

# Endothelial function and lipid profile of individuals with schizophrenia participating in a supported employment program

Função endotelial e perfil lipídico de pessoas com esquizofrenia participantes de um programa de emprego apoiado

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**ABSTRACT | Background:** The social function of individuals with schizophrenia is usually poor and this population exhibits a sedentary lifestyle. Social participation, inclusion in the world of work in particular, might favorably interfere with the lives of these individuals by reducing sedentarism and improving their state of health. **Objective:** To analyze the lipid profile and endothelial function markers among individuals with schizophrenia enrolled in a supported employment program. **Methods:** Quantitative quasi-experimental study conducted with 14 individuals with schizophrenia enrolled in a labor inclusion program. Participants were assessed before enrolment (time-point 1) and one year later (time-point 2). Total cholesterol and fractions, triglycerides, serum nitrates and nitrites (endothelial function markers) were measured. The data were analyzed with software SPSS 20. **Results:** The high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels exhibited significant changes one year after inclusion in the labor market. HDL increased from 82.30 to 98.60 mg/dL ( $p < 0.01$ ) and LDL decreased from 54.50 to 44.45 mg/dL ( $p < 0.02$ ). The triglyceride and total cholesterol levels remained stable. The nitrate and nitrite level exhibited significant reduction from 15.20 to 14.48  $\mu\text{Mol}$  ( $p < 0.01$ ). **Conclusion:** Participation in the supported employment program might have favorably influenced the participants' lipid profile and endothelial function. Nitrites have been described as mediators in the neural inflammatory process, and reduction of their levels is associated with better prognosis of chronic diseases such as schizophrenia.

**Keywords |** schizophrenia; endothelium; work; cholesterol.

**RESUMO | Introdução:** Pessoas com esquizofrenia habitualmente têm um funcionamento social empobrecido e são sedentárias. A participação social, especialmente a inclusão no universo do trabalho, pode interferir positivamente na vida dessas pessoas, reduzindo o sedentarismo e melhorando sua saúde. **Objetivo:** Avaliar o perfil lipídico e os marcadores da função endotelial de pessoas com esquizofrenia participantes de um programa de emprego apoiado. **Método:** Pesquisa quantitativa do tipo quase-experimental que avaliou um grupo de 14 sujeitos com esquizofrenia participantes de um programa de inclusão laboral. Os sujeitos foram avaliados antes de ingressarem no programa (momento 1) e um ano depois (momento 2). Foram dosados: colesterol total e frações, triglicérides, nitratos e nitritos séricos (marcadores da função endotelial). Os dados foram analisados com o auxílio do software SPSS 20. **Resultados:** As frações de colesterol *high density lipoprotein* (HDL-C) e *low density lipoprotein* (LDL-C) sofreram modificações significativas após o período de um ano de inserção no mercado de trabalho. O HDL aumentou de 82,30 para 98,60 mg/dL ( $p < 0,01$ ). Já o LDL apresentou uma redução de 54,50 para 44,45 mg/dL ( $p < 0,02$ ). Os triglicérides e o colesterol total mantiveram-se estáveis. Com relação aos nitritos e nitratos, houve diminuição significativa de 15,20 para 14,48  $\mu\text{mol}$  ( $p < 0,01$ ). **Discussão:** A participação no programa de emprego apoiado pode ter influenciado positivamente no perfil lipídico dos sujeitos e em sua função endotelial. Além disso, os nitritos também têm sido apontados como mediadores do processo inflamatório neural e sua diminuição está associada à melhora no prognóstico de doenças crônicas como a esquizofrenia.

**Palavras-chave |** esquizofrenia; endotélio; trabalho; colesterol.

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## INTRODUCTION

Schizophrenia is a serious and disabling mental disorder that impairs the global functioning of individuals; it affects about 1% of the world population<sup>1</sup>. The behavior of individuals with schizophrenia is quite peculiar, being characterized by isolation and sedentarism. Sedentarism is a considerable cause of concern, because added to the unquestionable need for antipsychotic medication, it usually leads to metabolic disorders that might shorten and threaten the lives of the affected individuals<sup>2</sup>.

