Increased cardiometabolic dysfunction in first-degree relatives of patients with psychotic disorders

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ABSTRACT

Introduction: Elevated prevalence of comorbid cardio-vascular and metabolic dysfunction (CMD) is consistently reported in patients with severe psychotic disorders such as schizophrenia (SZ), schizoaffective (SZA) and bipolar disorder (BP-P). Since both psychosis and CMD are substantively heritable in nature, we attempted to investigate the occurrence of CMD disorders in first-degree relatives of probands with psychosis.
Methods: Our sample included 861 probands with a diagnosis of SZ ($n = 354$), SZA ($n = 212$) and BP-P ($n = 295$), 776 first-degree relatives of probands and 416 healthy controls. Logistic regression was used to compare prevalence of any CMD disorders (diabetes, hypertension, hyperlipidemia or coronary artery disease) across groups. Post hoc tests of independence checked for CMD prevalence across psychosis diagnosis (SZ, SZA and BP-P), both in relatives of probands and within probands themselves.
Results: After controlling for potential confounders, first-degree relatives with ($p < 0.001$) and without ($p = 0.03$) Axis I non-psychotic or Axis- II cluster disorders were at a significant risk for CMD compared to controls. No significant difference ($p = 0.42$) was observed in prevalence of CMD between relatives of SZ, SZA and BP-P, or between psychosis diagnoses for probands ($p = 0.25$).
Discussion: Prevalence of CMD was increased in the first-degree relatives of psychosis subjects. This finding suggests the possibility of overlapping genetic contributions to CMD and psychosis. Increased somatic disease burden in relatives of psychotic disorder probands points to need for early detection and preventive efforts in this population.

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1. Introduction

Psychotic disorders such as schizophrenia (SZ), schizoaffective (SZA) and bipolar disorder (BP-P) are increasingly being viewed as 'multi-system' conditions, with disease burden extending beyond neurobiological and clinical dimensions (Kirkpatrick, 2009; Leboyer et al., 2012). Somatic comorbidities place patients at high-risk for premature death. Recent reviews show that individuals with psychosis are at least 3–4 times more likely than the general population to die due to natural causes (i.e. medical conditions excluding suicide and accidents) (Brown et al., 2010; Nordentoft et al., 2013). The mortality gap is between 20% and 25% compared to the general population

(Fleischhacker et al., 2008; Laursen, 2011; Laursen et al., 2014b) and has widened over time with improved treatments and availability of medical services that are less utilized by the severely mentally ill (Saha et al., 2007).

Cardio-vascular and metabolic (hereinafter called cardiometabolic) disorders (CMD) are known to be the leading medical cause of excess mortality in psychosis (Chwastiak et al., 2006; Osborn et al., 2008; Laursen et al., 2009; Woodhead et al., 2014). This is underscored by statistics reporting a 1.3 to 4.9 fold increase in morbidity and mortality resulting from coronary heart disease, diabetes and treatable risk factors such as hypertension and dyslipidemia (Jeste et al., 1996; McEvoy et al., 2005; Miller et al., 2008; Nordentoft et al., 2013; Laursen et al., 2014a).

A longitudinal analysis (Birkenaes et al., 2007) highlighted identical levels of cardiometabolic risk factors in SZ and BP-P, with both groups showing twice the prevalence compared to general population.

Investigations - both of drug naïve patients with SZ and with BP-P report worse glycemic control compared to healthy controls (Regenold et al., 2002; Ryan et al., 2003; Maina et al., 2008; Kim et al., 2009; Vancampfort et al., 2013). A more recent analysis in a younger first episode sample (mean age, 23.6) from the Recovery After an Initial Schizophrenia Episode (RAISE) study shows that cardiometabolic risk factors and abnormalities are present early in the illness, even before the onset of effects due to antipsychotics (Correll et al., 2014).

Psychotic and cardiometabolic disorders both have substantive heritability. This raises the question whether cardiometabolic risk is increased in relatives of people with psychosis. A few family studies have been conducted, albeit in a more narrow focus. Some studies (Spelman et al., 2007; Fernandez-Egea et al., 2008a) show impaired glucose tolerance in first-degree relatives of SZ compared to healthy controls. Two studies detected increased prevalence of diabetes mellitus type-II in first-degree relatives (Mukherjee et al., 1989; Fernandez-Egea et al., 2008b). Another study found associations in a larger sample, but also included second and third degree relatives in the investigation (van Welie et al., 2013). While these studies contribute to our knowledge about the relationship between psychosis and CMD, they were mostly small in sample size and restricted to non-affective psychoses.

