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Inverse Relationship Between Body Mass Index and Mortality in Older Nursing-Home Residents: A Meta-analysis of 19,538 Elderly Subjects

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To: David York, M.D.
Editor of Bone
RE: Manuscript reference OBR-2217

Dear Dr. York:

We thank you and the reviewers for evaluating our manuscript, entitled "**Inverse Relationship Between Body Mass Index and Mortality in Older Nursing-Home Residents: A Meta-analysis of 19,538 Elderly Subjects**" and appreciate the opportunity to submit a revised version.

We have made a point-by-point response to the Editor's comments and revised the manuscript accordingly.

We would like to acknowledge the helpful assessment of our manuscript provided by the Editor. Their insight has resulted in an improvement in the clarity and accuracy of our manuscript. We hope we have adequately addressed the concerns raised by the Editor in our response and in the changes made in the revised manuscript. Thank you for reconsidering our manuscript for publication in *Obesity Reviews*.

Sincerely,

Nicola Veronese, MD and Christoph U. Correll, MD

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Inverse Relationship Between Body Mass Index and Mortality in Older Nursing-Home Residents: A Meta-analysis of 19,538 Elderly Subjects

Running title: BMI and mortality in nursing home

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Key Words: Mortality; Elderly; Nursing-Home; Body Mass Index.

Conflict of interest: none.

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ABSTRACT

Body mass index (BMI) and mortality in old adults from general population have been related in a U-shaped or J-shaped curve. However, limited information is available for elderly nursing-home populations, particularly about specific cause death. A systematic PubMed/EMBASE/CINAHL/SCOPUS search until 05/31/2014 without language restrictions was made. As no published study reported mortality in standard BMI groups (<18.5, 18.5-24.9, 25-29.9, ≥30), the most adjusted hazard ratios (HRs) according to a pre-defined list of covariates were obtained from authors and pooled by random-effect model across each BMI category. Out of 342 hits, 20 studies including 19,538 older residents with 5,223 deaths and during a median of 2 years of follow-up were meta-analyzed. Compared to normal weight, all-cause mortality HRs were 1.41 (95%CI=1.26-1.58) for underweight, 0.85 (95%CI=0.73-0.99) for overweight and 0.74 (95%CI=0.57-0.96) for obesity. Underweight was a risk factor for higher mortality due to infections [HR=1.65 (95%CI=1.13-2.40)]. RR results corroborated primary HR results, with additionally lower infection-related mortality in overweight and obese than normal weight individuals.Like in the general population, underweight is a risk factor for mortality in old nursing-home residents. However, uniquely, not only overweight but also obesity is protective, which has relevant nutritional goal implications in this population/setting.

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INTRODUCTION

Body mass index (BMI) is the most common method to assess nutritional status in population studies.

In the adult general population, BMI was found to be associated with mortality in a U-shaped curve relationship in some studies [1,2] while others have suggested a J-shaped relationship.[3,4] In both cases, the evidence is that risk of death is increased in those having low or high BMI.

Older people are a continuously increasing population in developed/developing countries. Aging is substantially characterized by changes in body composition and muscle loss due to relevant changes of food intake and physical activity, multiple chronic diseases, hormonal changes and proneness to acute diseases and body weight loss. [5,6] Several studies in community-dwelling old adults demonstrated that overweight and mild obesity decrease mortality compared to normal or underweight status.[7-12] These contrasting findings compared to middle-aged populations were further confirmed by studies conducted in acute and sub-acute healthcare settings and in patients suffering from high-mortality risk diseases.[13-19]

The protective effect of overweight - but not of obesity – in adults aged ≥65 years has also recently been reported in a large meta-analysis of 97 studies.[20] However, no prior review or meta-analysis focused on nursing-home residents, and the relationship between BMI and mortality in this population is less clear. As the number of older people and those suffering from end-stage dementia and other non-communicable diseases, nutritional problems, sarcopenia, and low functioning continues to rise, the population of institutionalized old people will very likely too.[21,22] Furthermore, the high prevalence of chronic illness in nursing-home residents complicates the applicability of mortality risk associated with BMI from general population.

We conducted a meta-analysis of longitudinal studies in nursing-home residents to assess the role of overweight and obesity for all-cause and specific-cause mortality in this particular setting and population. Based on prior data in community dwelling populations and the higher prevalence of chronic disorders in nursing-home residents that are associated with weight loss and wasting, which in turn can lead to frailty and decreased immunity, we hypothesized that overweight and obesity may be protective of all-cause mortality in this old, high-risk mortality population.

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METHODS

This systematic review was conducted following the MOOSE guidelines,[23] and data reporting was performed in agreement with PRISMA statement.[24]

Data sources and literature search strategy

We created search strategies for the concepts of "nursing-home", "mortality", and "body weight", including "underweight", "body mass index", and "overweight", using a combination of standardized terms and keywords harvested from indices, thesauri, and on-topic articles. To exclude randomized controlled trials and clinical studies, we created a filter, using only standardized terminology tagged as "publication type" to not over-reduce the search recall. We searched Medline via PubMed, Embase, Scopus, CINAHL, Applied Social Sciences Index and Abstracts, and Social Work Abstracts from database inception until 05/31/2014 (see **Table S1** for search terms). We further conducted a manual search of reference lists of relevant articles. Conference abstracts were also considered. All articles were reviewed for inclusion by two independent reviewers (NV and MS). Any discrepancies were resolved by consensus.

Study selection

Inclusion criteria were: 1) prospective, observational cohort study; 2) study population's mean age ≥65 years, 3) nursing-home residents; and 4) assessment of BMI and all-cause and/or specific-cause mortality. Exclusion criteria were: 1) non-nursing home setting, including geriatric hospital units; 2) nursing-home residents admitted for a specific medical condition (e.g., after hip fracture) or being restricted to one disorder (e.g., dementia); and 3) intervention studies.

Data extraction

To be included in the quantitative analyses, we required data on either risk values (hazard ratios [HRs], primary analyses) or risk ratios (RRs, secondary analyses) together with precision estimates (95% confidence interval [CI]) comparing underweight (BMI=<18.5 kg/m^2), overweight (BMI=25-29.9 kg/m^2), or obesity (BMI=≥30 kg/m^2) against normal-weight (BMI=18.5-24.9 kg/m^2 [reference group])[25] regarding all-cause or specific-cause mortality. For each article, in addition to estimates, two investigators (NV and CC) extracted

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data about authors, publication year, study location, participants characteristics and their distribution among BMI categories, follow-up duration, number of deaths and covariates used in statistical analyses. When information on mortality and/or standard BMI groups, study authors were contacted to obtain unpublished data. These unpublished data were validated by the first or last authors of the studies from which these data were obtained. All these authors are coauthors of the present meta-analyses. When raw data were shared with us, these were independently analyzed by two authors of this meta-analysis (N.V. and E.C.). In addition to number of deaths per standard BMI category, we requested HR estimates adjusted for the maximum number of the following covariates: age (as continuous), gender, dementia, stroke, cancer, infectious diseases, diabetes, hypertension, established cardiovascular diseases, chronic obstructive pulmonary disease, disability (either categorical [i.e. disabled vs. non-disabled] or continuous [i.e. ADL score[26] or Barthel Index[27]]), and changes in BMI at last observation carried forward. Risks could be included in the analysis when ≥15 nursing-home residents were present in each compared BMI group.

Outcomes

The primary outcome was all-cause mortality. Secondary outcomes included mortality due to cardiovascular, cerebrovascular or infectious disease, and other causes, again taking normal-weight subjects as reference.

Assessment of study quality

The Newcastle-Ottawa Scale (NOS)[28] was used to evaluate study quality. The NOS assigns a maximum of 9 points to studies of highest quality according to three quality parameters: selection, comparability, and outcome. Any discrepancies were addressed by a joint re-evaluation of the article (NV, EC and CC).

