



# Association between anxiolytic/hypnotic drugs and suicidal thoughts or behaviors in a population-based cohort of students

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## ABSTRACT

**Aims:** To investigate the association between the use of anxiolytic/hypnotic drugs and suicidal thoughts and/or behavior (STB) in students.

**Methods:** 12,112 participants who completed the baseline questionnaire in the i-Share cohort between April 2013 and March 2017 were included. STB were defined at inclusion as suicidal thoughts over the previous year and/or a lifetime suicide attempt. The use of prescribed anxiolytic/hypnotic drugs over the previous 3 months was measured at baseline and follow-up time points (in 2,919 students). Psychiatric disorders were assessed through validated scales. Multivariate logistic regression models were run using disease risk score.

**Results:** At inclusion, 25.2% of students had STB and 10.3% used anxiolytics/hypnotics. STB at baseline were associated with a more frequent use of anxiolytics/hypnotics in the previous 3 months, after adjustment for covariates including anxiety, depression, sleep, impulsivity, and substance use. The use of anxiolytics/hypnotics at baseline was not associated with the occurrence, persistence or remission of STB one year later. STB at baseline were associated with a new anxiolytic/hypnotic treatment one year later.

**Conclusions:** Anxiolytic/hypnotic drug use was associated with STB in students independently of many risk factors of suicide and most psychiatric disorders that require such treatment, which raises drug safety concerns.

## 1. Introduction

Young adults are vulnerable to suicidal thoughts and behaviors with a short- and long-term impact (Goldman-Mellor et al., 2014; Mortier et al., 2015). According to the World Health Organization (WHO, 2014), suicide is the second cause of death among people 15–29 years old worldwide. Suicide attempts are also particularly frequent in this age group (Kessler et al., 1999). Thus, a meta-analysis estimated that 3.2% of students presented with a history of lifetime suicide attempt, and 10.6% with suicidal thoughts in the previous 12 months (Mortier et al., 2017). It therefore appears relevant to identify risk and protective factors for suicidal thoughts and behavior in this population such as prescription opioid misuse (Davis et al., 2019). Indeed, many drugs are labeled with warnings from regulatory agencies related to suicide risk. Paradoxically, many of these drugs are psychotropic drugs that are approved to treat psychiatric disorders or symptoms known to increase the occurrence of suicidal thoughts or behavior (Nazir et al.,

2014; Tournier, 2016).

Some recent studies have shown that benzodiazepines or Z-drugs have frequently been used prior to suicide death (Ahlm et al., 2013; Darke et al., 2012), thus suggesting that these drugs might trigger suicidal thoughts and/or behavior (Brower et al., 2010; Darke et al., 2012; Dodds, 2017; Saunders and Hawton, 2009; Shih et al., 2013). These studies found a positive and significant association between benzodiazepines and suicidal behaviors. However, they did not demonstrate any causality owing to methodological issues, such as confounding bias as suicidal behavior is a multifactorial process. Particularly, as suicidal behaviors might be linked to the condition treated, confounding by indication bias might occur (Costa et al., 2019; McCall et al., 2017; Panes et al., 2018; Zeng et al., 2018). Indeed, no study has shown a prospective association while controlling for depression, insomnia and anxiety symptoms (McCall et al., 2017). Furthermore, previous studies did not take into account other risk factors that may be associated both with medication use and suicide, e.g.

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substance use or temperament traits such as impulsivity, aggression and coping strategies (Conner et al., 2019; Gvion and Apter, 2011).

Mechanisms that might be involved in a potential causal association remain unclear. They might be direct (disinhibition, impairment of judgement through cognitive disturbances, dissociative behavior) or indirect (via depression, rebound insomnia or anxiety) (McCall et al., 2017). Some authors suggested that measuring this association might lead to a nocebo effect if patients knew about this potential and rare adverse event (Ruan et al., 2017). It was suggested that drugs targeting some GABA-A receptors might be involved (McCall et al., 2017). The roles of repeated withdrawal and of long-term lowering of the brain activation level that might limit the ability to compensate some pre-existing cognitive disturbances remain unknown (Pariente et al., 2016). Moreover, the relationship between zolpidem and suicide was shown cumulative, starting after 80 months of exposure (Cho et al., 2020). Similarly, patients with anxiety disorders had a decreased risk of suicide when they filled benzodiazepines in short-moderate compared with long-term treatment (Boggs et al., 2020). A dose effect was also shown with zolpidem related to the suicide risk in general population (Sun, 2016). Finally, concurrent use of benzodiazepines, antidepressants, and opioid analgesics with zolpidem increased the risk of suicide compared with the use of zolpidem alone (Sung HG, 2019). It was equally suggested that the use of other substances such as alcohol or MDMA might increase the risk of dissociative or impulsive behavior (Darke et al., 2012).

