**Supplementary Materials**

**Familial liability to psychosis is a risk factor for multimorbidity in people with psychotic disorders and their unaffected siblings**

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# 1. Supplementary Methods

In Genetic Risk and Outcome of Psychosis (GROUP) project, patients were identified through clinicians working in regional psychosis departments or academic centers, whose caseload was screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services either as outpatients or inpatients were recruited for the study from 2007 to 2008. Persons identified as potentially eligible were given a detailed explanation of the study procedures and were asked for informed consent for detailed assessment and for contacting their first-degree family members (brothers, sisters, parents). Controls were selected through a system of random mailings to addresses in the catchment areas of the cases [1].

The selection of the sample is depicted in Supplementary Figure S1. We followed sample selection procedure for 3684 participants, case by case, to retrieve information regarding lifetime diseases and complaints. Among them, 3468 participants filled in the Medical Questionnaire (MQ). We thoroughly scrutinized the MQ file, containing medical disease related data collected through a ‘Medische Vragenlijst (medical questionnaire)’. The checklist section contained information on 38 medical conditions in the form of ‘present/absent’. The narrative section provided a detailed medical, surgical, and medication history, as well as remarks on checklist status. We further retrieved compatible disease relevant information from narrative questions. Additionally, medication history was reviewed by the Anatomical Therapeutic Chemical (ATC) classification system and furthers the ICD-10 to obtain additional information to confirm evidence of the specific entities of the diseases derived from the medical questionnaire and registered diagnoses of the participants. According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) codes, and information either from the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) or the Comprehensive Assessment of Symptoms and History (CASH), five groups of psychiatric disorders (psychotic: including schizophrenia, schizoaffective and delusional; mood; anxiety and/or eating; substance, and others) were formed regarding patients, siblings and controls, respectively, at baseline. After gathering all information, we performed crosschecking across data domains to avoid duplication.

# 2. Supplementary Results

The observed prevalence of multimorbidity of complaints, physical health and lifetime diseases across familial liability groups by gender and age groups simultaneously are demonstrated in Supplementary Figures S2-S4. The comparisons between patient-control, sibling-control and patient-sibling on individual complaints are presented in Supplementary Table S1. More specifically, presence of the complaints angina pectoris, palpitation, short of breath, and dizziness were significantly different across the sibling-control, patient-control and patient-sibling groups (Supplementary Table S1). An overview of the group frequencies of all individual diseases is presented in Supplementary Table S2. However, a meaningful statistical analysis was not possible for the individual lifetime diseases due to very low numbers of subjects per group. Instead, the domains of lifetime diseases were compared across different familial liability subgroups, and are presented in Supplementary Table S3. Several domains of disease, such as diseases of the nervous system (35%), congenital mal/del-formations, and chromosomal abnormalities (12%), observed a *priori* in schizophrenia patients, also showed a significantly higher frequency compared to siblings and controls (Supplementary Table S3). The most prevalent lifetime diseases in patients, siblings and controls were concussion (24.4%, 15.3% and 19.3%), eczema (18.9%, 16.3% and 18.0%), migraine (8.8%, 10.1% and 10.2%), tonsillitis (9.3%, 12.5% and 8.1%), congenital defects (12.0%, 8.8% and 6.4%) and mood disorders (5.5%, 11.9% and 9.2%). The presence of concussion, mood disorders and congenital defects differed significantly between patients, and controls and siblings. Other diseases had an occurrence of less than 5% across the familial liability groups (Supplementary Table S4). Other schizophrenia studies showed different commonly co-occurring diseases such as hypertension, impaired glucose tolerance, diabetes, cardiovascular diseases, chronic infections and lung diseases, resulting overall in premature death, and particularly at a younger age [2-7]. Their results suggested a different profile of multimorbid diseases in younger patients with schizophrenia, who were already suffering from multiple medical conditions upon onset of their disease.

