STUDY PROTOCOL

BARIATRIC SURGERY IN PATIENTS WITH SCHIZOPHRENIA

Protocol version and date	Version: 2. Date: 06/02/2022
Protocol Code	IIBSP-BAR-2022-30
short title	SCHIZOBAR
Promoter	Research Institute of the Hospital de la Santa Creu i Sant Pau – IIB Sant Pau c/ Sant Quintí, 77-79 08041 Barcelona Phone: 93 553 78 69 Fax: 93 553 78 12
Coordinator Researcher	Inka Miñambres Donaire Endocrinology and Nutrition Hospital of Santa Creu i Sant Pau c/ Sant Antoni Maria Claret, 167 08025 Barcelona e-mail: iminambres@santpau.cat
Principal researchers	Maria del Mar Carceller Sindreu Psychiatry Hospital of Santa Creu i Sant Pau c/ Sant Antoni Maria Claret, 167 08025 Barcelona e-mail: mcarceller@santpau.cat **Members of the GOSEEN group (Working Group on Obesity of the Spanish Society of Endocrinology and Nutrition)**

1. SUMMARY:

Promoter Identification	Research Institute of the Hospital de la Santa Creu i Sant Pau – IIB Sant Pau c/Sant Quintí, 77-79 08041 Barcelona Phone : 93 553 78 69
study title	BARIATRIC SURGERY IN PATIENTS WITH SCHIZOPHRENIA
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Coordinating researcher	Inka Miñambres Donaire Endocrinology and Nutrition Hospital of Santa Creu i Sant Pau c/ Sant Antoni Maria Claret, 167 08025 Barcelona e-mail: iminambres@santpau.cat
Principal investigators and participating centers	**Maria del Mar Carceller Sindreu** Psychiatry Hospital of Santa Creu i Sant Pau **Albert Goday Arno:** Hospital del Mar. Barcelona **Alfonso Calañas Continent** : Reina Sofía University Hospital. Cordova **Assumpta Caixàs Pedragós** : Parc Taulí University Hospital **Fernando Cordido Carballido** : A Coruña University Hospital **Irene Bretón Lesmes:** Gregorio Marañón University Hospital, Madrid **Camilo Silva:** University of Navarra Clinic. Pamplona **Lilliam Flores** : Hospital Clínic, Barcelona **María Ballesteros Pomar:** León University Assistance Complex **Maria Jesus Diaz:** Valle del Nalón Hospital. Asturias **Maria Jose Morales Gorria:** Vigo University Hospital Complex, Pontevedra **Marta Bueno Díez:** Arnau de Vilanova University Hospital. Lleida **Miguel Angel Rubio:** San Carlos Clinical Hospital, Madrid **Nuria Vilarrasa:** Bellvitge University Hospital **Pedro Pablo Garcia Luna:** Hosp. Univ. Virgen del Rocio of Seville **Sergio Valdés:** Regional University Hospital of Malaga

	Silvia Pellitero: Germans Trias i Pujol University Hospital. badalona **María Tous :** Virgen de la Macarena Hospital, Málaga **Mª José Barahona** : Hospital Mutua de Terrassa, Terrassa. **Joana Nicolau** : Son Llàtzer Hospital, Majorca **David Pérez:** Trueta Hospital, Girona **Judith Lopez** : University Hospital of the Canary Islands, Tenerife. **Mubarak Aramadan** :H. Virgin of Light-Cuenca **José Ignacio Martínez** : H. University Virgen de la Victoria-Málaga. **Raúl Luque** : Reina Sofía-Córdoba University Hospital **Carlos Peteiro** : Viladecans Hospital, Barcelona **Carlos Morillas** : H. University Dr. Peset-Valencia: **Alejandra Durán** : H. San Carlos Clinic in Madrid **Liliana Gutierrez** : H. de Reus **Gloria Aranda** : H. General of Vic
Reference ethics committee	CEIM of the Hospital de la Santa Creu i Sant Pau
Main goal	To study the evolution after bariatric surgery in patients with obesity and schizophrenia
Design	Multicenter retrospective case control study.
Disease under study	Schizophrenia and Obesity
Methodology	Retrospective observational study
Study population and total number of subjects	Cases: Patients with schizophrenia and obesity undergoing bariatric surgery. (number: all cases collected within the GOSEEN group). Controls: Patients without psychiatric pathology matched by age, sex, BMI and type of surgery and in a 4:1 ratio to cases.
Calendar. Expected duration of the study.	12 months
ethical considerations	Informed consent will be obtained from patients who are currently being followed up at the reference centers.
Funding source	Not precise

