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ORIGINAL ARTICLE

The effect of age on the shape of the BMI–mortality relation and BMI associated with minimum all-cause mortality in a large Austrian cohort

RS Peter[1,2], B Mayer[2], H Concin[1] and G Nagel[1,2]

BACKGROUND: It is unclear if the body mass index (BMI) associated with minimum all-cause mortality is constant throughout adult life or increasing with age.

METHODS: We applied multivariable fractional polynomials to the data of the Vorarlberg Health Monitoring and Prevention Program to quantify the BMI associated with minimum mortality over age. The analysis included data of 129 904 never-smoking women and men (mean age: 45.4 years) who were followed for a median of 18.6 years.

RESULTS: Optimum BMI in women increased with age, lying within the normal BMI category (according to the World Health Organization definition) from the age of 20 years (23.3 kg m^{-2}, 95% confidence interval (CI): 22.2–24.3) to the age of 54 years and in the lower half of the overweight category from the age of 55 years onwards, reaching 26.2 kg m^{-2} (95% CI: 25.1–27.3) at the age of 69 years. In men, optimum BMI increased slightly from 23.7 kg m^{-2} (95% CI: 22.1–25.2) at the age of 20 years until the age of 59 years, reaching a BMI of 25.4 kg m^{-2} (95% CI: 24.8–26.0) and decreased afterwards to 22.7 kg m^{-2} (95% CI: 20.9–24.6) at the age of 80 years.

CONCLUSIONS: Our results indicate that BMI associated with minimum all-cause mortality changes with age and that patterns differ by sex. Sex- and age-independent BMI recommendations might therefore be inappropriate. Further studies using flexible methods instead of predefined categories are necessary to revise BMI recommendations.

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INTRODUCTION

The relationship between body mass index (BMI) and all-cause mortality is known to be U-shaped. Mortality is elevated in the lowest BMI categories as well as in higher BMI categories.[1–3] Most studies reported the BMI associated with minimum mortality to lie either in the normal range (BMI: 18.5–25 kg m^{-2})[2] or in the overweight range (BMI: 25–30 kg m^{-2}).[4,5] Differences in the optimum BMI between studies might be related to differences in the participants' baseline health status and age. Heiat *et al.*[6] did not find any evidence for increased all-cause mortality related to overweight in older individuals while reviewing 13 studies including up to 46 954 participants aged 65 years or older. Some studies in older subjects even found an inverse relation between BMI and mortality.[7,8] One very large study reported an increased risk for BMI $\geqslant$ 27 kg m^{-2} in participants aged 65 to 74 years but no association in participants older than 74 years, despite a large number of 5363 events in this age group.[9]

Populations are becoming older in western countries and the obesity prevalence is increasing even in old age. The level of BMI associated with lower mortality in older subjects is one of the unresolved questions in obesity research.[10] Whether the recommended BMI range shall be constant throughout adult life or be increased for higher age groups remains unclear.

The majority of studies used categories of BMI to model the relationship between BMI and mortality,[1–4,7–9,11,12] making it difficult to assess an optimal BMI range as categories are defined *a priori* and the optimum might lie anywhere within or near the category with the lowest mortality risk. Also, the number and definition of categories differs between studies from World Health Organization categories of BMI,[4] equally spaced categories,[1] to the use of quintiles,[7,8] limiting the comparability of results. Some authors assumed a specific functional form (e.g. quadratic) to assess the BMI associated with minimum mortality.[13,14] However, the relationship of BMI and mortality is usually not found to be completely symmetrical and the optimum of a fitted quadratic curve therefore does not match the 'real' optimum.

Our objective was to model the relation between BMI and mortality over adult life in a large cohort using a flexible data adaptive method without categorizing or implying a specific functional form for BMI, age and their interactive effect on mortality.