Data synthesis and statistical analysis

Analyses were performed by two independent investigators (NV, EC) using Comprehensive Meta-Analysis (CMA) 3 (http://www.meta-analysis.com). In primary analyses, pooled HRs and 95%CIs of all-cause and specific-cause mortality for standard BMI categories were calculated using DerSimonian-Laird random-effects models,[29] considered adequate, given study number and characteristics.[30] In secondary analyses, pooled, unadjusted RRs ±95%CIs were also calculated for providing additional information on proportions

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of deaths for every BMI category. Heterogeneity across studies was assessed by the Cochrane I^2 metric and chi square statistics. Given significant heterogeneity ($p<0.05$),[31] we conducted stratified analyses[30] exploring effects of the following pre-specified moderators: study origin (European vs. North-American vs. Australasian), study quality (median split of the NOS score [NOS=7]), median number of adjustments used in HR analysis (<8 vs. ≥8), follow-up duration (< 4 vs. ≥4 years), accurate BMI ascertainment (studies reporting weight and height measurement even in bedridden patients vs. those not reporting it), and most frequent sources of bias according to NOS. Additionally, we conducted meta-regression analyses (unrestricted maximum likelihood method) using the NOS score, number of covariates entered into the Cox regression HR analyses and duration of follow-up as continuous variables. Finally, we assessed the presence of publication bias by visual inspection of Funnel plots.

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RESULTS

Search

Altogether, 342 non-duplicated articles were identified. After excluding 290 articles based on title/abstract review, 52 articles were retrieved for full text review (**Figure S1**). Of these, 36 studies met inclusion criteria, but none reported mortality in relationship to standard BMI categories.[25] Instead, studies provided risk of mortality by study-specific BMI quantiles (quartiles, tertiles, etc) or continuous BMI. Therefore, we contacted authors ≥4 times asking them for information about the number of participants and deaths (overall and cause-specific) within each BMI category to calculate RRs and for the adjusted HRs including the maximum number of covariates. Among the potentially eligible studies, 16 authors (Asia, n=6; North America, n=6; Europe, n=4) could not be reached or were unable to provide the required information (**Table S2**), leaving 20 studies for this meta-analysis.[32-51]

Study and Population Characteristics

The 20 meta-analyzed studies[32-51] followed 19,538 participants (median=349 [interquartile range, IQR=193-1135]) in Europe (n=8), Asia (n=9), USA/Canada (n=2), and Australia (n=1). Participants were 84.2 (IQR=80.7-84.8) years old, 71.5% were females, with a median BMI=23.6 (IQR=21.7-25.1) kg/m^2, and a median follow-up duration of 2, IQR=1, 4.75 years. Altogether, 16% were underweight, 50% were normal weight, 24% were overweight, and 10% were obese (**Table 1**). Conversely, the 16 studies excluded from this analysis (data no longer available; **Table S2**) had a median age of 84.0 (IQR=82.5-86) years, 68.7% were females, with a median BMI=22.2 (IQR=21.3-23.2) kg/m^2, and a median follow-up duration of 0.5 (range: 0.5-2) years. Six studies included less than 349 residents, the median value of the studies included in our meta-analysis, while one followed prospectively more than one thousand residents.

The median NOS score was 7 (IQR=5-8). The most common sources of bias in prospective studies were the ascertainment of exposure and the length of follow-up. Particularly, although BMI was measured by trained personnel in all studies, appropriate assessment of BMI in all participants (including those bed-ridden) was reported only in 6 studies (30%) while duration of follow-up appeared adequate (≥5 years) in only 7 (35%) studies (**Table S3**).

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TABLE 1

All-Cause Mortality

Altogether, 5,223 deaths occurred. The raw numbers of deaths per BMI group were: underweight=1,500/4,194 (35.7%); normal weight=2,646/10,281 (25.7%); overweight=825/3,677 (22.4%); obese=252/1,386 (18.2%). Compared to normal weight status, underweight was associated with a significant higher risk for all-cause mortality (HR=1.41 [95%CI, 1.26-1.58], p<0.001), while a reduction in risk was observed for overweight (HR=0.85 [95%CI, 0.73-0.99], p=0.04) and obesity (HR=0.74 [95%CI, 0.57-0.96], p=0.02) (**Table 2; Table 3**). Funnel plot inspection indicated that publication bias was unlikely.

TABLE 2-3

Unadjusted RR analyses were consistent with HR results adjusted for potential confounders. However, all-cause mortality was reduced also with overweight (RR=0.80 [95%CI=0.72-0.88], p<0.001) (**Figure 1A**, **Figure S2A**).

FIGURE 1

Since HR results were significantly heterogeneous for all BMI categories, we investigated the role of potential moderators (**Table 4**). Study origin appeared to be a source of heterogeneity only for underweight estimates (p=0.001). Risk associated with all BMI categories remained significant only in studies performed in European countries. A consistent reduction in mortality risk heterogeneity was also observed. Among investigations conducted in Asia and Australia, significantly higher mortality risks for underweight and lower mortality risks for overweight were also confirmed, without heterogeneity. Heterogeneity was not associated with study quality. However, while underweight was associated with increased risk regardless of NOS score, a significant reduction in all-cause mortality associated with overweight and obesity was present only in high-quality (NOS≥7) studies. High study quality was also responsible for a consistent reduction in heterogeneity of all-cause mortality risk among underweight participants. The number of adjustments did not

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explain mortality risk heterogeneity. Besides, while a lower number of adjustment in the HR analyses confirmed risk estimates for all BMI categories and was associated with no/low heterogeneity, full adjustment appeared to result in no change in risk for overweight and obese participants. We evaluated also the role of follow-up duration and the ascertainment of BMI as they were the most frequent source of bias and determinants of study quality. Interestingly, the pooling of studies with follow-up ≥4 years[32,33,37,41,42,50,51] and accurate BMI ascertainment even of bedridden people[35-38,48,49] resulted in no heterogeneity in risk estimates for any of the BMI categories. Underweight still had a negative prognostic role in any strata investigated. Overweight status remained significantly associated with lower mortality in studies with longer duration and not reporting BMI ascertainment in bedridden residents, while obesity had a confirmed protective effect only in studies with duration ≥4 years and those including an accurate ascertainment of BMI even in bedridden people. Finally, meta-regression analyses using continuous variables as moderators substantially confirmed that study quality and duration and adjustment of analyses were not relevant sources of heterogeneity. Only study quality appeared to influence HR risk estimates in obese residents (p=0.04).

TABLE 4

Specific-Cause Mortality

The specific-cause mortality analysis included 9 studies[32,35-37,39,41,42,44,47] and 5,781 participants with 3,150 deaths (54.4%), which were due to cardio-vascular diseases in 705 residents (22.4%), cerebro-vascular conditions in 414 (13.0%), infections in 923 (29.0%), and other causes in 1,108 participants (35.6%).

Underweight was associated with a significant increased risk of mortality due to infections (+65%; p=0.010), and cardio-vascular (+34%; p=0.002) as well as cerebro-vascular diseases (+64%; p=0.003), while other causes of mortality were only marginally significantly increased (+29; p=0.060). Conversely, overweight and obesity did not affect any of the specific-cause mortality events using HR analyses (**Table 1**).

In RR analyses (**Figures 1 B-E**; **Figure S2 B-E**), underweight was only associated with higher specific-cause mortality due to infectious diseases (RR=1.47, 95%CI=1.12-1.92, p=0.006). Like in HR analyses, overweight and obesity did not differ from normal weight regarding cardiovascular, cerebrovascular and

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other-cause mortality. However, compared to normal weight status, mortality from infectious diseases was significantly reduced with overweight, and obesity.

The results of the HR analyses were not significantly heterogeneous, except when considering the comparison between underweight and normal weight for death from infections (I^2=61.6%). Only the number of adjustment used in the analyses appeared to be a source of heterogeneity (p=0.02). The increased risk of mortality due to infections associated with underweight status was confirmed in every strata (<8, HR=2.75 [95%CI, 1.54-4.90], p=0.001; ≥8, HR=1.24 [95%CI, 1.01-1.51], p=0.04). No meta-regression procedure was conducted for all other comparisons and causes of death. Funnel plots inspection indicated that publication bias was unlikely.

