Interrelations between Body Mass Index, Frailty, and Clinical Adverse Events in Older Community-Dwelling Women: The EPIDOS Cohort Study

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Abstract 288 words; word count: 5050

Running title: BMI, Frailty, and Clinical Events in Older Women

Conflicts of interest: None

Abstract

Background: The hypothesis of reverse epidemiology holds that, obesity may reduce the risk of clinical adverse events in older subjects. However, this association is controversial and rarely explored according to the underlying health status. We tested this phenomenon by assessing the association between body mass index (BMI) and clinical adverse events in community dwelling older women according to their frailty status.

Methods: EPIDOS is a multicenter prospective cohort of community-dwelling women aged 75 and older recruited between 1992 and 1994. At baseline, we collected demographics, BMI (<21 kg/m²: underweight; 21-24.9: normal weight: 25-29.9: overweight and ≥ 30: obesity), frailty through Fried model, and clinical characteristics. All-cause mortality, falls and hip fractures, and hospital admission were collected within 5 years of follow-up and were analyzed using univariate and multivariate survival analysis by using Kaplan-Meier methods and Cox Hazard Proportional models.

Results: Of 6662 women (mean age, 80.4 years), 11.6%; 95% Confidence Interval (95%CI) CI [10.8%-12.3%] were frail. By multivariate analysis, the risk of death in frail women (compared to not-frail normal weight women) decreases with increase of BMI: $aHR_{frail-underweight}$=2.04[1.23-3.39]; $aHR_{frail-normal\ weight}$ =3.07[2.21-4.26]; $aHR_{frail-overweight}$= 1.83[1.31-2.56]; $aHR_{frail-obese}$= 1.76 [1.15-2.70]; p<0.001). Frail overweight and obese women had a significant lower risk of death than frail normal- weight women (p=0.004). Similar features were found for fall risk and hip fracture and for not-frail women. The relative risks of hospital admission for normal weight, overweight and obese frail women were similar (aHR $_{frail-normal\ weight}$, 1.50[1.22-1.84], 1.48 $_{frail-overweight}$ [1.26-1.74] and 1.53 $_{frail-obese}$ [1.24-1.89], respectively).

Conclusion: Our results suggest that overweight and obesity reduce the risks of clinical adverse events in frail community-dwelling older women and that frailty definition through Fried model had to be re-calibrated for overweight and obese individuals.

Keywords: Body mass index, frailty, fall, death, hospital admission, older.

INTRODUCTION

Obesity and overweight are common in community-dwelling older people. In the United States, 28% of people aged 75 years or older were obese. In Europe, 48% of people aged 65 and older were overweight. Obesity is associated with higher mortality in middle-aged individuals(1–4), but whether the same is true in older people is unclear (1,5–9). Whether obesity is a risk factor for clinical adverse events such as death, falls, fracture or hospital admission remains controversial in older persons and may depend on the underlying medical condition. Indeed, some studies showed positive associations linking overweight and obesity to mortality and disability(6,10), whereas others found no associations or negative associations(1,5,7,8,11–13). Overweight and obesity are associated with better outcomes in various medical conditions(5,14–17).

Frailty is a state of general vulnerability associated with an increased risk for clinical adverse events (18–20). Although there is no consensus on the definition of frailty, the model developed by Fried et al. leading to the original definition in the CHS Study and adapted measures in different clinical settings is widely used (19,21). To our knowledge, potential interrelations linking obesity, frailty, and clinical adverse events in older people have been investigated in a single study: frail overweight individuals were less likely to fall compared to their thinner counterparts. However, the fall risk was the only outcome of interest(14).

Our hypothesis is that a protective effect of obesity, the so call obesity paradox or the paradox of reverse epidemiology(16) , may also be observed in the context of frailty.
In the present study, we investigated associations between 4 categories of BMI (underweight, normal weight, overweight and obesity) and clinical adverse events in community-dwelling older women according to their frailty status.

METHODS

Study design and population

We conducted a secondary analysis of the EPIDOS population (EPIdémiologie De l'OStéoporose, Epidemiology of Osteoporosis), which is a French multicenter prospective longitudinal cohort of 7598 women aged 75 years or older recruited in five French cities between 1992 and 1994.

