

Original Research

In patients with asthma, obesity status is associated with poor control and high exacerbation rates, which are reversed after bariatric surgery

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ABSTRACT

Background: In asthma, obesity status is associated with poor control and high exacerbation rates. The primary objective was to determine the effect of bariatric surgery (BS) on asthma control and exacerbations.

Methods: Retrospective study with a 3-year cohort of obese patients before and after BS: a baseline period (P0) covering the 12 months before BS and P1 and P2 periods covering the first and second years after BS, respectively. Asthma control was assessed from the use of relievers, and severe exacerbation rates, i.e. use of oral corticosteroids and asthma-related hospitalizations (ARHs). P1 and P2 measures were compared with those of P0. Patients were matched with non-obese patients and compared over P0 using a generalized linear mixed model with random effects.

Results: 2601 asthma patients undergoing BS were included. Of these, 2556 patients were matched with 2556 nonobese asthma patients. After BS, the risk of poor control decreased [OR = 0.26 (95 % CI: 0.21–0.32)] together with the mean exacerbation rate, with IRRs of 0.54 (95 % CI: 0.51–0.58) and 0.60 (95 % CI: 0.56–0.64) for P1 and P2, respectively, compared with P0. The incidence risk ratios (IRRs) were of 1.19 (95 % CI: 1.04–1.35) and 1.28 (95 % CI: 1.20–1.37) for poor control and severe exacerbation rates, respectively, in obese vs. nonobese asthma patients.

Conclusion: In patients with asthma, obesity is a major risk factor for poor control and increased exacerbation rates, with both outcomes highly reversible for at least two years following BS.

1. Introduction

Obesity is associated with high morbidity and mortality rates worldwide [1] as well as poor asthma control and severe exacerbation rates [2,3]. The relationship between obesity and asthma is supported by strong evidence, such as a dose-dependent relationship between body mass index (BMI) and the prevalence of asthma [2] and a high severity of asthma in patients with obesity [4,5], who experience an impaired response to controller therapy [6], decreased asthma-related quality of life [4,5] and frequent asthma-related hospitalizations [5]. In 2013, Moreira et al. [7] performed a systematic review of three large biomedical datasets to investigate the impact of weight change on asthma and concluded that weight management should be part of asthma care. Juel et al. [8] reached similar conclusions in another systematic review.

Currently, bariatric surgery (BS) is the most effective treatment for morbid obesity, leading to sustained weight loss and improvement in comorbidities [9], with maximal weight loss observed during the first 2 years following surgery [10,11]. Other studies have shown improvements in respiratory symptoms following BS [12–14], in addition to improved lung function and decreased numbers of mast cells in the airways after BS [15,16].

However, few studies have reported the effect of BS on the rate of asthma exacerbations [17]. Exacerbations play a major role in the morbidity and mortality of asthma, as they may lead to emergency department visits and hospitalizations, and their prevention is a key outcome in asthma therapeutic trials [18].

Given that France has universal healthcare coverage with a unified healthcare data system (covering 98 % of the total French population of approximately 66 million individuals), we designed a study with the

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primary objective of assessing whether BS has an effect on asthma control and exacerbation rates of asthma patients with obesity. The secondary objective consisted in verifying whether asthma patients with obesity have worse asthma control and more frequent exacerbations than nonobese asthma patients.

2. Methods

2.1. Data source

This study was based on digital data from the French National Health Insurance database (Système National des Données de Santé (SNDS)), which covers 98.8 % of the population living in France [19]. This real-world dataset contains comprehensive, anonymous, and individual information on sociodemographic characteristics; the date of death; out-of-hospital reimbursed public and private healthcare expenditures (including treatments, outpatient visits, medical procedures, medical devices and laboratory tests); and hospital discharge summaries with International Classification of Diseases (ICD)–10 codes. In addition, the SNDS contains information on medical diagnoses for patients who have full coverage for all medical expenses associated with the care of specific chronic conditions (“chronic disease” status), such as asthma.

