



# Metabolic abnormalities and low dietary Omega 3 are associated with symptom severity and worse functioning prior to the onset of psychosis: Findings from the North American Prodrome Longitudinal Studies Consortium

Kristin S. Cadenhead<sup>a,\*</sup>, Amedeo Minichino<sup>b</sup>, Skylar Kelsven<sup>a,l</sup>, Jean Addington<sup>c</sup>, Carrie Bearden<sup>d</sup>, Tyrone D. Cannon<sup>e</sup>, Barbara A. Cornblatt<sup>f</sup>, Dan Mathalon<sup>g</sup>, Thomas H. McGlashan<sup>e</sup>, Diana O. Perkins<sup>h</sup>, Larry J. Seidman<sup>i</sup>, Ming Tsuang<sup>a</sup>, Elaine F. Walker<sup>j</sup>, Scott W. Woods<sup>e</sup>, Jeff Yao<sup>k</sup>, the North American Prodromal Longitudinal Studies (NAPLS) consortium

<sup>a</sup> University of California San Diego, La Jolla, CA, United States

<sup>b</sup> Department of Psychiatry, University of Oxford, UK

<sup>c</sup> Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

<sup>d</sup> University of California Los Angeles, Los Angeles, CA, United States

<sup>e</sup> Yale University, New Haven, CT, United States

<sup>f</sup> The Zucker Hillside Hospital, New York, NY; Hofstra North Shore-LIJ School of Medicine, Hempstead, New York; The Feinstein Institute for Medical Research, Manhasset, NY, United States

<sup>g</sup> University of California San Francisco, San Francisco, CA, United States

<sup>h</sup> University of North Carolina, Chapel Hill, NC, United States

<sup>i</sup> Harvard, Boston, MA, United States

<sup>j</sup> Emory University, Atlanta, GA, United States

<sup>k</sup> VA Pittsburgh Healthcare System and University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

<sup>l</sup> San Diego State University/University of California-San Diego Joint Doctoral Program in Clinical Psychology, United States

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## ABSTRACT

**Objective:** Patients with schizophrenia have a high prevalence of metabolic disorders and cardiovascular mortality. It is possible that a vulnerability to metabolic abnormalities is associated with risk for psychosis, symptoms and functionality. In this study, we evaluate demographic information, cardiometabolic indices, symptoms and functioning in an antipsychotic free cohort at Clinical High Risk (CHR) for psychosis from the NAPLS Omega 3 fatty acid clinical trial.

**Method:** Subjects received physical exams and metabolic monitoring prior to randomization into the Omega 3 versus Placebo trial. Anthropometrical measures, vital signs, glucose, and lipids were assessed along with symptoms, functioning, dietary Omega 3 fatty acids, erythrocyte polyunsaturated fatty acid content and a measure of lipid peroxidation (TBARS, Thiobarbituric acid-reactive substances).

**Results:** The sample included 113 CHR subjects (42.1% female; 17.5% Latino) ages 12–29. The mean BMI was 24.3 with a trend toward higher BMI and a higher incidence of metabolic syndrome in Latino subjects; 36% of the sample was obese/overweight; 37.6% met criteria for prehypertension/hypertension; 4.2% met criteria for prediabetes/diabetes; 9.6% showed evidence of insulin resistance and 44.7% had dyslipidemia. The TBARS was elevated at  $9.8 \mu\text{M} \pm 6.1$  (normal 1.86–3.94  $\mu\text{M}$ ). Metabolic parameters and a diet low in Omega 3 rich foods were significantly associated with prodromal symptoms and poor functioning.

**Conclusions:** CHR subjects show a high percentage of metabolic abnormalities prior to exposure to antipsychotic medication. These findings reinforce that early detection of metabolic disturbances and food insecurity is crucial since these factors are modifiable with the potential for significant gains in terms of quality of life, physical and mental health.

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\* Corresponding author at: Department of Psychiatry, 0810, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0810, United States.  
E-mail address: [kcadenhead@ucsd.edu](mailto:kcadenhead@ucsd.edu) (K.S. Cadenhead).

## 1. Introduction

Meta-analyses report a 2.5- to 3-fold increase in mortality rate in schizophrenia (Brown, 1997; Bushe et al., 2010; McGrath et al., 2008)

with a 15–20 year shortened life expectancy compared to that of the general population (Bushe et al., 2010). Converging evidence suggests that schizophrenia and related psychotic disorders are systemic diseases in which metabolic abnormalities, inflammation and oxidative stress are intertwined with psychopathological features in a complex network (McCarthy, 2014; Steiner et al., 2014). The close mind-body connection that characterizes these disorders becomes clear when we look at the leading causes of death in this population. In addition to the higher suicide rate compared to that of the general population (Mitchell et al., 2013), the mortality and morbidity among individuals with schizophrenia are due to natural causes, such as cancer, respiratory diseases and cardiovascular disease (CVD) (Colton and Manderscheid, 2006; De Hert et al., 2011), with CVD mortality ranging from 40 to 50% in most studies (De Hert et al., 2011). One in three persons with schizophrenia meets criteria for metabolic syndrome, one in two is overweight, one in five have significant hyperglycemia (sufficient for a diagnosis of prediabetes) and at least two in five have lipid abnormalities (Mitchell et al., 2013). It is unclear whether this association is simply reflective of an unhealthy lifestyle (e.g., smoking, physical inactivity, poor diet, and obesity) or whether CVD and other metabolic abnormalities are due to the side effects of atypical antipsychotic medications (Buchholz et al., 2008; Stahl et al., 2009). However, metabolic abnormalities have also been reported in drug-naïve patients with schizophrenia (Chiu et al., 2009; Guest et al., 2010; Spelman et al., 2007) and their unaffected siblings (Fernandez-Egea et al., 2008), suggesting these findings are not solely due to antipsychotic medication. In this regard, it is intriguing to consider the hypothesis that suggests that inflammation and/or oxidative stress is a bridge between psychotic illness and CVD (McCarthy, 2014). Signs of oxidative stress, including depleted antioxidant defense enzymes, and increased lipid peroxidation products, (thiobarbituric acid-reactive substances; TBARS), are increasingly recognized in both CVD and psychiatric disorders (McCarthy, 2014). It is possible that CVD and psychiatric illness are causally related, with each problem stemming directly from the body's inability to manage oxidative stress (Assies et al., 2014).

