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Low cardiorespiratory fitness and physical functional capacity in obese patients with schizophrenia

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ABSTRACT

Background: Low cardiorespiratory fitness is a prominent behavioral risk factor for cardiovascular disease (CVD) morbidity and mortality, as cardiorespiratory fitness is strongly associated with CVD outcomes. High rates of CVD have been observed in the schizophrenia population, translating into a markedly reduced life expectancy as compared to healthy controls. Surprisingly however, while cardiorespiratory fitness is an eminent indicator for overall cardiovascular health as well as eminently modifiable risk factor for CVD, no studies have systematically assessed cardiorespiratory fitness in schizophrenia.

Methods: Community-dwelling schizophrenia patients underwent graded-exercise tests, to ascertain maximal oxygen uptake (Max Vo2), considered to be the gold standard for the evaluation of cardiorespiratory fitness and physical functional capacity. The modified Bruce protocol was used to ascertain cardiorespiratory fitness and physical functional capacity; data was normalized and compared to population standards derived from the ACLS (Aerobics Center Longitudinal Study) and the National Health and Nutrition Examination Surveys (NHANES), Cycles III and IV.

Results: Data for $n=117$ participants (41% male, 46% white) was analyzed. Mean age (y) was 43.2 ± 9.9, and mean BMI was 37.2 ± 7.3. Peak HR attained during exercise was 145.6 ± 19.6, after 8.05 ± 3.6 min, achieving 111.2 ± 44.2 W. Max Vo2 was 1.72 ± 6.6 l/min, MaxVCo2 1.85 ± 7.2 l/min, and minute ventilation (VE) was 55.6 ± 21.9 ml/s. PANSS Positive subscores (13.3 ± 4.4; $r=-0.21$, $p=0.024$) were inversely correlated with Max Vo2 $ml^{-1}min^{-1}kg^{-1}$. Neither PANSS Total (56.3 ± 12.3; $r=-0.105$, $p=0.72$), PANSS Negative (14 ± 5.1; $r=-0.52$, $p=0.57$) nor PANSS General Psychopathology (28.4 ± 7.4; $r=-0.28$, $p=0.76$) scores were correlated with Max Vo2 $ml^{-1}min^{-1}kg^{-1}$. Peak heart rate and duration of exercise were not correlated with PANSS scores. Compared to healthy controls derived from the ACLS and NHANES, respectively, 115 participants achieved 'low levels' of fitness only, as well as highly significantly reduced Max Vo2, across all age groups.

Conclusion: The test was generally well received and tolerated by those who elected to participate; and adherence to the protocol was good. Among participants with schizophrenia, most of whom were obese, and across all age groups, cardiorespiratory fitness was exceedingly poor. Only two participants in our entire sample fit the categorization of 'moderate fitness level'; that is, a fitness level at or above the 20th percentile of ACLS-derived population comparisons. Conversely, this left 98.3% of participants with schizophrenia below population standards. Low cardiorespiratory fitness emerges as an eminent modifiable risk factor for CVD mortality and morbidity in schizophrenia complicated by obesity.

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1. Introduction

High rates of cardiovascular disease (CVD) have been observed in the schizophrenia population, translating into a life expectancy that is reduced by as much as 20–25% in comparison with mentally healthy controls (Hennekens, 2007). The reasons are complex and include unhealthy lifestyles, poor diet, little exercise, and cigarette smoking (Brown et al., 1999; Strassnig et al., 2006), in addition to treatment with antipsychotic medication, which can add deleterious metabolic consequences by themselves (Newcomer, 2005).

This has lead to the untenable situation that, despite improved outcomes with respect to psychiatric symptoms, social functioning, and quality of life, the mortality gap for patients has not narrowed, but may actually be worsening (Saha, Chant & McGrath, 2007). A therapeutically unsustainable situation, it coincides with a relative lack of research into lifestyle-related adverse sequelae that would in all likelihood identify causative mechanisms and risk factors that could represent targets of intervention to mitigate, close or even reverse that gap (Koivukangas et al., 2010).

One lifestyle factor, low cardiorespiratory fitness has been recognized as a prominent behavioral risk factor for cardiovascular disease (CVD) morbidity and an independent risk factor for all-cause mortality in adults (Blair et al., 1989; Kampert et al., 1996). Higher cardiorespiratory fitness decreases overall mortality rates, and morbidity and mortality due to CVD in a dose–response fashion (CDC, 1996). These associations are quite robust and have been demonstrated to be largely independent from other major risk factors (Elekund et al., 1988; Blair et al., 1989, 1996). Together with anecdotal observations of sedentary behavior and lack of exercise in schizophrenia patients that may far exceed population standards (Faulkner et al., 2006; Lindamer et al., 2008, Sharpe et al., 2006), cardiorespiratory fitness in schizophrenia emerges as a major modifiable risk factor for CVD and overall morbidity and mortality (Vancampfort et al., 2010).