2.2. Study design and study population

This was a retrospective cohort study of asthma patients with obesity (i.e. patients undergoing BS) before and after BS. The study population consisted of patients who were likely to suffer from asthma, identified in the SNDS between January 1, 2012, and December 31, 2014, and who were undergoing any type of BS, such as gastrectomy, gastroplasty or bypass (see codes in the Supplementary Material, e-Table 1), between January and December 2014. Asthma patients were identified using ICD-10 codes (J45 and J46) from asthma-related hospitalizations, as

indicated by the main or related hospital diagnosis, and from “chronic disease status”, or by two or more dispensations of asthma controller therapy [inhaled corticosteroids (ICSs), fixed-dose combinations (FDCs) of long-acting-beta agonists (LABAs) and ICSs, leukotriene receptor antagonists (LTRAs) or omalizumab] (see codes in Supplementary Material, e-table 2), more than 90 days apart, over a one-year period. Similar definitions were used in other studies [20,21].

To ensure data exhaustivity, only patients who were continuously covered by the general health insurance scheme during the study period (January 1, 2012, to December 31, 2016) were included. Patients with a diagnostic code for chronic obstructive pulmonary disease (COPD) [i.e., ICD–10 codes: J41, J42, J44, J96.1 and J96.0 if together with J43 or J44 in associated diagnosis] during the study period were excluded, as were patients who underwent BS in 2012, 2013, 2015 or 2016 or with multiple BSs in 2014. Finally, patients without any dispensation of ICSs during the year before BS were excluded, as were patients who died within 2 years after BS.

With the date of BS defined as the index date, three periods were defined: a baseline period (P0) covering the 12 months before the index date (excluded), a first exposure period (P1) covering the 12 months after the index date (included) and a second exposure period (P2) covering the second 12-month period after the index date (Supplementary Material, e-Fig. 1).

2.3. Matched population

To verify whether the asthma patients with obesity included in the study had worse asthma control and more frequent exacerbations, they were individually matched to nonobese asthma patients selected at random in the overall dataset. Nonobese asthma patients were patients without markers of obesity over the study period, i.e., without BS, without hospitalization with a diagnosis of obesity [ICD–10 codes: E65 and E66], and without “chronic disease status” for obesity. Nonobese