Reductions in Red Blood Cell (RBC) membrane Polyunsaturated Fatty Acids (PUFAs) have also been reported in both chronic patients and unmedicated first episode patients with schizophrenia (Horrobin et al., 1994; Horrobin et al., 1991; Reddy et al., 2004; Yao et al., 1994), suggesting that PUFA metabolism may also be illness related and perhaps linked to the cardiometabolic abnormalities. Fish oil is the major source of the Omega-3 fatty acids, eicosapentaenoic acid [EPA, 20:5(*n*-3)] and docosahexaenoic acid [DHA, 22:6(*n*-3)]. Consumption of fish oil increases EPA- and DHA-containing phospholipids at the expense of decreased arachidonic acid (AA), an *n*-6 PUFA, incorporation into phospholipids (Capper and Marshall, 2001). DHA is the major Omega-3 fatty acid in the central nervous system (CNS) (Singh, 2005). A major benefit of Omega-3 fatty acids is their likely role in the prevention and treatment of CVD (Kris-Etherton et al., 2002). DHA and EPA decrease plasma very-low-density lipoprotein (VLDL), triglyceride levels, postprandial lipidemia and lead to antithrombotic changes (de Goede et al., 2010). Given the well-documented metabolic abnormalities that are present at the onset of illness and as a consequence of antipsychotic treatment, it is evident that PUFAs likely have a role in CVD risk associated with severe mental illness.

Despite the growing body of literature on medicated multi-episode patients with schizophrenia (Mitchell et al., 2013), less is known about the relationship between the cardio-metabolic risk and the different stages of the disorders (unmedicated, prodromal, first-episode, multi-episode). Correll and colleagues (Correll et al., 2014) found lipid abnormalities and elevated insulin resistance markers in the early phase of the psychotic illness and after only a few weeks of antipsychotic exposure. Distinguishing pretreatment status from treatment effects is important in understanding the source of CVD associated with psychosis and deciding the course of treatment. This etiological distinction can only be made at the very beginning of treatment in patients

with a first episode of psychosis or in subjects at Clinical High Risk (CHR) for psychosis who have not previously been exposed to antipsychotic drugs or who have been exposed for a short known period.

Cardiometabolic parameters, biomarkers of oxidative stress, lipid metabolism and dietary Omega 3 fatty acids may prove to be important risk factors for future psychosis in CHR individuals. Given that up to one third of clinically and demographically-defined CHR subjects later develop a psychotic illness (McGlashan et al., 2001), it is possible that the assessment of cardiometabolic measures, that can easily be assessed in a clinical setting, can add to the prediction of risk for psychosis and functional outcome in vulnerable individuals.

The aim of this study was to investigate baseline cardiometabolic, dietary Omega 3 fatty acids and oxidative stress indices in a cohort at Clinical High Risk (CHR) for psychosis from the North American Prodrome Longitudinal Study (NAPLS) Consortium who participated in a clinical trial of Omega-3 fatty acid versus placebo. The current report includes information from baseline assessment prior to starting the clinical trial.

Given the exploratory nature of the research question and the design of the parent study, we did not include healthy comparison subjects. Rather, we provided the first detailed report of the above-mentioned indices in CHR individuals. We further explored the association of the metabolic measures with baseline demographic, clinical, and functional characteristics of our CHR sample.

## 2. Method

Participants included 127 CHR participants enrolled in a double-blind Omega 3 fatty acid clinical trial (NCT01429454) of the North American Prodrome Longitudinal Study (NAPLS) Consortium. As part of the baseline assessment of the study, clinical, functional, metabolic, cardiovascular, RBC PUFA content and oxidative stress indices were collected from the enrolled participants prior to randomization. Baseline data were collected from January 2012 through April 2014.

The protocol was approved by Institutional Review Boards at the sites participating in NAPLS (Emory University, Harvard University, University of Calgary, University of California Los Angeles, University of California San Diego, University of North Carolina, Yale University, Zucker Hillside Hospital), and participants provided informed consent or assent (parental informed consent for minors).

### 2.1. Subjects

Individuals between the ages of 12 and 29 who met CHR diagnostic criteria for a possible prodromal psychosis syndrome were included. Psychosis- risk syndromal criteria were evaluated with the Structured Interview for Psychosis-risk Syndromes (SIPS) (McGlashan et al., 2010). Exclusion criteria were: a DSM-IV Axis I schizophrenia-spectrum disorder according to the Structured Clinical Interview for DSM-IV (SCID-IV), use of antipsychotic medication in the previous month, concomitant medical or neurological illness, history of significant head injury, alcohol or drug abuse (excluding nicotine) in the past month or dependence in the past three months, screening full scale estimated IQ < 80, active suicidal or homicidal ideation, pregnancy or lactation, and allergies to seafood or seafood related products or no history of seafood consumption.

All participants underwent assessments of height, weight, waist circumference, systolic and diastolic blood pressure as well as fasting phlebotomy for glucose, lipids, RBC PUFA Composition and Thiobarbituric Acid Reactive Substances (TBARS).

