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ARTICLE

Association between hospital admission for ketoacidosis and subsequent suicide attempt in young adults with type 1 diabetes

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Abstract

Aims/hypothesis The aim of this study was to examine the associations between hospitalisation for diabetic ketoacidosis and subsequent hospitalisation for suicide attempt in young adults with type 1 diabetes.

Methods This nationwide historical cohort study included hospital data on all young people hospitalised in France for type 1 diabetes in 2008. Epidemiological follow-up focused on hospitalisations (medical and psychiatric hospital data) from the index hospitalisation to 2017. Survival analyses were done using a Cox proportional hazards regression model to explore the association between hospitalisation for ketoacidosis and subsequent hospitalisation for a suicide attempt.

Results In 2008, 16,431 people aged 18–35 years had a hospitalisation mentioning type 1 diabetes. Among them, 1539 (9.4%) had at least one hospitalisation for ketoacidosis between 2008 and 2010. At 9 years, 7.2% of the group hospitalised for ketoacidosis had been hospitalised for a suicide attempt vs only 2.5% in the group not hospitalised for ketoacidosis. The association between hospitalisation for ketoacidosis and suicide attempt decreased over time and was no longer significant after 5 years.

Conclusions/interpretation We found that young adults admitted to hospital for diabetic ketoacidosis have an increased risk of being admitted to hospital for a subsequent suicide attempt. The risk of a suicide attempt was the highest in the 12 months following the ketoacidosis episode. Our findings support the recommendation that screening for depression and suicide risk should be part of the routine clinical assessment of individuals with type 1 diabetes and ketoacidosis.

Keywords Depression · Diabetes complications · Hospital data · Suicide attempt · Type 1 diabetes

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Abbreviations
PHQ Public Health Questionnaire

Introduction

Diabetic ketoacidosis is a frequent and serious complication in patients with type 1 diabetes mellitus. The most common precipitating causes of diabetic ketoacidosis are poor adherence to insulin therapy, infection and newly diagnosed diabetes mellitus [1]. In the same way, psychiatric disorders have a negative influence on blood glucose monitoring, which is also associated with an increased risk of diabetic ketoacidosis [2, 3]. A recent study suggested that people with type 1 diabetes and persistent elevated symptoms of depression were more likely to experience diabetic ketoacidosis [4]. Moreover, the risk of a

Research in context

What is already known about this subject?

- Psychiatric disorders have a negative influence on blood glucose monitoring and are associated with an increased risk of diabetic ketoacidosis
- Little is known regarding the risk of suicide attempts in young people with diabetes, particularly when there is past history of hospitalisation for diabetic ketoacidosis

What is the key question?

- Are episodes of ketoacidosis associated with the occurrence of suicide attempts in young people with type 1 diabetes?

What are the new findings?

- Our results showed that young people with type 1 diabetes and a history of hospitalisation for diabetic ketoacidosis have an increased risk of hospitalisation for suicide attempt in the 9 years following the index hospitalisation
- The risk of suicide attempt is highest in the 12 months following the ketoacidosis episode

How might this impact on clinical practice in the foreseeable future?

- Our findings fully support the recommendation that screening for depression and suicide risk evaluation should be part of the routine clinical assessment of patients with type 1 diabetes and ketoacidosis

suicide attempt is increased in individuals with depressive symptoms and psychiatric disorders, while the risk of suicidal/death ideation is higher in youths and young adults with type 1 diabetes [5]. These data indicate that there is a need for effective strategies to decrease suicide risk in this population, particularly because mental disorders tend to be a neglected comorbidity.

Suicide prevention could be improved if physicians were made aware of the specific warning signs for suicide risk in individuals with type 1 diabetes. Unfortunately, though it is recommended by the ADA, the symptoms of distress, depression and suicidal ideation in people with type 1 diabetes are not systematically assessed in Europe [6]. Thus, we lack reliable data regarding the risk of suicide attempt in this population, particularly when there is a past history of hospitalisation for diabetic ketoacidosis. For this reason, it seemed relevant to evaluate whether episodes of diabetic ketoacidosis could be warning signs for suicide risk. The aims of this study were therefore to examine the association between episodes of diabetic ketoacidosis and the occurrence of a suicide attempt in young adults with type 1 diabetes.