Overcoming this situation poses a major challenge, as the traditional healthcare model offers options almost exclusively based on pharmacological clinical approaches. Alternative strategies, following a model centered on rehabilitation and inclusion, have gradually emerged giving rise to positive expectations. One of such strategies is inclusion via work<sup>3</sup>. Participation in the world of work might result in several benefits for this population of individuals. First and foremost, having a job represents a considerable opportunity to break away from inactivity at home (which is usually the rule) and sedentarism. It is believed that physical activities of everyday social life — such as travelling to work, coming and going within the workplace, walking up and down stairs, catching a bus, etc. — might improve the physical functioning and health of this population and also reduce their cardiovascular risk<sup>4</sup>.

Coelho and Ornelas<sup>5</sup> observe that strategies such as supported employment are associated with reduction of psychiatric symptoms, isolation and exclusion, and provide opportunities for social reinforcement and improved personal empowerment. These strategies also result in higher levels of daily activity and reduction of sedentarism.

Sedentarism seems to be associated with endothelial dysfunction<sup>6</sup>. Abnormal endothelium (the internal layer of the blood vessels) function is characterized by imbalance in the production of the mediators that regulate the vascular tone, platelet aggregation, coagulation and fibrinolysis<sup>7</sup>. Endothelial dysfunction is frequently described as poor endothelium-dependent relaxation due to loss of nitric oxide (NO) bioavailability, even though also the secretion of other endothelium-derived vasoactive substances might be abnormal. A healthy endothelium is able to maintain vasodilation, inhibit platelet aggregation, leukocyte adhesion and the proliferation of smooth muscle cells<sup>8</sup>.

The endothelium of muscle and adipose tissue capillary vessels contains a surface enzyme involved in the intestinal pathway of lipoprotein degradation. Non-degraded, residual lipoproteins (as occur in cases of deficiency of this enzyme) are absorbed into the liver leading to the formation of very low-density lipoprotein (VLDL). In turn, among its actions, high-density lipoprotein (HDL) contributes to protect blood vessels against atherogenesis through removal of low-density lipoprotein (LDL) oxidized lipids, inhibition of the fixation of monocyte adhesion molecules to the endothelium and stimulation of NO release<sup>7</sup>. Therefore, there is a close relationship between endothelium and blood fats. Endothelial dysfunction, in association with dyslipidemia, might predispose to atherosclerotic plaque formation resulting in high-risk cardiovascular events, such as stroke and acute myocardial infarction<sup>9</sup>.

Endothelial dysfunction is probably a part of the picture exhibited by most individuals with schizophrenia. Reasons are sedentarism and metabolic diseases, such as overweight and dyslipidemias, which, as mentioned above, are frequent occurrences among this population<sup>2</sup>.

The aim of the present study precisely was to investigate the benefits that participation in the world of work might have for the cardiovascular health of individuals with schizophrenia through the study of specific factors, such as endothelial function and lipid profile. We are currently conducting a study in which we follow up a group of individuals with schizophrenia who participate in a labor inclusion program developed by Projeto Capacitar (Project To Capacitate) in Porto Alegre, Rio Grande do Sul, Brazil. Based on the Federal Law no. 8,231 (Law of Quotas for Individuals with Disabilities)<sup>10</sup> this program seeks to include individuals with schizophrenia into the formal labor market. Before enrolling in this program, these individuals exhibited an isolated and sedentary pattern of behavior, which changed after they started working on a daily basis.

## METHODS

### STUDY DESIGN

The present was a quantitative quasi-experimental study in which “a supported employment program” was the factor

considered. We analyzed several variables before the onset and during the program and compared them to establish the program's repercussion.

We assessed the impact of a supported employment program by comparing endothelial function markers and the lipid profile collected at two time-points:

1. before enrolment in the supported employment program;
2. after the end of the training and internship period in companies, which lasted about 12 months and was thus defined as the study period.

