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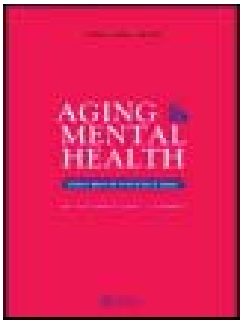

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Positive mental health in schizophrenia and healthy comparison groups: relationships with overall health and biomarkers

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ABSTRACT

Objective: Positive psychological factors (PPFs) have been reported to have a significant impact on health in the general population. However, little is known about the relationship of these factors with mental and physical health in schizophrenia.

Method: One hundred and thirty-five outpatients with schizophrenia and 127 healthy comparison subjects (HCs), aged 26–65 years, were evaluated with scales of resilience, optimism, happiness, and perceived stress. Measures of mental and physical health were also obtained. Regression analyses examined associations of a PPF composite with health variables.

Results: Relative to the HCs, the schizophrenia group had lower levels of PPFs. However, there was considerable heterogeneity, with over one-third of schizophrenia participants having values within the 'normative' range. The PPF composite was positively related to mental and physical health variables and with biomarkers of inflammation and insulin resistance. The relationship between PPFs and mental health was particularly strong for individuals with schizophrenia.

Conclusion: A sizable minority of adults with chronic schizophrenia have levels of resilience, optimism, happiness, and perceived stress similar to HCs. Psychosocial interventions to enhance PPFs should be tested in patients with serious mental illnesses, with the goal of improving their mental health (beyond controlling symptoms of psychosis) and their physical health.

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Resilience; happiness; quality of life/well-being; inflammation; schizophrenia

Introduction

Psychiatry has traditionally focused on the diagnosis and treatment of mental illnesses and study of risk factors. This approach ignores positive outcomes such as mental health, well-being, and positive psychological factors (PPFs). 'Positive psychiatry' is an emerging area of research and practice that focuses on understanding and promoting well-being (Blazer & Kinghorn, 2015; Jeste & Palmer, 2013; Shrivastava, Johnston, Shah, & Bureau, 2010; Summers & Lord, 2015). This movement originated in the field of psychology, where the term 'positive psychology' was coined to refer to the scientific study of positive experiences and positive traits, such as well-being, contentment, satisfaction, and happiness (Seligman & Csikszentmihalyi, 2000). There is accumulating evidence that PPFs can have a substantial impact on one's mental health, as they are associated with lower levels of depression and greater well-being (Lavretsky, 2014; Lavretsky, Small, Ercoli, & Merrill, 2013; Martin, Harmell, & Mausbach, 2015). In addition, PPFs can significantly impact one's physical health, as traits such as resilience and optimism have been associated with reduced mortality and biomarkers of physical health (Lavretsky, 2014; Martin et al., 2015; Moore et al., 2015). Well-being and optimism have also been linked to reduced risk of incident coronary heart disease in healthy adults (Boehm & Kubzansky, 2012; Davidson, Mostofsky, & Whang, 2010; Kubzansky & Thurston, 2007), reduced rates of hospitalization and mortality in cardiac patients (DuBois et al., 2015), lower incidence of stroke (Kim, Park, & Peterson, 2011; Ostir, Markides, Peek, & Goodwin, 2001), and reduced mortality in healthy populations (Chida & Steptoe, 2008). The beneficial effects of PPFs remain significant even after controlling for negative affect (Chida & Steptoe, 2008; Ostir et al., 2001). Positive affect can have an impact on neuroendocrine, autonomic, immune, and inflammatory pathways (Dockray & Steptoe, 2010). Studies have shown that positive affect and psychological well-being are related to lower concentrations of inflammatory biomarkers (e.g. interleukin-6, C-reactive protein) (Steptoe, Demakakos, de Oliveira, & Wardle, 2012; Steptoe, O'Donnell, Badrick, Kumari, & Marmot, 2008). In addition, biomarkers of metabolic dysfunction (e.g. insulin resistance) have been associated with PPFs. One study found an increase in psychological well-being and a decrease in homeostasis model assessment–insulin resistance (HOMA-IR) following weight loss in obese patients with type-2 diabetes (Osama & Shehab Ael, 2015). Similarly, a favorable metabolic profile was positively associated with mental health and well-being in middle-aged obese individuals (Phillips & Perry, 2015).

While there is increasing interest in the link between PPFs and health outcomes, research in this area has focused primarily on healthy samples or medical populations. Relatively little is known about PPFs in serious mental illnesses such as schizophrenia. Schizophrenia is a severe mental illness associated with cognitive and functional impairment (Green, Kern, Braff, & Mintz, 2000; Rajji, Miranda, & Mulsant, 2014),

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psychosocial dysfunction (Świtaj et al., 2012), and reduced quality of life (Pinikahana, Happell, Hope, & Keks, 2002). Given the negative outcomes associated with schizophrenia, it is perhaps not surprising that PPFs are rarely assessed or researched in this population. In an earlier report, our group examined individuals with chronic schizophrenia and found substantial heterogeneity in happiness levels of the sample (Palmer, Martin, Depp, Glorioso, & Jeste, 2014). Another study (Agid et al., 2012) showed that individuals with first-episode schizophrenia were as happy as control participants, despite their functional impairment. There is a dearth of studies examining other PPFs in schizophrenia.

In addition to negative functional and psychosocial outcomes, schizophrenia is also associated with premature physical decline, greater medical comorbidity, a higher mortality rate, and a decrease in lifespan by 15–20 years relative to the general population (Jeste, Wolkowitz, & Palmer, 2011; Kirkpatrick, Messias, Harvey, Fernandez-Egea, & Bowie, 2008). Individuals with schizophrenia experience physical decline in middle age and have high rates of disorders that are most commonly seen in older age (e.g. metabolic syndrome, diabetes, coronary heart disease) (Jeste et al., 2011; Kirkpatrick et al., 2008), suggesting the possibility of accelerated biological aging in schizophrenia. It is possible that these negative outcomes are influenced by antipsychotic medication use and/or poor health habits such as smoking and sedentary lifestyle. Insulin resistance is a major factor in the development of diabetes mellitus (Tang, Li, Song, & Xu, 2015), and inflammation plays a role in the pathogenesis of cardiovascular disease (Kanda & Takahashi, 2004; Ridker, Hennekens, Buring, & Rifai, 2000). These processes are highly relevant to schizophrenia, as this population has a high rate of obesity and cardiovascular disease (Azad et al., 2016; Ringen, Engh, Birkenaes, Dieset, & Andreassen, 2014; Ward & Druss, 2015), leading to increased morbidity and mortality relative to the general population. Although relationships have been discovered between PPFs, health variables, and blood-based biomarkers in other populations (i.e. healthy samples, medical populations), little is known about these relationships in schizophrenia.

