Role of body mass index in the prediction of all cause mortality in over 62 000 men and women. The Italian RIFLE Pooling Project

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Abstract

***Study objective*—To evaluate the relation of body mass index (BMI) to short-term mortality in a large Italian population sample.**

***Design*—Within the Italian RIFLE pooling project, BMI was measured in 47 population samples made of 32 741 men and 30 305 women aged 20–69 years (young 20–44, mature 45–69). Data on mortality were collected for the next six years.**

***Main outcome measures*—Age adjusted death rates in quintile classes of BMI and Cox proportional hazards models with six year all causes mortality as end point, BMI as covariate and age, smoking, systolic blood pressure as possible confounders were computed. Multivariate analysis was tested in all subjects and after the exclusion of smokers, early (first two years) deaths, and both categories.**

***Results*—The univariate analysis failed to demonstrate in all cases a U or inverse J shaped relation. The Cox coefficients for the linear and quadratic terms of BMI proved significant for both young and mature women. The minimum of the curve was located at 27.0 (24.0, 30.0, 95% confidence limits, CL) and 31.8 (25.5, 38.2, 95% CL) units of BMI, for young and mature women respectively. Similar findings were obtained even when exclusion were performed. No relation was found for young men while for mature adult men only the model for all subjects retained significant curvilinear relation (minimum 29.3; 22.4, 36.2, 95% CL).**

***Conclusion*—These uncommon high values of BMI carrying the minimum risk of death seems to be in contrast with weight guidelines. A confirmation of these findings in other population groups might induce the consideration of changes in the suggested healthy values of BMI.**

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Despite the large amount of medical literature available on the subject, the relations of body weight, body fatness, and related measures to disease and mortality require further investigation mainly in the search for optimal weight with regard to the best health status and health perspectives.[1–11]

On the other hand it has taken years for the acceptance of the concept of a J or U shaped relation of body weight and related measures to mortality,[4 8 9 12] and recently the desirable body weight for elderly people seems to be higher than previously claimed.

Extensive studies based on population samples with adequate follow up in Italy are limited. For example, the Italian cohorts of the Seven Countries Study could be followed up for 25 years,[13] but they were made only for middle aged men. A larger and more recent analysis, based on the pooling of a few studies, suggested the existence of a parabolic inverse J shaped relation of some parameters of obesity to 10 year mortality, although the step of the left branch of the curve could be reduced by the exclusion of smokers, early deaths, and people carrying serious health conditions at entry.[14]

The availability of data from the Italian RIFLE (Risk Factors and Life Expectancy) pooling project,[15] including many population samples spread all over the country and large numbers, offers the possibility to provide more consistent material although based on very simple measures of body fatness.The purpose of this analysis is to describe the relation of body mass index to short-term mortality in a large population sample of men and women in Italy.

Methods

STUDY POPULATION

The RIFLE Pooling Project includes epidemiological data from nine different large scale population studies started in Italy between 1978 and 1987 and focused on cardiovascular diseases or other chronic conditions.[15] The nine studies gathered 52 population samples of men and women in the age range of 20 to 69 years. Each sample, except two, were identified by electoral rolls (where all people aged 18 plus are enlisted) in defined geographical areas. Two samples were of occupational origin (large companies with a prevalence of sedentary employees), both located in Rome. The average participation rate was around 70%, while subjects lost to follow up at six years were 2.1%.

Only 47 cohorts, however, spread across 13 of the 20 Italian regions, were finally considered because, for the remaining five, a minimum follow up could not be completed.

These nine studies proved suitable for pooling because all of them were conducted or coordinated or methodologically advised by the same centre and most of the measurements were made using the same standardisation and quality control procedures.[15]

Table 1 Mean (SD) values of body mass index (BMI) and number of deaths in relation to sex and age group

Sex	Age (y)	No	BMI mean (SD)	No of deaths
Men	20–44	13150	25.5 (3.4)	85
Men	45–69	19591	26.8 (3.5)	950
Women	20–44	13827	24.7 (4.4)	37
Women	45–69	16468	27.8 (4.8)	301

Table 2 Smoking habits in the study population

Sex	Age (y)	No	Never smokers (%)	Ex-smokers (%)	Current smokers (%)
Men	20–44	13150	28.1	19.9	52.0
Men	45–69	19591	20.3	35.1	44.6
Women	20–44	13827	59.3	8.8	31.9
Women	45–69	16468	79.4	5.8	14.8

KEY POINTS

- The univariate approach suggest a U shaped or inverse J shaped relation of BMI with short-term all causes mortality.
- Multivariate models confirm this parabolic relation, at least in the age-sex group with a larger number of events.
- The high levels of BMI carrying the minimum risk of death in this study are rather high: 29 units for middle aged men, 27–29 for young women, and almost 32 for middle aged women.
- Similar findings are obtained even with the exclusion of smokers, former smokers, and early deaths.
- These results, if confirmed in other larger population groups, tend to underestimate the hazards of moderately high BMI levels.