Baseline data collection

Assessment of frailty

EPIDOS was conducted before the validation of the frailty criteria developed by Fried et al.(19). However, the standardized and systematic measures at baseline of grip strength walk speed, physical activity and anthropometric characteristics enable to build a frailty index very close of Fried model, the only adapted criteria being exhaustion. Therefore, frailty was defined as the presence of three or more of the following criteria:

1. Weight loss ≥4.5 kg from baseline to the end of the first study year;
2. Exhaustion was approximated by a "bad" or "very bad" answer to the question "In general, do you consider your current health very good, good, bad, or very bad?";
3. Weakness, i.e., mean grip strength on the left and right sides in the lowest 20% at baseline, as measured using a dynamometer (Takei Ltd, Tokyo, Japan). Women were classified as frail when grip strength was <43 kPa;
4. Low physical activity level, i.e., a "no" answer to two questions, "Do you regularly practice sport or have a physical activity such as recreational walking, gymnastics, cycling, swimming or gardening?" and "Do you do heavy housework on a regular basis, such as vacuum cleaning or floor washing?"; and

5. Slow walking speed, as measured during the baseline examination as the mean speed of two 6-meter walking tests, is defined by a walking speed≤0.65m/s for women≤159 cm and ≤0.76m/s for women>159 cm.

Instrumental Activities of Daily Living

The women were asked if they experienced difficulty in performing any of Lawton's eight Instrumental Activities of Daily Living (IADL). Altered IADL was considered when ≤ 7/8.

Anthropometric measurements

Body weight and height were measured at inclusion. BMI was calculated as weight (kg)/height² (m²). We classified the women into four BMI categories: underweight, BMI<21 kg/m²; normal weight, BMI=21.0-24.9 kg/m²; overweight, BMI=25.0-29.9 kg/m²; and obese, BMI≥30 kg/m² .

Waist circumference >88 cm was defined as abnormal. To assess body composition, dual-energy x-ray absorptiometry (DXA) was performed by trained technicians using QDR 4500 W Hologicmachines (Hologic, Waltham, MA) calibrated daily at each center and cross-calibrated across centers at regular intervals. Skeletal muscle mass (SMM) was computed as the ratio of appendicular skeletal mass over height in meters squared. We used two definitions of low SMM: <5.45 kg/m², and SMM within the lowest quartile (<5.80 kg/m² in our study). Sarcopenic obesity was defined by a SMM<5.45 kg/m² or <5.80 kg/m² and a BMI≥30 kg/m²(22,23). SMM data were available only for individuals recruited at the Lyon and Toulouse centers.

Demographic and socioeconomic factors

At baseline, age, level of education, and the fact of living alone were recorded. A physical examination and health status questionnaire were used to identify comorbidities

(≥2), past health issues, and treatments (≥2). Smoking status, and alcohol consumption were recorded.

Follow-up

We considered four outcomes: death, falls, hip fractures, and hospital admissions. Falls and hip fractures were assessed every 4 months for 4 years until 1998. All women had an annual evaluation.

Mortality was ascertained through the end of 1998 by telephone calls and mail to the proxies, primary-care physicians and Office Public Record.

Statistical analysis

Continuous variables are described as mean (SD) or median (25^{th}-75^{th} percentile) and categorical variables as n (%).

Baseline characteristics according to frailty status were compared using Student's *t* test or the Wilcoxon-Mann-Whitney test, the chi-square test or Fisher's exact test as appropriate.

Rates of death and of the other three outcomes within the 5 years of follow-up were determined using Kaplan-Meier survival method and expressed per 100 person-years. Factors associated with each of the four outcomes were identified using univariate Cox models. The main variable of interest was the frailty/BMI composite leading to 8 categories: underweight-not-frail (group1); underweight-frail (group 2); normal weight-not-frail (group 3); normal weight-frail (group 4); overweight-not-frail (group 5); overweight-frail (group 6); obese-not-frail (group 7); and obese-frail (group 8). The reference category was "group 3". We built four multivariate Cox models based on the variables associated with *P* values <0.20 by univariate analysis. Pairwise analyses were done to assess confounding factors, and interactions were sought. A trend test was used to assess the potential gradient between the 4 categories of BMI and the different outcomes.

An analysis stratified on waist circumference (≤ or > 88 cm) was carried out for death, fall, hip fracture and hospital admission.

All tests were two-sided. *P* values lower than 0.05 were considered significant, *P* values between 0.05 and 0.10 as trend. The analysis was conducted using Stata V12.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Study population

Among the 7598 women in the EPIDOS cohort, 936 were excluded because of missing data for assessing the frailty variable, leaving 6662 women for the analysis. The characteristics of the two groups, ie included *vs* excluded, were similar, except for age (mean, 80 years versus 81 years, $P<0.037$), the higher level of education (15.7% versus 12.7% had graduated from high school or obtained a higher education, $P<0.001$), and the functional status (median [quartile1-quartile3] IADL, 8 [7-8] versus 8 [7-8], $P=0.010$).