**Genetic Risk and Outcome of psychosis (GROUP) Study** **(N=3684)**

Controls (N=589)

Siblings (N=1057)

Patients (N=1119)

Parents (N=919)

Eligibility established by filling Medical Questionnaire **(N=3468)**

Controls (N=566)

Siblings (N=1024)

Patients (N=982)

Parents (N=896)

Participants included for the present study **(N=2584)**

**Controls (N=566)**

**Siblings (N=994)**

**Patients (N=1024**)

30 siblings and 12 parents were later reported as patients due to the diagnosis of non-affective psychosis

4 DSM-IV psychiatric diseases, validated by CASH and SCAN

Surgical, medical and self-reported details were thoroughly scrutinized case by case to retrieve additional diseases

38 self-reported somatic conditions were matched to the additional information to avoid overlap

Number of participants filled the specific parts of the questionnaire:

Surgical remarks (n=411)

Surgery specified (n=2,118)

Medical remarks (n=406)

Medication specified (n=1,613)

Self-reported status (n=996)

102 somatic diseases, retrieved through ATC classification system and specified by ICD-10 codes

**Multimorbidity (≥2) was counted based on 125 and 121 lifetime diseases**

19 conditions considered as complaints

**Multimorbidity (≥2) was counted based on 19 self-reported complaints**

19 conditions considered as lifetime diseases

**Medical Assessment**

Parents (N=884) were excluded from the study

# Supplementary Figure S1: Flowchart of inclusion of participants and retrieval of information on complaints and diseases.

# Supplementary Figure S2: Prevalence of multimorbidity of complaints across familial liability groups by gender and age groups simultaneously.

# Supplementary Figure S3: Prevalence of multimorbidity of physical health diseases across familial liability groups by gender and age groups simultaneously.

# Supplementary Figure S4: Prevalence of multimorbidity of lifetime diseases across familial liability groups by gender and age groups simultaneously.

# Supplementary Table S1: Relative frequencies (percentages) and patient-control, sibling-control and patient-sibling comparisons of complaints.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Name of Complaint | Familial liability group | | | | | |
| Control | Sibling vs. Control | | Patient vs. Control | | Patient vs. Sibling |
| N (%) | N (%) | P-value | N (%) | P-value | P-value |
| 1. Angina pectoris | 16 (2.8) | 48 (4.8) | 0.044 | 130 (12.7) | <0.001 | <0.001 |
| 2. Palpitation | 27 (4.8) | 84 (8.5) | 0.008 | 188 (18.4) | <0.001 | <0.001 |
| 3. Oedema | 16 (2.8) | 38 (3.8) | 0.307 | 50 (4.9) | 0.056 | 0.253 |
| 4. Short of breath | 15 (2.7) | 73 (7.3) | <0.001 | 187 (18.3) | <0.001 | <0.001 |
| 5. Hyperventilation | 28 (4.9) | 64 (6.4) | 0.230 | 124 (12.1) | <0.001 | <0.001 |
| 6. Dizziness | 41 (7.2) | 115 (11.6) | 0.007 | 238 (23.2) | <0.001 | <0.001 |
| 7. Perspiration | 32 (5.7) | 72 (7.2) | 0.242 | 172 (16.8) | <0.001 | <0.001 |
| 8. Pyrosis | 40 (7.1) | 81 (8.1) | 0.449 | 182 (17.8) | <0.001 | <0.001 |
| 9. Food allergy | 51 (9.0) | 84 (8.5) | 0.708 | 119 (11.6) | 0.106 | 0.017 |
| 10. Problematic bowel  movement | 57 (10.1) | 111 (11.2) | 0.514 | 163 (15.9) | 0.001 | 0.002 |
| 11. Jaundice | 7 (1.2) | 10 (1.0) | 0.674 | 10 (1.0) | 0.630 | 0.947 |
| 12. Paralysis | 7 (1.2) | 8 (0.8) | 0.405 | 22 (2.1) | 0.223 | 0.016 |
| 13. Pain in joints or  muscles | 99 (17.5) | 182 (18.3) | 0.676 | 220 (21.5) | 0.062 | 0.081 |
| 14. Limited movement of  joints (stiffness) | 30 (5.3) | 53 (5.3) | 0.982 | 69 (6.7) | 0.286 | 0.198 |
| 15. Loss of hearing | 32 (5.7) | 51 (5.1) | 0.606 | 89 (8.7) | 0.035 | 0.001 |
| 16. Loss of smell | 15 (2.7) | 32 (3.2) | 0.555 | 82 (8.0) | <0.001 | <0.001 |
| 17. ENT disorder (except  loss of hearing) | 39 (6.9) | 82 (8.2) | 0.338 | 92 (9.0) | 0.147 | 0.551 |
| 18. Allergy | 118 (20.8) | 166 (16.7) | 0.047 | 163 (15.9) | 0.015 | 0.625 |
| 19. Dermatology disorder  (except allergy) | 41 (7.2) | 95 (9.6) | 0.143 | 87 (8.5) | 0.396 | 0.436 |

