



## Effects of Bariatric Surgery on Influenza-Like Illness: a Two-Center Cross-sectional Study

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Dear Editor,

During the last months, the COVID-19 pandemic revealed the dramatic impact that respiratory viruses can generate on the overall population, with considerable consequences on social dynamics and health-care systems. Although it is generally less severely disrupting, influenza epidemic can nonetheless affect public health, communities, and economies worldwide. In fact, previous estimates indicated that almost 300,000–650,000 deaths occur annually worldwide due to seasonal influenza viruses [1], contributing to a substantial annual burden of deaths globally. Influenza is a highly contagious respiratory tract infection that affects millions of adults each year; recently, people suffering from obesity have been included in the high-risk population for seasonal influenza, together with children, elderly, and immunocompromised people [2].

The association between excess adiposity and pulmonary comorbidities has long been widely acknowledged, but the role of obesity as a risk factor for infectious diseases has been highlighted much more recently only [3, 4]. Obesity is indeed

characterized by an altered metabolic milieu, resulting in hormone dysregulation, derailment of the immune response, and creation of a pro-inflammatory environment, which can easily promote infections [5, 6].

The literature suggests that obesity delays the clearance of influenza viral load and prolongs shedding duration, resulting in long-term transmission and delayed recovery [7]. In actual fact, adults suffering from overweight and obesity, compared with normal-weight subjects, show higher risk of hospitalization for respiratory illness during seasonal influenza and, furthermore, of prolonged hospital stay [8]. Indeed, during the 2009 influenza pandemic, obesity was recognized as an independent risk factor for severe H1N1 pulmonary infection [9], as well as for the development of influenza-related systemic complications and for increased morbidity and mortality resulting from infection [10].

Moreover, as recently reported, obesity impairs vaccine response to several infectious diseases, affecting, in the case of influenza, the most efficient primary prevention [11].

It is therefore conceivable that, because of its favorable effects on weight loss, obesity-related comorbidities and on overall pulmonary function, bariatric surgery (BS) can contribute to reducing the incidence and improving the clinical course of influenza in patients suffering from obesity.

We investigated the impact of BS on influenza, by comparing the clinical course of influenza-like illness (ILI) in patients who had undergone BS to that in adult with obesity candidates for a bariatric procedure in a retrospective observational study involving 2 major centers of BS in Italy and France. Data regarding patients that had undergone a bariatric procedure were compared with those of subjects with obesity waiting for surgery in the above-mentioned hospitals. All the subjects completed a web-based questionnaire (Google® FORMS). Clinical expression of influenza virus infection was assessed by measuring illness-related symptoms and outcome parameters, including sick leaves. From the analysis, we

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excluded (a) patients  $\leq 18$ -year-old at the time of the survey; (b) subjects that had undergone a bariatric procedure other than adjustable gastric band (AGB), sleeve gastrectomy (SG), and Roux-en-Y Gastric By-pass (RYGB); (c) subjects that had undergone the intervention less than 12 months before the beginning of the 2018–2019 seasonal influenza epidemic, as this is considered the minimum time to reach weight loss stabilization and remission of comorbidities [12]. The enrolment period lasted 14 days starting 2 weeks after the end of the 2018–2019 seasonal influenza epidemic in both countries, as stated by the Joint ECDC-WHO Europe weekly Influenza Update report [13]. Data were collected between the 1st and the 14th of March 2019. As period prevalence for influenza-like illnesses in France and Italy during the 2018–2019 influenza season ranged around 13%, aiming to an absolute precision of 5% with a 95% confidence interval, a minimum sample size of 178 participants was calculated (<http://www.epicentro.iss.it/influenza/FluNews18-19>, <http://santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/grippe/documents/article/surveillance-de-la-grippe-en-france-saison-2018-2019>).

The bariatric procedures considered (AGB, SG, and RYGB) account for 89.2% of all bariatric procedures performed worldwide, being also representative of the Italian and French recent trends in BS [14, 15].

The web-based questionnaire consisted of 37 questions, mostly closed-ended. Data regarding anthropometric characteristics, vaccination history, BS history, comorbidities, influenza-related symptoms, clinical evaluation, and paid sick days were collected.