### 2.2. Body composition

Body mass index (BMI) was calculated as weight in Kg/height (cm) squared. To define BMI categories in subjects > 18 years, the following thresholds were used: underweight = BMI < 18.5, normal weight = BMI 18.5 < 25, overweight = BMI 25 < 30, obese = BMI ≥ 30. For

subjects < 18 years old, the respective BMI category was based on sex- and age-adjusted calculations using a web based calculator (<http://www.bcm.edu/cnrc/bodycomp/bmiz2.html>) and the following categories: underweight  $\leq$  5th BMI percentile, normal weight = 5–84.9th BMI percentile, overweight = 85–94.9th BMI percentile, obese  $\geq$  95th BMI percentile. Abdominal obesity was defined in males as waist circumference > 102 cm and in females as waist circumference > 88 cm. For subjects < 18 years old, we used a BMI percentile > 90% instead of age- and sex- adjusted waist circumference percentiles to define abdominal obesity, as done previously in a National Health and Nutrition Examination Survey (NHANES) study of metabolic syndrome in youth.

### 2.3. Lipid metabolism

For lipid parameters, the following thresholds were used: hypercholesterolemia = total cholesterol > 200 mg/dL; elevated low-density lipoprotein (LDL)-cholesterol > 130 mg/dL; elevated non-HDL-cholesterol > 130 mg/dL; low high-density lipoprotein (HDL)-cholesterol for males < 40 mg/dL and for females < 50 mg/dL; hypertriglyceridemia > 170 mg/dL. Dyslipidemia was defined according to NHANES as having either elevated triglycerides at the level of the metabolic syndrome criterion ( $\geq$ 150 mg/dL), elevated LDL-cholesterol, elevated non-HDL-cholesterol, or low HDL-cholesterol (as defined above).

### 2.4. Carbohydrate metabolism

For glucose parameters, prediabetes was defined as glucose 100–125 mg/dL, and diabetes was defined as glucose > 125 mg/dL. Insulin resistance was assessed with the proxy measure of triglyceride/HDL-cholesterol ratio (McLaughlin et al., 2005).

### 2.5. Metabolic syndrome

Metabolic syndrome was defined according to the modified Adult Treatment Panel III (ATPIII) guidelines, i.e., fulfilling  $\geq$  3 of the following criteria: abdominal obesity (as above); blood pressure > 130/85 mmHg; fasting triglycerides > 150 mg/dL; low HDL-cholesterol (as above); fasting glucose > 100 mg/dL. Note that per definition, the thresholds for triglyceride abnormality and elevated blood pressure in the metabolic syndrome criteria are lower than for established thresholds of hypertriglyceridemia and hypertension (Abduljawad et al., 2001; Grundy et al., 2005).

Treatment with lipid lowering medications, antihypertensives and anti-diabetic medications counted toward each of the respective criteria independent of the laboratory test result. Metabolic syndrome status was assigned taking the amount of missing data for specific criteria into account, i.e., if no criterion was positive, 1 or 2 variables could be missing to score as absent; if 1 criterion was positive, only one variable could be missing to score as absent; and if two criteria were positive, no variable could be missing to score metabolic syndrome as absent.

### 2.6. Dietary Omega 3, fasting erythrocyte Polyunsaturated Fatty Acid (PUFA) composition and Thiobarbituric Acid Reactive Substances (TBARS)

Baseline diet characterization was assessed using a systematic checklist provided by Vilma Gabbay (personal communication). The list includes foods that are rich in Omega-3 fatty acids. It was given to the family at the first screening visit. Intake was categorized as total Omega 3 rich foods consumed per week and was obtained from the sum of the individual item scores. Fasting RBC PUFA composition was quantified at baseline in the laboratory of Dr. Jeffery Yao at VA Pittsburgh Healthcare System (Reddy et al., 2004; Yao et al., 1994). Erythrocyte fatty composition was analyzed using capillary gas chromatography per established methods using an Agilent 7890A Series

capillary gas chromatograph, Model 7693, equipped with a hydrogen flame ionization detector. A 30-meter, fused silica SP-2380 column with an inner diameter of 0.25 mm and a 0.20- $\mu$ m film thickness (Supelco) was used. Each sample was run under a splitless injection mode with hydrogen as the carrier gas (30 mL/min) and with an inlet pressure of 6.5 psi. Oven temperature was programmed under three stages: stage 1, from 50 to 150 °C at a rate of 25 °C/min; stage 2, from 150 to 190 °C at a rate of 4 °C/min; and stage 3, from 190 to 250 °C at a rate of 6 °C/min, with a final time of 3 min at 250 °C. Peaks on the chromatograms were identified by comparing the retention times with those of standard mixtures (Supelco) and were calculated by an Agilent OpenLAB CDS ChemStation Edition for GC System (Product Version, A.01.02 [010]), using an internal standard mode. The following PUFAs were quantified: Total, Saturated, Monounsaturated, Polyunsaturated, arachidonic acid [20:4(n-6)], docosahexaenoic acid [22:6(n-3)], eicosapentaenoic acid [20:5(n-3)], linoleic acid [18:2 (n-6)], Total n-3 fatty acids, and n-3 Index (EPA + DHA).

Malondialdehyde (MDA) and 4-hydroxyalkenals are the major breakdown products following autooxidation of RBC PUFAs. Measurement of such aldehydes thus provides a convenient index for lipid peroxidation. Thiobarbituric acid (TBA) was measured by specific chromogenic reagent using a BIOXYTECH MDA-586 assay kit. This reagent reacts with both MDA and 4-hydroxyalkenals in the presence of methane-sulfonic acid (40 min. at 45 °C) and yields a stable chromophore with maximal absorbance at 586 nm wavelength. A standard curve in the range of 0 to 20  $\mu$ M is included for each assay series. The standard error of the mean values for between-run samples is <5%. All samples were assayed in two different batches. The first batch of samples was assayed in January 2014, and the second groups were assayed October 2015. 27 samples were chosen to be assayed 20 months apart. The correlations between these two batches are very good ( $p < 0.0001$ ,  $n = 27$ ).

