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The impact of a secondary diagnosis of Substance-Related Disorders as a comorbidity in Eating Disorders hospitalisations in public hospitalisations in Portugal from 2008 to 2015

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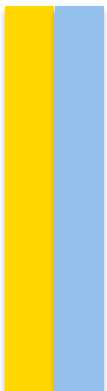

The impact of a secondary diagnosis of Substance-Related Disorders as a comorbidity in Eating Disorders hospitalisations in public hospitalisations in Portugal from 2008 to 2015

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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Porto, maio de 2025

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Resumo

Introdução: De acordo com a literatura, os pacientes com Perturbações Relacionadas com Substâncias (PRSs) e Perturbações do Comportamento Alimentar (PCAs) têm mais comorbilidades mentais e a sua coexistência afeta o prognóstico e evolução clínica dos pacientes, e acontece com alguma frequência, uma vez que partilham múltiplas caraterísticas, como a sensibilidade à recompensa, a impulsividade, défices da função executiva e desregulação emocional.

Objetivos: Este artigo teve como objetivo caraterizar o impacto do diagnóstico secundário de PRSs como comorbilidade nos internamentos públicos de PCAs a nível nacional. Para além disso, propusemo-nos também aprofundar e investigar este tema em particular, uma vez que raramente é alvo de investigação no nosso país.

Métodos: Realizámos uma análise observacional retrospetiva utilizando uma base de dados pública de hospitalizações que recolheu todos os episódios de internamento com um diagnóstico primário de PCAs de 2008 a 2015, disponibilizada pela Administração Central do Sistema de Saúde do Ministério da Sáude (ACSS).

Resultados: A nossa análise encontrou um total de 1517 episódios associados a PCAs, associados a 1042 doentes, durante um período de 7 anos, contemplado neste estudo. A maioria destes internamentos foi devido a pacientes do sexo feminino. Adicionalmente, verificámos que a probabilidade de coexistência de um diagnóstico secundário de PRSs e de um ICC superior ou igual a 1 está aumentada (aOR para a idade à admissão= 1,1; p-value <0,001). A aOR para o sexo de um episódio com diagnóstico secundário de PRSs estar associado a um Período de internamento superior ou igual a 22 dias, é superior a 1 (aOR=1,96; p-value <0,001).

Conclusões: Para elucidar os critérios de internamento e a sua relação com o prognóstico, são necessários mais estudos.

Palavras-chave: Perturbações do Comportamento Alimentar, Perturbações Relacionadas com Substâncias, Impacto, Evolução Clínica do Paciente, Diagnóstico Primário e Secundário, Hospitalizações

Abstract

Introduction: Patients with both Substance-related Disorders (SRD) and Eating Disorders (EDs), according to existing literature, have more mental comorbidities and impacts prognosis and outcomes and come often hand in hand, as they share multiple characteristics such as reward sensitivity, impulsivity, executive function deficits and emotional dysregulation.

Objectives: This article aimed to characterize the impact of a secondary diagnosis of SRD as a comorbidity in public ED hospitalisations on a national level. Furthermore, we also wanted to further explore and research this particular topic because this is rarely a research focus in our country.

Methods: We conducted a retrospective observational analysis using a public hospitalisations database that collected all inpatient episodes with a primary EDs diagnosis from 2008 to 2015, made available to us by the Authority for Health Services of the Portuguese Ministry of Health (ACSS).

Results: Our analysis has found a total of 1517 episodes associated with EDs, associated with 1042 patients, during a period of 7-year period contemplated in this study. Most of these hospitalisations were from women. Additionally, we found that the likelihood of a secondary diagnosis of SRD and a CCI superior or equal to 1 coexisting is increased (aOR for age at admission= 1.1; p-value <0.001). The aOR for sex of an episode with a secondary diagnosis of SRD being associated with a LoS superior or equal to 22, is superior to 1 (aOR=1.96; p-value <0.001).

Conclusion: To elucidate hospitalisation criteria and their relationship to prognosis, more research is required.