Among comorbidities and factors able to affect the clinical course of influenza infection, the following were considered: chronic cardiovascular disorders, such as hypertension, arrhythmia, and previous myocardial ischemia; diabetes; smoking habit; and chronic respiratory disorders, including COPD and asthma.

Along with seasonal influenza and pneumococcus vaccine for the examined period, past seasonal influenza vaccination history was recorded, assuming possible residual protection [16].

Influenza-related symptoms included the most predictive symptoms of influenza and other closely related ones, experienced from October 2018 to March 2019: fever ( $\geq 38$  °C), fever at rapid onset, shivering, cough, asthenia, myalgia, sore throat, running nose, nausea or vomit, and diarrhea [17].

Any influenza-related medical evaluation, hospital admission or intake of drugs was considered as indicator of severity of the disease. Sick leaves for any influenza-like symptom were considered as an outcome indicator too.

Consistently with the latest definitions given by the World Health Organization (WHO), ILI and Severe Acute Respiratory Infection (SARI) were considered in the analysis. In particular, ILI was defined as an acute respiratory illness with a measured temperature of  $\geq 38$  °C and cough, and SARI

as an acute respiratory illness with a history of fever or measured fever of  $\geq 38$  °C and cough, requiring hospitalization [17]. As per common practice for seasonal influenza, no confirmation laboratory test was considered.

Univariate comparisons were performed by means of chi-squared test with Yates correction for dichotomous variables, and with Student's unpaired *t* test for continuous variables. Four distinctive outcomes were assessed: (a) having received any bariatric surgery, (b) complaints fulfilling ILI definition, (c) any sick leave, and (d) any sick leave  $> 3$  days. Therefore, initially, we compared characteristics of operated and non-operated patients, including both demographic characteristics and complained signs/symptoms of seasonal influenza. Then, comparisons of individual characteristics were performed between cases of ILI vs. no-ILI, patients reporting sick leaves during the influenza season vs. cases not reporting sick leaves (any and  $> 3$  days).

In multivariate analyses, 4 models of binary logistic regression were assessed, which included all variables that, in univariate analysis, were associated with the respective outcome having *p* value  $< 0.2$ . Corresponding odds ratio (OR) values with their 95% confidence interval (CI95%) were then calculated accordingly.

Response rate to the questionnaire was 88%. Out of the 220 patients of 250 who responded to the questionnaire, 36 were excluded because they did not meet the inclusion criteria.

One hundred and three patients operated (Op) and 81 candidates for BS (C) were finally included in the statistical analysis. RYGB was the most common procedure performed (69.9%), followed by SG (26.2%), and AGB (3.9%). Op and C groups were similar for age and sex proportion (Table 1).

As predictable effect of BS, Op patients presented a significant lower BMI and lower incidence of metabolic comorbidities, such as diabetes (9.7% vs 29.6%, *p*: 0.001). No significant difference was found in smoking habits and in previous respiratory and cardiovascular disorders. Vaccination history was similar in the two groups, too. One hundred sixty-one patients (87.5%) reported at least one influenza-related symptom, 85.4% of Op patients and 90.1% of C patients (Table 1). In particular, among Op patients, we recorded lower incidence of fever, of fever with rapid onset (48.1% vs 20.4% and 44.4% vs 14.6%, *p*  $< 0.001$ , respectively), resulting in lower incidence of ILI among Op patients (13.6% vs 34.6%, *p*: 0.001). We reported a lower intake of non-steroid anti-inflammatory drugs (NSAIDs) among Op patients (20.4 vs 42.0%, *p*: 0.003), as well as a higher rate of evaluation by a general practitioner (GP) in C patients, both as practice and in-home assessment (45% vs 23.3%, *p*: 0.003 and 19.8% vs 2.9%, *p*  $< 0.001$ , respectively). A total of 13.6% of C patients was admitted to the emergency department vs 3.9% of Op patients (*p*: 0.034). A higher percentage of sick leave was found among C patients (42.0% vs 22.3%, *p*: 0.007), who had also a higher rate of prolonged ( $> 3$  days) leaves (22.2% vs 8.7%,