MEASUREMENTS

At baseline examination a large number of personal characteristics and risk factors were measured. Mortality follow up data were later collected for varying follow up periods.The present analysis deals with 47 cohorts of men (n=32 710) and women (n= 30 210). The following individual measurements were considered:age, computed in years, using the difference between the year of examination and the year of birth, and accepting a mean error of six months; height (cm) and weight (kg) were measured in light undergarments, using the technique described in the WHO Cardiovascular Survey Methods manual (WHO Manual),[16] and then compacted into body mass index (kg/m^2).

Moreover, systolic blood pressure, serum cholesterol, and the number of cigarettes smoked on the average per day, were used in multivariate analysis, as possible confounding covariates. Details on the measurement techniques can be found elsewhere.[15] Blood pressure was measured in sitting position, using the procedure recommended by the WHO Manual[16] ; serum cholesterol measurement was performed by laboratories under direct or indirect quality control from the WHO Lipid Reference Centre of Prague; and smoking habits were elicited by a questionnaire derived from that suggested by the WHO Manual.

MORTALITY FOLLOW UP

Mortality data used in this analysis cover a period of six years. Information on vital status and causes of death were collected by the responsible investigators of each cohort, while coding of causes of death was performed centrally, by a single nosographer, using the IX Revision of the WHO-ICD.[17] In case of multiple causes of death, a hierarchical order was adopted, with priority given to accidents, cancer, coronary heart disease and stroke, followed by other causes as listed.

STATISTICAL METHODS

Univariate analysis was made computing, separately for both sexes and for two age groups (20–44, young adults; 45–69, mature adults), age adjusted death rates from all causes in quintile classes of body mass index (BMI).

Multivariate analysis was run by the proportional hazards models,[18] using procedures available in BMDP2L statistical program,[19] with all cause mortality as dependent variable and BMI, age, systolic blood pressure, serum cholesterol, and cigarette smoking as continuous, independent variables. BMI was fed into the models both as linear and as quadratic term. Separate models were produced for both sexes and two age groups.

Models on all cause mortality were run on all subjects and then again after exclusion of smokers, of early deaths (two years), and of these two categories combined together. To control for heterogeneity, dummy variables were fed into the model to identify cohorts located in the northern, central, southern, and insular parts of the country. The proportional hazards assumption for BMI has been tested and confirmed for the five strata of the variable. The z^2 test,[20] gave a non-significant value of 1.35.

In the case of a clear cut parabolic relation between BMI and mortality, the BMI level associated with the minimum risk of death was estimated. The formula for identifying the minimum level of the parabola is: min = −b/2a, where "a" represents the coefficient of the quadratic term (BMI^2) and "b" the coefficient of the linear term (BMI). When the parabolic effect was not statistically significant the model was computed with the linear term only.

Table 3 Age adjusted, six year all cause death rates, per 1000, in body mass index (BMI) groups. Number of deaths in brackets

Sex	Age (y)	BMI group < 20	20–24	25–29	30–34	35+
Men	20-44	4.7 (6)	6.8 (40)	6.6 (38)	3.4 (4)	7.2 (1)
Men	45–69	51.5 (94)	52.6 (317)	44.5 (444)	50.9 (163)	64.4 (23)
Women	20–44	4.0 (9)	2.4 (17)	2.3 (9)	2.5 (3)	11.6 (5)
Women	45–69	19.7 (37)	20.9 (97)	18.2 (119)	14.4 (53)	22.5 (31)

Table 4 Multivariate coefficients (SE) for linear and quadratic terms of body mass index (BMI, treated as a continuous variable) estimated in proportional hazards models for six year all cause mortality, including all subjects and excluding smokers, early death, or both categories. Estimated BMI levels corresponding to the minimum risk when a U shaped relation is suggested