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DISCUSSION

To our knowledge, this is the first meta-analysis investigating the relationship between standard BMI categories and all-cause and specific-cause mortality in old nursing-home residents. As hypothesized, overweight status was protective for all-cause mortality compared to underweight and normal weight status. However, obesity was also associated with lower all-cause mortality. A series of meta-regression analyses was also conducted, but all-cause mortality risk was unlikely related to country of study conduct, study quality and adequate adjustment of estimates. Finally, underweight was a risk factor for death from infections and both cardio-vascular and cerebro-vascular diseases. Notably, in RR analyses of incidence rates, overweight and obese status were also associated with reduced mortality from infections compared to normal weight.

Underweight has consistently been associated with greater all-cause mortality, regardless of age but more likely in the old adults.[8,52-56] In fact, underweight is often related to cancer and consequently to higher mortality in younger populations as well as to frailty in the elderly. In contrast to present epidemiologic data, obesity has previously also been associated with higher future mortality compared to normal weight individuals[3,57-60] even independently of metabolic abnormalities.[61] Nevertheless, these studies mainly included middle aged participants, limiting the application of these results to older people and the growing nursing-home population. Consistent with prior meta-analyses in adult[20] and old[17] general population, overweight old nursing-home residents had a reduced all-cause mortality risk in our analyses. However, obesity was not protective of all-cause mortality as found in our main analyses and most sensitivity/moderator analyses.

Several reasons could explain our results. First, the median age of populations included in our meta-analysis was >80 years. In the meta-analysis of community dwelling adults[20] estimates were provided for people aged ≥65 years, but when looking at the few studies conducted in very old subjects, a protective effect of mild obesity was suggested.[4,12] Likely, with advancing age BMI decreases due to modifications of food intake and physical activity, multiple chronic and acute diseases, hormonal changes, and weight loss.[5,6] Second, although BMI is a useful marker of weight accumulation and adiposity, previous population data analyses

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have shown that the relationship between BMI and fat mass – particularly in the obesity range - is not linear, while the relationship between BMI and fat-free mass is linear.[62] Accordingly, higher BMI values are generally associated with higher fat-free mass, which is independently related to lower mortality.[63] Nonetheless, in catabolic conditions, higher fat mass could confer survival advantages.[41,64] However, there is also a physiological difference between older and younger people. In younger people, a large increase in fat mass could result in greater insulin resistance than in older subjects with an increased risk of unfavorable outcomes, like diabetes and cardiovascular diseases, which are characterized by high mortality.[65] Third, normal weight people at the time of death could represent a high-risk group for mortality because they may have been overweight or obese and lost unintentionally substantial weight due to decreased appetite and food intake and/or chronic (undetected) medical or mental illness, reducing resilience and immunity.[66,67] Fourth, old overweight and obese individuals could be survivors of detrimental effects of higher BMI at younger age, representing a selected subgroup of more resilient individuals. This issue, which may be a relevant factor for the analyzed population that is characterized by a mean age over 80 years, should be investigated in future studies. At least for HR calculations, it was not possible to obtain estimates for different degrees of obesity due to the limited number of cases. Fifth, the median follow-up period of 2 years (range=0.5-9 years) could have been too short to show detrimental effects of obesity. However, obesity had a confirmed protective effect in studies with longer follow-up duration. Nevertheless, some authors primarily focusing on subjects aged 18-60 years, proposed that it takes about 15 years or more for obesity to exert its full impact on mortality.[68,69] Finally, the lack of a significant association between increasing BMI and mortality found among studies with adequate adjustment could suggest that part of the protective effect of overweight and obesity may be mediated by interactions with comorbidities, although over-adjustment could also be taken into account.

Regarding underweight, the present meta-analysis confirms findings from almost all previous prospective investigations, regardless of study setting. The highest all-cause mortality rates were observed in underweight subjects, extending to each specific cause. Infections and cardiovascular disease are the leading causes of death in nursing-home residents.[70,71] Both of these mortality causes were significantly elevated in underweight individuals, while at least in RR analyses, overweight and obesity were protective regarding death from infectious diseases compared to normal weight status. Malnutrition is responsible for the

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impairment of immune functions.[72] Although urinary tract, skin and soft tissue infections are common, also due to the high prevalence of pressure ulcers and use of indwelling urinary catheters, pneumonia – frequently originating from aspiration in a highly neurologic and dysphagic population – is the most frequent cause and has the highest mortality.[70,71] This outcome is likely related also to the paucity of clinical signs characterizing pneumonia in nursing-homes.[70,72] Finally, although the association between vascular mortality and low body weight is intriguing - as it likely occurs in the absence of metabolic abnormalities – it may be explained by inflammatory and hormonal changes (e.g., glucocorticoids and catecholamines) and the dysregulation of the autonomic nervous system occurring with malnutrition and aging.[73-76]

This study has limitations. First, the most important shortcoming is that we excluded 16 potentially eligible studies since data were no longer available (see **Table S2**). In particular, we excluded six studies from North America where overweight and obesity are more common than in other continents, introducing a possible bias. However, the overall median BMI of the excluded studies was similar to or lower than ours, and the short follow-up duration compared to ours indicates that the excluded studies would have contributed less to clarifying the desired longer-term outcomes. Moreover, some of these studies seems to corroborate our and previous findings. Two studies,[77,78] reported that low BMI was associated to increased mortality compared to higher BMI, while another reported that higher BMI values resulted in decreased mortality.[79] Furthermore, Grabowski et al. reported that underweight and mild obesity were associated with increased and decreased all-cause, respectively, when compared to normal BMI.[80] Although a selection bias cannot be excluded, we also found that relevant characteristics features of participants from the excluded studies (age, BMI, gender) were similar to those included in our meta-analysis. However, the majority of studies without meta-analyzable data that had to be excluded (10/16) followed more than 349 participants, which is the median value of the studies included in our work. On the other hand, this potential advantage of the excluded studies is clearly off-set by the shorter follow-up. Nevertheless, even if the excluded studies may create a bias, it would be hard to argue that this bias would be systematic in one or another direction. Second, we could not control for some factors that are associated with mortality risk, including smoking, number/type of medical and psychiatric morbidities, socioeconomic status, duration of institutionalization, habitual BMI, unintentional weight loss, race, and frailty. Moreover, the indications for institutionalization might differ

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considerably across countries, although a large study from 8 European countries suggest that the most important predictors (i.e., neuropsychiatric symptoms, care dependency and poor cognitive status) were similarly prevalent and important across the different countries.[81] Another point is the possibly different life expectancy across countries included in our meta-analysis. However, as reported by the WHO,[82] the countries included in our study had an expected life expectancy ranging from 76 to 84 years suggesting that the risk of bias due to this factor is likely not very large. Furthermore, adjustment of mortality risks by relevant covariates was heterogeneous. Third, we considered only BMI and no other body composition parameters, including fat-free BMI indicators. However, BMI is an accepted proxy for other, more sophisticated or regionally specific indices of adiposity, performing generally equally well in predicting mortality in old adults.[11] Fourth, we could not assess different grades of obesity in HR analyses. However, consistent with our RR findings, the only study investigating high grade obesity in nursing-home residents detected an association between BMI≥40 and increased mortality,[80] indicating that high grade obesity is likely not protective and needs to be addressed adequately. Fifth, many studies were of relatively short duration and the median follow-up was only 2 years. However, we confirmed the findings in the studies with ≥4 years of follow-up and study duration was not a significant moderator of the results. Sixth, we included four studies with a NOS score <5, which is indicative of high risk of bias. However, although study quality appeared to be a relevant source of bias, sub-analyses of high-quality studies confirmed the estimates obtained from all studies with a partial reduction of heterogeneity. Finally, 11 out of 20 studies had less than 400 participants, and most were not powered to specifically address mortality, particularly due to specific causes. Despite these limitations, this is the first meta-analysis examining all-cause and specific-cause mortality in old nursing-home residents across standard BMI categories. Our results stress the importance of weighing nursing-home residents regularly, guarding against unintentional weight loss and focusing not only on underweight and its treatment by nutritional support, but also on normal weight individuals who may need to be reclassified as a moderate-risk group for mortality when cared for in nursing-home settings. This view is consistent with previous guidelines suggesting a BMI<21 kg/m^2 as an useful trigger for nutritional support.[35] Finally, obese nursing-home residents, who require more complex care, should likely not ubiquitously be encouraged to lose weight, although this may facilitate their physical handling and mobilization.

