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Meta-analyses

Dose–response relationship between body mass index and risks of all-cause mortality and disability among the elderly: A systematic review and meta-analysis

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SUMMARY

Background & aims: To establish the relationship between body mass index (BMI) and risks of mortality and disability among the Elderly.
Methods: A systematic review and dose–response meta-analysis was performed. PubMed, Embase, Cochrane library, and Google Scholar were searched systematically until December 2017 for relative studies reporting the hazard ratio (HR) and corresponding 95% confidence intervals (CIs) of all-cause mortality or disability across different BMI categories.
Results: 44 studies (37 studies on all-cause mortality and 9 studies on disability) were included in the meta-analysis. The restricted cubic spline model presents a U-shape trend, which suggests a relationship between BMI and all-cause mortality. As BMI increased, the all-cause mortality decreased from 1.49 (95% CI: 1.31, 1.71) to 0.96 (95% CI: 0.93, 0.98) in the 14.0–27.9 range and increased from 0.96 (95% CI: 0.94, 0.99) to 1.95 (95% CI: 1.37, 2.77) in the 28.0–47.9 range. In comparison with the reference BMI (23.0–23.9), the 24.0–29.0 BMI presented a significant protective effect, whereas <23.0 BMI and >33.0 BMI presented a significant risk effect on all-cause mortality. For disability, the restricted cubic spline model shows a nonlinear relationship. Individuals with >28.0 BMI and 33.0 BMI were 19% (95% CI: 1.01, 1.40) and 43% (95% CI: 1.13, 1.82) more prone to disability risks compared with those in the reference group, respectively.
Conclusions: The lower-end recommended BMI range, underweight, and obesity among the elderly is associated with significantly increased risks of mortality and disability. The 23.0–28.0 BMI range may be the healthy weight range for the elderly group.
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1. Introduction

Population aging is regarded a serious public health concern in developed and developing countries. The "Aging World: 2008" reported that population aging was a major global demographic trend in the first decade of the 21st century. The ≥80-year-old and ≥65-year-old age groups are even expected to increase by 233% and 160% from 2008 to 2040, respectively [1]. Moreover, the prevalence of obesity among the elderly has increased. In the 2007–2010 period, 40% of population aged 65–74 years and 29% of population aged ≥75 years were obese and the obesity rates represent an increase of 4% and 5% from the 2003–2006 period, respectively [2]. Consequently, the increase in chronic diseases and disabilities associated with population aging, as well as the rise in obesity rates, has become a major challenge to health care and social services worldwide.

Overweightness and obesity are important determinants of mortality and disability among young and middle-aged adults [3]. However, among the elderly, findings on mortality risk and its relation to overweightness and obesity were inconsistent [4–6]. For instance, some researchers suggested the inverse relationship between overweightness and mortality among the elderly [4–6]. In

Abbreviations: BMI, Body mass index; CIs, Confidence intervals; HR, Hazard ratio; MOOSE, Meta-analysis of Observation Studies in Epidemiology.

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other studies, mortality risks associated with BMI thresholds were reportedly higher among the elderly than those among the younger age groups [5,6]. In the meta-analysis of Winter et al., decreased mortality risks were observed among overweight ≥65-year-old adults, whereas increased mortality risks were linked to the low healthy range of recommended BMI [7].

Extensive research has been conducted on the relationship between BMI and mortality among the elderly. However, apart from mortality, other health variables such as disability should be considered [8]. The World Health Organization estimates that 650 million elderly live with disabilities or impairments [9]. Reports also showed that the number of people with disabilities has rapidly increased because of population aging, prevalence of chronic diseases, and inefficient medical care [9].

Studies on the relationship between BMI and disability among the elderly have been recently conducted, but their results are inconsistent. A study on self-reported weight, height, and disability proposed that obesity-related death is less significant than obesity-related disability among ≥70-year-old adults [10]. Another study using measured weight and height found that heavy weight is not associated with high incidence of disability among ≥65-year-old individuals [11]. Given the inconsistent results, the relationship between BMI and disability is currently unclear.

In this study, a meta-analysis is conducted to establish the dose–response relationship between BMI and risks of mortality and disability, as well as to determine the suitable healthy BMI range for the elderly group.

2. Methods

2.1. Search strategy and selection criteria

We performed this study followed the Meta-analysis of Observation Studies in Epidemiology (MOOSE) guidelines [12].

Under the guidance of professional librarian, we searched electronic databases (PubMed, Embase, Cochrane library, and Google Scholar) for prospective cohort studies and cross-sectional studies in English up to 31 October 2017 using a combined MeSH heading and text search strategy with the following terms: “body mass index” OR “BMI” OR “weight” OR “body weight” OR “obesity” OR “overweight” OR “underweight” AND “mortality” OR “disability” OR “death” OR “death rate” AND “old” OR “geriatric” OR “senior”. We also manually checked reference lists to identify other potential studies. Moreover, we contacted the authors of articles via e-mail when the required data was not reported in the articles to ensure that all necessary data were obtained. Websites of aging conferences since January 2010 were examined to identify current unpublished studies.

In conducting the meta-analysis, studies were selected on the basis of the following a-priori-defined inclusion criteria: (1) publications involving ≥65-year-old adults; (2) hazard ratio (HR) and corresponding 95% confidence intervals (CIs) of all-cause mortality or disability across different BMI categories were reported; (3) studies involving a follow-up time of more than five years; and (4) cohort studies on mortality and cohort studies and cross-sectional studies on disability. Studies were excluded if HRs were reported only for weight or weight change rather than BMI, and if a study reported less than three quantitative BMI categories. If study samples overlap in at least two publications, or if multiple publications describe the same study aspects, then only the publication with the largest sample was considered.

2.2. Data extraction and quality assessment

Data from original articles were independently extracted by two reviewers (Yuanfa Cai and Mingjun Jiang) who used a pretested data collection form. Any disagreement between the two reviewers was resolved through discussion with the third reviewer. The following data were collected for analysis: (1) author and publication year; (2) population information, including country, age, sex, sample size, and BMI; (3) study characteristics, including definition of disability, follow-up duration, adjusted risk factors, and event assessment; and (4) information on HR outcomes.

Methodological quality of studies was evaluated using the Newcastle–Ottawa scale [13]. Using the Newcastle–Ottawa scale, a study was assessed on the basis of selection (4 items, one star each), comparability (1 item, maximum of two stars), and exposure/outcome (3 items, one star each). Stars were assigned for studies that reported follow-up of at least 10 years; missed follow-ups were estimated to be less than 25%.

