Statistical approaches to explore clinical heterogeneity in psychosis

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CHAPTER 6

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

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Abstract

Background: Multimorbidity may impose an overwhelming burden on patients with psychosis and is affected by gender and age. Our aim is to study the independent role of familial liability to psychosis as a risk factor for multimorbidity

Methods: We performed the study within the framework of the Genetic Risk and Outcome of Psychosis (GROUP) project. Overall, we compared 1024 psychotic patients, 994 unaffected siblings and 566 controls on the prevalence of 125 lifetime diseases, and 19 self-reported somatic complaints. Multimorbidity was defined as the presence of two or more complaints/diseases in the same individual. Generalized linear mixed model (GLMM) were used to investigate the effects of gender, age (adolescent, young, older) and familial liability (patients, siblings, controls) and their interactions on multimorbidity.

Results: Familial liability had a significant effect on multimorbidity of either complaints or diseases. Patients had a higher prevalence of multimorbidity of complaints compared to siblings (OR 2.20, 95% CI 1.79-2.69, P<0.001) and to controls (3.05, 2.35-3.96, P<0.001). In physical health multimorbidity, patients (OR 1.36, 95% CI 1.05–1.75, P=0.018), but not siblings, had significantly higher prevalence than controls. Similar finding were observed for multimorbidity of lifetime diseases including psychiatric diseases. Significant results were observed for complaints and disease multimorbidity across gender and age groups.

Conclusion: Multimorbidity is a common burden, significantly more prevalent in patients and their unaffected siblings. Familial liability to psychosis showed an independent effect on multimorbidity; gender and age are also important factors determining multimorbidity.

Keywords: familial liability; multimorbidity; physical health; psychosis; schizophrenia

1. Introduction

Schizophrenia spectrum disorder is a complex, multifaceted disorder with a 10-20 year shorter life expectancy (Laursen, 2011; Korver et al., 2012; Walker et al., 2015; Lawrence et al., 2013). A recent meta-analysis (Walker et al., 2015) on mortality in schizophrenia indicates that comorbid health-conditions may contribute up to ~67 percent of the triple excess of premature mortality in schizophrenia and related psychotic disorders (De Hert et al., 2011). Indeed, up to 54 percent of patients with schizophrenia have metabolic syndrome (Bruins et al., 2016; Vancampfort et al., 2015) and a 2-3 fold higher risk of diabetes mellitus (Bushe and Holt, 2004; van Winkel et al., 2006; Vancampfort et al., 2016) and cardiovascular diseases (Bresee et al., 2010; Hennekens et al., 2005; Hoang et al., 2013; Vancampfort et al., 2015) compared to general population. Precisely, type 2 diabetes mellitus is higher (2.9 percent) in patients with severe mental illness who prescribed antipsychotics (Vancampfort et al., 2016). Also, an extensive study indicates that schizophrenia patients have a broad range of multiple physical-health conditions but are less likely to have cardiovascular diseases than people without schizophrenia (Smith et al., 2013). Other diseases have also been identified in psychotic patients, including cancers, chronic obstructive pulmonary disease (COPD), tuberculosis, hepatitis C virus and osteoporosis (De Hert et al., 2011; Iacovides and Siamouli, 2008). It has been established that physical comorbidity in people with severe mental illness leads to a lower quality of life than for people without mental illness (Barnett et al., 2012; Payne et al., 2013; Qin et al., 2014; Reilly et al., 2015). However, little is known about the risk factors for the co-occurrence of physical illness, unexplained physical symptoms, and psychiatric diseases.

Multimorbidity is defined as any co-occurrence of two or more medical conditions within the same person (Batstra et al., 2002; Feinstein, 1970; Tomasdottir et al., 2013). It affects more than two thirds of patients in general practice and half of the elderly population (Schafer et al., 2012). So far most studies (Bresee et al., 2010; De Hert et al., 2011; Hennekens et al., 2005; Taylor et al., 2010; van Winkel et al., 2006) have focused on lifetime diseases but not on medical complaints, even though these medical complaints in themselves may also lead patients to seek medical attention. Multiple factors play a role in multimorbidity: *e.g.* the side effects of psychotropic drugs, associations with lifestyle risk factors, particularly smoking and substance abuse, and inequitable access to preventative health care and medical treatment (De Hert et al., 2011; Lawrence and Kisely, 2010). Above all the factors gender and age are considered the main determinants of multimorbidity for many diseases (Agborsangaya et al., 2012; Britt et al., 2008; Fuchs et al., 2012; Rizza et al., 2012; van den Akker et al., 1998; van Oostrom et al., 2012; Schafer et al., 2012). However, with regard to schizophrenia, the role of gender and age in predisposing to multimorbidity in psychosis and in healthy population is unclear.

Notably, psychosis is more prevalent in men and has a typical onset in younger people between 20 and 40 years (McGrath et al., 2004; Batki et al., 2009; Taylor et al., 2010; Korver et al., 2012; Manuel et al., 2013; Smith et al., 2013). Men are more likely than women to have lifetime risk until age 45-50 years. After that age on (50-54 years), women reach almost the same as men lifetime risk. Consequently, lower age groups are certain to lead to a male predominance in the risk ratios (Häfner, 2003; Abel et al., 2010). Physical multimorbidity in psychosis or healthy controls, on the other hand, more often occurs in women (Schafer et al., 2012; Smith et al., 2013; Agur et al., 2016;

Stubbs et al., 2016) and is more typically seen in older people than in younger adults (Marengoni et al., 2011; Smith et al., 2013; Agur et al., 2016; Stubbs et al., 2016). If therefore, multimorbidity in psychosis has a different man/woman ratio, and that multimorbidity in psychosis emerges at a younger age, we can argue that genetic factors, family links, environmental factors (e.g. high rate of smoking and alcohol use in both patients and siblings) may play a greater role in liability to psychosis. This would suggest that family liability to psychosis is another important determinant for multimorbidity.

To study the effect of familial liability, we will evaluate a cohort of young psychotic patients and their unaffected siblings. Unaffected siblings of people with psychosis report increased numbers of subclinical psychotic symptoms (Chen et al., 2009; Genetic Risk and Outcome in Psychosis (GROUP) Investigators, 2011), have a 10-fold increased risk of developing schizophrenia (Gejman et al., 2011), and share ~50% of their genes with their ill relative, including a number of the schizophrenia risk genes (Gottesman and Gould, 2003). A large multinational study demonstrates that physical health multimorbidity is increased across the control, with subclinical psychosis and psychosis in 48 low- and middle-income countries (Stubbs et al., 2016). The study of siblings allows us to investigate the prevalence of multimorbidity in persons who to some extent share familial liability for psychosis, but by whom multimorbidity is related neither to the course of schizophrenia nor the use of antipsychotics. We will investigate the effects of gender, age, and familial liability on the prevalence of multimorbidity (of complaints, physical health and lifetime diseases including psychiatric diseases) and their possible two-way (*gender* x *age*; *age* x *familial liability*; *gender* x *familial liability*) and three-way (*gender* x *age* x *familial liability*) interactions.

The present study will examine (*i*) whether the liability to psychosis overrules the effect of gender and age on multimorbidity, whereby younger men with psychosis have an increased rate of multimorbidity, and (*ii*) whether the same effects hold for their unaffected siblings.