Frailty was noted in 771/6662 (11.6%; 95%CI, 10.8%-12.3%) women; 8.7% of women met three frailty criteria, 2.7% four criteria, and 0.2% five criteria. The proportion of weakness decreased with the increase of BMI, and the proportion of weight loss and slow walking speed increased with the increase of BMI (Table 1).

Compared to not-frail women, frail women were older, had a lower level of education, lived less frequently alone, consumed less alcohol, had a higher BMI, had a lower level of autonomy, had more comorbidities, took more medications, used more treatment with hypnotics, psychoactive drugs, and cardiovascular drugs including antihypertensive agents, had more fear of falling, had fallen more frequently in the last 6 months, had more often been admitted in hospital in the last 12 months, and had more previous fractures. No subject had sarcopenic obesity according to the definition 1 of sarcopenia and very few (0.4%) according to definition 2 (Table 2).

The proportion of frail women according to baseline BMI category indicates a J-shaped variation: the proportion of frail women was intermediate in the underweight category (n=89; 10.8%), the lowest in the normal-weight category (n=206; 8.5%), and highest in the overweight and obese categories (n=304; 12.1% and n=172; 20.3% respectively).

Death

Of the 6662 women include for the analysis, 520 died within the 5 years of follow-up (mortality rate: 1.88 per 100 persons-years; 95%CI: 1.6-2.2).

By univariate analysis, frailty was associated with death in the 4 BMI categories ($cHR_{group\ 4}$=5.20[3.79-5.14]; $cHR_{group\ 2}$=4.00[2.45-6.54]; $cHR_{group\ 6}$=3.14[2.29-4.31]; and $cHR_{group\ 8}$=2.88[1.92-4.32]). The risk of death decreased with the increase of BMI (p for trend=0.06). Other variables associated with death by univariate analysis were older age ($cHR_{per\ additional\ year}$=1.15[1.13-1.17]); low educational attainment (cHR=1.43[1.14-1.78]); number of comorbidities ≥2 ($cHR_{\geq 2\ vs.\ <2}$ =1.22[1.00-1.49]; treatment with hypnotics (cHR=1.22[1.03-1.45]), psychoactive drugs (cHR=1.25[1.01-1.54]), or cardiovascular drugs including antihypertensive agents (cHR=1.69[1.39-2.06]); fear of falling (cHR=1.30[1.09-1.54]); fall in the last 6 months (cHR=1.21[1.00-1.47]), hospital admission in the last 12 months (cHR=1.74[1.43-2.12]), low self-sufficiency ($cHR_{IADL<8\ vs.\ \geq 8}$=2.65[2.23-3.15.

By multivariate analysis adjusted for age, cardiovascular drugs including antihypertensive agents, hospital admission in the last 12 months, functional status, the association between frailty and death remained significant in the 4 categories of BMI (Figure

1). In the frail group, overweight and obese women had a significant lower risk of death than normal- weight women (p=0.004) (Figure 1).

Secondary analyses

Frail overweight or obese women with a normal waist circumference (≤88 cm) had similar risk of death than not-frail women with normal weight and normal waist circumference (aHR=1.30[0.72-2.34). Conversely, frail overweight or obese women with a waist circumference >88 cm had a higher risk of death (aHR=1.89[1.40-2.54]).

Falls

Of the 6662 women include for the analysis, 4061 fell within the 5 years of follow-up (fall rate: 17.9 per 100 persons-years; 95%CI:15.6-18.6).

By univariate analysis, frailty was associated with falls but not in the obese group ($cHR_{group\ 2}$=1.49[1.15-1.94]; $cHR_{group\ 4}$=1.55[1.30-1.84] and $cHR_{group\ 6}$=1.20[1.03-1.39]; $cHR_{group\ 8}$=1.04[0.86-1.27]; respectively). The risk of fall decreased with the increase of BMI (p for trend=0.10).

