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#### Healthcare utilisation and economic impact of non-treated obesity in Italy: findings from a retrospective administrative and clinical database analysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2016-013899
Article Type:	Research
Date Submitted by the Author:	15-Aug-2016
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<b>Primary Subject Heading</b> :	Diabetes and endocrinology
Secondary Subject Heading:	Health economics
Keywords:	Obesity, Body mass index, Healthcare resource consumption, Retrospective, Real-life study

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## Healthcare utilisation and economic impact of non-treated obesity in Italy: findings from a retrospective administrative and clinical database analysis

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#### Word count: 2897

**Keywords:** Obesity, body mass index, healthcare resource consumption, retrospective, real-life study

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## ABSTRACT

 **Objectives:** Aim of this study was to investigate the prevalence of obesity in Italy and to examine its resource consumption and economic impact on the Italian healthcare system.

Design: Retrospective, observational, real-life study

**Setting:** Data from three Italian local health units from northern, central, and southern Italy.

Participants: 20,159 adult subjects with at least one documented body mass index (BMI) measurement from three local health units. Subjects with BMI ≥30 kg/m<sup>2</sup> were defined as obese.

**Interventions:** Information retrieved from the databases included primary care data, medical prescriptions, specialist consultations, and hospital discharge records for the period 2009–2013. Costs associated with these data were also calculated. Data are presented for two time periods (1 year after the BMI measurement and at the end of the study).

**Primary and secondary outcome measures:** The primary outcome was health resources consumption and the associated economic impact on the Italian NHS. Secondary outcome measures were the prevalence and characteristics of subjects in relationship with the BMI category.

**Results:** The prevalence of obesity was 22.2% (N=4,471) and increased with age. At the 1-year observation period, obese subjects who did not receive treatment for

their obesity experienced longer durations of hospitalisation (median length: 5 vs 3 days), used more prescription drugs (75.0% vs 57.2%), required more specialised outpatient healthcare (mean number: 5.3 vs 4.4), and were associated with greater costs, primarily owing to prescription drugs and hospital admissions (mean annual cost per year per patient: €460.6 vs €290.9 for drug prescriptions, €422.7 vs €279.2 for hospitalisations, and €283.2 vs €251.7 for outpatient care), compared with normal-weight subjects. Similar findings were observed for the period up to data cut-off (mean follow-up of 2.7 years).

**Conclusions:** Untreated obesity has a significant economic impact on the Italian healthcare system, highlighting the need to raise awareness and proactively treat obese subjects.

Word count: 300

#### Strengths and limitations of this study

- Large study on more than 20,000 subjects
- Real-world data coming from local health units
- Data retrieved from different geographical areas
- Direct evaluation of costs by integrating multiple data sources
- Limitations due to the retrospective nature of the study

## INTRODUCTION

 Obesity is now widely regarded as a global epidemic; worldwide, obesity rates have more than doubled since 1980.<sup>1</sup> According to the World Health Organization (WHO), more than 1.9 billion adults were overweight in 2014. Of these, over 600 million (~13% of the world's population) were obese, defined as having a body mass index (BMI) of  $\geq$ 30 kg/m<sup>2</sup>.<sup>1</sup> Obesity is a major risk factor for various chronic diseases, particularly if it remains untreated. Globally, 44% of diabetes, 23% of ischaemic heart disease, and 7–41% of certain cancers are attributable to being overweight or obese.<sup>1</sup> Obesity-associated mortality rates are also alarmingly high, with at least 2.8 million deaths each year resulting from being overweight or obese.<sup>1</sup> Obesity was once considered to be an issue associated with high-income countries only; however, its prevalence is now also increasing in low- and middle-income countries.<sup>2</sup>

In Italy, WHO reports from 2014 showed that the prevalence of obesity was 20.4% among individuals aged  $\geq$ 18 years.<sup>3</sup> Childhood obesity is a particular concern in the Italian population.<sup>4-6</sup> As in other European countries, there are clear socioeconomic trends: those with a low educational status, from a low-income household, and from the southern regions of Italy are at higher risk of becoming obese.<sup>4 7-13</sup> Possible reasons for these trends are the decreased consumption of a Mediterranean diet and a more sedentary lifestyle.

Previous studies have shown that obesity and its associated comorbidities have a considerable economic impact on healthcare systems, primarily because of high costs for medication and hospitalisations.<sup>14-17</sup> However, in those studies, costs were only estimated indirectly. Alternatively, we report here on the findings from a study of

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over 20,000 adults that investigated the prevalence of, and direct costs associated with, untreated obesity in three distinct regions of Italy – which differ in terms of geography and nutritional traditions – in order to understand the healthcare utilisation and economic impact of obesity on the Italian national healthcare system (NHS).

### METHODS

#### Study design and population

This was a retrospective, observational, real-life study. To be eligible, individuals were required to be aged ≥18 years and to have at least one recorded BMI measurement between 1 January 2009 and 31 December 2012. The first recorded BMI was set as the index date. Eligible subjects were identified from registries at three Italian local health units that represent the primary Italian geographical areas: Bergamo, Lombardy (northern Italy), Grosseto, Tuscany (central Italy), and Naples, Campania (southern Italy).

BMI was classified as follows: underweight, <18 kg/m<sup>2</sup>; normal weight, ≥18 to <25 kg/m<sup>2</sup>; overweight, ≥25 to <30 kg/m<sup>2</sup>; obese, ≥30 kg/m<sup>2</sup>. Obesity was further classified as mild, moderate, and severe based on BMI levels of ≥30 to <35 kg/m<sup>2</sup>, ≥35 to <40 kg/m<sup>2</sup>, and ≥40 kg/m<sup>2</sup>, respectively.<sup>18</sup>

An anonymous data file is routinely used by regional health authorities for epidemiological and administrative purposes. No identifiers related to subjects were provided to the researchers. In accordance with Italian law regarding data confidentiality,<sup>19</sup> the ethics committee of each local health units was notified about the study. Neither ethics committee approval nor informed consent was required for using encrypted retrospective information.

#### Study objective

 The primary objective of the study was to estimate health resource consumption and the economic impact of obesity on the Italian NHS. The secondary objective was to assess the prevalence and characteristics of subjects in relationship with the BMI category.

#### Data sources and analysis

Primary care data for each subject were retrospectively collected from the Health Search Database of the Società Italiana di Medicina Generale (Italian Society of General Medicine) for the period 2009–2013. Using the numeric code assigned to each citizen by the local health units as a unique identifier, this database was linked to the following databases: i) Medications Prescription Database, which includes anatomical–therapeutic–chemical (ATC) codes; ii) Hospital Discharge Database, which includes dates of hospital admission and discharge, as well as discharge diagnosis codes according to the *International Classification of Diseases Ninth Revision, Clinical Modification* (ICD-9-CM); iii) Laboratory Tests and Specialist Visits Database; iv) Mortality Database, from which data on mortality, but not cause of death, were collected; and v) Beneficiaries' Database, from which data regarding date of birth, sex, and place of residence were collected.

Data on drug use, hospitalisations, use of specialist services, and treatment costs were evaluated from the index date until 31 December 2013, corresponding to a

period of at least 12 months and up to 5 years (the date of last enrolment was 31 December 2012). Specialist services encompassed all specialised outpatient healthcare, including diagnostic and laboratory tests (such as X-ray, ultrasound, magnetic resonance imaging, blood, and urinary tests), and consultations by specialist healthcare providers. Costs assigned to medical resources were based on publicly available market prices. Data were presented according to BMI class for the normal-weight, overweight, and obese (total and mild, moderate, and severe) cohorts for two time periods: at 1 year following the index date (1-year observation period) and at the time of data cut-off (31 December 2013). Underweight subjects were included for the prevalence analysis only.

#### Statistical analysis

To test normality assumption of data distribution, the Skewness-Kurtosis test was used. Continuous variables were reported as mean and standard deviation or median and interquartile range, as appropriate, and compared with analysis of variance (ANOVA) test, whereas categorical variables were expressed as numbers and percentages, and compared with the  $\chi^2$  test. Analyses were performed stratified for BMI groups. P-value ≤0.05 were considered statistically significant. All statistical analyses were conducted using Stata software version 12·0 (Stat Corp LP, College Station, TX, USA), data management will be carried out using Microsoft SQL Server 2012.

#### Role of funding source

Unrestricted financial support for the collection of data and for medical editorial assistance was provided by Johnson & Johnson Medical.

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### RESULTS

#### Subjects

Overall, 20,159 adults were included in the study. Table 1 shows the characteristics of subjects who were classified as underweight, normal weight, overweight, and obese at the index date. The prevalence of obesity was 22.2% (N=4471); of these, 3253 (72.8%) were classified as mildly obese, 898 (20.1%) as moderately obese, and 320 (7.2%) as severely obese. The mean length of follow-up was 2.6, 2.7, and 2.8 years for the normal-weight, overweight, and obese groups, respectively (p=NS). Within the obese group, the mean length of follow-up was 2.8 years across each of the mild-, moderate-, and severe-obesity cohorts; 1.1% of subjects died at 1 year following the index date (normal weight 1.1%, overweight 1.2%, obese 1.1%; p=NS). 