2.3. Statistical analysis

The HRs of all-cause mortality or disability across different BMI categories was obtained from original studies. The lowest BMI category range was used as the reference group, and the extracted HRs were then recalibrated for each original study. The potential nonlinear relation between BMI and all-cause mortality or disability was examined by a two-stage random-effects meta-analysis. Then, BMI was modeled with restricted cubic splines with three knots selected at the 5th, 50th, and 95th percentiles of the distribution. The pooled HRs of each 1-unit BMI increment was obtained using the 23.0–23.9 range as reference. The nonlinearity of the meta-analysis was assessed by testing the null hypothesis; that is, the coefficient of the second spline was equal to zero. The I^2 statistic describing the proportion of total variation caused by heterogeneity was used to assess statistical heterogeneity.

Apart from conducting a full meta-analysis, subgroup meta-analyses were performed for the following study aspects: sex, measured versus self-reported anthropometric variables, and non-smokers. Finally, using the BMI category range including 23.5 BMI as reference group, HRs was recalibrated for each original study to obtain the overall HR for the following BMI categories: <18.5, 18.5–22.9, 23.0–27.9, 28–32.9, and >33.

Publication bias was assessed with Egger's linear regression test and Begg's rank correlation test. All the analyses were conducted in STATA (version 11; Stata Corp., College Station, TX, USA). $P < 0.05$ was considered statistically significant, unless otherwise specified.

3. Results

Figure 1 illustrates the trial flow chart. The electronic and manual literature search yielded 6008 studies, of which 19 were excluded because of duplication. After the title and abstract search (i.e., preliminary screening), 5872 studies further were excluded. Thus, 117 full-text studies were screened for detailed evaluation. Of this number, 73 studies were excluded on the basis of the selection criteria: age (28 studies), short follow-up time (3 studies), duplication (7 studies), less than three BMI categories (1 study), missing data on all-cause mortality or disability (10 studies), and insufficient population or BMI information (24 studies). Consequently, 44 studies (including 37 studies on all-cause mortality and 9 studies on disability) were included in the meta-analysis [5,6,14–55]. Two of the studies reported on both all-cause mortality and disability [14,41]. According to the Newcastle–Ottawa scale, all studies were higher scoring studies because that they had more than six scores (data not shown).

Table 1 presents the characteristics of the BMI and mortality studies. The 37 studies on all-cause mortality involved 320,594 individuals (97,294 deaths) [5,6,14–48]. Of this number, 15 studies were conducted in the United States, 17 in Europe, 1 in Canada, 3 in

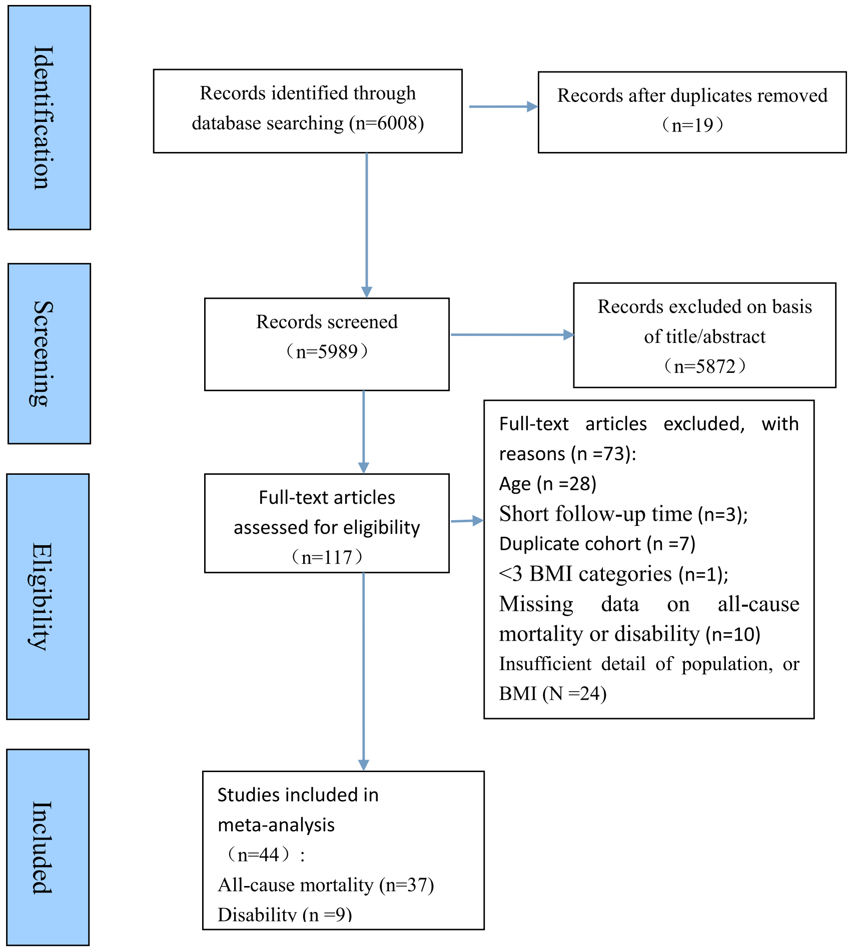

Fig. 1. Flow chart illustrating the selection process for articles included in the meta-analysis.

Australia, and 1 in Japan. The population cohorts of 6 studies involving <65-year-old (i.e., relatively younger) adults were included because subsequent subgroup analyses reported the HRs for >65-year-old adults in these studies. Female and male cohorts were reported in 20 and 16 studies, respectively. Non-smoking respondents were reported in 9 studies. Measured and self-reported height and weight for BMI calculation were highlighted in 24 and 13 studies, respectively. In these BMI and mortality studies, follow-up duration was 5–29 years.

The restricted cubic spline model in Fig. 2 presents a U-shape trend, which suggests a relationship between BMI and all-cause mortality (P-nonlinearity < 0.001). As BMI increased, the all-cause mortality decreased from 1.49 (95% CI: 1.31, 1.71) to 0.96 (95% CI: 0.93, 0.98) in the 14.0–27.9 range and increased from 0.96 (95% CI: 0.94, 0.99) to 1.95 (95% CI: 1.37, 2.77) in the 28.0–47.9 range. In comparison with the reference BMI (23.0–23.9), the 24.0–29.0 BMI presented a significant protective effect, whereas <23.0 BMI and >33.0 BMI presented a significant risk effect on all-cause mortality. Individuals with 27.0–28.0 BMI were least likely affected 5% mortality risks, whereas individuals with <20.0 BMI and >35.0 BMI were 14% and 20% more prone to mortality risks compared with those in the reference group. Both the subgroup meta-analyses on men–women and measured versus self-reported BMI did not show significant differences. The result of meta-analysis on non-smokers was similar to that on the entire population (Fig. 2).

The HRs was recalibrated using the reference range including 23.5 BMI for the reference group of each original study. Then, subgroup analyses were performed for the different BMI categories. The overall HRs were as follows: 1.69 (95% CI: 1.57, 1.83) for <18.5 BMI; 1.17 (95% CI: 1.12, 1.22) for 18.5–22.9 BMI; 0.91 (95% CI: 0.88, 0.94) for 23.0–27.9 BMI; 0.98 (95% CI: 0.94, 1.03) for 28.0–32.9 BMI; and 1.32 (95% CI: 1.15, 1.51) for >33.0 BMI.