The use of anxiolytic and hypnotic drugs is not infrequent in young adults. In the USA, 2.6% of people age 18–35 were prescribed benzodiazepine in 2008 with 14.7% of long-term use (Olsson et al., 2015). In college students, 1% and 2% of college students received anti-anxiety and sleep medication drugs respectively (Eisenberg et al., 2007). The College Student Life Survey (CSLS) was conducted during a one-month period, drawing on the total undergraduate population of full-time students attending a large public research university located in the Midwest United States in the winter semesters of the 2003, 2005, 2007, 2009, 2011 and 2013 school years (McCabe et al., 2014). Lifetime medical use of sleeping medication increased from 6.4% to 7.4%, and past-year medical use varied between 2.9% in 2003 and 4% in 2009. Lifetime medical use of anxiety medication increased from 6.7% to 8.8% and past-year medical use from 2.9% to 4.3%. As suicidal thoughts and behaviors are a major public health concern in this population, it is of utmost importance to clarify the role of anxiolytic and hypnotic drugs with respect to suicide risk, taking numerous confounding factors into account.

The study was conducted to assess the association between the use of prescribed anxiolytic or hypnotic drugs and suicidal thoughts or behaviors in a cohort of university students. To minimize confounding

by indication, we took numerous risk factors for suicide behaviors into account, in particular psychiatric symptoms or disorders that might require these treatments such as depression, anxiety, impulsivity, aggression, substance use and insomnia. Secondary objectives were to explore the association (i) between the use of anxiolytic or hypnotic drugs at baseline and the occurrence, persistence or remission of suicidal thoughts or behaviors at follow-up, and (ii) between the history of suicidal thoughts or behaviors at baseline and the occurrence of anxiolytic or hypnotic drug use at follow-up.

## 2. Methods

### 2.1. Study design and study population

Cross-sectional assessments were conducted in a national prospective population-based cohort study with public funding, the ongoing Internet-based Students Health Research Enterprise (i-Share) project (Montagni et al., 2016). This project assesses students' health in French-speaking universities and higher education institutions by self-administered online questionnaires (Figure S1). Students register voluntarily for the study and complete a mandatory baseline questionnaire online. An optional mental health survey is sent to them three months after completing the baseline questionnaire in order to investigate psychiatric disorders, personality and temperament traits using psychometric scales (see section "Other collected variables"). A follow-up questionnaire is then sent to them one year after inclusion to assess health care use, suicidal thoughts and behaviors among other items. Inclusion criteria for the i-Share cohort are the following: i) officially registered at a university or higher education institute, ii) at least 18 years old, iii) able to read and understand French. All participants provided informed consent. The study population included all participants who fully completed the baseline questionnaire between April 2013 and March 2017. Within the cohort, three populations were studied independently: all included students (i.e. students having completed the baseline questionnaire), those also having completed the optional mental health questionnaire and those having completed both baseline and follow-up questionnaires.

### 2.2. Exposure to anxiolytic/hypnotic drug, suicidal thoughts and behaviors

The main variables were exposure to anxiolytic/hypnotic drugs and suicidal thoughts and behaviors; points of measurement over the study period are shown in Fig. 1. They were explored through the baseline and follow-up questionnaires. Drug use was assessed within the previous three months at each contact. Anxiolytic drugs were defined as medications "against anxiety or stress (during the day)" and hypnotics

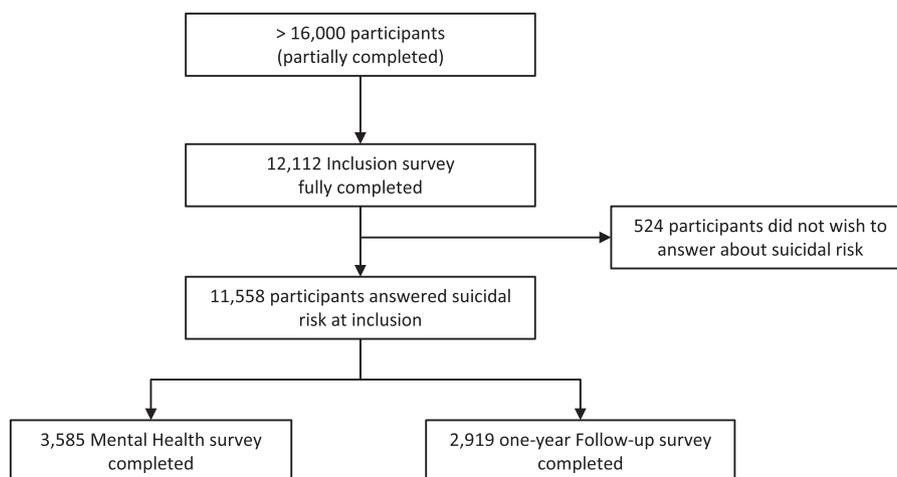


Fig. 1. Flowchart of the study population.

as medications “to sleep”: “Within the past 3 months, have you ever taken medications for anxiety, anguish or stress (in the day time) / to sleep? Was this drug obtained on medical prescription?”. Drug classes and names of products were unknown. Drugs were considered only when they were reported as prescribed to the participant by a physician. Thus, drugs obtained over the counter were not considered. The variable of interest was the use of at least one prescribed anxiolytic or hypnotic drug over the 3-month period.

