Genetic Predictors of Risk and Resilience in Psychiatric Disorders: A Cross-Disorder Genome-Wide Association Study of Functional Impairment in Major Depressive Disorder, Bipolar Disorder, and Schizophrenia

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Functional impairment is one of the most enduring, intractable consequences of psychiatric disorders and is both familial and heritable. Previous studies have suggested that variation in functional impairment can be independent of symptom severity. Here we report the first genome-wide association study (GWAS) of functional impairment in the context of major mental illness. Participants of European-American descent (N = 2,246) were included from three large treatment studies of bipolar disorder (STEP-BD) (N = 765), major depressive disorder (STAR*D) (N = 1091), and schizophrenia (CATIE) (N = 390). At study entry, participants completed the SF-12, a widely used measure of health-related quality of life. We performed a GWAS and pathway analysis of the mental and physical components of health-related quality of life across diagnosis (~1.6 million single nucleotide polymorphisms), adjusting for psychiatric symptom

severity. Psychiatric symptom severity was a significant predictor of functional impairment, but it accounted for less than one-third of the variance across disorders. After controlling for diagnostic category and symptom severity, the strongest evidence of genetic association was between variants in *ADAMTS16* and physical functioning ($P = 5.87 \times 10^{-8}$). Pathway analysis did not indicate significant enrichment after correction for gene clustering and multiple testing. This study illustrates a phenotypic framework for examining genetic contributions to functional impairment across psychiatric disorders.

Key words: SF-12; health-related quality of life; disability; genetics; *ADAMTS16*

INTRODUCTION

Functional impairment is one of the most enduring, intractable consequences of psychiatric disorders [Shippee et al., 2011; Awad and Voruganti, 2012; IsHak et al., 2012]. By the term "functional impairment," we refer to the persistent interference in daily life activities and role performance by psychiatric or related symptoms. Even when psychiatric symptoms abate through intervention, quality of life does not always improve [Harvey et al., 2012; IsHak et al., 2012]. Effective treatments for functional impairment have been scarce, making etiological studies valuable for informing novel treatment approaches.

Although functional impairment is a required dimension of DSM-IV psychiatric diagnoses, there are also individual differences in the extent of impairment, even for a given level of symptom severity [Eack and Newhill, 2007; Priebe et al., 2011; Verboom et al., 2011]. This evidence coincides with clinical observations that some patients are nearly incapacitated by relatively mild symptoms of psychiatric disorders while other patients are able to sustain activities of daily living despite moderate to severe psychiatric symptoms. This partial disassociation between psychiatric symptoms and disability has led to proposals for DSM-5 to separate and more clearly delineate the two dimensions [APA, 2010]. Our hypothesis is that individual variation in functional impairment, given a specific level of symptom severity, reflects an axis of risk/resilience that is partly distinct from risk for the psychiatric disorder itself.

Genetic contributions to functional impairment have not been extensively explored, but there is increasing interest in this topic [Sprangers et al., 2009; Raat et al., 2010]. There is evidence from twin and family studies in clinical and population samples to support a genetic contribution [Romeis et al., 2005; McGrath et al., 2009; Steenstrup et al., 2013]. Two large population-based twin studies (N $\sim$ 3,000, N $\sim$ 46,000) using the same functional impairment measures as the current study, reported heritability of the composite scores of $h^2 \sim 0.35$ (range 0.34–0.37) [Romeis et al., 2005] and $h^2 \sim 0.25$ (range 0.11–0.35) with variability due to age and gender [Steenstrup et al., 2013]. Two family studies have investigated the familial aggregation of functional impairment in relatives with schizophrenia. Both found strong evidence for the familiality of functional impairment ($h^2 \sim 0.60$) that was notably higher than for other behavioral traits more closely related to symptoms of schizophrenia [Kendler et al., 1995; McGrath et al., 2009].

This study is the first genome-wide association study (GWAS) of functional impairment in psychiatric disorders. We hypothesize an axis of risk/resilience for functional impairment that transcends diagnostic boundaries, allowing us to exploit the increased sample size of a cross disorder design to maximize power for gene finding under this set of assumptions. Our approach resonates with increasing interest in identifying fundamental dimensions of individual difference that transcend diagnostic boundaries as exemplified by the NIMH research domain criteria (RDoC) initiative [Insel et al., 2010]. This study used the three largest psychiatric treatment effectiveness studies for major depressive disorder, bipolar disorder, and schizophrenia (STAR*D, STEP-BD, and CATIE, respectively). Each of the studies collected extensive phenotypic data, including the SF-12 or SF-36, which are widely used, extensively validated, self-report measures of health-related quality of life [Ware and Sherbourne, 1992; McHorney et al., 1993, 1994; Ware et al., 1996; Contopoulos-Ioannidis et al., 2009]. The questionnaires measure general, rather than disease specific, health status.

Consistent with our conceptualization of an axis of risk/resilience that is partly independent from psychiatric symptom severity, we developed a functional impairment phenotype that controlled for psychiatric symptom severity. This phenotype captured the extent to which an individual was more or less impaired than expected given his/her specific psychiatric symptom profile. Here we report the results of the first GWAS and pathway (i.e., gene set) analysis of functional impairment across psychiatric disorders.

MATERIALS AND METHODS
Participants

Sample description. For each cohort, study protocols and informed consent procedures were approved by institutional review boards at each participating clinical site. Details regarding the primary clinical samples and genotyping have reported elsewhere as part of a GWAS of cross-disorder disease risk [Huang et al., 2010]. The following is a brief description.

*Major depressive disorder (Sequenced Treatment Alternatives to Relieve Depression [STAR*D]).* STAR*D was a multisite, prospective, randomized multiphase clinical trial of outpatients with nonpsychotic major depressive disorder that enrolled 4,041 participants over a 3-year period [Fava et al., 2003; Rush et al., 2004]. Eligibility required meeting DSM-IV criteria for a single or recurrent nonpsychotic major depressive episode coupled with a score of $\geq$14 on the 17 item Hamilton Depression Rating Scale [Hamilton, 1960, 1967]. The relevant exclusion criteria were: history of bipolar disorder, schizophrenia, schizoaffective disorder, or psychosis not otherwise specified. As previously described, 1,953 individuals from the larger study were enrolled in a genetic substudy [Garriock et al., 2010; Shyn et al., 2011].