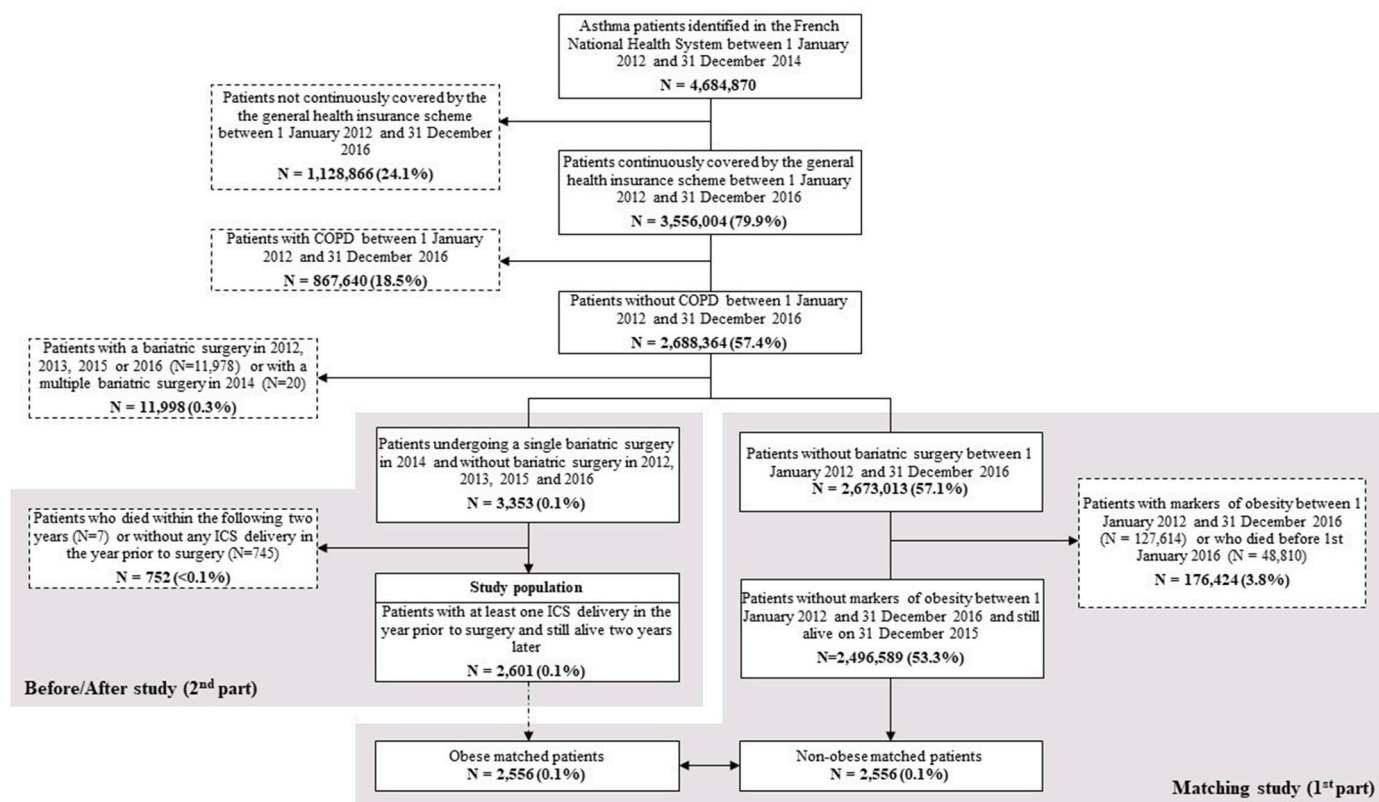


Fig. 1. Study flowchart.

asthma patients who died before 2016 were excluded from the matching. We carried out a 1:1 matching as the sample of cases was sufficient ($N = 2601$). This was an exact matching because we had a large number of controls (around 2.5 million). The approach was to search all pairs of matched case-controls on all matching criteria, then randomly select a control for each case. A control could be selected only once. In order to avoid cases without controls, the selection was made starting with the case with the fewest possible potential controls, then the second and so on. Patients were matched on year of birth, sex and variables recorded over the baseline period: free-access-to-care status (i.e., a proxy of social deprivation), asthma severity (see below), and comorbidities (diabetes, cancer, and mild liver disease). The index date of nonobese patients was the date of BS of their matched patients with obesity. To be included in this study, patients had to be followed for at least 2 years after the index date.

2.4. Asthma severity

Asthma severity was assessed on the basis of ICS use (monotherapy or FDCs) during the baseline period. The mean daily ICS consumption was computed for each patient and reported as a beclomethasone dipropionate (BDP)-equivalent dose, according to the equivalence table from British Thoracic Society guidelines (see method in Supplementary material, e-table 3) [22,23]. Patients with a mean daily consumption of strictly less than 500 mcg, between 500 mcg and 1000 mcg, or more than 1000 mcg were considered to have mild, moderate, or severe asthma, respectively.

2.5. Asthma control

Asthma control was assessed from the number of units of short-acting beta agonists (SABAs) dispensed over 12 months. Asthma was defined as uncontrolled when the number of units was ≥ 2 .

2.6. Severe exacerbation rate (SER)

The second outcome was the annual rate of severe exacerbation (SER), defined as either dispensation with oral or injectable corticosteroids or asthma-related hospitalization (ARH). Only exacerbations occurring more than 14 days apart were considered distinct outcomes.

2.7. Statistical analyses

Sociodemographic characteristics and clinical data are presented with descriptive statistics as follows: for quantitative variables, the mean, standard deviation (SD), median, first and third quartiles (Q1–Q3), minimum and maximum values were used; for qualitative variables, the frequency and percentage were reported for each modality. Sociodemographic characteristics, “chronic disease status” for asthma, type of BS, Charlson comorbidity index [24], major comorbidities, and asthma severity were described for the baseline period.

Asthma-related healthcare resource use (HCRU), asthma control, and SER were described during the three study periods. The level of asthma control and SER were compared between P1 and P2 versus P0 using a generalized linear mixed model (GLMM) with random effects. For the SER, a negative binomial distribution was used with a log link to account for data overdispersion. A mixed-effects logistic regression was used for asthma control. A random-effects model was applied to account for any correlation of repeated measurements over the three periods.

