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ORIGINAL ARTICLE

# Role of obesity on all-cause mortality in whites with type 2 diabetes from Italy

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**Abstract** Mortality rate of diabetic patients is twice as much that of non-diabetic individuals. The role of obesity on mortality risk in patients with type 2 diabetes is controversial. Aim of our study was to address the relationship between obesity and all-cause mortality in a real-life set of white patients with type 2 diabetes from central-southern Italy from the Gargano Mortality Study (GMS). In addition, we used genetic data from genome-wide association studies (GWAs)-derived single nucleotide polymorphisms (SNPs) firmly associated with body mass index (BMI), in order to investigate the intrinsic nature of reduced mortality rate we, in fact, observed in obese patients. Study subjects with type 2 diabetes ($n = 764$) are part of the GMS, which is aimed at unraveling predictors of incident all-cause mortality. Time-to-death analyses were performed by Cox regression. Association between genotype risk score and obesity was tested by logistic regression. Of the 32 SNPs firmly associated with BMI, we investigated those with BMI $\beta$ value $\geq$0.10 kg/m$^2$ and allele frequency $\geq$10 %. Genotyping was performed by KBioscience (http://www.lgcgenomics.com/). In GMS, obesity predicted a 45 % reduction in all-cause mortality. Individuals with high "obesity genetic load" (i.e., those carrying >9 risk alleles) were 60 % more likely to be obese as compared to individuals with low "obesity genetic load." Most importantly, mortality rate was not different in individuals with high and low "obesity genetic load," thus indicating no role of obesity genes on all-cause mortality and speaking against a cause–effect relationship underlying the association between obesity and reduced mortality rate.

**Keywords** Paradoxical effect · Reverse epidemiology · Mendelian randomization · Mortality prediction

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## Introduction

Mortality rate of diabetic patients is about twice as much that of non-diabetic individuals of similar age [1]. In order to target aggressive prevention strategies, a better understanding of predisposing factors to such an increased risk is timely and definitively needed. While there is no doubts that obesity is a major risk factor for all-cause mortality in otherwise healthy individuals [2], its role in patients with type 2 diabetes is controversial [3–7], with some studies showing a

deleterious [4] and others a protective, paradoxical [6–8] effect. To make this scenario even most confusing, some studies reported a divergent effect of obesity on all-cause mortality in type 2 diabetes, being protective only in elderly people (i.e., ≥65 years old) [3, 5]. Some of the observed inconsistencies might be due to a different effect of body mass index (BMI) on mortality risk across different study populations [9]. The aim of our study was to address the relationship between obesity and all-cause mortality in a real-life set of white patients with type 2 diabetes from central-southern Italy, as allowed by the Gargano Mortality Study (GMS) cohort [10]. In addition, we used genetic data from genome-wide association studies (GWAs)-derived single nucleotide polymorphisms (SNPs) firmly associated with BMI [11], in order to offer preliminary evidences about the intrinsic nature underlying the association we did find between obesity and reduced mortality rate.

## Methods

### The Gargano Mortality Study (GMS)

One thousand and twenty-eight whites with type 2 diabetes (according to ADA 2003 criteria) were consecutively recruited at Scientific Institute "Casa Sollievo della Sofferenza" in San Giovanni Rotondo (Apulia, central-southern Italy) from November 1, 2000, to September 30, 2005, for a study aimed at unraveling predictors of incident all-cause mortality [10]. The only exclusion criterion was the presence of poor life expectancy due to malignancies. Up to date, this cohort has been followed up for 7.5 ± 2.12 years (range 0.04–9.85) with the last information on vital status being obtained on November 30, 2010. After excluding patients whose information on baseline BMI, vital status at follow-up and DNA was not available, 764 subjects (74.3 % of the initial cohort) constituted the eligible sample for the present investigation. Of note, no differences in the most relevant baseline clinical features were observed between study individuals and those who were not included in the present investigation (data not shown).

### Ethics

Study protocol and the informed consent procedure were approved by the Institutional Ethic Committee of Scientific Institute "Casa Sollievo della Sofferenza" and have, therefore, been performed in accordance with the Declaration of Helsinki. All participants gave written informed consent.