2. Methods

2.1. Design and setting of the study

The study was conducted within the framework of the Genetic Risk and Outcome of Psychosis (GROUP) project (Data release version 3.02), a large prospective cohort study in the Netherlands and Belgium. The GROUP project has been described in detail elsewhere (Korver et al., 2012). From a total of 3684 participants at baseline, we included 2584 participants (1024 patients, 994 siblings, and 566 controls) in the present study. Persons identified as potentially eligible were given 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 (Korver et al., 2012). The GROUP study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute (Korver et al., 2012).

The selection of the sample is depicted in Supplementary Figure S1 and explained in Supplementary Methods. Participants were divided into three subgroups based on inheritance of liability to psychosis: 1) patients with a highest familial liability, 2) their corresponding unaffected

singleton of multiple siblings with an increased familial liability and 3) unrelated controls with no family history of psychosis as those with the lowest familial liability of psychosis.

2.2. Population demography

Socio-demographic characteristics used in the analysis were age, gender, ethnicity, educational attainment (adapted from Verhage (Verhage, 1964)), intelligence quotient (IQ) as estimated by The Wechsler Adult Intelligence Scale, third edition (WAIS-III) (Wechsler et al., 2008), marital and residential status, gross monthly income at the time of recruitment, smoking and alcohol consumption.

2.3. Characterization of complaints and lifetime diseases

Generally, a complaint is a symptom of which a person is aware or which causes discomfort. It is usually described from a patient's perspective and is often his/her key reason for seeking medical attention. On the other hand, lifetime disease is an illness or sickness characterized by specific signs and symptoms which people have developed and had diagnosed during their lifetime (Vos et al., 2013). Data on medical conditions, including complaints and lifetime diseases, were derived from two main resources: a medical questionnaire and pharmacy records. A Medical Questionnaire was designed for interviewing participants to identify their somatic comorbidities. It was noted that self-reported diseases were comparable with objectively diagnosed diseases in population-based studies (Lampe et al., 1999). We divided the questionnaire into two sections, including a 'checklist' of multiple choice questions and a 'narrative section,' consisting of open questions. The thirty-eight medical conditions from the checklist section were divided into 19 complaints and 19 lifetime diseases according to the 10th revision of the International Classification of Diseases (ICD-10). Another 102 lifetime diseases were retrieved from the narrative section; these were matched with the checklist of lifetime diseases to avoid duplication. Similarly, complaints were removed from the checklist if participants had received a medical diagnosis (e.g. lifetime diseases). In total, 121 physical health morbidity (excluding mental and behavioural disorders) were retrieved from the database. Note that at baseline, five groups of psychiatric disorders (psychotic disorder: schizophrenia, schizoaffective and delusional; mood; anxiety and/or eating; substance, and others) were formed regarding patients, siblings and controls, respectively. All patients were diagnosed with non-affective psychosis. The details has been depicted by a flow diagram in the Supplementary Figure S1. For simplicity of presentation, the observed 125 lifetime diseases including four mental and behavioural disorders were categorized into 16 disease domains based on the bodily organ system to which each disease belonged (Supplementary Table S1-S3).

2.4. Outcomes measure

For each subject, we counted the number of complaints and lifetime diseases (including and excluding mental and behavioural disorders) independently. We defined multimorbidity of complaints/diseases as the presence of two or more complaints/lifetime diseases in the same individual. We treated multimorbidity of complaints, physical morbidity and lifetime diseases as three separate outcomes throughout the study and as binary outcomes (i.e. present/absent). We did

not count psychotic disorder (e.g. schizophrenia, schizoaffective and delusional) in patients, as this was already their indexed disease. In summary, we collected 19 complaints and 125 lifetime diseases to measure multimorbidity regarding complaints, physical health multimorbidity and lifetime diseases separately (Supplementary Figure S1, Table S1 and Table S2).

2.5. Data analysis

We compared psychotic patients, their unaffected siblings and controls pairwise, for socio-demographic characteristics. We conducted independent group comparisons using Chi-square, T-test or Mann-Whitney U test, depending on the nature of variables; we compared correlated groups (e.g. patients and siblings) using the McNemar test or the Generalized Estimating Equations (GEEs) model. Moreover, we estimated the prevalence of multimorbidity of complaints and lifetime diseases in terms of percentages across familial liability groups by gender and age groups: adolescents ≤ 20 years, young adults 21-40 years, and older adults >40 years. Because age range is *a priori* factor involving more risk of multimorbidity, we categorized age into three meaningful groups (Batki et al., 2009; Marengoni et al., 2011; Manuel et al., 2013).

Since patients and siblings belonged to the same family, individuals within families were expected to be more homogenous than between families. To investigate the effects of gender, age, familial liability and their interactions on the prevalence of multimorbidity of complaints, physical health and lifetime diseases, we conducted a Generalized Linear Mixed Model (GLMM) (Molenberghs and Verbeke, 2006), taking the family into account as a random effect. We used an adaptive Gaussian quadrature with 20 quadrature points to estimate the parameters and their associate standard errors. If an interaction effect was not statistically significant, we reported only the main effect. In the model building process, we incorporated main (gender, age group and familial liability) and all possible two- and three-way interaction effects into the full model. We performed a backward elimination procedure and compared the models, using the corrected Akaike's Information Criterion (AICc) and the Bayesian information criterion (BIC). The smallest values of AICc and BIC concluded the final model. We used Type-III overall tests of fixed effect P-values to conclude the marginal effects of complaints and lifetime diseases on multimorbidity separately. We also conducted pairwise comparisons on main effects if they were significant. We also calculated the intraclass correlation coefficient (ICC) to measure the homogeneity of subjects within a family. We conducted all analyses using Statistical Analysis System (SAS Institute Inc., Cary, NC) version 9.4 with a two-tailed test at 5% level of significance.

3. Results

3.1. Descriptive of study population

Table 1 describes and compares the basic socio-demographics, risk factors and other subclinical characteristics among patients, siblings and controls. Overall, patients (age: mean 27.8± SD 8.2) and siblings (27.8±8.2) were significantly (P<0.001) younger than controls (30.5±10.6). In patients, the proportion of women (24.5%) was significantly lower (P<0.001) compared to siblings (54.3%) and controls (55.5%). Patients and siblings had significantly (P<0.001) less education, lower IQ's, and

higher use of alcohol and nicotine compared to controls. Moreover, 86.5% patients used antipsychotics while other two groups e.g. siblings and controls did not use any antipsychotic.

The prevalence of multimorbidity of complaints, physical and lifetime diseases across the familial liability subgroups (i.e. patients, siblings and controls) respectively, are depicted in the Figure 1-3. The occurrence of four or more complaints was 24.9%, 12.6% and 9.0% for patients, siblings and controls respectively. Multimorbidity of complaints was prevalent in 51.5% of the patients, 35.7% of the siblings and 31.3% of the controls (Figure 1). Physical health comorbidity was observed in 46.1% of the patients, 46.2% of the siblings and 45.6% of the controls (Figure 2). Multimorbidity of lifetime diseases was found in 47.2% of the patients, 47.0% of the siblings and 46.1% of the controls (Figure 3).

The observed prevalence of multimorbidity of complaints, physical health and lifetime diseases across familial liability subgroups by gender and age groups respectively are presented in Supplementary Results and are demonstrated in the Supplementary Figures S2-S4 and Tables S1-S4.

Table 1: Baseline socio-demographic characteristics for patients, siblings and controls[a].