The baseline questionnaire investigated the presence of suicidal thoughts over the previous 12 months (“Over the 12 preceding months, have you ever thought about killing yourself (suicidal thoughts)?”) as well as lifetime suicide attempts (“Over your lifetime, did you ever attempt suicide?”). Time windows were different since suicidal thoughts are more common and considered as less severe than suicide attempts. Suicide attempts are the main risk factor for suicide, even several years after (Bostwick et al., 2016; Suominen et al., 2004). The variable “suicidal thoughts and/or behaviors (STB)” was defined as the presence of at least one of the two factors. To select students at high and current suicide risk, a variable “suicidal thoughts and behaviors” was considered for sensitivity analyses and corresponded to students who had both suicide thoughts over the previous 12 months and at least a lifetime suicide attempt. The follow-up questionnaire investigated the presence of suicidal thoughts and attempts over the previous 12 months. Incident STB were identified in the sub-population having completed the follow-up questionnaire and were defined as the presence of suicidal thoughts and/or behaviors at follow-up (thoughts and/or attempt over the previous year) and none at baseline. In the same sub-population, persistent STB corresponded to the presence of STB at baseline and the presence of suicidal thoughts and/or suicide attempt over the previous year at follow-up, while remission corresponded to the presence of STB at baseline and their absence over the previous year at follow-up.

### 2.3. Other collected variables

Covariates were collected through the baseline and the mental health questionnaires. We selected *a priori* risk factors for STB that could also be associated with use of anxiolytics or hypnotics to limit confounding. They related to participants’ characteristics: i) socio-demographic characteristics: age, sex, year of study (categorized in four groups: 1st, 2nd, 3rd or higher year of university), scholarship, siblings, accommodation (with his/her parent(s), university residence, apartment), living alone, being an orphan, divorced parents, paid employment; ii) dissatisfaction with living conditions: regarding recreational opportunities, relationships with parents, social life and financial resources; iii) use of health care over the previous year: at least one consultation with a general practitioner (GP), at least one consultation with a psychiatrist, psychologist or psychotherapist, avoiding an appointment with the GP or not buying prescribed medication although it was necessary/recommended; iv) health status: disability, at least one physician-diagnosed somatic disease, at least one physician-diagnosed psychiatric disease, and exposure to a traumatic life event causing intense fear; v) family history: parental history of depression, anxiety disorders or alcoholism; vi) health behaviors: unhealthy BMI ( $\leq 18$  kg/m<sup>2</sup>, 18–30,  $\geq 30$  kg/m<sup>2</sup>), regular physical exercise (WHO, 2010), practicing a team sport; vii) sleep disturbances: global sleep quality (poor/not poor), difficulty in falling asleep/maintaining sleep (more/less than once a week), feeling extremely sleepy during the day (more/less than 3 to 5 times per week), usual lack of sleep with at least one hour less than necessary (more than a few times a week/once a week or less); and viii) substance use: smoking status, alcohol use (more than 4 times a week/3 times a week or less), cannabis use (more/less than once in the previous year), at least one lifetime use of another substance, or at least one use of doping products during competitions or exam periods. The use of other psychotropic medication drugs was not available in the database.

The mental health questionnaire consisted of nine psychometric scales: a perceived stress assessment adapted to the student population (17 items based on four main factors: academic stress, dysfunctions at university, feelings of loneliness, and problems with close relations) (Boujut and Bruchon-Schweitzer, 2009); a scale assessing coping strategies in 16 items divided in three parts: search for social support, emotional coping, festive and addictive coping (Boujut et al., 2012); the Spielberger trait anxiety inventory (STAI-YA): feelings of apprehension, tension, nervousness and anxiety (Spielberger and Vagg, 1984); the adolescent version of the Barratt Impulsivity Scale (BIS-11-A) based on a three-dimensional structure: motor (behavior), attentional (cognitive) and lack of planning (Baylé et al., 2000); the Life History of Aggression (LHA) including nine items considering aggressive behavior in adolescence and adulthood (Coccaro et al., 1997); the Patient Health Questionnaire (PHQ-9) based on DSM IV diagnostic criteria (Arthurs et al., 2012; Kroenke and Spitzer, 2002) to assess a current major depressive episode of at least moderate intensity (score  $\geq 10$ ); the Mood Disorder Questionnaire (MDQ) to screen bipolar disorders (at least 7 lifetime manic or hypomanic symptoms, several co-occurring symptoms, and moderate or serious associated functional impairment) (Weber Rouget et al., 2005); the Rosenberg self-esteem scale, which includes 10 items on a four-point Likert scale (Alessandri et al., 2015); and a short version of Cloninger’s Temperament and Character Inventory (TCI) with 56 items that allow the creation of 6 scores, including temperament traits (novelty-seeking, harm avoidance, dependence on reward and persistence), and character traits (determination and cooperation) (Pelissolo et al., 2005). Concerning MDQ and PHQ-9 scores, validated thresholds made it possible to obtain binary variables (presence/absence). For the other scales, quantitative scores were transformed into binary variables (high/low) using the median obtained in the study population as threshold, since thresholds validated in different populations might not be appropriate in students.