Our study sought to confirm and extend results from previous studies by including a large series of probands across the psychosis spectrum (SZ, SZA and BP-P), first-degree non-psychotic relatives of probands, and healthy controls from the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) study. As increased CMD abnormalities are well established in psychotic patients, the primary aim of the study was to test the hypothesis that first-degree relatives would have an elevated prevalence of CMD disorders compared to the healthy controls.

2. Methods

2.1. Participants

Our subject pool consisted of individuals recruited as part of the B-SNIP study, a multisite collaborative research consortium (Baltimore, Chicago, Dallas, Detroit, Boston and Hartford). Sites used identical diagnostic and clinical assessment techniques, and shared approaches to recruitment (Tamminga et al., 2013). All sites recruited 1) SZ, SZA, and BP-P probands; 2) first-degree relatives of probands; and 3) healthy comparison subjects to define the rates and severity of abnormalities in the patient and relative groups on measures of interest.

2.1.1. Probands

Patients with a history of psychotic symptoms were recruited if they had at least one available first-degree relative 15–65 years of age willing to participate in the study. A total of 861 probands with a diagnosis of SZ ($n = 354$), SZA ($n = 212$) and BP-P ($n = 295$) were included in the study.

Diagnosis was determined at consensus diagnostic meetings after review of data gathered using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 2012), information about the proband's medical and psychiatric history obtained from relatives, and available medical charts. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

2.1.2. First-degree relatives

First-degree relatives ($n = 776$) of probands were assessed with SCID and the Structured Interview for DSM-IV Personality (SIDP-IV) (Pfohl et al., 1997). Relatives with presence or past history of psychosis were excluded to avoid confounding due to anti-psychotics. For the sake of analysis in the present study, relatives were further stratified based on clinical diagnosis:

1) Affected family (AF): The affected group ($n = 442$) was diagnosed with Axis I non-psychotic or Axis II cluster A (odd or eccentric) or cluster B (dramatic, emotional, or erratic) personality disorders. First-degree relatives diagnosed with Axis I psychotic disorders were excluded from this group.
2) Non-affected family (NAF): First-degree relatives ($n = 334$) with no history of Axis I or Axis II diagnosis.

2.1.3. Healthy controls

Healthy volunteers ($n = 416$) were recruited through print and electronic media and research registries. Healthy comparison subjects were required to have no personal history of a psychotic disorder or recurrent depression (based on the SCID and consensus review) and no known immediate family history of these disorders.

2.2. Statistical methods

2.2.1. Group coding and characterization

The event/outcome variable for the analysis was a binary marker of cardiometabolic dysfunction (CMD). It was assessed across the sample based on self-reported medical history ("1 = yes" or "0 = no") or current use of medication/treatment for any of four cardiometabolic disorders: coronary artery disease, diabetes, hypertension or hyperlipidemia. A subject was considered as CMD + if reported to have at least one of the above conditions, CMD − if not. Trends in CMD + frequency across the 4 study groups (i.e., controls, NAF, AF and Probands) were assessed using the Cochran–Armitage trend test. Sample differences across groups were determined by chi-square tests for gender, race and site and Kruskal–Wallis test for mean age.

Table 1
Demographic characteristics of controls, non-affected first-degree relatives (NAF), affected first-degree relatives (AF) and Probands.

Variable	Controls ($n = 416$)		NAF[a] ($n = 334$)		AF[b] ($n = 442$)		Probands ($n = 861$)		X^2	p
	N	%	N	%	N	%	N	%		
Sex (M)	190	46	100	30	137	31	430	50	66.6	<0.001
Race[c]									29.8	<0.001
AA	122	29	94	28	116	26	310	36		
CA	256	62	217	65	310	70	492	57		
OT	38	9	23	7	16	4	59	7		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p
Age	37.15	12.69	41.09	16.6	42.75	14.99	36.1	12.52	27.7	<0.001
Family SES	39.76	14.35	42.66	14.31	41.49	14.78	41.512	14.81	2.57	0.052

[a] NAF = first-degree relatives with no history of Axis I or Axis II disorders.
[b] AF = first-degree relatives with Axis I or Axis II disorders.
[c] AA = African-American, CA = Caucasian and OT = others.