The aim of the current study was to examine PPFs in persons with schizophrenia and in healthy comparison subjects (HCs), and to explore the relationship of PPF to mental and physical health variables and blood-based biomarkers of insulin resistance and inflammation. The PPFs that we focused on were resilience, optimism, happiness, and low level of perceived stress. These factors were selected because they are among the variables that have been most studied in other populations, and they represent a range of positive traits and states. Our primary measures of mental and physical health were the overall component scores from the Short Form Health Survey (SF-36). We also included a number of additional health measures in order to examine more specific aspects of mental health (i.e. depression, anxiety, severity of psychopathology) and physical health (i.e. physical comorbidity, cardiovascular disease risk). We examined biomarkers of insulin resistance and inflammation due to their relevance to the health of persons with schizophrenia (Azad et al., 2016; Ringen et al., 2014; Ward & Druss, 2015), and because these two types of biomarkers have been found to be associated with positive psychological well-being and positive affect in other populations (Osama & Shehab Ael, 2015; Phillips & Perry, 2015; Steptoe et al., 2012; Steptoe et al., 2008). We hypothesized that the schizophrenia group would have lower mean levels of resilience, optimism, and happiness, and higher levels of perceived stress, relative to the HC group. We also predicted that PPFs would be related to better scores on measures of mental and physical health in both the schizophrenia and HC groups. Lastly, based on published findings (Steptoe et al., 2012; Steptoe et al., 2008), we expected that the PPFs would be associated with healthier levels on biomarkers of insulin resistance and inflammation.

Methods

Participants

Participants were 135 community-dwelling individuals with chronic schizophrenia receiving outpatient psychiatric treatment and 127 HCs. Data for the current study were drawn from an ongoing study of aging and schizophrenia conducted through the University of California, San Diego Center for Healthy Aging. We previously reported data on happiness in a smaller subsample from the ongoing project (Palmer et al., 2014); however, the present study is the first report on the association of several PPFs with objective biomarkers of health status. Diagnostic status was established with the semi-structured Clinical Interview for the DSM-IV-TR or DSM-5 (First, Spitzer, & Gibbon, 2002). Inclusion criteria were (1) age 26–65 years, (2) DSM-IV-TR (American Psychiatric Association, 2000) or DSM-5 (American Psychiatric Association, 2013) diagnosis of schizophrenia or, for HC subjects, absence of major neuropsychiatric disorders, (3) receiving outpatient psychiatric treatment (for the schizophrenia group), and (4) English fluency. Exclusion criteria were (1) alcohol or substance use disorders (other than nicotine or caffeine) within previous three months, (2) diagnosis of dementia, intellectual disability disorder, or other major neurological disorder, and (3) any medical condition that interfered with the ability to complete study assessments.

Recruitment was conducted using age bins as follows: 26–35, 36–45, 46–55, and 56–65 years, with attention to an even gender and ethnic distribution across bins and diagnostic groups. We recruited HCs using various methods including from an ongoing survey study of successful aging in healthy adults, ResearchMatch.org, recruitment flyers in the community, and word-of-mouth. HCs were screened for major neuropsychiatric illness using the MINI-International Neuropsychiatric Interview (Sheehan et al., 1998). This measure screens for lifetime occurrence of a DSM-IV-TR Axis 1 diagnoses. HCs were excluded if they had ever been diagnosed with a major neuropsychiatric illness. The study was approved by the university's Human Research Protections Program. All study participants provided written informed consent prior to participation.

Measures

Participants underwent a comprehensive psychological and physical assessment including the following measures:

Measures of positive psychological factors

Resilience: Participants' level of resilience was assessed using the 10-item Connor–Davidson Resilience Scale (CD-RISC) (Campbell—Sills & Stein, 2007; Connor & Davidson, 2003). This scale contains statements such as 'I am able to adapt to change,' 'I can deal with whatever comes my way,' and 'I am

not easily discouraged by failure.' Participants rated each statement on a scale from 0 (not true at all) to 4 (true nearly all the time). Scores can range from 0 to 40, with higher scores reflecting greater resilience.

Optimism: Individuals' optimism was measured using the 6-item Life Orientation Test-Revised (LOT-R) (Scheier, Carver, & Bridges, 1994). This measure assesses individual differences in optimism versus pessimism, with statements such as 'In unclear times, I usually expect the best,' 'I am always hopeful about my future,' and 'I rarely count on good things happening to me.' Items were rated on a scale from 1 (strongly disagree) to 5 (strongly agree). Scores can range from 6 to 30. Pessimism items are reverse scored; thus, higher total scores indicate greater optimism.

Happiness: Participants' happiness was measured using the Center for Epidemiologic Studies – Depression, 4-item Happiness subscale (CESD-HS) (Radloff, 1977). The items assess participants' level of happiness during the last week. Statements such as 'I felt happy' and 'I enjoyed life' were rated on a scale from 0 (rarely or none of the time) to 3 (most or all of the time). Scores can range from 0 to 12, with higher scores indicating greater happiness. These items have been shown to be valid for measuring positive affect (Fowler & Christakis, 2008; Sheehan, Fifield, Reisine, & Tennen, 1995).

Perceived stress: The 10-item Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983) was used to assess participants' level of perceived stress. This measure asks participants to evaluate their feelings and thoughts during the past month. Items include 'How often have you been upset because of something that happened unexpectedly?' and 'How often have you felt difficulties were piling up so high that you could not overcome them?' Responses were given using a scale from 0 (never) to 4 (very often). Scores can range from 0 to 40, with lower scores indicating less perceived stress.

Mental health

Primary measure. *Short Form Health Survey (SF-36)* mental component score (Ware & Sherbourne, 1992): The SF-36 yields a mental health component summary which includes four subscales: vitality, social functioning, role-emotional, and mental health. Reliability statistics for the mental health component scores routinely exceed 0.90 (Ware, 2000). Lower scores on this measure indicate poorer mental health.

Additional measures. *Depression*: The Calgary Depression Scale (Addington, Addington, & Schissel, 1990) was designed as a measure of level of depression in persons with schizophrenia and has demonstrated high interrater reliability, as well as high internal reliability and validity (Addington & Addington, 1991). In addition, the Calgary Depression Scale appears to distinguish between depression and negative and extrapyramidal symptoms in individuals with schizophrenia (Addington, Addington, & Maticka-Tyndale, 1993). Higher scores on this measure indicate worse depression.

Anxiety: The Brief Symptom Inventory Anxiety Scale (Derogatis & Melisaratos, 1983) is a subscale of the Brief Symptom Inventory which includes six items clinically associated with anxiety (e.g. nervousness, fear, restlessness, tension) (Derogatis, 1979). Each question is rated on a 5-point Likert scale of distress (0–4) with higher scores indicating worse anxiety.