For the matching study, the matching variables, level of asthma control and SER were described in both groups of patients for P0. The levels of asthma control and SER were subsequently compared during P0 between the two groups of patients via the models developed for the first part of the project.

All the statistical analyses were performed via SAS (SAS Institute, North Carolina, US), version 9.4.

3. Results

3.1. Study population

The flowchart of patient selection is shown in Fig. 1. Almost 4.7 million asthma patients were identified in the SNDS between January 1, 2012, and December 31, 2014. After applying successive selection criteria, the study population consisted of 2601 patients who were likely to suffer from asthma and who were undergoing BS in 2014. Among the asthma patients, nearly 2.5 million (53.3 %) presumed nonobese patients were eligible for matching. Finally, 2556 patients with obesity were matched to 2556 nonobese patients (matching study). Forty-five asthma patients with obesity could not be matched due to their comorbidities.

Among 2601 patients with obesity, 87.6 % were female, with a mean age of 42.5 years at the time of BS (± 11.3 ; Table 1). The most frequent interventions were gastrectomy (60.7 %) and bypass (29.7 %). Asthma was considered mild for 76.5 % of the patients, and 69.7 % of the patients had a Charlson score < 2 . Notably, 16.4 % of the patients had diabetes, 23.8 % hypertension, and 17.6 % hypertriglyceridemia.

3.2. Before/after BS study

The number of patients with uncontrolled asthma, as assessed from the number of SABA dispensations, decreased over the three periods P0, P1 and P2: 28.4 %, 18.2 % and 17.5 %, respectively (Table 2). The mean SER was greater in P0 (1.2) than in P1 (0.7), and it remained stable in P1 and P2 (0.7).

There was a protective effect of undergoing BS on asthma control (the number of SABA dispensations), with ORs of 0.26 (95 % CI: 0.21–0.32) for P1 and 0.23 (95 % CI: 0.19–0.29) for P2 compared with P0 (Fig. 2). After BS, the annual SER decreased significantly, with IRRs of 0.54 (95 % CI: 0.51–0.58) and 0.60 (95 % CI: 0.56–0.64) for P1 and P2, respectively, compared with P0.

Overall, the percentage of users and the mean number of units of asthma treatments dispensed was lower in P1 and P2 compared to P0, as well as the number of distinct treatment classes used (Table 2): this was

Table 1

Baseline characteristics of patients with asthma who underwent bariatric surgery ($n = 2601$).

Characteristics	Population
Sex, n (%)	
Male	323 (12.4 %)
Female	2278 (87.6 %)
Age at index date (in years)	
Mean (SD)	42.5 (11.3)
Median (Q1 - Q3)	42.0 (34.0–51.0)
Min - Max	16.0–87.0
Type of bariatric surgery, n (%)	
Bypass	772 (29.7 %)
Gastrectomy	1578 (60.7 %)
Gastroplasty	251 (9.7 %)
Severity of asthma^a, n (%)	
Mild	1991 (76.5 %)
Moderate	375 (14.4 %)
Severe	235 (9.0 %)
Charlson comorbidity index, n (%)	
0	433 (16.6 %)
1–2	1814 (69.7 %)
3–4	309 (11.9 %)
≥ 5	45 (1.7 %)
Comorbidities	
Diabetes, n (%)	427 (16.4 %)
Mild liver disease, n (%)	217 (8.3 %)
Cancer, n (%)	55 (2.1 %)
Hypertension, n (%)	618 (23.8 %)
Hypertriglyceridemia, n (%)	458 (17.6 %)

^a Assessed from ICS use (monotherapy or FDC).

Table 2
Asthma-related HCRU and asthma control during periods P0, P1 and P2 in patients undergoing bariatric surgery (N = 2601).