With regard to the 9 studies on BMI and disability, 5 were cohort studies and 4 were cross-sectional studies involving 96,213 individuals (Table 2) [14,41,49–55]. 3 studies were conducted in the United States, whereas 1 study each was conducted in England, Canada, China, Australia, and Brazil. One of the studies (Al Snih et al.) focused on BMI and disability in seven Latin American cities, namely, Buenos Aires (Argentina), Bridgetown (Barbados), Sao Paulo (Brazil), Santiago (Chile), Havana (Cuba), Mexico City (Mexico), and Montevideo (Uruguay). In terms of sex, 4 studies were on females whereas 3 studies were on males. All 9 studies involved smokers and non-smokers. In 8 studies, the measured height and weight were used for BMI calculation. In these BMI and disability studies, follow-up duration was 5–14 years.

The restricted cubic spline model in Fig. 3 shows a nonlinear relationship between BMI and disability (P-nonlinearity = 0.004). The 24.0–28.0 BMI presented a decreasing risk effect on disability compared with the reference BMI (23.0–23.9). Individuals with >28.0 BMI and 33.0 BMI were 19% (95% CI: 1.01, 1.40) and 43% (95% CI: 1.13, 1.82) more prone to disability risks compared with those in the reference group, respectively. The independent meta-analysis on men and women did not show a significant difference. The analytical results of 8 studies with measured BMI were similar to that of the entire population (Fig. 3).

Table 1
Main characteristic of the included articles on mortality and body mass index.

First author, year	Cohort, country, and study period	Sample size (death)	Years of follow-up	Age (y)	BMI	HR (95%CI)	Adjusted variable
Al Snih, 2007	EPESE study, USA, 1982–1989; 1986–1993; 1993–2000	12,725 (2019)	7 (max)	≥65	<18.5	1.53 (1.31,1.8)	Age, sex, race, marital status, education, smoking status, comorbidity, EPESE site
					18.5–24.9	1.00	
					25.0–29.9	0.78 (0.72,0.85)	
					30.0–34.9	0.8 (0.72,0.9)	
					35.0–39.9	1.02 (0.84,1.24)	
					≥40	1.13 (0.79,1.6)	
Atlantis, 2010	MELSHA, Australia, 1994–2006	1000 (409)	12 (max)	≥65	<18.5	2.15 (1.15,4.02)	Sex, age, smoking status, instrumental ADLs, timed up and, social activity, cognitive impairment, CVD
					18.5–24.9	1.00	
					25.0–29.9	0.96 (0.77,1.2)	
					≥30	1.04 (0.76,1.42)	
Berraho, 2010	Personness Ages QUID (PAQUID) study, France, 1988–2001	3646 (1973)	13 (max)	75.25 ± 6.78	<18.5	1.45 (1.17,1.78)	Sex, age, physical activities, smoking status, and comorbidity
					18.5–21.9	1.27 (1.12,1.43)	
					22.0–24.9	1.00	
					25.0–29.9	0.98 (0.88,1.1)	
					≥30	1.06 (0.89,1.27)	
Berrington de Gonzalez, 2010	PAQUID cohort study, France, 1988–2001	28,446 (5160)	13 (max)	19-84; subgroup (70–84)	15.0–18.4	1.65 (1.39,1.95)	Sex, age, physical activity, smoking status, comorbidity (diabetes, dyspnea, hypertension, ischemic heart disease, antecedent stroke antecedent, number of medications)
					18.5–19.9	1.32 (1.15,1.51)	
					20.0–22.4	1.06 (0.97,1.16)	
					22.5–24.9	1.00	
					25.0–27.4	1.04 (0.96,1.13)	
					27.5–29.9	1.15 (1.04,1.26)	
					30.0–34.9	1.24 (1.12,1.38)	
					35.0–39.9	1.59 (1.33,1.9)	
					40.0–49.9	1.91 (1.44,2.52)	
Blain, 2010	EPIDOS, France, 1992/1993-2001	1300 (410)	8 (max)	≥75	<18	1.33 (0.62,2.83)	Age
					18–25	1.00	
					25–30	0.88 (0.71,1.09)	
					≥30	1.18 (0.89,1.55)	
Breeze, 2006	Male civil servants, UK, 1997–2002	4862 (1075)	5 (max)	67–96.4	<22.7	1.22 (1,1.4)	Age, marital status, employment grade, smoking, alcohol, disable, poor physical performance
					22.7–24.3	1.00	
					24.3–26.1	0.92 (0.8,1.1)	
					≥26.1	1.09 (0.9,1.3)	
Moore, 2008	BCDDP follow-up study, United States, 1997–2007	50,186 (5201)	10	67	15.0–18.4	1.43 (1.19,1.72)	Age, menopausal hormone use, annual household income, education level, race, smoking, physical activity
					18.5–20.9	1.07 (0.98,1.17)	
					21.0–23.4	1.00	
					23.5–24.9	1.1 (1,1.2)	
					25.0–27.4	1.2 (1.11,1.31)	
					27.5–29.9	1.23 (1.11,1.37)	
					30.0–34.9	1.6 (1.44,1.77)	
					35.0+	1.92 (1.64,2.24)	
Cesari, 2009	Invecchiare in Chianti study, Italy, 1998/2000–2001/2003-2004/2006	934 (263)	5.1 (mean)	≥65	<25	1.00	Age, gender, site, education, Mini-Mental State Examination score, ESD scale score, physical activity, congestive heart failure, coronary artery disease, hypertension, peripheral artery disease, respiratory disease, osteoarthritis, stroke, interleukin-6, C-reactive protein, tumor
					25–30	1.33 (0.77,2.27)	
					≥30	1.09 (0.58,2.07)	
Corrada, 2006	Leisure World Cohort Study, U.S.A, 1981–2004	13,451 (11,203)	13 y (mean); 23 (max)	73 (mean,44–101)	<18.5	1.53 (1.4,1.67)	Age; gender; smoking status; active activities; hypertension, angina, myocardial infarction, stroke, diabetes, arthritis, and cancer.
					18.5–24.9	1.00	
					25–29.9	1.12 (1.01,1.24)	
					≥30	0.97 (0.93,1.01)	
Dahl, 2013,	OCTO-twin, Gender, and NONA, Sweden, NM	882 (667)	18 (max)	80.1 ± 5.7; range 70–95;	<25	1.00	Age, education, multi morbidity
					25.0–29.9	0.8 (0.67,0.95)	
					≥30.0	0.93 (0.71,1.22)	

