their overlapping symptomology. The observed traits are shown in the rectangles. Similarly, the latent variables (additive genetic factors: A, and unique environmental factors: E) are depicted by circles. The arrows depict the relationship between the variables. The genetic and environmental correlations between MiDD and fatigue were 1.00 (0.43-1.00) and 0.11 (0.00-0.43), respectively.