# Supplementary Table S2: Relative frequencies (percentages) of all lifetime diseases for controls, siblings and patients.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Name of lifetime diseases | Familial liability group | | | | | | |
|  | Control  (N=566) | | | | Sibling (N=994) | | Patient  (N=1024) |
| **Mental and behavioural disorders** | |  | | |  |  | |
| Psychotic disorders (Schizophrenia, schizoaffective and delusional) | | … | | | … | 1024 (39.6)\* | |
| 1. Mood Disorder | | 52 (9.2) | | | 118 (11.9) | 56 (5.5) | |
| 1. Anxiety and/or Eating Disorder | | 1 (0.2) | | | 10 (1.0) | 6 (0.6) | |
| 1. Substance Disorder | | 0 | | | 4 (0.4) | 21 (2.1) | |
| 1. Other Disordersa | | 10 (1.8) | | | 19 (1.9) | 20 (2.0) | |
| **Diseases of the circulatory system** | |  | | |  |  | |
| 1. Ischemic Heart Disease | | 2 (0.4) | | | 4 (0.4) | 7 (0.7) | |
| 1. Aneurysm | | 0 | | | 1 (0.1) | 0 | |
| 1. Myocarditis | | 0 | | | 0 | 0 | |
| 1. Cardiomyopathy | | 0 | | | 0 | 1 (0.1) | |
| 1. Kawasaki Disease | | 0 | | | 1 (0.1) | 0 | |
| 1. Heart Failure | | 0 | | | 0 | 0 | |
| 1. Arrhythmia | | 3 (0.5) | | | 1 (0.1) | 1 (0.1) | |
| 1. Heart Valve Disease | | 2 (0.4) | | | 1 (0.1) | 2 (0.2) | |
| 1. Hypertension | | 5 (0.9) | | | 8 (0.8) | 12 (1.2) | |
| 1. Hypotension | | 1 (0.2) | | | 4 (0.4) | 0 | |
| 1. Stroke | | 1 (0.2) | | | 1 (0.1) | 6 (0.6) | |
| 1. Transient Ischemic Attack | | 1 (0.2) | | | 2 (0.2) | 2 (0.2) | |
| 1. Deep Vein Thrombosis | | 0 | | | 1 (0.1) | 1 (0.1) | |
| 1. Pulmonary Embolism | | 0 | | | 2 (0.2) | 1 (0.1) | |
| 1. Phlebitis | | 0 | | | 1 (0.2) | 0 | |
| 1. Hemorrhoids/Varices | | 0 | | | 2 (0.2) | 0 | |
| 1. Varicosity | | 7 (1.2) | | | 7 (0.7) | 2 (0.2) | |
| **Endocrine, nutritional and metabolic diseases** | | | | |  |  | |
| 1. Dyslipidaemia | 5 (0.9) | | | | 5 (0.5) | 6 (0.6) | |
| 1. Obesity | 23 (4.1) | | | | 38 (3.8) | 62 (6.1) | |
| 1. Diabetes | 3 (0.5) | | | | 8 (0.8) | 16 (1.6) | |
| 1. Hypothyroidism | 3 (0.5) | | | | 9 (0.9) | 8 (0.8) | |
| 1. Hyperthyroidism | 1 (0.2) | | | | 0 | 3 (0.3) | |
| 1. Thyroiditis (not specified) | 4 (0.7) | | | | 7 (0.7) | 10 (1.0) | |
| 1. Goiter | 2 (0.4) | | | | 0 | 0 | |
| 1. Addison’s Disease | 0 | | | | 0 | 1 (0.1) | |
| **Diseases of the respiratory system** | | | |  |  |  | |
| 1. Chronic Obstructive Pulmonary Disease | 26 (4.6) | | | | 52 (5.2) | 74 (7.2) | |
| 1. Asthma | 10 (1.8) | | | | 17 (1.7) | 5 (0.5) | |
| 1. Pneumothorax | 0 | | | | 2 (0.2) | 1 (0.1) | |
| 1. Bronchitis | 0 | | | | 1 (0.1) | 1 (0.1) | |
| 1. Pneumonia | 0 | | | | 0 | 1 (0.1) | |
| 1. Sleep Apnea | 0 | | | | 0 | 1 (0.1) | |
| 1. Sarcoidosis | 1 (0.2) | | | | 0 | 0 | |
| 1. Nasal Polyps | 3 (0.9) | | | | 8 (0.8) | 4 (0.4) | |
| 1. Deviated Nasal Septum | 5 (0.9) | | | | 7 (0.7) | 6 (0.6) | |
| 1. Epistaxis | 0 | | | | 1 (0.1) | 2 (0.2) | |
| 1. Chronic Sinusitis | 0 | | | | 4 (0.4) | 2 (0.2) | |
| 1. Tonsillitis | 46 (8.1) | | | | 124 (12.5) | 95 (9.3) | |