	No	Death rate per 1000	BMI		BMI^2		BMI with minimum risk (95% CI)
			Coefficient (SE)	p	Coefficient (SE)	p	
Men 20–44 y							
All subjects	13150	6.5	−0.0599 (0.0356)	0.0925	—		NA
Smokers excluded	6211	5.5	−0.0506 (0.0576)	0.3797	—		NA
Early deaths excluded	13120	4.3	−0.0126 (0.0428)	0.7685	—		NA
Both excluded	6200	3.7	−0.0293 (0.0697)	0.6742	—		NA
Men 45–69 y							
All subjects	19591	48.5	−0.1876 (0.0806)	0.0199	0.0032 (0.0015)	0.0329	29.3 (22.4,36.2)
Smokers excluded	10740	41.1	−0.0023 (0.0139)	0.8686	—		NA
Early deaths excluded	19261	32.2	0.0033 (0.0113)	0.7703	—		NA
Both excluded	10583	26.9	0.0088 (0.0172)	0.6089	—		NA
Women 20–44 y							
All subjects	13827	2.2	−0.4315 (0.2290)	0.0595	0.0080 (0.0038)	0.0353	27.0 (24.0,30.0)
Smokers excluded	9168	2.5	−0.6736 (0.2731)	0.0136	0.0119 (0.0045)	0.0082	28.3 (23.4,33.3)
Early deaths excluded	13816	1.9	−0.4857 (0.2694)	0.0714	0.0088 (0.0045)	0.0505	27.6 (22.9,32.3)
Both excluded	9168	2.5	−0.8897 (0.2982)	0.0028	0.0153 (0.0049)	0.0018	29.0 (23.6,34.5)
Women 45–69 y							
All subjects	16468	18.3	−0.2611 (0.0917)	0.0044	0.0041 (0.0016)	0.0104	31.8 (25.5,38.2)
Smokers excluded	13554	16.9	−0.2303 (0.1068)	0.0311	0.0036 (0.0018)	0.0455	32.0 (26.8,37.1)
Early deaths excluded	16375	12.7	−0.3014 (0.1076)	0.0051	0.0047 (0.0018)	0.0090	32.1 (27.2,36.9)
Both excluded	13483	11.7	−0.2523 (0.1265)	0.0461	0.0040 (0.0021)	0.0568	31.5 (26.0,37.1)

NA = not applicable.

Similar models were solved with BMI expressed as a categorical variable corresponding to five arbitrary classes, that is, <20 units, 20–24, 25–29, 30–34, and 35 and over, limited to groups where the parabolic effect was found. This permited us to compute hazards ratios between the BMI class associated with the minimum risk and other classes.

Results

Overall 32 741 men and 30 305 women were included in the analysis. Table 1 gives the age and sex distribution, together with mean values of BMI and crude death rates from all causes in six years. Among young adults (aged 20–44 years), average BMI in women was lower than in men, whereas the opposite was the case in mature adults (aged 45–69 years). In six years, there were 1037 fatal events among men and 338 among women. Death rates in men, in each age group, were more than twofold compared with women.

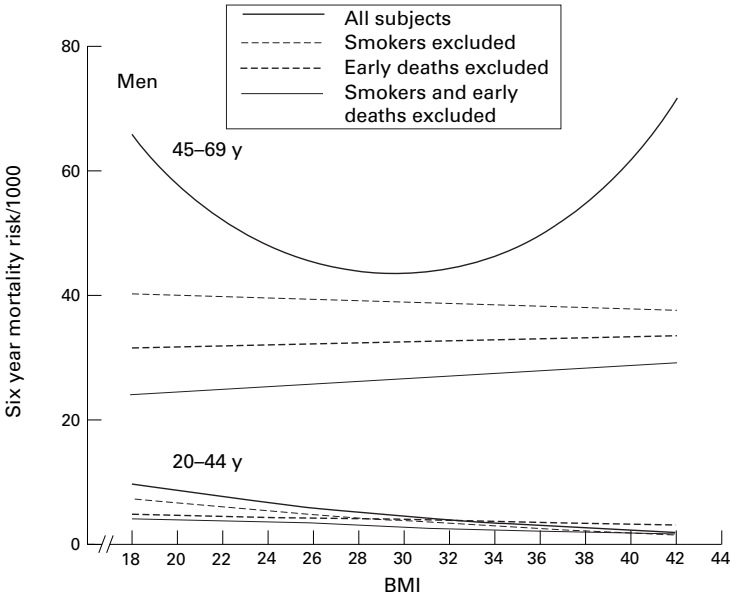

Figure 1 Six year mortality risk as a function of BMI (kg/m²) levels in men aged 20–44 and 45–69. Estimates adjusted for age, systolic blood pressure, serum cholesterol, and cigarette consumption. Four curves are reported corresponding to all subjects, all subjects minus smokers, or early deaths or both categories.