2. THEORETICAL FRAMEWORK. PROBLEM STATEMENT:

Background

Obesity affects approximately 45-55% of patients with schizophrenia (1). Weight gain in these patients may be due to different factors such as the use of antipsychotic drugs with an unfavorable metabolic profile, the coexistence of sleep disorders or negative cognitive symptoms that often translate into a more sedentary lifestyle and alterations in eating behavior, among others (2). The coexistence of obesity and its comorbidities in this group of patients significantly worsens both their physical and mental health (3). In fact, cardiovascular disease is one of the main causes of mortality in patients with schizophrenia (4).

Lifestyle interventions, while they may be effective in people with schizophrenia (5), often fall short of achieving weight goals. At present, obesity surgery represents the most effective treatment in terms of weight loss and resolution of comorbidities, being indicated in cases of patients with a body mass index (BMI) > 35 kg/m2 with comorbidities or BMI > 40 Kg/m2 with/without comorbidities. However, the access of patients with schizophrenia to bariatric surgery techniques is usually limited by different factors such as fear of a possible worsening of the underlying disease, or a lower weight loss in this population, among others. In addition, clinical practice guidelines recommend that all patients with psychiatric pathologies be evaluated in a regulated manner prior to surgery (6), although the content of this evaluation and the criteria for declining or accepting surgery are not clear. Although the course of schizophrenia is variable and its symptoms may be stable without being a clear contraindication for bariatric surgery, in actual practice, a considerable number of professionals contraindicate bariatric surgery in the presence of a psychotic disorder (7).

For these reasons, data on the efficacy of bariatric surgery in patients with schizophrenia are scarce and limited to very small case series with short-term follow-up (2,8,9). Our objective is therefore to carry out a multicenter retrospective study that allows us to study the long-term evolution after bariatric surgery in a large series of patients, focusing not only on weight evolution but also on the long-term evolution of psychiatric pathology.

Justification

It is necessary to have information about the prognosis of subjects with severe obesity and schizophrenia who undergo bariatric surgery. This knowledge will make it possible to establish clear guidelines for action in these cases.

Research questions

What is the long-term outcome after bariatric surgery in subjects with schizophrenia?

Hypothesis

Bariatric surgery in subjects with schizophrenia leads to an improvement in weight and cardiometabolic comorbidities similar to that of subjects without schizophrenia

3. GOALS:

Main goal:

To study the short (first year after bariatric surgery) and long-term (up to 5 years of follow-up after bariatric surgery) evolution in terms of weight loss of patients with obesity and schizophrenia who underwent bariatric surgery in Spain and compare it with the evolution of patients without psychiatric disorder.

Secondary objectives:

- Determine the casuistry of patients, with special interest in the characteristics of the underlying psychiatric pathology (years of evolution, clinical stability criteria, pharmacological treatment...).
- To Analyze the evolution of obesity comorbidities.
- To Analyze the evolution of psychiatric pathology after bariatric surgery: (decompensation, drug treatment...)
- To analyze the frequency of early (<30 days post-surgery) or late (>30 days post-surgery) post-surgical complications.

4. METHODS:

Study design

Retrospective case-control study.

Study population. Inclusion, exclusion criteria

Cases:

Inclusion) Both criteria must be met:

1.- Patients with severe obesity undergoing bariatric surgery and with follow-up in Spanish territory.

2.- Patient with schizophrenia or schizoaffective disorder.

Exclusion)

Subjects who do not meet any of the two inclusion criteria

Controls: in a 4:1 ratio with cases

Inclusion) Both criteria must be met:

1.- Patients with severe obesity undergoing bariatric surgery and with follow-up in Spanish territory.

2.- Absence of psychiatric pathology

3.- Paired with the cases by age, sex, BMI before surgery and type of surgery.

Exclusion)

Subjects who do not meet any of the two inclusion criteria

Definition of variables

Main variables:

- weight
- size
- BMI

- TWL (total weight loss)
- EWL (excess weight loss)

Secondary variables:

- Age, ethnicity, educational level
- Type of surgery
- psychiatric dx
- Years of evolution of the psychiatric disorder at the time of IQ
- Psychiatric drug treatment, lithemia, medication load.
- Number of psychiatric admissions prior to IQ.
- Number of psychiatric admissions/psychiatric emergencies after surgery (relapses): In-hospital relapses, Relapses < 30d, relapses during follow-up.
- Criteria for approval of surgery (in each center).
- Biochemical parameters: glucose, HbA1c, total cholesterol, triglycerides, HDL, LDL.
- Early and late postoperative complications and death of the patient.
- Presence of diabetes, arterial hypertension, dyslipidemia, OSAS and liver disease and treatments for these pathologies.
- Adherence to follow-up in endocrinology and dietetics (Number of visits attended/Number of scheduled visits)
- Lost to follow-up.