| 1. Chronic Laryngitis | 1 (0.2) | | | | 1 (0.1) | 0 | |
| 1. Hay Fever | 49 (8.7) | | | | 65 (6.5) | 51 (5.0) | |
| **Neoplasms** | | | |  |  |  | |
| 1. Cancer (not specified) | 4 (0.7) | | | | 9 (0.9) | 9 (0.9) | |
| **Diseases of the musculoskeletal system and connective tissue** | | | | | | | |
| 1. Rheumatoid Arthritis | 2 (0.4) | | | | 2 (0.2) | 0 | |
| 1. Systemic lupus Erythematosus | 1 (0.2) | | | | 0 | 0 | |
| 1. Multiple Sclerosis | 0 | | | | 0 | 0 | |
| 1. Psoriatic Arthritis | 0 | | | | 0 | 0 | |
| 1. Osteoarthritis | 3 (0.5) | | | | 7(0.7) | 12 (1.2) | |
| 1. Frozen Shoulder | 0 | | | | 0 | 0 | |
| 1. Gout | 1 (0.2) | | | | 0 | 0 | |
| 1. Fibromyalgia | 4 (0.7) | | | | 6 (0.6) | 3 (0.3) | |
| 1. Back & Neck Pain | 16 (2.8) | | | | 16 (1.6) | 9 (0.9) | |
| 1. Scoliosis & Kyphosis | 4 (0.7) | | | | 6 (0.6) | 1 (0.1) | |
| 1. Carpal Tunnel Syndrome | 2 (0.4) | | | | 2 (0.2) | 2 (0.2) | |
| 1. Osteoporosis | 2 (0.4) | | | | 1 (0.1) | 0 | |
| 1. Osteomyelitis | 1 (0.2) | | | | 0 | 0 | |
| **Diseases of the digestive system** |  | | | |  |  | |
| 1. Chronic Gastritis | 6 (1.1) | | | | 10 (1.0) | 16 (1.6) | |
| 1. Helicobacter Pylori | 0 | | | | 1 (0.1) | 0 | |
| 1. Lactose Intolerance | 4 (0.7) | | | | 7 (0.7) | 4 (0.4) | |
| 1. Diverticulitis | 0 | | | | 0 | 0 | |
| 1. Celiac Disease | 0 | | | | 1 (0.1) | 0 | |
| 1. Diarrhea | 0 | | | | 4 (0.4) | 3 (0.3) | |
| 1. Constipation | 2 (0.4) | | | | 5 (0.5) | 10 (1.0) | |
| 1. Peritonitis | 0 | | | | 0 | 1 (0.1) | |
| 1. Pancreatitis | 0 | | | | 0 | 0 | |
| 1. Irritable Bowel Syndrome | 4 (0.7) | | | | 8 (0.8) | 2 (0.2) | |
| 1. Inflammatory Bowel Disorder | 7 (1.2) | | | | 4 (0.4) | 1 (0.1) | |
| 1. Gall Bladder Diseases | 6 (1.1) | | | | 9 (0.9) | 13 (1.3) | |
| 1. Diseases of Appendix | 27 (4.8) | | | | 60 (6.0) | 47 (4.6) | |
| 1. Hernia | 22 (3.9) | | | | 32 (3.2) | 34 (3.3) | |
| 1. Anal Fistula | 2 (0.4) | | | | 3 (0.3) | 3 (0.3) | |
| 1. Teeth Abnormalities | 12 (2.1) | | | | 16 (1.6) | 12 (1.2) | |
| **Pregnancy, childbirth and the puerperium** | | | | |  |  | |
| 1. Abortion/Recurrent Abortion | 1 (0.2) | | | | 4 (0.4) | 6 (0.6) | |
| 1. Ectopic Pregnancy | 2 (0.4) | | | | 2 (0.2) | 0 | |
| 1. Other Obstetric Complications | 1 (0.2) | | | | 2 (0.2) | 0 | |
| **Diseases of the genitourinary system** |  | | | |  |  | |
| 1. Diseases of Genital Organ | 3 (0.5) | | | | 5 (0.5) | 3 (0.3) | |
| 1. Infertility | 2 (0.4) | | | | 2 (0.2) | 1 (0.1) | |
| 1. Endometriosis | 0 | | | | 3 (0.3) | 1 (0.1) | |
| 1. Menopausal Syndrome | 1 (0.2) | | | | 0 | 0 | |
| 1. Prolapse | 0 | | | | 1 (0.1) | 0 | |
| 1. Menstrual Abnormalities | 1 (0.2) | | | | 0 | 1 (0.1) | |
| 1. Pelvic Inflammatory Disease | 0 | | | | 1 (0.1) | 1 (0.1) | |
| 1. Chronic Cystitis (>3/years) | 18 (3.2) | | | | 40 (4.0) | 31 (3.0) | |
| 1. Kidney Stone | 11 (1.9) | | | | 13 (1.3) | 8 (0.8) | |
| 1. Chronic Kidney Disease | 0 | | | | 1 (0.1) | 0 | |