Characteristics	Familial liability group		
	Control (N=566)	Sibling (N=994)	Patient (N=1024)
Age in years			
Overall, mean±sd (Range)	30.5±10.6 (15-56)	27.8±8.3 (14-60)^{3†}	27.8±8.2 (15-68)^{3†}
Age in category (years)			
Adolescents, N (mean±sd)	130 (18.2±1.2)	204 (18.1±1.6)	163 (18.5±1.4)$^{2\dagger 2*}$
Young adults, N (mean±sd)	300 (29.0±6.0)	703 (28.3±5.2)	778 (27.7±5.2)$^{2\dagger 2*}$
Older adults, N (mean±sd)	136 (45.6±3.3)	87 (45.8±4.3)	83 (46.7±5.9)
Gender, % Women	55.5	54.3	24.5$^{3\dagger 3*}$
Ethnicity, % Caucasian	92.1	83.7^{3†}	79.0$^{3\dagger 3*}$
Education[1], mean±sd	5.4±1.8	5.1± 2.1^{3†}	4.1±2.1$^{3\dagger 3*}$
IQ, estimated[2], mean±sd	109.6±14.7	102.8±15.4^{3†}	95.3 ±16.1$^{3\dagger 3*}$
Married/Living together, %	40.7	39.9	9.5$^{3\dagger 3*}$
Living with partner/family, %	46.5	46.0	10.7$^{3\dagger 3*}$
Income minimal, % (€<1264.80)	35.3	28.9†	63.0$^{3\dagger 3*}$
Nicotine use, %	27.1	41.5^{3†}	61.9^{3†}
Alcohol use, %	62.7	73.7^{3†}	71.2$^{3\dagger 3*}$
Current use of Antipsychotics, %	-	-	86.5

[a]Table presents Mean±SD or numbers (in %); Adolescents ≤ 20 years, young adults = 21-40 years, older adults >40 years; [1]Education (Verhage): range 0 (no education), 3-5 (school diploma) to 8 (university degree); [2]IQ: Wechsler Adult Intelligence Scale-III (WAIS-III).

†Patient or sibling compared to control (using Chi-square and/or Mann-Whitney test): †P<0.05, ^{2†}P<0.01 and ^{3†}P<0.001. *Patient compared to sibling (using Generalized Estimating Equations): ^{2*}P<0.01 and ^{3*}P<0.001.

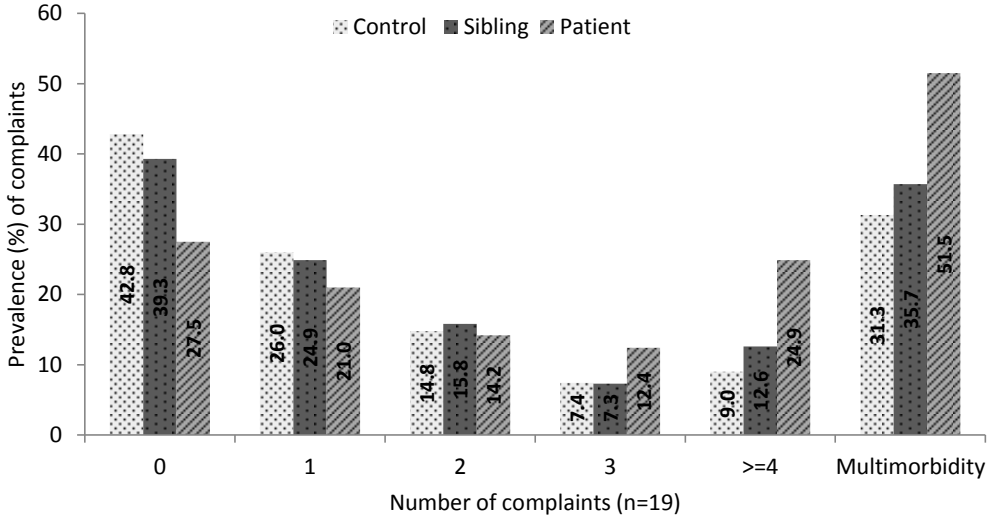

Figure 1: Prevalence of occurrence of complaints for different groups of subjects.

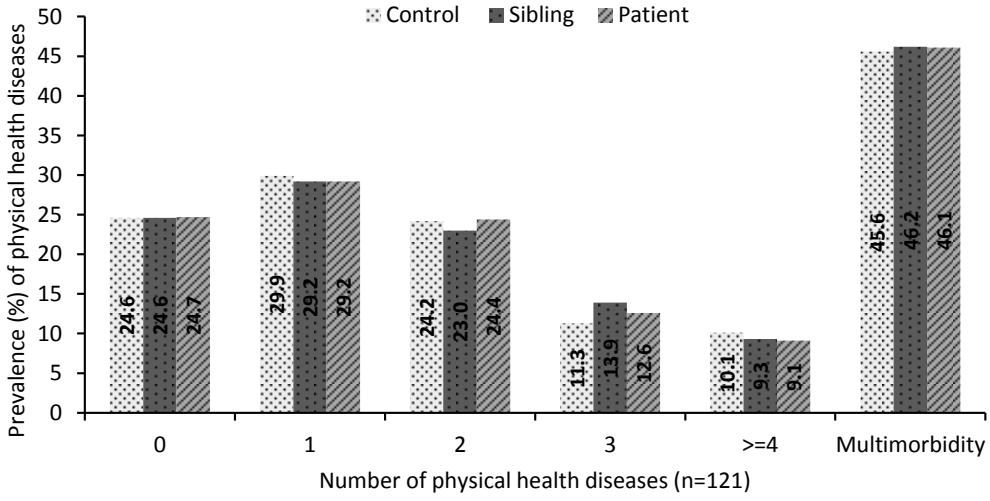

Figure 2: Prevalence of occurrence of physical health diseases for different groups of subjects.

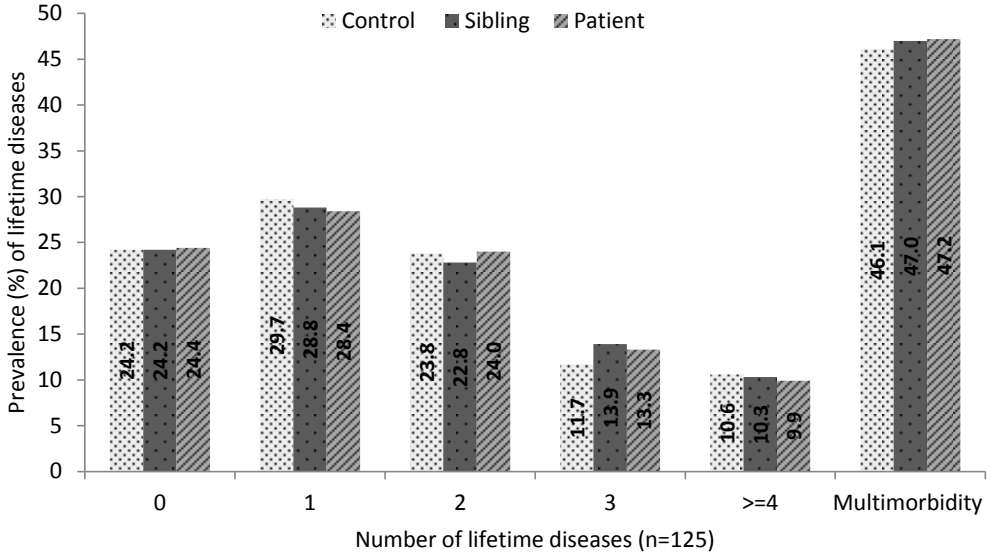

Figure 3: Prevalence of occurrence of lifetime diseases for different groups of subjects.