### 2.7. Clinical and functional assessment

Demographic data, medical history and medications history were obtained at baseline assessment. Any treatment received prior to study participation or assessment was based on the community clinician's and/or patient's choice. Prodromal symptoms were assessed with the Scale of Prodromal Symptoms (SOPS) from the SIPS interview. Overall functioning was measured using the Global Assessment of Functioning (GAF), Global Role and Global Social scales (Cornblatt et al., 2012).

### 2.8. Statistical analysis

All analyses were conducted in SPSS, version 21.0 (SPSS, Inc., Chicago). Beyond descriptive analyses, cardiovascular variables were compared by sex, race, ethnicity, antipsychotic-naïve versus antipsychotic-exposed status using a *t*-test and analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. The threshold for statistical significance was set at 0.05 (two-tailed,  $p < 0.05$ ); values between 0.05 and 0.10 are reported as trends. Normality was assessed by the Kolmogorov–Smirnov test. Because of non-normal distribution of BMI, glucose blood levels and Frequency of Omega-3FA assumption, Spearman  $\rho$  was used to assess correlations between these variables and continuous clinical and functioning variables.

## 3. Results

### 3.1. Sample

The sample consisted of 127 subjects; 14 (10.2%) of the CHR subjects dropped out of the study prior to baseline assessment; 113 (89.8%) had 1 or more baseline assessments of BMI, blood pressure, or metabolic assessment, composing the study sample; 95 had never been exposed to

antipsychotic medications. Of those 16 subjects who had previously been exposed to antipsychotic medication, the mean exposure was  $32.42 \pm 59.38$  weeks. As part of clinical consensus procedures, all subjects on antipsychotic medication were reviewed carefully to assure that the use of antipsychotics was not associated with a full psychotic syndrome. Typically antipsychotics were used in this population for behavioral issues or mood stabilization rather than the subsyndromal symptoms of psychosis. Given the well-known influence of antipsychotic medications on metabolic and cardiovascular parameters, we analyzed the sample first with all participants and then the 95 antipsychotic naive participants separately.

The mean (SD) age of subjects was 18.7 (4.6) years; 42.1% of subjects were female; 17.5% of subjects were Latino and 66.7% identified white. 17.4% reported a history of smoking tobacco, 33% using alcohol and 23.1% had a history of drug use. No sex differences were found for age, alcohol use, drug use or exposure to antipsychotic medication. There were sex differences in history of tobacco use, with more males than females reporting tobacco use within the past month (Male = 23.8% vs. Female = 8.7%;  $p = 0.04$ ). (Table 1).

### 3.2. Body composition

The mean (SD) BMI was 24.3 (6.5); 36% of subjects were obese or overweight. Latino subjects showed a trend (Cohen  $d = 0.57$ ) toward higher BMI values compared to non-Latino (Table 2).

### 3.3. Blood pressure

Among the CHR subjects, 31.3% had prehypertension and 6.3% hypertension, 3.5% received antihypertensive drugs. Blood pressure was significantly higher in males ( $p < 0.01$ ), who received more antihypertensive medication ( $p < 0.05$ ) than females. No differences were found in blood pressure parameters between Latino and Non-Latino individuals (Table 2).

### 3.4. Lipid metabolism

Altogether, 44.7% of CHR subjects showed evidence of dyslipidemia (at least 1 abnormality in LDL-C, n-HDL-C, HDL-C, or triglycerides levels), but no subjects received lipid lowering medications. Males had lower HDL-C ( $p < 0.01$ ). Lipid parameters abnormalities were equally distributed between males and females, Latino and non-Latino (Table 2) groups.

**Table 1**  
Demographic characteristics.

Characteristic	Total (N = 113)	Males (N = 65)	Females (N = 48)	p Value
Age, mean (SD), y	18.7 ± 4.6	18.5 ± 4.5	19.0 ± 4.7	NS
Non-Hispanic ethnicity, No. (%)	94 (82.5%)	54 (81.8%)	40 (83.3%)	NS
Race, No. (%)				
White	76 (66.7%)	47 (71.2%)	29 (60.4%)	NS
Black	15 (13.2%)	6 (9.1%)	9 (18.8%)	
Asian	7 (6.1%)	2 (3.0%)	5 (10.5%)	
Native American	2 (1.8%)	2 (3.0%)	None	
Interracial	10 (8.8%)	6 (9.1%)	4 (8.3%)	
Educational level				
Years, mean (SD)	11.1 ± 2.95	10.8 ± 2.8	11.3 ± 3.1	NS
Antipsychotic treatment, No. (%)				
No exposure	95 (84.8%)	54 (83.1%)	41 (87.2%)	NS
Exposure	16 (14.3%)	10 (15.4%)	6 (12.8%)	
Substance use				
Tobacco	19 (17.4%)	15 (23.8%)	4 (8.7%)	0.04*
Alcohol	36 (33.0%)	20 (31.7%)	16 (34.8%)	NS
Illicit Drug	25 (23.1%)	14 (22.2%)	11 (24.4%)	NS

\*  $p < 0.05$ .

### 3.5. Carbohydrate metabolism

Despite the fact that a history of diabetes was an exclusion criteria, based on fasting glucose level, prediabetes and diabetes were present in 4.2% of subjects. Insulin resistance based on the triglycerides to HDL-C ratio  $> 3.5$  was present in 9.6% of subjects. Males showed a significantly higher prevalence of proxy insulin resistance. A significant difference was found in fasting glucose blood levels between Latino versus non-Latino participants, with the latter group receiving more anti-diabetic medications (Table 2).

### 3.6. Metabolic syndrome

Among the CHR subjects, 6.5% met criteria for metabolic syndrome. The abdominal obesity criterion was close to three times more common in females versus males and a trend toward higher values was found in Latino when compared to non-Latino individuals (Table 2). Significantly more male subjects had blood pressure above the metabolic syndrome criterion threshold compared to female subjects.