At the same time, the literature regarding cardiorespiratory fitness in schizophrenia remains insufficient. No studies have systematically assessed cardiorespiratory fitness in patients treated for schizophrenia, facing known deleterious lifestyles and chronic treatment with antipsychotic medication. Moreover, to our knowledge, neither the response to structured physical exercise nor its tolerability has been systematically examined in patients with schizophrenia. This would aid in the development of targeted interventions to improve cardiorespiratory fitness and physical health in patients with schizophrenia, and identify specific subgroups that may be at especially high risk for CVD due to low cardiorespiratory fitness.

2. Methods

2.1. Study population

Between 2005 and 2008, overweight and obese community-dwelling patients with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder and psychotic disorder NOS were recruited from the outpatient clinic and partial hospital at the Schizophrenia Treatment and Research Center, at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, PA, for a clinical trial on weight loss. The subjects in the parent study were asked if they were willing to participate in graded-exercise tests (GXTs), but this was not a requirement for continuing in the parent protocol. Less than half of the individuals in the clinical trial agreed to undergo GXT. Reasons for accepting or declining, were not tracked. The GXT is considered to be the gold standard for the evaluation of cardiovascular fitness and overall physical functional capacity, and a standardized GXT protocol at the University of Pittsburgh Medical Center's ONRC (Obesity and Nutrition Research Center), using the Bruce protocol (Myers et al., 1991), was used.

The University of Pittsburgh IRB approved the study; all of the participants gave written consent prior to the GXT. The GXT was completed at baseline before any behavioral weight loss intervention took place. Each individual was asked to verify demographic, clinical and medication information with regard to history of chronic disease, current medications, and cigarette smoking habits. Information was verified by chart review. Subjects received a physical examination and baseline electrocardiogram (ECG), and those deemed to have a medically unstable condition or ECG abnormalities were excluded from the GXT. Body weight and height were recorded. BMI was calculated.

2.2. Graded-exercise test (GXT) procedure

Participants, dressed lightly, completed the GXT on a stationary cycle ergometer, and those deemed to exceed the ergometer safety weight limits (>400 lbs; $n=2$) were asked to complete the GXT on a treadmill. Preparation was as follows: The subjects were asked to sit down comfortably on the ergometer after removing excess clothing, were then connected to a 12 lead ECG and an automatic sphygmomanometer, and had a rubber face mask fitted to comfortably enclose their mouth and nose. The facemask was then connected via flexible tubes to an open-circuit spirometer for the measurement of gas exchange. Prior to each test session, the gas analyzers were calibrated with certified gases of known standard concentration.

After a brief rest period to get familiarized with the setup and adjusted to the facemask, the exercise test was initiated; speed remained constant throughout each subsequent 2 min testing stage while resistance was increased. During the last 10 s of each exercise stage and at the point of test termination, heart rate was measured from a 12 lead ECG, blood pressure was measured by an automatically inflating sphygmomanometer, and rating of perceived exertion (RPE) was obtained using the 6–20 category Borg Scale (Borg, 1974). For safety, blood pressure was measured during the last 45 s of each even minute exercise stage (i.e., stages 2, 4, 6, etc.) and for a defined period after test termination using a manual sphygmomanometer. Using the standard test termination criteria of the American College of Sports Medicine (ACSM, 2005; Gibbons et al., 2002), the test was terminated at voluntary exhaustion or if the patient reported signs or symptoms of exercise intolerance (i.e., muscular fatigue, significant ST depression and ischemia, or complex arrhythmias).

Cardiorespiratory fitness was expressed as maximal oxygen uptake (Vo2max $ml^{-1}min^{-1}kg^{-1}$). Peak exercise time was recorded in minutes; peak exercise capacity was estimated as metabolic equivalents (METs). One MET is defined as the energy expended at rest, which is equivalent to an oxygen consumption of 3.5 ml kg^{-1} of body weight per minute and peak exercise capacity as MET (metabolic equivalent) was estimated from speed and resistance using standardized quotations where V02 (ml $kg^{-1}min^{-1}$)/ [0.1 ml kg^{-1} m^{-1} s(m min^{-1})] + [1.8 ml kg^{-1} m^{-1} s(m min^{-1})G] + 3.5 mL kg^{-1} min^{-1}; s = speed and r = resistance in percent. METS = Vo2 (ml kg^{-1} min^{-1})/3.5 ml kg min^{-1}. Predicted Vo2max was calculated as follows, for males: VO2max = 14.76 − (1.379 × time) + (0.451 × $time^2$) − (0.012 × $time^3$) and for females: VO2max = (4.38 × time) − 3.90, whereas time = max time. Predicted maximum heart rate was calculated as follows: 220 − age.

To ascertain cardiovascular fitness and exercise capacity among study participants, study results categorized by age and gender were compared to reference data derived from US population surveys including the Aerobics Center Longitudinal Study (ACLS; Blair et al., 1989), and the National Health and Nutrition Examination Survey (Duncan et al., 2005; Wang et al., 2010; Sanders and Duncan, 2006).