| 1. Pyelonephritis | 1 (0.2) | | | | 1 (0.1) | 0 | |
| 1. Hydrocele | 1 (0.2) | | | | 1 (0.1) | 0 | |
| 1. Benign Prostatic Hyperplasia | 1 (0.2) | | | | 1 (0.1) | 0 | |
| 1. Epididymitis | 1 (0.2) | | | | 0 | 0 | |
| **Certain infectious and parasitic diseases** |  | | | |  |  | |
| 1. Tuberculosis lifetime | 5 (0.9) | | | | 3 (0.3) | 10 (1.0) | |
| 1. Viral Hepatitis | 2 (0.4) | | | | 2 (0.2) | 3 (0.3) | |
| 1. Hepatitis (not specified) | 1 (0.2) | | | | 0 (0.0) | 4 (0.4) | |
| 1. Cytomegalovirus | 1 (0.2) | | | | 1 (0.1) | 0 | |
| 1. Infectious Mononucleosis | 0 | | | | 7 (0.7) | 0 | |
| 1. Tropical Diseases (not specified) | 1 (0.2) | | | | 8 (0.8) | 2 (0.2) | |
| 1. Other Bacterial Infection | 1 (0.2) | | | | 1 (0.1) | 3 (0.3) | |
| 1. Infectious Diseases (not specified) | 15 (2.7) | | | | 22 (2.2) | 38 (3.7) | |
| 1. Parasitic Infestation | 0 | | | | 3 (0.3) | 2 (0.2) | |
| 100. Childhood Infectious Diseases | 1(0.2) | | | | 1 (0.1) | 1(0.1) | |
| **Diseases of the skin and subcutaneous tissue** | | | | |  |  | |
| 101. Eczema | 102 (8.0) | | | | 162 (6.3) | 194 (8.9) | |
| 102. Acne | 10 (1.8) | | | | 6 (0.6) | 8 (0.8) | |
| 103. Lichen Planus | 0 | | | | 0 | 1 (0.1) | |
| 104. Psoriasis | 3 (0.2) | | | | 5 (0.5) | 4 (0.4) | |
| 105. Pigment Disorders | 0 | | | | 0 | 2 (0.2) | |
| **Diseases of the eye and adnexa** | | |  | |  |  | |
| 106. Vision Reduction | 18 (3.2) | | | | 27 (2.7) | 18 (1.8) | |
| 107. Lazy Eye | 3 (0.5) | | | | 5 ( 0.5) | 3 (0.3) | |
| 108. Coordination Abnormalities | 2 (0.4) | | | | 1 (0.1) | 4 (0.4) | |
| 109. Glaucoma | 1 (0.2) | | | | 1 (0.1) | 0 | |
| 110. Others Eye Disorders | 0 | | | | 3 (0.3) | 1 (0.1) | |
| **Diseases of the ear and mastoid process** |  | | | |  |  | |
| 111. Hearing Impairment (diagnosed) | 4 (0.7) | | | | 10 (1.0) | 8 (0.8) | |
| 112. Chronic Suppurative Otitis Media | 16 (2.8) | | | | 29 (2.9) | 19 (1.9) | |
| 113. Cholesteatoma | 1 (0.2) | | | | 1 (0.1) | 0 | |
| 114. Otosclerosis | 1 (0.2) | | | | 0 | 0 | |
| **Diseases of the nervous system (+ due to injury)** | | | | |  |  | |
| 115. Epilepsy | 7 (1.2) | | | | 9 (0.9) | 24 (2.3) | |
| 116. Concussion | 109 (19.3) | | | | 152 (15.3) | 250 (24.4) | |
| 117. Meningitis | 5 (0.9) | | | | 7 (0.7) | 13 (1.3) | |
| 118. Migraine | 58 (10.2) | | | | 100 (10.1) | 90 (8.8) | |
| 119. Insomnia | 0 | | | | 1 (0.1) | 1 (0.1) | |
| 120. Chronic Fatigue Syndrome | 1 (0.2) | | | | 0 | 0 | |
| 121. Impaired Smell | 0 | | | | 0 | 6 (0.6) | |
| **Diseases of blood & blood-forming organs and certain disorders involving the immune mechanism** | | | | | | | |
| 122. Anemia | 2 (0.4) | | | | 7 (0.7) | | 1 (0.1) |
| **Congenital malformations, deformations and chromosomal abnormalities** | | | | | | | |
| 123. Congenital Defect | 36 (6.4) | | | | 87 (8.8) | | 123 (12.0) |
| 124. Sex-linked Diseases | 0 | | | | 0 | | 0 |
| 125. Sexual Dysfunction | 0 | | | | 2 (0.2) | | 0 |