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In conclusion, as in the general population, underweight is a risk factor for increased all-cause and specific cause mortality in nursing-home residents. Conversely, both overweight and obesity are likely protective for survival in this population. Thus, pros and cons of intended weight loss in obese old subjects need to be weighed carefully. Future studies should assess the effects of body composition parameters, weight trajectories, immobility, duration of institutionalization, comorbidities, and medications, and should evaluate death from specific infections, in order to provide explanations of the observed findings. Despite the protective effect, one also needs to consider the negative impact of high BMI on co-morbidities, disability, poor physical performance and low quality of life.[66,67] Further research is needed to identify ways to prevent elevated mortality in underweight as well as normal weight individuals, with nutritional support being an obvious target.[35]

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FIGURE LEGEND

Figure 1. Pooled estimates (RRs) and 95%CI for mortality risk associated with underweight, overweight and obesity compared to normal weight status (*Plot A*, all-cause mortality; *Plot B*, mortality due to infectious disease; *Plot C*, mortality due to cardiovascular causes; *Plot D*, mortality due to cerebrovascular causes; *Plot E*, mortality due to other causes).

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Table 1. Characteristics of the studies included

Study/Country	Sample size	Number of deaths	Baseline age	Percentage of females	Baseline BMI	Percent in Specific BMI Category	Years of follow-up	Newcastle-Ottawa Scale	Number of adjustments *
Abe, 2011 Japan [32]	244	173	84.7±7.5	81.1	19.3±3.5	Underweight: 46% Normal Weight: 47% Overweight: 6% Obese: 1%	4	8	9
Allard,2004 Canada [33]	495	147	85.1±7.8	67.2	24.4±5.6	Underweight: 13% Normal Weight: 42% Overweight: 29% Obese: 16%	1.7	4	4
Beck, 2008 Denmark [34]	428	109	85.4±7.0	79.9	23.5±5.0	Underweight: 15% Normal Weight: 49% Overweight: 25% Obese: 11%	1	5	12
Cereda, 2011 Italy [35]	519	409	84.0±8.4	90.2	23.1±4.7	Underweight: 15% Normal Weight: 55% Overweight: 22% Obese: 8%	5.7	9	11
Chan, 2010 Singapore [36]	158	41	77.0±12.0	51.0	18.7±3.6	Underweight: 51% Normal Weight: 41% Overweight: 7% Obese: 1%	2	8	3
Hsu, 2013 Taiwan [37]	336	155	79.1±7.2	46.1	21.7±4.8	Underweight: 21% Normal Weight: 57% Overweight: 18 % Obese: 4%	5	8	6
Kaiser, 2010 Germany [38]	200	47	85.5±7.8	73.5	26.3±5.3	Underweight: 5% Normal Weight: 40% Overweight: 30% Obese: 25%	1	5	4
Kimyagarov, 2010 Israel [39]	82	24	84.8±7.1	57.3	25.2±4.1	Underweight: 1% Normal Weight: 52% Overweight: 35% Obese: 12%	1	3	10

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Study/Country	Sample size	Number of deaths	Baseline age	Percentage of females	Baseline BMI	Percent in Specific BMI Category	Years of follow-up	Newcastle-Ottawa Scale	Number of adjustments *
Kuikka, 2009 Finland [40]	191	25	84.9±4.6	82.7	22.8±4.6	Underweight: 15% Normal Weight: 59% Overweight: 17% Obese: 9%	0.7	5	5
Lee, 2014 China [41]	1614	1261	83.7±8.4	69.5	21.7±4.8	Underweight: 26% Normal Weight: 51% Overweight: 18% Obese: 5%	9	8	11
Lin, 2010 Taiwan [42]	354	219	78.4±7.8	55.9	21.7±4.2	Underweight: 20% Normal Weight: 54% Overweight: 22% Obese: 4%	5	8	6
Lok, 2009 China [43]	525	67	81.0±7.9	60.0	22.4±4.3	Underweight: 21% Normal Weight: 56% Overweight: 18% Obese: 5%	1	4	7
Miller, 2009 Australia [44]	1827	613	80.6±1.3	77.4	23.7±4.6	Underweight: 12% Normal Weight: 53% Overweight: 26% Obese: 9%	2	7	5
Nakazawa, 2013 Japan [45]	8179	1081	84.3±8.1	77.2	20.6±3.8	Underweight: 30% Normal Weight: 58% Overweight: 11% Obese: 1%	1	7	3
Smiley, 2012 USA [46]	1339	193	79.7±12.0	58.9	25.7±6.9	Underweight: 10% Normal Weight: 42% Overweight: 28% Obese: 20%	2	3	9
Sund-Levander, 2007 Sweden [47]	234	132	84.6±6.8	66.7	25.4±4.9	Underweight:16% Normal Weight: 47% Overweight: 27% Obese: 10%	3	6	11

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Study/Country	Sample size	Number of deaths	Baseline age	Percentage of females	Baseline BMI	Percent in Specific BMI Category	Years of follow-up	Newcastle-Ottawa Scale	Number of adjustments *
Torma, 2013 Sweden [48]	172	41	86.3±7.7	61.0	23.7±5.1	Underweight: 6% Normal Weight: 39% Overweight: 35% Obese: 10%	1	7	11
Valentini, 2009 Germany [49]	2116	192	84.3±9.1	79.3	24.9±5.4	Underweight: 9% Normal Weight: 47% Overweight: 28% Obese: 15%	0.5	7	9
Veronese, 2013 Italy [50]	181	115	81.3±8.4	80.1	25.4±4.8	Underweight: 4% Normal Weight: 47% Overweight: 34% Obese: 15%	5	9	7
Volpato, 2004 Italy [51]	344	179	82.1±7.1	79.1	24.1±4.6	Underweight: 10% Normal Weight: 53% Overweight: 26% Obese: 11%	4	7	11
All studies: 20 Europe= 9 studies Asia=7 studies USA/Canada=2 studies Australia=1 study Israel=1 study	***19538 (median=349; IQR=193.3-1135)***	***5223***	***Median=84.2 (IQR=80.7-84.8)***	***71.5***	***Median=23.6 (IQR=21.7-25.1)***	***Underweight: 16% Normal Weight: 50% Overweight: 24% Obese: 10%***	***Median=2 (IQR=1.0-4.8)***	***Median=7 (IQR=5-8)***	***Median=8 (IQR=5-11)***

* number of baseline variables that the hazard ratios were adjusted for in Cox regression analyses

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Table 2. Pooled hazard ratio estimates for all-cause and specific-cause mortality risk associated with underweight, overweight and obese BMI categories compared to normal-weight status

		Mortality causes				
Category of BMI	**Analysis details**	**All-cause**	**Infections**	**Cardio-vascular**	**Cerebro-vascular**	**Others**
<18.5	***Pooled estimate***, HR (95%CI)	**1.41 (1.26-1.58)**	**1.65 (1.13-2.40)**	**1.34 (1.11-1.62)**	**1.64 (1.18-2.28)**	1.29 (0.99-1.67)
	P-value for HR	<0.001	0.010	0.002	0.003	0.06
	Heterogeneity, I^2 (P-value)	40.8 % (0.04)	61.6 % (0.01)	0 % (0.94)	9.8 % (0.35)	35 % (0.15)
	Number of studies	18	8	8	7	8
	Number of events	4106	737	481	288	747
	Number of participants	14338	3958	3791	3647	3791
25-30	***Pooled estimate***, HR (95%CI)	**0.85 (0.73-0.99)**	0.77 (0.58-1.05)	1.07 (0.90-1.27)	0.90 (0.69-1.16)	0.92 (0.76-1.11)
	P-value for HR	0.04	0.10	0.46	0.41	0.38
	Heterogeneity, I^2 (P-value)	61.1 % (<0.001)	23.2% (0.25)	0 % (0.80)	0 % (0.77)	0 % (0.67)
	Number of studies	20	7	8	6	8
	Number of events	3463	547	507	263	689
	Number of participants	13949	3780	3856	3780	3856
≥30	***Pooled estimate***, HR (95%CI)	**0.74 (0.57-0.96)**	0.93 (0.64-1.36)	0.97 (0.66-1.42)	0.79 (0.49-1.26)	0.96 (0.68-1.35)
	P-value for HR	0.02	0.71	0.87	0.32	0.82
	Heterogeneity, I^2 (P-value)	67.1 % (<0.001)	0 % (0.99)	13.6 % (0.33)	0 % (0.93)	1 % (0.41)
	Number of studies	17	4	6	4	6
	Number of events	2784	403	372	178	517
	Number of participants	11338	2496	2921	2713	2921

Bolded HR values: p<0.05

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Table 3. Adjusted hazard ratios of each study by BMI categories compared to normal-weight residents for all-cause and specific cause mortality.