Severity of psychopathology: The Scales for Assessment of Positive Symptoms and Negative Symptoms (SAPS and SANS, respectively) (Andreasen, Arndt, Miller, Flaum, & Nopoulos, 1995; Andreasen and Olsen, 1982) assess a total of 49 individual signs and symptoms. Individual items are grouped together to include five positive symptoms (hallucinations, delusions, positive formal thought disorder, bizarre behavior, and catatonic motor behavior) and five negative symptoms (alogia, affective blunting, avolition, anhedonia, attentional impairment) for which global ratings are designated. Higher scores on these scales indicate more severe symptoms.

Physical health

Primary measure. *Short Form Health Survey (SF-36)* physical component score (Ware & Sherbourne, 1992): Lower scores on this measure indicate poorer physical health.

Additional measures. *Physical comorbidity*: Total score and severity score on Cumulative Illness Rating Scale (CIRS) (Linn, Linn, & Gurel, 1968). Higher scores on this measure indicate greater comorbidity.

Cardiovascular disease risk: Framingham Coronary Heart Disease (CHD) Risk Score (Wilson et al., 1998). Higher scores on this measure indicate greater risk of CHD.

Blood-based biomarkers

Participants underwent a blood draw for analysis of systemic blood-based biomarkers within two to four weeks of completing the assessments of PPFs and mental/physical health. These included biomarkers of insulin resistance (HOMA-IR) (Matthews et al., 1985) and inflammation (interleukins IL-6; high-sensitivity C-reactive protein or hs-CRP) (Pepys & Hirschfield, 2003; Signorelli, Fiore, & Malaponte, 2014). HOMA-IR was calculated as (Fasting insulin) $\times$ (Fasting glucose)/405. IL-6 was quantified using Meso Scale Discovery Multi-Spot Assay System (MSD, Rockville, MD, USA). Levels of hs-CRP were processed with a commercially available (MSD) enzyme-linked immunosorbent assay.

Statistical analyses

Characteristics of the schizophrenia and HC groups were compared using independent samples *t*-tests and Pearson chi-squares. We also examined what proportion of schizophrenia participants scored within a 'normative' range on measures of PPFs; this was operationalized as having a score within 1 SD of the HC mean. Since the four PPFs are likely to be highly correlated with one another, we created a Positive Psychological Factor Index (PPFI), which was a composite score of averaged *z*-scores of the four scales (the perceived stress scale was reversed scored so it went in the same direction as the other measures). Regression analyses were conducted for the two primary measures of mental and physical health (SF-36 component scores) and the three biomarker variables. The regression models included Group and PPFI (Model 1), and the addition of the Group $\times$ PPFI interaction (Model 2). Scatterplots are presented for those variables showing a significant Group $\times$ PPFI interaction. In addition, for primary variables with a significant PPFI or Group $\times$ PPFI effect, we explored whether these effects persisted after adjusting for education as a covariate. Education was chosen for examination because it differed between the two groups and was correlated with all of the primary outcome measures (data not shown). Specifically, we conducted an additional regression model in which

education was added to Model 2. Biomarker data were log transformed prior to analyses to reduce significant skew of the distributions of these variables in their raw-value form. Regression analyses (Models 1 and 2) were repeated for the additional mental health and physical health measures.

Results

Differences between schizophrenia and healthy comparison groups

There were no significant differences between the schizophrenia and HC groups on age or gender (see Table 1); thus, the sample used in this analysis was well matched on these variables. The schizophrenia group had less education and fewer Caucasian participants than the HC group. Relative to the HCs, the schizophrenia participants had lower mean levels of PPFs (see Table 1). However, there was considerable heterogeneity and some overlap in scores between the two groups on all of these measures. In fact, over one-third of the schizophrenia participants had scores within 1 SD of the HC mean on scales of resilience (33.3%), optimism (35.6%), happiness (37.8%), and perceived stress (39.3%). The schizophrenia group had more severe symptoms of psychopathology and poorer physical health, including greater physical comorbidity and higher values on the Framingham CHD Risk Score (see Table 1). With regard to biomarkers, the schizophrenia group demonstrated higher levels of HOMA-IR, IL-6, and hs-CRP (see Table 1). The schizophrenia group had a mean hs-CRP level of 4.5 mg/L, which exceeds the cutoff value of >3 mg/L based on the American Heart Association guidelines indicating high cardiovascular risk (Yeh & Willerson, 2003). Validated diagnostic cutoffs that can be broadly applied are not available for HOMA-IR or IL-6. The suggested cutoff values for HOMA-IR differ for different races, ages, genders, diseases, and complications (Tang et al., 2015).

Relationship among the positive psychological factors

The four PPFs were highly correlated with one another in both the schizophrenia (r values ranged from .45 to .58; $p < .001$) and the HC (r values ranged from .51 to .65; $p < .001$) groups. The PPFI, a composite score of averaged z-scores of the four scales, was highly correlated with the individual PPFs in both groups (schizophrenia: r values ranged from .79 to .80; $p < .001$; HC: r values ranged from .77 to .88; $p < .001$). This composite score was used as the independent variable in all further analyses.

Relationship of positive psychological factors with primary measures of mental and physical health (SF-36 component scores) and biomarkers

Regression analyses showing significant results for PPFI or the Group × PPFI interaction are presented in Table 2. For mental health, results showed that Group and PPFI significantly predicted SF-36 mental health component scores ($F(2, 258) = 171.15$, $p < .001$, $r^2 = .57$). Including the Group × PPFI interaction in the model accounted for additional variance ($R^2_{change} = .02$, $F_{change}(1, 257) = 13.84$, $p_{change} < .001$). A scatterplot of the interaction showed that the relationship between PPFI and SF-36 mental health component scores was stronger in the schizophrenia group relative to the HCs (see Figure 1(a)). There was no effect of adjusting for education on the PPFI or PPFI × Group effects (see Supplemental Table 1). For physical health, PPFI significantly predicted SF-36 physical health component scores ($F(2, 258) = 45.94$, $p < .001$, $r^2 = .26$). There was no significant Group × PPFI interaction and adjusting for education did not diminish the PPFI relationship.

For the biomarker variables, PPFI significantly predicted participants' HOMA-IR level ($F(2, 225) = 14.34$, $p < .001$, $r^2 = .11$). Adding the Group × PPFI interaction did not improve the model and adjusting for education did not diminish the PPFI relationship. For IL-6, Group and PPFI were significant predictors ($F(2, 234) = 11.33$, $p < .001$, $r^2 = .09$); there was no significant interaction and adjusting for education did not diminish the PPFI relationship. For hs-CRP, Group significantly predicted hs-CRP values ($F(2, 247) = 20.05$, $p < .001$, $r^2 = .14$); there was no relationship with PPFI or the Group × PPFI interaction.