We therefore used the multivariable fractional polynomials (MFP) procedure invented by Royston and Altman,[15] and modified by Sauerbrei and Royston.[16] MFP combines the determination of fractional polynomial functions of continuous variables with backward elimination. MFP has previously been used to model the U-shaped relationship of hematocrit and mortality,[17] maternal age and blood pressure,[18] BMI and all-cause mortality in patients with established coronary artery disease,[19] and BMI and risk of work disability due to cardiovascular disease or cancer.[20]

Wong *et al.*[21] investigated the use of MFP to model the BMI all-cause mortality relation using data of national health surveys and concluded, 'the MFP method identified improvements in model fit compared with other commonly used models that estimate the

[1]Agency for Preventive and Social Medicine, Bregenz, Austria and [2]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany. Correspondence: RS Peter, Institute of Epidemiology and Medical Biometry, Ulm University, Helmholtzstrasse 22, Ulm 89081, Germany,
E-mail: raphael.peter@uni-ulm.de
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BMI–mortality relationship, and is a robust method to determine the functional form for BMI'.

We focused on all-cause mortality as the criterion for defining a healthy weight should be the weight range corresponding to lowest all-cause mortality.[22]

SUBJECTS AND METHODS

The Vorarlberg Health Monitoring and Prevention Program (VHM&PP) is a risk factor surveillance program in Vorarlberg, the westernmost province of Austria. Health examinations were routinely performed by the Agency of Social and Preventive Medicine and addressed all adults (aged $\geqslant 19$ years) of the entire province. Participation in the health examination was voluntary and was conducted by local physicians. The program includes a physical examination, a blood test, and a consultation with a physician. Costs are covered by the participant's (compulsory) health insurance. A detailed description of the program can be found elsewhere.[23,24] Height, weight and smoking status among other variables were documented. The data set was linked to the Vorarlberg death index and to the Vorarlberg cancer registry. During the study period of 20 years (from January 1985 to August 2005), the participants underwent an unequal number of examinations from 1 up to 21. More than 55% of the general population in the eligible age range participated in the program at least once.[12]

Height and weight were measured in a standardized manner; participants did not wear shoes and had only light clothing. Height was measured by trained stuff according to a standardized procedure with precision of 1 cm and weight with precision of 1 kg.

Ethical approval was obtained by the ethics committee of the province of Vorarlberg.

The study population consists of 185367 individuals with 7 15 414 examinations. We excluded examinations of current or former smokers, examinations where the individual died within the following 3 years and examinations in individuals with prevalent cancer (identified via linkage to the Vorarlberg cancer registry). Information on diagnosis of cancer has been available since January 1985; mortality follow-up was conducted until December 2009. Missing data on BMI lead to loss of additional 33 individuals and 118 examinations. In all, 129 904 individuals with 459 740 examinations were remaining for the analysis. Reasons for exclusion from the study population and corresponding portions are shown in Table 1.

STATISTICAL METHODS

Model selection

We used MFP with Cox regression to model the relation between BMI, age and all-cause mortality for men and women separately.

In the first step, we applied the MFP procedure to select significant polynomial terms of BMI and age. We considered second-degree polynomials for BMI and age by choosing from power transformations of (−2, −1, −0.5, 0, 0.5, 1, 2, 3), where 0 denotes the natural logarithm.

The MFP procedure was carried out using the ra2 algorithm implementing a closed testing procedure, which maintains approximately the predefined type I error (usually 5%) rate for each component test and thus provides some protection against overfitting.[25] A prespecified nominal level of $\alpha = 0.05$ was used for choosing the best-fitting MFP model. Variables were rescaled and centered in the selection process to provide numerical stability. In the second step, we refitted the models identified by the MFP procedure using sandwich variance estimation to account for the correlated structure of multiple measurements within individuals, and kept terms still significant on $\alpha = 0.05$. In step three, we included possible interaction terms of BMI and age. The final model was determined via backward elimination of interaction terms. A summary of the model selection can be found in Supplementary Tables 1 and 2.

BMI associated with minimum mortality

BMI associated with minimum mortality as a function of age was determined by setting the derivative of the final model with respect to BMI to zero and solving subsequently for BMI.