### 3.7. Dietary fatty acids, fasting erythrocyte Polyunsaturated Fatty Acid (PUFA) composition and Thiobarbituric Acid Reactive Substances (TBARS)

According to the Omega-3 fatty acid dietary checklist, females had a significantly higher frequency of Omega-3 fatty acids consumption compared to males (Table 2). Ethnic groups did not differ in frequency of Omega 3 consumption. Omega 3 intake was significantly lower in CHR subjects with a history of antipsychotic exposure compared to antipsychotic naive subjects (Table 2).

The composition of RBC PUFAs significantly differed between Latino and non-Latino subjects while trends were noted between male and female subjects (Table 2). Overall, Latinos had a significantly lower percentage of saturated fatty acids and higher levels of PUFAs compared to non-Latino subjects. The same pattern was seen in female subjects (less saturated and more PUFAs). The Omega 3 and Omega 6 fatty acid content was higher in Latinos relative to non-Latinos.

The self-reported Omega 3 fatty acids in the diet were significantly correlated with RBC membrane Omega 3 composition variables, providing evidence of validity for the Dietary Scale (Table 3).

A total of 95 subjects had assays for malodialdehyde (as measured by TBARS). 92.6% of CHR subjects had an MDA level above the normal range for this index. The mean MDA was 9.84  $\mu\text{M/L}$  (Range 2.45–43.23  $\mu\text{M/L}$ ), (normal values 1.86–3.94  $\mu\text{M/L}$ ) (Richard et al., 1992; Yagi, 1998). MDA was negatively correlated with RBC Omega 3 variables (Table 3).

### 3.8. Clinical and functional assessment. Association with cardiometabolic measures and Omega 3 fatty acid consumption

In exploratory correlational analyses shown in Table 4, total SOPS was significantly correlated with serum glucose and BMI. SOPS subscale correlations revealed that this association was most accounted for by SOPS negative and general symptoms with serum glucose and SOPS general and disorganized symptoms with BMI. Greater SOPS general symptoms was also significantly associated with greater abdominal circumference and lower RBC Omega 3 composition (DHA, Total Omega 3). Better functioning (GAF, GFR and GFS) was significantly associated with lower BMI, smaller abdominal circumference, greater frequency of Omega 3 intake and greater RBC EPA composition.

### 3.9. Antipsychotic exposure and cardio-metabolic risk

Although no significant differences were found in blood pressure, lipids, carbohydrate metabolism, or Metabolic Syndrome parameters between antipsychotic-naïve and non-naïve CHR individuals (Table 2), these variables were less favorable in the antipsychotic-naïve group.