\*Out of 2584 subjects, aOther disorders= Adjustment disorder, bereavement, personality disorder, Autism, Deferred.

# Supplementary Table S3: Relative frequencies (percentages) and patient-control, sibling-control and patient-sibling comparisons per domain for the lifetime diseases.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Domaina | Familial liability group | | | | | |
| Control | Sibling vs. Control | | Patient vs. Control | | Patient vs. Sibling |
| N (%) | N (%) | P-value | N (%) | P-value | P-value |
| 1. Mental and behavioral disorders | 61 (10.8) | 144 (14.5) | 0.038 | 103 (10.1) | 0.659 | 0.003 |
| 2. Diseases of circulatory system | 22 (3.9) | 35 (3.5) | 0.720 | 35 (3.4) | 0.627 | 0.882 |
| 3. Endocrine, nutritional and  metabolic diseases | 37 (6.5) | 64 (6.4) | 0.937 | 95 (9.3) | 0.066 | 0.015 |
| 4. Diseases of respiratory system | 179 (31.6) | 348 (35.0) | 0.162 | 298 (29.1) | 0.292 | 0.003 |
| 5. Neoplasms | 4 (0.7) | 9 (0.9) | 0.679 | 9 (0.9) | 0.716 | 0.950 |
| 6. Diseases of musculoskeletal  system and connective tissue | 34 (6.0) | 39 (3.9) | 0.067 | 27 (2.6) | 0.001 | 0.950 |
| 7. Diseases of digestive system | 80 (14.1) | 138 (13.9) | 0.865 | 125 (12.2) | 0.290 | 0.089 |
| 8. Pregnancy, childbirth and the  Puerperium | 4 (0.7) | 8 (0.8) | 0.831 | 6 (0.6) | 0.771 | 0.265 |
| 9. Diseases of genitourinary system | 39 (6.9) | 64 (6.4) | 0.730 | 44 (4.3) | 0.028 | 0.555 |
| 10. Certain infectious and parasitic  diseases | 24 (4.2) | 44 (4.4) | 0.833 | 58 (5.7) | 0.226 | 0.034 |
| 11. Diseases of the skin and  subcutaneous tissue | 114 (20.1) | 175 (17.6) | 0.191 | 208 (20.3) | 0.979 | 0.223 |
| 12. Diseases of the eye and adnexa | 24 (4.2) | 37 (3.7) | 0.616 | 25 (2.4) | 0.051 | 0.105 |
| 13. Diseases of the ear and mastoid process | 22 (3.9) | 40 (4.0) | 0.920 | 26 (2.5) | 0.145 | 0.089 |
| 14. Diseases of the nervous system  (+ due to injury) | 169 (29.9) | 264 (26.6) | 0.165 | 358 (35.0) | 0.041 | 0.067 |
| 15. Diseases of blood & blood-forming organs and certain disorders involving the immune mechanism | 2 (0.4) | 7 (0.7) | 0.389 | 1 (0.1) | 0.293 | <0.001 |
| 16. Congenital mal/de-formations and chromosomal abnormalities | 36 (6.4) | 87 (8.8) | 0.096 | 123 (12.0) | <0.001 | 0.064 |