**Table 1** Demographics, symptoms, outcomes

	Total (N = 184)	Op (N = 103)	C (N = 81)	P value
Gender (N, %)				0.458
Male	44 23.9	22 21.4	22 27.2	
Female	140 76.1	81 78.6	65 72.8	
Age (years; average ± SD)	48.0 ± 10.8	48.6 ± 10.4	47.2 ± 11.2	0.380
left (N, %)				0.014
Italy	110 59.8	53 51.5	57 70.4	
France	74 40.2	50 48.5	24 29.6	
Surgical procedure (N, %)				
RYGB	72 39.1	72 69.9	-	
SG	27 14.7	27 26.2	-	
AGB	4 2.2	4 3.9	-	
BMI (kg/m <sup>2</sup> ; average ± SD)	35.6 ± 9.6	29.4 ± 5.6	43.4 ± 7.6	< 0.001
Status by BMI (N, %)				< 0.001
Normal weight (< 25 kg/m <sup>2</sup> )	23 12.5	23 22.3	0 -	
Overweight (25–29.9 kg/m <sup>2</sup> )	36 19.6	36 35.0	0 -	
Obesity 1st class (30–34.9 kg/m <sup>2</sup> )	33 17.9	26 25.2	7 8.5	
Obesity 2nd class (35–39.9 kg/m <sup>2</sup> )	38 20.7	13 12.6	25 30.9	
Obesity 3rd class (≥ 40 kg/m <sup>2</sup> )	54 29.3	5 4.9	49 60.5	
Vaccination history (N, %)				
SIV during previous winter season	44 23.9	24 23.3	20 24.7	0.964
Any uptake of SIV, previous years	54 29.3	32 31.1	22 27.2	0.678
Pneumococcal vaccination, any	5 2.7	2 1.9	3 3.7	0.785
Comorbidities (N, %)				
Any respiratory disorder	29 15.8	17 16.5	12 14.8	0.914
Any cardiovascular disorder	49 26.9	27 26.5	22 27.5	1.000
Diabetes	34 18.5	10 9.7	24 29.6	0.001
Smoking history (N, %)	112 60.9	62 60.2	50 61.7	0.953
Symptoms (N, %)				
Fever (body temperature > 38°C)	60 32.6	21 20.4	39 48.1	< 0.001
Fever, sudden onset	51 27.7	15 14.6	36 44.4	< 0.001
Sore throat	100 54.3	48 46.6	52 64.2	0.026
Running nose	11 63.0	63 61.2	53 65.4	0.659
Cough	93 50.5	45 43.7	48 59.3	0.051
Shivering	86 46.7	48 46.6	38 46.9	1.000
Muscle pain	90 48.9	47 45.6	43 54.1	0.392
Nausea	53 29.0	26 25.2	27 33.8	0.274
Diarrhea	74 40.2	40 38.8	34 42.0	0.780
Asthenia	91 49.5	50 48.5	41 50.6	0.896
ILI (fever + cough)	42 22.8	14 13.6	28 34.6	0.001
SARI (ILI + hospital admission)	12 6.5	4 3.9	8 9.9	0.182
Any symptom	161 87.5	88 85.4	73 90.1	0.466
More than 3 symptoms	115 62.5	57 55.3	58 71.6	0.035
Drug uptake (N, %)				
Paracetamol	126 69.6	71 68.9	55 70.5	0.948
Painkillers	94 51.1	49 47.6	45 55.6	0.354
NSAIDS	55 29.9	21 20.4	34 42.0	0.003
Antibiotics	60 32.8	28 27.2	32 40.0	0.094
Antiviral drugs	7 3.8	2 1.9	5 6.2	0.271
Antitussive drugs	56 30.4	27 26.2	29 35.8	0.214

**Table 1** (continued)

	Total (N = 184)	Op (N = 103)	C (N = 81)	P value
Nasal sprays	62 33.7	29 28.2	33 40.7	0.102
Medical evaluation (N, %)				
Assessment by GP for any malaise	60 32.8	24 23.3	36 45.0	0.003
Home assessment by GP	19 10.3	3 2.9	16 19.8	< 0.001
Evaluation by a medical specialist	14 7.6	6 5.8	89.9	0.454
Admission to emergency department	15 8.2	4 3.9	11 13.6	0.034
Sick leave (N, %)	57 31.0	23 22.3	34 42.0	0.007
Length of sick leave (days; mean ± SD)	4.6 ± 4.9	3.1 ± 1.9	5.7 ± 6.0	0.028
Sick leave > 3 days (N, %)	27, 14.7	9, 8.7	18, 22.2	0.018

Op operated patients, C candidates for surgery, RYGB Roux-en-Y Gastric Bypass, SG sleeve gastrectomy, AGB adjustable gastric banding; BMI body mass index, SIV seasonal influenza vaccination, ILI influenza-like illness, SARI severe acute respiratory syndrome, NSAID non-steroid anti-inflammatory drug, GP general practitioner

$p$ : 0.018). Fever, sore throat, in-home assessment by GPs, and sick leaves > 3 days showed to be inversely associated with BS also at multivariate analysis.