BMI categories recommended by the World Health Organization[26] were used for comparison with optimum BMI identified in our data.

Hazard relative to optimum BMI

For calculation of the hazard relative to BMI associated with minimum mortality, the linear predictor at optimum BMI (f(age, bmi_{min}(age))) was subtracted from the linear predictor (f(age, bmi)) and exponentiated subsequently.

$$\text{HR}(\text{age}, \text{bmi}) = exp(f(\text{age}, \text{bmi}) - f(\text{age}, \text{bmi}_{\text{min}}(\text{age})))$$

R (R Foundation for Statistical Computing, Vienna, Austria) version 2.11.0 and the R package mfp version 1.4.9 were used for analyses.

RESULTS

Characteristics of the study population consisting of 76 590 women and 53 314 men can be found in Table 2. Mean age at baseline (first examination of an individual) was 46.4 years in women and 44.1 years in men. Women had a mean baseline BMI of 24.9 kg m^{-2} and men of 25.6 kg m^{-2}. Death occurred in 8860 women and 5855 during median follow-up of 18.6 years. Multiple examinations over age were available for 64% of participants. A descriptive figure illustrating the associations between BMI, age and survival time can be found in the Supplementary Information (Supplemental Figure 1).

Final models

Final models for women and men included a second- and third-order term for age. Selected BMI terms differed for women (orders: −2, 1) and men (orders: −1, −0.5). However, we identified significant BMI–age interaction terms for both sexes (two in the

Table 1. Selection of the study population

	Women		*Men*	
	Participants	*Examinations*	*Participants*	*Examinations*
Initial	99 894	406 348	85 473	309 066
Exclusion of	*Remaining (%)*			
Ever smokers	77 727 (77.8)	299 552 (73.7)	54 298 (63.5)	174 693 (56.5)
Death within 3 years	77 072 (77.2)	296 494 (73.0)	53 598 (62.7)	171 950 (55.6)
Prevalent cancer	76 609 (76.7)	291 043 (71.6)	53 328 (62.4)	168 815 (54.6)
Missing BMI	76 590 (76.7)	290 962 (71.6)	53 314 (62.4)	168 778 (54.6)

Abbreviation: BMI, body mass index.

Table 2. Characteristics of the study population

	Women	*Men*
N	76 590	53 314
Death	8860	5855
	Mean (s.d.)	
Age (years) at baseline	46.4 (14.7)	44.1 (13.7)
BMI (kg m^{-2}) at baseline, overall	24.9 (4.7)	25.6 (3.5)
BMI (kg m^{-2}), by age group (years)		
25–34	22.7 (4.1)	24.5 (3.3)
35–44	24.4 (4.5)	25.6 (3.5)
45–54	26.0 (4.8)	26.4 (3.4)
55–64	26.8 (4.7)	26.6 (3.6)
65–74	26.6 (4.5)	26.4 (3.6)
75–84	25.6 (4.3)	25.6 (3.3)
	Median (Q1, Q3)	
Measurements per participant	2 (1, 5)	2 (1, 4)
Follow-up (years)		
From first measurement	19.2 (12.6, 22.6)	17.6 (11.0, 21.8)
From last measurement	8.0 (5.3, 14.6)	8.2 (5.3, 15.1)

Abbreviation: BMI, body mass index.

Table 3. Cox regression coefficients and standard errors of the final models including age–BMI interaction terms

Term	μ^a	β	*Robust s.e. of* β
Women			
$(Age/100)^2$	0.277	23.92	1.259
$(Age/100)^3$	0.164	−0.21	0.797
$(Bmi/10)^{-2}$	0.174	8.03	1.263
$(Bmi/10)^1$	2.507	1.33	0.186
$(Age/100)^2 \times (bmi/10)^1$	0.716	−1.76	0.386
$(Age/100)^3 \times (bmi/10)^{-2}$	0.026	−10.97	3.263
Men			
$(Age/100)^2$	0.253	7.85	4.50
$(Age/100)^3$	0.144	−28.74	10.89
$(Bmi/10)^{-1}$	0.396	63.78	7.52
$(Bmi/10)^{-0.5}$	0.628	−83.96	9.39
$(Age/100)^2 \times (bmi/10)^{-1}$	0.099	27.01	11.20
$(Age/100)^3 \times (bmi/10)^{-1}$	0.056	−106.83	27.26
$(Age/100)^3 \times (bmi/10)^{-0.5}$	0.090	95.69	31.02