The Borg Scale is a 15-point linear Likert scale and measures subjective, i.e., perceived exertion/exercise intensity (including heart rate, respiration effort, soreness and fatigue). Exertion is rated on a scale of 6–20; between 7 and 8 is 'very light' exertion. Eleven is a light level of exertion. Fifteen would be consistent with a level of heavy resistance. A level of 20 cannot be sustained.

2.3. Statistics

The NHANES survey design is a stratified probability sample of the US population. Details of the NHANES protocol and testing procedures are available elsewhere (http://www.cdc.gov/nchs/abutmajro/nhanes/datalink.htm#1999%20Current%20NHANES). All individuals aged 12–49 years were eligible to participate in the cardiovascular fitness component of NHANES. The final sample consisted of 1978 adults who had complete data available for the analysis (Duncan et al., 2005).

The ACLS (Blair et al., 1989; Mahler et al., 1995) stratifies data according to fitness levels. Low cardiovascular fitness is defined as MET below the 20th percentile of the same sex and age group, a moderate fitness levels is a value between the 20th and 59th percentile; and a high fitness level is at or above the 60th percentile (also see Table 2 later).

SPSS (for windows) software was employed for data analysis. Descriptive analysis including mean, range and standard deviation for continuous variables was carried out to determine whether the variables were normally distributed and frequency counts for categorical data (for example gender, race, etc) were done to examine the proportions of the GXT were examined for the whole group, for males and females and for Caucasians and African Americans. Individual GXT values such as max Vo2, METs, were categorized according to standard fitness-level cut-offs derived corresponding values observed in the National Health and Nutrition Examination Survey, Cycle III (NHANES III; Alaimo et al., 1994; McDowell et al., 1994). Student t-tests and where appropriate Fisher's exact tests, chi-square tests and ANOVA were employed to look for statistical differences between the means of 2 variables. Confidence interval was 95% throughout.

3. Results

3.1. Exercise capacity

From among n = 260 subjects who were recruited to participate in the behavioral weight loss trial, n = 117 subjects (41% male, 46% white) were elected to participate in the GXT. Mean age (y) of those subjects was 45.1 ± 10.1, and mean BMI was 36.7 ± 7.5. Antipsychotic medications included clozapine (n = 21), olanzapine (n = 15), risperidone (n = 28), quetiapine (n = 10), ziprasidone (n = 7), aripiprazole (n = 19), and antipsychotic polypharmacy (n = 19). Psychopathology was measured with the Positive and Negative Symptom Rating Scale (PANSS; Kay et al., 1987) and scores were as follows: PANSS Positive subscores were 13.3 ± 4.4, PANSS Negative subscores 14 ± 5.1, PANSS General Psychopathology subscores were 28.4 ± 7.4, and PANSS Total scores were 56.3 ± 12.3.

Resting BP was 124 (11)/80(10), and resting HR was 88 ± 14. Peak HR attained during exercise was 142 ± 21, after 7.7 ± 3.4 min, and peak BP was 161 ± 21 and 82 ± 9. Maximal watt attained was 103.4 ± 45.2; corresponding to a Vo2max of 1635 ± 687 ml/min, a VCo2 max of 1741 ± 731 l/min and a minute ventilation (VE) max of 49 ± 19.9 ml/s. This equates to a max MET of 4.4 ± 1.75. The anaerobic threshold (AT) amongst all participants was surpassed at 1.06 ± 0.5. The rate of perceived exertion was 15(±2), indicating 'hard to very hard work' (Table 1).

Compared to individual age-predicted maximal values (ACLS derived), study subjects achieved 38 ± 16% of maximal MET 12 ± 3; 83% of maximal predicted heart rate (171 ± 7); and 42 ± 11% of maximal V02 uptake, 2648 ± 916 ml/min. One hundred and fifteen (n = 115; 98.3%) out of the total participant number of 117 fell in the age-adjusted ACLS 'low fitness category'. Two participants fell in the 'moderate fitness category'. No participant reached the ACLS 'high fitness category' (Table 2).

Age was inversely correlated with Max Vo2 $ml^{-1}min^{-1}$ kg^{-1} (r = −0.184, *p = 0.047*), max watt attained (r = −0.215, *p = 0.021*), duration of exercise (r = −0.315, *p = 0.001*); peak heart rate (r = −0.261, *p = 0.024*), but not with RPE (r = 0.151, *p = 0.104*). BMI was inversely correlated with Max Vo2 ml^{-1} $min^{-1}kg^{-1}$ (r = −.0207, *p = 0.025*), but not with max minutes (exercise time; r = 0.038, *p = 0.691*), or RPE (r = −0.54, *p = 0.561*). PANSS Positive subscores (13.3 ± 4.4; r = −0.21, *p = 0.024*) were inversely correlated with Max Vo2 ml^{-1} min^{-1} kg^{-1}. Neither PANSS total scores (56.3 ± 12.3; r = −0.105, *p = 0.72*), PANSS Negative (14 ± 5.1; r = −0.52, *p = 0.57*), nor PANSS General Psychopathology (28.4 ± 7.4; r = −0.28, *p = 0.76*) subscores were correlated with Max Vo2 $ml^{-1}min^{-1}kg^{-1}$. Peak heart rate, duration of exercise, and RPE were not correlated with PANSS total scores, PANSS Positive, Negative, and General Psychopathology subscores.