### SNPs selection and genotyping

Of the 32 SNPs associated with BMI from the most recent and largest GWAs in white Europeans [11], we only investigated those whose risk allele increase in BMI was ≥0.10 kg/m$^2$ and allele frequency was ≥10 % [11, 12] ($n = 20$). Genotyping was performed by KBioscience (Hertsfordshire, UK), which designed and used assays based on either their proprietary competitive allele-specific PCR (KASPar) method or a modified TaqMan-based assay, details of which are available on the company Web site (http://www.lgcgenomics.com/). Genotype success rate of each individual SNP was >95 %. All SNPs, but rs12444979 at *GPRC5B* locus and rs2112347 at *FLJ35779* locus, were in HWE (all $p > 0.01$). Of the 764 study patients, 77 (10 %) had some missing genotypes (SNPs missingness median 5 %, lower quartile 5 %, upper quartile 10 %). The supervised survival random forest algorithm was employed to impute missing SNPs data on such patients, on the basis of their mortality outcome [13].

### Statistical analysis

Patients' baseline characteristics were reported as frequencies (%) and mean ± SD, for categorical and continuous variables, respectively. Time-to-death analyses were performed using multivariate Cox proportional hazards regression models, and risks were reported as hazards ratios (HR) along with their 95 % confidence intervals (95 % CI). The overall survival was defined as the time between enrollment and death. For subjects who did not experience the end point, survival time was censored at the time of the last available follow-up attempt. Univariate logistic regression analysis was used to test the association between GRS and obesity, and results were reported as odds ratios (OR) along with their 95 % CI.

Observed and expected associations between the obesity genetic load and risk of all-cause mortality were compared using one-sample $t$ test. Genotype risk score (GRS) was obtained by counting the number of risk alleles [11] carried by each individual. Only SNPs obeying Hardy–Weinberg equilibrium (HWE, $n = 18$) were used for further analyses. A weighted genotype risk score was obtained by summing the risk alleles from each SNP weighted by their estimated effect sizes (i.e., by univariate logistic regressions) on the presence of obesity from current data.

## Results

### Effect of obesity on all-cause mortality

Clinical features of the 764 study patients are reported in Table 1. Four hundred and nine patients (53.5 %) were obese (i.e., BMI ≥30 kg/m$^2$). During the 7.46 ± 2.13-year follow-up, 149 (19.5 %) patients died. Annual incidence rates were 2.6, 3.4 and 1.9 for 100 person-years in the whole

**Table 1** Clinical characteristics of patients from GMS

| | Whole sample ($n = 764$) | Survived ($n = 615$) | Died ($n = 149$) |
|---|---|---|---|
| Males (%) | 379 (49.6) | 303 (49.3) | 76 (51.0) |
| Age (years) | 62.5 ± 9.7 | 60.9 ± 9.3 | 68.9 ± 8.7 |
| Smokers | | | |
| Present | 95 | 81 (13.2) | 14 (9.4) |
| Former | 70 | 51 (8.3) | 19 (12.8) |
| Never | 598 | 482 (78.4) | 116 (77.9) |
| Diabetes duration (years) | 10.9 ± 9.1 | 10.0 (8.7) | 14.4 ± 10.2 |
| BMI (kg/m$^2$) | 31.0 ± 5.6 | 31.3 (5.4) | 29.9 ± 6.0 |
| $HbA_1c$ (%) | 8.7 ± 1.9 | 8.6 ± 1.9 | 8.9 ± 2.0 |
| Glucose-lowering therapy | | | |
| Diet only (%) | 105 (14.2) | 91 (15.3) | 14 (9.6) |
| Oral agents (%) | 319 (43.0) | 280 (47.1) | 39 (26.7) |
| Insulin with or w/o oral agents (%) | 317 (42.8) | 224 (37.6) | 93 (63.7) |
| Antihypertensive therapy (%) | 406 (57.8) | 304 (53.7) | 102 (75) |
| Antidyslipidemic therapy (%) | 220 (28.9) | 174 (28.4) | 46 (30.9) |

Continuous variables were reported as mean ± SD, whereas categorical variables as total frequency and percentages