Methods

Study population The principle of this nationwide historical cohort study was to examine the hospital data of all young adults (aged 18–35 years) hospitalised for type 1 diabetes in France in 2008. Data from the French hospital database were provided by the French national agency for the management of hospitalisation data (*Agence Technique de l'Information sur l'Hospitalisation* [ATIH] no. 2015-111111-47-33). The French hospital database includes discharge abstracts for people hospitalised in all public or private hospitals in France. The discharge abstract contains individual information, including the WHO ICD-10 codes (http://apps.who.int/classifications/icd10/browse/2016/en) for the main and associated diagnoses.

People with type 1 diabetes were identified on discharge abstracts with the codes E10 ('insulin-dependent diabetes mellitus'), E12 ('malnutrition-related diabetes mellitus'), E13 ('other specified diabetes mellitus') and E14 ('unspecified diabetes mellitus') as the main, related or associated diagnoses.

To reduce the risk of including people with type 2 diabetes, we only recruited individuals aged 35 years or younger. We used age in addition to ICD-10 codes in order to comply with the findings of the REDSIAM network working group dedicated to endocrine disorders. REDSIAM was set up to promote the collaboration of teams working on the French national information system and it develops and validates algorithms used to identify specific diseases [7]. The 'endocrine disorders' working group has collated, described and analysed some of the algorithms used to identify people with diabetes in France.

For each individual, the first hospitalisation in 2008 mentioning type 1 diabetes was considered the index hospitalisation. People who died during the index hospitalisation were excluded. This hospitalisation was either the first hospitalisation for the diagnosis of type 1 diabetes or a follow-up for previously diagnosed type 1 diabetes. Among the people included following hospitalisation in 2008, we identified subsequent hospitalisations for non-inaugural ketoacidosis (ICD-10 codes E10.1, E12.1, E13.1 or E14.1 as the main,

related or associated diagnoses) until 2010. We then defined two groups: young adults with hospitalisation for ketoacidosis and young adults without hospitalisation for ketoacidosis. Epidemiological follow-up focused on medical and psychiatric hospital data from the index hospitalisation to 2017.

Outcomes The main outcome of interest was hospitalisation for a suicide attempt, identified by at least one main, related or associated ICD-10 diagnosis code from X60 to X84. As this study was retrospective and registry based, we were unable to assess the degree of suicidal intent present in those with self-injury and these presentations were likely along the spectrum from suicide attempt to self-harm with no suicidal intent at all. We use the term 'suicide attempt' to cover this range of intent underlying the behaviour in the absence of a preferred term.

Confounding variables

The following variables were assessed during the index hospitalisation for all people included in the study: age and sex. Psychiatric disorders were identified for the years 2007 and 2008, before or during the index hospitalisation. Psychiatric history included acute or chronic depressive disorders and psychosis (ICD-10 codes F20 ['schizophrenia'], F32 ['depressive episode'], F33 ['recurrent depressive disorder'], F31.3 ['bipolar affective disorder, current episode mild or moderate depression'], F31.4 ['bipolar affective disorder, current episode severe depression without psychotic symptoms'], F31.5 ['bipolar affective disorder, current episode severe depression with psychotic symptoms']).

Statistical analysis Qualitative variables were expressed as percentages. Comparisons were made between persons with and without ketoacidosis using the Pearson χ^2 test or Fisher's exact test as appropriate. The groups were compared at 1, 2, 3 and 9 years after the index hospitalisation. Then, after adjustment for age, sex and history of psychiatric disorders, survival analyses were performed using a Cox proportional hazards regression model to explore the association between hospitalisation for ketoacidosis and subsequent hospitalisation for a suicide attempt. We followed individuals until hospitalisation for a suicide attempt, the end of the 9 year follow-up period, or death, whichever came first.

A ketoacidosis event that occurred during the epidemiological follow-up was considered a time-dependent covariate, meaning that it was only considered if it occurred before a potential hospitalisation for a suicide attempt. We then included an interaction between time and the exposure to ketoacidosis. The time lapse was the period of time between the first hospitalisation for ketoacidosis and the first hospitalisation for a suicide attempt. To estimate the risk of a recurrent ketoacidosis event, we created a second model in which we added both the first and the second ketoacidosis exposure as time-dependent covariates. We were then able to estimate, both separately and overall, the impact of the first and the second ketoacidosis events on the risk of hospitalisation for a suicide attempt. The results are reported as adjusted HRs and 95% CIs. Statistical significance was set at a p value of 0.05 for all analyses. SAS software was used for the data analyses (SAS Institute, Version 9.4, Cary, NC).