Other variables associated with falls by univariate analysis were older age ($cHR_{per\ additional\ year}$=1.03[1.02-1.04]), low educational attainment (cHR=0.82[0.75-0.89], living alone (cHR=1.12[1.05-1.20]), smoking (cHR=1.15[1.05-1.25]), having ≥2 comorbidities (cHR=1.24[1.15-1.33], having ≥2 treatments (cHR=1.09[1.00-1.19], treatment with hypnotics (cHR= 1.21[1.14-1.29]) or psychoactive drugs (cHR=1.16[1.08-1.26]), fear of falling (cHR=1.27[1.20-1.36]), fall in the last 6 months (cHR=1.48[1.38-1.58]), previous fracture (cHR=1.33[1.25-1.41], and functional status ($cHR_{IADL<8\ versus\ \geq 8}$=1.09[1.02-1.17]).

By multivariate analysis adjusted for age, educational level, living alone, smoking, number of chronic comorbidities, treatment with hypnotics, psychoactive drugs, fear of falling, fall in the last 6 months and previous fracture, frailty in underweight and normal-weight women remained significantly associated with falling. Frail overweight and obese women had a lower risk of fall, similar to not-frail women (Figure 2).

Secondary analyses

Frail overweight or obese women with a waist circumference ≤88 cm or a waist circumference>88 had similar risk of fall compared to not-frail women with normal weight and normal waist circumference (aHR=1.06[0.82-1.36] and 0.95[0.82-1.09], respectively).

Hip fractures

Of the 6662 women include for the analysis, 298 has a hip fracture within the 5 years of follow-up (hip fracture rate: 1.33; 95%CI:1.04-1.69).

By univariate analysis, frailty was associated with hip fracture but not in the obese group ($cHR_{group\ 2}$ =3.38[1.76-6.50]; $cHR_{group\ 4}$ =2.71[1.64-4.50]), $cHR_{group\ 6}$ =2.56[1.68-3.92]; $cHR_{group\ 8}$=0.92 [0.40-2.11]). Other variables associated with hip fractures by univariate analysis were older age ($cHR_{per\ additional\ year}$=1.12[1.09-1.15]), ≥2 daily medications (cHR=1.33[1.00-1.78], use of hypnotics (cHR=1.65[1.31-2.08]), fear of falling (cHR=1.78[1.41-2.26]), fall in the last 6 months (cHR=1.45[1.13-1.86], previous fracture (cHR=1.55[1.23-1.95]), and low functional status ($cHR_{IADL<8\ vs.\ \geq 8}$=2.16[1.72-2.71]).

By multivariate analysis adjusted for age, use of hypnotics, fear of falling, and functional status and previous fracture, frailty was not associated with hip fracture in any of the BMI categories. In the not-frail women, obese had a decreased risk of hip fracture (Figure 3).

Secondary analyses

Frail overweight or obese women with a waist circumference ≤88 cm or a waist circumference>88 had similar risk of hip fracture compared to not-frail normal weight and normal waist circumference women (aHR=0.80[0.32-1.98] and 1.20[0.78-1.85], respectively).

Hospital admission

Of the 6662 women included for the analysis, 2673 were admitted for an hospitalization within 5 years of follow-up (Hospital admission rate:13.4 per 100 persons-years; 95%CI:10.5-15.2).

By univariate analysis, frailty was associated with hospital admissions in the 4 BMI categories (cHR_{group2}=1.43[1.07-1.91], $cHR_{group\ 4}$=1.74[1.44-2.11], $cHR_{group\ 6}$=1.86[1.59-2.17], and $cHR_{group\ 8}$=1.73[1.42-1.2.12]). Other variables associated with hospital admission by univariate analysis were older age ($cHR_{per\ additional\ year}$=1.02[1.01-1.03]); living alone (cHR=1.17[1.09-1.26]); smoking (cHR=1.12[1.01-1.23]); alcohol use (cHR=0.92[0.85-0.98]); ≥2 comorbidities (cHR=1.43[1.32- 1.55]); ≥2 daily medications (cHR=1.11[1.01-1.22]); use of hypnotics (cHR=1.23[1.15-1.32]), psychoactive agents (cHR=1.19[1.09-1.29]), or cardiovascular drugs including antihypertensive drugs (cHR=1.23[1.15-1.33]), fear of falling (cHR=1.25[1.16-1.33]), fall in the last 6 months (cHR=1.19[1.10-1.28]), hospital admission in the last 12 months (cHR=1.52[1.40-1.65]), previous fracture (cHR=1.13[1.06-1.21]), and low functional status ($cHR_{IADL<8\ versus\ \geq 8}$=1.19[1.11-1.28]).

By multivariate analysis adjusted for age, living alone, smoking, number of chronic comorbidities, number of treatment, use of hypnotics, cardiovascular drugs including antihypertensive drugs, fear of falling, fall in the last 6 months, hospital admission in the last 12 months and previous fracture, frailty was associated with hospital admission in the normal-weight, overweight, and obese categories compared to not-frail normal-weight women with similar level of association strengths in the 3 categories (Figure 4).