*GMS* Gargano Mortality Study, *BMI* body mass index, *$HbA_{1C}$* glycated hemoglobin

sample, in non-obese and obese individuals, respectively. Obese patients had 45 % decreased risk of all-cause mortality as compared to non-obese individuals (Fig. 1a, HR = 0.55, 95 % CI 0.40–0.76; $p = 0.0004$). This association remained significant after adjusting for age, sex, smoking habit and exercise (HR = 0.62, 95 % CI 0.44–0.87, $p = 0.006$). Similarly, no further change was observed when hypertension (yes/no), dyslipidemia (yes/no), diabetes duration and $HbA_{1C}$ were added into the multivariate model (HR = 0.60, 95 % CI 0.42–0.85, $p = 0.004$). Thus, our results resemble those recently obtained in large studies [6–8] and point to a paradoxical effect of obesity on all-cause mortality in type 2 diabetes.

No major differences were observed when the association between obesity and all-cause mortality was evaluated after stratifying the whole study sample according to smoking habit, diabetes duration and age (see Supplementary material).

On the contrary, when the entire cohort was stratified according to glycemic control (i.e., $HbA_{1C} \leq$ or >8.4 %, the median value), the risk of all-cause mortality in obese versus non-obese individuals was significantly different between patients with relatively low and high $HBA_1c$ levels: HR = 0.80, 95 % CI 0.50–1.30, $n = 381$ versus HR = 0.41, 95 % CI 0.25–0.65, $n = 368$, respectively; $p$ for HRs heterogeneity = 0.045.

When normal weight individuals (i.e., BMI <25 kg/m$^2$, $n = 88$) were considered as the reference group, HR (95 % CI) for all-cause mortality was 0.77 (0.48–1.21) and 0.45 (0.29–0.72) in overweight (i.e., BMI = 25.0–29.9 kg/m$^2$, $n = 267$) and obese (i.e., BMI ≥30 kg/m$^2$, $n = 409$) individuals, respectively.

## Associations between GWAs-derived SNPs and BMI and between obesity and all-cause mortality

Of the 20 SNPs that were typed, 2 (i.e., rs12444979 at *GPRC5B* locus and rs2112347 at *FLJ35779* locus) did not obey the HWE and were, therefore, not used in further analyses. The 18 SNP-derived GRS (as calculated by simply counting the number of risk alleles carried by each individual) was significantly associated with obesity with an OR equal to 1.07 for one risk allele (95 % CI 1.01–1.12, $p = 0.02$). In contrast, when attempting a Mendelian randomization approach aimed at addressing the biology underlying obesity–mortality association, the 18 SNP-derived GRS was not associated with all-cause mortality (HR = 1.00, 95 % CI 0.94–1.06, $p = 0.97$).

When looking at individual SNP data, 10 of them showed a trend of association toward the expected direction (with rs713586 at *RBJ* locus and rs2815752 at *NEGR1* locus reaching nominal statistical significance) (Table 2), while the remaining 8 were either neutral (i.e., defined as a BMI $\beta$ value ranging from −0.005 to +0.005 kg/m$^2$; $n = 5$) or showed an association toward the opposite direction to that expected ($n = 3$) (Table 2).

In order to increase the strength of our instrument for the Mendelian randomization approach, we focused on the former SNPs so to obtain a 10 SNP-derived GRS. This was significantly associated with obesity (OR = 1.17, 95 % CI 1.08–1.26, $p = 4.6 \times 10^{-5}$) but not with all-cause mortality (HR = 0.96, 95 % CI 0.88–1.04, $p = 0.28$). To further strengthen our genetic instrument, we calculated an individual "obesity genetic load," so to have patients with