There was no difference across antipsychotic medications in Max Vo2 ml^{-1} min^{-1} kg^{-1} (F = 0.942, *p = 0.47*), max VE (F = 0.427, *p = 0.86*), RQ (F = 0.28, *p = 0.94*), max watt attained (F = 0.91, *p = 0.49*), max minutes (F = 1.25, *p = 0.29*) or RPE (F = 0.54, *p = 0.78*).

Males (n = 46) had higher Max Vo2 $ml^{-1}min^{-1}kg^{-1}$ than females (n = 71, 18.7 ± 6.8 vs. 13.4 ± 4.6; *p = 0.017, t = 2.45*), maximum MET (5.4 ± 1.9 vs. 3.8 ± 1.3; *p = 0.017, t = 2.43*) but not maximum minutes (8.9 ± 3.9 vs. 7 ± 2.8; *p = 0.104, t = 1.65*), and peak heart rate (144 ± 20 vs. 140 ± 21; *p = 0.5, t = 0.68*), RPE (15.6 ± 1.7 vs,14.5 ± 2; *p = 0.96, t = −0.46*).

There were no differences in BMI (27.1 ± 7 vs. 37.4 ± 6.9; *p = 0.92, t = −0.106*), Max Vo2 $ml^{-1}min^{-1}kg^{-1}$ (19.1 ± 7.3 vs. 17.9 ± 5.7; *p = 0.6, t = 0.527*) and RPE (15.6 ± 1.8 vs. 15.8 ± 1.7; *p = 0.69, t = −0.4*) between white (n = 32) and black

Table 1
Population distribution, cardiorespiratory fitness.

Cardiovascular fitness level	Population males	Population females
	(age) 20–39	
Low	<10.8	<8.6
Moderate	10.9–13.3	8.7–10.8
High	>13.3	>10.8
	40–49	
Low	<9.9	<8.1
Moderate	10–12.4*	8.2–9.9
High	>12.4	>9.9
	50–59	
Low	<8.9	<7.2
Moderate	9.0–11.3+	7.3–8.9
High	>11.3	>8.9
	60+	
Low	<8.1	<6.3
Moderate	8.2–10.3	6.4–8.1
High	>10.3	>8.1

Maximal MET cutoff points for low, moderate and high cardiovascular fitness, adapted from the Aerobics Center Longitudinal Study (2002).
*, + One male study participant each, in the 40–49 year group (n = 1) and 50–59 year group (n = 1), respectively, reached moderate levels of fitness, respectively; all other participants (n = 115), male and female, age-adjusted, only reached low levels of fitness.

males (n = 14). White males exercised longer (max minutes 9.7 ± 4.2 vs. 7.1 ± 3.2; *p = 0.039*, *t = 2.12*). Among females, white females (n = 23) had significantly lower BMI (33.8 ± 9.8 vs. 37.7 ± 6.4; *p = 0.049, t = −2*) than black females (n = 48) and significantly higher Max Vo2 ml^{-1}min^{-1}kg^{-1} (15.3 ± 5.5 vs. 12.6 ± 3.9; *p = 0.017, t 2.45*). There was no difference in maximum minutes spent exercising (7.8 ± 3.1 vs. 6.5 ± 2.6; *p = 0.1, t = 1.65*) or RPE (14.4 ± 2.3 vs. 14.5 ± 1.9; *p = 0.96, t = −0.46*).

3.2. Tolerability

Termination reason was muscular soreness (n = 52, 44.5%), shortness of breath (n = 10, 8.5%), physical fatigue n = 32, 27.3%, dry mouth (n = 3, 2.6%), medical (n = 1; 0.8%), and other (n = 21, 18%). Nineteen subjects developed ECG changes during the GXT (16.2%), eleven of which (9.4%) showed ST-wave changes (10 nonspecific, 1 terminated) and ten of which showed rhythm abnormalities (i.e., extrasystoles, PVCs). No subject had to be terminated due to GXT-induced rhythm abnormalities, but one subject presented to the GXT lab with a previously undetected baseline sinus arrhythmia and had to be referred to emergency care after ECG leads were placed and before the protocol was started.

4. Conclusions

The graded-exercise test, considered the 'gold standard' for examination of cardiorespiratory fitness, was generally well received and tolerated by those who elected to participate and their adherence to the rather demanding protocol was good. Among the study participants, all of whom were suffering from schizophrenia of various illness durations, cardiovascular fitness was exceedingly poor. All but two participants met ACLS criteria for 'low fitness' levels, referring to the lowest quintile of age and sex adjusted fitness levels according to a standardized US population sample.