Because of the important role of smoking habits in this analysis, a summary on their distribution is reported in table 2.The univariate analysis given in table 3 suggests a non-uniform relation of BMI with mortality in different age-sex classes. In men aged 20–44 the trend of mortality with increasing levels of BMI is irregular and a minimum death rate is located in the fourth class (BMI 30–34). In men aged 45–69 the relation has a parabolic shape with the lowest risk of death in the intermediate class, corresponding to BMI values of 25–29 units.

In women aged 20–44 the trend seems parabolic, with a peak in the highest class, but this finding should be considered with caution because of the small number of events. In women aged 45–69, the lowest death rate is located in the fourth class of BMI, with higher rates at the extremes.

Table 4 gives a summary of proportional hazards models with BMI treated as a continuous variable, giving coefficients and their standard error. All regression coefficients are adjusted for age, systolic blood pressure, serum cholesterol, and the number of cigarettes smoked per day.

For men, a definite, statistically significant parabolic U shaped relation of BMI with mortality was only seen in the mature adult group. In women this finding was seen for both age groups.

Models excluding cigarette smokers, or early deaths (first two years), or both categories were also computed and graphs showing the relation of BMI with mortality are shown in figures 1 and 2. When exclusions are made, the U shaped relation of BMI to mortality completely disappears in men (fig 1).

Despite exclusions, both in young and mature women, the shape of the relation of BMI with mortality remains parabolic and the coefficients are always significant. In mature

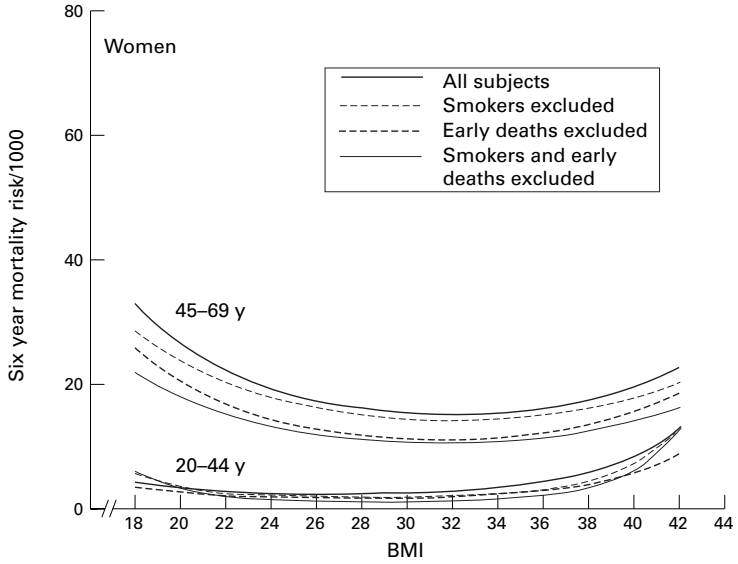

Figure 2 Six year mortality risk as a function of BMI (kg/m²) levels in women aged 20–44 and 45–69. Estimates adjusted for age, systolic blood pressure, serum cholesterol, and cigarette consumption. Four curves are reported corresponding to all subjects, all subjects minus smokers, or early deaths or both categories.

women the exclusions of smokers, early deaths or both categories, are associated with a reduction in the step of the left branch of the parabola, suggesting that an excess of high risk subjects (smokers or carriers of morbid conditions rapidly leading to death) are mainly located in the left branch. This is not the case for young women (fig 2).

Curvilinear relations were judged significant when both linear and quadratic components were so. However, when the linear and quadratic coefficients of BMI were statistically significant, or at least not too small, the values of BMI associated with the minimum risk was estimated (table 4). This was not done for the category of younger men because none of the coefficients was statistically significant. Among older men the BMI value corresponding to minimal risk is high (29.3 units) but the confidence intervals are large (22.4 to 36.2). However the minimum risk can be identified only in the model without exclusions because in the models with exclusions the parabolic effect is not present and the linear term is not significant. In the four subgroups of younger women the value of BMI carrying the minimum risk ranges between 27 and 29 units, again with large confidence intervals. These values, however, are not influenced by the exclusions. Finally among older women these estimates are again not influenced by the exclusions and the BMI value carrying the minimum risk is extremely high—that is, around 32 units.