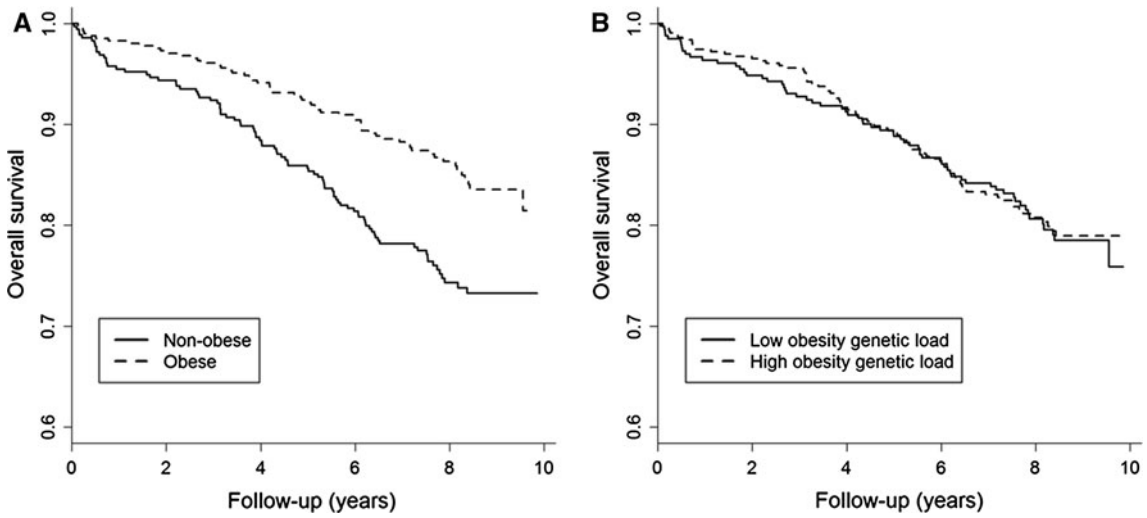


**Fig. 1** **a** Survival *curves* for all-cause mortality in patients with type 2 diabetes according to obesity status. Overall survival for all-cause mortality during follow-up in non-obese ($n = 355$, *dotted line*) and obese ($n = 409$, *black line*) diabetic patients, obtained by using Cox regression analysis. **b** Survival *curves* for all-cause mortality in patients with type 2 diabetes according to high and low "obesity genetic load." Overall survival for all-cause mortality during follow-up in diabetic patients with high ($n = 437$, *dotted line*) and low ($n = 333$, *black line*) "obesity genetic load," obtained by using Cox regression analysis

**Table 2** Association between GWAs-derived SNPs and BMI in GMS

| SNP | Locus | RAF (%) | $\beta$ (kg/m$^2$) | $p$ value | Direction of association |
|---|---|---|---|---|---|
| rs7359397 | *SH2B1* | 30 | −0.037 | 0.19 | Opposite |
| rs2867125 | *TMEM18* | 81 | −0.033 | 0.32 | Opposite |
| rs13078807 | *CADM2* | 21 | −0.031 | 0.32 | Opposite |
| rs2241423 | *MAP2K5* | 16 | −0.002 | 0.948 | Neutral |
| rs9816226 | *ETV5* | 82 | −0.001 | 0.98 | Neutral |
| rs10938397 | *GNPDA2* | 44 | 0.002 | 0.95 | Neutral |
| rs887912 | *FANCL* | 29 | 0.004 | 0.90 | Neutral |
| rs543874 | *SEC16B* | 16 | 0.005 | 0.88 | Neutral |
| rs2287019 | *QPCTL* | 44 | 0.014 | 0.68 | Expected |
| rs987237 | *TFAP2B* | 20 | 0.018 | 0.58 | Expected |
| rs7138803 | *FAIM2* | 37 | 0.019 | 0.47 | Expected |
| rs10968576 | *LRRN6C* | 20 | 0.027 | 0.39 | Expected |
| rs10150332 | *NRXN3* | 16 | 0.034 | 0.33 | Expected |
| rs571312 | *MC4R* | 24 | 0.036 | 0.23 | Expected |
| rs10767664 | *BDNF* | 73 | 0.041 | 0.15 | Expected |
| rs1558902 | *FTO* | 52 | 0.047 | 0.06 | Expected |
| rs2815752 | *NEGR1* | 71 | 0.060 | 0.03 | Expected |
| rs713586 | *RBJ* | 44 | 0.062 | 0.02 | Expected |

Out of 20 typed SNPs, only those ($n = 18$) obeying HWE are shown

Direction of association is described as compared to that previously reported in GWAs. Neutral direction was defined as $\beta$ value ranging from −0.005 to +0.005 kg/m$^2$

*GWAs* genome-wide association studies, *BMI* body mass index, *GMS* Gargano Mortality Study, *RAF* risk allele frequency, $\beta$ risk allele

either low or high load (i.e., 10 SNP-derived GRS being $<$ or $\geq 9$, the median value of whole sample). These latter patients were more likely to be obese (OR 1.61, 95 % CI 1.21–2.12, $p = 0.001$) as compared to those with low "obesity genetic load."