The collection of variables will be carried out pre-surgery and 1 month, 6 months, 12 months and subsequently annually until a maximum of 5 years of follow-up.

Expected sample size

All cases detected in Spanish territory

The minimum number of cases expected will be 10 patients based on the low casuistry of the problem. The number of patients in the control group will be x4 that in the study group.

Methodology. Information sources

The study population will be identified in each center in the usual specialty consultations or by searching the databases of each center. Review of medical records in search of the specified variables (retrospective observational study).

Data Management and Analysis

The coordinating researcher (Dra Inka Miñambres Donaire) will be responsible for the creation of the database and its exploitation. The database will be created in Excell format and the SPSS program will be used for statistical analysis. The statistics will be mainly descriptive. For cases in which it is decided to compare groups, normality tests will be used to establish the behavior of the variables and parametric/non-parametric tests will be used as appropriate.

Data collection

The researcher will guarantee the accuracy and integrity of the data, as well as all the reports that are required. The data included in the Data Collection Notebook (CRD), which are derived from source documents, will be consistent with those documents or otherwise the discrepancies will be justified.

The researcher will keep the study documents until at least 5 years after completion.

At the request of the monitor, auditor, ethics committee or health authority, the researcher will have available all the files related to the study, allowing direct access to the data or source documents for monitoring, auditing, review by the ethics committee, as well as the inspection of the trial by the competent authorities.

Limitations of the design, the source of information and the methods of analysis

The main limitation of the study is its retrospective nature. However, the study design is adequate given the low frequency of the pathology.

5. WORK PLAN (tasks, milestones and timeline of the study):

month 1

Elaboration of the protocol. Edition of study materials. base design data. Meeting of researchers to resolve doubts. Preparation of the logistical aspects for the start-up of the study.

month 2-4

Presentation to the ethics committee.

month 4-8

Registration in ISRCTN

Start of study. Patient identification. Collection and introduction of data.

month 8-12

Data purification and analysis. Meeting of researchers to discuss the results and close the study. Preparation of the final report. Preparation of a manuscript for publication of the results.

Duration: 12 months

6. ETHICAL ASPECTS:

Research benefit-risk assessment

The present investigation, given its retrospective nature, does not pose a risk to the study patients. The expected benefits of it are a better knowledge of the risks and benefits of bariatric surgery in subjects with schizophrenia. This will allow in the future to establish the risk-benefit of bariatric surgery in these patients.

Ethical considerations, on information to the subjects and informed consent

The study will be carried out strictly following the international ethical recommendations for medical research in humans. The investigator will be responsible for ensuring that the study is carried out in accordance with the standards contained in the Declaration of Helsinki.

Before starting the study, the Ethics Committee of the Hospital de la Santa Creu i Sant Pau must approve the study protocol, the information that will be given to the subject and the informed consent model that will be used.

The CEIC will be informed of any subsequent amendment to the protocol and its opinion should be requested in the event that a new evaluation of the ethical aspects of the study is necessary.

It is the responsibility of the investigator to obtain the informed consent of the patient. The patient will not be able to participate in any study-specific procedure without obtaining their consent, or that of their legal guardian/family member when the patient is unable to give consent due to their clinical situation.

Before including any subject in the study and before obtaining informed consent, the investigator or the person designated by the investigator will explain to the potential participating subject or their legal guardian/family member the objectives, methods, and potential risks of the study and any inconvenience it may cause. The explanation about the nature, scope and possible consequences of the study will be made in an understandable language.

The prospective participant or their legal guardian/family member should have time to consider their decision to participate in the study, and have the opportunity to ask questions. After this explanation, and before entering the study, the consent must be properly recorded by the signature of the subject or their legal guardian/family member.

Given the retrospective nature of the study, it is likely that some patients to be included have died or are no longer seen at their referral center. In this case, informed consent will not be obtained, but the research team undertakes to verify that there is no record of the subjects' express opposition in the clinical history and to comply with the confidentiality regulations.

In addition, since the use of pseudonymized personal data for biomedical research purposes requires technical and functional separation between the research team, and those who perform the pseudonymization and keep the information that enables re-identification, the person who performs the pseudonymization for this study does not will be part of the research team.