Multivariate models were also calculated including BMI as a categorical variable made of to five classes. Hazard ratios and their confidence intervals computed from these models (not reported in detail) are given in table 5. Tests were performed, for each model where the parabolic effect was significant, comparing classes including the minimum risk (taken as reference and derived from the analysis on continuous variable) with the others. In the four models for men aged 20–44 and in three of four models for men aged 45–69, a level carrying the minimum risk could not be identified in the absence of a clear cut parabolic shape.

In these particular cases linear models, instead of parabolic models, have been used and reference class has been arbitrary chosen as the lower BMI category (<20 units). However, for men aged 20–44 smokers excluded and both smokers and early deaths excluded, the models did not converge. For all the other linear models, the lower category of BMI taken as reference, represents the class with the highest risk of dying, even if this excess result is statistically significant only for men aged 45–69 when smokers and both smokers and early deaths are excluded. Dealing with

Table 5 Hazard ratios (95% confidence intervals) between pairs of body mass index (BMI) classes, derived from proportional hazards models with BMI treated as a categorical variable. The reference class is that carrying the minimum risk of death when the model shows a parabolic shape. In the linear models (*) the reference class is the lowest (BMI < 20 units)

	BMI				
	< 20	*20–24*	*25–29*	*30–34*	*35+*
Men 20–44 y					
All subjects*	Ref	0.80 (0.24, 2.60)	0.69 (0.21, 2.28)	0.33 (0.07, 1.54)	0.64 (0.06, 6.40)
Smokers excluded*	The model does not converge				
Early deaths excluded*	Ref	0.42 (0.13, 1.47)	0.48 (0.14, 1.65)	0.35 (0.08, 1.64)	0.73 (0.07, 7.34)
Both excluded*	The model does not converge				
Men 45–69 y					
All subjects	1.62 (1.10, 2.38)	1.12 (0.97, 1.30)	Ref	1.04 (0.86, 1.24)	1.30 (0.84, 1.99)
Smokers excluded*	Ref	0.39 (0.20, 0.74)	0.37 (0.20, 0.70)	0.42 (0.22, 0.81)	0.47 (0.20, 1.09)
Early deaths excluded*	Ref	0.73 (0.44, 1.22)	0.69 (0.42, 1.15)	0.78 (0.46, 1.32)	0.95 (0.47, 1.94)
Both excluded*	Ref	0.31 (0.14, 0.67)	0.33 (0.15, 0.70)	0.41 (0.19, 0.91)	0.32 (0.10, 0.95)
Women 20–44 y					
All subjects	1.83 (0.52, 6.39)	1.32 (0.56, 3.12)	Ref	1.18 (0.31, 4.49)	4.42 (1.28, 15.28)
Smokers excluded	4.03 (0.84, 19.26)	1.97 (0.61, 6.40)	Ref	1.43 (0.26, 7.89)	6.18 (1.32, 29.04)
Early deaths excluded	1.97 (0.44, 8.85)	1.47 (0.50, 4.27)	Ref	1.20 (0.23, 6.24)	4.70 (1.06, 20.97)
Both excluded	7.34 (1.19, 48.11)	2.73 (0.55, 13.43)	Ref	1.34 (0.12, 14.90)	10.14 (1.56, 65.91)
Women 45–69 y					
All subjects	2.47 (1.39, 4.37)	1.50 (1.05, 2.14)	1.30 (0.93, 1.81)	Ref	1.40 (0.88, 2.22)
Smokers excluded	2.19 (1.05, 4.55)	1.56 (1.04, 2.35)	1.39 (0.96, 2.02)	Ref	1.61 (0.98, 2.66)
Early deaths excluded	2.50 (1.26, 4.98)	1.46 (0.95, 2.24)	1.37 (0.92, 2.03)	Ref	1.37 (0.78, 2.39)
Both excluded	1.92 (0.73, 5.04)	1.63 (0.99, 2.68)	1.55 (0.99, 2.44)	Ref	1.75 (0.96, 3.19)

* Model linear.
Age, systolic blood pressure, serum cholesterol, and cigarette smoking were fed into the model as possible confounding variables.

parabolic models, among men aged 45–69 the BMI class carrying the minimum risk was that of 25–29 units. The only significant hazard ratio was that of BMI class of less than 20 units. Among women aged 20–44 the minimum risk was located in the mid class (25 to 29 units) and significant excess risks compared with the reference class were found in the upper class of four models and in the lowest class of one model (that with the exclusions of early deaths and smokers).

Among women aged 45–69 the minimum risk was located, in all models, in the BMI class of 30–34 units. Significant excess risk of dying was found in the lower two classes for the models with all subjects and with smokers exclusion, and in the lowest BMI class in the model with early deaths exclusion.