	Period 0		Period 1		Period 2	
	No. of users (%)	Mean (SD)	No. of users (%)	Mean (SD)	No. of users (%)	Mean (SD)
HCRU						
Medications						
ICS	1068 (41.1 %)	1.0 (1.9)	510 (19.6 %)	0.5 (1.5)	382 (14.7 %)	0.4 (1.4)
ICS/LABA FDCs	1951 (75.0 %)	3.2 (4.0)	1156 (44.4 %)	2.0 (3.5)	931 (35.8 %)	1.6 (3.2)
LABA	142 (5.5 %)	0.3 (1.6)	73 (2.8 %)	0.2 (1.4)	70 (2.7 %)	0.1 (1.1)
LTRA	593 (22.8 %)	1.3 (3.2)	406 (15.6 %)	0.9 (2.8)	315 (12.1 %)	0.8 (2.7)
OCS	1491 (57.3 %)	1.4 (2.6)	902 (34.7 %)	0.7 (2.3)	952 (36.6 %)	0.8 (2.4)
SABA	1554 (59.7 %)	2.6 (4.4)	1037 (39.9 %)	1.6 (3.4)	1007 (38.7 %)	1.5 (3.5)
Respiratory antibiotics	2097 (80.6 %)	5.2 (5.4)	1687 (64.9 %)	3.4 (5.7)	1623 (62.4 %)	3.2 (4.6)
Nasal corticosteroids	2097 (80.6 %)	5.2 (5.4)	1687 (64.9 %)	3.4 (5.7)	1623 (62.4 %)	3.2 (4.6)
Antihistamines	1749 (67.2 %)	4.0 (5.9)	1442 (55.4 %)	3.1 (5.4)	1314 (50.5 %)	3.1 (5.8)
Number of therapeutic classes^a						
0	0 (0 %)		624 (24.0 %)		801 (30.8 %)	
1	388 (14.9 %)		681 (26.2 %)		662 (25.5 %)	
2	874 (33.6 %)		683 (26.3 %)		592 (22.8 %)	
3	801 (30.8 %)		451 (17.3 %)		396 (15.2 %)	
4	426 (16.4 %)		122 (4.7 %)		120 (4.6 %)	
≥ 5	112 (4.3 %)		40 (1.5 %)		30 (1.2 %)	
Medical contacts						
Independent general practitioner	2571 (98.8 %)	9.9 (7.3)	2528 (97.2 %)	9.0 (6.9)	2473 (95.1 %)	7.8 (6.6)
Independent respiratory physician	383 (14.7 %)	0.2 (0.6)	173 (6.7 %)	0.1 (0.4)	75 (2.9 %)	0.0 (0.3)
Outpatients visits to hospital practitioners	1751 (67.3 %)	3.2 (3.9)	1565 (60.2 %)	2.3 (3.5)	1530 (58.8 %)	2.3 (4.1)
Visits to emergency room ^b	720 (27.7 %)	0.5 (1.0)	821 (31.6 %)	0.5 (1.1)	812 (31.2 %)	0.6 (1.1)
Hospitalization for asthma	19 (0.7 %)	0.0 (0.1)	5 (0.2 %)	0.0 (0.1)	2 (0.1 %)	0.0 (0.0)
Asthma control markers						
Number of SABA dispensation						
Poor control	739 (28.4 %)		473 (18.2 %)		454 (17.5 %)	
Good control	1862 (71.6 %)		2128 (81.8 %)		2147 (82.5 %)	
Number of exacerbations						
0	1597 (61.4 %)	1.2 (1.5)	1014 (39.0 %)	0.7 (1.2)	1056 (40.6 %)	0.7 (1.3)
1	1004 (38.6 %)		1587 (61.0 %)		1545 (59.4 %)	
2	785 (30.2 %)		624 (24.0 %)		622 (23.9 %)	
3	430 (16.5 %)		241 (9.3 %)		240 (9.2 %)	
4	226 (8.7 %)		82 (3.2 %)		99 (3.8 %)	
≥ 5	86 (3.3 %)		28 (1.1 %)		55 (2.1 %)	
	70 (2.7 %)		39 (1.5 %)		40 (1.5 %)	

^a Except respiratory antibiotics, nasal corticosteroids and antihistamines.

^b Not followed by a hospitalization.