Relationship of positive psychological factors with additional measures of mental and physical health

On additional measures of mental health, regression analyses showed that PPFI significantly predicted scores on measures of depression ($F(2, 256) = 65.53$, $p < .001$, $r^2 = .34$) and anxiety ($F(2, 258) = 88.02$, $p < .001$, $r^2 = .41$). Including the Group × PPFI interaction in the models accounted for some additional variance in depression ($R^2_{change} = .02$, $F_{change}(1, 255) = 6.80$, $p_{change} = .01$) and anxiety ($R^2_{change} = .02$, $F_{change}(1, 257) = 7.23$, $p_{change} = .008$). Scatterplots of the interactions showed that there was a stronger negative relationship between PPFI and depression/anxiety scores in the schizophrenia group relative to the HCs (see Figure 1(b,c).

On additional measures of physical health, regression analyses showed that Group and PPFI significantly predicted CIRS–Total Scores ($F(2, 220) = 24.05$, $p < .001$, $r^2 = .18$). For the CIRS–Severity Index, significant predictors were Group, PPFI, and the Group × PPFI interaction ($F(3, 219) = 16.96$, $p < .001$, $r^2 = .19$). A scatterplot of the interaction showed that the negative relationship between PPFI and CIRS–Severity Index scores was stronger in the HCs relative to the schizophrenia group (see Figure 1(d)). For Framingham CHD Risk Scores, Group was a significant predictor ($F(2, 225) = 7.49$, $p < .001$, $r^2 = .06$), but there was no relationship with PPFI or the Group × PPFI interaction.

Discussion

We compared a composite score of PPFs (which included resilience, optimism, happiness, and low perceived stress) in schizophrenia and HC subjects, and examined the association of this composite with mental and physical health status, and biomarkers of insulin resistance and inflammation. This study extended our previous work by: (1) including a larger sample of schizophrenia and HC participants, (2) examining a composite score that included multiple PPFs, and (3) investigating associations between PPFs and biomarkers of insulin resistance and inflammation.

As hypothesized, the schizophrenia group had lower mean levels of PPFs relative to the HCs. However, these group comparisons do not capture the considerable variability observed within the schizophrenia group. A major finding of this study was that over one-third of schizophrenia participants had values on measures of PPFs that were within the 'normative' range (i.e. within 1 SD of the HC mean). This finding has

Table 1. Characteristics of schizophrenia and healthy comparison groups.

	Schizophrenia ($n = 135$)		Healthy comparison ($n = 127$)			
	Mean	SD	Mean	SD	t or χ^2	p
Demographics						
Age (years)	48.2	10.1	48.6	11.2	$t = .28$	.777
Gender (% female)	46.7%	–	52.0%	–	$\chi^2 = .74$	.460
Education (years)	12.5	2.0	14.6	2.2	$t = 7.82$	<.001
Ethnicity					$\chi^2 = 12.58$	.028
Caucasian	43.0%	–	62.2%	–		
African American	18.5%	–	11.8%	–		
Hispanic	31.9%	–	19.7%	–		
Asian	4.4%	–	4.7%	–		
Native American/other Pacific Islander	1.5%	–	0.0%	–		
Bi/Multiracial	0.7%	–	1.6%	–		
Positive psychological factors						
Resilience (CD-RISC)	22.8	8.4	32.7	6.1	$t = 11.08$	<.001
Optimism (LOT-R)	19.9	3.8	24.0	3.7	$t = 8.86$	<.001
Happiness (CESD-HS)	7.2	3.5	10.8	2.1	$t = 10.32$	<.001
Perceived stress (PSS)	18.7	6.1	11.0	6.1	$t = 10.23$	<.001
Psychopathology						
Duration of illness (SZ)	23.4	12.2	–	–	–	–
Total antipsychotic dose (DDD) SZ	1.7	1.4	–	–	–	–
Positive symptoms (SAPS)	6.5	4.2	0.3	.72	$t = 17.04$	<.001
Negative symptoms (SANS)	7.4	4.4	1.3	2.2	$t = 14.23$	<.001
SF-36 – mental component	43.0	11.2	54.7	5.9	$t = 10.66$	<.001
Depression (CDRS)	3.6	4.1	0.6	1.5	$t = 7.95$	<.001
Anxiety (BSI)	7.4	6.6	1.4	2.5	$t = 9.90$	<.001
Physical health						
SF-36 – physical component	43.1	10.2	51.3	9.3	$t = 6.80$	<.001
Number of comorbid physical illnesses (CIRS–total)	6.7	4.9	3.2	3.4	$t = 6.31$	<.001
Severity of comorbid physical illnesses (CIRS–severity)	1.5	0.6	1.0	0.7	$t = 6.00$	<.001
Framingham CHD risk score	1.4	0.8	1.1	0.6	$t = 3.77$	<.001
Blood-based biomarkers						
HOMA-IR	3.7	5.2	1.8	1.6	$t = 4.16$[a]	<.001
IL-6 (pg/mL)	1.1	0.9	0.9	1.4	$t = 4.27$[a]	<.001
hs-CRP (mg/L)	4.5	5.4	2.0	2.9	$t = 6.05$[a]	<.001

[a]Means (and SDs) are provided as raw values; t-test comparisons reflect the log-transformed values.

CD-RISC, Connor–Davidson Resilience Scale – 10-item version; LOT-R, Life Orientation Test – Revised; CESD-HS, Center for Epidemiologic Studies-Depression – Happiness subscale; PSS, Perceived Stress Scale; SZ, schizophrenia; DDD, defined daily dose (WHO, 2010); SAPS/SANS, assessment of positive symptoms and negative symptoms; SF-36, Short-Form Health Survey; CDRS, Calgary Depression Rating Scale; BSI, Brief Symptom Inventory; CIRS, Cumulative Illness Rating Scale; CHD, coronary heart disease; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; IL, interleukin; hs-CRP, high-sensitivity C-reactive protein.

important implications, namely that individuals with schizophrenia can be resilient, optimistic, happy, and have low perceived stress regardless of their chronic illness.

The second major finding of this study was that the PPF composite was positively related to mental and physical health variables, even after adjustment for the potential confound of education. The relationship between the PPF composite and mental health measures was particularly strong for individuals with schizophrenia. Given the cross-sectional nature of the study, the direction of the relationship between PPFs and mental health is unclear. It is possible that individuals with better mental health and well-being tended to rate themselves more highly on the measures PPFs. On the other hand, it may be that PPFs lead to improvements in one's mental health, including a reduction or prevention of depression and anxiety. A relationship between resilience and mental health was also demonstrated in a study of a community-based sample of adults (Jeste et al., 2013), which found that greater resilience and lower depression levels were associated with higher well-being. While there may be some conceptual overlap between PPFs such as happiness and psychopathologic dimensions such as depression, there is literature supporting the notion that positive affect and negative affect can coexist. Studies have shown that positive mental health and mental illness represent two separate unipolar dimensions (Keyes, 2005; Westerhof & Keyes, 2010). A meta-analysis examining factor analyses of various measures of depression also found that positive affect was independent from other factors measuring depressive symptoms (Shafer, 2006).