For access to the pseudonymous data, an express commitment of confidentiality and not to carry out any re-identification activity is sent, and that specific security measures will be adopted to avoid re-identification and access by unauthorized third parties.

The Model Patient Information Sheet and the Consent Form are presented as an Annex.

Considerations on the treatment of biological samples

Does not apply

Data confidentiality

Regarding the confidentiality of the study data, the provisions of Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights and the General Regulation (EU) on Data Protection will be followed. 2016/679.

Interference with physician's prescribing habits

As it is a retrospective study, there will be no interference with the prescribing habits of the doctor.

7. PLANS FOR DISSEMINATION OF RESULTS:

An oral presentation is planned within the framework of the Congress of the Spanish Society of Endocrinology and Nutrition. The results will be published in a journal of the Specialty, prioritizing those in the first quartile.

8. RESOURCES FOR CARRYING OUT THE STUDY AND FINANCING:

This study will ask the Spanish Society of Endocrinology and Nutrition (SEEN) for funding to cover the possibility of publication fess in an online journal.

9. MODIFICATIONS TO THE PROTOCOL:

Any modification to the study protocol will always take the form of a written amendment or addendum. For its formalization, the approval of all the people responsible for the study will be required. In the case of relevant modifications, the express approval of the Clinical Research Ethics Committee will be requested.

10. PRACTICAL CONSIDERATIONS:

Start, follow-up and end reports

The start of the study will be notified to the ethics committee. Subsequently, annual monitoring reports will be sent.

After obtaining the conclusions of the study, a final report will be prepared and presented to the ethics committee.

11. BIBLIOGRAPHY:

1. De Hert M, Schreurs V, Vancampfort D, et al. Metabolic syndrome in people with schizophrenia: a review. World Psychiatry. 2009;8(1) : 15–22

2. Brito ME, Sampaio IM, Ferreira AC, Lorencetti PG, Celeri EHRV, Azevedo RCS, Noto CS, Gadelha A, Chaim FDM, Cazzo E, Ramos AC, Velloso LA, Chaim EA, Dalgalarrondo P, Dos Santos-Júnior A. Patients with Schizophrenia Undergoing Gastric Bypass Surgery: a Case Series Study. Obes Surg. 2020 Oct;30(10):3813-3821.

3. Dixon L, Postrado L, Delahanty J, et al. The association of medical comorbidity in schizophrenia with poor physical and mental health. J Nerv Ment Dis. 1999;187(8):496–502

4. Newcomer JW, Hennekens CH. Severe mental illness and risk of cardiovascular disease. NEVER. 2007;298(15):1794–6

5. McKibbin CL, Patterson TL, Norman G, et al. A lifestyle intervention for older schizophrenia patients with diabetes mellitus: a randomized controlled trial. Schizophr Res. 2006;86(1–3):36–44.

6. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient 2013 update. Cosponsored by the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic and Bariatric Surgery. Obesity (Silver Spring). 2013;21(0 1):S1–27

7. Fabricatore AN, Crerand CE, Wadden TA, Sarwer DB, Krasucki JL. How do mental health professionals evaluate candidates for bariatric surgery? Survey results. Obes Surg. 2006 May;16(5):567-73.

8. Archid R, Archid N, Meile T, Hoffmann J, Hilbert J, Wulff D, Teufel M, Muthig M, Quante M, Königsrainer A, Lange J. Patients with Schizophrenia Do Not Demonstrate Worse Outcome After Sleeve Gastrectomy: a Short-Term Cohort Study. Obes Surg. 2019 Feb;29(2):506-510

9. Kouidrat Y, Amad A, Stubbs B, Moore S, Gaughran F. Surgical Management of Obesity Among People with Schizophrenia and Bipolar Disorder: a Systematic Review of Outcomes and Recommendations for Future Research. Obes Surg. 2017 Jul;27(7):1889-1895.

ANNEXES:

Annex 1: Study evaluations
Annex 2: Information sheet for subjects (presented in a separate document)
Annex 3: Informed consent form (presented in a separate document)

Appendix 1

STUDY EVALUATION SCHEME

Visit / Procedure	V0	V1
Sign informed consent		x (in patients who are still being monitored at their center)
Inclusion/exclusion criteria	x	
Retrospective collection of variables	x	
Collection of anthropometric and sociodemographic variables	x	
Collection of laboratory variables	x	
Collection of post-surgical clinical evolution variables	x	