Bipolar disorder (Systematic Treatment Enhancement Program for Bipolar Disorder [STEP-BD]). STEP-BD was a national, longitudinal public health initiative which including randomized and standard care components designed to evaluate

the effectiveness of bipolar treatments [Sachs et al., 2003; Kogan et al., 2004]. Over a 7-year period, 4,361 participants were enrolled across 20 sites and followed for up to 2 years. Eligibility required a consensus DSM-IV bipolar spectrum diagnosis (bipolar I, bipolar II, bipolar not otherwise specified, or cyclothymia) on both the Affective Disorders Evaluation and Mini-International Neuropsychiatric Interview-PLUS semistructured interviews [Sachs et al., 2003]. As previously described, 2,089 individuals from the larger study were enrolled in a genetic sub-study [Sklar et al., 2008].

Schizophrenia (Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE]). CATIE was a multiphase randomized controlled trial of antipsychotic medications comprising 1,460 individuals with schizophrenia followed for up to 18 months [Stroup et al., 2003; Lieberman et al., 2005]. Final study diagnoses of DSM-IV schizophrenia were established by CATIE clinicians using the Structured Clinical Interview for DSM-IV [First et al., 1994] and review of clinical records. Relevant exclusion criteria were: diagnosis of schizoaffective disorder, pervasive developmental disorder, mental retardation, other cognitive disorder, or single psychotic episode; history of treatment resistance; and serious adverse reaction to the study treatments [Stroup et al., 2003]. As previously described, 738 individuals from the larger study were enrolled in a genetic sub-study [Sullivan et al., 2008].

Genotyping

As previously described, genotyping of STEP-BD and CATIE samples was performed using the Affymetrix GeneChip Human Mapping 500K Array Set (Affymetrix, Inc., Santa Clara, CA) [Huang et al., 2010]. Approximately half of the STAR*D samples were genotyped with the same 500K array and the second half with the Affymetrix Human Single Nucleotide Polymorphism (SNP) Array 5.0. Genotyping of the STEP-BD samples was performed at the Broad Institute [Sklar et al., 2008]. Genotyping of the CATIE samples was performed at Perlegen Sciences (Mountain View, CA) [Sullivan et al., 2008]. Genotyping of the STAR*D samples run on the Affymetrix 500K array was performed at Affymetrix, and genotyping of the STAR*D samples run on the Affymetrix 5.0 array was performed at the University of California, San Francisco [Garriock et al., 2010; Shyn et al., 2011].

Quality control and harmonization of genotype data. Quality control (QC) of the genotypic datasets was first performed within each study and then across the combined genotypic dataset. QC procedures were performed using PLINK 1.07 (http://pngu.mgh. harvard.edu/purcell/plink/) [Purcell et al., 2009] using standard thresholds [Sklar et al., 2008; Huang et al., 2010]. Briefly, individuals were excluded if they had overall call rates <95%, excess or insufficient heterozygosity, inconsistent gender between genotype and phenotype data, or apparent relatedness. We only included non-Hispanic Caucasian individuals with European ancestry based on self-reported race and ethnicity information. We then confirmed the self-reported ancestry using the PLINK nearest neighbor method [Purcell et al., 2007] to detect potential ancestry outliers based on the first 10 multidimensional scaling (MDS) factors. We also visually inspected the clustering of samples with HapMap populations to identify any additional outliers. The QC sample size eligible for further analysis was 3,102 (1,507 from STEP-BD, 1,199 from STAR*D, and 396 from CATIE). This sample size was further reduced based on availability of clinical phenotypes (see the Phenotypic Definition Section).

SNPs were excluded if they had a call rate <95%, had a minor allele frequency <1%, failed Hardy–Weinberg equilibrium at a P-value of $<1 \times 10^{-6}$, showed haplotype-based nonrandom missingness, or showed differential rates of missingness in patients and controls [Sklar et al., 2008; Huang et al., 2010]. Note that the control dataset was not employed in the current quantitative case-only analyses, but these SNPs were excluded to maintain consistency with previous QC procedures [Huang et al., 2010].

A total of 224,826 genotyped SNPs passed QC criteria across each of the samples. We used BEAGLE, Version 3.1.0, (http://www.stat. auckland.ac.nz/~bbrowning/beagle/beagle.html) to impute missing genotypes, with HapMap2 (Centre d'Etude du Polymorphisme Humain from Utah population, release 23, forward strand) as the reference panel (hg18). Individuals were imputed in 10 separate sets that were composed of randomly selected individuals from each study. We selected only the highest quality imputed SNPs based on a plink imputation quality score (INFO) between 0.8 and 1.2 and minor allele frequency >2%. The INFO metric is based on the ratio of empirical and expected variance in dosage where better imputation quality is expected for values closer to 1. Values greater than 1 indicate strong departure from Hardy–Weinberg equilibrium. After QC, a total of 1,633,452 SNPs were available for final analysis using the imputed dosages.

Phenotypic Definition

The current study focuses on the baseline measurement of functional impairment that was given at entry into each treatment study. STEP-BD administered the SF-36 [Ware et al., 1994], while STAR*D and CATIE administered the SF-12 (version 1), which is a subset of the SF-36 items [Ware et al., 1995]. The SF-12 score can be obtained using the SF-36 by scoring only the 12 overlapping items [Ware et al., 1995]. The SF-12 is further divided into two subdimensions, each with six items, the Mental Component Summary (MCS) scale and the Physical Component Summary (PCS) scale. As part of the scoring algorithm, the MCS and PCS scales are transformed to have a mean of 50 and a standard deviation of 10 in the general U.S. population. The MCS and PCS were developed to be independent measures of health-related quality of life with a negligible correlation in population samples [Ware et al., 2002]. The reliability and validity of the SF-12 has been found to be satisfactory for psychiatric clinical samples [Russo et al., 1998; Tunis et al., 1999; Salyers et al., 2000]. In the current sample, Cronbach's alpha was in the satisfactory range for the MCS and PCS of each study (STEP-BD MCS $\alpha = 0.84$, PCS $\alpha = 0.84$; STAR*D MCS $\alpha = 0.68$, PCS $\alpha = 0.85$; CATIE MCS $\alpha = 0.79$, PCS $\alpha = 0.82$). The convergent validity of the SF-12/SF-36 in the current sample has been demonstrated in previous reports from STEP-BD and STAR*D showing that poorer health-related quality of life was associated with clinical and demographic characteristics, such as depression severity and disadvantaged sociodemographic background [Trivedi et al., 2006; Zhang et al., 2006; Daly et al., 2010]. Table I shows the means and standard deviations of the MCS and PCS in the final sample included in the analysis.