First author, publication year	BMI category	All-cause HR (95%CI)	Infections HR (95%CI)	Cardio-vascular HR (95%CI)	Cerebro-vascular HR (95%CI)	Others HR (95%CI)	Adjustments
Abe, 2011 [32]	Underweight	1.04 (0.69-1.56)	0.83 (0.47-1.46)	1.69 (0.18-16.10)	1.34 (0.32-5.65)	1.47 (0.71-3.05)	Age, gender, dementia, stroke, cancer, infectious diseases, CVD, COPD, changes in BMI at LOCF.
	Overweight	1.83 (0.83-4.06)	1.37 (0.39-4.75)	6.99 (0.35-140.17)	No cases	2.40 (0.71-8.10)	
	Obese	Not computed [a]	Not computed [a]	Not computed [a]	Not computed [a]	Not computed [a]	
Allard, 2004 [33]	Underweight	0.80 (0.50-1.27)	Not available	Not available	Not available	Not available	Age, gender, infectious diseases, disability
	Overweight	0.75 (0.49-1.11)	Not available	Not available	Not available	Not available	
	Obese	0.57 (0.28-1.18)	Not available	Not available	Not available	Not available	
Beck, 2008 [34]	Underweight	1.81 (1.17-2.80)	Not available	Not available	Not available	Not available	Age, gender, dementia, stroke, cancer, infectious diseases, diabetes, hypertension, CVD, COPD, disability, changes in BMI at LOCF
	Overweight	0.62 (0.33-1.16)	Not available	Not available	Not available	Not available	
	Obese	0.72 (0.34-1.54)	Not available	Not available	Not available	Not available	
Cereda, 2011 [35]	Underweight	1.29 (0.97-1.71)	1.09 (0.55-2.17)	1.49 (1.03-2.15)	1.31 (0.68-1.55)	1.03 (0.53-1.97)	Age, gender, dementia, stroke, cancer, infectious diseases, diabetes, hypertension, CVD, COPD, disability
	Overweight	0.97 (0.76-1.24)	0.44 (0.21-0.93)	1.16 (0.85-1.58)	1.02 (0.58-1.79)	0.75 (0.43-1.32)	
	Obese	0.66 (0.44-0.98)	0.93 (0.42-2.08)	0.57 (0.32-1.04)	0.71 (0.28-1.79)	0.56 (0.24-1.31)	
Chan, 2010 [36]	Underweight	2.47 (1.11-5.48)	3.73 (0.82-16.97)	0.45 (0.23-8.87)	Only 1 death due to stroke in the cohort	2.16 (0.76-6.08)	Age, gender, disability
	Overweight	6.13 (0.84-71.42)	No events	0.98 (0.40-2.37)		0.86 (0.34-2.16)	
	Obese	Not computed [a]	Not computed [a]	Not computed [a]		Not computed [a]	
Hsu, 2013 [37]	Underweight	1.37 (0.91-2.07)	5.96 (1.89-18.80)	1.31 (0.63-2.73)	3.32 (1.20-9.19)	0.47 (0.16-1.36)	Age, gender, dementia, stroke, cancer, disability
	Overweight	0.87 (0.53-1.43)	1.07 (0.21-5.60)	1.26 (0.52-3.03)	0.76 (0.16-3.62)	1.07 (0.51-2.25)	
	Obese	0.88 (0.36-2.19)	No events	1.56 (0.35-6.86)	No events	0.42 (0.06-3.19)	
Kaiser, 2010 [38]	Underweight	Not computed [a]	Not available	Not available	Not available	Not available	Age, gender, dementia, disability
	Overweight	0.75 (0.36-1.57)	Not available	Not available	Not available	Not available	

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First author, publication year	BMI category	All-cause HR (95%CI)	Infections HR (95%CI)	Cardio-vascular HR (95%CI)	Cerebro-vascular HR (95%CI)	Others HR (95%CI)	Adjustments
	Obese	0.52 (0.19-1.43)	Not available	Not available	Not available	Not available	
Kimyagarov, 2010 [39]	Underweight	Not computed [a]	Not computed [a]	Not computed [a]	Not computed [a]	Not computed [a]	Age, gender, dementia, stroke, cancer, infectious diseases, CVD, COPD, disability, changes in BMI at LOCF
	Overweight	0.26 (0.04-1.52)	No events	0.33 (0.01-6.98)	2.00 (0.07-88.05)	2.00 (0.07-88.05)	
	Obese	3.83 (0.66-23.64)	No events	3.00 (0.15-84.79)	0.50 (0.01-13.89)	0.50 (0.01-13.89)	
Kuikka, 2009 [40]	Underweight	1.22 (0.47-3.16)	Not available	Not available	Not available	Not available	Age, gender, dementia, stroke, cancer
	Overweight	0.66 (0.21-2.01)	Not available	Not available	Not available	Not available	
	Obese	Not computed [a]	Not available	Not available	Not available	Not available	
Lee, 2014 [41]	Underweight	1.48 (1.30-1.69)	1.32 (1.05-1.66)	1.12 (0.79-1.58)	1.35 (0.92-1.97)	1.54 (1.24-1.66)	Age, gender, dementia, stroke, cancer, infectious diseases, diabetes, hypertension, CVD, COPD, disability
	Overweight	0.73 (0.62-0.85)	0.66 (0.49-0.90)	1.18 (0.83-1.69)	0.89 (0.56-1.40)	0.82 (0.63-1.07)	
	Obese	0.72 (0.54-0.97)	0.96 (0.55-1.67)	1.27 (0.65-2.46)	0.61 (0.19-1.96)	1.18 (0.75-1.84)	
Lin, 2010 [42]	Underweight	1.49 (1.00-2.22)	5.44 (1.88-15.75)	1.42 (0.70-2.88)	3.50 (1.30-9.42)	0.70 (0.30-1.74)	Age, gender, dementia, stroke, cancer, disability.
	Overweight	0.81 (0.50-1.32)	0.88 (0.18-4.39)	1.10 (0.46-2.63)	0.78 (0.16-3.75)	1.01 (0.49-2.11)	
	Obese	0.77 (0.31-1.93)	No events	1.31 (0.30-5.71)	No events	0.42 (0.06-3.11)	
Lok, 2009 [43]	Underweight	2.52 (1.35-4.72)	Not available	Not available	Not available	Not available	Age, gender, dementia, stroke, cancer, diabetes, COPD.
	Overweight	1.35 (0.60-3.03)	Not available	Not available	Not available	Not available	
	Obese	2.14 (0.62-7.15)	Not available	Not available	Not available	Not available	
Miller, 2009 [44]	Underweight	1.52 (1.22-1.89)	1.44 (0.94-2.20)	1.50 (1.05-2.15)	1.31 (0.64-2.68)	1.17 (0.67-2.02)	Age, gender, dementia, stroke, disability
	Overweight	0.70 (0.58-0.86)	1.15 (0.76-1.74)	0.88 (0.61-1.26)	1.01 (0.64-1.61)	1.19 (0.72-1.95)	
	Obese	0.36 (0.24-0.54)	0.95 (0.39-2.34)	1.96 (0.62-6.21)	0.84 (0.38-1.85)	1.46 (0.59-3.67)	
Nakazawa, 2013 [45]	Underweight	1.61 (1.42-1.83)	Not available	Not available	Not available	Not available	Age, gender, disability
	Overweight	0.76 (0.56-1.04)	Not available	Not available	Not available	Not available	
	Obese	1.07 (0.51-2.27)	Not available	Not available	Not available	Not available	
Smiley, 2012 [46]	Underweight	0.91 (0.65-1.26)	Not available	Not available	Not available	Not available	Age, gender, dementia, stroke,
	Overweight	1.44 (1.16-1.79)	Not available	Not available	Not available	Not available	