de Hollander, 2012	SENECA study, Netherlands, 1988/1989–1998/1999	1970 (751)	10 (max)	70–75	<20.0	1.06 (0.73,1.55)	Sex, smoking status, educational level, age at baseline
					20.0–25.0	1.00	
					25.0–30.0	0.92 (0.78,1.09)	
					≥30.0	1.05 (0.89,1.29)	
Dey, 2001	Sweden, three birth cohort 1971/1972–1986/1987; 1976/1977–1991/1992; 1981/1982–1996/1997	2590 (1333)	15 (max)	70–75	14.0–22.6	1.2 (0.96,1.51)	Birth cohort, smoking habits at age 70 y
					22.7–24.6	1.07 (0.85,1.34)	
					24.7–26.4	1.00	
					26.5–28.5	1.01 (0.81,1.26)	
					28.6–39.2	1.19 (0.95,1.49)	
					14.1–22.5	1.49 (1.14,1.96)	
					22.6–24.5	1.16 (0.88,1.53)	
					24.6–26.5	1.00	
					26.6–29.2	1.16 (0.88,1.52)	
					29.3–39.8	1.25 (0.95,1.64)	
Dolan, 2007	Osteoporotic Fractures Study, U.S.A, 1986–1997	8029 (945)	8 (mean)	≥65	≤22.38	1.00	Age; smoking status; self-reported health status; grip strength; non–thiazide diuretic use; femoral neck bone mineral density
					22.38–24.56	0.8 (0.65,0.96)	
					24.56–26.73	0.7 (0.57,0.87)	
					26.73–29.82	0.72 (0.58,0.89)	
					>29.82	0.89 (0.72,1.1)	
Flicker, 2010	Health in Men and Longitudinal Study of Women's Health, Australia, 1996–2006	9240 (2308)	10 (max)	women 72.1; men 72.3	<18.5	1.76 (1.39,2.22)	Age, sex
					18.5–24.9	1.00	
					25.0–29.9	0.87 (0.78,0.94)	
					≥30	0.98 (0.85,1.11)	
Freedman, 2006	U.S. Radiologic Technologists (USRT) Study, US, 1983/1989-2002	4572 (743)	19 (max)	≥65	18.0–24.9	1.00	Race-ethnicity, education, alcohol behavior, year first worked as a radiologic technologist
					25.0–29.9	0.77 (0.57,1.03)	
					30.0–34.9	1.15 (0.7,1.89)	
					≥35.0	3.16 (1.27,7.84)	
					18.0–24.9	1.00	
					25.0–29.9	1.09 (0.89,1.33)	
					30.0–34.9	1.44 (1.08,1.92)	
					≥35.0	2.57 (1.68,3.95)	
Gale, 2007	Department of health and social security survey, UK, 1973/1974-1998	348 (315)	24 (max)	≥65	<18.5	1.41 (0.9,2.38)	Age, height, smoking, social class, physical activity, diagnosed disease, calorie intake, weight loss, body composition
					18.5–24.9	1.00	
					25.0–29.9	1 (0.74,1.34)	
					≥30	1.14 (0.76,1.71)	
Grabowski, 2001	Longitudinal Study of Aging, USA, 1984–1991	7527 (2860)	8 (max)	70	<19.0	2 (1.2,3.2)	Age, health care use, functional limitations, sex, race, private health insurance, region of country, education, self-rated health, lives alone, need for proxy, married
					19.0–21.9	1.00	
					22.0–24.9	0.9 (0.7,1.1)	
					25.0–26.9	0.9 (0.7,1.2)	
					27.0–28.9	0.7 (0.5,1)	
					29.0–31.9	0.8 (0.5,1.1)	
					≥32.0	0.8 (0.4,1.2)	
					<19.0	1.4 (1.1,1.8)	
					19.0–21.9	1.00	
					22.0–24.9	0.9 (0.7,1.1)	
					25.0–26.9	0.7 (0.5,1)	
					27.0–28.9	0.9 (0.7,1.2)	
					29.0–31.9	0.6 (0.4,0.8)	
					≥32.0	0.8 (0.4,1.2)	
Gulsvik, 2009	Bergen Clinical Blood Pressure Study, Norway, 1965–2007	788 (231)	women:29 (mean); men:25 (mean)	20-75; subgroup: 65-74	<22.0	1.58 (1.11,2.25)	Sex, hypertension, cholesterol, smoking, activity, CVD, diabetes, pulmonary disease, socioeconomic status
					22.0–24.9	1.00	
					25.0–27.9	0.86 (0.64,1.16)	
					≥28.0	1.1 (0.83,1.46)	
Janssen, 2007	Cardiovascular health study, US, 1989–1998	4968 (1464)	9 (max)	≥65	20.0–24.9	1.00	Sex, age, race, socioeconomic status, smoking, activity, prevalent disease
					25.0–29.9	0.89 (0.8,0.99)	
					≥30.0	0.83 (0.71,0.97)	

(*continued on next page*)

Table 1 (*continued*)