TABLE I. Phenotypic Descriptives Across Samples

	STAR*D	STEP-BD	CATIE	Total
Sample size, N	1,091	765	390	2,246
MCS, M [SD]	26.1 [8.3]	32.6 [12.3]	40.0 [11.6]	30.7 [11.6]
PCS, M [SD]	50.9 [11.8]	47.0 [10.9]	47.8 [10.3]	49.0 [11.4]

The population mean and standard deviation for the SF-12 is M = 50, SD = 10.

A primary concern for our phenotypic conceptualization was that, to the extent possible, ratings of mental and physical health-related quality of life should be independent from the current severity of psychiatric symptoms. As a result, we constructed novel phenotypes which were derived from the residuals of independent regressions of the MCS and PCS on psychiatric symptom severity, age, and gender (details below). To capture psychiatric symptom severity, we selected constructs that captured the defining features of the primary disorders: depressed mood, irritability, elevated mood, and psychosis. Across samples, we selected the most comparable items from the available measures (see Supplementary Table I).

We selected one among several possible strategies for constructing residuals. For example, one might consider controlling for an entire psychiatric measure (i.e., the *Hamilton Depression Rating Scale* in STAR*D, the *Positive and Negative Syndrome Scale* in CATIE, the *Young Mania Rating Scale* and *Montgomery–Asberg Depression Rating Scale* in STEP-BD) rather than individual items as in the current study. This approach of regressing out different measures across studies has the potential benefit of controlling for psychiatric symptom severity more comprehensively, but two important limitations. First, this approach would increase the conceptual heterogeneity of the residuals since different symptoms would be regressed out across studies, making the interpretability of results more difficult. Secondly, many of the scales include items that are related to functional impairment. As such, we wanted to retain this variance of interest while still controlling for severity of core psychiatric symptoms and the correlated functional impairment attributable to these core symptoms.

A 14-day window was used to ensure broadly concurrent administration of the SF-12 and psychiatric symptom measures, while simultaneously minimizing missing data. The sample sizes reported in Table I reflect the total number of individuals in the final analysis who passed QC and had concurrent SF-12 and psychiatric symptom measures.

The MCS and PCS phenotypes for genetic analysis consisted of residuals from the previously described regressions, standardized within study. Supplementary Tables II and III present the regression results along with the adjusted model R^2. As expected, more of the variance was shared with psychiatric symptoms for the MCS than for the PCS. Standardized residuals were chosen in order to equate the units for a cross-disorder analysis and control for mean differences between disorders. This standardized residual represents a within-disorder statistic that captures the deviation of an individual from an expected functional impairment score given their level of psychiatric symptom severity. We conceptualize this quantitative phenotype as an index of functional risk/resilience in the context of a psychiatric disorder.

Analysis

Control for confounding by population stratification was performed by calculating the first 10 MDS components for all those individuals in the merged genotypic dataset who had complete SF-12 phenotypes and concurrent psychiatric measures. To examine the effect of each of the 10 MDS components (C1–C10), we calculated the genomic inflation factor (λ) from a GWAS using each component (C1–C10) as the dependent variable as described by Huang et al. [2010]. We plotted the λ's against each of the components (analogous to a scree plot) and found excessive values only for C1–C3. Thus, we used these first three MDS components as covariates in our GWAS.

Quantitative genetic association analyses were performed with PLINK, version 1.07 [Purcell et al., 2007] using linear regression of the MCS or PCS standardized residuals on single SNP allelic dosage, adjusting for the first three MDS components and a dummy variable denoting each contributing study. The alpha level for genome-wide significance was set at $P < 2.5 \times 10^{-8}$ which represents the conventional genome-wide significance level ($P < 5 \times 10^{-8}$) [Pe'er et al., 2008] corrected for two phenotypes tested.

Genotyping Confirmation of Top GWAS Imputed Signal

Because the top signal from the cross-disorder GWAS was primarily imputed, we selected six SNPs for confirmation genotyping in the linkage disequilibrium (LD) block identified by the imputed dataset. Primers were designed using MassARRAY Assay Design (Sequenom, San Diego, CA) and run through e-PCR using an in-house alignment tool highly sensitive for short primer sequences (A. Kirby, unpublished work).

SNP genotyping was performed on the Sequenom MassArray platform at the Massachusetts General Hospital Center for Human Genetic Research. Following DNA amplification by multiplex PCR, a pooled single base extension reaction was performed using the Sequenom iPLEX Gold assay. Allelic differentiation was detected with MassARRAY MALDI-TOF mass spectrometry. After baseline correction and peak identification, the spectra were analyzed using Sequenom MassARRAY Typer 4. The following QC thresholds were used for exclusion: sample pass rate <90%, SNP pass rate <90%, minor allele frequency <0.01, and Hardy–Weinberg equilibrium (HWE) value $<1 \times 10^{-5}$ (actual HWE P values were $P > 0.3$ for the six SNPs). Genotyping concordance rate for duplicate samples after removal of low quality data (n = 22 pairs) was 100%. All six of the selected SNPs passed QC criteria. Two individuals failed QC resulting in a final dataset of 2,244 individuals.

Pathway Analysis

Meta-Analysis Gene-set Enrichment of variaNT Associations (MAGENTA; http://www.broadinstitute.org/mpg/magenta) [Segre et al., 2010] was used to test whether specific biological pathways were enriched for associations to the phenotypes of MCS and PCS

(separately). MAGENTA assigns scores to specific genes based on the most significant SNP in the gene and user-specified flanking regions (35 kb upstream, 10 kb downstream). The resulting gene score is corrected for important confounders such as gene size, SNP density, LD properties, and recombination hotspots. We removed the HLA region from the analysis due to high LD and gene density in this region (MAGENTA default chr6:29,710,331–33,150,000 hg18). MAGENTA requires user-specified thresholds for nominal significance of gene-level P values in order to calculate pathway significance. We used the MAGENTA defaults of the 95th and 75th percentile cut-offs. We chose to analyze pathways in the Kyoto Encyclopedia of Genes and Genomes (KEGG) (N = 186 pathways, mean # of genes per pathway = 86 (SD = 68), range 10–389) because they are curated with high standards for evidence. See Segre et al. [2010] for other details about the MAGENTA method.