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First author, publication year	BMI category	All-cause HR (95%CI)	Infections HR (95%CI)	Cardio-vascular HR (95%CI)	Cerebro-vascular HR (95%CI)	Others HR (95%CI)	Adjustments
	Obese	1.35 (1.02-1.79)	Not available	Not available	Not available	Not available	cancer, diabetes, hypertension, COPD.
Sund-Levander, 2007 [47]	Underweight	1.78 (0.92-3.43)	1.81 (0.52-6.34)	1.29 (0.45-3.76)	1.80 (0.51-6.40)	2.33 (0.76-7.11)	Age, gender, dementia, stroke, cancer, infectious diseases, diabetes, hypertension, CVD, COPD, disability
	Overweight	0.88 (0.59-1.31)	0.63 (0.25-1.55)	0.89 (0.50-1.57)	0.47 (0.19-1.14)	1.01 (0.46-2.20)	
	Obese	0.83 (0.49-1.41)	0.80 (0.28-2.30)	0.87 (0.41-1.83)	0.97 (0.37-2.53)	0.61 (0.19-1.96)	
Torma, 2013 [48]	Underweight	0.80 (0.23-2.83)	Not available	Not available	Not available	Not available	Age, gender, dementia, stroke, cancer, infectious diseases, diabetes, hypertension, CVD, COPD, disability
	Overweight	1.12 (0.36-3.49)	Not available	Not available	Not available	Not available	
	Obese	0.56 (0.14-2.20)	Not available	Not available	Not available	Not available	
Valentini, 2009 [49]	Underweight	1.64 (1.09-2.45)	Not available	Not available	Not available	Not available	Age, gender, dementia, stroke, cancer, diabetes, hypertension, CVD, COPD
	Overweight	0.54 (0.37-0.79)	Not available	Not available	Not available	Not available	
	Obese	0.31 (0.17-0.57)	Not available	Not available	Not available	Not available	
Veronese, 2013 [50]	Underweight	1.97 (0.89-4.38)	Not available	Not available	Not available	Not available	Age, gender, dementia, cancer, diabetes, hypertension, disability
	Overweight	0.93 (0.61-1.42)	Not available	Not available	Not available	Not available	
	Obese	0.58 (0.30-1.10)	Not available	Not available	Not available	Not available	
Volpato. 2004 [51]	Underweight	1.21 (0.76-1.92)	Not available	Not available	Not available	Not available	Age, gender, dementia, stroke, cancer, infectious diseases, diabetes, hypertension, CVD, COPD, disability
	Overweight	0.83 (0.56-1.22)	Not available	Not available	Not available	Not available	
	Obese	1.09 (0.63-1.89)	Not available	Not available	Not available	Not available	

Abbreviations: **BMI**, body mass index; **CVD**, cardiovascular diseases; **COPD**, chronic obstructive pulmonary disease; **LOCF**, last observation carrying forward; **HR (95%CI)**, hazard ratio and 95% confidence interval

[a] Could not be computed due to limited number of residents (<15) in the BMI category.

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Table 4. All-cause mortality risk for strata of different moderators

			BMI Category		
Moderator	**Strata**	**Analysis details**	**Underweight** (BMI<18.5)	**Overweight** (BMI, 25-29.9)	**Obesity** (BMI≥30)
Ethnicity	**Europe**	***Pooled estimate***, HR (95%CI)	**1.45 (1.22-1.72)**	**0.83 (0.72-0.96)**	**0.65 (0.49-0.86)**
		P-value for HR	<0.001	0.010	0.002
		Heterogeneity, I^2 (P-value)	0 % (0.72)	0 % (0.43)	33.1 % (0.16)
		Number of studies	8	9	8
	Asia + Australia	***Pooled estimate***, HR (95%CI)	**1.53 (1.39-1.68)**	**0.80 (0.67-0.95)**	0.82 (0.52-1.30)
		P-value for HR	<0.001	0.011	0.40
		Heterogeneity, I^2 (P-value)	17.2 % (0.29)	36.7 % (0.16)	66.9 % (0.006)
		Number of studies	8	9	7
	North America	***Pooled estimate***, HR (95%CI)	0.87 (0.66-1.14)	1.07 (0.57-2.02)	0.94 (0.41-2.16)
		P-value for HR	0.30	0.84	0.88
		Heterogeneity, I^2 (P-value)	0 % (0.66)	86.8 % (0.006)	78.6 % (0.03)
		Number of studies	2	2	2
		P-value [a]	0.001	0.68	0.54
Study quality[b]	**NOS score <7**	***Pooled estimate***, HR (95%CI)	1.35 (0.92-1.98)	0.89 (0.65-1.23)	0.96 (0.65-1.42)
		P-value for HR	0.13	0.47	0.83
		Heterogeneity, I^2 (P-value)	68.3 % (0.007)	61.7 % (0.01)	52.1 % (0.05)
		Number of studies	6	8	7
	NOS score ≥7	***Pooled estimate***, HR (95%CI)	**1.50 (1.39-1.61)**	**0.80 (0.70-0.91)**	**0.63 (0.48-0.83)**
		P-value for HR	<0.001	0.001	0.001
		Heterogeneity, I^2 (P-value)	0 % (0.57)	37.0 % (0.10)	54.9 % (0.02)
		Number of studies	12	12	10
		P-value [a]	0.59	0.55	0.09

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			BMI Category		
Moderator	**Strata**	**Analysis details**	**Underweight** (BMI<18.5)	**Overweight** (BMI, 25-29.9)	**Obesity** (BMI≥30)
Number of adjustments[b]	**<8**	***Pooled estimate***, HR (95%CI)	**1.51 (1.29-1.78)**	**0.78 (0.68-0.88)**	**0.66 (0.45-0.96)**
		P-value for HR	<0.001	<0.001	0.03
		Heterogeneity, I^2 (P-value)	37.3 % (0.12)	0 % (0.53)	47.2 % (0.07)
		Number of studies	9	10	8
	≥8	***Pooled estimate***, HR (95%CI)	**1.33 (1.13-1.55)**	0.88 (0.68-1.13)	0.80 (0.57-1.11)
		P-value for HR	<0.001	0.31	0.17
		Heterogeneity, I^2 (P-value)	38.7% (0.11)	76.8% (<0.001)	71.5% (<0.001)
		Number of studies	9	10	9
		P-value [a]	0.25	0.39	0.46
Follow-up duration	**<4**	***Pooled estimate***, HR (95%CI)	**1.45 (1.24-1.70)**	0.83 (0.67-1.02)	0.73 (0.51-1.04)
		P-value for HR	<0.001	0.08	0.08
		Heterogeneity, I^2 (P-value)	57.4 % (0.009)	70.1 % (<0.001)	78.0 % (<0.001)
		Number of studies	11	13	11
	≥4	***Pooled estimate***, HR (95%CI)	**1.41 (1.27-1.56)**	**0.82 (0.74-0.92)**	**0.74 (0.61-0.90)**
		P-value for HR	<0.001	0.001	0.003
		Heterogeneity, I^2 (P-value)	0.0% (0.64)	28.1% (0.21)	0.0% (0.72)
		Number of studies	7	7	6
		P-value [a]	0.58	0.65	0.90
Accurate ascertainment of BMI in bedridden residents	**Not reported**	***Pooled estimate***, HR (95%CI)	**1.41 (1.24-1.60)**	**0.83 (0.69-0.99)**	0.78 (0.57-1.06)
		P-value for HR	<0.001	0.03	0.12
		Heterogeneity, I^2 (P-value)	51.6 % (0.16)	70.3 % (<0.001)	76.2 % (<0.001)
		Number of studies	13	14	12
	Reported	***Pooled estimate***, HR (95%CI)	**1.40 (1.13-1.73)**	0.95 (0.79-1.14)	**0.64 (0.48-0.87)**
		P-value for HR	0.002	0.58	0.004
		Heterogeneity, I^2 (P-value)	0.0% (0.44)	0.0% (0.65)	0.0% (0.95)
		Number of studies	5	6	5
		P-value [a]	0.89	0.44	0.50

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Bolded HR values: p<0.05

Abbreviations: NOS, Newcastle-Ottawa Scale

[a] The P-value for the t-test between the two statistical analysis strata according to meta-regression procedure.