The study was approved by the research ethics committee of Methodist University Center, Porto Alegre Institute (Instituto Porto Alegre – IPA) no. 12382013.5.0000.5308 and complied with Resolution no. 466/12<sup>11</sup>.

## STUDY SETTING

The study was entirely conducted in Porto Alegre, a city located in Southern Brazil. The initial setting was Center of Prevention and Intervention in Psychoses (CPIP), namely, a non-profit charity devoted to teaching, technical development and social work from a biopsychosocial perspective. CPIP has large experience in rehabilitation of individuals with severe mental disorders, and starting 2009 it launched a supported employment program.

CPIP receives, interviews and follows up interested individuals. Companies that participate in Projeto Capacitar and hire these new employees are contacted by CPIP staff. These are companies from various economic areas and systematically seek to adjust jobs to the profile of the project participants.

Blood sample collection and analysis of biological samples were performed at the laboratory of Methodist University Center – IPA.

## DESCRIPTION OF THE STUDY POPULATION

Participants were individuals diagnosed with schizophrenia from both sexes, over 18 years old, not exhibiting a psychotic crisis, under psychiatric medical treatment and who did not consume alcohol or other drugs at the time of the study. In addition, participants could not receive disability pension, should deliver a medical certificate authorizing them to attend the course and name a relative or guardian committed to the proposal. All candidates ought to recognize and accept themselves as having

a mental disorder and manifest the will for, or have as personal project, inclusion via work.

The selected population initially included 20 participants. However, some losses occurred along the study due to therapeutic interventions and dropouts. Therefore, the final sample comprised 14 participants.

## DEVELOPMENT OF PROJETO CAPACITAR

This supported employment program begins by the selection of candidates. Divulcation is accomplished through mass media. Individuals who meet the inclusion criteria are referred to a training program developed by professionals who participate in Projeto Capacitar on a voluntary basis.

The training program consists of courses with 400 hours of theoretical and 400 hours of practical (so-called internship) teaching. These 800 hours are distributed across 12 months (6-month theoretical teaching and 6-month internship at partner companies). Theoretical teaching addresses subjects related to the behavior required by the social function of work with emphasis on the development of autonomy, hygiene, good manners and responsibility, among others. It also seeks to develop the ability to perform activities required in the workplace (e.g., how to use a cashier register, package food, organize stored items, etc.). Practical teaching is configured as internship at a company, during which participants perform job activities under continued supervision by the training team. Participants are paid a salary from the time of initial enrolment, and are hired by partner companies as disabled apprentices as per the Consolidation of Labor Laws article 428, §5<sup>12</sup>.

## PROCEDURES FOR DATA COLLECTION AND ANALYSIS

As the present study involved evaluating a supported employment program, the aforementioned Projeto Capacitar, we complied with the program's schedule. As planned, a group was enrolled in March 2015. This was the moment when we began our research activities, following formal approval documented by means of an institutional authorization form. All the subjects who agreed to participate in the study signed an informed consent form. Data collection and interviews corresponding to time-point 1 were performed one week before the onset of the

program, and the ones corresponding to time-point 2 one week after its end.

During interviews the participants were requested to respond psychological evaluation scales and a questionnaire on sociodemographic data. Blood samples were collected for biochemical analysis for measurement of endothelial function markers and lipid profile. These data were used to draw the participants' physical and mental health profile as a part of the larger research project of broad scoped evaluation of the impacts of Projeto Capacitar on the participants' lives.

Blood samples were collected by a duly accredited professional by means of venipuncture with syringe and needle and in compliance with all recommendations for asepsis. Ten mL of blood were collected on the cubital fossa. This procedure lasted about 15 minutes. All the participants received orientation as to the care required after the procedure. They had been previously informed they should fast 12, minimum, to 14, maximum, hours before the procedure. Samples corresponding to time-point 1 were collected on April 2015, and the ones corresponding to time-point 2 on May 2016. On both occasions collection of biological materials was performed in the morning between 7:00 and 8:00.