RESULTS

The regression analyses to derive the MCS and PCS functional impairment residuals, controlling for psychiatric symptom severity, age, and gender are reported in Supplementary Tables II and III. From these analyses, it is clear that psychiatric symptom severity and demographic variables were significant predictors of functional impairment, but these variables accounted for less than one-third of the variance in both measures, across the three cohorts (MCS 20–31%, PCS 5–19%). The fact that more of the variance in MCS than PCS was accounted for by psychiatric symptoms is consistent with the item content of the MCS in which three of the six items are closely related to symptoms of depression (i.e., sadness, fatigue, calmness). Overall, these analyses indicated that there is variance remaining in functional impairment scores after controlling for psychiatric symptoms and demographic variables. The rest of our analyses utilized the residuals from these regressions standardized within disorder.

To establish the validity of these functional impairment residuals, we also tested for a relationship with a widely used objective measure of functional impairment, current employment status. In each cohort, we conducted a logistic regression of employment status on MCS and PCS residual scores. Individuals who reported full-time or part-time employment were grouped together and compared to those who were unemployed. Both the MCS and PCS

residuals showed significant relationships with employment status across all three disorder samples, with the exception of the MCS in CATIE. Because the sample size is smallest and employment rates were lowest in CATIE (15% compared to 49% in STEP-BD and 58% in STAR*D), power was limited in this sample, but the odds ratio (OR) of the effect for MCS in CATIE (OR = 1.13) was comparable to the other samples (ORs = 1.13–1.18). Across samples, the PCS residual was more strongly related to occupational status (ORs = 1.4–1.8) than the MCS residual (see Supplementary Table IV).

The top 10 GWAS results using the MCS and PCS residuals as phenotypes in the combined psychiatric sample are reported in Tables II and III as LD clumped regions. Supplementary Tables V and VI report all regions with $P < 10^{-4}$. Supplementary Figures 1–4 show Q-Q and Manhattan plots (λ MCS = 1.007, λ PCS = .995). The strongest association evidence was between SNPs in the gene *ADAMTS16* with the PCS. Figure 1 shows the regional plot of this gene. The top association signal ($P = 5.87 \times 10^{-8}$) approached genome-wide significance, although it did not meet our strict alpha criteria of 2.5×10^{-8}. Further investigation of this region indicated that the strongest signal was derived from imputed SNPs with only modest evidence from the nearby genotyped SNPs (see Fig. 1). Follow-up genotyping of the top imputed SNPs confirmed the signal with a similar effect size and P-value, ruling out technical or imputation artifacts as a source of the signal (see Supplementary Table VII and diamonds denoted in Fig. 1). Figure 2 shows the forest plot of the effect sizes for the top SNP, rs16875288, across the three psychiatric disorders. There was no statistically significant evidence of heterogeneity according to the Cochrane's Q statistic ($P = .34$), which was supported by the I^2 heterogeneity index ($I^2 = 7.35$).

Pathway analysis did not reveal any significant enrichment after correction for gene clustering and multiple testing (2 phenotypes (MCS, PCS), 2 thresholds (75%, 95%), and 186 pathways; corrected alpha threshold = 6.7×10^{-5}) (Supplementary Tables VIII and IX). Before accounting for gene clustering, two pathways related to inflammation and autoimmune disorders showed evidence of enrichment of genetic associations to PCS (Supplementary Table VIII). However, these two pathways shared 13 interferon alpha genes, 12 of which (IFNA genes: 2, 4, 5, 6, 7, 8, 10, 13, 14, 16, 17, 21) are clustered in a gene dense, LD block on chromosome 9 (Supplementary Fig. 5). Because pathway analysis statistics can be inflated by gene dense areas with strong LD, we completed a

TABLE II. Loci Showing Strongest Evidence of Association With MCS

Chromosome	SNP	P	Additional SNPs ($P < 0.0001$), $r^2 > 0.25$	Nearest genes (within 50 kb)
3	rs4681346	2.61E−06	32	[ ]
1	rs7535475	3.23E−06	5	[HSPA6, FCGR3A, FCGR2A]
8	rs2736871	3.42E−06	4	[ST3GAL1]
12	rs10878563	1.10E−05	1	[ ]
10	rs10883890	1.59E−05	3	[SH3PXD2A, NEURL]
5	rs888643	1.63E−05	5	[ ]
9	rs988954	1.81E−05	2	[PTPRD]
22	rs5993665	2.04E−05	14	[UFD1L, MRPL40, HIRA, CLDN5, CDC45L, C22orf39]
3	rs6809127	2.22E−05	6	[ ]
3	rs10513787	2.42E−05	17	[ ]

Chromosome	SNP	P	Additional SNPs ($P < 0.0001$), $r^2 > 0.25$	Nearest genes (within 50 kb)
5	rs16875288	5.87E−08	4	[ADAMTS16]
17	rs7221595	4.53E−06	32	[ZZEF1, CYB5D2, ANKFY1]
3	rs9877870	1.28E−05	30	[LPP]
4	rs6848750	2.05E−05	7	[MGC48628]
8	rs2737327	2.38E−05	1	[WRN]
11	rs10890798	2.43E−05	7	[RAB39, CUL5, ACAT1]
4	rs17015692	2.63E−05	1	[ ]
8	rs10095012	2.91E−05	6	[ ]
18	rs550139	3.30E−05	6	[MAPRE2]
20	rs6095959	3.67E−05	3	[PTPN1]

secondary analysis in which we excluded all but the most significant gene in the interferon alpha region. Although this was a conservative approach, it was justified by the fact that conditional SNP analysis did not reveal any evidence of independent signals in the region. Following this correction, the P-values of the previously significant pathways decreased by several orders of magnitude and were no longer significant (Supplementary Table VIII).