First author, year	Cohort, country, and study period	Sample size (death)	Years of follow-up	Age (y)	BMI	HR (95%CI)	Adjusted variable
Janssen, 2008	Framingham Heart Study, US, initiated 1948	4982 (3224)	70s:10.8 (median); 80s: 4.8 (median)	70–89	70s:<=24.9	1.00	Sex, age, smoking, alcohol
					25.0–29.9	0.99 (0.9,1.09)	
					≥30.0	1.22 (1.08,1.38)	
					80s:<24.9	1.00	
					25.0–29.9	0.9 (0.78,1.04)	
					≥30.0	0.96 (0.79,1.19)	
Keller, 2005	Canadian Study of Health & Aging, Canada, 1991–2001	539 (207)	10 (max)	≥65	<18.5	1.00	Age, sex, smoking, educational level, marital status, cognitive impairment at first follow-up
					18.5–24.9	0.51 (0.16,1.65)	
					25–29.9	0.36 (0.11,1.14)	
					≥30	0.47 (0.13,1.66)	
Kulminski, 2008	National Long Term Care Survey (NLTCS), USA, 1994–2003	4791 (2956)	9 (max)	≥65	<18.5	1.86 (1.62,2.14)	Sex, age, smoking, drinking, heart attack, other heart problems, stroke, cancer, and race (white, black, and other)
					18.5–21.9	1.27 (1.14,1.41)	
					22.0–24.9	1.00	
					25.0–29.9	0.82 (0.74,0.91)	
					30.0–34.9	0.78 (0.68,0.91)	
					≥35	1.05 (0.87,1.26)	
Kvamme, 2012	4th Troms study; Norway, 1994/1995-	16,711 (7474)	9.3 (mean)	≥65	<18.5	2.07 (1.47,2.92)	Age, marital status, education and smoking, study site
					18.5–19.9	1.14 (0.89,1.46)	
					20.0–22.4	1.1 (0.98,1.24)	
					22.5–24.9	1.00	
					25.0–27.4	0.89 (0.82,0.97)	
					27.5–29.9	0.94 (0.86,1.03)	
					30.0–32.4	1.06 (0.94,1.2)	
					32.5–34.9	1.17 (0.98,1.4)	
					≥35	1.37 (1.07,1.75)	
					<18.5	1.62 (1.19,2.21)	
					18.5–19.9	1.43 (1.14,1.79)	
					20.0–22.4	1.2 (1.06,1.36)	
					22.5–24.9	1.00	
					25–27.4	0.91 (0.82,1.01)	
					27.5–29.9	0.96 (0.86,1.07)	
					30.0–32.4	0.91 (0.81,1.03)	
					32.5–34.9	1.08 (0.93,1.25)	
					≥35	1.32 (1.11,1.57)	
Mazza, 2007	CASTEL, Italy, 1979–1991	Men:3257 (1275); women:1599 (713)	12 (max)	65-95; 73.8 (mean)	<22.7	1.27 (1.01,1.59)	Age; pulmonary disease; smoking; alcohol; serum total cholesterol; coronary heart disease; arterial hypertension; diabetes; serum creatinine
					22.7–24.9	1.00	
					25.0–26.5	0.94 (0.74,1.19)	
					26.6–29.0	0.91 (0.72,1.15)	
					>29.0	0.78 (0.62,0.99)	
McAuley, 2009	Veterans Exercise Testing Study, US, 1987–2004	981 (208)	6.9 (mean)	≥65	<20.0	2.51 (1.26,4.98)	Age, ethnicity, hypertension, cholesterol, smoking, physical activity
					20.0–24.9	1.00	
					25.0–29.9	0.66 (0.48,0.9)	
					30.0–34.9	0.5 (0.31,0.78)	
					≥35.0	0.44 (0.2,0.97)	
McTigue, 2006	Women's health Initiative Study, US, 1993–2004	18,651 (1876)	9.9 (max); 7 (mean)	50-79; subgroup analysis:70-79	18.5–24.9	1.00	Age, tobacco use, education, US region, physical activity level
					25.0–29.9	0.86 (0.77,0.96)	
					30.0–34.9	0.99 (0.87,1.15)	
					35.0–39.9	1.16 (0.94,1.44)	
					≥40	1.26 (0.92,1.72)	
Miller, 2002	ALSA, Australia, 1992/1993 –2000/2001	1396 (579)	8 (max)	≥70	<20	1.36 (0.94,1.99)	Sex, age group, marital status, smoking status, health, comorbid conditions, cognitive performance, ADLs, depression.
					20–25	1.00	
					25–30	0.99 (0.82,1.21)	
					>30	1.13 (0.86,1.49)	
Price, 2006	Medical Research Council General Practice Research Framework, UK, 1995/1998	9984 (4077)	5.8 (mean)	≥75	15.9–23.0	1.00	Serious illness in loved one in past year, depression, cognitive impairment, unexplained recent weight loss > 3.2 kg, housing type, alcohol use, former smoking
					23.0–25.0	0.81 (0.69,0.94)	
					25.0–26.7	0.73 (0.63,0.85)	

					26.7–29.0	0.67 (0.57,0.78)	
					29.0–40.4	0.64 (0.55,0.75)	
					14.7–22.3	1.00	
					22.3–24.6	0.94 (0.84,1.05)	
					24.6–26.8	0.74 (0.65,0.83)	
					26.8–29.7	0.75 (0.65,0.87)	
					29.7–45.2	0.72 (0.62,0.84)	
Reis, 2009	NHANES III, US, 1988–1994	3748 (1593)	12 (max)	30-102; subgroup analysis:≥65	<18.5	2.46 (1.39,4.37)	Age, race, education, smoking status, alcohol use, heart disease, stroke, respiratory disease, cancer
					18.5–24.9	1.00	
					25.0–29.9	0.88 (0.7,1.11)	
					30.0–34.9	0.74 (0.54,1.02)	
					≥35.0	0.7 (0.37,1.34)	
					<18.5	2.32 (1.49,3.62)	
					18.5–24.9	1.00	
					25.0–29.9	0.88 (0.7,1.11)	
					30.0–34.9	0.91 (0.68,1.21)	
					≥35.0	0.87 (0.58,1.3)	
Rillamas-Sun, 2014	WHI Observational Study and Clinical Trial programs, US, 1998–2005	36,611 (8975)	7	72.4	<18.5	2.09 (1.54,2.85)	Age, study membership, baseline hormone therapy use, race, education, marital status, smoking status, alcohol, physical activity, and depression status. BMI
					18.5–<25	1.00	
					25–<30	1.09 (1.01,1.18)	
					30–<35	1.72 (1.55,1.92)	
					35–<40	3.28 (2.69,4.01)	
					≥40	3.48 (2.52,4.8)	
Stessman, 2009	Jerusalem Longitudinal Study, Israel, 1990–2008	2403 (733)	18 (max)	≥70	<25.0	1.00	Perceived economic hardship, health, physical activity, smoking, ADL, hypertension, diabetes, ischemic heart disease, cancer
					25.0–29.9	0.93 (0.63,1.7)	
					≥30.0	1.03 (0.59,1.79)	
					<25.0	1.00	
					25.0–29.9	0.55 (0.33,0.92)	
					≥30.0	0.45 (0.25,0.83)	
Tamakoshi, 2010	Collaborative Cohort Study, Japan, 1988/1990-2003	26,747 (9256)	11.2 (mean)	65–79	<16.0	1.89 (1.44,2.48)	Smoking, drinking, physical activity, sleep duration, stress, education, marital status, green vegetables, stroke, MI, cancer
					16.0–16.9	1.77 (1.45,2.17)	
					17.0–18.4	1.23 (1.1,1.38)	
					18.5–19.9	1.19 (1.08,1.31)	
					20.0–22.9	1.06 (0.98,1.14)	
					23.0–24.9	1.00	
					25.0–27.4	0.98 (0.88,1.09)	
					27.5–29.9	0.95 (0.78,1.15)	
					≥30.0	0.99 (0.7,1.4)	
					<16.0	2.66 (1.99,3.56)	
					16.0–16.9	1.53 (1.2,1.94)	
					17.0–18.4	1.48 (1.29,1.7)	
					18.5–19.9	1.27 (1.13,1.43)	
					20.0–22.9	1.04 (0.95,1.14)	
					23.0–24.9	1.00	
					25.0–27.4	1.05 (0.94,1.18)	
					27.5–29.9	1.02 (0.86,1.2)	
					≥30.0	1.27 (0.32,5.1)	
Tayback, 1990	NHANWS I and NHEFS, US, 1971–1984	2568 (792)	12 (max); 8.7 (ave)	55-74, subgroup analysis: 65–74	<22.0	1.3 (1,1.6)	Smoking, elevated blood pressure, age and poverty
					22.0–30.0	1.00	
					>30.0	1.1 (1,1.2)	
					<22.0	1.3 (1,1.7)	
					22.0–30.0	1.00	
					>30.0	1 (1,1.1)	

(*continued on next page*)

Table 1 (*continued*)