Table 2
Frequency of cardiometabolic disorder (CMD+).

	Controls ($n = 416$)		NAF($n = 334$)		AF($n = 442$)		Probands($n = 861$)		X^2	p^a
	N	%	N	%	N	%	N	%		
Coronary artery disease	2	0.5%	9	2.7%	16	3.6%	7	0.8%	0.0196	0.8
Diabetes	8	1.9%	19	5.7%	37	8.4%	106	12.3%	43.3	<0.01
Hyperlipidemia	30	7.2%	40	12%	68	15.4%	168	19.5%	36.1	<0.01
Hypertension	34	8.2%	49	14.7%	93	21%	192	22.3%	40.6	<0.01
Event of CMD (presence of at least 1 of the above conditions)										
CMD+	57	13.7%	87	26%	141	31.9%	318	36.9%	73.1	<0.01
CMD−	359	86.3%	247	74%	301	68.1%	543	63.1%	-	-

[a] Cochran–Armitage trend test at 0.05 alpha.

2.2.2. Socio-economic status

As a socio-economic gradient has been demonstrated related to cardio-vascular and diabetes factors, (Chaturvedi et al., 1998; Kanjilal et al., 2006; Saydah et al., 2013) with both education and income playing important determinants, for our analysis we used the Family Hollingshead Index Score. This was computed by summing the Hollingshead occupation score multiplied by 7 and the Hollingshead education score multiplied by 4; higher score indicates lower social class. The Hollingshead Socio-Economic Status (SES) score was not available and missing at random in 134 subjects (<10%). It has been shown that properly performed multiple imputations give less biased results compared to traditional complete case analysis (van der Heijden et al., 2006). Therefore, to account for missing values, we used a multivariate normal imputation method. The event variable CMD was used as a predictor variable because multiple imputations with the outcome have been shown to yield more valid results (Moons et al., 2006). Imputation for Hollingshead SES was performed using the Comprehensive R Archive Network (CRAN) package Amelia. One-way ANOVA was used to check the difference in mean family SES across subject groups.

2.2.3. Main analysis

A logistic regression was performed to evaluate the risk of CMD+ occurrence based on subject status (i.e., control, NAF, AF and Proband) while controlling for age, sex, race, site and SES differences. A type-1 error rate of 0.05 was applied. Adequacy of the regression model fit was evaluated using the Hosmer–Lemeshow calibration test (Hosmer et al., 2013). All statistical analysis was performed using the R statistical programming package (Vienna, Austria; 2013, http://www.R-project.org, version 2.15.3). As a post hoc comparison, a test of independence was performed to compare CMD+ prevalence in relatives of SZ, SZA and BP probands to identify if any specific group influenced results. Similar post hoc tests of independence were performed across diagnostic groups in probands.

3. Results

Analysis of variance revealed a significant difference in age between all groups ($F = 27.7$, $p < 0.001$), with the AF reporting highest mean age with a 6.6 year difference from the youngest group (Probands) (Table 1). Family groups are older as the majority of relative recruited into the study were parents of probands. The distribution of the Family SES score was similar between the groups. The sex and race ratios significantly differed between groups ($p < 0.001$).

Prevalence of CMD frequency is shown in Table 2 and Fig. 1. On visual inspection of Fig. 1, except for coronary artery disease which was not common, all the other conditions (i.e., diabetes, hyperlipidemia and hypertension) showed an increasing trend in prevalence from controls to relatives to probands. Subsequent testing for a linear trend in CMD frequency resulted in a highly significant trend increasing from controls to probands with the NAF and the AF groups as intermediaries (Cochran–Armitage trend test $X^2 = 73.1$, $p < 0.001$).

After adjusting for age, sex, race, site and SES, overall CMD rates were significantly different from the control population in all study groups. The results are shown in Table 4. For unaffected family the OR = 1.6 (95% CI = 1.03, 2.3; $p = 0.03$), affected family OR = 2.6 (95% CI = 1.55, 3.03; $p < 0.001$) and proband OR = 4.8 (95% CI = 3.48, 6.96; $p < 0.001$). Since both age and SES were significant covariates in the model, we evaluated them as modifiers of the effect of participant group (using an interaction term). No significant interactions were observed.