DISCUSSION

Mood and psychotic disorders are known to be associated with substantial disability, but prior research and clinical experience suggest that variation in functional impairment does not necessarily track with symptom severity. We hypothesized that there is an axis of functional risk/resilience in the presence of psychiatric illness that is separable from symptom burden and diagnostic category. In
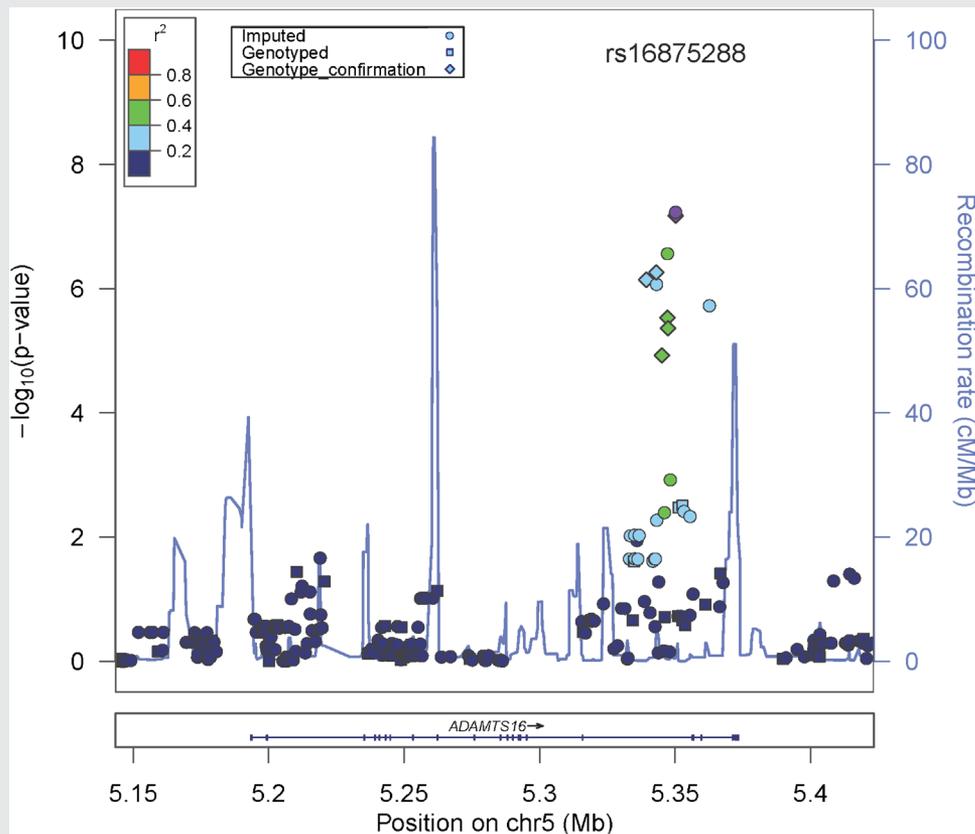

FIG. 1. Regional plot of the strongest associated SNPs in *ADAMTS16* with the PCS. Marker shapes indicate whether the SNP was genotyped, imputed, or confirmed with follow-up genotyping. Plotted using LocusZoom [Pruim et al., 2010].
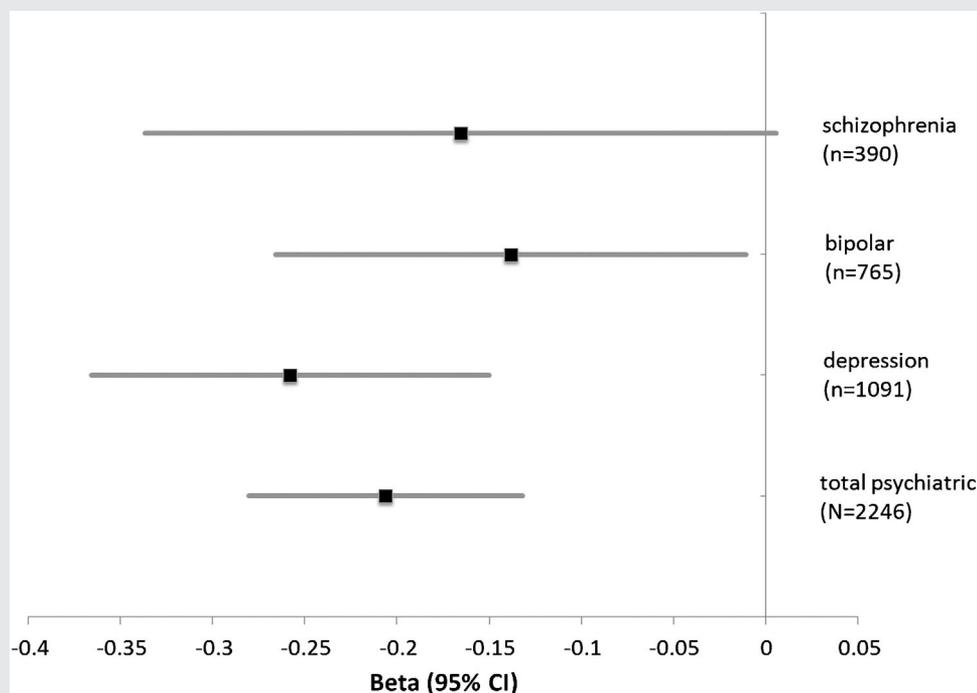
FIG. 2. Forest plot of effect sizes across the psychiatric samples for rs16875288 in the gene ADAMTS16.

light of prior evidence that functional status (indexed by the SF-36) is moderately heritable, we conducted a genome-wide search for variants associated with this phenotype.

To isolate genetic influences on mental and physical functioning, we controlled for psychiatric symptom severity, diagnostic group, and other relevant covariates. These analyses revealed that psychiatric symptom severity accounted for a minority of the variance in functional impairment, consistent with our hypothesis that there is an axis of risk/resilience that is distinct from severity of the disorder. In essence, our phenotypic approach was designed to identify genetic modifiers that affect the functional impact of psychiatric disorder irrespective of whether they influence risk for the disorder itself [Fanous and Kendler, 2005].