3.2. Effects of gender, age groups and familial liability on the prevalence of multimorbidity

We found no significant interaction effects of gender, age groups and familial liability groups on the prevalence of multimorbidity, either of complaints or physical health multimorbidity or lifetime diseases. The main effects from type III overall tests indicated that gender (P=0.003), age group (P<0.001) and familial liability (P<0.001) were significantly related to the prevalence of multimorbidity of complaints. Table 2 presents the pairwise comparisons, odds ratios, their 95% confidence interval and ICC for multimorbidity. In model-1, both being a patient with the highest liability of psychosis (OR 3.05, 95% CI 2.35-3.96, P<0.001) and being a sibling with increased familial liability of psychosis (OR 1.39, 95% CI 1.08–1.78, P=0.01) had a significant effect on having more complaints, as compared to those with the lowest familial liability for psychosis (i.e. controls). Also, patients had significantly, 2.20 (95% CI 1.79-2.69, P<0.001), times more multimorbid complaints than their corresponding siblings. Older adults had 2.24 times (95% CI 1.60–3.13, P<0.001) higher prevalence of multimorbidity of complaints compared to adolescents. Older adults had more multimorbid complaints than young adults (OR 1.86, 95% CI 1.39-2.47, P<0.001). The odds of women having multimorbidity of complaints were 1.33 (95% CI 1.11–1.61, P=0.003) times higher than for men (Table 2, model-1).

Similarly, in model-2, psychotic patients had 1.36 (95% CI 1.05–1.75, P=0.018) times higher odds for physical health multimorbidity compared to controls. Young adults and older adults were significantly associated with 1.55 (95% CI 1.23–1.97, P<0.001) and 3.83 (95% CI 2.69–5.46, P<0.001) times higher for physical multimorbidity than adolescents. Women had significantly higher (OR 1.70, 95% CI 1.41-2.06, P<0.001) physical health multimorbidity than for men (Table 2, model-2).

Additionally, in model-3, type III overall tests of fixed effects showed that gender (P<0.001), age group (P<0.001) and familial liability (P=0.038) were significantly associated with the prevalence of multimorbidity of lifetime diseases. Patients had 1.39 (95% CI 1.08–1.79, P=0.011) times higher prevalence of lifetime diseases compared to controls. Young adults (OR 1.59, 95% CI 1.25–2.02, P<0.001) and older adults (OR 4.06, 95% CI 2.84–5.80, P<0.001) had significantly more disease multimorbidity than adolescents. Older adults also had more multimorbid diseases than young adults (OR 2.56, 95% CI 1.88-3.47, P<0.001). Likewise, the odds of women having disease multimorbidity were 1.68 (95% CI 1.39–2.03, P<0.001) times higher than for men (Table 2, model-3).

The intraclass correlation coefficients (ICC) between subjects within a family were 0.11 (95% CI 0.03-0.19) for multimorbidity of complaints, 0.15 (95% CI 0.07-0.23) for physical health multimorbidity and 0.16 (95% CI 0.08-0.24) for multimorbidity of lifetime diseases, meaning that proportion of the total variance (11%, 15% and 16%) in multimorbidity of complaints, physical and lifetime diseases, respectively, that were accounted for by the family effect (Table 2).

Table 2: Pairwise comparisons, odds ratios, their 95% confidence interval and ICC for multimorbidity[a].

Factors	Odds Ratio (95% C.I)	P-value
Model-1: Multimorbidity of complaints		
Patient vs. Control	3.05 (2.35-3.96)	<0.001
Sibling vs. Control	1.39 (1.08-1.78)	0.010
Patient vs. Sibling	2.20 (1.79-2.69)	<0.001
Young adult vs. adolescent	1.21 (0.96-1.52)	0.114
Older adult vs. adolescent	2.24 (1.60-3.13)	<0.001
Older adult vs. young adult	1.86 (1.39-2.47)	<0.001
Women vs. Men	1.33 (1.11-1.61)	0.003
Model-2: Physical health multimorbidity (excluding psychiatric diseases)		
Patient vs. Control	1.36 (1.05-1.75)	0.018
Sibling vs. Control	1.18 (0.92-1.52)	0.188
Patient vs. Sibling	1.15 (0.94-1.41)	0.178
Young adult vs. adolescent	1.55 (1.23-1.97)	<0.001
Older adult vs. adolescent	3.83 (2.69-5.46)	<0.001
Older adult vs. young adult	2.46 (1.82-3.34)	<0.001
Women vs. Men	1.70 (1.41-2.06)	<0.001
Model-3: Multimorbidity of lifetime disease (including psychiatric diseases)		
Patient vs. Control	1.39 (1.08-1.79)	0.011
Sibling vs. Control	1.21 (0.94-1.55)	0.143
Patient vs. Sibling	1.15 (0.94-1.41)	0.165
Young adult vs. adolescent	1.59 (1.25-2.02)	<0.001
Older adult vs. adolescent	4.06 (2.84-5.80)	<0.001
Older adult vs. young adult	2.56 (1.88-3.47)	<0.001
Women vs. Men	1.68 (1.39-2.03)	<0.001
Variance:	Estimate	ICC[b] (95% C.I)
Model-1: Intercept (Family effect)	0.40	0.11 (0.03-0.19)
Model-2: Intercept (Family effect)	0.59	0.15 (0.07-0.23)
Model-3: Intercept (Family effect)	0.60	0.16 (0.08-0.24)

[a]Table presents the GLMM pairwise comparison results; Adolescents ≤ 20 years, young adults = 21-40 years, older adults>40 years; [b]ICC: Intraclass correlation coefficient = [Variance of random intercept/(Variance of random intercept+π^2/3)]. Model-1: AICc=3384.07, BIC=3421.12; Model-2: AICc= 3459.76, BIC= 3496.81.; Model-3: AICc=3462.42, BIC=3499.47.

4. Discussion

This study described the prevalence of multimorbidity in psychotic patients, their unaffected siblings and controls, and investigated the role of familial liability to psychosis as a determinant of multimorbidity, next to gender and age.

In all three groups, women showed a higher prevalence of multimorbidity for both complaints and diseases with/without psychiatric diseases, and the prevalence of multimorbidity increased with age. Also, the prevalence of multimorbidity was increased by the degree of familial liability for psychosis. Studying the two- and three-way interactions, this study demonstrates familial liability to psychosis to be a consistent determinant of the risk of multimorbidity across gender and age groups. For medical complaints, we found the pain of joints or muscles, allergy, problematic bowel movement, dizziness and palpitation to be the most prevalent medical complaints of all three groups. These complaints also prevailed in general population studies (den Boeft et al., 2016). Note that pain prevalence of psychotic patients in the current study did not differ significantly either from controls or siblings, which was in line with the recent meta-analysis studied by Stubbs et al (Stubbs et al., 2014). Since medical complaints were based on self-reported data, lack of pain sensitivity measure yielded the same conclusion, which might be under-estimate. There might be other factors e.g. impaired prefrontal, medial temporal functioning (Keshavan et al., 2008), use of antipsychotics (Seidel et al., 2013; Stubbs et al., 2015) and alterations in the cortical dopamine system (Jarcho et al., 2012) which reduced pain sensitivity in people with schizophrenia. However, a meta-analysis of clinical pain induction studies demonstrated that higher psychiatric symptoms moderated increased pain threshold, and younger patient age moderated increased pain tolerance (Stubbs et al., 2015).