Annual incidence rates of all-cause mortality were 2.65 and 2.58 for 100 person-years in individuals with high and low "obesity genetic load," respectively. As compared to individuals with low "obesity genetic load," the HR for all-cause mortality in those with high load was 0.97 (95 % CI

0.70–1.33, $p = 0.877$) (Fig. 1b). This association did not change much after adjusting for age, sex, smoking habit and exercise, four potential confounders possibly affecting mortality independently of the obesity genetic background (HR = 1.02, 95 % CI 0.74–1.41, $p = 0.91$). Although the observed HR was not significantly different from the expected one (HR = 0.75; $p = 0.12$), its approaching the value of 1, strongly suggest that no causality underlies the association between obesity and reduced mortality risk.

Very similar results were observed when weighted 18 and 10 SNP-derived GRS, as well as weighted "obesity genetic load" were computed and used to evaluate their association with both obesity and all-cause mortality (data not shown).

## Discussion

The role of obesity on mortality rate in patients with type 2 diabetes is a matter of debate [3–5, 7]. The major finding of our study is that in a real-life clinical set of white diabetic patients from central-southern Italy, obesity is associated with 45 % reduction in all-cause mortality. This association was independent of all clinical variables taken into account. Of note, most of the association was observed in individuals with relatively high $HbA_{1C}$ levels, thus suggesting that glycemic control acts as a modifier on the role of obesity on all-cause mortality. Our data are along the same line of three recent studies from the USA and the UK [6–8], and all together strongly point to a paradoxical protective role of obesity on mortality rate in diabetic patients.

The biology underlying such unexpected association is totally unknown. It can be hypothesized that lack of obesity among patients affected by a disease known to be strongly associated with excess adiposity (i.e., type 2 diabetes in our case) is simply a marker of pathogenic factors increasing the risk of mortality, including advanced cardiovascular and/or respiratory diseases [2]. One could, also, speculate that excess adiposity is a marker either of better nutrition or of socioeconomics differences affecting access to health care [14]. Alternatively, in the specific context of heavily treated diabetic individuals, drugs known to favorably affect adipokines profiles like metformin [15, 16], ACE inhibitors [17], sartans [18, 19] and statins [20–22] might have helped switch the overall adipose tissue effect on metabolic milieu, endothelial function and chronic low-grade inflammation toward a positive direction, thus allowing a real direct beneficial action of obesity on mortality risk. Of note, since BMI is only a proxy of body fatness, caution should be used when extrapolating our epidemiological observation to a biological role played by excess adiposity.

To give our own contribution in addressing this fascinating and poorly understood scenario, we carried out exploratory analyses using genetic tools of body weight modulation. Such an approach, referred to as Mendelian randomization, makes a strong case about a cause–effect relationship underlying associations between two variables whose biological link is questioned [23]. In our specific context, we took advantage by several GWAs-derived SNPs firmly associated with BMI [11] as an instrument to infer a possible causal role of obesity on reduced mortality risk. In other words, if the association between obesity and reduced mortality risk had been a causal one, obesity genetic markers should have been associated with reduced mortality risk. Our data, quite clearly, indicate no role of obesity genes on all-cause mortality and speaks, therefore, against a cause–effect relationship underlying the association between obesity and reduced mortality rate. We acknowledge that our genetic evidences derive from a small sample, which affects study statistical power, thus making impossible to exclude a false-negative result. In addition, no replication of our finding in an independent sample is offered. Therefore, our genetic data have to be viewed as preliminary and interpreted with caution. Nonetheless, while waiting for replication in further and possibly large studies, our present findings play the important function of new hypothesis generating for better addressing a clinically important issue.

In conclusion, obesity is associated with reduced mortality risk in white patients from central-southern Italy. Further studies are needed to get deeper insights about the biological link between obesity and all-cause mortality in diabetic patients.

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