A Hosmer–Lemeshow test for the model was not significant ($p = 0.379$) indicating good model calibration. Furthermore, the Mc-Fadden pseudo R^2 and chi-square statistics both increase with the log functional form indicating that the overall model is superior in terms of model fit in comparison to a model without covariates. Results from post hoc tests comparing prevalence of CMD across diagnostic groups of probands and relatives of SZ, SZA and BP are shown in Table 3. No significant differences in CMD prevalence were observed in relatives ($X^2 = 1.73$, $p = 0.42$) or probands across diagnostic groups ($X^2 = 2.72$, $p = 0.25$).

4. Discussion

As predicted, our findings indicate that probands with psychotic disorders are at significantly increased risk for overall cardiometabolic dysfunction (OR = 4.8) compared to healthy controls. The unaffected family group, independent of any psychiatric problems and drug effects, reported 1.6 times the risk compared to healthy controls. This is in agreement with findings from another large sample analysis looking at associations between diabetes and relatives of patients but was restrictive to non-affective psychosis (van Welie et al., 2013). In comparison, our finding is novel due to the inclusion of multiple diagnostic categories (both affective and non-affective psychosis) and is suggestive
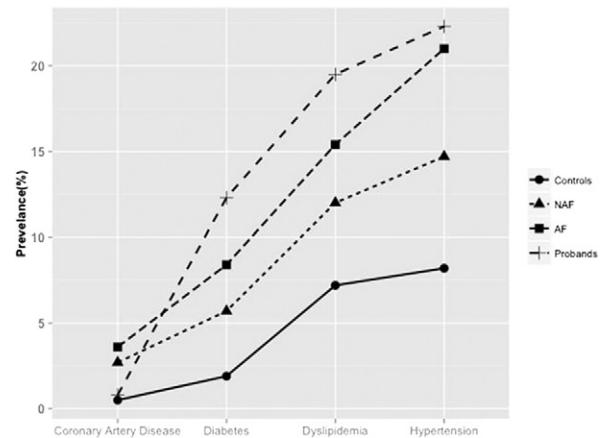
Fig. 1. Point prevalence of CMD conditions across groups. (Figure not adjusted for age effects. NAF = first-degree relatives with no history of Axis I or Axis II disorders. AF = first-degree relatives with Axis I or Axis II disorders.).

Table 3
Frequency of cardiometabolic dysfunction across probands and relatives of SZ, SZA and BP.

		BP		SZA		SZ		X^2	p
Relatives	CMD+	76	27%	56	29%	96	32%	1.73	0.42
	CMD−	206	73%	137	71%	205	68%		
Probands	CMD+	99	34%	78	37%	141	40%	2.72	0.25
	CMD−	196	66%	134	63%	213	60%		

of CMD prevalence as trans-diagnostic and not restricted to non-affective psychosis. What is also unique to our findings is that the first-degree relatives diagnosed with Axis I or Axis II non-psychotic disorders had an increased risk for CMD compared to healthy relatives.

Our observations of increased CMD in unaffected relatives point to the possibility that psychosis and CMD may share risk factors that are familial. This vulnerability could be due to common risk factors linking CMD and psychosis, such as common genetic liability, shared environmental factors and epigenetic interactions. Regarding common genetic liability, there is emerging literature regarding shared loci in SZ or bipolar disorder and cardiometabolic disorders (Gough and O'Donovan, 2005; Andreassen et al., 2013; Liu et al., 2013). For example, Liu et al. performed a pathway analysis of type 2 diabetes and schizophrenia risk genes, identifying several 'hub proteins', such as GRB2 and PLCG1, which may interact with networks of proteins in both disorders (Liu et al, 2013). Future genetic investigations should continue to explore a possible link between psychosis and CMD risk alleles.

Shared environmental factors could also contribute to the elevated prevalence of CMD among relatives. Similar to psychotic probands, first-degree relatives affected with non-psychotic disorders may also suffer from poor health habits and decreased access to or compliance with medical care. This possibility is further supported by numerous studies demonstrating an association between cardiometabolic risk and depression (Rudisch and Nemeroff, 2003). Environmental factors that could account for the elevated prevalence of CMD among non-affected first-degree relatives are less clear, but could include caretaker burden (Schulz et al., 1997; Möller-Leimkühler and Wiesheu, 2012) or even social network phenomena (Christakis and Fowler, 2007).