**Table 2**  
Cardiometabolic risk status by gender, ethnicity and antipsychotic exposure.

Variable name	CHR Total N = 113	CHR Male N = 65	CHR Female N = 48	Cohen's d	p	CHR Latino N = 20	CHR Non-Latino N = 93	Cohen's d	p	CHR AP Naïve N = 95	CHR AP Non-Naïve N = 16	Cohen's d	p
Body mass index (BMI; kg/m <sup>2</sup> ± SD)	24.3 ± 6.5	24.5 ± 5.9	24.1 ± 7.4	0.06	0.75	27.3 ± 8.4	23.6 ± 5.9	0.57	0.08 <sup>+</sup>	24.5 ± 6.62	22.5 ± 5.90	0.31	0.29
Weight status category (n, %)													
Underweight	9 (8.1%)	3 (4.8%)	6 (12.5%)		0.34	None	9 (10.0%)		0.19	6 (6.3%)	3 (21.4%)		0.24
Normal	61 (55%)	34 (54%)	27 (56.3%)			9 (45.0%)	52 (57.1%)			53 (55.8%)	7 (50%)		
Overweight	17 (15.3)	12 (19.0%)	5 (10.4%)			4 (20.0%)	13 (14.3%)			16 (16.8%)	1 (7.1%)		
Obese	24 (21.6%)	14 (22.2%)	10 (20.8%)			7 (35%)	17 (18.7%)			20 (21.1%)	3 (21.4%)		
Obese or Overweight	41 (36.9%)	26 (41.2%)	15 (31.2%)		0.28	11 (55%)	30 (33%)		0.07 <sup>+</sup>	36 (37.9%)	4 (28.6%)		0.50
Systolic (mm Hg ± SD)	114.5 ± 14	118.4 ± 14.1	109.3 ± 12.1	0.65	<0.001**	118.5 ± 13.6	113.6 ± 14.0	0.35	0.15	114.6 ± 14.70	113.2 ± 9.90	0.10	0.73
Diastolic (mm Hg ± SD)	71.9 ± 9.4	71.5 ± 8.6	72.4 ± 10.4	0.10	0.62	73.5 ± 8.0	71.6 ± 9.7	0.20	0.42	71.8 ± 8.90	72.4 ± 13.30	0.06	0.83
Hypertension status (n, %)													
Pre-hypertension (mm Hg)	35 (31.3%)	24 (37.5%)	11 (22.9%)		0.10	7 (35.0%)	28 (30.4%)		0.69	30 (31.6%)	4 (28.6%)		0.82
Hypertension (mm Hg)	7 (6.3%)	6 (9.4%)	1 (14.3%)		0.12	3 (15.0%)	4 (4.3%)		0.07 <sup>+</sup>	7 (7.4%)	0 (0.0%)		0.29
Pre or hypertension	42 (37.5%)	30 (46.9%)	12 (25.0%)		0.02*	10 (50.0%)	32 (34.8%)		0.20	37(38.9%)	4 (28.6%)		0.45
Total cholesterol, mg/dL, mean ± SD	158.7 ± 29.8	158.2 ± 29.1	157.8 ± 31.1	0.01	0.96	162.9 ± 36.8	157.3 ± 28.6	0.19	0.52	158.9 ± 30.1	152.8 ± 30.0	0.20	0.49
Hypercholesterolemia, total cholesterol ≥ 200 mg/dL, (n, %)	8 (8.4%)	3 (5.5%)	5 (12.5%)		0.22	1 (7.1%)	7 (8.6%)		0.85	7 (9.0%)	1 (7.1%)		0.82
LDL-C, mg/dL, mean ± SD	89.3 ± 23.2	90.8 ± 23.2	87.2 ± 23.5	0.16	0.47	91.9 ± 27.2	88.8 ± 22.6	0.13	0.64	90.3 ± 23.7	84.1 ± 20.9	0.27	0.37
Elevated LDL-C, ≥130 mg/dL, (n, %)	6 (6.3%)	4 (7.3%)	2 (5.0%)		0.65	1 (7.1%)	5 (6.2%)		0.89	5 (6.4%)	1 (7.1%)		0.91
HDL-C, mg/dL, mean ± SD	51.4 ± 12.1	48.6 ± 10.5	55.2 ± 13.1	0.55	<0.01**	51.9 ± 9.3	51.3 ± 12.5	0.05	0.87	51.1 ± 12.3	50.9 ± 11.4	0.02	0.28
Reduced HDL-C < 40 M, <50 F (n, %)	27 (28.4%)	13 (23.6%)	14 (35%)		0.23	2 (14.3%)	25 (30.9%)		0.20	22 (28.2%)	5 (35.7%)		0.57
Non-HDL-C, mg/dL, mean ± SD	106.7 ± 27.9	109.6 ± 29.0	102.7 ± 26.1	0.25	0.24	111.0 ± 34.3	106.0 ± 26.9	0.18	0.54	107.7 ± 28.7	101.9 ± 25.2	0.21	0.48
Elevated non-HDL-C ≥ 130 mg/dL, (n, %)	14 (14.7%)	9 (16.4%)	5 (12.5%)		0.60	2 (14.3%)	12 (14.8%)		0.96	13 (16.7%)	1 (7.1%)		0.36
Triglycerides, mg/dL, mean ± SD	85.2 ± 42.0	91.1 ± 46.0	77.2 ± 34.8	0.33	0.11	95.3 ± 57.5	83.4 ± 38.9	0.28	0.33	84.7 ± 43.7	88.2 ± 37.0	−0.08	0.77
Hypertriglyceridemia, triglycerides ≥ 170 mg/dL, (n, %)	5 (5.3%)	4 (7.3%)	1 (2.5%)		0.30	2 (14.3%)	3 (3.7%)		0.10	5 (6.4%)	None		0.33
Dyslipidemia, (n, %)	42 (44.7%)	21 (38.9%)	21 (52.5%)		0.19	5 (35.7%)	37 (46.3%)		0.46	36 (46.2%)	6 (42.9%)		0.82
Glucose, mg/dL, mean ± SD	84.5 ± 18.4	83.7 ± 12.6	85.6 ± 24.5	0.10	0.64	94.2 ± 40.1	83.0 ± 11.5	0.61	0.04*	84.2 ± 19.7	86.4 ± 11.3	0.12	0.69
Triglycerides to HDL-C ratio													
Mean ± SD	1.8 ± 1.05	2.0 ± 1.2	1.5 ± 0.8	0.48	0.01**	1.9 ± 1.06	1.8 ± 1.1	0.08	0.74	1.8 ± 1.07	1.9 ± 1.09	0.10	0.82
Ratio ≥ 3.5, (n, %)	9 (9.6%)	8 (14.8%)	1 (2.5%)		<0.05*	2 (14.3%)	7 (8.8%)		0.52	7 (9.1%)	2 (14.3%)		0.55
Prediabetes, glucose 100–125 mg/dL, (n, %)	2 (2.1%)	2 (3.7%)	None		0.45	None	2 (2.5%)		0.31	1 (1.3%)	1 (7.1%)		0.33
Diabetes, glucose >125 mg/dL, (n, %)	2 (2.1%)	1 (1.9%)	1 (2.4%)			1 (7.1%)	1 (1.2%)			2 (2.6%)	0 (0%)		
Metabolic syndrome	6 (6.5%)	4 (7.7%)	2 (4.9%)		0.58	2 (14.3%)	4 (5.1%)		0.20	6 (7.7%)	None		0.28
Fasting glucose ≥ 100 mg/dL per ATP III, (n, %)	4 (4.2%)	3 (3.3%)	1 (1.1%)		0.45	1 (1.1%)	3 (3.3%)		0.55	3 (3.8%)	1 (7.1%)		0.58
Low HDL-C, <40 mg/dL in M and <50 mg/dL in F, (n, %)	27 (28.4%)	13 (23.6%)	14 (35%)		0.23	2 (14.3%)	25 (30.9%)		0.20	22 (28.2%)	5 (35.7%)		0.57
Abdominal obesity, waist circumference > 102 cm M and > 88 cm F, (n, %)	19 (17.4%)	6 (9.8%)	13 (27.1%)		0.02*	6 (31.6%)	13 (14.4%)		0.07 <sup>+</sup>	17 (18.1%)	1 (7.1%)		0.31
Elevated BP ≥ 130/80 mmHg, or antihypertensive treatment, (n, %)	19 (17.4%)	16 (25.8%)	3 (6.4%)		<0.01**	4 (20.0%)	15 (16.9%)		0.74	16 (17.0%)	3 (21.4%)		0.69
Elevated triglycerides, ≥150 mg/dL, (n, %)	7 (7.4%)	5 (9.3%)	2 (5.0%)		0.44	2 (14.3%)	5 (6.3%)		0.29	6 (7.8%)	1 (7.1%)		0.93
Antihypertensive, (n, %)	5 (3.9%)	5 (6.9%)	None		<0.05*	1 (5.0%)	4 (4.3%)		0.87	3 (2.9%)	2 (10.5%)		0.12
Antidiabetic, (n, %)	1 (0.8%)	None	1 (1.8%)		0.25	None	1 (5.0%)		0.03	1 (1.0%)	None		0.67
TBARS - MDA concentration (µM)	9.8 ± 6.1	9.5 ± 5.2	10.3 ± 7.3	0.13	0.54	8.78 ± 6.5	10.1 ± 6.0	0.22	0.41	9.9 ± 6.3	10.1 ± 5.6	0.03	0.91
Saturated %total	41 ± 4.3	41 ± 4.3	42 ± 4.3	0.23	0.06	39 ± 1.9	42 ± 4.5	0.70	<0.001**	41.1 ± 4.3	43.1 ± 4.3	0.47	0.11
Monounsaturated %total	22 ± 2.5	22 ± 2.7	22 ± 2.3	0.00	0.97	21 ± 2.3	22 ± 2.6	0.40	0.67	21.6 ± 2.4	21.6 ± 3.2	0.00	0.99
Polyunsaturated %total	58 ± 4.2	59 ± 4.3	57 ± 4.1	0.48	<0.05*	61 ± 2.1	58 ± 4.4	0.71	<0.001**	58.7 ± 4.2	56.9 ± 4.2	0.43	0.14
Arachidonic acid, 20:4, (n = 6) %total	13 ± 2.6	13 ± 2.6	13 ± 2.6	0.00	0.39	14 ± 1.8	13 ± 2.7	0.38	0.01**	13.0 ± 2.6	11.9 ± 2.9	0.42	0.15
Linoleic acid, 18:2 (n = 6) %total	16 ± 2.1	17 ± 2.2	16 ± 1.8	0.48	0.17	17 ± 2.0	16.3 ± 2.1	0.33	0.41	16.4 ± 2.0	16.3 ± 3.0	0.05	0.84
Docosahexaenoic acid (DHA), 22:6(n = 3) %total	2.5 ± 1.0	2.6 ± 1.0	2.5 ± 1.0	0.10	0.75	3.2 ± 0.7	2.4 ± 1.0	0.80	<0.001**	2.7 ± 1.0	2.1 ± 0.9	0.60	0.05*
Eicosapentaenoic acid (EPA), 20:5(n = 3) %total	0.4 ± 0.3	0.4 ± 0.3	0.4 ± 0.4	0.03	0.82	0.4 ± 0.3	0.5 ± 0.2	0.20	0.36	0.5 ± 0.26	0.3 ± 0.13	0.67	0.02*
Total Omega 3 %total	4.8 ± 1.7	5 ± 1.7	4.7 ± 1.7	0.18	0.42	5.9 ± 1.3	4.6 ± 1.7	0.76	<0.01**	5.0 ± 1.7	4.1 ± 1.5	0.53	0.05*
Omega 3 index (EPA + DHA) %total	3.0 ± 1.1	3 ± 1.1	3 ± 1.2	0.00	0.74	3.7 ± 0.8	2.8 ± 1.1	0.82	<0.001**	3.1 ± 1.1	2.4 ± 0.9	0.64	0.04*
Weekly frequency of Omega-3FA consumption, mean ± SD	13.9 ± 10.7	11.8 ± 10.3	16.7 ± 10.8	0.46	0.02*	12.5 ± 8.7	14.1 ± 11.1	0.15	0.56	14.8 ± 11.0	7.3 ± 2.1	0.70	0.02*