Abbreviation: BMI, body mass index. [a]Mean used to center the data.

female sample, three in the male sample). Regression coefficients and corresponding standard errors can be found in Table 3.

BMI associated with minimum mortality

The BMI associated with minimum mortality as a function of age is shown in Figure 1 (corresponding equations may be found as Supplementary Equations 1 and 2). Optimum BMI in women increased with age, lying in the normal BMI category from the age of 20 years (23.3 kg m^{-2}, 95% CI: 22.2–24.3) to the age of 54 years (24.9 kg m^{-2}, 95% CI: 24.1–25.7) and in the lower half of the overweight category from the age of 55 years onwards, reaching 26.2 kg m^{-2} (95% CI: 25.1–27.3) at the age of 69 years. Optimum BMI still increased from the age of 70 years onwards, but the confidence band became increasingly wide. In men, optimum BMI increased from 23.7 kg m^{-2} (95% CI: 22.1–25.2) at the age of 20 years until the age of 59 years, reaching a BMI of 25.4 kg m^{-2} (95% CI: 24.8–26.0) and decreased afterwards to 22.7 kg m^{-2} (95% CI: 20.9–24.6) at the age of 80 years. These variations with age in men were modest with an overall optimum of 24.3 kg m^{-2} (95% CI: 23.6–25.0).

Shape of the association

The association between BMI and mortality was clearly U-shaped for both women and men (Figure 2), while the strength of the association was stronger in men. The strength of the association between BMI and mortality decreased with age, particularly in women, represented by a flattening in the curves. The excess risk associated with a BMI of 30.0 kg m^{-2} (the lower limit of the obesity category) relative to the optimum was 1.25 kg m^{-2} (95% CI: 1.15–1.36), 1.13 kg/m^2 (95% CI: 1.08–1.18), 1.03 (95% CI: 1.01–1.05) at age of 30, 50 and 70 years in women, and 1.31 kg m^{-2} (95% CI: 1.15–1.48), 1.17 kg m^{-2} (95% CI: 1.11–1.23), 1.13 kg m^{-2} (95% CI: 1.09–1.18) in men, respectively. A BMI value of 20 kg m^{-2} (lying within the normal BMI category) was associated with a significant excess risk even in young women (at 30 years of age: 1.13, 95% CI: 1.04–1.22) and men (at 30 years of age: 1.30, 95% CI: 1.12–1.52).

DISCUSSION

Shape of the association

Our results are consistent with the well-known U-shaped BMI mortality relationship.[1,2] The U-shaped pattern is unlikely to be fully the result of reverse causation, as the U-shaped relation persisted in studies attempting to minimize the effect of reverse causation.[3] Also, different causes of death with opposed associations to BMI are not a sufficient explanation, as a U-shaped association has been reported for cardiovascular mortality as well.[11,12] Opposite effects of fat mass and fat-free mass on health could be a plausible explanation, as BMI is an additive measure of fat mass and fat-free mass.[13]

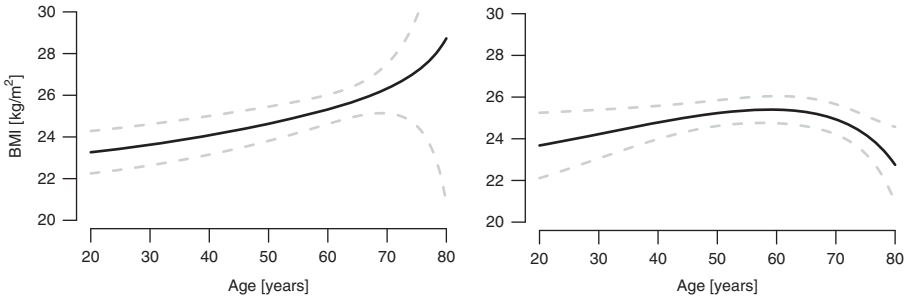

Figure 1. BMI associated with minimum mortality and 95% confidence bands (dashed lines) for women (left) and men (right).