Furthermore, studies of relatives of people with psychosis have reported higher emotional, economic and social distress (Reinares et al., 2006; Caqueo-Urízar et al., 2009, 2011; Perlick et al., 2010). The results from our study highlight an additional need to incorporate somatic disease burden in these investigations.

In comparison to past investigations, our inclusion of BP-P patients and their relatives stands apart. When comparing the CMD occurrence between proband groups for relatives, we report no significant differences ($p = 0.43$). Our findings here indicate that the familial risk for CMD spreads across the psychosis spectrum and is not restricted to relatives of non-affective psychosis.

Any confounding due to antipsychotic usage in the first-degree relatives can be ruled out, as any family member with a psychosis diagnosis was excluded from the analysis. However, since the affected relatives had a diagnosis of cluster A or cluster B personality disorders, a few of them received antipsychotics, possibly leading to elevated odds for CMD. Our study is reasonably representative of the general population of patients with psychotic disorders, their first-degree relatives and healthy controls. By contrast, the van Welie et al. study (van Welie

et al., 2013) had a much higher mean age (62.5) and included only a Caucasian population, and Mukherjee et al. (Mukherjee et al., 1989) used data from a population registry, and lacked a comparable control group.

The results of this study should be interpreted in the view of the following limitations. First, we could not establish the presence or severity of comorbid metabolic disorders based on laboratory confirmation, and relied on patient self-report and review of medication treatments for comorbid disease status; this could raise the possibility of selective recall bias. With that said, studies have shown that information provided by psychiatric patients about medical diagnoses is reliable, valid, and useful (Linet et al., 1989; Bergmann et al., 1998; Selim et al., 2004). Second, we also could not distinguish between type 1 and type 2 diabetes in the patient population. Third, no data were collected on current tobacco and alcohol use, which are common in schizophrenia and bipolar populations and act as independent risk factors for cardiometabolic dysfunction. Effects due to substance abuse may be less likely as we excluded participants meeting the DSM-4 criteria for current or recent (within the past month) substance abuse or past dependence within the last 6 months. However, the effects of past substance abuse cannot be ruled out. Fourth, we could not address the influence of BMI on the obtained results, as data on weight and height of the participants were not recorded. Since obesity runs in families, inclusion of BMI data could have increased the explanatory power. Finally, we also could not control for the effects of shared living situation as some probands may live with first-degree relatives, and others may not.

The results from our analysis elucidate that boundaries for disease-burden in psychosis should be re-thought, for the sake of both etiology and disease prognosis. Our findings suggest several lines of future investigation. First, the observed familial association suggests that cardiometabolic markers (e.g. heart rate variability, HbA1C Levels, lipid profile etc.) should be explored as potential heritable markers for psychosis. Second, genetic studies should focus on the possible pleiotropic effects of CMD and psychosis risk genes, with the goal of isolating genes that may contribute to elevated prevalence of CMD in psychosis. Finally, our data suggest that the substantive medical morbidity in families of psychosis probands should motivate studies of somatic disease burden and avenues for early detection and preventive efforts not only in patients but in their relatives.

Contributors

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Conflict of interest

GP has served on an advisory panel for Bristol-Myers Squibb. JS has been on advisory boards for Bristol-Myers Squibb, Eli Lilly, Pfizer, Roche, and Takeda and has received grant support from Janssen. CT has the following disclosures to make: Intracellular Therapies (ITI, Inc.)—Advisory Board, drug development; PureTech Ventures—Ad Hoc Consultant; Eli Lilly Pharmaceuticals—Ad Hoc Consultant; Sunovion—Ad Hoc Consultant; Astellas—Ad Hoc Consultant; Cypress Bioscience—Ad Hoc Consultant; Merck—Ad Hoc Consultant; International Congress on Schizophrenia Research—Organizer, unpaid volunteer; National Alliance on Mental Illness—Council Member, unpaid volunteer; American Psychiatric Association—Deputy Editor. MSK has received research support from Sunovion and GlaxoSmithKline. Other authors report no disclosures.

Table 4
Adjusted odds ratio and 95% confidence interval estimates predicting likelihood of CMD occurrence by subject status.

	N	OR[a]	95% CI		p
Controls	416	1.0	–	–	–
NAF	334	1.6	1.03	2.3	0.03
AF	442	2.6	1.55	3.03	<0.01
Probands	861	4.8	3.48	6.96	<0.01

[a] Adjusted for age, sex, race and SES.

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