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### Table 1. Baseline characteristics and demographics at the index date

	Weight		Total		
4	Under	Normal	Over	Obese	
	(BMI <18)	(BMI ≥18	(BMI ≥25 to <30)	(BMI ≥30)	
		to <25)			
Patients,	282 (1·4)	7861 (39·0)	7545 (37·4)	4471 (22·2)	20,159 (100)
n (%)					
Males:females, n:n	42:240	3002:4859	3996:3549	2048:2423	9088:11,071
Mean age ± SD, years	44.4 ± 21.0*	53.4 ± 17.3 <sup>†</sup>	59.3 ± 15.2 <sup>‡</sup>	58.1 ± 15.1	56.5 ± 16.4
SD, standard deviation *p<0.001 vs normal weight, o	overweight, and obes	e; <sup>†</sup> p<0.001 vs overwei	ght and obese; <sup>‡</sup> p<0.001 vs o	obese	

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#### Prevalence of obesity by age

 The proportion of subjects who were overweight or obese increased with age, while it decreased for normal weight subjects (p<0.001) (table 2). Among subjects aged >30 years, more than half were classified as overweight or obese (table 2). In particular, among subjects aged between 30 and 64 years, 36.1 and 22.6% were overweight and obese, respectively; among subjects aged 65+ years, 44 and 23.6% were overweight and obese, respectively (table 2).

# Table 2. Proportions of patients classified as being of normal weight, overweight, and obese, stratified by age at the index date

	Normal	Over		
Prevalence	weight	weight	Obese	Total
18–29 years, n	786	267	189	1242
(%)	(63.3)*	(21.5)*	(15.2)*	(100.0)
30–64 years, n	4801	4195	2627	11623
(%)	(41.3) <sup>†</sup>	(36.1) <sup>†</sup>	(22.6) <sup>†</sup>	(100.0)
	2274	3083	1655	7012
65+ years, n (%)	(32.4)	(44.0)	(23.6)	(100.0)
Total	7861	7545	4471	

\*p<0.0001 vs 30–64 years and +65 years; <sup>†</sup>p<0.0001 vs +65 years

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#### Use of prescription medication

In total, 13,060 subjects from the normal weight, overweight and obese groups (65.7%) received at least one prescription drug treatment during the 1-year observation period. 3,353 were obese subjects (75%), 4,495 were normal-weight subjects (57.2%) and 5,212 were overweight subjects (69.1%). These differences were significant (p<0.0001 among groups); 14,888 (74.9%) subjects had received at least one drug treatment at data cut-off; 3,666 were obese subjects (82%), 5,357 were normal-weight subjects (68.1%) and 5,865 were overweight subjects (77.7%). Again, these differences were significant (p<0.0001 among groups). During the 1year observation period, anti-hypertensive drugs were the most common drug class received (43.5% of subjects); 31.2% of subjects received gastrointestinal drugs, 28.6% received anti-inflammatory drugs, 23.3% received antiplatelet drugs, 17.6% received statins, and 0.7% received antineoplastic drugs. Obese patients received each class of drug more frequently than normal-weight or overweight subjects (p<0.001 for all drug classes except antineoplastic among all groups and statins between overweight and obese subjects [p=NS]) (figure 1a). The largest difference in drug use between subjects who were obese and of normal weight was observed for the antidiabetic drug class (301% increase in obese subjects; p<0.001). Results were similar for the period up to data cut-off (p<0.001 for all drug classes except antineoplastic among all groups and stating between overweight and obese subjects [p=NS]) (figure 1b).

#### **Duration of hospitalisation**

In total, 1431 subjects (7.2%) were hospitalised at least once during the 1-year observation period and this increased to 3,231 subjects (16.3%) for the period up to data cut-off. In normal-weight, overweight, and obese subjects, hospitalisation rates were 7.4%, 8.7%, and 8.8%, respectively, at 1 year, and 19.0%, 23.0%, and 23.8%, respectively, at data cut-off. Obese and overweight subjects had a higher hospitalisation rate in comparison with normal weight individuals (p=0.006 and 0.03, at 1-year follow-up and data cut-off, respectively). In the 1-year observation period, the mean duration of hospitalisation was 3 (interguartile range; IQR 7) days in normal-weight subjects, 4 (IQR 7) days in overweight subjects, and 5 (IQR 8) days in obese subjects (p=NS). Within the group of obese subjects, median duration of hospitalisation was not different among the severe (4.5 [IQR 8] days), mild- (5 [IQR 8] days) and moderate-obese (4.5 [IQR 9.5] days) groups. The most common reasons for hospitalisation in the mild- and moderate-obese groups were type 2 diabetes and essential hypertension (not specified; 0.8% each). For severe-obese patients, the most common reasons for hospitalisation were severe obesity and benign essential hypertension (1.6% and 0.9%, respectively). Similarly, the median duration of hospitalisation for the period up to data cut-off did not show significant differences among groups (obese subjects, 5 [IQR 7] days; normal-weight subjects, 3 [IQR 7] days; and overweight subjects 4 [IQR 7] days, respectively; p=NS), as well as among obese subgroups (mild-obesity 4 [IQR 7] days; medium-obesity 5 [IQR 9] days; severe obesity 5 [IQR 7.5] days; p=NS).

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#### Use of specialist services

During the 1-year observation period, an average of 5.3 ( $\pm$  7.0) specialist services were required overall for obese subjects; the mean number of specialist services required was higher in the moderate-obese group (5.8  $\pm$  9.5) than in the other BMI groups (4.4  $\pm$  5.5, 5.0  $\pm$  7.2, 5.2  $\pm$  6.3, and 5.0  $\pm$  5.8 for normal-weight, overweight, mild-obese, and severe-obese groups, respectively, p<0.001). At the point of data cut-off, the mean number of specialist services required was 18.8 ( $\pm$  26.8) in the moderate-obese group, compared with 12.6 ( $\pm$  16.0), 15.8 ( $\pm$  21.3), 16.6 ( $\pm$  18.8), and 15.9 ( $\pm$  18.5) for the normal-weight, overweight, mild-obese, and severe-obese group.

#### Costs

During the observation period, the mean annual healthcare costs per subject was €821.80 for normal-weight group, €1,015.19 for overweight group and €1,166.52 for obese group, respectively. The mean healthcare cost per subject for the period up to data-cut-off was €2,468.27 for normal-weight group, €3,417.81 for overweight group and €3,782.21 for obese group, respectively. Mean healthcare costs during the 1year observation period were higher in obese than in non-obese subjects (p<0.001), while no differences were observed at data cut-off point (p=NS) (figure 2a and figure 2b). During the 1-year observation period, the highest mean annual costs per individual in the obese group were associated with drug prescriptions (€461), followed by hospitalisation costs (€423) and specialised outpatient services (€283). Subjects with moderate obesity generated higher costs than the mild- and severeobese groups, primarily owing to higher hospitalisation costs (p<0.01). Compared

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with normal-weight controls over 1 year, costs were higher by 23.5% for overweight subjects (34.3% when considering drug costs only), 34.8% for patients with mild obesity (47.0% for drug costs only), 70.4% for those with moderate obesity (90.1% for drug costs only), and 33.9% for patients with severe obesity (83.9% for drug costs only) (all values: p<0.01). At the point of data cut-off, the mean annual costs in the obese group had increased to  $\leq$ 1544,24 for drug prescriptions,  $\leq$ 1256,41 for hospitalisation costs, and  $\leq$ 981,56 for outpatient services (figure 2b). Similar to the 1year observation, costs were higher for obese patients in comparison with normal weight controls (p<0.01) (figure 2b). Again, patients with moderate obesity generated higher costs, mainly due to outpatient costs (p<0.05) (figure 2b).

### DISCUSSION

There are still limited data on healthcare resources utilisation for untreated obesity and its economic impact on healthcare systems. We report here on the prevalence and associated costs of obesity in an Italian population of over 20,000 individuals. Our study represents one of the largest European population studies on obesity and provides a real-life assessment of the economic impact of this increasingly prevalent condition. The findings of our study show that obese adults who did not receive treatment for their underlying obesity used more prescription drugs, experienced longer durations of hospitalisation, required more specialised outpatient healthcare and were associated with substantially greater costs compared with normal-weight adults.

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Our study directly evaluated the economic impact of comorbidities associated with obesity on the Italian healthcare system by integrating multiple data sources, taking into account the true costs of pharmaceutical treatments, the use of diagnostic and specialist services, and hospitalisations over a period of up to 5 years. Importantly, as a result of the structure of the Italian national healthcare system and the multiple data sources available, the healthcare resources and costs reported in this study are a true and accurate reflection of the real-life costs for each subject. Previous studies have been limited by the fact that they were based on resources used at a single point in time or restricted to a single hospital department. Our study in real-world setting helps to identify the actual consumption of resources by obese patients. However, as with any retrospective observational study, it should be noted that limitations might exist as a result of the variability of professional practice and information bias.

Obese subjects used a wide range of drugs, including antihypertensive, gastrointestinal, anti-inflammatory, antiplatelet, and antidiabetic drugs. Our study showed that obese subjects generally received each class of drug more frequently than normal-weight or overweight subjects, with the exception of antidepressant. This is likely to reflect the various comorbidities that obese subjects commonly experience if their underlying condition remains untreated, such as diabetes and hypertension. Notably, antidiabetic and antihypertensive drugs were used in around twice as many obese as normal-weight subjects. Overall healthcare costs were substantially higher for obese than for non-obese individuals. Prescriptions represented the greatest overall costs, highlighting the economic impact that obesityrelated comorbidities have on healthcare systems.