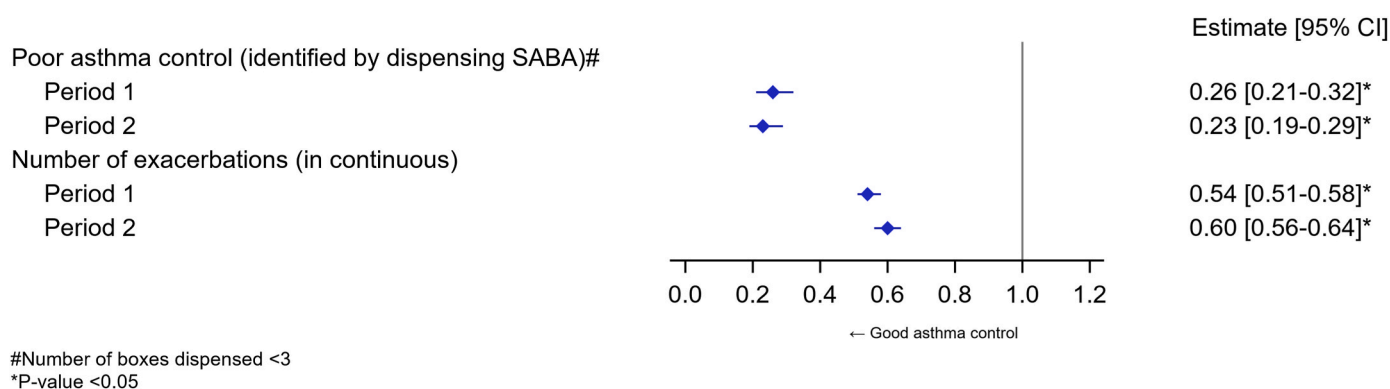


Fig. 2. Forest plot for the estimation of asthma control and severe exacerbation rates in patients with asthma undergoing bariatric surgery for the first (P1) and second (P2) years after their surgery compared with the year before surgery (before/after study, N = 2601).

the case for all asthma controller therapies (ICS, FDCs of ICS/LABAs, LABAs, and LTRA) and antiallergic treatments (nasal corticosteroids and antihistamines). Notably, the use of ICS decreased across the three periods (P0, P1, and P2) from 41.1 % to 19.6 % and 14.7 %. Similarly, the percentage of ICS/LABA use declined from 75.0 % in P0 and 44.4 % in P1 to 35.8 % in P2.

With respect to the use of oral corticosteroids (OCSs), SABAs and oral respiratory antibiotics, differences were more pronounced between P0 and P1 than between P1 and P2. The mean numbers of visits to GPs, respiratory physicians, and hospital practitioners, i.e., outpatient

visits—were lower in P1 and P2 than in P0.

3.3. Matching study

The matching variables of asthma patients with and without obesity were similar (Supplementary Material, e-Table 4). According to SABA dispensation data, a total of 28.4 % of patients with obesity had uncontrolled asthma, whereas 25.4 % of nonobese asthma patients did (Table 3). The mean annual rates of severe exacerbations were 1.2 and 0.9 for patients with and without obesity, respectively.

Table 3
Markers of asthma control and severe exacerbation rates in matched patients with and without obesity (N pairs = 2556).

	Asthma patients with obesity (N = 2556)	Nonobese asthma patients (N = 2556)
Asthma Control, n (%)		
Good control	1830 (71.6 %)	1906 (74.6 %)
Poor control	726 (28.4 %)	650 (25.4 %)
Severe exacerbation rate, n (%)		
0	985 (38.5 %)	1264 (49.5 %)
1	775 (30.3 %)	684 (26.8 %)
2	424 (16.6 %)	340 (13.3 %)
3	219 (8.6 %)	160 (6.3 %)
4	83 (3.2 %)	60 (2.3 %)
≥ 5	70 (2.7 %)	48 (1.9 %)
Mean (SD)	1.2 (1.5)	0.9 (1.4)

There was a significant association between obesity and uncontrolled asthma, with ORs of 1.15 (95 % CI: 1.02–1.28) for the ratio of controllers-to-total asthma therapy and 1.19 (95 % CI: 1.04–1.35) for the number of SABA dispensations (Fig. 3).

The mean annual SER was also greater in patients with obesity than in nonobese patients, with an IRR of 1.28 (95 % CI: 1.20–1.37).