Discussion

In this analysis dealing only with BMI, the univariate approach suggested U shaped or inverse J shaped relation of BMI with all cause mortality, and therefore the multivariate models were solved with the inclusion of both linear and quadratic terms of BMI. This provided a confirmation of the parabolic relation between BMI and mortality at least in the sex-age subgroups with relatively large number of events. This means that instead of the monotone increasing or decreasing relation of risk factor with mortality, this relation permits identification of a level associated with a minimum amount of risk, which becomes higher and higher when moving in either direction along the scale of BMI. An unexpected finding is the high level of BMI corresponding to the minimum risk, in both univariate and multivariate analyses, the latter even after adjustment for age, systolic blood pressure, serum cholesterol, and cigarette consumption.

It is possible that the high risk in the left branch of the parabola is a result of the concentration, in that area, of people with special conditions. This was partly confirmed in men when, in the multivariate analysis, different models were solved after the exclusion of smokers, or early deaths (that is, of people who are probable carriers of some conditions that rapidly leads to death) or of both sub-groups. In fact the left branch of the parabola levelled off almost completely. However the same occurred to the right branch cancelling any real predicting power of BMI in middle aged men. This was not the case for women where the parabolic shape remained almost unchanged. This is shown by the changing shapes of curves in figures 1 and 2.

To make our findings comparable with a large study from Manson *et al*,[21] conducted on women, the multivariate analysis on women was re-run for the age range of 30–55 years and for the most similar types of inclusions-exclusions. Clear cut significant parabolic estimates of coefficients were found for all subjects, for all subjects after exclusion of prevalent cases, for all subjects after exclusion of ex-smokers and prevalent cases, for ex-smokers only, but not for all subjects after exclusion of current and ex-smokers, nor for current smokers only. In the latter case the number of events was 68 only. These findings do not fully compare with those reported by Manson *et al*, but the persistence of a curvilinear relation in our data contrasts with its disappearance in the Manson's data when several confounders were not taken into account.[21]

The interpretation of figures 1 and 2 should take into account that people located in the extreme BMI classes represent a minority. Among people aged 20–44 only 1.3% of men and 4.8% of women have a BMI smaller than 20 units, whereas the corresponding proportions of those having levels of 35 or more are 1.7 % and 4.0% respectively. In the age group 45–69 years, 0.7% of men and 1.2% of women have a BMI smaller than 20 units, while 3.1% of men and 11.3% of women have a BMI of 35 units or more.

The levels of BMI carrying the minimum risk of death are higher than expected—that is, about 29 units of BMI for middle aged men, 27 to 29 units for young women, and nearly 32 units for middle aged women. At the same time the confidence intervals around these estimates are also wider than expected. This suggests that the deviation from the level carrying the minimum risk must be rather large before becoming a hazard to health.

This analysis has obvious limitations including the fact that the only indicator of obesity was the body mass index. However other studies in the past were characterised by similar limitations. The advantage of this study is linked to the size of the population, which is the largest ever studied in Italy in this context. The medical literature in this area is extensive and cannot be quoted or commented on in detail. The indications provided by the Consensus Conference on Obesity of the NIH,[22] and the parallel conference held more recently in Italy,[23] tend to emphasise that obesity is a health hazard. Other authors,[11] emphasise the poor outcome for severely obese subjects who, on the other hand, represent a small fraction of the general population. Especially among middle aged women, however, the proportion of those who can be classified as definitely obese is comparatively large and poses a public health problem. This also highlights the difficulties in showing such findings with relatively small samples. Our main interest was to study the predictive role of body mass index in short-term survival and mortality over a wide spectrum of general population and therefore these findings must be evaluated from a broader point of view.

In a review of the medical literature on body weight and longevity made in 1987,[24] it was emphasised that valuable conclusions cannot be reached if cigarette smoking and hypertension are not properly taken into account, together with weight loss possibly caused by sub-clinical disease. The exclusion of smokers, of people who died within two years from entry examination, together with the multivariate control of age, systolic blood pressure, and serum cholesterol puts our findings within these guidelines.

Despite this we do not recommend weight guidelines on the basis of these results, which seem relatively uncommon considering the high levels of BMI corresponding to the lowest death rate, although projected only into the next six years. The impression is, however, that, if confirmed, such results tend to underestimate the hazards of moderately high BMI levels which, to date, have been considered to be of importance.

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Conflicts of interest: none.

Appendix

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