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There were also significant costs associated with hospitalisation, particularly for the moderate-obese group; this may be related to the longer mean duration of hospitalisation in these patients compared with severe-obese and non-obese subjects. The relatively short hospital stay observed in the severe-obesity group should be highlighted as this may suggest that many institutions within the Italian healthcare system are not adequately equipped to diagnose and treat morbidly obese subjects, such as radiological instruments not being suitable to host severely obese patients, or a lack of specialists with sufficient experience to prescribe suitable therapies to address the different comorbidities. This could result in these patients being discharged from hospital earlier than should be expected. It is also possible that, as severely obese people are frequently depressed,<sup>20-22</sup> they may refuse to leave home to go to hospital at all, unless they have an acute condition.

The prevalence of obesity reported in this study ( $22 \cdot 2\%$ ) is in line with the current WHO estimation of the prevalence of obesity in Italy ( $21 \cdot 0\%$ ),<sup>3</sup> but higher than other estimates (~10%).<sup>7 13</sup> The proportion of subjects who were overweight or obese increased with age, with more than half of adults aged ≥30 years being overweight or obese. Similar findings have previously been reported in Italy,<sup>6</sup> based on data from five surveys conducted between 2006 and 2010, the prevalence ratios for overweight/obesity in individuals aged ≥65 versus 18–24 years were 2.01 in men and 2.65 in women.<sup>7</sup> These data suggest that it may be important to target and educate individuals who are overweight or have mild obesity and are of working age, with the aim of preventing them from becoming more obese later in life.

It is important to raise awareness that the direct treatment of patients who are severely obese would help to reduce the economic impact of the condition on

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healthcare systems.<sup>23</sup> The initial costs associated with treatment, such as bariatric surgery, would probably be offset by the subsequent savings made on drug prescriptions, hospitalisation costs, and outpatient care related to the treatment of comorbidities.<sup>24 25</sup> Indeed, a recent meta-analysis, comprising 37,720 patients across 11 studies, showed that bariatric surgery significantly reduces drug use and costs.<sup>26</sup> In addition, the direct treatment of obesity would likely help to reduce the burden on physicians who spend a substantial amount of time treating the comorbidities associated with obesity. The value of preventative strategies for obesity is an important consideration for decision makers, particularly given the increasing concern over the sustainability of the healthcare system and the ageing population. Measures such as advocating the value of a healthy and balanced diet with regular exercise as part of an early obesity prevention strategy are likely to be important.

In conclusion, our data highlight the need to develop public health policies that aim to prevent the development of obesity at an early age and also to proactively and effectively treat severely obese patients, thereby reducing the overall economic burden of this condition.

### ACKNOWLEDGEMENTS

We thank Vito Basile, Chairman of Burson-Marsteller Italy, for his commitment in the design of the project and for his assistance. We also thank Andrew Jones, PhD, from Mudskipper Business Ltd, for medical editorial assistance with this manuscript. Special thanks are given to the general practitioners (Medico di Medicina Generale BMJ Open: first published as 10.1136/bmjopen-2016-013899 on 24 February 2017. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

[MMG]) and the three Italian local health authorities (ASL) for making available the data analysed in the study:

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#### ASL: Dott. Antonio Stellato

MMG: Enrico Benedetto, Giovanni Paudice, Antonio Mura, Vincenzo Piramide, Salvatore Scapolatello, Antonio Ambrosanio, Mario Avano, Irene Caruso, Giuseppe Crispano, Eliseo De Leo, Emilia De Simone, Salvatore Falanga, Giovanni Ferrara, Pasquale Festa, Massimo Maddaloni, Giovanni Mansueto, Pasqualino Mastromo, Francesco Carmine Miniello, Giovanni Piccolo Raffaele Napoli, Franco Schiano, and Angela Zappa

#### ASL Grosseto

ASL: Dott. Fabio Lena

MMG: Alessio Bonadonna, Massimo Olivoni, Franca Castellani, Gino Maestrini, Valeria Rombai, Laura Bellangioli, Gabriele Guidoni, Giancarlo Vitillo, Tommaso locca, Anna Pia Capperucci, Luca Pianelli, Ugo Simoni, Sandro Monaci, Marilena Del Santo, Andrea Salvetti, Giuseppe Virgili, Rolando Zullo, and Nicola Briganti

#### ASL Bergamo

#### ASL: Dott. Marco Gambera

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MMG: Elio Pinotti, Giuliana Giunti, Paola Fausta Tagliabue, Monica Rovelli, Francesca Marchesi, Alessandro Filippi, Marino Zappa, Anna Scorpiniti, Alex Fulgosi, Manuela Mariuz, Luca Benedetti, Lina Magrì, Angela Milesi, Pierrentao Pernici, Annamaria Cremaschi, Paola Bocchi, Mahmoud Mazid, Luigi Donzelli, Fulvio Patelli, Lucilla Luderin, Giovanni Argenti, Alfredo Di Landro, Carmela Neotti, and Sergio Nicoli

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## CONTRIBUTOR STATEMENT

Chiara Veronesi, Valerio Blini, and Luca Degli Esposti contributed to the design and conduct of the study, data collection and management, analysis and interpretation of the data, and preparation of the manuscript. Annamaria Colao, Marcello Lucchese, Monica D'Adamo, Silvia Savastano, Enrico Facchiano and Paolo Sbraccia contributed to clinical evaluation and data interpretation and investigated all aspects of the work, ensuring that guestions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors critically revised the manuscript for important intellectual content; all authors approved the final version of the manuscript.

## FUNDING

Unrestricted financial support for the collection of data and for medical editorial assistance was provided by Johnson & Johnson Medical.

## **COMPETING INTERESTS**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi disclosure.pdf and declare: all authors had financial support from Johnson & Johnson Medical for the submitted work; no financial relationship with any organisations that might have an interest in the submitted work in the previous three

years; no other relationship or activities that could appear to have influenced the submitted work.

## DATA SHARING

No additional data available. data a... BMJ Open: first published as 10.1136/bmjopen-2016-013899 on 24 February 2017. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de Enseignement Superieur (ABES)

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# Fig 1. Patients exposed to treatment, by BMI category and drug class, during (a) the 1-year observation period and (b) the period up to data cut-off

- (a) \*p<0.001 vs overweight and obese subjects; <sup>†</sup>p<0.001 vs obese subjects
- (b) \*p<0.001 vs overweight and obese subjects; <sup>†</sup>p<0.001 vs obese subjects

# Fig 2. Mean annual costs per surviving individual, by BMI category, during (a) the 1-year observation period and (b) the period up to data cut-off

- (a) Overall costs: p<0.001 vs overweight and obese subjects; p<0.01 vs mild and severe obese subjects. Drug costs: p<0.001, p<0.01; Hospitalisation costs: p<0.01, p=NS; Outpatient costs: p<0.01, p=NS</li>
- (b) Overall costs: p<0.001 vs overweight and obese subjects; p<0.01 vs mild and severe obese subjects. Drug costs: p<0.001, p=NS; Hospitalisation costs: p<0.001, p=NS; Outpatient costs: p<0.001, p<0.05</li>





## Patients exposed to treatment, by BMI category and drug class, during (a) the 1-year observation period and (b) the period up to data cut-off !! + (a) \*p < 0.001 vs overweight and obese subjects; $^{\dagger}p < 0.001$ vs obese subjects

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Figure 2a

**Mean annual costs per surviving individual, by BMI category, during (a) the 1-year observation period and (b) the period up to data cut-off** (a) Overall costs: p<0.001 vs overweight and obese subjects; p<0.01 vs mild and severe obese subjects. Drug costs: p<0.001, p<0.01; Hospitalisation costs: p<0.01, p=NS; Outpatient costs: p<0.01, p=NS BMJ Open: first published as 10.1136/bmjopen-2016-013899 on 24 February 2017. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de I Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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Figure 2b

**Mean annual costs per surviving individual, by BMI category, during (a) the 1-year observation period and (b) the period up to data cut-off** (b) Overall costs: p<0.001 vs overweight and obese subjects; p<0.01 vs mild and severe obese subjects. Drug costs: p<0.001, p=NS; Hospitalisation costs: p<0.001, p=NS; Outpatient costs: p<0.001, p<0.05

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## **BMJ Open**

#### Healthcare utilisation and economic impact of non-treated obesity in Italy: findings from a retrospective administrative and clinical database analysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2016-013899.R1
Article Type:	Research
Date Submitted by the Author:	24-Nov-2016
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<b>Primary Subject Heading</b> :	Diabetes and endocrinology
Secondary Subject Heading:	Health economics
Keywords:	Obesity, Body mass index, Healthcare resource consumption, Retrospective, Real-life study

SCHOLARONE<sup>™</sup> Manuscripts

## Healthcare utilisation and economic impact of non-treated obesity in Italy: findings from a retrospective administrative and clinical database analysis

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#### Word count: 3068

**Keywords:** Obesity, body mass index, healthcare resource consumption, retrospective, real-life study

#### ABSTRACT

 **Objectives:** Investigate the prevalence of obesity in Italy and examine its resource consumption and economic impact on the Italian healthcare system.