Univariate analysis indicated BMI and obesity (body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>) as related to ILI ( $p$ : 0.046 and  $p$ : 0.017, respectively), to sick leave ( $p$ : 0.007 and  $p$ : 0.001, respectively), and to prolonged leaves ( $p$ : 0.003 and  $p$ : 0.004, respectively) (Table 2). Diabetes showed a significant correlation with sick leave and prolonged leaves ( $p$ : 0.001 and  $p$ : 0.003, respectively).

At multivariate analysis, both obesity and diabetes confirmed to be associated with sick leave and to prolonged leaves, while the presence of underlying respiratory diseases showed a correlation with ILI (Table 3).

The lower incidence of influenza-related symptoms and ILI among Op patients in our series are consistent with recently

published data [18], reporting significantly lower risk of respiratory infections in a cohort of Taiwanese patients who underwent BS.

The effect of BS on weight loss and improvement in the main obesity-related comorbidities is undoubted. Moreover, it is conceivable that BS could decrease the risk of respiratory infectious diseases, even though, to date, available evidence in the literature is limited.

Severe obesity could promote the clinical expression of influenza viruses, as recently reported for Sars-CoV-2 infection [19, 20]. Obesity is in fact characterized by chronic low-grade inflammation, with subsequent impairment of the immune system, and it is also associated with reduced lung function and decreased respiratory compliance, leading to higher risk of obstructive syndrome and pneumonia [5, 6]. The literature gives clear evidence that sustained weight loss after BS is associated with reduced

**Table 2** Univariate analysis

	ILI			Sick leave			Sick leave > 3 days		
	Pos. (N = 42)	Neg. (N = 142)	P value	Pos. (N = 57)	Neg. (N = 127)	P value	Pos. (N = 27)	Neg. (N = 157)	P value
Male gender (N, %)	9 21.4	35 24.6	0.823	13 22.8	31 24.4	0.961	5 18.5	39 24.8	0.640
Age (ys, average ± S.D.)	48.7 ± 10.6	45.7 ± 10.9	0.109	46.6 ± 10.3	48.7 ± 10.9	0.275	48.7 ± 10.9	43.9 ± 9.2	0.030
BMI (average ± S.D.)	38.0 ± 8.6	34.9 ± 9.8	0.046	38.3 ± 8.3	34.4 ± 9.9	0.007	40.1 ± 7.6	34.8 ± 9.7	0.003
Obesity (N, %)	35 83.3	88 62.0	0.017	48 84.2	75 59.1	0.001	25 92.6	98 62.4	0.004
SIV during previous winter season (N, %)	8 19.0	36 25.4	0.525	11 19.3	34 26.9	0.426	5 18.5	39 24.8	0.640
Any previous uptake of SIV (N, %)	11 26.2	43 30.3	0.750	12 21.1	42 33.1	0.139	5 18.5	49 31.2	0.267
Pneumococcal vaccine (N, %)	2 4.8	3 2.1	0.698	0 -	5 3.9	0.304	0 -	5 3.2	0.765
Respiratory disease (N, %)	10 23.8	19 13.4	0.165	12 21.1	17 13.4	0.271	4 14.8	25 15.9	1.000
Diabetes (N, %)	11 26.2	23 16.2	0.215	19 33	15 11.8	0.001	11 40.7	23 14.6	0.003
Cardiovascular disease (N, %)	8 19.5	41 29.1	0.310	16 28.6	33 26.2	0.878	8 29.6	41 26.5	0.914
Smoking history (N, %)	26 61.9	86 60.6	1.000	37 64.9	75 59.1	0.556	19 70.4	93 59.2	0.378