Of all the comorbid diseases, we found concussion, eczema, migraine, tonsillitis, congenital defects, mood disorders and COPD across the familial liability groups to be the most prevalent lifetime diseases. Other diseases had an occurrence of less than 5% (Supplementary Table S1 and S4). The current study found higher levels of migraine in siblings and controls but not in patients. This might be due to under-reporting clinical symptoms and diseases in patients which reduced pain sensitivity as patients used antipsychotics, higher levels of nicotine and alcohol.

Different operational definitions of multimorbidity have been used in the literature (Willadsen et al., 2016). The majority of studies have defined multimorbidity as two or more, whereas others counted three or more, concurrent diseases (Fortin et al., 2005; Jacobi et al., 2004; Fuchs et al., 2012). A medical complaint is in itself a symptom or a set of symptoms, not a disease. The present study extracted 19 such complaints or symptoms independently and had formed a separate definition of multimorbidity of complaints, leading to another dimension for studying multimorbidity and finding their determinants. This approach is in line with the suggestions of Willadsen et al., based on the data from their recent meta-analysis, including severity and symptoms, making the existing definitions more suitable for epidemiologists than for clinicians (Willadsen et al., 2016). Along with this meta-analysis, the separation of multimorbidity into complaints, physical health and lifetime diseases has made the present study more comprehensive and clinically relevant. Examining comorbidity through the mechanism of multimorbidity allows for evaluation of the overall health of a familial liability group and avoids the complexity of comparing many specific diseases, particularly those with a low prevalence. The current study was the first to make a more clear

distinction between complaints and diseases, thus providing a novel comparison of physical health between patients with non-affective psychosis and their unaffected siblings.

In our study, healthy controls reported overall prevalence of 31.3 percent multimorbidity for complaints, 45.6 percent for physical health, and 46.1 percent for lifetime diseases. A recent systematic review demonstrated a prevalence rate of 13.1 to 71.8 percent for the general population across studies (Fortin et al., 2012). For example, in Switzerland, the prevalence of multimorbidity ranged from 47 to 97 percent in medical inpatient records (Schneider et al., 2012), comparable to 36 to 43 percent of the older population in a German national health survey (Fuchs et al., 2012). Other studies showed a lower prevalence of multimorbidity, such as the 17 percent frequency of all ages based on an Australian biomedical cohort study (Taylor et al., 2010). In the Netherlands, Van den Akker et al. (1998) reported a 29 percent overall multimorbidity of diseases in Registration Network Family Practice data (van den Akker et al., 1998). Although comparisons with other cohorts were hampered by a lack of a standard definition of multimorbidity, the percentages of complaints and diseases in our healthy controls were within the range of studies in the general population, adding to the validation of our sample. When looking at gender, several population based studies (Agborsangaya et al., 2012; Britt et al., 2008; Marengoni et al., 2011; O'Kelly et al., 2011; Rizza et al., 2012; van Oostrom et al., 2012) reported an increased proportion of multimorbidity in women compared to men in general. Additionally, gender difference was also observed in three other studies (Smith et al., 2013; Crump et al., 2013; Stubbs et al., 2016) where women with schizophrenia were more likely to have physical multimorbidity than men. Interestingly, women showed a tendency to have a longer life expectancy, but also a lower quality of health compared to men (Foguet-Boreu et al., 2014; Ha et al., 2015). In line with these literatures, our study also showed multimorbidity to be more common in women than in men. In our study, the gender difference might be explained by the fact that women were older on average (29.37±9.6) than men (27.59±8.22) and women more often consult with their general practitioner (Smith et al., 2013; Crump et al., 2013). We also observed this pattern across familial liability classes, meaning that women more often had multimorbidity of diseases and complaints than did men. However, within both genders, patients more often had multimorbidity than their siblings and the latter more often than controls. Thus, gender was confirmed as a major determinant of multimorbidity. At the same time, these data suggested that the effect of familial liability was independent of gender.

Like previous studies, our study showed that age was associated with multimorbidity of complaints as well as of physical and lifetime diseases (Agborsangaya et al., 2012; Schafer et al., 2012; Stubbs et al., 2016). When studying older control groups, we observed 42.3 to 69 percent multimorbidity, which differed from previous studies reporting 32 to 36 percent for the 40-59 year age group (Taylor et al., 2010; Marengoni et al., 2011). We also found that the prevalence of lifetime disease multimorbidity increased with increasing age. In older patients, we found a 68.1 to 72.2 percent multimorbidity of lifetime diseases for both genders (mainly within 40-50 years), which was higher than age-matched unaffected siblings and controls; further unaffected siblings showed trends similar to those of controls when compared to the findings from previous studies (Fortin et al., 2005; Marengoni et al., 2011; Taylor et al., 2010). Thus, we found that having schizophrenia showed an effect on multimorbidity independent of age, suggesting that the presence of schizophrenia may

trigger a primed susceptibility to multiple diseases at a younger stage of life. In physical health multimorbidity, patients but not siblings had more risk on having diseases than controls. This result was in line with a recent large study confirming that schizophrenia patients had multiple physical health diseases than healthy people (Smith et al., 2013). Also, prevalence of lifetime diseases including psychiatric diseases demonstrated a slightly increasing trend (controls<siblings<patients), but here only the difference between patients and controls reached statistical significance (Figure 3). Regarding the multimorbidity of complaints, patients had a significantly higher number of complaints than their siblings, who in turn had a significantly higher number of complaints than controls. Therefore, the estimated prevalence of multimorbidity was higher in patients with schizophrenia compared to siblings and controls, but it followed similar increasing trends with ageing, as reported in other studies (Agborsangaya et al., 2012; Britt et al., 2008; O'Kelly et al., 2011; Rizza et al., 2012; Schneider et al., 2012; van Oostrom et al., 2012). A large multi nation-wide study also showed that the prevalence of physical health multimorbidity was increased across the psychosis-spectrum e.g. 11.4 in controls, 21.8 percent in subclinical psychosis (more than one psychotic symptom in the past 12 months, but no lifetime diagnosis of psychosis) and 36.0 percent in lifetime diagnosis of psychosis. Although the prevalence was lower than the current study but the risks of subclinical psychosis and psychosis for multimorbidity were comparable with the present study (Stubbs et al., 2016).

Although this study was based on a large cohort of patients and their unaffected siblings, these data needed to be interpreted with some caution. This study focused on the main determinants of gender, age and new discoveries of familial liability, leaving out other reported multiple risk factors (Agborsangaya et al., 2012; De Hert et al., 2011) for multimorbidity. We showed that familial liability is one of the main determinants of multimorbidity which acts independently of the other major risk factors of age and gender. It is essential to perform additional genetic analysis to distinguish between the effects of genetic liability and intra-familial environmental susceptibility. Some other risk factors, *e.g.* psychotropic drugs, applied only to the patients; others such as nicotine, alcohol use, and IQ were described in the population characteristics. The present study was based mainly on self-reported diseases, clinical complaints, and medication history. For the selected population with psychotic disorders, there might be a reporting bias due to the diagnosis of the disease. Comparison to their siblings and matched healthy controls could lead to underrepresentation of the numbers, rather than an indication of the presence of other psychiatric symptoms like mood disorders, anxiety or eating disorders. A major methodological concern is how to deal with other psychiatric disorders. The inclusion of those disorders could be problematic; *e.g.* it is not uncommon for people with psychotic disorders to receive a diagnosis of mood disorder at some time in their lives because of the different presentation of symptoms at different times in the course of the disease. What presents may not always be a distinct disease but may have symptoms of the psychotic disorder. Mood disorder in patients was the most frequently co-occurring psychiatric disorder. However, only 5.5% of the patients received a mood disorder diagnosis, while depressive symptoms were more prevalent (62.0%) indicating that in our sample depressive symptoms are considered by and large to be an integrated part of the psychotic disorder. It must be noted that we did not include psychotic disorders in patients while estimating multimorbidity, as we wished to give the latter similar weight as in the other participants (siblings and controls). Another concern is that

we formed anxiety and eating disorders together as anxiety disorders co-occur with eating disorders. In fact, the existence of anxiety disorders can often lead to the development of an eating disorder i.e. anxiety precedes an eating disorder. Although anxiety and eating disorders are in different diagnosis groups with high comorbidity, both act similar clinical features (Hocaoglu, 2017).