Keywords: Eating Disorders, Substance-Related Disorders, Impact, Patient's Outcomes, Primary and Secondary Diagnosis, Hospitalisations

Abreviaturas

EDs- Eating Disorders

SRDs- Substance-Related Disorders

ACSS- Authority for Health Services of the Portuguese Ministry of Health

LoS- Length of Stay

DRG- Diagnostic-Related Groups

CCI- The Charlson Comorbidity Index

ECI- The Elixhauser Comorbidity Index

OR- Odds-Ratio

aOR- adjusted Odds-Ratio

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Introduction

In a society where the *media* and the Internet create a constant pressure for thinness and looking "good", Eating Disorders (EDs) have been increasingly mentioned in the scientific literature [1].

A chronic disturbance in eating behaviour that affects one's health or psychosocial functioning is what defines eating disorders. Anorexia nervosa, binge eating disorder, bulimia nervosa, pica, rumination disorder, other specified feeding and eating disorder, as well as avoidant/restrictive food intake disorder are among these disorders [2].

There are many different biological, social, and psychological components that contribute to eating disorders. Anorexia nervosa appears to have the highest genetic risk, although binge eating disorder and bulimia nervosa also tend to run in the family.

Risk factors for eating disorders might be unique to eating disorders or nonspecific, linked to the risk of psychiatric illness in general. Nonspecific risk factors include, but are not limited to, dysfunctional parenting practices and exposure to physical and/or sexual trauma [3].

According to Cruz and Gonçalves-Pinho et al., whose study contemplated data from Portuguese hospitals from 2000 to 2014, a total of 4,485 hospitalisations was found linked with EDs, representing 3,237 individuals. Over the course of the study period, the overall number of hospitalisations with related EDs stayed constant. However, there was an increase in the number of hospitalisations for both nonspecific ED and *Anorexia Nervosa*. For the first, there were 0.5 hospitalisations per 1 M people in 2000 and 9.8 in 2014, and for the latter, there were 12.8 in 2000 and 23.7 in 2014 [4].

These results, obtained in 2017, correspond to the last estimate found on the number of hospitalisations in Portugal for EDs, and it is not possible to obtain up-to-date information after this year, on the prevalence of this diagnosis in Portugal.

In the general population, this problem also persists and, according to a study published in 2021, which had the main objective of updating the prevalence of EDs in the general population, having 18 epidemiological studies carried out around the world as a reference, it was concluded that the lifetime and 1-year prevalence of these disorders in Western countries was 1.89% and 0.68%, respectively. However, this study also states that the prevalence of this type of disorder is probably underestimated and that not all types of EDs were included in the research [5].

Moreover, the literature shows that this diagnosis is often associated with other psychiatric disorders, in particular Substance-Related Disorders (SRDs). There are multiple characteristics

shared between these two, such as reward sensitivity, impulsivity, executive function deficits and emotional dysregulation [6].

Also, the self-medication hypothesis which states that people with eating disorders start misusing drugs to try to address their eating issues and to relieve the anxiety these issues generate may account another way to theoretically co-relate EDs with SRDs [7].

Excessive use of any substance can directly trigger the brain's reward system, which plays a role in creating memories and reinforcing behaviour. Rather than eliciting the reward system through adaptive behaviour, these drugs cause the reward system to become so strongly activated that regular activities can be disregarded. This is what defines the physiological mechanism of SRDs.

Ten distinct drug classes are included: alcohol; caffeine; cannabis; inhalants; opioids; sedatives, hypnotics, or anxiolytics; stimulants (as amphetamines, cocaine and others); hallucinogens (including distinct categories for phencyclidine [or similarly acting arylcyclohexylamines] and other hallucinogens); tobacco as well as other substances [2].

The European Commission's 2023 Report indicates that around 4% of Portugal's population suffers from alcohol and drug-related disorders, the latest epidemiological data specifically on SRD [8].

As for alcohol-related disorders as a comorbidity of EDs, a lifetime co-occurrence of around 25 to 34 per cent has been demonstrated, and alcohol is the substance most associated with EDs, particularly *binge eating*, which is mainly reported throughout adolescence [9]. In the case of *bulimia nervosa*, the substances of choice are cocaine, amphetamines and other stimulants [10].