4. Discussion

In this population-based study, over a twelve-month period, asthma control was lower in patients with obesity than in matched nonobese asthma patients, as assessed from SABAs, with 71.6 % vs. 74.6 % of well-controlled patients with obesity and nonobese patients, respectively. Similarly, the annual rates of severe exacerbations were higher in asthma patients with obesity than in nonobese asthma patients, at 1.2 and 0.9, respectively. Asthma control clearly improved after BS in asthma patients with obesity, with percentages of appropriate control increasing from 71.6 %, 81.8 %, and 82.5 % before, one year and two years after surgery, respectively; in parallel, the annual rates of severe exacerbations largely decreased, from 1.2 % before BS to 0.7 % both one and two years after surgery.

Our findings are in line with available evidence showing that asthma patients with obesity benefit from BS, as assessed from their level of control, their quality of life, the therapeutic load—i.e., the number of distinct treatment classes—and the rate of exacerbation [25–27]. Similar to our study, Hasegawa et al. demonstrated that in patients with obesity, the risk of an emergency department visit or asthma-related hospitalization was halved after BS [17]. After 8 years of follow-up, although the sample size was small, Witte et al. emphasized the interest in the use of BS to treat obesity-related asthma, which has long-lasting effects [28]. Interestingly, a systematic review comparing BS to nonsurgical techniques for weight loss has suggested that BS leads to greater weight loss (22–36 %) than nonsurgical programs (4.1–14.2 %) and is consistently associated with decreased medication use, airway hyperresponsiveness, hospitalization rate, and emergency department

attendance and improved lung function, despite variable changes in inflammatory markers [29]. In addition to the impact of BS on asthma control, our data suggest that surgery could have an effect on health care utilization, with decreased numbers of visits to primary or secondary care: fewer family physician visits, fewer outpatient visits, and fewer asthma-related hospitalizations.

In our study, when the use of OCSs, SABAs and respiratory antibiotics was analyzed, there was a marked decrease in the first year after BS, followed by stable figures in the second year. The same trend was observed for drugs related to allergies, i.e., nasal corticosteroids and antihistamines. Overall, our results are in line with the study of Gueron et al., where undergoing BS was associated with decreased asthma medication use starting 30 days postoperation, with a reduction sustained for up to 3 years [30], as also shown by Sikka et al. [31]. Our study also highlights a large reduction in ICS use, which may be clinically relevant given the potential systemic and metabolic side effects of ICS in these patients with obesity [32,33].

As a rule, our population made high use of OCSs (57 % of patients before BS), with a mean number of 1.4 annual dispensations. This could be due to the phenomenon of steroid resistance commonly observed in individuals with obesity, with patients inclined to increase the doses of ICS before possibly adding OCS. This regimen in turn facilitates the development of insulin resistance and diabetes, among other adverse effects of high-dose steroid use [34]. In our study, after surgery, OCS use decreased markedly, down to 34.7 % and 36.6 % of patients after 1 and 2 years, respectively, with lower numbers of dispensations, further supporting the benefits of BS.

Our study had several strengths. This population-based study was conducted with data recording the healthcare consumption of almost all French citizens (over 67 million inhabitants) without distinguishing age, sex, ethnicity, residency, income and social status in a large country with a single universal healthcare system. It is particularly valuable as this cohort spans both hospital and general practice settings, which provides an important addition to previous studies that primarily focused on secondary care. These assets allowed us to overcome the limitations of other studies on asthma care, such as distinct health care coverage for different patient groups or missing information as a result of fragmented care. It is also likely that our study included almost all asthma patients undergoing BS in France at the time of the study, regardless of their social and economic status or their usual asthma care. This study provides a robust and detailed description of this specific population, their treatment patterns and their outcomes, in addition to a valid comparison between asthma patients with and without obesity. The validity of our results is also supported by the robustness of the self-controlled design for the study before/after BS, in particular for a study in asthma, where the adjustments for confounding factors are complex.