**Design:** Retrospective, observational, real-life study

**Setting:** Data from three health units from Northern (Bergamo, Lombardy), Central (Grosseto, Tuscany), and Southern (Naples, Campania) Italy.

Participants: All patients aged ≥18 years with at least one recorded BMI measurement between January 1st 2009 and December 31st 2012 were included.

**Interventions:** Information retrieved from the databases included primary care data, medical prescriptions, specialist consultations, and hospital discharge records from 2009–2013. Costs associated with these data were also calculated. Data are presented for two time periods (1 year after BMI measurement and study end).

**Primary and secondary outcome measures:** Primary – to estimate health resources consumption and the associated economic impact on the Italian NHS. Secondary – the prevalence and characteristics of subjects by BMI category.

**Results:** 20,159 adult subjects with at least one documented BMI measurement. Subjects with BMI  $\geq$ 30 kg/m<sup>2</sup> were defined as obese. The prevalence of obesity was 22.2% (N=4,471) and increased with age. At the 1-year observation period, obese subjects who did not receive treatment for their obesity experienced longer durations of hospitalisation (median length: 5 vs 3 days), used more prescription drugs (75.0% vs 57.7%), required more specialised outpatient healthcare (mean number: 5.3 vs

4.4), and were associated with greater costs, primarily owing to prescription drugs and hospital admissions (mean annual cost per year per patient:  $\in$ 460.6 vs  $\in$ 288.0 for drug prescriptions,  $\in$ 422.7 vs  $\in$  279.2 for hospitalisations, and  $\in$ 283.2 vs  $\in$ 251.7 for outpatient care), compared with normal-weight subjects. Similar findings were observed for the period up to data cut-off (mean follow-up of 2.7 years).

**Conclusions:** Untreated obesity has a significant economic impact on the Italian healthcare system, highlighting the need to raise awareness and proactively treat obese subjects.

#### Strengths and limitations of this study

- Large study on more than 20,000 subjects
- Real-world data coming from local health units
- Data retrieved from different geographical areas
- Direct evaluation of costs by integrating multiple data sources
- Limitations due to the retrospective nature of the study

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## INTRODUCTION

Obesity is now widely regarded as a global epidemic; worldwide, obesity rates have more than doubled since 1980.<sup>12</sup> According to the World Health Organization (WHO), more than 1.9 billion adults were overweight in 2014. Of these, over 600 million (~13% of the world's population) were obese, defined as having a body mass index (BMI) of  $\geq$ 30 kg/m<sup>2</sup>.<sup>1</sup> In Italy, WHO reports from 2014 showed that the prevalence of obesity was 20.4% among individuals aged  $\geq$ 18 years.<sup>3</sup> Obesity is a major risk factor for various chronic diseases, particularly if it remains untreated. Globally, 44% of diabetes, 23% of ischaemic heart disease, and 7–41% of certain cancers are attributable to being overweight or obese.<sup>1</sup> Obesity-associated mortality rates are also alarmingly high, with at least 2.8 million deaths each year resulting from being overweight or obese.<sup>1</sup> Obesity was once considered to be an issue associated with high-income countries only; however, its prevalence is now also increasing in lowand middle-income countries.<sup>4</sup>

Previous studies have shown that obesity and its associated comorbidities have a considerable economic impact on healthcare systems, primarily because of high costs for medication and hospitalisations.<sup>5-8</sup> However, in those studies, costs were only estimated indirectly. In contrast, we report here on the findings from a study of over 20,000 adults that investigated the prevalence of, and direct costs associated with, untreated obesity in three distinct regions of Italy – which differ in terms of geography and nutritional traditions – in order to understand the healthcare utilisation and economic impact of obesity on the Italian national healthcare system (NHS).
## **METHODS**

## Study design and population

This was a retrospective, observational, real-life study. To be eligible, individuals were required to be aged ≥18 years and to have at least one recorded BMI measurement between 1 January 2009 and 31 December 2012. The first recorded BMI was set as the index date. Eligible subjects were identified from registries at three Italian local health units that represent the primary Italian geographical areas: Bergamo, Lombardy (northern Italy), Grosseto, Tuscany (central Italy), and Naples, Campania (southern Italy).

BMI was classified as follows: underweight, <18.5 kg/m<sup>2</sup>; normal weight, ≥18.5 to <25 kg/m<sup>2</sup>; overweight, ≥25 to <30 kg/m<sup>2</sup>; obese, ≥30 kg/m<sup>2</sup>. Obesity was further classified as grade I, II and III based on BMI levels of ≥30 to <35 kg/m<sup>2</sup>, ≥35 to <40 kg/m<sup>2</sup>, and ≥40 kg/m<sup>2</sup>, respectively.<sup>9</sup>

An anonymous data file is routinely used by regional health authorities for epidemiological and administrative purposes. No identifiers related to subjects were provided to the researchers. In accordance with Italian law regarding data confidentiality,<sup>10</sup> the ethics committee of each local health units was notified about the study. Neither ethics committee approval nor informed consent was required for using encrypted retrospective information.

## Study objective

The primary objective of the study was to estimate health resource consumption and the economic impact of obesity on the Italian NHS. The secondary objective was to assess the prevalence and characteristics of subjects in relationship with the BMI category.

## Data sources and analysis

 Primary care data for each subject were retrospectively collected from the Health Search Database of the Società Italiana di Medicina Generale (Italian Society of General Medicine) for the period 2009–2013. Using the numeric code assigned to each citizen by the local health units as a unique identifier, this database was linked to the following databases: i) Medications Prescription Database, which includes anatomical–therapeutic–chemical (ATC) codes; ii) Hospital Discharge Database, which includes dates of hospital admission and discharge, as well as discharge diagnosis codes according to the *International Classification of Diseases Ninth Revision, Clinical Modification* (ICD-9-CM); iii) Laboratory Tests and Specialist Visits Database; iv) Mortality Database, from which data on mortality, but not cause of death, were collected; and v) Beneficiaries' Database, from which data regarding date of birth, sex, and place of residence were collected.

Data on drug use, hospitalisations, use of specialist services, and treatment costs were evaluated from the index date until 31 December 2013, corresponding to a period of at least 12 months and up to 5 years (the date of last enrolment was 31 December 2012). Specialist services encompassed all specialised outpatient healthcare, including diagnostic and laboratory tests (such as X-ray, ultrasound, magnetic resonance imaging, blood, and urinary tests), and consultations by specialist healthcare providers. The cost analysis was conducted from the perspective of the NHS. Costs are reported in Euros ( $\in$ ). Drug costs were evaluated

based on the Italian NHS costs at the time of the analysis. Outpatient services costs were evaluated according to regional tariffs. Hospitalisation costs were calculated using the Diagnosis-Related Group (DRG) tariff. Data were presented according to BMI class for the normal-weight, overweight, and obese (total and grade I, II and III) cohorts for two time periods: at 1 year following the index date (1-year observation period) and at the time of data cut-off (31 December 2013). Underweight subjects were included for the prevalence analysis only. Costs were also analysed according to age (using a cut-off of 65 years).

## Statistical analysis

To test normality assumption of data distribution, the Skewness-Kurtosis test was used. Continuous variables were reported as mean and standard deviation or median and interquartile range, as appropriate, and compared with analysis of variance (ANOVA) test, whereas categorical variables were expressed as numbers and percentages, and compared with the  $\chi^2$  test. Analyses were performed stratified for BMI groups. P-value ≤0.05 were considered statistically significant. All statistical analyses were conducted using Stata software version 12·0 (Stat Corp LP, College Station, TX, USA), data management was carried out using Microsoft SQL Server 2012.

## Role of funding source

Unrestricted financial support for the collection of data and for medical editorial assistance was provided by Johnson & Johnson Medical.

## RESULTS

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Overall, 20,159 adults were included in the study. Table 1 shows the characteristics of subjects who were classified as underweight, normal weight, overweight, and obese at the index date. The prevalence of obesity was 22.2% (N=4471); of these, 3253 (72.8%) were classified as grade I obesity, 898 (20.1%) as grade II obesity, and 320 (7.2%) as grade III obesity. The mean length of follow-up was 2.6, 2.7, and 2.8 years for the normal-weight, overweight, and obese groups, respectively (p=NS). Within the obese group, the mean length of follow-up was 2.8 years across each of the grade I, II and III obesity cohorts; 1.1% of subjects died at 1 year following the index date (normal weight 1.1%, overweight 1.2%, obese 1.1%; p=NS).

## Table 1. Baseline characteristics and demographics at the index date

		v	Veight		Total
	Under	Normal	Over	Obese	
	(BMI <18 <mark>.5</mark> )	(BMI ≥18 <mark>.5</mark>	(BMI ≥25 to <30)	(BMI ≥30)	
		to <25)			
Patients,	475 (2.3)	7686 (38.1)	7545 (37·4)	4471 (22·2)	20,159 (100)
n (%)					
Males:females, n:n	67:390	2977:4709	3996:3549	2048:2423	9088:11,071
Mean age ± SD, years	44.6 ± 20.4*	53.6 ± 17.2 <sup>†</sup>	59.3 ± 15.2 <sup>±</sup>	58.1 ± 15.1	56.5 ± 16.4
SD, standard deviation				7/	
*p<0.001 vs normal weight,	overweight, and obes	se; <sup>†</sup> p<0.001 vs overwei	ght and obese; <sup>‡</sup> p<0.001 vs c	obese	
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# Prevalence of obesity by age

The proportion of subjects who were overweight or obese increased with age, while it decreased for normal weight subjects (p<0.001) (table 2). Among subjects aged >30 years, more than half were classified as overweight or obese (table 2). In particular, among subjects aged between 30 and 64 years, 36.4 and 22.8% were overweight and obese, respectively; among subjects aged 65+ years, 44.2 and 23.7% were overweight and obese, respectively (table 2).