<sup>+</sup> p = 0.05–1.0

\* p < 0.05

\*\* p < 0.01

**Table 3**  
Correlational analysis oxidative stress and Omega 3 MEASURES.

	RBC %EPA	RBC %DHA	RBC Omega 3 Fatty Acid Index (%EPA + DHA)	RBC %total O3	Self report Dietary Omega 3 Fatty Acid Diet
Malondialdehyde content	−0.07	−0.24*	−0.24*	−0.20 <sup>+</sup>	−0.16
Self report Dietary Omega 3 Fatty Acid Diet	0.26*	0.23*	0.24*	0.21*	

RBC = Red blood cell; EPA = Eicosapentaenoic acid; DHA = Docosahexaenoic acid.

<sup>+</sup> p = 0.06.

\* p &lt; 0.05.

#### 4. Discussion

Teenagers and young adults at CHR for psychosis, with little or no history of antipsychotic exposure, have high rates of cardiometabolic abnormalities including obesity, dyslipidemia and hypertension that are independent of antipsychotic history. To our knowledge, this is the first study reporting detailed cardiometabolic measures in antipsychotic-naïve CHR subjects. These values approach those observed in an older first episode psychosis sample from the RAISE study with minimal antipsychotic exposure (Correll et al., 2014) and are greater than those observed in the general population of adolescents and young adults across multiple national surveys (Gordon-Larsen et al., 2010; Ogden et al., 2012; Organization, 2014). The cardiometabolic abnormalities were more prevalent in Latino CHR subjects as well as male subjects. The high prevalence of cardiometabolic abnormalities in the CHR population does not appear to be related to side effects of psychotropic medication, but may be related to unhealthy life-style and perhaps pathophysiological mechanisms innate to early psychosis. The higher rate of cardiometabolic abnormalities and low rate of Omega 3 intake in the Latino CHR population is consistent with that of the general population of Latino youth (Dong et al., 2016) and suggests that underserved populations at risk for psychosis are particularly vulnerable to morbidity and mortality.