### 2.4. Statistical method

All statistical analyses were performed by using SAS (version 9.4; SAS Institute Inc, Cary, NC, USA) statistical software. First, we carried out descriptive analyses of the study population. Participants who had also completed the mental health questionnaire were compared with those who did not using univariate tests, the Pearson Chi2 test for qualitative variables and the Student test for quantitative variables. Completers of the follow-up questionnaire were compared with non-completers. Second, covariates were summarised in disease risk scores (DRS) in order to control for a large number of confounding variables (Tadrous et al., 2013). Then, several multivariate logistic regression models were run to assess the association between prescribed anxiolytic/hypnotic drugs and STB.

The first model assessed the association between STB and the use of prescribed anxiolytic/hypnotic drugs at baseline in the whole population, adjusting for a DRS including all covariates explored through the baseline questionnaire. Three sensitivity analyses were performed for this model: i) for the first one, “suicidal thoughts and/or behaviors”, i.e. STB, were replaced by “suicidal thoughts and behaviors”; ii) the second one was conducted in participants having completed the optional mental health questionnaires to add these covariates to the DRS for this model; and iii) for the third one, all covariates were individually included in the model (TableS1).

The three other models were run for participants who had completed the follow-up questionnaire. The first one assessed the association between incident STB (absence at baseline and presence at follow-up) and the use of prescribed anxiolytics/hypnotics at baseline, adjusting for a DRS including all covariates explored through the baseline questionnaire, in students without STB at baseline. The second one assessed the association between persistent STB (presence at baseline and at follow-up) and the use of prescribed anxiolytics/hypnotics at baseline, adjusting for a DRS including all covariates explored through

the baseline questionnaire, in students with STB at baseline. The last one investigated the association between the use of prescribed anxiolytic/hypnotic drugs at follow-up and STB at baseline, adjusting for a DRS including all covariates explored through the baseline questionnaire. For these models, sensitivity analyses were performed individually including covariates in the models (Table 5).

All covariates were defined *a priori* according to their clinical relevance. Variables with more than 20% missing data were eliminated from all models. For sensitivity analyses individually including all covariates, all interactions were tested and the suitability of the model was verified with the Hosmer-Lemeshow test, and its discriminating power was calculated by computing the area under the ROC curve.

### 3. Results

A total of 12,112 students completed the i-Share baseline questionnaire. Among them, 3585 students fully completed the mental health questionnaire and were then identified as the “mental health subgroup”. Finally, 2919 students completed the follow-up questionnaire and were considered as the “follow-up subgroup”. flowchart is shown in Fig. 1.

#### 3.1. Description of study population

Among the 12,112 students enrolled in the i-Share cohort, 97.5% students answered questions on suicide thoughts and attempts ( $n = 11,588$ ). STB were identified in 2916 students (25.2%), nearly 22% reporting suicidal thoughts in the past 12 months, and 6.2% a lifetime suicide attempt (Table 1). These students are described in Table 2 according to the presence or not of STB. In both groups, most participants were women, and more than one-third were in the first year. Both groups were similar in terms of age (mean 20.4 years; SD 2.6). Students with or without STB at baseline had different characteristics regarding nearly all sociodemographics, health care use and health status, apart from age, having siblings and a paid job. In particular, the use of prescribed anxiolytic and/or hypnotic was nearly three times higher among students with STB than among students without STB (Table 2).

#### 3.2. Description of sub-population who completed the mental health questionnaire

The sub-sample who completed the mental health questionnaire was compared to the students who did not (data not shown). Completers

were slightly different from the others. The main differences concerned scholarship (62% in whole group vs 67% in mental health subgroup,  $p < 0.0001$ ) and smoking (34% vs 26%,  $p < 0.0001$ ). Almost all mental health scores were very different in students with or without STB at baseline, with poorer mental health in students with STB than in those without (Table 3). However, seeking social support as a coping strategy and planning difficulties were similar across the groups, as well as some temperament traits such as novelty-seeking, harm avoidance and reward dependence.

#### 3.3. Cross-sectional association between use of anxiolytic/hypnotic drugs and STB

STB at baseline were associated with the use of prescribed anxiolytic/hypnotic medications at baseline, after adjustment for all covariates (Table 4). This association persisted in sensitivity analyses after adjustment for mental health characteristics in the subgroup of students who completed the mental health questionnaire. The co-existence of suicidal thoughts and behaviors was also associated with the use of anxiolytic/hypnotic drugs. Similar results were found when covariates were individually included in the models sensitivity analyses (Table 5).