The present study was approved by the French Institute of Health Data and by the French data protection authority, which did not require informed consent for the use of registry data.

Results

In 2008, 16,431 persons aged 18–35 years were admitted to hospital with type 1 diabetes. Between 2008 and 2010, 1539 (9.4%) individuals from the initial population had at least one hospitalisation for ketoacidosis. The individuals' characteristics at the index hospitalisation are presented in Table 1. People with ketoacidosis were younger and more likely to have a history of psychiatric illness. There was no significant difference for gender.

At nine years, individuals with type 1 diabetes who were hospitalised for ketoacidosis were more likely to have been hospitalised for a subsequent suicide attempt (7.2% vs 2.5%). The number of hospitalisations for a suicide attempt was significantly higher in the ketoacidosis group (Table 1). In individuals with ketoacidosis, 4.7% were hospitalised once for a suicide attempt and 2.5% at least twice. Comparatively, only 1.8% of patients without a ketoacidosis event were hospitalised once for a suicide attempt and 0.8% at least twice ($p < 0.0001$) (Table 1). Table 2 shows the risk of hospitalisation for suicide attempt associated with recurrent episodes of ketoacidosis. The rate of hospitalisation for a suicide attempt in people with vs without ketoacidosis was 2.2% vs 0.5% at 1 year of follow-up, 3.0% vs 0.8%. at 2 years of follow-up and 4.5% vs 1.1% at 3 years of follow-up. The methods used for suicide attempts were not significantly different between the two groups: nearly 90% of the entire population hospitalised for suicide attempt used self-poisoning (Table 3).

Psychiatric history was strongly associated with subsequent hospitalisation for a suicide attempt. During the 9 years of follow-up, 16.2% of people with a past history of psychiatric disorders and diabetic ketoacidosis were hospitalised for a suicide attempt.

The survival analyses are presented in Table 4. After adjustment for age, sex and psychiatric history, at least one hospitalisation for ketoacidosis was associated with subsequent hospitalisation for a suicide attempt (HR 2.22 [95% CI 1.73, 2.83]). Sex and age at index hospitalisation were not associated with a subsequent hospitalisation for suicide attempt but a psychiatric history was strongly associated with

Table 1 Characteristics of diabetic individuals hospitalised for ketoacidosis and frequency of hospitalisation for suicide attempt over 9 years of follow-up

Characteristic	Ketoacidosis ($N = 1539$)		No ketoacidosis ($N = 14,892$)		p value
	n	%	n	%	
Age, years					
18–22	577	37.5	3542	23.8	<0.0001
23–27	422	27.5	3671	24.7	
28–31	309	20.1	3337	22.4	
32–35	231	15.0	4342	29.2	
Sex					
Male	710	46.1	7223	48.5	0.08
Female	829	53.9	7669	51.5	
Subsequent hospitalisation for suicide attempt					
Any attempt	111	7.2	383	2.5	<0.0001
0 attempts	1428	92.8	14,509	97.4	<0.0001
1 attempt	73	4.7	263	1.8	
≥2 attempts	38	2.5	120	0.8	
History of psychiatric disorders	162	10.5	662	4.5	<0.0001

The p value was determined by χ^2 test for categorical data

this event (HR 5.27 [95% CI 4.23, 6.53]). At 1 year, the risk of hospitalisation for suicide attempt for people with type 1 diabetes previously hospitalised for ketoacidosis was 4.68 (95% CI 2.59, 8.48) after adjustment, and it was 3.19 (95% CI 2.25, 4.52) at 3 years.

When we added an interaction between time and the exposure to ketoacidosis to the model, the association between hospitalisation for ketoacidosis and suicide attempts decreased over time and was no longer significant after 5 years (Table 5 and Fig. 1). When we included both the first and the second ketoacidosis exposure in a model as time-dependent covariates, the risk of hospitalisation for suicide attempt after the first ketoacidosis event was not significantly modified after accounting for the second ketoacidosis event. The risk for a second ketoacidosis event was similar to the risk for a single ketoacidosis event (data not shown).