Patients with both SRD and ED have more mental comorbidities, leading to increased prescription of mood stabilizers and increased reward-sensitivity compared to those with only an ED. This comorbidity also has a reported impact in prognosis and outcome, higher frequency of recurrence, aggravated health issues, have trouble responding to treatment, greater disability, and a high probability of early death [11-15].

The lack of extensive research on this particular topic may be limiting the discovery of more clinically relevant associations. Having this in mind, this article aims to characterize the impact of a secondary diagnosis of SRDs as a comorbidity in all public EDs hospitalisations registered in between the years of 2008 and 2015 on a national level.

Methods

Using a public hospitalisation database that collected all inpatient episodes with a primary EDs diagnosis from 2008 to 2015, we conducted a retrospective observational analysis.

The hospitalisation database in Portugal uses the International Classification of Diseases—Ninth Revision—Clinical Modification (ICD-9-CM). Both Table I and II show the codes used to retrieve the primary diagnosis and secondary diagnosis, in order of appearance.

As the code 307.59 (Other ED) covers many EDs, it was not used in our analysis.

The Portuguese hospitalisation database, which collects clinical and administrative data from hospitalisation episodes that took place in public hospitals, was made available to us by the Authority for Health Services of the Portuguese Ministry of Health (ACSS). Using an anonymous patient identification approach, the study unit was the hospitalisation episode for one part of the analysis and the patient for the other. Three variables were cross-referenced, namely sex, birth date, and place of residence (district, county, and parish), to determine the number of readmissions that took place during the study period. The data included only incorporates hospitals from the mainland, excluding Azores and Madeira.

Confounders, information bias, and selection bias were considered. Regarding selection bias, the researchers were not involved in clinical coding, and all data was anonymised.

Age at admission (all ages), sex, primary and secondary diagnosis of SRD, Length of stay (LoS), place after discharge, admission type, estimated hospital costs and the Charlson Comorbidity Index were among the characteristics considered.

In this study, the hospitalisations with a primary diagnosis of ED and with a secondary diagnosis of SRD were quantified, analysed and compared with those who only have a primary diagnosis and variables such as in-hospital mortality, length of stay (LoS), and Estimated Hospital costs for each episode, categorizing them into scheduled (elective) and unscheduled (urgent) admissions were used as outcomes and as impact influencers.

To determine the normality of the samples, we asked for kurtosis and skewness for numerical and scale variables in which the non-normal distribution was unclear, as it was the case of Age at admission.

For non-normally distributed continuous variables (Age at Admission, LoS, and Estimated hospital costs), the Mann Whitney-U test was employed, while the Chi-square ($\chi 2$) test was utilised for categorical variables (Sex, Place after discharge, Charlson Comorbidity Index (CCI),

Admission Type). When more than 20% of cells have expected cell count less than 5, the Fisher test was the one used in analysis.

For the estimated hospital costs, we used the respective Diagnostic-Related Groups (DRG) codes, being the Portuguese denomination "Grupos de Diagnóstico Homogéneos", that each episode was classified with and each one of them has an associated estimated weight and cost or DRG rate, having utilized only the latter for analysis. On the one hand, the clinical variables that influence the diagnosis grouping are the primay diagnosis, the surgical procedures, additional diagnosis. On the other hand, the administrative variables that affect these grouping are age, sex, place after discharge and weight (in new-borns) [16].

We also considered two comorbidity measurement tools invented by Charlson et al. and by Elixhauser et al., The Charlson Comorbidity Index (CCI) and The Elixhauser Comorbidity Index (ECI), respectively, frequently found codified in administrative data. The first one includes 17 diseases and takes into consideration the number and the severity of comorbid diseases and is a validated applicable method that rates them by their likely impact in prognostic, determining the survival rate in 1 year and 10 years in patients with multiple chronic conditions [17]. As for the second one, composed of 30 illnesses, was created to respond to some of the limitations of other measures, such as the one previously mentioned [18]. It is predicated on a thorough method of identifying comorbidities and distinguishes them from the main cause of hospitalisation, producing a broader set of comorbidities that can be applied to administrative data for a variety of conditions without additional refinement. The Enhanced ICD-9-CM Classification was used in this data base to codify both Elixhauser and Charlson list of comorbidities [19].