For physical health variables, higher scores on the PPF composite were related to physical well-being on both a subjective measure (i.e. SF-36) and a more objective measure (i.e. CIRS–Total Scores). PPFs were more strongly associated with reduced medical severity (i.e. CIRS-Severity Index) in the HCs relative to the schizophrenia group. One possible explanation for this is that the schizophrenia participants had more severe medical/physical conditions, as reflected by higher CIRS scores, and it is possible that the impact of psychological variables on physical health is reduced in the presence of more severe medical problems.

The PPF composite was a significant predictor of IL-6 and HOMA-IR levels, even after adjustment for the potential confound of education. These findings are consistent with previous studies showing that blood-based biomarkers of inflammation and insulin resistance are related to positive affect/happiness (Matsunaga et al., 2011; Steptoe et al., 2008), well-being (Boehm & Kubzansky, 2012; Osama & Shehab Ael, 2015; Phillips & Perry, 2015; Steptoe et al., 2012), optimism (Ikeda et al., 2011; Roy et al., 2010), psychological resilience or 'hardiness' (Fields, Hoyt, Linnville, & Moore, 2015; Sandvik et al., 2013), and perceived stress (Aschbacher et al., 2013; Barbosa−Leiker et al., 2014; Shimanoe et al., 2014). Although longitudinal research is needed, our findings suggest the possibility that resilience, optimism, happiness, and low

Table 2. Regression results for variables with significant findings for PPFI or the Group × PPFI interaction.

	Model 1				Model 2			
	B	SE *B*	*β*	*t*	*B*	SE *B*	*β*	*t*
SF-36 mental component								
Group	−2.95	1.11	−.14	−2.66**	−3.50	1.09	−.16	−3.21**
PPFI	8.26	.64	.66	12.84***	.68	2.13	.05	.32
Group × PPFI					4.76	1.28	.61	3.72***
SF-36 physical component								
Group	−2.64	1.43	−.13	−1.85	−2.56	1.45	−.12	−1.77
PPFI	5.23	.83	.43	6.30***	6.40	2.82	.52	2.27*
Group × PPFI					−.74	1.69	−.10	−.44
HOMA-IR								
Group	.08	.06	.10	1.25	.06	.07	.08	.98
PPFI	−.13	.04	−.27	−3.42***	−.28	.13	−.59	−2.19*
Group × PPFI					.10	.08	.32	1.25
IL-6								
Group	.09	.04	.17	2.09*	.08	.04	.15	1.85
PPFI	−.05	.03	−.17	−2.10*	−.15	.09	−.46	−1.65
Group × PPFI					.06	.05	.29	1.10
Calgary Depression Scale								
Group	.92	.44	.14	2.10*	1.08	.44	.16	2.46*
PPFI	−1.94	.25	−.49	−7.62***	.19	.86	.05	.22
Group × PPFI					−1.34	.51	−.54	−2.61**
BSI Anxiety Scale								
Group	2.60	.71	.22	3.67***	2.86	.71	.25	4.04***
PPFI	−3.22	.41	−.48	−7.83***	.33	1.38	.05	.24
Group × PPFI					−2.22	.83	−.53	−2.69**
CIRS – Total Score								
Group	2.31	.72	.25	3.21**	2.12	.72	.23	2.93**
PPFI	−1.20	.43	−.22	−2.83**	−3.63	1.45	−.67	−2.50**
Group × PPFI					1.51	.86	.45	1.75
CIRS – Severity Index								
Group	.42	.11	.30	3.81***	.37	.11	.27	3.37***
PPFI	−.10	.07	−.12	−1.52	−.76	.22	−.93	−3.49***
Group × PPFI					.41	.13	.81	3.18**

*$p<.05$; **$p<.01$; ***$p<.001$

PPFI, Positive Psychological Factor Index; SF-36, Short-Form Health Survey; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; IL, interleukin; CIRS, Cumulative Illness Rating Scale; BSI, Brief Symptom Inventory.