Discussion

To the best of our knowledge, this is the largest study aiming to determine whether diabetic ketoacidosis episodes could be associated with hospitalisation mentioning a suicide attempt. Our results showed that people with type 1 diabetes and a history of hospitalisation for diabetic ketoacidosis have an increased risk of being hospitalised for a suicide attempt in the 9 years following the index hospitalisation. The risk of suicide attempt is highest in the 12 months following the ketoacidosis episode, and 7% of the total type 1 diabetes population was hospitalised for at least one suicide attempt within the study period. We also observed that during the 9 years of follow-up, an alarming 16.2% of people with a past history of psychiatric disorders and ketoacidosis hospitalisation were hospitalised for suicide attempt. Approximately 0.2% of people living in France are hospitalised for a suicide attempt every year [8]. Our study found a strongly increased prevalence of suicide attempts in people with type 1 diabetes and ketoacidosis hospitalisation as well as in people with type 1 diabetes without ketoacidosis hospitalisation, as previously reported [9].

It is clear that the functional disabilities and comorbidities that often accompany diabetes can lead to a decreased quality of life that could increase the risk of depression and suicidal thoughts [10]. In type 1 diabetes, depression and psychiatric disorders are associated not only with an increased risk of suicide attempts but also with an increased risk of hospitalisation for glycaemic disorders [4, 11]. Suicidal ideation is a common feature of depression and it is well known that depression is two to three times more prevalent in people

Table 2 Hospitalisation for suicide attempt associated with recurrent episodes of ketoacidosis

Hospitalisation for suicide attempt	No. of ketoacidosis episodes			
	0	1	2	≥3
Individuals hospitalised for suicide attempt, n (%)	382 (2.6)	67 (6.5)	23 (8.2)	21 (9.1)

Risk of hospitalisation for suicide attempts associated with recurrent episodes of ketoacidosis

Table 3 Self-harm methods in people hospitalised for suicide attempts in the groups with or without ketoacidosis

Self-harm method	Suicide attempt in people with ketoacidosis ($N = 111$)		Suicide attempt in people without ketoacidosis ($N = 382$)		p value
	n	%	n	%	
Self-poisoning	97	87.4	344	90.1	0.42
Self-harm by sharp or blunt objects	5	4.5	23	6.0	0.39
Hanging, strangulation and suffocation	3	2.7	5	1.3	0.65
Other method	6	5.4	10	2.6	0.22

p value was determined by χ^2 or the Fisher's exact probability test for categorical data

with type 1 diabetes than it is in the general population [11–14]. Major depressive disorders have been found in 11.4% of patients with diabetes and clinically significant depressive symptoms appear to be more common in people with diabetes, affecting an estimated 31.0% [13]. As expected, the increased prevalence of depression in type 1 diabetes is also associated with an increased risk of suicide [10, 14–16]. A recent meta-analysis suggested that the RR of suicide associated with type 1 diabetes is 2.25 [10], yet the underlying mechanism remains poorly understood.

This study found no association between female sex and suicide attempts. Though it may seem surprising, this observation does not appear to be specific to people with type 1 diabetes since previous studies in populations with specific psychiatric and physical disorders did not find an increased risk of suicide attempt in women compared with men [17]. Johnson et al. found consistent evidence that severe symptoms of depression were associated with higher levels of HbA_{1c} in people with type 1 diabetes [11]. One recognised pathway between depression, suicidal ideation and ketoacidosis is impaired glycaemic control, and a recent longitudinal study has suggested a relationship between depression symptoms and blood-glucose-related outcomes over time [18]. The authors found a relationship between changes in depression symptom status and likelihood of diabetic ketoacidosis (diabetic ketoacidosis in 10.0% with persistent elevated depressive symptoms and 6.5% with new-onset elevated depressive symptoms vs 1.6% in non-depressed group, $p < 0.001$) [18]. In the Type 1 Diabetes Exchange Clinic Registry, participants with higher depression scores were more likely to miss insulin doses and experience diabetic ketoacidosis [4]. Likewise, the results of the Diabetes-specific Cognitive Behavioral Treatment Program (DIAMOS) study suggested that reduced depression symptoms could explain improved glycaemic control [19]. One explanation for our results is that higher incidence of diabetic ketoacidosis and suicide attempts were both related to depression and mental illnesses. In young adults with diabetes, depression has a clear influence on glycaemic control and the occurrence of diabetic ketoacidosis, and at the same time it encourages suicidal ideation. This may explain the association between hospitalisation for diabetic ketoacidosis and the higher incidence of suicide attempts observed in our results.