# Table 2. Proportions of patients classified as being of normal weight, overweight, and obese, stratified by age at the index date

	Normal	Over		
Prevalence	weight	weight	Obese	Total
18–29 years, n	743	267	189	1199
(%)	(62.0)*	(22.3)*	(15.8)*	(100.0)
30–64 years, n	4701	4195	2627	11523
(%)	(40.8) <sup>†</sup>	(36.4) <sup>†</sup>	(22.8) <sup>†</sup>	(100.0)
	2242	3083	1655	6980
65+ years, n (%)	(32.1)	(44.2)	(23.7)	(100.0)
Total	7686	7545	4471	

\*p<0.0001 vs 30–64 years and +65 years; <sup>†</sup>p<0.0001 vs +65 years

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## Use of prescription medication

In total, 13,002 subjects from the normal weight, overweight and obese groups (66%) received at least one prescription drug treatment during the 1-year observation period. 3,353 were obese subjects (75%), 4,437 were normal-weight subjects (57.7%) and 5,212 were overweight subjects (69.1%). These differences were significant (p<0.0001 among groups); 14,807 (75.2%) subjects had received at least one drug treatment at data cut-off; 3,666 were obese subjects (82%), 5,276 were normal-weight subjects (68.6%) and 5,865 were overweight subjects (77.7%). Again, these differences were significant (p<0.0001 among groups). During the 1year observation period, anti-hypertensive drugs were the most common drug class received (43.8% of subjects); 31.3% of subjects received gastrointestinal drugs, 28.8% received anti-inflammatory drugs, 23.4% received antiplatelet drugs, 17.7% received statins, and 0.7% received antineoplastic drugs. Obese patients received each class of drug more frequently than normal-weight or overweight subjects (p<0.001 for all drug classes except antineoplastic among all groups and statins between overweight and obese subjects [p=NS]) (figure 1a). The largest difference in drug use between subjects who were obese and of normal weight was observed for the antidiabetic drug class (30.1% increase in obese subjects; p<0.001). Results were similar for the period up to data cut-off (p<0.001 for all drug classes except antineoplastic among all groups and stating between overweight and obese subjects [p=NS]) (figure 1b).

## **Duration of hospitalisation**

In total, 1416 subjects (7.2%) were hospitalised at least once during the 1-year observation period and this increased to 3,204 subjects (16.3%) for the period up to data cut-off. In normal-weight, overweight, and obese subjects, hospitalisation rates were 6.5%, 7.7%, and 7.6%, respectively, at 1 year, and 14.8%, 17.3%, and 17.0%, respectively, at data cut-off. Obese and overweight subjects had a higher hospitalisation rate in comparison with normal weight individuals (p=0.006 and 0.03, at 1-year follow-up and data cut-off, respectively). In the 1-year observation period, the mean duration of hospitalisation was 3 (interguartile range; IQR 7) days in normal-weight subjects, 4 (IQR 7) days in overweight subjects, and 5 (IQR 8) days in obese subjects (p=NS). Within the group of obese subjects, median duration of hospitalisation was not different among the grade III (4.5 [IQR 8] days), grade I (5 [IQR 8] days) and grade II obese (4.5 [IQR 9.5] days) groups. The most common reasons for hospitalisation in the grade I and II obese groups were type 2 diabetes and essential hypertension (not specified; 0.8% each). For grade III obese patients, the most common reasons for hospitalisation were severe obesity and benign essential hypertension (1.6% and 0.9%, respectively). Similarly, the median duration of hospitalisation for the period up to data cut-off did not show significant differences among groups (obese subjects, 5 [IQR 7] days; normal-weight subjects, 3 [IQR 7] days; and overweight subjects 4 [IQR 7] days, respectively; p=NS), as well as among obese subgroups (grade I obesity 4 [IQR 7] days; grade II obesity 5 [IQR 9] days; grade III obesity 5 [IQR 7.5] days; p=NS).

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During the 1-year observation period, an average of 5.3 ( $\pm$  7.0) specialist services were required overall for obese subjects; the mean number of specialist services required was higher in the II grade obese group (5.8  $\pm$  9.5) than in the other BMI groups (4.4  $\pm$  5.5, 5.0  $\pm$  7.2, 5.2  $\pm$  6.3, and 5.0  $\pm$  5.8 for normal-weight, overweight, grade I obese, and grade III obese groups, respectively, p<0.001). At the point of data cut-off, the mean number of specialist services required was 18.8 ( $\pm$  26.8) in the grade II obese group, compared with 12.7 ( $\pm$  16.1), 15.8 ( $\pm$  21.3), 16.6 ( $\pm$  18.8), and 15.9 ( $\pm$  18.5) for the normal-weight, overweight, grade I and II obese groups, respectively, p<0.001.

## Costs

During the observation period, the mean annual healthcare costs per subject was €819.03 for normal-weight group, €1,015.19 for overweight group and €1,166.52 for obese group, respectively. The mean healthcare cost per subject for the period up to data-cut-off was €2,465.01 for normal-weight group, €3,417.81 for overweight group and €3,782.21 for obese group, respectively. Mean healthcare costs during the 1year observation period were higher in obese than in non-obese subjects (p<0.001), while no differences were observed at data cut-off point (p=NS) (figure 2a and figure 2b). During the 1-year observation period, the highest mean annual costs per individual in the obese group were associated with drug prescriptions (€461), followed by hospitalisation costs (€423) and specialised outpatient services (€283). Subjects with grade II obesity generated higher costs than the grade I and grade III obese groups, primarily owing to higher hospitalisation costs (p<0.01). Compared

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with normal-weight controls over 1 year, costs were higher by 23.5% for overweight subjects (34.3% when considering drug costs only), 34.8% for patients with grade I obesity (47.0% for drug costs only), 70.4% for those with grade II obesity (90.1% for drug costs only), and 33.9% for patients with grade III obesity (83.9% for drug costs only) (all values: p<0.01). At the point of data cut-off, the mean annual costs in the obese group had increased to €1544,24 for drug prescriptions, €1256,41 for hospitalisation costs, and €981,56 for outpatient services (figure 2b). Similar to the 1year observation, costs were higher for obese patients in comparison with normal weight controls (p<0.01) (figure 2b). Again, patients with grade II obesity generated higher costs, mainly due to outpatient costs (p<0.05) (figure 2b).

The possible effect of age, when comparing the impact of obesity on healthcare costs, is reported in Figure 3.

## DISCUSSION

There are still limited data on healthcare resources utilisation for untreated obesity and its economic impact on healthcare systems. We report here on the prevalence and associated costs of obesity in an Italian population of over 20,000 individuals. Our study represents one of the largest European population studies on obesity and provides a real-life assessment of the economic impact of this increasingly prevalent condition. The findings of our study show that obese adults who did not receive treatment for their underlying obesity used more prescription drugs, experienced longer durations of hospitalisation, required more specialised outpatient healthcare

and were associated with substantially greater costs compared with normal-weight adults.

Our study directly evaluated the economic impact of comorbidities associated with obesity on the Italian healthcare system by integrating multiple data sources, taking into account the true costs of pharmaceutical treatments, the use of diagnostic and specialist services, and hospitalisations over a period of up to 5 years. Importantly, as a result of the structure of the Italian national healthcare system and the multiple data sources available, the healthcare resources and costs reported in this study are a true and accurate reflection of the real-life costs for each subject. To our knowledge, at present only few studies have evaluated data on real-life healthcare costs from obesity associated with BMI.<sup>11-13</sup> Previous studies have been limited by the fact that they were based on resources used at a single point in time or restricted to a single hospital department. Our study in real-world setting helps to identify the actual consumption of resources by obese patients. However, as with any retrospective observational study, it should be noted that limitations might exist as a result of the variability of professional practice and information bias.

Obese subjects used a wide range of drugs, including antihypertensive, gastrointestinal, anti-inflammatory, antiplatelet, and antidiabetic drugs. Our study showed that obese subjects generally received each class of drug more frequently than normal-weight or overweight subjects, with the exception of antidepressant. This is likely to reflect the various comorbidities that obese subjects commonly experience if their underlying condition remains untreated, such as diabetes and hypertension. Notably, antidiabetic and antihypertensive drugs were used in around twice as many obese as normal-weight subjects. Overall healthcare costs were

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substantially higher for obese than for non-obese individuals. Prescriptions represented the greatest overall costs, highlighting the economic impact that obesityrelated comorbidities have on healthcare systems.