The strongest association evidence we observed was between variants in *ADAMTS16* (ADAM metallopeptidase with thrombospondin type 1 motif, 16) and physical health-related quality of life (PCS) ($P = 5.87 \times 10^{-8}$). We interpret these results cautiously given that the association signal did not exceed genome-wide significance. This gene has been previously implicated in hypertension via converging evidence from fine mapping of quantitative trait loci in rats and association and linkage analyses in humans [Joe et al., 2009], although *ADAMTS16* did not emerge as a candidate in the recent large-scale GWAS for hypertension involving 200,000 individuals [Ehret et al., 2011]. *ADAMTS16* is expressed in the adult brain, but has had limited biological characterization to date [Cal et al., 2002; Porter et al., 2005; Surridge et al., 2009]. In our study, SNPs with the strongest association signals in *ADAMTS16* are intronic and do not have documented eQTL annotations in brain

tissue [Myers et al., 2007; Gibbs et al., 2010] or in lymphoblastoid cell lines [Yang et al., 2010; Stranger et al., 2012] leaving the functional implications of these SNPs unknown. Further biological and genetic studies are needed to understand the potential role of *ADAMTS16* in functional impairment and resilience. Future analyses may also examine the genetic and phenotypic relationship between risk/resilience for functional impairment in the context of psychiatric disorders and other traits that may impact health-related quality of life, including personality traits [e.g., Kentros et al., 1997], motivation [e.g., Foussias et al., 2011], social-cognition [e.g., Hoertnagl et al., 2011; Maat et al., 2012], and neurocognitive functioning [e.g., Green, 1996; Depp et al., 2012; Tolman and Kurtz, 2012].

After careful correction for multiple testing and gene clustering, there was no evidence of association for any of the KEGG pathways. Although there was an initial signal in autoimmune and inflammatory processes for PCS, follow-up analyses suggested that results were artifactually driven by a single signal within the interferon alpha gene cluster on chromosome 9. These results emphasize the importance of controlling for LD patterns in pathway analyses and suggest that, like the HLA region, the interferon alpha region on chromosome 9 can be problematic.

Our results should be interpreted in the context of their limitations. First, based on the available sample size, we had >80% power to detect a locus explaining 2% or more of the variance in MCS or PCS scores. Our strongest result approached but did not exceed a genome-wide threshold of statistical significance. Thus, analyses in larger samples will be essential to clarify our findings. To

our knowledge, there are no comparable psychiatric samples with functional impairment measures and GWAS data available. As a result, we could not attempt replication of these results or examine cross-sample correspondence via more advanced statistical genetic approaches [i.e., polygenic scoring, Purcell et al., 2009]. Fortunately, there is an ongoing data collection effort aimed at examining genetic predictors of quality of life, the GENEQOL consortium [Sprangers et al., 2009], so future datasets with rich quality of life and genetic data will become available to examine correspondence with these results.

Second, self-report measures are only one strategy among many for measuring functional status [Bromley and Brekke, 2010; Awad, 2011; Harvey et al., 2012]. Alternative measures include real-world outcomes (i.e., occupational status, residential status, educational attainment) and functional capacity (i.e., ability to perform real-world skills such as managing money, paying bills). Of note, our derived mental and physical functioning measure was significantly associated with employment status across the three disorders, after controlling for psychiatric symptom severity, supporting their relevance to real world outcomes. Recently, functional capacity, with an emphasis on performance-based testing, has been advanced as a candidate endophenotype for genetic studies of severe mental illness [Harvey et al., 2012]. Genetic investigations of alternative measures of functional impairment will be complementary to the current analyses and important for characterizing genetic effects on functional vulnerability/resilience in the context of psychopathology.

Third, the psychiatric symptom measures were different across the three disorder samples which may have provided different degrees of control for psychiatric symptom severity across the disorders. To address this limitation, we chose clinician-rated scales with similar wording and scales wherever possible (see Supplementary Table I). Moreover, mental functioning, as measured by the SF-12, was more difficult to distinguish from psychiatric symptom severity than physical functioning given the overlap of constructs, particularly with depressive features (i.e., fatigue, calmness, sadness). This fact may have differentially diminished our power for the MCS analyses relative to the PCS.

Despite these limitations, we believe these results contribute to the emerging literature on genetic risk factors for functional impairment in psychiatric disorders. Our phenotypic approach of capturing functional impairment independent of concurrent psychiatry symptom severity provides a model for future genetic studies. The overall approach of identifying modifier genes that impact functional impairment across psychiatric disorders could provide valuable insight into novel treatment approaches that might directly impact functional impairment in the context of psychopathology.

ACKNOWLEDGMENTS

REFERENCES

APA. 2010. Impairment and Disability Assessment Study Group White Paper: Mental Disorders: Separating Symptoms and Disabilities in the DSM-5 American Psychiatric Association.

Awad AG. 2011. Quality-of-life assessment in schizophrenia: The unfulfilled promise. Expert Rev Pharmacoecon Outcomes Res 11(5):491–493.

Awad AG, Voruganti LN. 2012. Measuring quality of life in patients with schizophrenia: An update. Pharmacoeconomics 30(3):183–195.

Bromley E, Brekke JS. 2010. Assessing function and functional outcome in schizophrenia. Curr Top Behav Neurosci 4:3–21.

Cal S, Obaya AJ, Llamazares M, Garabaya C, Quesada V, Lopez-Otin C. 2002. Cloning, expression analysis, and structural characterization of seven novel human ADAMTSs, a family of metalloproteinases with disintegrin and thrombospondin-1 domains. Gene 283(1–2):49–62.

Contopoulos-Ioannidis DG, Karvouni A, Kouri I, Ioannidis JP. 2009. Reporting and interpretation of SF-36 outcomes in randomised trials: Systematic review. BMJ 338:a3006.

Daly EJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Gaynes BN, Warden D, Morris DW, Luther JF, Farabaugh A, Cook I, et al. 2010. Health-related quality of life in depression: A STAR*D report. Ann Clin Psychiatry 22(1):43–55.

Depp CA, Mausbach BT, Harmell AL, Savla GN, Bowie CR, Harvey PD, Patterson TL. 2012. Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. Bipolar Disord 14(3):217–226.

Eack SM, Newhill CE. 2007. Psychiatric symptoms and quality of life in schizophrenia: A meta-analysis. Schizophr Bull 33(5):1225–1237.

Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, Smith AV, Tobin MD, Verwoert GC, Hwang SJ, et al. 2011. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature 478(7367):103–109.