Both the quantity and severity of comorbid conditions are taken into consideration in the weighted index that was created, when regarding the CCI. The assigned weight for diseases was 1 (conditions with a relative risk $\geq 1.2 < 1.5$) for Myocardial infarct, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Dementia Chronic pulmonary disease, Connective tissue disease, Ulcer disease and Mild liver disease Diabetes.

As for conditions with a relative risk $\geq 1.5 < 2.5$ such as Hemiplegia, Moderate or severe renal disease, Diabetes with end organ damage, Any tumor, Leukemia and Lymphoma the value assigned was 2. As for Moderate or severe liver disease, as its weight is $\geq 2.5 < 3.5$. Lastly, the diseases Metastatic solid tumor and AIDS that had a weight of 6 or more, were scored with a weight of 6 [17].

In this article, we used the Chi-Square test between LoS and the Comorbidities present in the Charlson and Elixhauser lists and only the comorbidities with a statistical significance were

included in the analyses. As for the CCI, it was included as part of the logistical regression, as explained next.

We also dichotomized outcomes as present or absent. The variable LoS was cut at the overall sample median (<22 vs ≥22 days). All analyses were two-tailed. A p-value inferior to 0.05 was considered as statistically significant.

To measure associations between the secondary diagnosis of SRD and LoS or Admission type, we used logistic regression to calculate the Odds- Ratio (OR) and Odds-Ratio adjusted for age and sex (aOR). The T-Test was performed to compare the means of two groups in independent variables such as age at admission and sex, giving sense to how these variables are distributed on those groups. The dependent variables are the LoS (<22 vs ≥22 days), Admission type and CCI (<1 vs ≥1). This last variable was dichotomized this way has it translates has an episode being associated with one or more Charlson Comorbidities, ergo, expressing a different one year mortality rate, having a relative risk of at least 1.2 [17].

The IBM SPSS Statistics® v.30.0.0.0. for Windows (Armonk, NY: IBM Corp) was the tool selected to perform the statistical analysis.

Results

From 2008 to 2015, there were 1517 hospitalisations with a primary diagnosis of EDs.The year with the highest number of episodes recorded was 2013 (N=210) and the one with a lowest number of episodes was 2015 (N=174), the last year analysed (Table III). The total estimated cost of all the episodes was 9,549,501.7 €.

Table IV displays the primary characteristics of the population studied in this research.

The age mean of our sample is 22.7 years old, with a range of 0 to 95 years old and a standard deviation of 13.1. The majority of episodes were due to female patients (N=1372). The age at admission had a peak of episodes from 15 to 20 years old, therefore, during the last years of adolescence.

Only 2 patients dying from 2008 and 2015. Hence, the in-hospital mortality was not considered in any further analysis. The mean of Length of Stay (LoS) was 29.97 days. In terms of sex, women were associated with a longer LoS (p-value <0.001) when compared with men.

Also, using this statistical test, we were able to estimate that there is an association with statistical significance between Diabetes without complications (CCI) (p-value=0.014) or Diabetes, uncomplicated (ECI) (p-value=0.017), and the LoS (<22 vs ≥22 days). The episodes with

this comorbidity were associated with a LoS inferior to 22 days. Adding to this, we found the same association with Fluid and electrolyte disorders (ECI) (p-value=0.003) and Deficiency anemia (ECI) (p-value=0.04).

The frequency of episodes for each primary diagnosis code is as follows: for 307.1 is 1125, for 307.50 is 173, for 307.51 is 137, 307.52 is 3, 307.53 is 5 and, at last, for 307.54 is 74. Accordingly, the most prevalent ED is *Anorexia Nervosa,* followed by *Unspecified ED* and *Bulimia Nervosa*.

Out of totality of hospitalisations, 3.9% had a secondary diagnosis of SRD, as can be seen in Table III. 92,98% of the episodes with a secondary diagnosis analysed were of female sex (N=53). The trends in hospitalisations with SRD were the same as without SRD, as 2013 and 2015 were once again the years the highest and lowest number of episodes, respectively.