ILI influenza-like illness, BMI body mass index, SIV seasonal influenza vaccination

**Table 3** Multivariate analysis

	BS		ILI		Sick leave		Sick leave > 3 days	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Obesity	-	-	1.116	0.412 3.027	3.151	1.352 7.342	9.097	1.859 44.519
Respiratory disease	-	-	2.783	1.100 7.044	-	-	-	-
Diabetes	0.359	0.092 1.404	-	-	3.569	1.534 8.300	4.231	1.533 11.678
Previous SIV	-	-	-	-	0.538	0.247 1.174	0.658	0.217 1.992
Fever	0.097	0.010 0.967	-	-	-	-	-	-
Fever–sudden onset	0.306	0.083 1.129	-	-	-	-	-	-
Sore throat	0.102	0.021 0.489	-	-	-	-	-	-
Cough	1.355	0.493 3.726	-	-	-	-	-	-
More than 3 symptoms	0.090	0.018 0.442	-	-	-	-	-	-
ILI	0.172	0.019 1.567	-	-	-	-	-	-
SARI	0.857	0.068 10.857	-	-	-	-	-	-
Uptake of NSAIDs	0.575	0.221 1.492	-	-	-	-	-	-
Uptake of antibiotics	1.785	0.661 4.891	-	-	-	-	-	-
Nasal sprays	0.560	0.232 1.354	-	-	-	-	-	-
Assessment by GP	0.771	0.252 2.361	-	-	-	-	-	-
Home assessment by GP	0.240	0.042 0.963	-	-	-	-	-	-
Admission to emergency department	0.439	0.044 4.332	-	-	-	-	-	-
Any sick leave	0.543	0.144 2.051	-	-	-	-	-	-
Sick leave > 3 days	0.198	0.038 0.930	-	-	-	-	-	-

BS bariatric surgery, ILI influenza-like illness, SIV seasonal influenza vaccination, SARI severe acute respiratory syndrome, NSAID non-steroid anti-inflammatory drug, GP general practitioner

low-grade inflammation markers and improved pulmonary function, thus ameliorating symptomatic asthma and obstructive sleep apnea syndrome [21].

In the light of the above, an improvement in outcome parameters was expected in our series and has been confirmed by the better performance of Op patients in NSAIDs and antiviral drug use, evaluation by GP and admission to the emergency department.

The difference among Op and C patients in sick leaves and prolonged leaves confirms the outcome trend, highlighting the social and economic implications of the disease.

Comorbidity resolution could also contribute to the better clinical outcome of Op patients.

Individuals with obesity are indeed at higher risk of other chronic diseases, such as hypertension, dyslipidemia, insulin resistance, and metabolic syndrome, which can be responsible

for a more severe course of respiratory tract infections. In particular, both univariate and multivariate analyses suggest a correlation of diabetes with sick leave and prolonged leaves, in line with previous studies reporting a higher risk for diabetic patients to suffer from more severe influenza, to be hospitalized, or to require ICU care [22, 23].

Vaccination before seasonal influenza outbreaks is still the most effective preventive measure. Nevertheless, studies of vaccine efficacy have shown a significant interindividual variability, on which obesity could play a role. In particular, increased BMI is associated with a reduction in the protective immune response over time, because of decreased activation of immunocompetent cells [11]; as a consequence, vaccinated patients suffering from obesity have a twofold risk of developing influenza or ILI compared with vaccinated healthy weight adults [24]. Paradoxically, the population with obesity, who would benefit the most from the

influenza vaccine, at the same time shows a lower response to it. Indeed, in our series, we did not observe any correlation of vaccination history with ILI or with parameters of severe infection, probably due to the small sample size. Larger series should assess whether a vaccination strategy mainly focused on patients with obesity may be reasonable.

Despite the limits of the study, including the small sample size, the self-completion of the questionnaire leading to a not “clinical” diagnosis of ILI, and the lack of a laboratory confirmation of influenza, our series suggests a protective role of BS against ILI.

Further studies are needed to better define the role of weight loss and, in particular, of BS, among the preventive measures against influenza and respiratory tract infections.

The questionnaire will be made available on request by the corresponding author.

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**Declarations** Informed consent was obtained from all individual participants included in the study.

All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Conflict of Interest** The authors declare no competing interests.

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