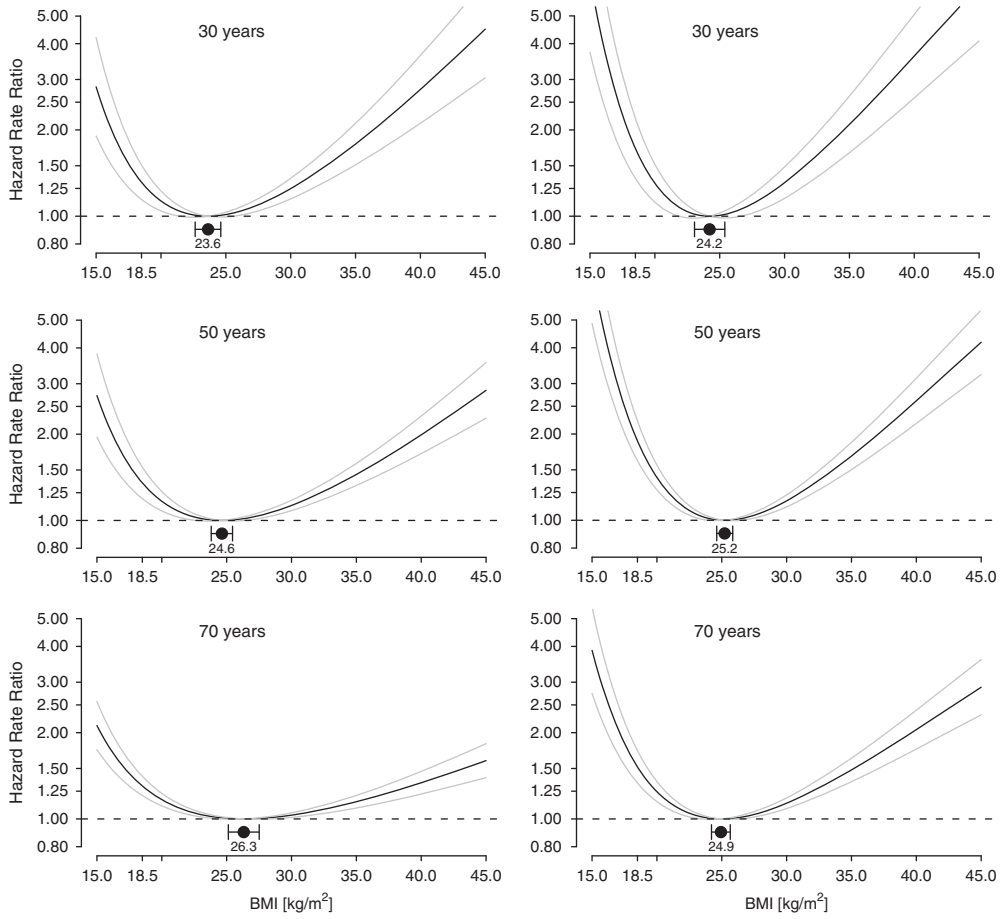

Figure 2. Hazard relative to optimum BMI and 95% confidence bands in women (left) and men (right) at different ages. The black dot represents the BMI associated with minimum mortality.

Our finding of a decreasing strength of association with higher age is consistent with previously published literature.[1,2,6] One possible explanation may be selective survival, as subjects susceptible to the adverse effects of obesity have died already because of obesity or obesity-associated complications at younger age.[27] Another possible explanation might be accumulated confounding throughout the lifespan.[10] Examples include exposure to endogenous and exogenous hormones, as well as physical activity and nutritional patterns throughout life. It is difficult to accurately measure and control for these factors.