[b] Stratification was performed by median NOS score and number of adjustments as appropriate.

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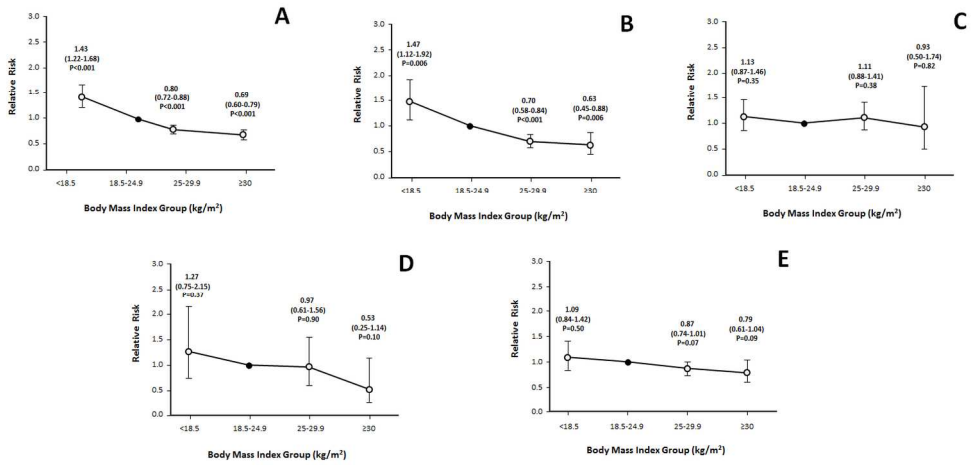

Pooled estimates (RRs) and 95%CI for mortality risk associated with underweight, overweight and obesity compared to normal weight status (Plot A, all-cause mortality; Plot B, mortality due to infectious disease; Plot C, mortality due to cardiovascular causes; Plot D, mortality due to cerebrovascular causes; Plot E, mortality due to other causes).
327x163mm (300 x 300 DPI)

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SUPPLEMENTARY DATA

Inverse Relationship Between Body Mass Index and Mortality in Older Nursing-Home Residents: A Meta-analysis of 19,538 Elderly Subjects

Running title: BMI and mortality in nursing home

Nicola Veronese[1], Emanuele Cereda[2], Marco Solmi [3], Susan A. Fowler[4], Enzo Manzato [1,5], Stefania Maggi [5], Peter Manu [6-9], Eiko Abe[10], Kunihiko Hayashi[10], Johane Allard [11,12], Bianca Arendt [11], Anne Marie Beck [13], Mark Chan [14], Yeo Jing Ping Audrey[14], Wen-Yuan Lin [15], Hua-Shui Hsu[15], Cheng-Chieh Lin[15], Rebecca Diekmann[16], Simca Kimyagarov[17], Michelle Miller[18], Ian Cameron[19], Kaisu H. Pitkälä[20], Jenny Lee [21], Jean Woo[21], Kazutoshi Nakamura[22], Dawn Smiley[23], Guillermo Umpierrez[23], Mariangela Rondanelli[24], Martha Sund-Levander[25], Luzia Valentini[26], Karin Schindler[27], Johanna Törmä[28], Stefano Volpato[29], Giovanni Zuliani[29], Moses Wong[30], Kris Lok[30], John M. Kane[6-9], Giuseppe Sergi[1], Christoph U. Correll [6-9]

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Table S1. Search strategies

PubMed, Filters activated: English, 113 results found 05/31/2014 ("Nursing Homes"[Mesh] OR "Nursing Homes" OR "Nursing Home" OR “Intermediate Care Facilities” OR “Intermediate Care Facility” OR “Skilled Nursing Facilities” OR “Skilled Nursing Facility” OR “Extended Care Facilities” OR “Extended Care Facility” OR “convalescence home” OR “convalescence hospital”) AND ("Body Mass Index"[Mesh] OR "Obesity"[Mesh] OR "Overweight"[Mesh] OR "Thinness"[Mesh] OR "Emaciation"[Mesh] OR "Cachexia"[Mesh] OR "Body Mass Index" OR “Quetelet Index” OR “Quetelet's Index” OR “Quetelets Index” OR “BMI” OR "Obesity" OR “Obesities” OR “obese” OR “adipose tissue hyperplasia” OR “adipositas” OR “adiposity” OR “excess body weight” OR “obesitas” OR “overweight” OR “weight insufficiency” OR “leanness” OR “Underweight” OR "Emaciation" OR "Emaciated” OR "Cachexia" OR “cachectic”) AND ("Mortality"[Mesh] OR "mortality" [Subheading] OR “Mortality” OR “Mortalities” OR “Case Fatality Rate” OR “Case Fatality Rates” OR “Death Rate” OR “Death Rates” OR “survival”) NOT ("Controlled Clinical Trial"[Publication Type] OR "Randomized Controlled Trial" [Publication Type] "Clinical Trial" [Publication Type] OR "Clinical Trial, Phase IV" [Publication Type] OR "Clinical Trial, Phase III" [Publication Type] OR "Clinical Trial, Phase II" [Publication Type] OR "Clinical Trial, Phase I" [Publication Type])
Embase, 172 results found 05/31/2014 'nursing home'/exp OR ‘Nursing Homes’ OR ‘Nursing Home’ OR ‘Intermediate Care Facilities’ OR ‘Intermediate Care Facility’ OR ‘Skilled Nursing Facilities’ OR ‘Skilled Nursing Facility’ OR ‘Extended Care Facilities’ OR ‘Extended Care Facility’ OR ‘convalescence home’ OR ‘convalescence hospital’ AND ('body mass'/exp OR 'obesity'/exp OR 'underweight'/exp OR 'cachexia'/exp OR ‘Body Mass Index’ OR ‘Quetelet Index’ OR ‘Quetelets Index’ OR ‘BMI’ OR ‘body ban mass’ OR ‘Obesity’ OR ‘Obesities’ OR ‘obese’ OR ‘adipose tissue hyperplasia’ OR ‘adipositas’ OR ‘adiposity’ OR ‘excess body weight’ OR ‘fat overload syndrome’ OR ‘obesitas’ OR ‘overweight’ OR ‘weight insufficiency’ OR ‘leanness’ OR ‘Underweight’ OR ‘Emaciation’ OR ‘Emaciated’ OR ‘Cachexia’ OR ‘cachectic’) AND ('mortality'/exp OR ‘Mortality’ OR ‘Mortalities’ OR ‘Case Fatality Rate’ OR ‘Case Fatality Rates’ OR ‘Death Rate’ OR ‘Death Rates’ OR ‘survival’) NOT (‘controlled clinical trial’/it OR ‘randomized controlled trial’/it OR 'controlled clinical trial'/exp OR 'randomized controlled trial'/exp OR 'clinical trial'/exp)

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Table S2. Excluded eligible studies due to lack of mortality data in standardized BMI groups (Authors did not answer).

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13. Sullivan DH, Morley JE, Johnson LE, Barber A, Olson JS, Stevens MR, et al. The GAIN (Geriatric Anorexia Nutrition) registry: the impact of appetite and weight on mortality in a long-term care population. J Nutr Health Aging. 2002; 6: 275-81
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risk-predicting ability in institutionalised older Taiwanese. J Clin Nurs. 2010; 19: 2493-2499.