In table V, we can see the prevalence of a comorbid diagnosis of SRDs by diagnostic code related to the primary diagnosis of EDs. The ED codes most associated with a secondary diagnosis of SRD are 307.1, 307.51 and 307.50, respectively. These are the same codes already reported above, but the order of prevalence has switched in between Unspecified ED and *Bulimia Nervosa*, therefore, the second-mentioned has a higher frequency of SRD comorbid diagnosis.

When considering the frequency of episodes with any ICD9-CM Codes for Substance-Related Disorders individually, we found that there were 9 episodes coded with 303.X, 2 with 304.0X, 3 with 304.2X, 2 with 304.3X, 1 with 304.4X, 3 with 304.7X, 1 with 304.9X, 4 with 305.0X, 34 with 305.1X, 4 with 305.4X and 6 with 305.59X. This means that the substance most associated with hospitalisations was tobacco, followed by alcohol and other, mixed, or unspecified drugs.

No episodes were classified with the following codes: 304.1X, 304.6X, 304.8X, 305.3X, 305.5X, 305.6X, 305.7X nor 305.8X.

By running the Mann-Whitney U Test, it was possible to observe, with statistical significance (p-value <0.001), that the mean rank of the age at admission of the episodes with a secondary diagnosis of SRD (N=1215.5) is higher than the ones without this comorbidity (N=741.2), therefore these are associated with older ages. In fact, the median age in episodes with an absent SRD diagnosis was 17 years old compared to the other group, which was 35 years old.

About 66,7% of the episodes with a secondary diagnosis had a LoS of less than 22 days.

Using again the Mann-Whitney U Test, we found that the mean rank of the LoS of the episodes with a secondary diagnosis of SRD (N=640.4) was inferior to the other group of episodes (N=763.63), again with statistical significance (p-value=0.04).

After studying the association in between LoS (<22 vs ≥22 days) and the Secondary Diagnosis of SRDs (Absent or Present), we were able to show with a p- value=0.01 of significance that there is an association between the absence of the secondary diagnosis of SRD and a LoS inferior to 22 days. Neither this association or the one previously mentioned between sex and LoS are not statistically significative in hospitalisations with a secondary diagnosis of SRD.

The Odds-ratio of an episode with a secondary diagnosis of SRD being associated with a LoS superior or equal to 22, as described in Table VI, adjusted to sex, it is superior to 1 (aOR=1.96). Therefore, when sex is taken in consideration as a confounder, the presence of a secondary diagnosis of SRD is associated with an increased likelihood of a more extended stay (p-value <0.001).

When analysing the Odds-ratio adjusted to the age of admission of a hospitalisation with a secondary diagnosis of SRD being associated with an Unscheduled/Urgent admission, adjusted to the age at admission, it is inferior to 1 (aOR=0.99), that translates to episodes with this comorbid diagnosis being considered less urgent then without SRDs (p-value=0.02).

Furthermore, when taking into consideration the same confounder as above, the likelihood of an episode with the diagnosis of SRD being linked to a CCI superior or equal to 1 is increased (aOR= 1.1; p-value <0.001).

Regarding the estimated costs of hospitalisation, in 1260 episodes, it was estimated that their price was 7322. 9 € (83.1%). As seen in Table VII, 89.5% of the hospitalisations with a secondary diagnosis of SRD present had an estimated price of 7322. 9 €, as for the ones without a secondary diagnosis, the percentage was 82.8%. The DRG codes associated with more episodes were 753 (Rehabilitation for compulsive nutritional disorders), followed by 432 (Other mental disorders diagnosis) and 427 (Neurosis except the depressive ones).

The estimated totality of costs for episodes with a secondary diagnosis of SRD was 386,671.1€, compared to 9,162,830.6€ of the episodes without SRD.

In terms of median of Estimated costs, without SRD it was 6275.9 € (Standard deviation= 2305.8) and with SRD was superior, equal to 6783.7 (Standard deviation= 1664.5). Table VII illustrates the ED hospitalisation estimated costs, with or without SRD, by cost of episode.