It is possible, however, that the emotional distress linked to hospitalisation for ketoacidosis induces or aggravates depressive symptoms, leading to an increased risk of suicide attempts. Unfortunately, causality cannot be determined in this study: we do not know whether a hospital stay for ketoacidosis increases the likelihood of depression and suicide attempt or whether being depressed and at increased risk of suicide influences self-care, leading to hospital admission for ketoacidosis.

Table 4 Survival analyses adjusted for age, sex and history of psychiatric disorders on the risk of suicide attempt at 9 years in individuals with type 1 diabetes hospitalised vs not hospitalised for ketoacidosis

Adjustment	HR	95% CI
One ketoacidosis episode before first SA (ref. = 0)	2.22	1.73, 2.83
Age, years (ref. ≥23 years to 27 years)		
18–22	0.93	0.72, 1.21
28–31	1.00	0.78, 1.31
32–35	1.26	0.99, 1.59
Sex (ref. = female)	0.92	0.77, 1.10
History of psychiatric disorders (ref. = 0)	5.27	4.23, 6.53

SA, suicide attempt

Table 5 Survival analyses adjusted for age, sex and history of psychiatric disorders on the risk of hospitalisation for suicide attempt with interaction between time and the time lapse between the first hospitalisation for ketoacidosis and a subsequent hospitalisation for a suicide attempt

Adjustment	p value
Ketoacidosis	<0.0001
Ketoacidosis × time lapse	0.0006
Age (classes)	0.12
Sex	0.14
History of psychiatric disorders	<0.0001

The data in the table are for a time lapse of 1 month. To explore the time variation between the first hospitalisation for ketoacidosis and the first hospitalisation for a suicide attempt, the time lapse was varied between 1 month and 108 months (see Fig. 1)

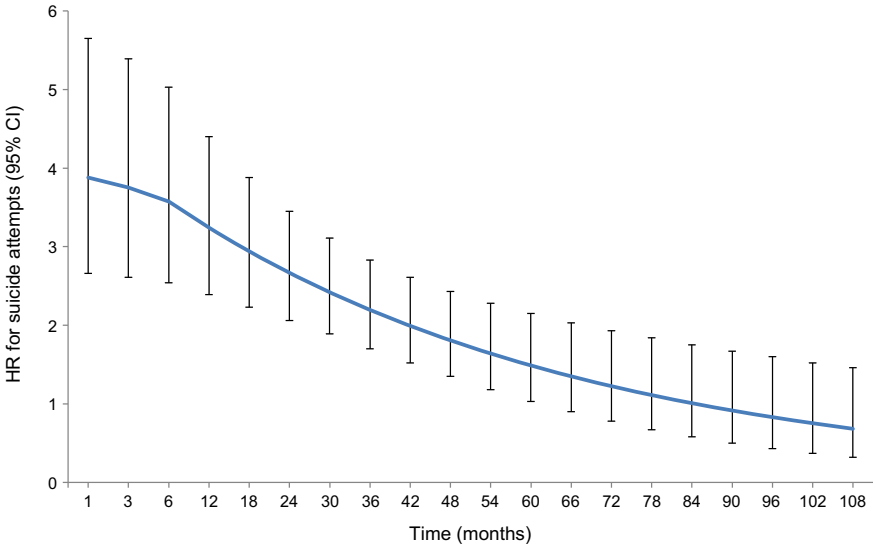

Fig. 1 Interaction between time and the time lapse between the first hospitalisation for ketoacidosis and a subsequent hospitalisation for a suicide attempt. Results are statistically significant when the CI does not include or cross 1

