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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 centres 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 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 two 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 [14, 15].

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 [16, 17].

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; 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 [18].

Influenza related symptoms included the most predictive symptoms of influenza and other closely related ones, experienced from October 2018 to March 2019: fever ($\geq 38^{\circ}\text{C}$), fever at rapid onset, shivering, cough, asthenia, myalgia, sore throat, running nose, nausea or vomit and diarrhoea [19].

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 $\geq 38^{\circ}\text{C}$ and cough, and SARI as an acute respiratory illness with a history of fever or measured fever of $\geq 38^{\circ}\text{C}$ and cough, requiring hospitalization [19]. 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. 4 distinctive outcomes were assessed: a) having received any bariatric surgery; b) complaints fulfilling ILI definition; c) any sick leave; 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). 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 %, $p: 0.018$). 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 $BMI \geq 30 \text{ kg/m}^2$) 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 [20], 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 [21, 22]. 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 low-grade inflammation markers, and improved pulmonary function, thus ameliorating symptomatic asthma and obstructive sleep apnea syndrome [23].

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 drugs 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.

Comorbidities 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, dyslipidaemia, 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 [24, 25].

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 [26]. 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.

Marina Valente, Giorgio Dalmonte, Matteo Ricco', Tarek Debs, Jean Gugenheim, Antonio Iannelli, Maria Marcantonio, Alfredo Annicchiarico, Paolo Del Rio, Gabriele Luciano Petracca, Francesco Tartamella, Federico Marchesi have no conflicts of interest or financial ties to disclose.

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.

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