Table 2
Study participants, cardiorespiratory fitness.

	Schizophrenia		Healthy controls	
	Males	Females	Males	Females
	(age) 20–29		20–29	
	n = 5	*n = 7*	*n = 675*	*n = 576*
BMI	44.1 ± 3 9	39.5 ± 9.5		
Vo2 ml^{-1}min^{-1}kg^{-1}	18.5 ± 5.9	14.9 ± 4.3	44.5 ± 0.4 p<0.0001 t = 95.9	36.5 ± 0.4 p<0.0001 t = 83.7
Minute ventilation (VE)	62.3 ± 26	44 ± 17		
Watt	150 ± 66	107 ± 31		
Minutes	12 ± 4.2	8.6 ± 3		
MET	5.3 ± 1.7	4.2 ± 1.2		
%PredMaxHR [a]	82.4 ± 11	80 ± 10		
%PredMaxVo2 [+]	65 ± 8.1	44.5 ± 4.5		
	30–39		30–39	
	n = 10	*n = 14*	*n = 574*	*n = 542*
BMI	42 ± 7.8	38.9 ± 8.6		
Vo2 ml^{-1}min^{-1}kg^{-1}	22.3 ± 6.2	15.6 ± 5.2	42.8 ± 0.5 p<0.0001 t = 63.6	35.4 ± 0.4 p<0.0001 t = 82.3
VE	64 ± 13	47.6 ± 10.8		
Watt	138 ± 32	96 ± 35		
Minutes	10 ± 2.8	8.5 ± 3.2		
MaxMet	6.4 ± 1.8	4.5 ± 1.5		
%PredMaxHR	87 ± 1.4	78 ± 8		
%PredMaxVo2	66.5 ± 18	69 ± 21.6		
	40–49		40–49	
	n = 19	*n = 29*	*n = 458*	*n = 425*
BMI	37.6 ± 6	35.8 ± 5.3		
Vo2 ml^{-1}min^{-1}kg^{-1}	19.8 ± 7.1	13.3 ± 4.7	42.2 ± 0.6 p<0.0001 t = 96.4	34.4 ± 0.5 p<0.0001 t = 86.8
VE	66 ± 17.1	36.4 ± 9.6		
Watt	142 ± 53	83 ± 25.1		
Minutes	8.6 ± 4.1	6.2 ± 1.7		
MaxMet	5.6 ± 2.1	3.8 ± 1.3		
%PredMaxHR	80 ± 13	80.5 ± 10		
%PredMaxVo2	65.4 ± 23.5	61.6 ± 16		
	50–59		50–59	
	n = 21	*n = 23*		
BMI	33.8 ± 4.3	34. ± 8 9		
Vo2 ml^{-1}min^{-1}kg^{-1}	17.1 ± 6.5	12 ± 3.7	[b]	
VE	59.7 ± 22	38 ± 13.7		
Watt	116 ± 38	75 ± 33		
Minutes	7.2 ± 3.3	6.5 ± 3.2		
MaxMet	4.9 ± 1.9	3.4 ± 1		
%PredMaxHR	81.7 ± 8.4	81 ± 15.3		
%PredMaxVo2	58 ± 23	62 ± 18		

[a] %PredMaxHR = Percentage of expected maximal heart rate.
[+] PredMaxVo2 = percentage of expected maximal Vo2 ml^{-1}min^{-1}kg^{-1}.
[b] NHANES population GXT data available until age 49 (Duncan et al., 2005).

Looking more closely, there was a highly significant difference in Vo2max – hallmark of cardiorespiratory fitness – between subjects and population comparisons. Even more worrisome yet, the lack of cardiorespiratory fitness among participants was not confined to older age groups, but was present in the youngest age group as well. These findings are consistent with those of a handful of recent studies that have investigated fitness levels; in early psychosis patients, reporting poor cardiorespiratory fitness and little habitual physical activity (Koivukangas et al., 2010); and among hospitalized patients with schizophrenia, showing low physical activity and fitness levels (Chamove, 1986).

High rates of subjectively perceived exertion (RPE) together with a Respiratory Quotient that indicates that the participants had, on average, reached the anaerobic threshold (Wasserman et al., 1973) during the GXT, i.e., had exceeded their sustainable exercise performance capabilities, indicating that most participants exerted themselves up to close to their physiological limitations. In the subset of participants who gave no physical termination reasons (18%), motivational and self-efficacy issues may have imparted limitations on their exercise capacity, that is, they may have been able to continue longer with the GXT before terminating. Overall however, because the average cardiovascular fitness among participants is so low, functional capacity, i.e., the physical 'functional reserve' is reached quickly and indicates a state of marked physical deconditioning, mostly observed in chronic medical — as opposed to psychiatric illness (Fleg et al., 2000).