The venous blood samples were stored in tubes containing EDTA K3 and homogenized gently by inverting the tubes. Next the samples were centrifuged at 5000 rpm for 5 minutes. The serum was removed and stored in Eppendorf microtubes at -80°C until the time of analysis.

Measurement of nitrates and nitrites (NO<sub>x</sub>) was performed by means of the Griess test, which reaction gives rise to a purple hued compound that might be read on spectrophotometry at 450-nm wavelength<sup>13,14</sup>. For this reaction, 100 mL of serum were added 50 mL of solution 1 (1% sulfanilamide in 2.5% phosphoric acid solution) After a waiting time of 10 minutes, 50 µL of solution 2 (0.1% N-naphthyl-ethylenediamine in 2.5% phosphoric acid) were added. The samples were homogenized and read with an enzyme-linked immunosorbent assay (ELISA) reader. The results were expressed as µMol.

Total cholesterol (TC) was measured by means of the enzymatic cholesterol oxidase/peroxidase method also with spectrophotometer. HDL was measured by means of the reactive precipitation method. LDL and VLDL were

calculated with the Friedwald equation. The triglyceride (TG) levels were measured by means of the glycerol enzymatic method.

Analysis involved calculation of measures of central tendency (mean) and variability (standard deviation) as the variables of interest were quantitative. Mean values of continuous variables were compared with Student's t-test when the distribution was normal and the Mann-Whitney test when it was not normal. The significance level was set to  $p < 0.05$ . Analysis was performed with software Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows.

## RESULTS

Fourteen subjects successfully completed the 12-month intervention. The sample characterization is described in Table 1.

As shown in Table 2, as concerns the endothelial function on time-point 2, i.e., after the end of intervention, the NO<sub>x</sub> levels significantly decreased from 15.20 to 14.48 µMol ( $p < 0.01$ ).

The HDL and LDL levels only exhibited significant changes one year after the participants joined the labor market. The HDL level increased from 82.30 to 98.60 mg/dL ( $p < 0.01$ ) and the LDL level decreased from 54.50 to 44.50 mg/dL ( $p < 0.02$ ). We did not find significant difference in the TG and TC levels, the corresponding p-value being statistically irrelevant. These results are described in Table 2.

## DISCUSSION

The results of the present pioneering study indicate that endothelial markers and the lipid profile might change in individuals with schizophrenia in association with work. While the average age of the participants ( $37 \pm 12.3$  years old) was within the economically active range, until enrolment in the program they were isolated and had no job activity whatsoever. Most participants were female (more than 64%) which possibly reflects the better social adjustment of women with schizophrenia, and thus corroborates reports in the literature<sup>15</sup>.

Another relevant aspect deserving of discussion is the marital status of the participants. One European study entitled Schizophrenia Outpatient Health Outcomes (SOHO), which included more than 10,000 individuals with schizophrenia from 10 countries from all continents, found that only 18.6% had some form of conjugal relationship<sup>16</sup>. These data agree with the results of the present study, as only 1 out of the 14 participants (7.1%) had a partner. Louzã Neto and Elkis<sup>17</sup> observe that individuals with schizophrenia have

difficulty to maintain affective relationships, particularly as a function of their personality traits predominantly schizoid and with tendency to withdraw.

In regard to their financial conditions, at the time of enrolment in the program most participants depended on their families. This finding was expected, since as a rule individuals with schizophrenia have much difficulty to join the labor market. As a result, their families or the government end by providing for their material needs<sup>16</sup>.

Relative to their educational level, most participants (more than 57%) had completed secondary school. This is an interesting finding vis-à-vis a group of Brazilian individuals with schizophrenia. Traditionally, this population has difficulty to continue formal education and usually attain only low educational levels, especially as a function of the cognitive impairment that develops together with the progression of disease<sup>18</sup>. The participants in the present study might represent a differentiated group from the perspective of functioning. Despite living with the disease and its implications, they were eager for personal and professional growth, and this differential aspect might had been the very reason that led them to Projeto Capacitar in the first place.