#### 3.4. Longitudinal associations between use of anxiolytic/hypnotic drugs and STB

At the follow-up, incident STB were 7.1% and almost 47% of students with STB at baseline still had them. The sub-sample who completed the follow-up questionnaire was compared to students who did not (data not shown). Completers were slightly different from the others. The main differences concerned scholarship (60% among non-completers vs 78% among follow-up subgroup,  $p < 0.0001$ ) and smoking (35% vs 26%,  $p < 0.0001$ ).

No association was found between the prescription of anxiolytic/hypnotic medication at baseline and incident STB one year later in students without STB at inclusion or the persistence of STB at follow-up (Table 4). On the contrary, there was a significant association between STB at baseline and a new use of prescribed anxiolytic/hypnotic drugs at follow-up (aOR 1.80; 95%CI 1.20–2.71). This model showed a 80% increase in new use of prescribed anxiolytic/hypnotic at follow-up after self-reported STB at baseline. The same result was found when covariates were individually included in the model in sensitivity analysis (aOR 1.9; 95%CI 1.1–3.3).

**Table 1**  
Suicidal thoughts and behaviors at baseline and at follow-up.

	Number of students with available information	N	(%)
<b>At baseline (n = 12,112)</b>			
Suicidal thoughts in previous 12 months	11,664	2603	22.3
Lifetime suicide attempt	11,791	732	6.2
Total suicidal thoughts and/or behaviors (STB) <sup>a</sup>	11,588	2916	25.2
Suicidal thoughts and behaviors <sup>b</sup>	11,867	419	3.5
<b>At time of follow-up in whole population (n = 2919)</b>			
Suicidal thoughts in previous 12 months	2799	483	17.3
Suicide attempt in previous 12 months	2812	18	0.6
Suicide attempt and/or thoughts in previous 12 months	2799	491	17.5
<b>At time of follow-up in students with suicide risk at baseline (n = 718)</b>			
Persistent suicidal thoughts and/or behaviors <sup>c</sup>	685	321	46.9
<b>At time of follow-up in students with no suicide risk at baseline (n = 2106)</b>			
Suicidal thoughts in previous 12 months	2029	139	6.8
Suicide attempt in previous 12 months	2037	6	0.3
Incident suicidal thoughts and/or behaviors <sup>d</sup>	2029	145	7.1

<sup>a</sup> suicidal thoughts in preceding year and/or lifetime suicide attempt.

<sup>b</sup> suicidal thoughts in preceding year and lifetime suicide attempt.

<sup>c</sup> Suicidal thoughts and/or behaviors at baseline and suicidal thoughts and/or attempt in preceding year at follow-up.

<sup>d</sup> No suicidal thoughts nor behaviors at baseline and suicidal thoughts and/or attempt in preceding year at follow-up.

**Table 2**Description of the whole study population according to presence of suicidal thoughts and/or behaviors at baseline ( $n = 11,588$ ).