There were also significant costs associated with hospitalisation, particularly for the grade II obese group; this may be related to the longer mean duration of hospitalisation in these patients compared with grade III obese and non-obese subjects. The relatively short hospital stay observed in the grade III obesity group should be highlighted as this may suggest that many institutions within the Italian healthcare system are not adequately equipped to diagnose and treat morbidly obese subjects, such as radiological instruments not being suitable to host severely obese patients, or a lack of specialists with sufficient experience to prescribe suitable therapies to address the different comorbidities. This could result in these patients being discharged from hospital earlier than should be expected. It is also possible that, as severely obese people are frequently depressed,<sup>14-16</sup> they may refuse to leave home to go to hospital at all, unless they have an acute condition.

The prevalence of obesity reported in this study  $(22 \cdot 2\%)$  is in line with the current WHO estimation of the prevalence of obesity in Italy  $(21 \cdot 0\%)$ ,<sup>3</sup> but higher than other estimates (~10%).<sup>17 18</sup> The proportion of subjects who were overweight or obese increased with age, with more than half of adults aged ≥30 years being overweight or obese. Similar findings have previously been reported in Italy;<sup>19</sup> based on data from five surveys conducted between 2006 and 2010, the prevalence ratios for overweight/obesity in individuals aged ≥65 versus 18–24 years were 2.01 in men and 2.65 in women.<sup>17</sup> These data suggest that it may be important to target and

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educate individuals who are overweight or have grade I obesity and are of working age, with the aim of preventing them from becoming more obese later in life.

Since older subjects are likely to consume more healthcare resources, we have also analysed the possible effect of age when comparing the impact of obesity on healthcare costs. The results highlight that healthcare costs did not increase just because obese patients were older than normal weight patients, but that in each age group, the costs of obese patients were higher than other patients.

It is important to raise awareness that the direct treatment of patients who are severely obese would help to reduce the economic impact of the condition on healthcare systems.<sup>20</sup> The initial costs associated with treatment, such as bariatric surgery, would probably be offset by the subsequent savings made on drug prescriptions, hospitalisation costs, and outpatient care related to the treatment of comorbidities.<sup>21 22</sup> Indeed, a recent meta-analysis, comprising 37,720 patients across 11 studies, showed that bariatric surgery significantly reduces drug use and costs.<sup>23</sup> In addition, the direct treatment of obesity would likely help to reduce the burden on physicians who spend a substantial amount of time treating the comorbidities associated with obesity. The value of preventative strategies for obesity is an important consideration for decision makers, particularly given the increasing concern over the sustainability of the healthcare system and the ageing population. Measures such as advocating the value of a healthy and balanced diet with regular exercise as part of an early obesity prevention strategy are likely to be important.

Although in our study we used the healthcare databases of Lombardy, Tuscany and Campania, three Italian Regions localised from north to south of Italy, including data

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> for a total population of about 2.3 million, and Health Search Database of the Società Italiana di Medicina Generale, larger studies are needed to confirm and to enhance the generalisability of the findings.

> In conclusion, our data highlight the need to develop public health policies that aim to prevent the development of obesity at an early age and also to proactively and effectively treat severely obese patients, thereby reducing the overall economic burden of this condition.

# ACKNOWLEDGEMENTS

We thank Vito Basile, Chairman of Burson-Marsteller Italy, for his commitment in the design of the project and for his assistance. We also thank Andrew Jones, PhD, from Mudskipper Business Ltd, for medical editorial assistance with this manuscript. Special thanks are given to the general practitioners (Medico di Medicina Generale [MMG]) and the three Italian local health authorities (ASL) for making available the data analysed in the study:

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MMG: Enrico Benedetto, Giovanni Paudice, Antonio Mura, Vincenzo Piramide, Salvatore Scapolatello, Antonio Ambrosanio, Mario Avano, Irene Caruso, Giuseppe Crispano, Eliseo De Leo, Emilia De Simone, Salvatore Falanga, Giovanni Ferrara, Pasquale Festa, Massimo Maddaloni, Giovanni Mansueto, Pasqualino Mastromo,

## ASL Grosseto

## ASL: Dott. Fabio Lena

MMG: Alessio Bonadonna, Massimo Olivoni, Franca Castellani, Gino Maestrini, Valeria Rombai, Laura Bellangioli, Gabriele Guidoni, Giancarlo Vitillo, Tommaso locca, Anna Pia Capperucci, Luca Pianelli, Ugo Simoni, Sandro Monaci, Marilena Del Santo, Andrea Salvetti, Giuseppe Virgili, Rolando Zullo, and Nicola Briganti

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## **CONTRIBUTOR STATEMENT**

Chiara Veronesi, Valerio Blini, and Luca Degli Esposti contributed to the design and conduct of the study, data collection and management, analysis and interpretation of the data, and preparation of the manuscript. Annamaria Colao, Marcello Lucchese, Monica D'Adamo, Silvia Savastano, Enrico Facchiano and Paolo Sbraccia contributed to clinical evaluation and data interpretation and investigated all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors critically revised the manuscript for important intellectual content; all authors approved the final version of the manuscript.

# FUNDING

Unrestricted financial support for the collection of data and for medical editorial assistance was provided by Johnson & Johnson Medical.

# **COMPETING INTERESTS**

All authors have completed the ICMJE uniform disclosure form at <u>www.icmje.org/coi\_disclosure.pdf</u> and declare: all authors had financial support from Johnson & Johnson Medical for the submitted work; no financial relationship with any organisations that might have an interest in the submitted work in the previous three years; no other relationship or activities that could appear to have influenced the submitted work.

# **DATA SHARING**

No additional data available.

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# **FIGURE LEGENDS**

# Fig 1. Patients exposed to treatment, by BMI category and drug class, during (a) the 1-year observation period and (b) the period up to data cut-off



\*p<0.001 vs overweight and obese subjects; <sup>†</sup>p<0.001 vs obese subjects

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\*p<0.001 vs overweight and obese subjects; <sup>†</sup>p<0.001 vs obese subjects

Fig 2. Mean annual costs per surviving individual, by BMI category, during (a) the 1-year observation period and (b) the period up to data cut-off



Overall costs: p<0.001 vs overweight and obese subjects; p<0.01 vs grade I and grade II obese subjects. Drug costs: p<0.001, p<0.01; Hospitalisation costs: p<0.01, p=NS; Outpatient costs: p<0.01, p=NS

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Overall costs: p<0.001 vs overweight and obese subjects; p<0.01 vs grade I and grade II obese subjects. Drug costs: p<0.001, p=NS; Hospitalisation costs: p<0.001, p=NS; Outpatient costs: p<0.001, p<0.05



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173x105mm (300 x 300 DPI)

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Figure 2a

Fig 2a

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Figure 2b

Fig 2b

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Figure 3

Fig 3

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	nt—Check	list of items that should be included in reports of <i>conort studies</i>
	ltem No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		The title on page 1 in the main manuscript states the study design:
		"Healthcare utilisation and economic impact of non-treated obesity in Ital findings from a retrospective administrative and clinical database analysis"
		(b) Provide in the abstract an informative and balanced summary of wh was done and what was found
		The Abstract in the main manuscript provides a balanced summary of wh was done and what was found:
		ABSTRACT
		<b>Objective:</b> Aim of this study was to investigate the prevalence of obesity Italy and to examine its resource consumption and economic impact on the Italian healthcare system.
		Design: Retrospective, observational, real-life study
		<b>Setting:</b> Analysis of data performed by integrating administrative database that included a total of approximately 2.3 million health-assisted individua from three Italian Local Health Units from northern (Bergamo, Lombardy
		central (Grosseto, Tuscany), and southern (Naples, Campania) Italy.
		<b>Participants:</b> All patients aged $\geq 18$ years with at least one recorded BM measurement between January 1 <sup>st</sup> 2009 and December 31st 2012 we included.
		Main outcome measures: The primary outcome was health resource consumption and the associated economic impact on the Italian NH Secondary outcome measures were the prevalence and characteristics subjects in relationship with the BMI category.
		<b>Results:</b> 20,159 adult subjects with at least one documented body maindex (BMI) measurement from three local health units. Subjects with BI
		≥30 kg/m <sup>4</sup> were defined as obese. The prevalence of obesity was 22.2 (N=4,471) and increased with age. At the 1-year observation period, obe subjects who did not receive treatment for their obesity experienced long
		durations of hospitalisation (median length: 5 vs 3 days), used mo prescription drugs (75.2% vs 57.7%), required more specialised outpatie healthcare (mean number: 5.3 vs 4.4), and were associated with great
		costs, primarily owing to prescription drugs and hospital admissions (mea annual cost per year per patient: €460.6 vs €288.0 for drug prescription €422.7 vs €279.2 for hospitalisations, and €283 vs €251.7 for outpatie
		care), compared with normal-weight subjects. Similar findings were observe