The subjects in this study were all overweight or obese, and questions may arise as to whether obesity itself explains the lowered fitness of the schizophrenia subjects. In general, overweight and obese subjects may not have an impaired Vo2max (Leger, 1996). The limiting factor in aerobic activities of the obese individual is not usually the cardiorespiratory system but rather a limitation in their sub-maximal aerobic capacity, as indicated by higher sub-maximal heart and respiratory exchange rates, and a shorter time to exhaustion (Goran et al., 2000). Stated differently, maximal oxygen consumption of fat free tissue (predominantly muscle) is mostly independent of body fat mass. Thus, we suspect that obesity, by itself, does not explain the poor physical fitness of our subjects.

Health implications are profound. Low cardiorespiratory fitness predicts an 8 to 9 fold increased risk of cardiovascular death over a follow-up period of 8.2 years (Blair et al., 1989). Physical activity is inversely correlated with morbidity and mortality from several chronic diseases, including CVD (Harrington et al., 2009). Strong evidence supports that increased cardiorespiratory fitness improves several parameters of physical health including body weight and composition (Rippe and Hess, 1998), glucose control (Boulé et al., 2001), blood pressure (Kokkinos et al., 2009), and lipid profile (Kelley et al., 2005). These associations of sedentary habits to health risk are independent of confounding by other well-established risk factors, such as smoking, diet, or socioeconomic status (Blair et al., 1989).

At least two important conclusions can be drawn, relevant for obese patients with schizophrenia. 1) Low cardiorespiratory fitness is an eminently modifiable risk factor, as it closely correlates with habitual physical activity. Because maximal aerobic capacity (i.e., Vo2max) at any given time is inversely related to the initial level of fitness (Astrand, 1976), a previously sedentary person may experience a highly relevant – as much as a 25% – increase in VO2max after as little as 8 weeks of structured training (Wilmore et al., 2001), that is, receive substantial health benefits from only a short period of physical exercise. Data from the ACLS indicate that moderately fit men and women have approximately half the risk (e.g., 50% lower) of all-cause mortality compared with their low fit counterparts. Because the level of cardiorespiratory fitness may be extremely low in patients with schizophrenia, amounting to a state of deconditioning and a very low capacity for sustained physical activity that is high in intensity, activities promoting low to moderate activity levels may serve the population well and lead to highly relevant improvements in health prospects.

2) On a more fundamental level, cardiorespiratory fitness translates directly into the ability to engage in aerobic, i.e., oxygen-using, work, and as such, is a requirement for all activities of daily living (Levinger et al., 2009; Fleg et al., 2000). Cardiorespiratory fitness, in this context, becomes an important predeterminant for health-related quality of life, and increases in cardiorespiratory fitness commensurately increase functional capacity (Fleg et al., 2000). In addition, several studies point to a relationship of physical activity and mental health, that is, they have shown how physical activity improves mental health status in a variety of domains, including depression, anxiety and overall mental well-being (Moses et al., 1989; Babyak et al., 2000; Mather et al., 2002; Acil et al., 2008; Schmitz et al., 2004). Regular physical exercise to improve cardiorespiratory fitness practiced by patients with schizophrenia can be a useful non-pharmacological application to improve their mental states, quality of life, and functional capacity (Faulkner and Biddle, 1999; Menza et al., 2004; Fogarty and Happel, 2005; Lindenmayer et al., 2009). A handful of small studies confirm positive outcomes in these domains, most notably in the physical fitness of residents (Fogarty and Happell, 2005), overall however, physical exercise prescription remains a neglected intervention in schizophrenia (Callaghan, 2004).

There are several limitations of this study. The subjects were all overweight or obese with the mean BMI for the group in the moderate to severe range. This was not a random sample drawn from the population, nor a random sample from a defined clinic population, but a subset of individuals who had initially volunteered to take part in a weight loss study. Accordingly, caution is recommended in generalizing the results to all or most persons with schizophrenia. The results are most likely to be applicable to obese individuals with schizophrenia, which does, however represent a large proportion of people suffering from this disorder. Unfortunately neither NHANES nor ACLS provides BMI stratified exercise data, limiting our ability to draw conclusions from our own data, which is derived from overweight and obese patients. On the other hand, most of the exercise capacity/physical fitness literature available reports Max Vo2 $ml^{-1}min^{-1}kg^{-1}$, that is, uses Vo2max data relative to body weight. This is an accepted method when analyzing and reporting exercise comparisons between exercise performance of normal weight and obese subjects (Goran et al., 2000).

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Contributors

Dr Rohan Ganguli obtained funding for the study and, as Principal Investigator, over saw the conduct of the research. Dr Ganguli and Dr Jaspreet Brar designed the study and wrote the protocol. Dr Martin Strassnig supervised the graded-exercise tests, undertook the statistical analysis, and

wrote the first draft of the report. All authors contributed to and have approved the final manuscript.