First author, year	Cohort, country, and study period	Sample size (death)	Years of follow-up	Age (y)	BMI	HR (95%CI)	Adjusted variable
Visscher, 2004	Social Insurance Institution's Mobile Clinic Unit, Finland, 1973–1977	1559 (731)	15 (max)	65–92	18.5–24.9	1.00	Age, educational level, geographic region, alcohol use
					25.0–29.9	0.9 (0.7,1.2)	
					≥30.0	1.4 (1,2)	
					18.5–24.9	1.00	
					25.0–29.9	0.9 (0.7,1.1)	
					≥30.0	0.9 (0.8,1.2)	
Walter, 2009	Rotterdam Study cohort, Netherland, 1991–2006	4620 (1530)	15	68.85	18.5–25	1.00	Smoking status, smoke, alcohol consumption, education, income and living situation.
					25–30	0.96 (0.86,1.07)	
					30–35	1.06 (0.89,1.25)	
					35+	1.31 (0.86,1.99)	
Wee, 2011	Medicare Current Beneficiary Survey, US, 1994/2000-2008	20,975 (11,093)	14 (max)	≥65	<18.5	2.37 (1.84,3.07)	Baseline age, smoking status, education, proxy response, chronic health conditions
					18.5–21.9	1.24 (1.12,1.37)	
					22.0–24.9	1.00	
					25.0–27.4	0.84 (0.77,0.92)	
					27.5–29.9	0.83 (0.74,0.92)	
					30.0–34.9	0.91 (0.82,1.02)	
					≥35.0	1.53 (1.2,1.95)	
					<18.5	1.75 (1.51,2.02)	
					18.5–21.9	1.13 (1.03,1.25)	
					22.0–24.9	1.00	
					25.0–27.4	0.88 (0.8,0.97)	
					27.5–29.9	0.82 (0.73,0.92)	
					30.0–34.9	0.99 (0.89,1.1)	
					≥35.0	1.21 (1.04,1.42)	
Zunzunegui, 2012	Aging in Leganes, Spain, 1993–2006	1008 (672)	16 (max); 11.6 (median)	≥65	<18.5	2.47 (1.36,4.5)	Age, sex, education, physical activity, smoking, chronic conditions, and ADL
					18.5–24.9	1.00	
					25–29.9	0.9 (0.76,1.07)	
					30.0–34.9	0.87 (0.7,1.09)	
					≥35	1.09 (0.78,1.53)	

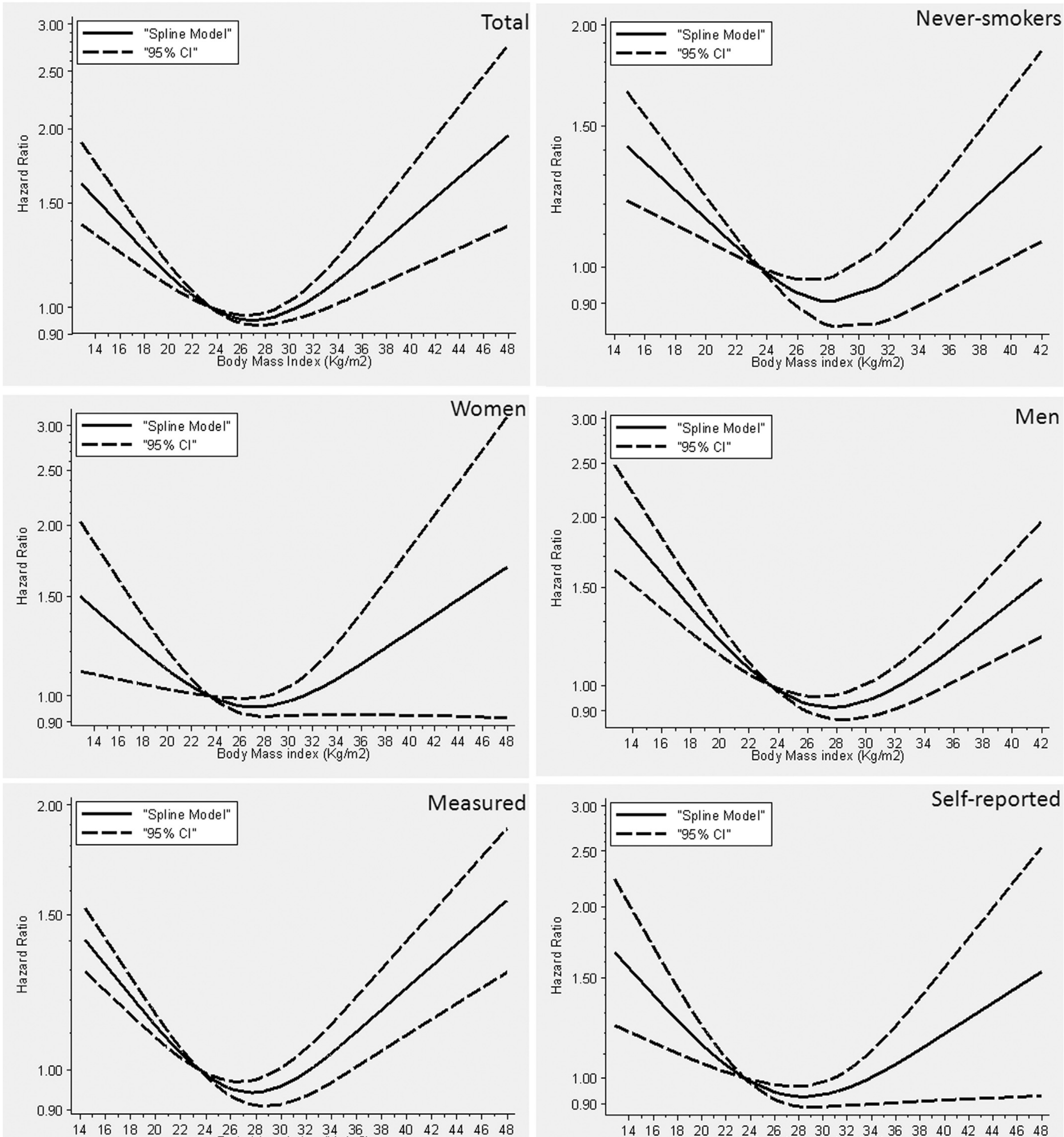

Fig. 2. The restricted cubic spline model presents a U-shape relationship between BMI and all-cause mortality for ≥65-year-old adults. The subgroup meta-analyses on non-smokers, men–women, or measured versus self-reported BMI did not show significant differences.

The HRs was recalibrated using the reference range including 23.5 BMI for the reference group of each original study. Then, subgroup analyses were performed for the different BMI categories. The overall HRs for disability were as follows: 1.54 (95% CI: 1.26, 1.87) for <18.5 BMI; 1.12 (95% CI: 0.84, 1.51) for 18.5–22.9 BMI; 1.06 (95% CI: 0.99, 1.13) for 23.0–27.9 BMI; 1.68 (95% CI: 1.43, 1.97) for 28.0–32.9 BMI; and 2.96 (95% CI: 2.06, 4.33) for >33.0 BMI.