As concerns the variables of interest in the present study, we now address the reduction of the serum NOx that occurred after intervention. Most studies compare NO products as chemical mediators or neurotransmitters, but do not measure their serum levels as we did. An interesting perspective for discussion is the possible relationship between reduced serum NOx levels and the mechanisms that underlie oxidative stress. We found

**Table 1.** Sociodemographic profile of participants, Porto Alegre, Rio Grande do Sul, 2016 (n=14).

Characteristics	Participants
Age (years), mean±SD	37±12.3
Sex, n (%)	
Male	5 (35.8)
Female	9 (64.2)
Marital status, n (%)	
With partner	1 (7.1)
Without partner	13 (92.9)
Social security status, n (%)	
Receiving benefit	2 (14.3)
Family dependent	12 (85.7)
Educational level, n (%)	
Elementary school	5 (35.7)
Secondary school	8 (57.1)
Higher education	1 (7.2)

SD: standard deviation.

**Table 2.** Comparison of serum variables between time-points 1 and 2, Rio Grande do Sul, 2016 (n=14).

	TP1		TP2		p value
	Mean	Standard deviation	Mean	Standard deviation	
Endothelial profile					
NOx	15.20	0.52	14.48	0.86	0.01*
Lipid profile					
Total cholesterol	166.35	39.39	171.65	37.11	0.24
LDL	54.50	21.72	44.45	21.61	0.02*
HDL	82.30	45.13	98.60	41.33	0.01*
Triglycerides	172.35	66.74	173.40	56.61	0.88
VLDL	34.45	13.33	34.75	11.36	0.83

TP1: time-point 1; TP2: time-point 2; NOx: serum nitrates and nitrites; LDL: low-density lipoprotein; HDL: high-density lipoprotein; VLDL: very low-density lipoprotein; \*p<0.05.

significant reduction of the serum NOx from 15.20 to 14.48  $\mu\text{Mol}$  ( $p < 0.01$ ). This finding might be related to increase of the emotional stress levels in association with the fact of undergoing a new experience. As such, this finding was expectable, since before their experience with work the participants had settled in.

Stressful events at the behavioral level compel individuals to react through one of the following three types of response: confrontation, avoidance or passivity<sup>19</sup>. The selected response defines the physiological resources that will be mobilized. In the first case, confrontation elicits anxiety, which in turn triggers a series of body changes (elevation of the blood pressure, tachycardia, vasodilation in skeletal muscles and vasoconstriction in the skin and viscera). These phenomena increase the oxygenation of muscles and the brain, as well as events related to oxidative stress<sup>20</sup>.

Oxidative stress develops following imbalance between prooxidants (such as large amounts of free radicals) and antioxidants (substances able to delay or inhibit oxidation, such as enzymes, vitamins and mineral salts)<sup>21</sup>. Reduction reactions (addition of an electron to an oxygen molecule) result in the production of superoxide anion, which rapidly reacts with nitric oxide inhibiting its bioactivity. It also inhibits secondary reactive species, such as peroxynitrite (NOx-derived oxidant) which generates the hydroxyl radical which in turn is converted into NOx. As a result, the serum production of NOx decreases, which is precisely what we found in the present study. Physical activity-induced shear stress (caused by increase of the blood circulation within vessels) is a powerful stimulus for the release of vasorelaxant factors synthesized in the vascular endothelium, such as NOx, resulting in reduction of the blood pressure among other benefits<sup>22</sup>. However, NOx functions might be antagonistic. This molecule might be beneficial or also potentially toxic as a function of its concentration or tissue clearance<sup>23</sup>. NOx contributes to improve some pathological conditions, especially when derived from inflammation in immune system. Loss of control over the nitric oxide synthesis is a mechanism involved in the pathogenesis of cardiovascular autoimmune diseases, transplant rejection, sepsis and genotoxicity. Also neuronal injury and neurodegenerative diseases, such as Parkinson's and Alzheimer's, are associated with increased synthesis of NOx<sup>24,25</sup>.