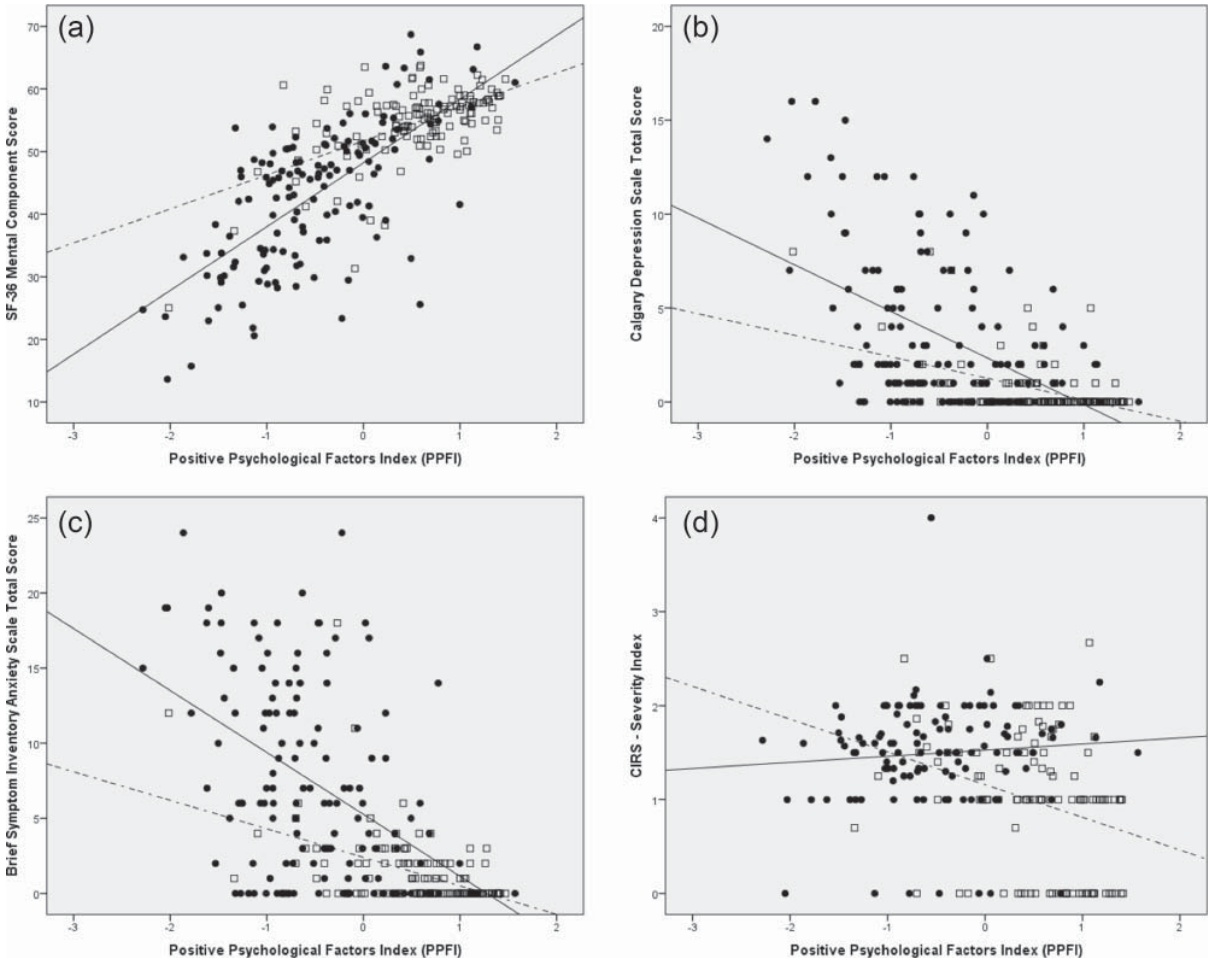

Figure 1. Scatterplots showing the group × PPFI interaction for (a) SF-36 mental health component scores, (b) Calgary Depression Scale scores, (c) BSI Anxiety Scale scores, and (d) CIRS–Severity Index scores. The filled circles and solid lines represent the schizophrenia group while the open squares and dashed lines represent the HC group. Regression lines are shown for the schizophrenia and HC group.

perceived stress might serve as protective factors against insulin resistance and inflammation and their associated negative health outcomes in both schizophrenia and HCs.

Strengths of the current study include the broad age range, systematic assessment of PPF using standardized rating scales, the examination of blood-based biomarkers, and the use of multivariate analysis. There are also several limitations to consider. These include the cross-sectional nature of the study, and the significant difference between the schizophrenia and HC groups in ethnicity. In addition, it is possible that other measures of PPFs might have produced a different pattern of results. Additional studies employing alternative instruments for measuring PPFs are needed to demonstrate generalizability of our findings. The schizophrenia group consisted of relatively stable outpatients on antipsychotic medications. Findings might vary among first-episode patients or those who are treatment-resistant, or among patients with comorbidities that were excluded for in the current study (e.g. alcohol or drug abuse).

In sum, results revealed a notable overlap in PPF scores between schizophrenia and HC groups, as well as significant relationships between PPFs and better mental and physical health. The association between PPFs and mental health was particularly strong for individuals with schizophrenia, while the HCs showed a stronger relationship between PPFs and severity of physical symptoms relative to those with schizophrenia. If our ongoing longitudinal studies suggest that the observed cross-sectional associations are due to an effect of PPFs on subsequent health, this could have direct clinical implications. Treatment for schizophrenia typically focuses on correcting deficits surrounding positive and negative symptoms, cognitive impairments, and relapse (Dixon et al., 2010). However, interventions for schizophrenia should move beyond these traditional methods and emphasize enhancing PPFs such as resilience, optimism, and happiness, and lowering perceived stress, perhaps via methods such as mindfulness meditation or cognitive reappraisals (Moore et al., 2015). This type of intervention would be consonant with the conceptualization of positive psychiatry (Jeste, 2015; Jeste & Palmer, 2013; Jeste, Palmer, Rettew, & Boardman, 2015), and would contrast with traditional psychiatric interventions focused primarily on decreasing negative affect.

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The authors, Ms Daly and Mr Reuter have no conflicts of interest to declare.

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References

Addington, D., Addington, J., & Maticka-Tyndale, E. (1993). Assessing depression in schizophrenia: The Calgary Depression Scale. *The British Journal of Psychiatry, 22*, 39–44.

Addington, D., Addington, J., & Schissel, B. (1990). A depression rating scale for schizophrenics. *Schizophrenia Research, 3*(4), 247–251.

Addington, J., & Addington, D. (1991). Positive and negative symptoms of schizophrenia: Their course and relationship over time. *Schizophrenia Research, 5*(1), 51–59.

Agid, O., McDonald, K., Siu, C., Tsoutsoulas, C., Wass, C., Zipursky, R.B., … Remington, G. (2012). Happiness in first-episode schizophrenia. *Schizophrenia Research, 141*(1), 98–103.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: Fourth edition – Text revision (DSM-IV-TR)*. Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: Fifth edition (DSM-5)*. Arlington, VA: American Psychiatric Publishing.

Andreasen, N.C., Arndt, S., Miller, D., Flaum, M., & Nopoulos, P. (1995). Correlational studies of the scale for the assessment of negative symptoms and the scale for the assessment of positive symptoms: An overview and update. *Psychopathology, 28*(1), 7–17.

Andreasen, N.C., & Olsen, S. (1982). Negative v positive schizophrenia: Definition and validation. *Archives of General Psychiatry, 39*(7), 789–794.

Aschbacher, K., O'Donovan, A., Wolkowitz, O.M., Dhabhar, F.S., Su, Y., & Epel, E. (2013). Good stress, bad stress and oxidative stress: Insights from anticipatory cortisol reactivity. *Psychoneuroendocrinology, 38*(9), 1698–1708.

Azad, M.C., Shoesmith, W.D., Al Mamun, M., Abdullah, A.F., Naing, D.K., Phanindranath, M., & Turin, T.C. (2016). Cardiovascular diseases among patients with schizophrenia. *Asian Journal of Psychiatry, 19*, 28–36. doi:10.1016/j.ajp.2015.11.012

Barbosa−Leiker, C., Roper, V., McPherson, S., Lei, M., Wright, B., Hoekstra, T., & Kostick, M. (2014). Cross−sectional and longitudinal relationships between perceived stress and C−reactive protein in men and women. *Stress and Health, 30*(2), 158–165. doi:10.1002/smi.2507

Blazer, D.G., & Kinghorn, W.A. (2015). Positive Social Psychiatry. In D.V. Jeste & B.W. Palmer (Eds.), *Positive psychiatry: A clinical handbook* (pp. 71–87). Arlington, VA: American Psychiatric Publishing.

Boehm, J.K., & Kubzansky, L.D. (2012). The heart's content: The association between positive psychological well-being and cardiovascular health. *Psychological Bulletin, 138*(4), 655–691. doi:10.1037/a0027448

Campbell−Sills, L., & Stein, M.B. (2007). Psychometric analysis and refinement of the Connor–Davidson resilience scale (CD−RISC): Validation of a 10−item measure of resilience. *Journal of Traumatic Stress, 20*(6), 1019–1028. doi:10.1002/jts.20271

Chida, Y., & Steptoe, A. (2008). Positive psychological well-being and mortality: A quantitative review of prospective observational studies. *Psychosomatic Medicine, 70*(7), 741–756.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24*(4), 385–396. doi:10.2307/2136404

Connor, K.M., & Davidson, J.R. (2003). Development of a new resilience scale: The Connor−-Davidson resilience scale (CD−RISC). *Depression and Anxiety, 18*(2), 76–82. doi:10.1002/da.10113

Davidson, K.W., Mostofsky, E., & Whang, W. (2010). Don't worry, be happy: Positive affect and reduced 10-year incident coronary heart disease: The Canadian Nova Scotia Health Survey. *European Heart Journal, 31*(9), 1065–1070.