The strength of this study was that it allowed for investigation of a large number of lifetime diseases and complaints in a large sample of psychotic patients, siblings, and controls. In fact, no previous study has dealt with a comprehensive list of diseases, either somatic or psychiatric, in people with psychotic disorders while counting multimorbidity in a cumulative way rather than focusing only on pairwise comorbidities (Nuyen et al., 2006; Oreski et al., 2012). The most informative feature of this study was the sibling model; whereas most studies emphasized multimorbidity either in healthy subjects or the disease population, this is the first study to consider multimorbidity of siblings of people with psychotic disorders.

4.1. Conclusions

Multimorbidity is a clinical burden not only for people with psychotic disorders but also for their family members. In psychosis, multimorbidity was strongly associated with women and was not limited to the elderly but also affected young individuals. This information may be vital to quantify the burden of multimorbidity on patients and, most importantly, on unaffected siblings. The risk of multimorbidity caused by familial liability for psychosis was consistent across gender and age group, meaning that familial liability for psychosis is in itself a strong independent determinant of multimorbidity. Future studies could investigate the role of heritability and genetic factors in multimorbidity to confirm our findings and gain more insight into causal factors.

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Supplementary Materials

Supplementary Methods

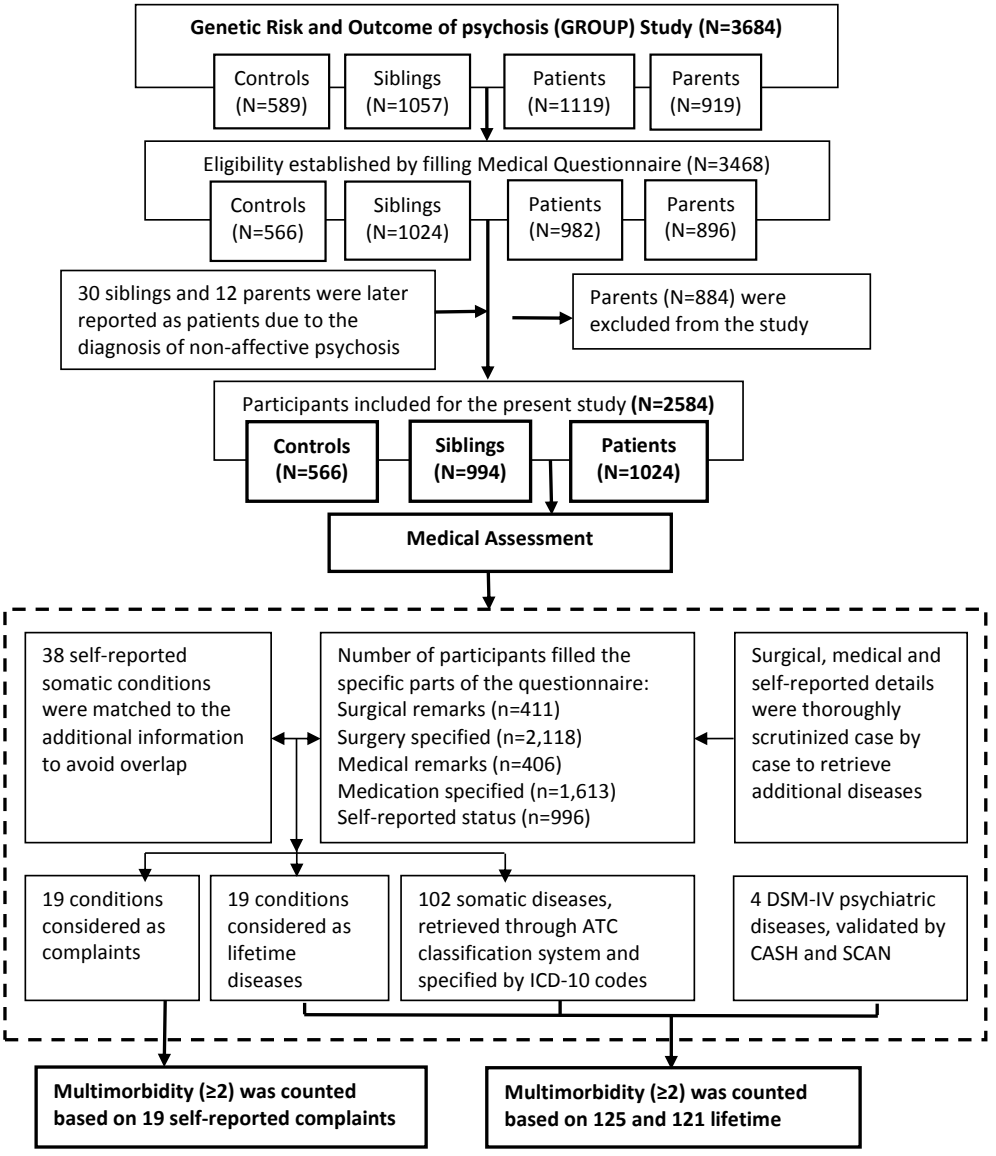
In Genetic Risk and Outcome of Psychosis (GROUP) project, patients were identified through clinicians working in regional psychosis departments or academic centers, whose caseload was screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services either 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 (Korver et al., 2012).

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.