The potential bias of the publications in the meta-analysis was evaluated using Egger's test and Begg's test. Egger's and Begg's tests did not indicate any publication bias (data not shown).

Table 2
Main characteristic of the included articles on disability and body mass index.

First author, year	Study type and country	Sample size	Years of follow-up	Age	BMI groups	HR (95%CI)	Adjusted variables	Disability standards
Lang, 2008	Cohort, England	3793	5	≥65	20.0–24.9	1.00	Year of entry into the study	One or more problems in following ADLs: dressing, including putting on shoes and socks; walking across a room; bathing or showering; eating; getting in or out of bed; and using the toilet, including getting up or down were classified as having impaired physical function.
					30.0–34.9	1.99 (1.42,2.78)		
					>35.0	5.26 (2.21,9.97)		
					20.0–24.9	1.00		
					30.0–34.9	1.66 (1.25,2.19)		
					>35.0	2.69 (1.81,4.01)		
Backholer, 2012	Cohort, Austrilia	6300	5	≥70	18.5–22.5	1.00	Prevalence of angina, asthma, diabetes, arthritis, cancer, heart attack, stroke and hypertension at baseline.	Limitations to self-care activities of daily living (ADLs) and self-care plus mobility activities
					22.5–25	0.87 (0.58,1.29)		
					25–27.5	1 (0.68,1.46)		
					27.5–30	1.27 (0.86,1.87)		
					30–35	1.55 (1.04,2.34)		
					35+	2.68 (1.35,5.33)		
					18.5–22.5	1.00		
					22.5–25	1.19 (0.92,1.53)		
					25–27.5	1.72 (1.35,2.2)		
					27.5–30	2.55 (1.96,3.3)		
					30–35	3.21 (2.47,4.19)		
					35+	4.74 (3.31,6.78)		
Danielewicz 2014	Cross-sectional, Brazil	477		60–100	<22	1.15 (0.76,1.75)	Age, gender, education, currently work, living arrangements, cognitive function and number of morbidities	The difficulty in performing one or more self-reported tasks related to basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs)
					22–27	1.00		
					>27	1.46 (1.11,1.92)		
Chen, 2008	Cross-sectional, USA	3295		70.8	<24.3	1.00	Age, gender, ethnicity, education, smoking, alcohol consumption, and physical activity, presence of individual chronic diseases, waist circumference	Having any difficulty in performing one or more activities within a given domain
					24.3–27.5	0.9 (0.5,1.4)		
					27.6–31.3	0.8 (0.4,1.5)		
					≥31.4	1.1 (0.5,2.3)		
					<24.3	1.00		
					24.3–27.5	1.1 (0.6,2.1)		
					27.6–31.3	1.1 (0.5,2.3)		
					≥31.4	2 (0.8,4.8)		
Chou, 2012	Cohort, CHINA	5591	9	≥65	≤18.5	1.12 (0.72,1.76)	Age, sex, and education, chronic conditions, smoking, and insurance status.	They needed help or could not dress, walk, use the toilet, bathe, and eat at all
					18.5–22.9	1.00		
					23.0–24.9	0.58 (0.36,0.96)		
Rillamas-Sun, 2014	Cohort, USA	36,611	14	72.4 (mean)	<18.5	1.11 (0.73,1.7)	Age, study membership, hormone therapy use, race, education, marital status, smoking status, alcohol, physical activity, depression status.	Need crutches, a walker, or a wheelchair to walk on a level surface or who self-reported on the RAND 36-Item Health Survey17 that their health greatly limited their ability to walk one block or up one
					18.5–<25	1.00		
					25–<30	1.64 (1.5,1.79)		
					30–35	3.22 (2.87,3.61)		
					35–40	6.62 (5.41,8.09)		
					≥40	6.65 (4.8,9.21)		
Al snih, 2007	Cohort, USA	12,725	7	≥65	<18.5	1.52 (1.28,1.79)	Age,sex,race, marital status, level of formal education, smoking status,comorbidity, and EPESE site	ADL included bathing, grooming, dressing, eating, using the toilet, walking across a small room, and transferring from a bed to a chair. Activity of daily living disability was dichotomized as needing no help v sneeding help with performing or being unable to perform 1 or more of the 7 ADL activities.
					18.5 to <25	1.00		
					25 to <30	1.02 (0.94,1.1)		
					30 to <35	1.31 (1.19,1.45)		
					35 to <40	1.94 (1.65,2.27)		
					≥40	2.49 (1.92,3.22)		
AL Snih, 2010	Cross-sectional, Latin American	6166		≥65	<18.5	1.25 (0.91,1.71)	Age, gender, marital status, education, smoking status, and city.	Having difficulty or no difficulty in performing following activities: walking across a small room, bathing, dressing, eating, getting into and out of bed, and using the toilet
					18.5–<25	1.00		
					25–<30	1.1 (0.93,1.3)		
					30–<35	1.11 (0.89,1.36)		
					>35	1.63 (1.26,2.11)		
Gadalla, 2010	Cross-sectional, Canada	21,255		≥65	<18.5	1.94 (4.58,2.38)	Social economic and health characteristics	They needed help with IADL, such as preparing meals, getting to appointments, doing everyday housework, shopping for groceries and other necessities, personal care, or moving about inside their home
					18.5–25	1.00		
					25–30	1.04 (0.96,1.11)		
					≥30	1.72 (1.57,1.89)		