This study has several limitations. As the SNDS does not contain clinical or biological information (no results of tests or dosages or numerical ‘asthma control’ tools, no diagnoses except those associated with hospital stays), we used an algorithm to identify patients with asthma, but this algorithm has already been used in previous work [35, 36]. However, the absence of these data also led us to use different

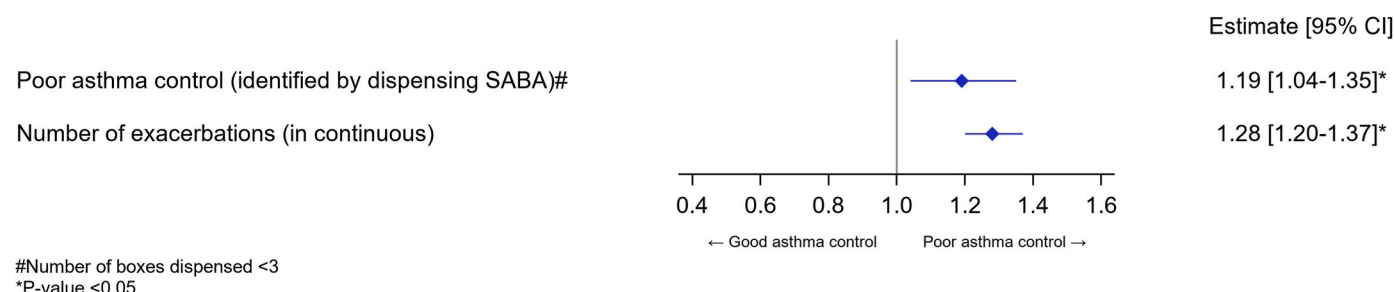


Fig. 3. Forest plot for the estimation of asthma control and severe exacerbation rates in asthma patients with and without obesity (matching study, N pairs = 2556).

criteria from the clinical practice guidelines to define asthma control and severity, as well as severe exacerbations [37]. Another limitation was that short courses of OCS could not be distinguished from maintenance OCS, leading to a potential overestimation of exacerbations. Additionally, the SNDS does not contain information on smoking status, pulmonary function or BMI. This prevents the identification of specific subgroups that might obtain an optimal benefit from BS; it may also lead to some misclassification if undiagnosed patients with obesity are included in the control group. However, if that was the case, our findings can be considered robust, as this would have decreased the effects of BS in a conservative way. While the effects of confounding factors were taken into account as thoroughly as possible, residual confounding effects may still be present due to the study design.

Treating patients with obesity, particularly those with asthma, is a complex objective that requires an individually tailored approach. Obesity is a multifactorial condition that should be managed with the same efforts as other medical conditions. Indeed, in addition to asthma, obesity affects rhinosinusitis, gastroesophageal reflux disease, obstructive sleep apnea, hypertension, anxiety, and depression, and it also increases morbidity due to cardiovascular/cerebrovascular diseases, metabolic syndrome, diabetes, breast and bladder cancer, and migraines, among other conditions [38].

5. Conclusion

In conclusion, our population-based study confirms that obesity is a major risk factor for uncontrolled asthma and high rates of severe exacerbations and that BS leads to improved control and lower rates of severe exacerbations in the two years following the intervention. Patients with overweight or obesity must be carefully addressed in asthma care. BS is therefore a key player in asthma treatment in patients with asthma and obesity.

CRedit authorship contribution statement

Manon Belhassen: Writing – original draft, Validation, Supervision, Methodology, Funding acquisition, Conceptualization. **Clarisse Marchal:** Writing – review & editing, Validation, Project administration, Methodology. **Floriane Deygas:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Flore Jacoud:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Eric Van Ganse:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Data availability

Owing to NHS and SNDS regulations, no data sharing is possible since access to data and data management is restricted to habilitated and qualified researchers (Floriane Deygas and Flore Jacoud are habilitated and qualified).

Institutional review board statement

This study was approved by the French Institute for Health Data (approval no. 133 from June 9, 2015). It was conducted with anonymized data, as requested by the National Informatics and Liberty Commission [CNIL], approval from Dec 24, 2015.

Guarantor statement

Manon Belhassen is the guarantor of the content of the manuscript, including the data and analysis.

Role of sponsors

PELyon developed the protocol of this study and performed all the

analyses as well as the interpretation of the results.

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Declaration of competing interest

Nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2024.107917>.

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