Over 90% of CHR subjects demonstrated evidence of elevated oxidative stress. In addition, RBC Omega 3 index (%EPA + DHA) was relatively low (<4%) in CHR subjects and this measure, like oxidative stress, is associated with CVD in general population studies (Harris and Von Schacky, 2004). Evidence of increased oxidative stress (Reddy et al., 2003; Yao and Reddy, 2011) and reduced Omega 3 PUFAs (16–19) has been found in both chronic and first episode patients with schizophrenia. The significant association of cardiometabolic abnormalities, lower levels of Omega 3 intake and increased severity of symptoms and poorer functioning, suggests that systemic illness and dietary factors may play a crucial role in the psychosis disease process. The association of RBC PUFA reductions and increased symptom severity is consistent with prior studies in chronic schizophrenia that showed

similar associations with positive and negative symptoms, cognitive impairment, and tardive dyskinesia (Yao et al., 1999).

Importantly, MDA levels in CHR subjects were inversely correlated with RBC Omega 3 levels, consistent with the findings of Arvindakshan et al. (Arvindakshan et al., 2003) who found an inverse relationship between levels of lipid peroxides (index of free radical-mediated fatty acid damage) and RBC DHA and AA in never-medicated patients. It is therefore possible that PUFA reductions in schizophrenia may in part be due to oxidative stress.

Changes in oxidative stress have been attributed to dietary factors and physical activity levels. Diets high in saturated fatty acids, sugar and alcohol as well as low in fresh fruits and vegetables (antioxidants) are thought to intensify oxidative stress. In addition, physical inactivity, smoking, and severe psychological stress contribute to oxidative stress (Roberts and Sindhu, 2009; Schiavone et al., 2012). Oxidative stress induces alterations in the methionine, or the 1–Carbon cycle, and fatty acid metabolism and thereby may play an integrative role in oxidative-stress-associated pathophysiology of psychiatric disorders and CVD (Assies et al., 2014). Elevated oxidative stress also precedes insulin resistance, the first manifestation of CVD risk. Increased oxidative stress is likely the causal pathway that links excess caloric intake to insulin resistance (Urakawa et al., 2003). A central role of oxidative stress in the link between psychiatric and CVD stresses the need for monitoring of signs of oxidative stress (e.g. waist circumference) in psychiatric patients and treatment aimed at preventing oxidative stress development (e.g. diet, exercise, cognitive therapy). Future randomized controlled trials that combine add-on lifestyle interventions (e.g. diet, physical exercise) and investigation of (adjuvant) novel oxidative-stress-relieving treatments (e.g. N-acetylcysteine) are therefore urgently needed.

There is increasing evidence that cardiometabolic abnormalities are associated with brain structural abnormalities and associated networks noted to be affected in psychotic illness (Minichino et al., 2017; Sun et al., 2016). In addition, weight gain-related brain abnormalities are associated with poor cognitive and functional outcomes in the general population (Jauch-Chara and Oltmanns, 2014; Miller and Spencer, 2014) and worse prognostic outcomes in psychotic patients

**Table 4**  
Correlational analysis symptoms and functioning vs. cardiometabolic and Omega 3 measures.

	Serum glucose	BMI	Abdominal circum	Omega 3 Fatty Acid Diet	RBC EPA	RBC DHA	RBC Omega 3 Fatty Acid Index (EPA + DHA)	RBC total Omega 3 Fatty Acid
SOPS total	0.29**	0.26**						
Positive								
Negative	0.18 <sup>+</sup>	0.18 <sup>+</sup>		−0.18 <sup>+</sup>				
Disorganized		0.19*						
General	0.22*	0.33**	0.22*			−0.21*	−0.24*	−0.27*
GAF	−0.19 <sup>+</sup>	−0.19*		0.37**	0.21*			
Global social			−0.20*					
Global role							0.17 <sup>+</sup>	

SOPS = Scale of Psychosis Risk Syndromes; GAF = Global Assessment of Functioning;

BMI = Body Mass Index; RBC = Red Blood Cell; DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; BMI: Body Mass Index.

<sup>+</sup> p = 0.05–0.10.

\* p &lt; 0.05.

\*\* p &lt; 0.01.

(Rashidrashid et al., 2013). Of relevance, longitudinal studies in otherwise healthy individuals show that obesity/overweight-related brain structural abnormalities might be reversible with weight loss and dietary interventions, in particular when adolescents and young adults are targeted (Gomez-Pinilla, 2011; Haltia et al., 2007; Mueller et al., 2015).

#### 4.1. Limitations

The current manuscript examines baseline cardiometabolic and dietary characteristics of a CHR population prior to participation in a clinical trial. A primary limitation of this study was lack of healthy comparison group. Because there was not a normal comparison sample, it was not possible to easily compare the rate of metabolic abnormalities to a general population. Because of the exploratory nature of the correlational analyses we did not correct for multiple comparisons; therefore, these results need replication and should be considered as preliminary. Finally, since the participants in this study were part of a randomized clinical trial, it is not possible to rule out effects of self selection bias in those individuals who chose to participate.

#### 4.2. Conclusions

Early identification of individuals at high risk for psychosis and decreasing the duration of untreated psychosis are important goals in reducing the impact of mental illness in vulnerable young people. Based on the data presented here, it is also likely that evidence of early systemic disease is also present before the onset of psychotic illness and can serve as an additional risk factor for future mental illness along with associated morbidity. Prevention and early detection of metabolic disturbances in this population is crucial since they are modifiable with the potential for significant gains in terms of clinical, cognitive and functional outcomes.

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##### Author contributions

The NAPLS PIs (Addington, Bearden, Cadenhead, Cannon, Cornblatt, Mathalon, McGlashan, Perkins, Seidman, Walker, Woods) were all involved in designing the trial. Drs. Cadenhead, Minichino and Ms. Kelsven were responsible for the majority of the writing and data analysis. The late Dr. Yao was involved in Fatty Acid analysis and measures of Oxidative stress. All authors were involved in editing the manuscript and approved its content.

##### Conflicts of interest

Authors report no conflicts of interests related to this study.

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