Derogatis, L., 1979. *Brief severity index (BSI)*. Minneapolis, MN: Pearson, Inc.

Derogatis, L.R., & Melisaratos, N. (1983). The brief symptom inventory: An introductory report. *Psychological Medicine, 13*(3), 595–605.

Dixon, L.B., Dickerson, F., Bellack, A.S., Bennett, M., Dickinson, D., Goldberg, R.W., … Pasillas, R.M. (2010). The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophrenia Bulletin, 36*(1), 48–70. doi:10.1093/schbul/sbp115

Dockray, S., & Steptoe, A. (2010). Positive affect and psychobiological processes. *Neuroscience & Biobehavioral Reviews, 35*(1), 69–75.

DuBois, C.M., Lopez, O.V., Beale, E.E., Healy, B.C., Boehm, J.K., & Huffman, J. C. (2015). Relationships between positive psychological constructs and health outcomes in patients with cardiovascular disease: A systematic review. *International Journal of Cardiology, 195*, 265–280.

Fields, A.J., Hoyt, R.E., Linnville, S.E., & Moore, J.L. (2015). Physical activity, sleep, and C-reactive protein as markers of positive health in resilient older men. *Journal of Health Psychology, 21*(9), 1928–1938. doi:10.1177/1359105314568578

First, M.B., Spitzer, R.L., & Gibbon, M. (2002). *Structured clinical interview for DSM-IV-TR Axis I disorders, reserach version, patient edition (SCID-I/P)*. New York: New York State Psychiatric Institute, Biometrics Research.

Fowler, J.H., & Christakis, N.A. (2008). Dynamic spread of happiness in a large social network: Longitudinal analysis over 20 years in the Framingham Heart Study. *BMJ (Clinical Research Ed.), 337*, a2338.

Green, M.F., Kern, R.S., Braff, D.L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the" right stuff"? *Schizophrenia Bulletin, 26*(1), 119–136.

Ikeda, A., Schwartz, J., Peters, J.L., Fang, S., Spiro III, A., Sparrow, D., … Kubzansky, L.D. (2011). Optimism in relation to inflammation and endothelial dysfunction in older men: The VA Normative Aging Study. *Psychosomatic Medicine, 73*(8), 664–671. doi:10.1097/PSY.0b013e3182312497

Jeste, D.V. (2015). A fulfilling year of APA presidency: From DSM-5 to positive psychiatry. *American Journal of Psychiatry, 170*(10), 1102–1105.

Jeste, D.V., & Palmer, B.W. (2013). A call for a new positive psychiatry of ageing. *The British Journal of Psychiatry, 202*(2), 81–83. doi:10.1192/bjp.bp.112.110643

Jeste, D.V., Palmer, B.W., Rettew, D.C., & Boardman, S. (2015). Positive psychiatry: Its time has come. *The Journal of Clinical Psychiatry, 76*(6), 478–683.

Jeste, D.V., Savla, G.N., Thompson, W.K., Vahia, I.V., Glorioso, D.K., Martin, A. S., … Depp, C.A. (2013). Association between older age and more successful aging: Critical role of resilience and depression. *American Journal of Psychiatry, 170*(2), 188–196. doi:10.1176/appi.ajp.2012.12030386

Jeste, D.V., Wolkowitz, O.M., & Palmer, B.W. (2011). Divergent trajectories of physical, cognitive, and psychosocial aging in schizophrenia. *Schizophrenia Bulletin, 37*(3), 451–455. doi:10.1093/schbul/sbr026

Kanda, T., & Takahashi, T. (2004). Interleukin-6 and cardiovascular diseases. *Japanese Heart Journal, 45*(2), 183–193.

Keyes, C.L. (2005). Mental illness and/or mental health? Investigating axioms of the complete state model of health. *Journal of Consulting and Clinical Psychology, 73*(3), 539–548. doi:10.1037/0022-006x.73.3.539

Kim, E.S., Park, N., & Peterson, C. (2011). Dispositional optimism protects older adults from stroke. The health and retirement study. *Stroke, 42*(10), 2855–2859.

Kirkpatrick, B., Messias, E., Harvey, P.D., Fernandez-Egea, E., & Bowie, C.R. (2008). Is schizophrenia a syndrome of accelerated aging? *Schizophrenia Bulletin, 34*(6), 1024–1032. doi:10.1093/schbul/sbm140

Kubzansky, L.D., & Thurston, R.C. (2007). Emotional vitality and incident coronary heart disease: Benefits of healthy psychological functioning. *Archives of General Psychiatry, 64*(12), 1393–1401.

Lavretsky, H. (2014). *Resilience and aging: Research and practice* (1st ed.). Baltimore, MD: Johns Hopkins University Press.

Lavretsky, H., Small, G., Ercoli, L., & Merrill, D.A. (2013). Lifestyle behaviors promoting mental health in older adults. *The American Journal of Geriatric Psychiatry, 21*(3), S22.

Linn, B.S., Linn, M.W., & Gurel, L. (1968). Cumulative illness rating scale. *Journal of the American Geriatrics Society, 16*(5), 622–626.

Martin, A.S., Harmell, A.L., & Mausbach, B.T. (2015). Positive psychological traits. In D.V. Jeste & B.W. Palmer (Eds.), *Positive psychiatry: A clinical handbook* (pp. 19–43). Arlington, VA: American Psychiatric Publishing.

Matsunaga, M., Isowa, T., Yamakawa, K., Tsuboi, H., Kawanishi, Y., Kaneko, H., … Ohira, H. (2011). Association between perceived happiness levels and peripheral circulating pro-inflammatory cytokine levels in middle-aged adults in Japan. *Neuroendocrinology Letters, 32*(4), 458–463.

Matthews, D., Hosker, J., Rudenski, A., Naylor, B., Treacher, D., & Turner, R. (1985). Homeostasis model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia, 28*(7), 412–419.

Moore, R.C., Eyler, L.T., Mills, P.J., O'Hara, R.M., Wachmann, K., & Laveretsky, H. (2015). Biology of positive psychiatry. In D.V. Jeste & B.W. Palmer (Eds.), *Positive psychiatry: A clinical handbook* (pp. 261–284). Arlington, VA: American Psychiatric Publishing.

Osama, A.J., & Shehab Ael, K. (2015). Psychological wellbeing and biochemical modulation in response to weight loss in obese type 2 diabetes patients. *African Health Sciences, 15*(2), 503–512. doi:10.4314/ahs.v15i2.25

Ostir, G.V., Markides, K.S., Peek, M.K., & Goodwin, J.S. (2001). The association between emotional well-being and the incidence of stroke in older adults. *Psychosomatic Medicine, 63*(2), 210–215.

Palmer, B.W., Martin, A.S., Depp, C.A., Glorioso, D.K., & Jeste, D.V. (2014). Wellness within illness: Happiness in schizophrenia. *Schizophrenia Research*, *159*(1), 151–156.