Out of the 1517 episodes, 74 had an associated Charlson Index equal or superior to 1, as seen in Table IV. In table VIII, we can see the episode distribution by CCI.

The statistical analysis has shown a significant association between having a secondary diagnosis of SRD and having AIDS/HIV (CCI) with a p- value =0.04. The same has been shown with Renal Disease (CCI) (p-value=0.009).

It what regards the Place after Discharge, out of the 57 episodes with a comorbid diagnosis of SRD, 4 episodes continued in another in-patient institution and other 4 left the hospital against medical advice.

To estimate the number of episodes that may be due to the same patient, this study used a statistical method that accounts for the number of episodes that may be associated with the same age at admission, sex and place of birth, as previously mentioned in the methods section. With this method, we estimate that there were 475 duplicated cases and 1042 primary cases, which can translate in the fact that the estimated number of individuals responsible for the 1517 episodes is 1042.

Adding to this, thanks to a MatchSequence Sequential count of matching cases, it was possible to create a variable, within groups of identified duplicate cases, having accredited a sequential number which describes the order of each duplicate case within its group. Therefore, roughly calculating the number of readmissions per patients, earlier mentioned in the methods of this article. So, we found out that the maximum number of episodes corresponding to one patient was 15 and that 790 patients were associated with the minimum of 1 episode.

Out of the total number of duplicated episodes, 28.1% had a secondary diagnosis of SRD, compared to the 31.4% seen in the absence of this comorbid diagnosis. However, there was no statistically significant difference between the two groups.

Discussion

Our analysis has found a total of 1517 episodes associated with EDs, associated with 1042 patients, during a period of 7-year period contemplated in this study. Most of these hospitalisations were from women, as already seen in 2017 by Cruz and Gonçalves-Pinho et al.

The mean age at admission is 22.7 years old and the median was 18, meaning that 50% of the hospitalisations happened while the patient was underage. This is compatible with existing literature, emphasizing puberty as critical period for the development of this disorders [20]. Clearly, a younger population that compared to the one in the article mentioned (mean age of 25.7 years old). Also, the median LoS was 22 days, 10 days superior to what was registered by these authors.

The most common diagnosis out of all of the ED hospitalisations was *Anorexia Nervosa* followed by Unspecified ED and *Bulimia Nervosa*, the same reported in the previously mentioned bibliography [4].

Unlike seen in existing published articles, there was a low mortality rate, which may be explained by the low number of episodes associated with a secondary diagnosis of SRD [12,21].

When considering the variable sex in ED-SRD hospitalisations, there were more episodes attributed to female patients than to males, data concordant with existing literature. This can also be since most episodes in our studied sample (with or without SRD comorbid diagnosis) were also due to females [22].

Additionally, the LoS median for ED-SRD episodes is inferior to just ED episodes, however, 4 of these episodes were very short due to Discharge against medical advice, as the median of LoS of these 4 episodes was 1.5 days. This can be one of the reasons that justifies this difference, as this is a known Place after discharge, mentioned in existing articles [23].

The OR adjusted for age at admission has shown to be > 1 when the secondary diagnosis of SRD and a CCI superior or equal to 1 are linked. This means that the likelihood of both coexisting is increased (aOR= 1.1; p-value <0.001). The increased comorbidity rate in patients with SRD diagnosis has already been discussed in articles, such as Bahorik et al.. However, there is not a much research documenting the prevalence of comorbidities in patients with coexisting ED and SRD [24].

When touching the important topic of the limitations of this work, one that deserves a special note is the under registration and mis or under diagnosis of SRDs, as they can be sometimes overlooked, resulting in “diagnosis overshadowing”, where some symptoms of SRDs are wrongly attributed to the existing mental or physical disease of the patient, or even not questioned when the patients are hospitalised, besides the fact that the ICD-9-CM is outdated [25,26]. As well as the fact that many patients might not know the exact amount of different substances that were consumed if, for example, they have purchased “mixtures” from drug dealers, or even the consumed substance not being yet codified, has New Psychoactive Substances (NPSs) are identified every year by the European Union Drugs Association, thus resulting in the episode being mis-classified [27].