Conflict of Interest

Dr. Ganguli has no current relevant conflicts of interest to report. In the past he has received research grant funding from Bristol Myers-Squibb, Janssen, Pfizer, and Lilly. In the past he has also served as a consultant or received honoraria from Bristol Myers-Squibb, Janssen, Pfizer, and Lilly.

Drs. Strassnig and Brar have no relevant conflicts of interest to report.

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References

Acil, A.A., Dogan, S., Dogan, O., 2008. The effects of physical exercises to mental state and quality of life in patients with schizophrenia. J. Psychiatr. Ment. Health Nurs. 15 (10), 808–815.

Alaimo, K., McDowell, M.A., Briefel, R.R., et al., 1994. Dietary Intake of Vitamins, Minerals, and Fiber of Persons Ages 2 Months and Over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988-91. Advance data from vital and health statistics; No 258. Hyattsville, Maryland: National Center for Health Statistics.

American College of Sports Medicine, 2005. American College of Sports Medicine: Guidelines of Exercise Testing and Prescription, 7th edition. Williams & Wilkins, Baltimore, pp. 93–114.

Astrand, P.O., 1976. Quantification of exercise capability and evaluation of physical capacity in man. Prog. Cardiovasc. Dis. 19 (1), 51–67.

Babyak, M., Blumenthal, J.A., Herman, S., et al., 2000. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psychosom. Med. 62 (5), 633–638.

Blair, S.N., Kohl III, H.W., Paffenbarger, R.S., et al., 1989. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 262 (17), 2395–2401.

Blair, S.N., Kampert, J.B., Kohl III, H.W., et al., 1996. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA 276 (3), 205–210.

Borg, G.A., 1974. Perceived exertion. Exerc. Sport Sci. Rev. 2, 131–151.

Boulé, N.G., Haddad, E., Kenny, G.P., et al., 2001. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA 286 (10), 1218–1227.

Brown, S., Birtwistle, J., Roe, L., et al., 1999. The unhealthy lifestyle of people with schizophrenia. Psychol. Med. 29 (3), 697–701.

Callaghan, P., 2004. Exercise: a neglected intervention in mental health care? J. Psychiatr. Ment. Health Nurs. 11 (4), 476–483.

Centers for Disease Control And Prevention, 1996. US Department of Health and Human Services. Physical Activity and Health: A Report of the Surgeon General. Atlanta, Ga: US Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion.

Chamove, A.S., 1986. Positive short-term effects of activity on behaviour in chronic schizophrenic patients. Br. J. Clin. Psychol. 25 (2), 125–132.

Duncan, G.E., Li, S.M., Zhou, X.H., 2005. Cardiovascular fitness among U.S. adults: NHANES 1999–2000 and 2001–2002. Med. Sci. Sports Exerc. 37 (8), 1324–1328.

Elekund, L.G., Haskell, W.L., Johnson, J.L., et al., 1988. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. The Lipid Research Clinics Mortality Follow-up Study. N Engl J. Med. 319 (21), 1379–1384.

Faulkner, G., Biddle, S., 1999. Exercise as an adjunct treatment for schizophrenia: a review of the literature. J. Ment. Health 8, 441–457.

Faulkner, G., Cohn, T., Remington, G., 2006. Validation of a physical activity assessment tool for individuals with schizophrenia. Schizophr. Res. 82 (2–3), 225–231.

Fleg, J.L., Pina, I.L., Balady, G.J., et al., 2000. Assessment of functional capacity in clinical and research applications. Circulation 102, 1591–1597.

Fogarty, M., Happell, B., 2005. Exploring the benefits of an exercise program for people with schizophrenia: a qualitative study. Issues Ment. Health Nurs. 26 (3), 341–351.

Gibbons, R.J., Balady, G.J., Bricker, J.T., et al., 2002. ACC/AHA 2002 Guidelines Update for Exercise Testing: Summary Article. A report of the American College of Cardiology/American heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 106, 1883–1892.

Goran, M., Fields, D.A., Hunter, G.R., Herd, S.L., Weinsier, R.L., 2000. Total body fat does not influence maximal aerobic capacity. Int. J. Obes. 24, 841–848.

Harrington, M., Gibson, S., Cottrell, R.C., 2009. A review and meta-analysis of the effect of weight loss on all-cause mortality risk. Nutr. Res. Rev. 22 (1), 93–108.

Hennekens, C.H., 2007. Increasing global burden of cardiovascular disease in general populations and patients with schizophrenia. J. Clin. Psychiatry 68 (Suppl 4), 4–7.

Kampert, J.B., Blair, S.N., Barlow, et al., 1996. Physical activity, physical fitness, and all-cause cancer mortality: a prospective study of men and women. Ann. Epidemiol. 6 (5), 452–457.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Kelley, G.A., Kelley, K.S., Vu, Tran Z., 2005. Aerobic exercise, lipids and lipoproteins in overweight and obese adults: a meta-analysis of randomized controlled trials. Int. J. Obes. 29 (8), 881–893.