According to some studies, this type of mechanism is also involved in schizophrenia<sup>26,27</sup>. Some authors argue that

NOx do not only behave as endothelial function mediators, but also as reactive nitrogen species and neuromediators. From this perspective, high NOx levels might paradoxically indicate increase of free radicals and progression/severity of disease<sup>28</sup>. In turn, reduction might denote attenuation of disease progression.

Vetter et al.<sup>29</sup> performed a case-control study with 51 healthy subjects and 51 individuals with schizophrenia and found significant impairment of the microvascular function among the latter. According to these authors, impaired endothelial function might be an early indicator of cardiovascular risk in schizophrenia.

Further relevant findings concern the HDL and LDL levels, which exhibited significant changes one year after the participants joined the labor market. HDL increased from 82.30 to 98.60 mg/dL ( $p < 0.01$ ). HDL removes cholesterol from tissues and transports it to the liver, which in turn eliminates it through the intestine. The higher the HDL level, the lower the odds of cardiovascular events<sup>9</sup>. We located several studies which showed that patients with schizophrenia tend to exhibit low HDL levels<sup>30,31</sup>. These phenomena is possibly related to the patients' lifestyle and chronic use of antipsychotic agents, resulting in worrisome metabolic disorders that impair the longevity of this population.

The LDL level exhibited significant reduction from 54.50 to 44.45 mg/dL ( $p < 0.02$ ). This finding points to a favorable change in the participants' lipid profile, especially when considered together with the results discussed above. This is a relevant finding, as this population of individuals is particularly susceptible to elevation of the LDL levels in association with chronic use of antipsychotic drugs<sup>32</sup>. In opposition to HDL, LDL transports the blood cholesterol and TG to the tissues and facilitates the deposition of fat on the blood vessel walls, with consequent formation of atheroma plaques and development of atherosclerosis.

Brown and Estoup<sup>33</sup> reviewed the medical records of 191 patients treated with antipsychotic drugs for 22 months and found 11% increase of the LDL levels, elevation of other harmful lipoproteins and reduction of the beneficial ones. Another study conducted with individuals with schizophrenia found that most participants exhibited overweight, larger waist circumference and high LDL levels<sup>34</sup>.

We understand that the job-related activities performed by the participants in the present study posed several daily challenges: waking up in the morning, travelling and the activities as such, characteristically of physical rather than of intellectual nature. Physically active individuals exhibit higher HDL and lower TG, LDL and VLDL levels compared to sedentary individuals<sup>35</sup>. Higher HDL and lower TG and LDL levels are associated with regular performance of physical activity, which increases the utilization of fatty acids and the effects of enzyme lipoprotein lipase on the muscle tissue<sup>36</sup>. Although the other lipoproteins analyzed in the present study did not exhibit significant changes, the aforementioned findings suffice to suggest that daily job activities had favorable influence on the lipid profile.

## CONCLUSION

Participation in the supported employment program might have had favorable influence on the subjects' lipid

profile and endothelial function, reducing the cardiovascular risk among this population of individuals. However, one should take also the limitations of the present study into consideration. Its internal validity should be analyzed as a function of the non-random nature of the sample and the lack of a control group. Also its external validity is limited, and thus caution is required in the generalization of the results. Larger studies with better methodological rigor are needed in order to make assertions instead of inferences and suppositions.

Continuous participation of the study participants in the world of work might reveal new repercussions in their lives, which should be followed up over a long period of time and with better control of confounding variables.

One further relevant issue concerns the NOx levels and the understanding of the relevance of these molecules as mediators in the pathogenesis of and inflammation in schizophrenia. The study of this research question opens a full scope of inquiries which future studies might come to elucidate.

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