Also, using the DRG codes, we only have an estimate value of costs and not the real one, which can affect our results. Since 2016, these codes are created based on the ICD-10-CM, instead of the ICD-9-CM, which can impact this estimate. Besides these, and in spite the fact that there are

several internal and external audits from the Portuguese Health Ministry to control the quality of the clinical registration of the episodes, the DRG codes depend on the quality of these. For that reason, if it has not been done correctly, it may have impacted the estimation of the costs analysed in this article.

Although in the context of our country, most ED hospitalisations are in the public system, given that our sample only consists of inpatients treated in public hospitals and excludes hospitalisations in the private sector, the research unit and the patient identifier method are significant limitations.

The number of duplicated episodes can be explained by the fact that EDs are diseases that are difficult to manage. There are no specific guidelines to follow when it comes to its treatment, so the patients will have to learn how to live with the disease and create coping mechanisms to adapt, resulting in dealing with it for most of their lives and having perhaps multiple episodes due to it [2]. However, it is only an estimate based on the almost impossibility of the coexistence of two patients of the same sex, age and place of birth; therefore, it is not an absolute number. Moreover, the primary cases may be duplicate cases from the years prior to the study period.

Now, addressing the strengths of this article, it is to our knowledge that this is the first time that both ED-SRD episodes are thoroughly and specifically analysed using this data base, as well as in this study period, at a national level.

The pros of having data from all the Portuguese hospitals in the mainland is that they are more comprehensive and therefore more representative of the population of Portugal, resulting in a more accurate set of findings.

Conclusions

Information about ED-related hospitalisations in Portuguese public hospitals associated with a secondary diagnosis of SRD is provided by our study. To elucidate hospitalisation criteria and their relationship to prognosis, more research is required.

To overcome the constraints imposed by their lesser prevalence, it would be crucial to compare the trends reported in other nations with our own. Also, it would be crucial to analyse more recent data, as the last year analysed in this article is 2015, which was 10 years ago, and the population characteristics may have significantly changed by now.

Appendix

ICD-9-CM code	Classification
307.1	*Anorexia Nervosa*
307.50	Unspecified ED
307.51	*Bulimia Nervosa*
307.52	Pica
307.53	Rumination Disorder
307.54	Psychogenic Vomiting

Table I: ICD-9-CM related to EDs and used for Primary Diagnosis [28].

ICD-9-CM code	Classification
303	Alcohol dependence syndrome
303.0X	Acute alcoholic intoxication
303.9X	Other and unspecified alcohol dependence
304	Drug dependence
304.0X	Opioid type dependence
304.1X	Sedative, hypnotic or anxiolytic dependence
304.2X	Cocaine dependence
304.3X	Cannabis dependence
304.4X	Amphetamine and other psychostimulant dependence
304.5X	Hallucinogen dependence
304.6X	Other specified drug dependence
304.7X	Combinations of opioid type drug with any other
304.8X	Combinations of drug dependence excluding opioid type drug
304.9X	Unspecified drug dependence
305	Nondependent abuse of drugs
305.0X	Alcohol abuse
305.1	Tobacco use disorder
305.3X	Hallucinogen abuse
305.4X	Sedative, hypnotic or anxiolytic abuse
305.5X	Opioid abuse

305.6X	Cocaine abuse
305.7X	Amphetamine or related acting sympathomimetic abuse
305.8X	Antidepressant type abuse
305.9X	Other, mixed, or unspecified drug abuse

Table II: ICD-9-CM related to SRDs and used for Secondary Diagnosis [28].

Year	Studied Population (Total) (N)	Hospitalisations without secondary SRD (N)	Hospitalisations with secondary SRD (N)	Hospitalisations with secondary SRD (%)
2008	188	184	4	2.17
2009	186	181	5	2.76
2010	182	177	5	2.83
2011	184	178	6	3.37
2012	201	189	12	6.35
2013	210	196	14	7.14
2014	192	184	8	4.3
2015	174	171	3	1.75
Total	**1517**	**1460**	**57**	**3.9**

N: Number of hospitalisation episodes; SRD: Substance-Related Disorder

Table III: Trends in hospitalisations with and without a comorbid Substance-Related Disorder per year (2008–2015)