Pepys, M.B., & Hirschfield, G.M. (2003). C-reactive protein: A critical update. *The Journal of Clinical Investigation, 111*(12), 1805–1812. doi:10.1172/jci18921

Phillips, C.M., & Perry, I.J. (2015). Depressive symptoms, anxiety and well-being among metabolic health obese subtypes. *Psychoneuroendocrinology, 62*, 47–53. doi:10.1016/j.psyneuen.2015.07.168

Pinikahana, J., Happell, B., Hope, J., & Keks, N.A. (2002). Quality of life in schizophrenia: A review of the literature from 1995 to 2000. *International Journal of Mental Health Nursing, 11*(2), 103–111. doi:10.1046/j.1440-0979.2002.00233.x

Radloff, L.S. (1977). The CES-D scale a self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385–401.

Rajji, T.K., Miranda, D., & Mulsant, B.H. (2014). Cognition, fonction et incapacité chez des patients souffrant de schizophrénie: une revue des études longitudinales [Cognition, function, and disability in patients with schizophrenia: A review of longitudinal studies/cognition]. *Canadian Journal of Psychiatry, 59*(1), 13.

Ridker, P.M., Hennekens, C.H., Buring, J.E., & Rifai, N. (2000). C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *The New England Journal of Medicine, 342*(12), 836–843. doi:10.1056/nejm200003233421202

Ringen, P.A., Engh, J.A., Birkenaes, A.B., Dieset, I., & Andreassen, O.A. (2014). Increased mortality in schizophrenia due to cardiovascular disease – a non-systematic review of epidemiology, possible causes, and interventions. *Frontiers in Psychiatry, 5*, 137. doi:10.3389/fpsyt.2014.00137

Roy, B., Diez-Roux, A.V., Seeman, T., Ranjit, N., Shea, S., & Cushman, M. (2010). The association of optimism and pessimism with inflammation and hemostasis in the multi-ethnic study of atherosclerosis (MESA). *Psychosomatic Medicine, 72*(2), 134–140. doi:10.1097/PSY.0b013e3181cb981b.

Sandvik, A.M., Bartone, P.T., Hystad, S.W., Phillips, T.M., Thayer, J.F., & Johnsen, B.H. (2013). Psychological hardiness predicts neuroimmunological responses to stress. *Psychology, Health & Medicine, 18*(6), 705–713. doi:10.1080/13548506.2013.772304

Scheier, M.F., Carver, C.S., & Bridges, M.W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A reevaluation of the Life Orientation Test. *Journal of Personality and Social Psychology, 67*, 1063–1063. doi:10.1037/0022-3514.67.6.1063

Seligman, M.E., & Csikszentmihalyi, M. (2000). Positive psychology. An introduction. *The American Psychologist, 55*(1), 5–14.

Shafer, A.B. (2006). Meta-analysis of the factor structures of four depression questionnaires: Beck, CES-D, Hamilton, and Zung. *Journal of Clinical Psychology, 62*(1), 123–146. doi:10.1002/jclp.20213

Sheehan, D.V., Lecrubier, Y., Harnett-Sheehan, K., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. (1998). The mini international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview. *Journal of Clinical Psychiatry, 59*(20), 22–33.

Sheehan, T.J., Fifield, J., Reisine, S., & Tennen, H. (1995). The measurement structure of the Center for Epidemiologic Studies Depression Scale. *Journal of Personality Assessment, 64*(3), 507–521. doi:10.1207/s15327752jpa6403_9

Shimanoe, C., Otsuka, Y., Hara, M., Nanri, H., Nishida, Y., Nakamura, K., … Sakamoto, T. (2014). Gender-specific associations of perceived stress and coping strategies with C-reactive protein in middle-aged and older men and women. *International Journal of Behavioral Medicine, 21*(5), 821–832. doi:10.1007/s12529-013-9341-y

Shrivastava, A., Johnston, M., Shah, N., & Bureau, Y. (2010). Redefining outcome measures in schizophrenia: Integrating social and clinical parameters. *Current Opinion in Psychiatry, 23*(2), 120–126.

Signorelli, S.S., Fiore, V., & Malaponte, G. (2014). Inflammation and peripheral arterial disease: The value of circulating biomarkers (Review). *International Journal of Molecular Medicine, 33*(4), 777–783. doi:10.3892/ijmm.2014.1657

Steptoe, A., Demakakos, P., de Oliveira, C., & Wardle, J. (2012). Distinctive biological correlates of positive psychological well-being in older men and women. *Psychosomatic Medicine, 74*(5), 501–508.

Steptoe, A., O'Donnell, K., Badrick, E., Kumari, M., & Marmot, M. (2008). Neuroendocrine and inflammatory factors associated with positive affect in healthy men and women the Whitehall II Study. *American Journal of Epidemiology, 167*(1), 96–102.

Summers, R.F., & Lord, J.A. (2015). Positivity in supportive and psychodynamic therapy. In D.V. Jeste & B.W. Palmer (Eds.), *Positive psychiatry: A clinical handbook* (pp. 167–192). Arlington, VA: American Psychiatric Publishing.

Świtaj, P., Anczewska, M., Chrostek, A., Sabariego, C., Cieza, A., Bickenbach, J., & Chatterji, S. (2012). Disability and schizophrenia: A systematic review of experienced psychosocial difficulties. *BMC Psychiatry, 12*(1), 193.

Tang, Q., Li, X., Song, P., & Xu, L. (2015). Optimal cut-off values for the homeostasis model assessment of insulin resistance (HOMA-IR) and pre-diabetes screening: Developments in research and prospects for the future. *Drug Discoveries & Therapeutics, 9*(6), 380–385. doi:10.5582/ddt.2015.01207

Ward, M., & Druss, B. (2015). The epidemiology of diabetes in psychotic disorders. *Lancet Psychiatry, 2*(5), 431–451. doi:10.1016/s2215-0366(15)00007-3

Ware, J.E. Jr. (2000). SF-36 health survey update. *Spine, 25*(24), 3130–3139.

Ware, J.E. Jr, & Sherbourne, C.D. (1992). The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical Care, 30*(6), 473–483. doi:10.1097/00005650-199206000-00002

Westerhof, G.J., & Keyes, C.L. (2010). Mental illness and mental health: The two continua model across the lifespan. *Journal of Adult Development, 17*(2), 110–119. doi:10.1007/s10804-009-9082-y

World Health Organization. (2010). *Guidelines for ATC classification and DDD assignment*. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2009.

Wilson, P.W., D'Agostino, R.B., Levy, D., Belanger, A.M., Silbershatz, H., & Kannel, W.B. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation, 97*(18), 1837–1847. doi:10.1161/01.CIR.97.18.1837

Yeh, E.T., & Willerson, J.T. (2003). Coming of age of C-reactive protein: Using inflammation markers in cardiology. *Circulation, 107*, 370–371.