Note: The 16 domains were based on 125 lifetime diseases.

# Supplementary Table S4: Top 10 lifetime diseases ranked by controls.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Comorbid Diseases | Familial liability group | | | | | |
| Control | Sibling vs. Control | | Patient vs. Control | | Patient vs. Sibling |
| % | % | P-value | % | P-value | P-value |
| 1. Concussion | 19.3 | 15.3 | 0.046 | 24.4 | 0.019 | <0.001 |
| 2. Eczema | 18.0 | 16.3 | 0.362 | 18.9 | 0.641 | 0.097 |
| 3. Migraine | 10.2 | 10.1 | 0.916 | 8.8 | 0.314 | 0.280 |
| 4. Mood Disorders | 9.2 | 11.9 | 0.105 | 5.5 | 0.006 | <0.001 |
| 5. Hay Fever | 8.7 | 6.5 | 0.745 | 5.0 | 0.069 | 0.009 |
| 6. Tonsillitis | 8.1 | 12.5 | 0.013 | 9.3 | 0.424 | 0.029 |
| 7. Congenital defect | 6.4 | 8.8 | 0.096 | 12.0 | 0.001 | 0.016 |
| 8. Appendicitis | 4.8 | 6.0 | 0.297 | 4.6 | 0.862 | 0.135 |
| 9. COPDa | 4.6 | 5.2 | 0.572 | 7.2 | 0.045 | 0.066 |
| 10. Obesity | 4.1 | 3.8 | 0.855 | 6.1 | 0.088 | 0.014 |

Note: Table presents the percentages; aCOPD=Chronic Obstructive Pulmonary Disease

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