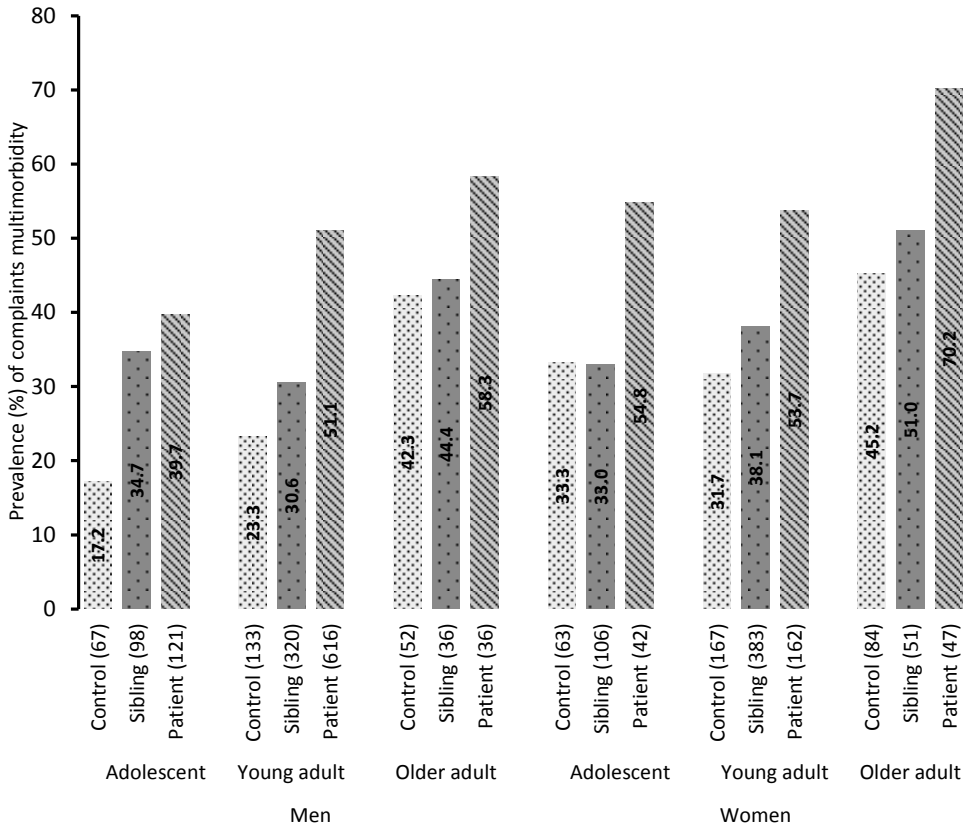
Supplementary Results

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

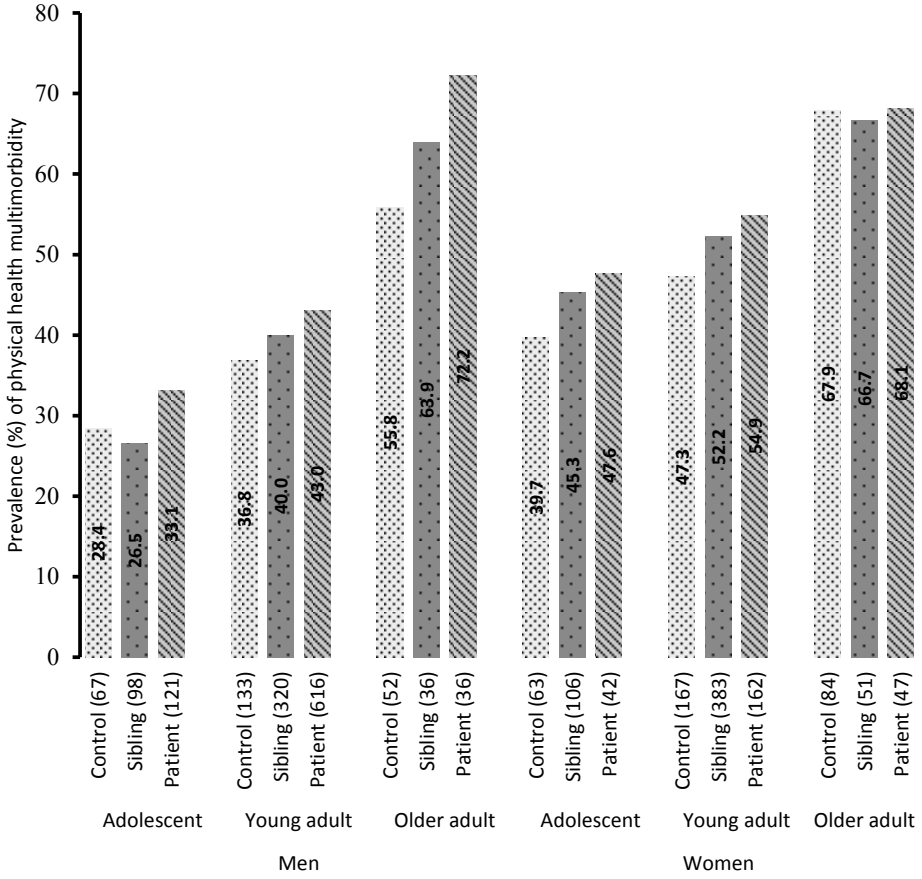
Table S3. Several domains of disease, such as diseases of the nervous system (35%), congenital mal/del-formations, and chromosomal abnormalities (12%), observed a *priori* in schizophrenia patients, also showed a significantly higher frequency compared to siblings and controls (Supplementary Table S3). 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 (Bresee et al., 2010; Bushe and Holt, 2004; De Hert et al., 2009; Hennekens et al., 2005; Iacovides and Siamouli, 2008; van Winkel et al., 2006). 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.



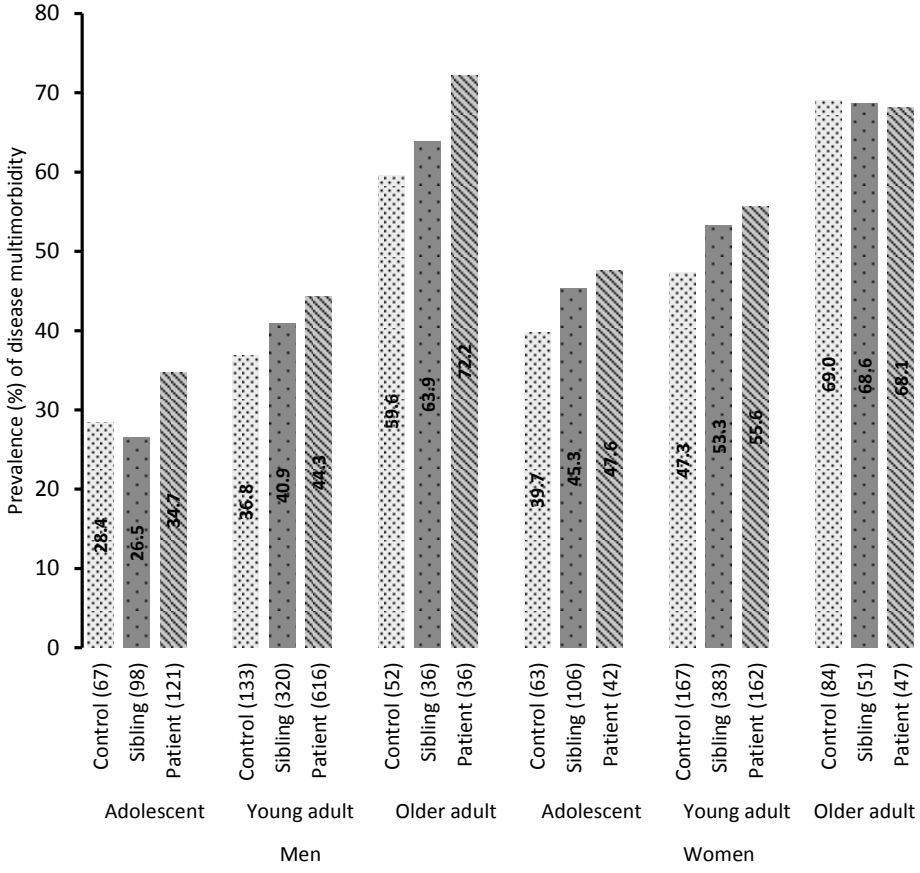
Supplementary Figure S1: Flowchart of inclusion of participants (GROUP version 3.2) and retrieval of information on complaints and diseases.