	n <sup>a</sup>	Students without STB (n = 8672) n (%)	Students with STB (n = 2916) n (%)	Chi-2 T-test p
<b>Prescribed anxiolytics/hypnotics in preceding 3 months</b>	11,588	643 (7.4)	554 (19.0)	< 0.0001
<b>Sociodemographic characteristics</b>				
Age [mean (SD)]	11,588	20.4 (2.6)	20.4 (2.7)	0.67
Sex (woman)	11,588	6412 (73.9)	2254 (77.3)	0.0003
Year of study	11,588			< 0.0001
1		3321 (38.3)	1289 (44.2)	
2		1691 (19.5)	556 (19.1)	
3		1324 (15.3)	394 (13.5)	
4 or more		2336 (26.9)	677 (23.2)	
Scholarship	11,316	5361 (63.2)	1898 (67.0)	0.0003
Siblings	11,459	7838 (91.4)	2611 (90.5)	0.1
Accommodation	11,588			< 0.0001
With his/her parent(s)	2770 (31.9)	868 (29.8)		
University residence	943 (10.9)	428 (14.7)		
Apartment		4655 (53.7)	1503 (51.5)	
Orphan (at least one parent)	11,588	413 (4.8)	179 (6.1)	0.004
Divorced parents	11,235	2502 (29.7)	1095 (39.0)	< 0.0001
Paid employment	11,588	2951 (34.0)	1010 (34.6)	0.6
<b>Dissatisfaction with living conditions</b>				
Relationship with parents	11,588	634 (7.3)	567 (19.4)	< 0.0001
Financial resources	11,588	1614 (18.6)	837 (28.7)	< 0.0001
Recreational opportunities	11,588	1885 (21.7)	954 (32.7)	< 0.0001
Social life	11,588	1215 (14.0)	787 (27.0)	< 0.0001
<b>Use of health care over previous year</b>				
Consultation with GP	11,587	7436 (85.7)	250 (87.1)	0.07
Consultation with mental health professional	11,467	741 (8.6)	770 (26.8)	< 0.0001
Avoiding GP consultation	11,588	2804 (32.3)	1445 (49.6)	< 0.0001
Not buying prescribed medications	11,588	1726 (19.9)	926 (31.8)	< 0.0001
<b>Health status</b>				
Somatic illness <sup>b</sup>	11,588	3030 (34.9)	1257 (43.1)	< 0.0001
Psychiatric illness <sup>c</sup>	11,588	1417 (16.3)	1250 (42.9)	< 0.0001
Parental history of depression /anxiety/alcohol use disorder	10,243	3321 (42.9)	1614 (64.7)	< 0.0001
Disability	11,588	230 (2.7)	128 (4.4)	< 0.0001
Traumatic event that caused intense fear	11,481	2646 (30.8)	1315 (45.6)	< 0.0001
<b>Health behavior</b>				
Physical regular activity	11,566	8135 (94.0)	2667 (91.7)	< 0.0001
Practicing a team sport	11,588	1235 (14.2)	302 (10.4)	< 0.0001
BMI	10,962			< 0.0001
≤ 18 kg/m <sup>2</sup>	706 (8.6)	277 (10.1)		
18 - 30 kg/m <sup>2</sup>	7323 (89.7)	2344 (85.6)		
≥ 30 kg/m <sup>2</sup>		194 (2.36)	118 (4.3)	
<b>Sleep disturbances</b>				
Poor quality of sleep	11,588	1556 (17.9)	949 (32.5)	< 0.0001
Difficulty falling asleep/maintaining sleep	11,585	3522 (40.6)	1703 (58.4)	< 0.0001
Daytime sleepiness	11,586	3586 (41.4)	1712 (58.7)	< 0.0001
Usual lack of sleep	11,588	4227 (48.7)	1764 (60.5)	< 0.0001
<b>Substance use</b>				
Doping products	11,588	1874 (21.6)	776 (26.6)	< 0.0001
Tobacco	11,588	2468 (28.5)	1114 (38.2)	< 0.0001
Alcohol	11,588	351 (4.1)	150 (5.1)	0.01
Cannabis	9187	2143 (31.2)	969 (41.9)	< 0.0001
Other drugs <sup>d</sup>	11,570	3016 (34.8)	1085 (37.3)	0.02

STB: suicidal thoughts and/or behaviors; GP: general practitioner.

<sup>a</sup> Number of students with available information;<sup>b</sup> including migraine, chronic inflammatory bowels disease, multiple sclerosis, type 1 diabetes, asthma, juvenile arthritis;<sup>c</sup> including depression, attention deficit/hyperactivity disorder, obsessive compulsive disorder, anxiety disorders or anorexia;<sup>d</sup> at least one lifetime use of another substance among ecstasy, MDMA, amphetamines, nitrous oxide, inhalant, cocaine, magic mushrooms (or other hallucinogenic plants), crack, free-base, heroin, LSD, or ketamine.

## 4. Discussion

### 4.1. Main findings

This study conducted in a large student population is the first one to show an association between the use of prescribed anxiolytic/hypnotic medication and STB, even when considering psychiatric disorders and symptoms including depression, anxiety, perceived stress, sleeping disorders, impulsivity and substance use. Another striking finding is the high number of students found to have STB.

Indeed, more than one out of five students reported suicidal

thoughts over the year preceding the baseline questionnaire. This rate was higher than in a recent meta-analysis assessing suicidal thoughts among college students (10.6%, 95%CI 9.10;12.25) (Mortier et al., 2017), but similar to the frequency described among US undergraduate students (24%) (Liu et al., 2019) or in medical students over the same duration (24.2%, 95%CI 13.0;40.5) (Rotenstein et al., 2016). The frequency of lifetime suicide attempts was also nearly two-fold higher in the present study than in the findings of the meta-analysis (1.2%, 95%CI 0.83;1.59) (Mortier et al., 2017) but lower than in a study using the same design (9%) (Liu et al., 2019). As inclusion in the i-Share cohort is voluntary and its objective is to assess students' health

**Table 3**  
Description of mental health characteristics according to presence of suicidal thoughts and/or behaviors at baseline (n = 3585).

N = 3585	Students without STB (n = 2566) - n (%)	Students with STB (n = 898) - n (%)	Chi-2 p
<b>High level of perceived stress</b>	1250 (46.5)	577 (64.3)	<0.0001
<b>Coping strategies</b>			
Emotional	1315 (48.9)	591 (65.8)	<0.0001
Festive-addictive	1320 (49.1)	475 (52.9)	0.05
Seeking social support	1707 (63.5)	571 (63.6)	0.9
<b>High level of impulsivity</b>			
Motor	1546 (57.5)	574 (63.9)	0.0008
Cognitive	1350 (50.2)	605 (67.4)	<0.0001
Planning difficulties	1541 (57.4)	490 (54.6)	0.2
<b>Low self-esteem</b>	1103 (41.1)	537 (59.8)	<0.0001
<b>High level of anxiety</b>	1283 (47.8)	559 (62.3)	<0.0001
<b>Bipolar disorder</b>	102 (3.8)	108 (11.7)	<0.0001
<b>Major depressive episode</b>	421 (15.7)	372 (41.4)	<0.0001
<b>High level of aggression</b>	1243 (46.3)	558 (62.1)	<0.0001
<b>Temperament and character</b>			
Novelty-seeking	1425 (53.0)	492 (54.8)	0.4
Persistence	1318 (49.1)	486 (54.1)	0.009
Harm avoidance	1369 (51.0)	460 (51.2)	0.9
Determination	1214 (45.2)	653 (72.7)	<0.0001
Reward dependence	1718 (63.9)	576 (64.1)	0.9
Cooperation	1343 (50.0)	564 (62.8)	<0.0001