		for the period up to data cut-off (mean follow-up of 2.7 years).
		<b>Conclusions:</b> Untreated obesity has a significant economic impact on the Italian healthcare system, highlighting the need to raise awareness and proactively treat obese subjects.
Introduction		
Background/	2	Explain the scientific background and rationale for the investigation being reported
		In the introduction in the main manuscript a scientific background and rationale is provided:
		Obesity is now widely regarded as a global epidemic; worldwide, obesity rates have more than doubled since 1980. <sup>12</sup> According to the World Health Organization (WHO), more than 1·9 billion adults were overweight in 2014. Of these, over 600 million (~13% of the world's population) were obese, defined as having a body mass index (BMI) of $\geq$ 30 kg/m <sup>2</sup> . <sup>1</sup> In Italy, WHO reports from 2014 showed that the prevalence of obesity was 20.4% among individuals aged $\geq$ 18 years. <sup>3</sup> Obesity is a major risk factor for various chronic diseases, particularly if it remains untreated. Globally, 44% of diabetes, 23% of ischaemic heart disease, and 7–41% of certain cancers are attributable to being overweight or obese. <sup>1</sup> Obesity-associated mortality rates are also alarmingly high, with at least 2.8 million deaths each year resulting from being overweight or obese. <sup>1</sup> Obesity was once considered to be an issue associated with high-income countries only; however, its prevalence is now also increasing in low- and middle-income countries. <sup>4</sup>
		Previous studies have shown that obesity and its associated comorbidities have a considerable economic impact on healthcare systems, primarily because of high costs for medication and hospitalisations. <sup>5-8</sup> However, in those studies, costs were only estimated indirectly. In contrast, we report here on the findings from a study of over 20,000 adults that investigated the prevalence of, and direct costs associated with, untreated obesity in three distinct regions of Italy – which differ in terms of geography and nutritional traditions – in order to understand the healthcare utilisation and economic impact of obesity on the Italian national healthcare system (NHS).
Objectives	3	State specific objectives, including any prespecified hypotheses
		The objectives are stated in both the Introduction and Methods sections:
		we report here on the findings from a study of over 20,000 adults that investigated the prevalence of, and direct costs associated with, untreated obesity in three distinct regions of Italy – which differ in terms of geography and nutritional traditions – in order to understand the healthcare utilisation and economic impact of obesity on the Italian national healthcare system (NHS)

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	The primary objective of the study was to estimate health re- consumption and the economic impact of obesity on the Italian NH secondary objective was to assess the prevalence and characterist subjects in relationship with the BMI category.	source S. The tics of
Methods		
Study design	4 Present key elements of study design early in the paper	
	The key elements are presented in the method section of the manuscript:	main
	Study design and population	
	This was a retrospective, observational, real-life study. To be en individuals were required to be aged ≥18 years and to have at leas recorded BMI measurement between 1 January 2009 and 31 Dec 2012. The first recorded BMI was set as the index date. Eligible subjects identified from registries at three Italian local health units that represe primary Italian geographical areas: Bergamo, Lombardy (northern Grosseto, Tuscany (central Italy), and Naples, Campania (southern Italy	ligible, st one ember s were ent the Italy), ).
	BMI was classified as follows: underweight, <18.5 kg/m <sup>2</sup> ; normal w ≥18.5 to <25 kg/m <sup>2</sup> ; overweight, ≥25 to <30 kg/m <sup>2</sup> ; obese, ≥30 l Obesity was further classified as grade I, II and III based on BMI levels to <35 kg/m <sup>2</sup> , ≥35 to <40 kg/m <sup>2</sup> , and ≥40 kg/m <sup>2</sup> , respectively. <sup>9</sup>	veight, kg/m². of ≥30
	An anonymous data file is routinely used by regional health authorit epidemiological and administrative purposes. No identifiers relat subjects were provided to the researchers. In accordance with Italia regarding data confidentiality, <sup>10</sup> the ethics committee of each local units was notified about the study. Neither ethics committee approv informed consent was required for using encrypted retrosp information.	ies for ed to In law health Inor pective
	Data sources and analysis	
	Primary care data for each subject were retrospectively collected fro Health Search Database of the Società Italiana di Medicina Generale ( Society of General Medicine) for the period 2009–2013. Using the nu code assigned to each citizen by the local health units as a unique ide	m the Italian ımeric ntifier.
	this database was linked to the following databases: i) Medic Prescription Database, which includes anatomical–therapeutic–che (ATC) codes; ii) Hospital Discharge Database, which includes dates of he	ations emical ospital
	admission and discharge, as well as discharge diagnosis codes accord the International Classification of Diseases Ninth Revision, C Modification (ICD-9-CM); iii) Laboratory Tests and Specialist Visits Data iv) Mortality Database, from which data on mortality, but not can dooth ware collected, and v) Datafining (2014)	ling to Clinical abase; use of
	regarding date of birth, sex, and place of residence were collected.	uutu
	Data on drug use, hospitalisations, use of specialist services, and trea costs were evaluated from the index date until 31 December	tment 2013,