BMI associated with minimum mortality

Durazo-Arvizu *et al.*[28] derived the optima using power transformations of BMI to model the relation between BMI and mortality. Their study included 7861 women (mean age: 48 years) and 5381 men (mean age: 52 years) regardless of smoking status and found the BMI associated with minimum mortality to be 24.3 kg m^{-2} (95% CI: 23.2–25.4) in women and 24.8 kg m^{-2} (95% CI: 23.8 25.9) in men. Although, Durazo-Arvizu *et al.*[28] did not model the optimum as a function of age, our results for an overall optimum of 24.3 kg m^{-2} in men and an optimum of 24.6 in women aged 50 years are similar. The Diverse Populations Collaborative Group quantified the optimum BMI in 6 populations of white women and 15 populations of white men using data of 15 studies (mean age ranging from 41 to 55 years).[29] This study assumed a relation between BMI and mortality of the form log(HR) = 1/BMI+1/BMI^2 allowing non-symmetric U-shaped curves and found optima ranging from 22.1 to 25.2 kg m^{-2} in women and from 20.9 to 29.4 kg m^{-2} in men. Differences between optima found in those studies might be related to differences in the populations (e.g. ethnicity, lifestyle), in the age distribution, in the exposure assessment (self-reported vs measured) or the result of different inclusion and exclusion criteria.

Wong *et al.*[21] applied fractional polynomials to the data of 65 412 women (mean age: 47 years) and 52 549 men (mean age: 45 years) who participated in a National Health Household Survey. Different to our study was the inclusion of smokers but exclusion of underweight subjects. They found the optimum BMI in men to be constant over age, whereas the optimum in women was increasing with age, which is in line with our results. However, the optima found by Wong *et al.*,[21] an optimum of 27.0 kg m^{-2} (95% CI: 26.4–27.5) in men and 22.3 kg m^{-2} (95% CI: 20.1–24.6) in 50 year old women, differ somewhat from the optima found in our study.

The slight decrease in optimum BMI in men starting at the age of 60 years observed in our study was unexpected. Other studies should be conducted to test these results.

Strength and limitations

An obvious strength of our study is the large number of participants (about 130 000) and the long follow-up (median: 18.6 years). We used all available BMI measurements of participants as compared with only the first one, to reduce misclassification of weight status at later time points.[22] Weight and height were measured rather than self-reported. Self-reported weight tends to be underreported,[30] and could potentially lead to an underestimation of the BMI associated with minimum mortality. We excluded examinations of participants with

prevalent cancer, examinations that were within 3 years before the end of follow-up or death, and examinations in ever smokers to reduce the effect of reverse causation. We have not attempted to control statistically for physiologic effects of body fat-like blood pressure, fasting glucose and blood lipids as they lie on the casual pathway and thus adjustment would attenuate the association between overweight and mortality.[22]

We used BMI as continuous variable while accounting for the shape of the BMI mortality relation, which allowed it to quantify the optimum and reserves statistical power compared with the traditional method of categorizing BMI.

Besides those strengths, our study has limitations, mainly the lack of information on prevalent chronic diseases other than cancer, which might have affected the participants' weight. We addressed this shortcoming by exclusion of examinations within 3 years before death or end of follow-up. However, some diseases might affect weight long before leading to death.

Generalizability

Although a large proportion of the general population participated in the VHM&PP, the cohort is relatively healthy. However, quantification of an optimum BMI range should be based on healthy individuals. Participants may differ from non-participants (e.g. lifestyle, immigration, dietary habits), which might possibly alter the relation between BMI and mortality. We excluded current and former smokers; therefore, our results can only be generalized to never smokers.

CONCLUSION

Our results indicate that BMI associated with minimum all-cause mortality changes with age and that patterns differ by sex. Sex- and age-independent BMI recommendations might therefore be inappropriate. Further studies using flexible methods instead of predefined categories are necessary to revise BMI recommendations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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