STB: suicidal thoughts and/or behaviors.

conditions, students concerned about health or having health problems, especially mental health disorders, might be over-represented in the sample. However, we cannot exclude an especially high frequency of suicide behaviors in French students compared with other countries, as already reported for deliberate self-harm (Brunner et al., 2014).

STB at baseline were associated with the use of a prescribed anxiolytic or hypnotic drug at inclusion when taking all other variables into account, including psychiatric disorders, anxiety, sleep disturbances, impulsivity and substance use. This minimized confounding and particularly confounding by indication. The association persisted when considering the co-existence of suicidal thoughts and behaviors. When students presented a history of suicide attempt and recent suicidal thoughts, they might be offered care more easily or they might be more likely to seek professional support.

STB at baseline were also associated with a new prescription of anxiolytic/hypnotic drugs at follow-up. Students with mental distress, and particularly suicidal thoughts or attempts, were likely to seek mental health care and, among other treatments, to receive a

**Table 4**  
Association between use of anxiolytic or hypnotic drugs at baseline and suicidal thoughts and/or behaviors at baseline or at follow-up (multivariate models).

	N <sup>a</sup>	n <sup>b</sup>	Use of anxiolytic or hypnotic drugs at baseline aOR <sup>c</sup>	95%CI	
STB at baseline	8073	1994	1.36	1.12	1.65
Suicidal thoughts and behaviors at baseline	7363	248	2.03	1.48	2.80
STB at baseline in students having completed mental health survey <sup>d</sup>	2277	527	1.33	1.05	1.69
Incident STB at follow-up in students with no STB at baseline	1353	101	1.09	0.50	2.38
Persistent STB at follow-up in students with STB at baseline	409	189	1.04	0.61	1.80

STB: suicidal thoughts and/or behaviors.

<sup>a</sup> Number of students with available information;

<sup>b</sup> Number of students with suicidal thoughts and/or behaviors;

<sup>c</sup> Odds ratio adjusted on all covariates: sociodemographic characteristics, dissatisfaction with living conditions, use of health care over previous year, health status, health behaviors, sleep disturbances and substances use;

<sup>d</sup> Odds ratio adjusted on all these covariates and on perceived stress, coping strategies, trait-anxiety, impulsivity, aggression, current major depressive episode, bipolar disorder, self-esteem, temperament and character traits.

prescription for anxiolytic/hypnotic drugs. This request for health care might be deferred and be formulated later than suicidal thoughts, because students might lack information about the availability of health care services (Montagni et al., 2017), or they might be worried about or suspicious of psychiatry and psychotropic drugs. They might wait until their distress is overwhelming before consulting. Moreover, only a few students with STB sought health care. Conversely, we did not find any association between the use of prescribed anxiolytic/hypnotic medication within the three months preceding the baseline questionnaire and the occurrence of STB or the persistence or remission at follow-up of STB already identified at the time of inclusion (Ribeiro et al., 2016). This suggests that the use of these drugs did not attenuate the students' STB.

Following the increase in suicide rates among young adults, the association between suicide and prescription drug use and misuse was assessed by few studies. Non-medical use of prescription drugs increased over years in college students except from painkillers (McCabe et al., 2014). A recent study carried on in college students found an association between suicidal ideation, suicide planning or suicide attempts with prescription opioid misuse (any use not prescribed) (Davis et al., 2020). Another study considered misuse of several drug classes and showed a unique association between suicidal ideation and misuse of stimulants (Zullig and Divin, 2012). In particular, misuse of benzodiazepines was not associated with suicidal ideation or suicide attempts. However, none of these studies investigated the impact of medical use of anxiolytics or hypnotics on STB in students.

#### 4.2. Limitations and strengths

These longitudinal analyses were performed in an exploratory way and several methodological limitations might have hampered the identification of such an association. A depletion of susceptible bias might be suspected, since considering only the occurrence of incident STB at follow-up excluded all students who presented with suicidal thoughts in the year prior to inclusion and who used anxiolytic/hypnotic drugs in the preceding three months; in other words, all students likely to present suicidal thoughts and/or behaviors when exposed to these drugs. Furthermore, a selection bias might be suspected, as many students were lost to follow-up. However, only slight differences were identified between completers and non-completers. Some other limitations should be considered. First, the abovementioned selection bias (registration in the cohort on a voluntary basis) might have modified the association only if it was differential. Second, students less likely to participate might have been students with STB (Mortier et al., 2018) and non-users of prescribed medications, which would tend to reduce the strength of the association that we identified. Third, there may have been a competitive risk because students who died by suicide were not

**Table 5**  
Association between use of anxiolytic or hypnotic drugs at baseline and suicidal thoughts and/or behaviours at baseline or at follow-up (multivariate models).