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19 20 21			subjects were included for the prevalence analysis only. Costs were also analysed according to age (using a cut off of 65-years).
21 22 23 24 25 26 27 28	Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection The setting, locations and relevant dates are presented in the method section (paragraphs "Study design and population" "Data sources and analysis") of the main manuscript:
29 30 31 32 33			The data used for the analysis were obtained from the healthcare databases of three Local Health Units (LHUs), whose databases included a total population of about 2.3 million health-assisted individuals, in the Italian regions of Lombardy, Tuscany and Campania.
34 35 36	Participants	6	( <i>a</i> ) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
37 38 39			(b) For matched studies, give matching criteria and number of exposed and unexposed
40 41 42			The participants are described in the methods section (paragraph "Study design and populations") of the main manuscript:
43 44 45 46 47 48 49 50 51 52			This was a retrospective, observational, real-life study. To be eligible, individuals were required to be aged $\geq 18$ years and to have at least one recorded BMI measurement between 1 January 2009 and 31 December 2012. The first recorded BMI was set as the index date. () BMI was classified as follows: underweight, <18.5 kg/m <sup>2</sup> ; normal weight, $\geq 18.5$ to <25 kg/m <sup>2</sup> ; overweight, $\geq 25$ to <30 kg/m <sup>2</sup> ; obese, $\geq 30$ kg/m <sup>2</sup> . Obesity was further classified as grade I, II and III based on BMI levels of $\geq 30$ to <35 kg/m <sup>2</sup> , $\geq 35$ to <40 kg/m <sup>2</sup> , and $\geq 40$ kg/m <sup>2</sup> , respectively.
53 54			The methods of follow-up are described in the methods section (paragraph
55 56			"Data sources and analysis") of the main manuscript:
57 58 59 60			Data on drug use, hospitalisations, use of specialist services, and treatment costs were evaluated from the index date until 31 December 2013,
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1 2 3 4 5 6 7 8 9 10 11 12 13	Variables	7	corresponding to a period of at least 12 months and up to 5 years (the date of last enrolment was 31 December 2012). () Data were presented according to BMI class for the normal-weight, overweight, and obese (total and grade I, II and III) cohorts for two time periods: at 1 year following the index date (1-year observation period) and at the time of data cut-off (31 December 2013). Underweight subjects were included for the prevalence analysis only. Costs were also analysed according to age (using a cut off of 65-years). Clearly define all outcomes, exposures, predictors, potential confounders,	
14 15			and effect modifiers. Give diagnostic criteria, if applicable	
16 17			The outcomes are described in the methods section of the main manuscript:	7
18			manuscript:	
19			Data on drug use, hospitalisations, use of specialist services, and	
20			treatment costs were evaluated from the index date until 31 December 2013,	
21			corresponding to a period of at least 12 months and up to 5 years (the date	
22			of last enrolment was 31 December 2012). Specialist services encompassed	
24			all specialised outpatient healthcare, including diagnostic and laboratory	
25			tests (such as X-ray, ultrasound, magnetic resonance imaging, blood, and	
26			urinary tests), and consultations by specialist healthcare providers. The cost	
28			analysis was conducted with the perspective of the National Health System.	
29			costs are reported in Euros $(\mathbf{E})$ currency. () Data were presented according	
30			I and III) cohorts for two time periods: at 1 year following the index date (1-	
31			vear observation period) and at the time of data cut-off (31 December 2013)	
32			Underweight subjects were included for the prevalence analysis only. Costs	
33 34			were also analysed according to age (using a cut off of 65-years).	
35	Data asumas (	0*	For each unstable of interest, size country of data and data its of mother do of	
36	Data sources/	8*	For each variable of interest, give sources of data and details of methods of	
37	measurement		if there is more than one group	
38			If there is more than one group	
39 40			Data sources and details of methods of assessment are given in the	
41			methods section:	
42				
43			This was a retrospective, observational, real-life study. To be eligible,	
44 15			inuiviuuuis were required to be aged 218 years and to have at least one recorded BMI measurement between 1 January 2000 and 21 December	-
45 46			2012 The first recorded BMI was set as the index data. Eligible subjects were	5
47			2012. The just recorded birth was set as the index date. Engible subjects were identified from registries at three Italian local health units that represent the	
48			nimary Italian geographical greas: Bergamo Lombardy (northern Italy)	
49			Grosseto, Tuscany (central Italy), and Nanles, Campania (southern Italy)	
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วา 52			BMI was classified as follows: underweight, <18.5 kg/m <sup>2</sup> ; normal weight,	
53			$\geq$ 18.5 to <25 kg/m <sup>-</sup> ; overweight, $\geq$ 25 to <30 kg/m <sup>+</sup> ; obese, $\geq$ 30 kg/m <sup>4</sup> .	
54			Obesity was jurtner classified as grade I, II and III based on BMI levels of $\geq 30$	
55			to <35 kg/m , 235 to <40 kg/m , and 240 kg/m , respectively.	
56			Primary care data for each subject were retrospectively collected from the	c
5/ 59			Health Search Database of the Società Italiana di Medicina Generale (Italian	O
00 59				
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		Society of General Medicine) for the period 2009–2013. ()	
		Data on drug use, hospitalisations, use of specialist services, and treatment costs were evaluated from the index date until 31 December 2013, corresponding to a period of at least 12 months and up to 5 years (the date of last enrolment was 31 December 2012). Specialist services encompassed all specialised outpatient healthcare, including diagnostic and laboratory tests (such as X-ray, ultrasound, magnetic resonance imaging, blood, and urinary tests), and consultations by specialist healthcare providers. The cost analysis was conducted with the perspective of the National Health System. Costs are reported in Euros ( $\pounds$ ) currency. Drug costs were evaluated using the Italian National Health Service purchase both at the time of analysis. Outpatient services costs were evaluated according to regional tariffs. Hospitalization costs were calculated using the Diagnosis-Related Group (DRG) tariff. Data were presented according to BMI class for the normal- weight, overweight, and obese (total and grade I, II and III) cohorts for two time periods: at 1 year following the index date (1-year observation period) and at the time of data cut-off (31 December 2013). Underweight subjects were included for the prevalence analysis only. Costs were also analysed according to age (using a cut off of 65-years).	
Bias	9	Describe any efforts to address potential sources of bias	
		This is addressed by the design of the study and the clearly defined data selection specifications	
Study size	10	Explain how the study size was arrived at	
		How the study size was arrived at is described in the methods section	
		Sample size dictated by the source databases	
Quantitative variables	11	Sample size dictated by the source databases Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Quantitative variables	11	Sample size dictated by the source databases Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why The handling of the variables is described in the "Statistical analysis" paragraph:	
Quantitative variables	11	Sample size dictated by the source databasesExplain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and whyThe handling of the variables is described in the "Statistical analysis" paragraph:To test normality assumption of data distribution, the Skewness-Kurtosis test was used. Continuous variables were reported as mean and standard deviation or median and interquartile range, as appropriate, and compared with analysis of variance (ANOVA) test, whereas categorical variables were expressed as numbers and percentages, and compared with the $\chi^2$ test.	
Quantitative variables Statistical methods	11	Sample size dictated by the source databasesExplain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and whyThe handling of the variables is described in the "Statistical analysis" paragraph:To test normality assumption of data distribution, the Skewness-Kurtosis test was used. Continuous variables were reported as mean and standard deviation or median and interquartile range, as appropriate, and compared with analysis of variance (ANOVA) test, whereas categorical variables were expressed as numbers and percentages, and compared with the $\chi^2$ test.(a) Describe all statistical methods, including those used to control for confounding	
Quantitative variables Statistical methods	11	Sample size dictated by the source databasesExplain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and whyThe handling of the variables is described in the "Statistical analysis" paragraph:To test normality assumption of data distribution, the Skewness-Kurtosis test was used. Continuous variables were reported as mean and standard deviation or median and interquartile range, as appropriate, and compared with analysis of variance (ANOVA) test, whereas categorical variables were expressed as numbers and percentages, and compared with the $\chi^2$ test.(a) Describe all statistical methods, including those used to control for confounding(b) Describe any methods used to examine subgroups and interactions	
Quantitative variables Statistical methods	11	<ul> <li>Sample size dictated by the source databases</li> <li>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</li> <li>The handling of the variables is described in the "Statistical analysis" paragraph:</li> <li>To test normality assumption of data distribution, the Skewness-Kurtosis test was used. Continuous variables were reported as mean and standard deviation or median and interquartile range, as appropriate, and compared with analysis of variance (ANOVA) test, whereas categorical variables were expressed as numbers and percentages, and compared with the \chi<sup>2</sup> test.</li> <li>(a) Describe all statistical methods, including those used to control for confounding</li> <li>(b) Describe any methods used to examine subgroups and interactions</li> <li>(c) Explain how missing data were addressed</li> </ul>	
		( <u>e</u> ) Describe any sensitivity analyses	7, 8
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		The statistical methods are given in the "Statistical analysis" paragraph:	
		To test normality assumption of data distribution, the Skewness-Kurtosis test was used. Continuous variables were reported as mean and standard deviation or median and interquartile range, as appropriate, and compared with analysis of variance (ANOVA) test, whereas categorical variables were expressed as numbers and percentages, and compared with the $\chi^2$ test. Analyses were performed stratified for BMI groups. P-value $\leq 0.05$ were considered statistically significant. All statistical analyses were conducted using Stata software version 12-0 (Stat Corp LP, College Station, TX, USA), data management will be carried out using Microsoft SQL Server 2012.	
Results	C		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		The numbers of individuals are given in the Results section	9–14
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		The characteristics of study participants are given in Tables 1 and 2.	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	
		() cohorts for two time periods: at 1 year following the index date (1-year observation period) and at the time of data cut-off (31 December 2013). (follow-up period)	7
		The mean length of follow-up was 2.6, 2.7, and 2.8 years for the normal-weight, overweight, and obese groups, respectively	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	
		Numbers of outcome events were reported in the Results section, and in Figures 1 and 2	8, 9, 1: 13, 14
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	

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		Variables defined in Statistical analysis section and analyses reported in Figure 1 and 2	11,13, 14, 26– 29
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8, 11,12
Discussion	C		
Key results	18	Summarise key results with reference to study objectives	
		Key results are summarized as follows in the Discussion:	14,15
		() The findings of our study show that obese adults who did not receive treatment for their underlying obesity used more prescription drugs, experienced longer durations of hospitalisation, required more specialised outpatient healthcare and were associated with substantially greater costs compared with normal-weight adults.	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
		Limitations are summarized as follows in the Discussion:	15
		as with any retrospective observational study, it should be noted that limitations might exist as a result of the variability of professional practice and information bias.	13
		Although in our study we used the healthcare databases of Lombardy, Tuscany and Campania, three Italian Regions localized from north to south of Italy, including data for a total population of about 2.3 million, and Health Search Database of the Società Italiana di Medicina Generale larger studies are needed to confirm and to enhance the generalizability of the findings.	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
		The interpretation is given as follows in the Discussion:	
		There are still limited data on healthcare resources utilisation for untreated obesity and its economic impact on healthcare systems. We report here on the prevalence and associated costs of obesity in an Italian population of over 20,000 individuals. Our study represents one of the largest European population studies on obesity and provides a real-life assessment of the economic impact of this increasingly prevalent condition. () The findings of	14–17

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our study show that obese adults who did not receive treatment for their underlying obesity used more prescription drugs, experienced longer durations of hospitalisation, required more specialised outpatient healthcare and were associated with substantially greater costs compared with normalweight adults.

Our study directly evaluated the economic impact of comorbidities associated with obesity on the Italian healthcare system by integrating multiple data sources, taking into account the true costs of pharmaceutical treatments, the use of diagnostic and specialist services, and hospitalisations over a period of up to 5 years. Importantly, as a result of the structure of the Italian national healthcare system and the multiple data sources available, the healthcare resources and costs reported in this study are a true and accurate reflection of the real-life costs for each subject. To our knowledge, at present only few studies have evaluated data on real-life healthcare costs from obesity associated with body mass index (BMI).<sup>11-13</sup> Previous studies have been limited by the fact that they were based on resources used at a single point in time or restricted to a single hospital department. Our study in real-world setting helps to identify the actual consumption of resources by obese patients. However, as with any retrospective observational study, it should be noted that limitations might exist as a result of the variability of professional practice and information bias.

These data suggest that it may be important to target and educate individuals who are overweight or have grade I obesity and are of working age, with the aim of preventing them from becoming more obese later in life.

It is important to raise awareness that the direct treatment of patients who are severely obese would help to reduce the economic impact of the condition on healthcare systems.<sup>14</sup> (....) In addition, the direct treatment of obesity would likely help to reduce the burden on physicians who spend a substantial amount of time treating the comorbidities associated with obesity. The value of preventative strategies for obesity is an important consideration for decision makers, particularly given the increasing concern over the sustainability of the healthcare system and the ageing population. Measures such as advocating the value of a healthy and balanced diet with regular exercise as part of an early obesity prevention strategy are likely to be important.

Generalisability

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Discuss the generalisability (external validity) of the study results

#### The issue of generalisability is addressed as follows in the Discussion:

18

Although in our study we used the healthcare databases of Lombardy, Tuscany and Campania, three Italian Regions localized from north to south of Italy, including data for a total population of about 2.3 million, and Health Search Database of the Società Italiana di Medicina Generale larger studies are needed to confirm and to enhance the generalizability of the findings.

Despite these limitations, our study indicates that in a "real-world" setting,

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our data highlight the need to develop public health policies that aim to prevent the development of obesity at an early age and also to proactively and effectively treat severely obese patients, thereby reducing the overall economic burden of this condition.

# Other information

Funding	22	Give the source of funding and the role of the funders for the present study	
		and, if applicable, for the original study on which the present article is based	
		Such information is given in the Funding section:	21
		Role of funding source	
		Unrestricted financial support for the collection of data and for medical editorial assistance was provided by Johnson & Johnson Medical.	

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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http://www.who.int/mediacentre/factsheets/fs311/en/.

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- World Health Organization. Global Health Observatory Data Repository. Obesity, data by country. 2015.
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