The identification of risk factors is crucial for developing effective suicide prevention strategies, and healthcare professionals need to be made aware of the higher risk of suicide in certain subgroups of patients. The primary implication of our study is that all people with type 1 diabetes hospitalised for diabetic ketoacidosis and hyperglycaemic coma should be screened for depressive symptoms and suicidal ideation. It is also important to find the most appropriate tools with which to screen and detect depression and suicidal ideation in these patients. The ADA recommends the Patient Health Questionnaire (PHQ) as a valid and relevant depression screening and monitoring tool for people with diabetes [6]. The PHQ-8 is a standardised and validated measure of self-reported depression symptoms and their severity. It has been used in numerous patient-based studies, including several focused on diabetes [4, 5, 18, 20]. Suicidal ideation can be measured using item nine of the nine-item PHQ-9, which asks respondents to rate the frequency of 'thoughts that you would be better off dead, or of hurting yourself in some way' over the previous 2 weeks [21]. With the PHQ-9, a suicidal ideation rate of 14.3% was observed in people with diabetes (sevenfold higher than in the general population) [13]. The Position Statement of the ADA recommends an assessment of symptoms of diabetes distress, depression and anxiety during the initial medical consultation, at periodic intervals, and when there is a change in disease, treatment or personal circumstances [6]. Considering the increased risk of suicide attempt following hospitalisation for ketoacidosis, our results suggest the need for systematic evaluation of depression symptoms and suicidal ideation whenever a person with type 1 diabetes is hospitalised for ketoacidosis.

Moreover, in our study, we found that people with a history of psychiatric disorders and ketoacidosis had an extremely high risk of attempting suicide in the year following their hospital stay. We showed previously that people diagnosed with both type 1 diabetes and schizophrenia had a higher risk of hospitalisation for acute diabetes complications, suicide and hospital mortality [3]. Our results strongly suggest that any hospitalisation for ketoacidosis in people with type 1 diabetes and a history of psychiatric illness should automatically lead to a psychiatric assessment in an effort to minimise the risk of suicide after hospital discharge. Collaboration between endocrinologists and mental health professionals should also be promoted.

One of the strengths of this study is the population-based design using the French hospital databases, which provided detailed epidemiological information and allowed us to collect 9 years of follow-up data after the index hospitalisation. We do acknowledge that our work has limitations. First, we limited patient age to 35 years in an attempt to select only those with type 1 diabetes mellitus. We cannot exclude that a few individuals with type 2 diabetes may also have been mistakenly included in our study. However, because type 2 diabetes is rare in individuals under 35 years of age, the number possibly included in our study is likely to be limited. Second, the diagnoses were based on hospital reports only, and the quality of these diagnoses cannot be guaranteed. Third, we did not have access to information about other comorbidities such as previous suicide attempts, drug addiction, alcohol abuse, socioeconomic status, glycaemic control, blood glucose monitoring or the frequency of missed insulin doses. These confounding factors could limit the interpretation of our results. Fourth, we did not include the whole population of individuals with type 1 diabetes in France in our study. According to data from the French national information system, published by The National Agency for Public Health, 40,382 patients aged 18–34 years were treated with insulin in 2012. Thus, the 16,431 patients hospitalised in 2008 and included in our study represent approximately 40% of people with type 1

diabetes aged 18–34 years in France. However, the French hospital database used in our study includes discharge abstracts for people hospitalised in all public or private hospitals in France. Thus, we can assume that all people with type 1 diabetes hospitalised in France for ketoacidosis were included in our study. Fifth, hospitalisation for suicide attempt might be considered to represent the greatest severity in either lethality of injury or severity of mental disorder considering that treatment for a suicide attempt does not systematically result in hospitalisation. Consequently, the suicide attempts that were not severe enough to warrant admission to hospital were not included in our study. Finally, our data source limited our analysis to hospitalised individuals only, and the occurrence of death from suicide without hospital admission was not detected. These limitations must be considered.

In conclusion, our study suggests that hospitalisation for ketoacidosis is a warning sign for suicide risk in young adults with type 1 diabetes. Our findings fully support the recommendation that screening for depression and suicide risk should be part of the routine clinical assessment of patients with type 1 diabetes and ketoacidosis. This paper represents an important step in better defining the prevalence of suicide attempts in this at-risk population and we believe that our findings are significant as they are based on data from all young people hospitalised in France for type 1 diabetes. We expect that the identification and treatment of depression in younger adults with diabetic ketoacidosis could lead to a reduction in suicide attempts.

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Data availability The use of these data by our department was approved by the National Committee for data protection. We are not allowed to transmit these data. PMSI (Programme de médicalisation des systèmes d'information) data are available for researchers who meet the criteria for access to these French confidential data (this access is subject to the approval of the National Committee for data protection) from the national agency for the management of hospitalisation (ATIH: *Agence Technique de l'Information sur l'Hospitalisation*).

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