Variable	Studied Population (Total)	Without	With SRD
Hospitalisation Episodes, N	1517	1460	57
Age at admission, years old, Median (Q1;Q3)	18 (14;27)	17 (14;26)	35 (27.5;39.5)
Sex, N (%)			
Female	1372 (90.44%)	1319 (90.34%)	53 (92.98%)
Male	145 (9.56%)	141 (9.66%)	4 (7.02%)
Admission type, N (%)			
Scheduled	565 (37.2%)	539 (36.9%)	26 (45.6%)
Unscheduled/ Urgent	952 (62.8%)	921 (63.1%)	31 (54.4%)
Place after discharge, N (%)			
Home	1393 (91.8%)	1344	49

Other in-patient institution	71 (4.7%)	67	4
Home Service	2 (0.1%)	2	0
Discharge against medical advice	49 (3.2%)	45	4
Death	2 (0.1%)	2	0
Length of Stay (LoS), days, Median (Q1;Q3)	22 (8;42)	22 (8;42)	17 (5;27.5)
Estimated costs, €, Median, (Q1;Q3)	7322.9 (7322.9; 7322.9) *	7322.9 (7322.9; 7322.9) *	7322.9 (7322.9; 7322.9) *
The Charlson Comorbidity Index (CCI), N (%)			
0	1443	1392 (95.3%)	51 (89.5%)
≥ 1	74	68 (4.7%)	6 (10.5%)

N: number of hospitalisations

*Q1 and Q3 are equal to the median as 83.1% of the total amount of episodes have the same DRG code (753), and so the same estimated cost.

Table IV: Population characteristics.

ED diagnosis	Without SRD diagnosis	Percent (%)	With SRD diagnosis	Percent (%)	Total
Anorexia Nervosa	1083	96.3	42	3.7	1125
Unspecified ED	170	98.3	3	1.7	173
Bulimia Nervosa	127	92.7	10	7.3	137
Pica	3	100	0	0	3
Rumination Disorder	4	80	1	20	5
Psychogenic Vomiting	73	98.7	1	1.3	74
Total	**1460**		**57**		**1517**

Table V: Prevalence of a comorbid diagnosis of SRDs by diagnostic code related to the primary diagnosis of EDs.

	LoS ≥ 22	Unscheduled/ Urgent admission (2)	Charlson Index ≥ 1

	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value
Any ICD9-CM Codes for SRDs	0.5(0.3–0.9) 0.3	0.8(0.5-1.3) 0.4	1.4(0.6-3.4) 0.5
	LoS ≥ 22	**Unscheduled/ Urgent admission (2)**	**Charlson Comorbidity Index (CCI) ≥ 1**
	aOR(95%CI) p-value	**aOR(95%CI) p-value**	**aOR(95%CI) p-value**
Age at admission	0.99(0.98-0.99) 0.3	0.99 (0.98-0.999) 0.02	1.1(1.0-1.1) <0.001
Sex	1.96(1.4-2.8) <0.001	0.7(0.5-1.1) 0.1	0.998(0.4-2.5) 0.1

LoS: Length iof stay; OR: Odds Ratio; aOR: Adjusted Odds Ratio; CI: Confidence Interval.

Table VI: Outcomes in ED hospitalisations considering the presence of comorbid SRD.

Estimated Costs (€)	Without SRD	Percent (%)	With SRD	Percent (%)
1061.54	169	11.6	2	3.5
1471.30	77	5.3	2	3.5
1879.38	3	0.2	0	0
2717.35	0	0	1	1.8
5418.16	1	0.1	1	1.8
5649.88	1	0.1	0	0
7322.94	1209	82.8	51	89.5
Total	**1460**	**100.0**	**57**	**100.0**

Table VII: Costs of ED hospitalisations with or without the secondary Diagnosis of SRD.

CCI	N	Percent (%)
0,00	1443	95.1
1,00	45	3.0
2,00	16	1.1
3,00	10	0.7
4,00	1	0.1
5,00	1	0.1
6,00	1	0.1
Total	**1517**	**100.0**

Table VIII: Number of Episodes associated with a CCI.

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