Fanous AH, Kendler KS. 2005. Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness: Searching for a framework. Mol Psychiatry 10(1):6–13.

Fava M, Rush AJ, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, Quitkin FM, Wisniewski S, Lavori PW, Rosenbaum JF, et al. 2003. Background and rationale for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Psychiatr Clin North Am 26(2):457–494, x.

First M, Spitzer R, Gibbon M, Gibbon M, Williams J. 1994. Structured Clinical Interview for DSM-IV Axis I Disorders - Administrative Booklet. Washington, DC: American Psychiatric Press Inc.

Foussias G, Mann S, Zakzanis KK, van Reekum R, Agid O, Remington G. 2011. Prediction of longitudinal functional outcomes in schizophrenia: The impact of baseline motivational deficits. Schizophr Res 132(1):24–27.

Garriock HA, Kraft JB, Shyn SI, Peters EJ, Yokoyama JS, Jenkins GD, Reinalda MS, Slager SL, McGrath PJ, Hamilton SP. 2010. A genomewide association study of citalopram response in major depressive disorder. Biol Psychiatry 67(2):133–138.

Gibbs JR, van der Brug MP, Hernandez DG, Traynor BJ, Nalls MA, Lai SL, Arepalli S, Dillman A, Rafferty IP, Troncoso J, et al. 2010. Abundant quantitative trait loci exist for DNA methylation and gene expression in human brain. PLoS Genet 6(5):e1000952.

Green MF. 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153(3):321–330.

Hamilton M. 1960. A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62.

Hamilton M. 1967. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 6(4):278–296.

Harvey PD, McClure MM, Patterson TL, McGrath JA, A EP, Bowie CR, Siever LJ. 2012. Impairment in functional capacity as an endophenotype candidate in severe mental illness. Schizophr Bull 38(6):1318–1326.

Hoertnagl CM, Muehlbacher M, Biedermann F, Yalcin N, Baumgartner S, Schwitzer G, Deisenhammer EA, Hausmann A, Kemmler G, Benecke C, et al. 2011. Facial emotion recognition and its relationship to subjective and functional outcomes in remitted patients with bipolar I disorder. Bipolar Disord 13(5–6):537–544.

Huang J, Perlis RH, Lee PH, Rush AJ, Fava M, Sachs GS, Lieberman J, Hamilton SP, Sullivan PF, Sklar P, et al. 2010. Cross-disorder genome-wide analysis of schizophrenia, bipolar disorder, and depression. Am J Psychiatry 167(10):1254–1263.

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. 2010. Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. Am J Psychiatry 167(7):748–751.

IsHak WW, Brown K, Aye SS, Kahloon M, Mobaraki S, Hanna R. 2012. Health-related quality of life in bipolar disorder. Bipolar Disord 14(1):6–18.

Joe B, Saad Y, Dhindaw S, Lee NH, Frank BC, Achinike OH, Luu TV, Gopalakrishnan K, Toland EJ, Farms P, et al. 2009. Positional identification of variants of Adamts16 linked to inherited hypertension. Hum Mol Genet 18(15):2825–2838.

Kendler KS, McGuire M, Gruenberg AM, Walsh D. 1995. Schizotypal symptoms and signs in the Roscommon Family Study. Their factor structure and familial relationship with psychotic and affective disorders. Arch Gen Psychiatry 52(4):296–303.

Kentros MK, Terkelsen K, Hull J, Smith TE, Goodman M. 1997. The relationship between personality and quality of life in persons with schizoaffective disorder and schizophrenia. Qual Life Res 6(2):118–122.

Kogan JN, Otto MW, Bauer MS, Dennehy EB, Miklowitz DJ, Zhang HW, Ketter T, Rudorfer MV, Wisniewski SR, Thase ME, et al. 2004. Demographic and diagnostic characteristics of the first 1000 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Bipolar Disord 6(6):460–469.

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, et al. 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353(12):1209–1223.

Maat A, Fett AK, Derks E. 2012. Social cognition and quality of life in schizophrenia. Schizophr Res 137(1–3):212–218.

McGrath JA, Avramopoulos D, Lasseter VK, Wolyniec PS, Fallin MD, Liang KY, Nestadt G, Thornquist MH, Luke JR, Chen PL, et al. 2009. Familiality of novel factorial dimensions of schizophrenia. Arch Gen Psychiatry 66(6):591–600.

McHorney CA, Ware JE, Raczek AE. 1993. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 31(3): 247–263.

McHorney CA, Ware JE, Lu JF, Sherbourne CD. 1994. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 32(1):40–66.

Myers AJ, Gibbs JR, Webster JA, Rohrer K, Zhao A, Marlowe L, Kaleem M, Leung D, Bryden L, Nath P, et al. 2007. A survey of genetic human cortical gene expression. Nat Genet 39(12):1494–1499.

Pe'er I, Yelensky R, Altshuler D, Daly MJ. 2008. Estimation of the multiple testing burden for genomewide association studies of nearly all common variants. Genet Epidemiol 32(4):381–385.

Porter S, Clark IM, Kevorkian L, Edwards DR. 2005. The ADAMTS metalloproteinases. Biochem J 386(Pt 1):15–27.

Priebe S, McCabe R, Junghan U, Kallert T, Ruggeri M, Slade M, Reininghaus U. 2011. Association between symptoms and quality of life in patients with schizophrenia: A pooled analysis of changes over time. Schizophr Res 133(1–3):17–21.

Pruim RJ, Welch RP, Sanna S, Teslovich TM, Chines PS, Gliedt TP, Boehnke M, Abecasis GR, Willer CJ. 2010. LocusZoom: Regional visualization of genome-wide association scan results. Bioinformatics 26(18):2336–2337.

Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, et al. 2007. PLINK: A tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 81(3):559–575.

Purcell S, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P. 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460(7256):748–752.

Raat H, van Rossem L, Jaddoe VW, Landgraf JM, Feeny D, Moll HA, Hofman A, Mackenbach JP. 2010. The Generation R study: A candidate gene study and genome-wide association study (GWAS) on health-related quality of life (HRQOL) of mothers and young children. Qual Life Res 19(10):1439–1446.