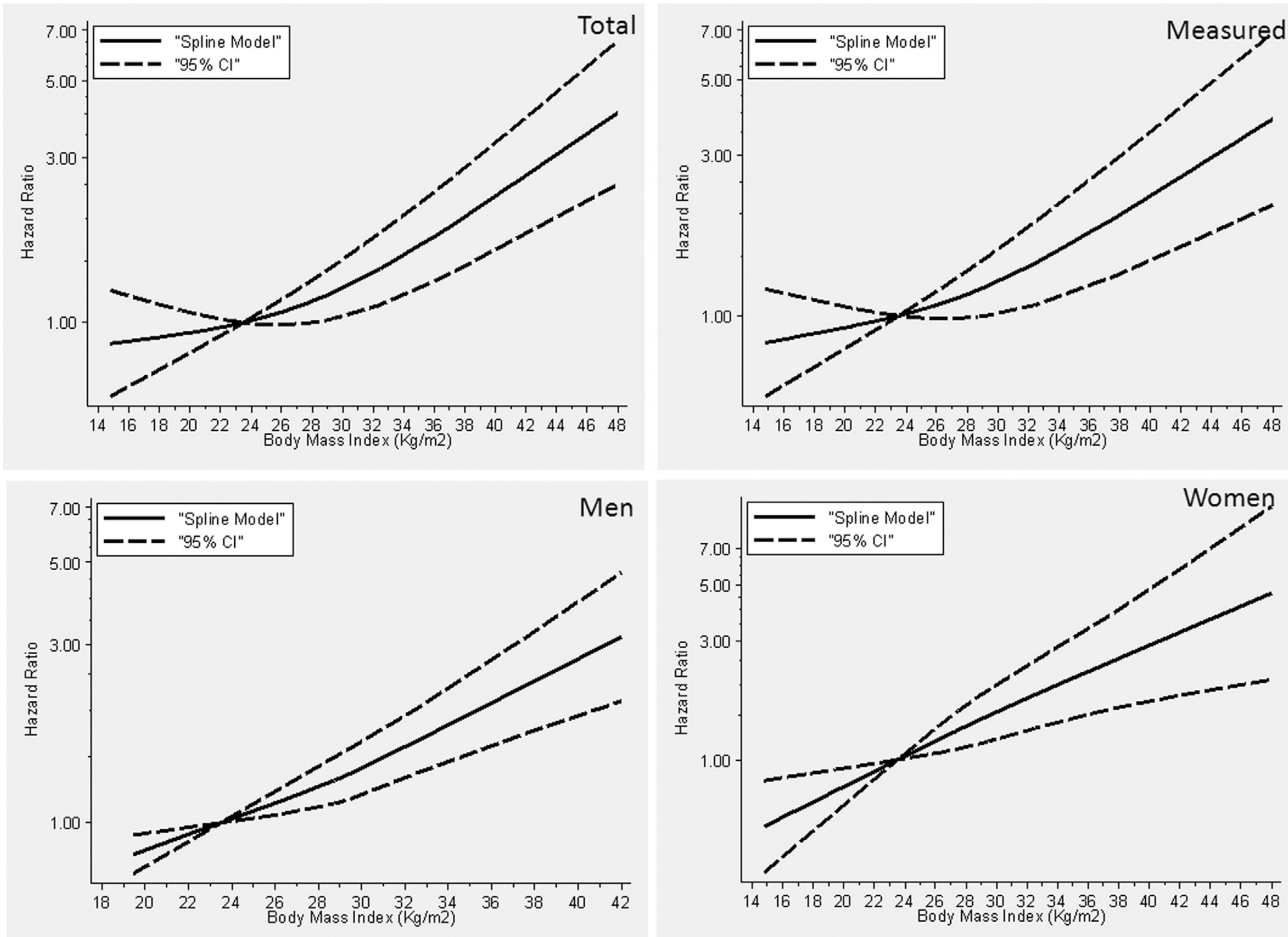

Fig. 3. The restricted cubic spline model presents a nonlinear relationship between BMI and disability for ≥65-year-old adults. The subgroup meta-analyses on men–women or measured BMI did not show significant differences.

4. Discussion

Overweightness and obesity contributes to high incidences of mortality, disability, and risks of chronic diseases such as diabetes and some cancers among young and middle-aged adults. However, the same assumptions have been challenged among ≥65-year-old adults. This meta-analysis clarified for the first time the relationship between body weight and risks of mortality and disability among ≥65-year-old individuals. The restricted cubic spline model established the U-shaped association between BMI and all-cause mortality and the nonlinear association between BMI and disability.

The meta-analysis did not find any significant association between overweightness-related BMI and increased all-cause mortality risk. The 27.0–28.0 BMI was least affected by mortality risk at 5%, whereas the >35.0 BMI was associated with 20% increase in mortality risk. Our findings were consistent with previous studies. For instance, Janssen and Mark conducted a meta-analysis on >65-year-old adults and found that BMIs in the obese range not in the overweight range was associated with increased risks of all-cause mortality [56]. Similarly, the recent meta-analysis by Flegal et al. showed a significant decrease in all-cause mortality for the overweight 65-year age group [57]. In addition to the obesity range, the underweight range and the lower-end recommended BMI range (<23.0) were also prone to all-cause mortality risk. The <20.0 BMI was associated with 14% mortality risk.

Similar to the findings on body weight and mortality, we found that obese and underweight elderlies had elevated risks of disability for the first time. The <23.0 BMI and >28.0 BMI were associated with 12% and 68% increase in disability risks, respectively. This finding is congruent to those results of other researchers. Approximately 59% and 45% of underweight and obese individuals experienced limited activities in daily living, respectively [54].

Previous studies on BMI–mortality and BMI–disability among elderlies focused on risks associated with being underweight, overweight, and obese. However, our interest was on the “healthy weight range” and its suitability to the elderly group. In the present meta-analysis, both all-cause mortality and disability risks decreased starting at 23.0 BMI, which falls within WHO's recommended healthy weight range for adults (18.5–24.9 BMI). In our meta-analysis, the 23.0–28.0 BMI was regarded the healthy weight range of elderlies in terms of all-cause mortality and disability; thus, the WHO healthy weight range may not be suitable for the elderly group.

BMI is a reflection of body fat and lean mass. Previous studies have proven the inverse association between lean mass and mortality risks, in which lean mass acted as a nutritional preserve during prolonged periods of disease among elderlies [58]. The preservation of high lean mass may become increasingly important in old age in order for elderlies to counteract illnesses and diseases.

However, lean mass decreases during old age, even in the presence of stable BMI [59]. Thus, among elderlies, a higher lean mass for the overweight BMI range and a lower lean mass for the lower-end recommended BMI range or underweight BMI range may offer some protection or risk against mortality and disability, respectively.

Nonetheless, the meta-analysis has a number of limitations. The studies focused solely on the relationship between BMI and mortality and disability risks. By contrast, a number of literature has linked BMI with various health problems, including diabetes, coronary heart disease, and arthritis, among the elderly [60,61]. The results of this meta-analysis are further limited by selective survival, inappropriate adjustment factors, and smoking status; these parameters can alter the relationship between BMI and risks of mortality and disability. Moreover, the calculated BMIs from the self-reported height and weight were lower than those from the measured counterpart studies owing to the tendency of respondents to overestimate their height and underestimate their weight [62]. However, none of our subgroup analyses altered the overall results.

Understanding the association between BMI and risks of mortality and disability is very important because various interpretations can lead to conflicting recommendations of ideal BMIs among the elderly. The results of this meta-analysis suggest that the lower-end recommended BMI range, underweight, and obesity among the elderly is associated with significantly increased risks of mortality and disability. However, further big cohort studies are needed to compare BMI–mortality and BMI–disability relationships among the elderly, and to prove whether the 23.0–28.0 BMI range is the healthy weight range for the elderly group.

Conflict of interest

None of authors declared a conflict of interest.

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Defu Ma designed this manuscript. Mingjun Jiang, Yongqiu Zou, and Yuanfa Cai selected articles for inclusion, extracted data, and assessed risk of bias. Qinghua Xin and Ying Wang planned the statistical analyses with advice from Xueying Qin. Mingjun Jiang wrote the first draft of the paper and all authors revised it critically for important intellectual content. All authors have read and approved the final manuscript.

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