	N <sup>a</sup>	n <sup>b</sup>	Use of anxiolytic or hypnotic drugs at baseline aOR <sup>c</sup> 95%CI		
STB at baseline	8073	1994	1.46	1.2	1.8
Suicidal thoughts and behaviours at baseline <sup>e</sup>					
Parents not divorced	5162	142	1.26	0.8	2.0
Parents divorced	2201	106	2.48	1.5	4.1
STB at baseline in students having completed mental health survey <sup>d</sup>	2277	527	1.57	1.1	2.3
Incident STB at follow-up in students with no STB at baseline	1353	101	1.25	0.6	2.9
Persistent STB at follow-up in students with STB at baseline	409	189	1.04	0.6	2.0

STB: suicidal thoughts and/or behaviours.

<sup>a</sup> Number of students with available information;

<sup>b</sup> Number of students with suicidal thoughts and/or behaviors;

<sup>c</sup> Odds ratio adjusted on all covariates: sociodemographic characteristics, dissatisfaction with living conditions, use of health care over previous year, health status, health behaviours, sleep disturbances and substances use;

<sup>d</sup> Odds ratio adjusted on all these covariates and on perceived stress, coping strategies, trait-anxiety, impulsivity, aggression, current major depressive episode, bipolar disorder, self-esteem, temperament and character traits;

<sup>e</sup> a significant interaction led to stratification on having divorced parents or not.

identified. In fact, there was a 97% risk that a maximum of two students might have died from suicide during the follow-up. Fourth, the vagueness of the questions concerning drug use may have created an information bias. However, to minimize this risk, we considered only prescribed medications in order to exclude over-the-counter drugs such as herbal medicine and to select high-potency drugs. Similarly, STB were not assessed with a validated scale. Moreover, misuse of anxiolytics/hypnotics, defined as a use non-compliant with guidelines, was not considered in the study. A misuse similar to the one of opioid painkillers could happen among our population study and might have led to overestimate the association between STB and drug use. This bias was minimized as only drug use from medical prescription was selected, excluding the one borrowed from the entourage or used over the counter. Finally, residual confounding by indication bias might have led us to conclude erroneously about an association between drug use and suicide risk, since these drugs and suicide risk might be independently associated with the condition treated. Although most indications of these drugs were adjusted for, as well as other confounding factors, further studies are warranted to investigate clinical events occurring when such treatments are initiated and during the following weeks (Millner et al., 2017).

The main strengths of the study are its large number of participants and the number of explored variables. Many risk factors were assessed with validated tools including psychiatric disorders and symptoms, substance abuse and chronic somatic diseases. Many suicide protective factors such as social and family support and coping strategies were also investigated. In fact, the study was conducted in a large cohort who completed many relevant items. The use of a composite criterion (thoughts and/or behaviors) made it possible to consider those who had made an attempt without suicidal thoughts, which can be associated with the use of medication in youth (Copelan, 2017). Finally, the online self-administered assessment could be a strength by circumventing disclosure barriers such as shame.

In conclusion, this large community-based cohort study found a cross-sectional association between the use of anxiolytics/hypnotics and STB, with an approximately 50% increase in the risk of the latter. This association was independent from many risk factors of suicide and from most psychiatric disorders that require such treatments. Even if residual confounding cannot be excluded, these findings should alert prescribers to this potential risk and at least to the lack of demonstrated effectiveness of these drugs on suicidal thoughts or behaviors and encourage them to weigh up the expected benefit and risks when prescribing anxiolytics or hypnotics, even to young patients. Therapeutic alternatives might be considered such as psychotherapy and other psychotropic drugs when relevant.

### Ethics approval

The i-Share project from which this study was derived was approved by the Commission Nationale de l'Informatique et des Libertés (CNIL) [DR. – 2013–019].

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### CRediT authorship contribution statement

**Nicolas Lecat:** Conceptualization, Methodology, Formal analysis, Writing - original draft. **Annie Fourier-Réglat:** Conceptualization, Supervision, Validation, Writing - review & editing. **Ilaria Montagni:** Data curation, Supervision, Validation, Writing - review & editing, Project administration. **Christophe Tzourio:** Data curation, Supervision, Validation, Writing - review & editing, Project administration. **Antoine Pariente:** Supervision, Validation, Methodology, Writing - review & editing. **Hélène Verdoux:** Supervision, Validation, Methodology, Writing - review & editing. **Marie Tournier:** Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing, Validation.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2020.113276.

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