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 behavioral disorders			
Psychotic disorders (Schizophrenia, schizoaffective and delusional)	…	…	1024 (39.6)*
1. Mood Disorder	52 (9.2)	118 (11.9)	56 (5.5)
2. Anxiety and/or Eating Disorder	1 (0.2)	10 (1.0)	6 (0.6)
3. Substance Disorder	0	4 (0.4)	21 (2.1)
4. Other Disorders[a]	10 (1.8)	19 (1.9)	20 (2.0)
Diseases of the circulatory system			
5. Ischemic Heart Disease	2 (0.4)	4 (0.4)	7 (0.7)
6. Aneurysm	0	1 (0.1)	0
7. Myocarditis	0	0	0
8. Cardiomyopathy	0	0	1 (0.1)
9. Kawasaki Disease	0	1 (0.1)	0
10. Heart Failure	0	0	0
11. Arrhythmia	3 (0.5)	1 (0.1)	1 (0.1)
12. Heart Valve Disease	2 (0.4)	1 (0.1)	2 (0.2)
13. Hypertension	5 (0.9)	8 (0.8)	12 (1.2)
14. Hypotension	1 (0.2)	4 (0.4)	0
15. Stroke	1 (0.2)	1 (0.1)	6 (0.6)
16. Transient Ischemic Attack	1 (0.2)	2 (0.2)	2 (0.2)
17. Deep Vein Thrombosis	0	1 (0.1)	1 (0.1)
18. Pulmonary Embolism	0	2 (0.2)	1 (0.1)
19. Phlebitis	0	1 (0.2)	0
20. Hemorrhoids/Varices	0	2 (0.2)	0
21. Varicosity	7 (1.2)	7 (0.7)	2 (0.2)
Endocrine, nutritional and metabolic diseases			
22. Dyslipidaemia	5 (0.9)	5 (0.5)	6 (0.6)
23. Obesity	23 (4.1)	38 (3.8)	62 (6.1)
24. Diabetes	3 (0.5)	8 (0.8)	16 (1.6)
25. Hypothyroidism	3 (0.5)	9 (0.9)	8 (0.8)
26. Hyperthyroidism	1 (0.2)	0	3 (0.3)
27. Thyroiditis (not specified)	4 (0.7)	7 (0.7)	10 (1.0)
28. Goiter	2 (0.4)	0	0
29. Addison's Disease	0	0	1 (0.1)
Diseases of the respiratory system			
30. Chronic Obstructive Pulmonary Disease	26 (4.6)	52 (5.2)	74 (7.2)
31. Asthma	10 (1.8)	17 (1.7)	5 (0.5)
32. Pneumothorax	0	2 (0.2)	1 (0.1)
33. Bronchitis	0	1 (0.1)	1 (0.1)
34. Pneumonia	0	0	1 (0.1)
35. Sleep Apnea	0	0	1 (0.1)
36. Sarcoidosis	1 (0.2)	0	0
37. Nasal Polyps	3 (0.9)	8 (0.8)	4 (0.4)
38. Deviated Nasal Septum	5 (0.9)	7 (0.7)	6 (0.6)
39. Epistaxis	0	1 (0.1)	2 (0.2)
40. Chronic Sinusitis	0	4 (0.4)	2 (0.2)
41. Tonsillitis	46 (8.1)	124 (12.5)	95 (9.3)
42. Chronic Laryngitis	1 (0.2)	1 (0.1)	0
43. Hay Fever	49 (8.7)	65 (6.5)	51 (5.0)

Neoplasms			
44. Cancer (not specified)	4 (0.7)	9 (0.9)	9 (0.9)
Diseases of the musculoskeletal system and connective tissue			
45. Rheumatoid Arthritis	2 (0.4)	2 (0.2)	0
46. Systemic lupus Erythematosus	1 (0.2)	0	0
47. Multiple Sclerosis	0	0	0
48. Psoriatic Arthritis	0	0	0
49. Osteoarthritis	3 (0.5)	7(0.7)	12 (1.2)
50. Frozen Shoulder	0	0	0
51. Gout	1 (0.2)	0	0
52. Fibromyalgia	4 (0.7)	6 (0.6)	3 (0.3)
53. Back & Neck Pain	16 (2.8)	16 (1.6)	9 (0.9)
54. Scoliosis & Kyphosis	4 (0.7)	6 (0.6)	1 (0.1)
55. Carpal Tunnel Syndrome	2 (0.4)	2 (0.2)	2 (0.2)
56. Osteoporosis	2 (0.4)	1 (0.1)	0
57. Osteomyelitis	1 (0.2)	0	0
Diseases of the digestive system			
58. Chronic Gastritis	6 (1.1)	10 (1.0)	16 (1.6)
59. Helicobacter Pylori	0	1 (0.1)	0
60. Lactose Intolerance	4 (0.7)	7 (0.7)	4 (0.4)
61. Diverticulitis	0	0	0
62. Celiac Disease	0	1 (0.1)	0
63. Diarrhea	0	4 (0.4)	3 (0.3)
64. Constipation	2 (0.4)	5 (0.5)	10 (1.0)
65. Peritonitis	0	0	1 (0.1)
66. Pancreatitis	0	0	0
67. Irritable Bowel Syndrome	4 (0.7)	8 (0.8)	2 (0.2)
68. Inflammatory Bowel Disorder	7 (1.2)	4 (0.4)	1 (0.1)
69. Gall Bladder Diseases	6 (1.1)	9 (0.9)	13 (1.3)
70. Diseases of Appendix	27 (4.8)	60 (6.0)	47 (4.6)
71. Hernia	22 (3.9)	32 (3.2)	34 (3.3)
72. Anal Fistula	2 (0.4)	3 (0.3)	3 (0.3)
73. Teeth Abnormalities	12 (2.1)	16 (1.6)	12 (1.2)
Pregnancy, childbirth and the puerperium			
74. Abortion/Recurrent Abortion	1 (0.2)	4 (0.4)	6 (0.6)
75. Ectopic Pregnancy	2 (0.4)	2 (0.2)	0
76. Other Obstetric Complications	1 (0.2)	2 (0.2)	0
Diseases of the genitourinary system			
77. Diseases of Genital Organ	3 (0.5)	5 (0.5)	3 (0.3)
78. Infertility	2 (0.4)	2 (0.2)	1 (0.1)
79. Endometriosis	0	3 (0.3)	1 (0.1)
80. Menopausal Syndrome	1 (0.2)	0	0
81. Prolapse	0	1 (0.1)	0
82. Menstrual Abnormalities	1 (0.2)	0	1 (0.1)
83. Pelvic Inflammatory Disease	0	1 (0.1)	1 (0.1)
84. Chronic Cystitis (>3/years)	18 (3.2)	40 (4.0)	31 (3.0)
85. Kidney Stone	11 (1.9)	13 (1.3)	8 (0.8)
86. Chronic Kidney Disease	0	1 (0.1)	0
87. Pyelonephritis	1 (0.2)	1 (0.1)	0
88. Hydrocele	1 (0.2)	1 (0.1)	0
89. Benign Prostatic Hyperplasia	1 (0.2)	1 (0.1)	0
90. Epididymitis	1 (0.2)	0	0
Certain infectious and parasitic diseases			
91. Tuberculosis lifetime	5 (0.9)	3 (0.3)	10 (1.0)
92. Viral Hepatitis	2 (0.4)	2 (0.2)	3 (0.3)
93. Hepatitis (not specified)	1 (0.2)	0 (0.0)	4 (0.4)

94. Cytomegalovirus	1 (0.2)	1 (0.1)	0
95. Infectious Mononucleosis	0	7 (0.7)	0
96. Tropical Diseases (not specified)	1 (0.2)	8 (0.8)	2 (0.2)
97. Other Bacterial Infection	1 (0.2)	1 (0.1)	3 (0.3)
98. Infectious Diseases (not specified)	15 (2.7)	22 (2.2)	38 (3.7)
99. 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, [a]Other 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.

Domain	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. COPD[a]	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; [a]COPD=Chronic Obstructive Pulmonary Disease