Koivukangas, J., Tammelin, T., Kaakinen, M., et al., 2010. Physical activity and fitness in adolescents at risk for psychosis within the Northern Finland 1986 Birth Cohort. Schizophr. Res. 116, 152–158.

Kokkinos, P., Manolis, A., Pittaras, A., et al., 2009. Exercise capacity and mortality in hypertensive men with and without additional risk factors. Hypertension 53, 494–499.

Leger, L., 1996. Aerobic performance. In: Docherty, D. (Ed.), Measurement in pediatric exercise science: Human Kinetics: Champaign, 16, pp. 183–223.

Levinger, C., Goodman, D., Hare, G., et al., 2009. Functional capacity and quality of life in middle-age men and women with high and low number of metabolic risk factors. Int. J. Cardiol. 133 (2), 281–283.

Lindamer, L.A., McKibbin, C., Norman, G.J., et al., 2008. Assessment of physical activity in middle-aged and older adults with schizophrenia. Schizophr. Res. 104 (1–3), 294–301.

Lindenmayer, J.P., Khan, A., Wance, D., et al., 2009. Outcome evaluation of a structured educational wellness program in patients with severe mental illness. J. Clin. Psychiatry 70 (10), 1385–1396.

Mahler, D.A., Froelicher, V.F., Miller, N.H., et al., 1995. ACSM's Guidelines for Exercise Testing and Prescription, 5th ed. Williams & Wilkins, Media, PA, pp. 113–118.

Mather, A.S., Rodriguez, C., Guthrie, M.F., et al., 2002. Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder: randomised controlled trial. Br. J. Psychiatry 180, 411–415.

McDowell, M.A., Briefel, R.R., Alaimo, K., et al., 1994. Energy and Macronutrient Intakes of Persons Ages 2 Months and Over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988-91. Advance data from vital and health statistics; No 255. Hyattsville, Maryland: National Center for Health Statistics.

Menza, M., Vreeland, B., Minsky, S., et al., 2004. Managing atypical antipsychotic-associated weight gain: 12-month data on a multimodal weight control program. J. Clin. Psychiatry 65, 471–477.

Moses, J., Steptoe, A., Mathews, A., Edwards, S., 1989. The effects of exercise training on mental well-being in the normal population: a controlled trial. J. Psychosom. Res. 33 (1), 47–61.

Myers, J., Buchanan, N., Walsh, D., et al., 1991. Comparison of the ramp versus standard exercise protocols. J. Am. Coll. Cardiol. 17, 1334–1342.

Newcomer, J.W., 2005. Metabolic risk during antipsychotic treatment. Clin. Ther. 26 (12), 1936–1946.

Rippe, J.M., Hess, S., 1998. The role of physical activity in the prevention and management of obesity. J. Am. Diet. Assoc. 98 (10 Suppl 2), S31–S38.

Saha, S., Chant, D., McGrath, J., 2007. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch. Gen. Psychiatry 64 (10), 1123–1131.

Sanders, L.F., Duncan, G.E., 2006. Population-based reference standards for cardiovascular fitness among U.S. adults: NHANES 1999–2000 and 2001–2002. Med. Sci. Sports Exerc. 38 (4), 701–707.

Sharpe, J.K., Stedman, T.J., Byrne, N.M., et al., 2006. Energy expenditure and physical activity in clozapine use: implications for weight management. Aust. N. Z. J. Psychiatry 40 (9), 810–814.

Schmitz, N., Kruse, J., Kugler, J., 2004. The association between physical exercises and health-related quality of life in subjects with mental disorders: results from a cross-sectional survey. Prev. Med. 39 (6), 1200–1207.

Strassnig, M., Brar, J.S., Ganguli, R., et al., 2006. Increased caffeine and nicotine consumption in community-dwelling patients with schizophrenia. Schizophr. Res. 86 (1–3), 269–275.

Vancampfort, D., Knapen, J., Probst, M., et al., 2010. Considering a frame of reference for physical activity research related to the cardiometabolic risk profile in schizophrenia. Psychiatry Res. 177, 271–279.
Wang, C.Y., Haskell, W.L., Farrell, S.W., et al., 2010. Cardiorespiratory fitness levels among US adults 20–49 years of age: findings from the 1999–2004 National Health and Nutrition Examination Survey. Am. J. Epidemiol. 171 (4), 426–435.
Wasserman, K., Whipp, B.J., Koyal, S.N., et al., 1973. Anaerobic threshold and respiratory gas exchange during exercise. J. Appl. Physiol. 35 (2), 236–243.
Wilmore, J.H., Green, J.S., Stanforth, P.R., et al., 2001. Relationship of changes in maximal and submaximal aerobic fitness to changes in cardiovascular disease and non-insulin-dependent diabetes mellitus risk factors with endurance training: the HERITAGE Family Study. Metabolism 50 (11), 1255–1263.