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Table S3. Methodological quality of cohort studies included in the meta-analysis*

First author, publication year	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure†	Outcome of interest not present at start of study††	Control for important factor or additional factor†††	Assessment of outcome	Follow-up long enough for outcomes to occur††††	Adequacy of follow-up of cohorts	Total quality scores
Abe, 2011 [32]	*	*	-	*	**	*	*	*	8
Allard, 2004 [33]	*	*	-	-	-	*	-	*	4
Beck, 2008 [34]	*	*	-	*	-	*	-	*	5
Cereda, 2011 [35]	*	*	*	*	**	*	*	*	9
Chan, 2010 [36]	*	*	*	*	**	*	-	*	8
Hsu, 2013 [37]	*	*	*	-	**	*	*	*	8
Kaiser, 2010 [38]	*	*	*	-	-	*	-	*	5
Kimyagarov, 2010 [39]	*	*	-	-	-	*	-	*	3
Kuikka, 2009 [40]	*	*	-	*	-	*	-	*	5
Lee, 2014 [41]	*	*	-	*	**	*	*	*	8
Lin, 2010 [42]	*	*	-	*	**	*	*	*	8
Lok, 2009 [43]	*	*	-	-	-	*	-	*	4
Miller, 2009 [44]	*	*	-	*	**	*	-	*	7
Nakazawa, 2013 [45]	*	*	-	*	**	*	-	*	7
Smiley, 2012 [46]	-	*	-	-	-	*	-	*	3
Sund-Levander, 2007 [47]	-	*	-	*	**	*	*	-	6
Torma, 2013 [48]	*	*	*	*	*	*	-	*	7
Valentini, 2009 [49]	*	*	-	*	**	*	-	*	7
Veronese, 2013 [50]	*	*	*	*	**	*	*	*	9
Volpato, 2004 [51]	*	*	-	*	**	*	-	*	7

Original studies were analyzed in the quality assessment.

* A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor. The definition/explanation of each column of the Newcastle-Ottawa Scale is available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

† For this index, one star was given if in Method section was indicated if weight and height were taken in bedridden patients.

†† Being outcome of interest mortality, we took as outcome of interest for assessment of quality if the presence of cognitive impairment, disability or frailty was assessed.

††† A maximum of 2 stars could be awarded for this item. Studies that controlled for at least three confounders or including disability or frailty indexes received one star, whereas studies that controlled their survival analysis for more than 4 confounders received an additional star.

†††† A cohort study with a mean/median follow-up time ≥5 y was assigned one star.

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FIGURE LEGENDS

Figure S1. PRISMA flow-chart.

Figure S2. Relationship between mortality risk and baseline body mass index levels.

Plot A, all-cause: slope= -0.07, 95% CI= -0.08, -0.05, p-value<0.001. Plot B, infectious disease: slope= -0.07, 95% CI= -0.09, -0.04, p-value<0.001. Plot C, cardiovascular causes: slope= -0.003, 95% CI= -0.04, 0.03, p-value=0.86. **Plot D, cerebrovascular causes: slope= -0.04, 95% CI= -0. 02, -0.07, p-value=0.02.**
Plot E, other causes: slope= 0.01, 95% CI= -0.04, 0.002; p-value=0.08.

Significant associations (p<0.05) were typed in bold.
The gray lines indicate the 95% CIs around the regression line..

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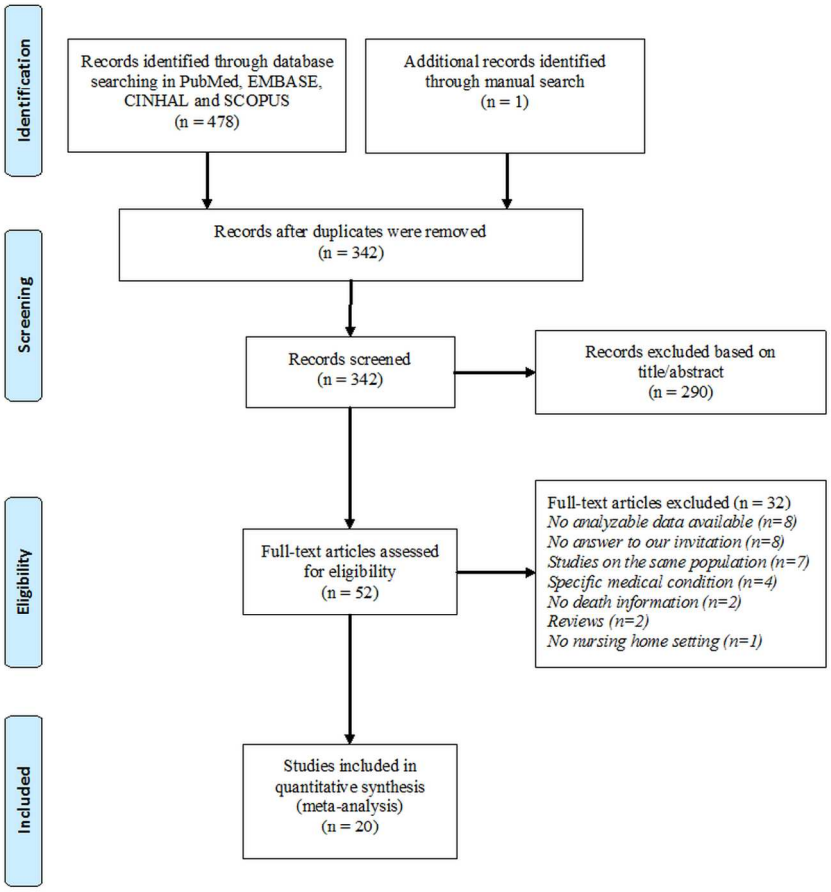

PRISMA flow-chart.
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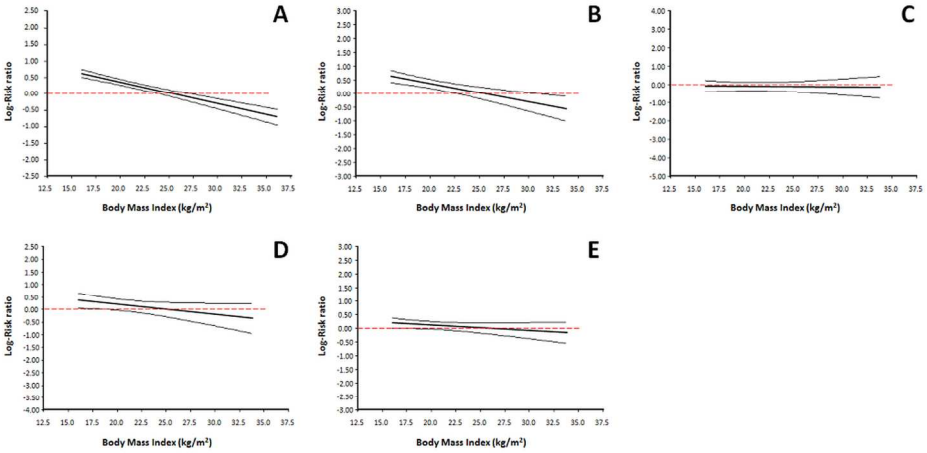

Relationship between mortality risk and baseline body mass index levels.

Plot A, all-cause: slope= -0.07, 95% CI= -0.08, -0.05, p-value<0.001. Plot B, infectious disease: slope= -0.07, 95% CI= -0.09, -0.04, p-value<0.001. Plot C, cardiovascular causes: slope= -0.003, 95% CI= -0.04, 0.03, p-value=0.86. Plot D, cerebrovascular causes: slope= -0.04, 95% CI= -0. 02, -0.07, p-value=0.02. Plot E, other causes: slope= 0.01, 95% CI= -0.04, 0.002; p-value=0.08.

Significant associations (p<0.05) were typed in bold.
The gray lines indicate the 95% CIs around the regression line.
231x117mm (300 x 300 DPI)

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