Romeis JC, Heath AC, Xian H, Eisen SA, Scherrer JF, Pedersen NL, Fu Q, Bucholz KK, Goldberg J, Lyons MJ, et al. 2005. Heritability of SF-36 among middle-age, middle-class, male-male twins. Med Care 43(11):1147–1154.

Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, Thase ME, Nierenberg AA, Quitkin FM, Kashner TM, et al. 2004. Sequenced Treatment Alternatives to Relieve Depression (STAR*D): Rationale and design. Control Clin Trials 25(1):119–142.

Russo J, Trujillo CA, Wingerson D, Decker K, Ries R, Wetzler H, Roy-Byrne P. 1998. The MOS 36-Item Short Form Health Survey: Reliability, validity, and preliminary findings in schizophrenic outpatients. Med Care 36(5):752–756.

Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, Lavori P, Lebowitz B, Rudorfer M, Frank E, et al. 2003. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 53(11):1028–1042.

Salyers MP, Bosworth HB, Swanson JW, Lamb-Pagone J, Osher FC. 2000. Reliability and validity of the SF-12 health survey among people with severe mental illness. Med Care 38(11):1141–1150.

Segre AV, Groop L, Mootha VK, Daly MJ, Altshuler D. 2010. Common inherited variation in mitochondrial genes is not enriched for associations with type 2 diabetes or related glycemic traits. PLoS Genet 6(8):1–19.

Shippee ND, Shah ND, Williams MD, Moriarty JP, Frye MA, Ziegenfuss JY. 2011. Differences in demographic composition and in work, social, and functional limitations among the populations with unipolar depression and bipolar disorder: Results from a nationally representative sample. Health Qual Life Outcomes 9:90.

Shyn SI, Shi J, Kraft JB, Potash JB, Knowles JA, Weissman MM, Garriock HA, Yokoyama JS, McGrath PJ, Peters EJ, et al. 2011. Novel loci for major depression identified by genome-wide association study of Sequenced Treatment Alternatives to Relieve Depression and meta-analysis of three studies. Mol Psychiatry 16(2):202–215.

Sklar P, Smoller JW, Fan J, Ferreira MA, Perlis RH, Chambert K, Nimgaonkar VL, McQueen MB, Faraone SV, Kirby A, et al. 2008. Whole-genome association study of bipolar disorder. Mol Psychiatry 13(6):558–569.

Sprangers MA, Sloan JA, Veenhoven R, Cleeland CS, Halyard MY, Abertnethy AP, Baas F, Barsevick AM, Bartels M, Boomsma DI, et al. 2009. The establishment of the GENEQOL consortium to investigate the genetic disposition of patient-reported quality-of-life outcomes. Twin Res Hum Genet 12(3):301–311.

Steenstrup T, Pedersen OB, Hjelmborg J, Skytthe A, Kyvik KO. 2013. Heritability of Health-Related Quality of Life: SF-12 Summary Scores in a Population-Based Nationwide Twin Cohort. Twin Res Hum Genet 16(3):670–678.

Stranger BE, Montgomery SB, Dimas AS, Parts L, Stegle O, Ingle CE, Sekowska M, Smith GD, Evans D, Gutierrez-Arcelus M, et al. 2012. Patterns of cis regulatory variation in diverse human populations. PLoS Genet 8(4):e1002639.

Stroup TS, McEvoy JP, Swartz MS, Byerly MJ, Glick ID, Canive JM, McGee MF, Simpson GM, Stevens MC, Lieberman JA. 2003. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: Schizophrenia trial design and protocol development. Schizophr Bull 29(1):15–31.

Sullivan PF, Lin D, Tzeng JY, van den Oord E, Perkins D, Stroup TS, Wagner M, Lee S, Wright FA, Zou F, et al. 2008. Genomewide association for schizophrenia in the CATIE study: Results of stage 1. Mol Psychiatry 13(6):570–584.

Surridge AK, Rodgers UR, Swingler TE, Davidson RK, Kevorkian L, Norton R, Waters JG, Goldring MB, Parker AE, Clark IM. 2009. Characterization and regulation of ADAMTS-16. Matrix Biol 28(7):416–424.

Tolman AW, Kurtz MM. 2012. Neurocognitive predictors of objective and subjective quality of life in individuals with schizophrenia: A meta-analytic investigation. Schizophr Bull 38(2):304–315.

Trivedi MH, Rush AJ, Wisniewski SR, Warden D, McKinney W, Downing M, Berman SR, Farabaugh A, Luther JF, Nierenberg AA, et al. 2006. Factors associated with health-related quality of life among outpatients with major depressive disorder: A STAR*D report. J Clin Psychiatry 67(2):185–195.

Tunis SL, Croghan TW, Heilman DK, Johnstone BM, Obenchain RL. 1999. Reliability, validity, and application of the medical outcomes study 36-item short-form health survey (SF-36) in schizophrenic patients treated with olanzapine versus haloperidol. Med Care 37(7):678–691.

Verboom CE, Sentse M, Sijtsema JJ, Nolen WA, Ormel J, Penninx BW. 2011. Explaining heterogeneity in disability with major depressive disorder: Effects of personal and environmental characteristics. J Affect Disord 132(1–2):71–81.

Ware JE, Sherbourne CD. 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30(6):473–483.

Ware JE, Kosinski M, Keller SD. 1994. SF-36 Physical and Mental Health Summary Scale: A user's manual. Boston, MA: Health Assessment Lab.

Ware JE, Kosinski M, Keller SD. 1995. How to score the SF-12 physical and mental health summary scales. Lincoln, RI: QualityMetric Incorporated.

Ware JE, Kosinski M, Keller SD. 1996. A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. Med Care 34(3):220–233.

Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. 2002. User's manual for the SF-12v2 health survey with a supplement documenting SF-12 health survey. Lincoln, RI: QualityMetric Incorporated.

Yang TP, Beazley C, Montgomery SB, Dimas AS, Gutierrez-Arcelus M, Stranger BE, Deloukas P, Dermitzakis ET. 2010. Genevar: A database and Java application for the analysis and visualization of SNP-gene associations in eQTL studies. Bioinformatics 26(19):2474–2476.

Zhang H, Wisniewski SR, Bauer MS, Sachs GS, Thase ME. 2006. Comparisons of perceived quality of life across clinical states in bipolar disorder: Data from the first 2000 Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) participants. Compr Psychiatry 47(3):161–168.

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