Secondary analyses

Frail overweight or obese women with a waist circumference ≤88 cm had similar risk of hospitalization compared to not-frail normal weight and normal waist circumference women (aHR=1.14[0.86-1.49]). Conversely, frail overweight or obese women with a waist circumference >88 cm had a higher risk of hospitalization (aHR=1.56[1.35-1.81]).

DISCUSSION

Our results suggest that association between frailty and clinical adverse events (fall, hip fracture, hospital admission and death) is affected by overweight and obesity in older community-dwelling women. Indeed, overweight and obese frail women are at lower risk of death and fall than normal- weight frail women. Moreover, frailty was associated with increased hospital admission risk but normal-weight, overweight, and obese frail women had similar level of risk of hospital admission. However, frail overweight or obese women with a waist circumference > 88 cm had higher risk of death and hospital admission than not-frail normal weight women.

The 11.6% prevalence of frailty in our population of individuals aged 75 years or older is close to that reported in other studies (11,14,15,20,21). Frailty and BMI category showed a J-shaped association in our study. This finding agrees with earlier reports with frailty being more prevalent in obese and underweight individuals than in their normal-weight counterparts(14,24–26).

In a recent study of 606 older people, frail overweight individuals were less likely to fall compared to their thinner counterparts, in keeping with our results(14). In another study, walking speed was diminished in obese older adults(27), suggesting a possible explanation of the decreased risk of fall risk in this category.

In the Korean Living Profiles of Older People survey, frail underweight or normal-weight individuals had higher mortality rates compared to not-frail normal-weight individuals (28). Mortality was higher in frail underweight, but not normal-weight, participants in an others studies (29,30). Both underweight and normal weight were associated with a higher risk of death in our study. The association between low BMI and increased risk of death may be mediated by reduced reserve capacity. A decrease risk of death in obese women had already been found in the EPIDOS study(9). Consistent with previous results(1), among frail obese or overweight women, those with a waist circumference >88 cm had a higher risk of death, whereas those with smaller waist circumferences did not. In contrast, another study showed no independent association linking BMI, waist circumference, and death in individuals >65 years(31). However, this study did not include stratification on the underlying health profile.

Our findings are in line with earlier results in frail individuals showing lower mortality among obese or overweight compared to normal-weight participants, after adjustment for age, functional status, and comorbidities(30,32). First, the fat mass may provide an energy reserve, to be mobilized against acute stress events like an acute illness. Second, obese patients may present with symptoms and morbidities earlier, and therefore earlier medical management. Another possible explanation is that frailty assessments based on Fried model may overestimate frailty in older obese individuals**:** indeed, obese women have more frequently ≥4.5-kg weight loss and a slower gait speed, two criteria of the frailty Fried model, leading to higher proportion of frail women in obese groups compared to others. However, it is questionable that these two criteria are relevant frailty markers for obese women. Accordingly~~,~~ the ≥4.5-kg weight loss criterion may spuriously result in better outcomes in the obese and overweight groups, as losing this amount of weight would have less impact than in thinner individuals. Similarly, obese individuals had lower speed walking in mean therefore the cut-offs for defining low walking speed for identifying frailty in obese individuals may be different compared to thinner. Studies using other measures of frailty, such as the Rockwood Frailty Index, would be useful. Finally, selective survival bias may lead to apparently better outcomes in overweight and obese individuals, as only individuals who have not died from complications of their excess weight can be included in a study.

In a prospective cohort study of 246 361 people age ≥45 years, in accordance with our results, there was a substantial increase of hospitalization risk in younger mid-age adults with above-normal BMI while the pattern of increasing relative risk of hospitalization with increasing above-normal BMI is fairly weak in older people(33).

Our study has several strengths. EPIDOS is a large prospective cohort of community-dwelling older women. It is one of the few cohorts with such a high mean age. To our knowledge, this is the first study of potential interrelations linking frailty to 4 clinical adverse events, death, falls, hip fractures, hospital admissions according to BMI and waist circumference(25).

Our study also has limitations. We used a Fried-adapted definition of frailty as the frailty criteria developed by Fried et al. did not exist at the time of completion of the study. However, only one criterion (exhaustion) was adapted. In many other clinical studies several criteria had to be adapted due to non-availability of grip-strength, walk speed, weight loss or anthropometric measurements and despite these proxys, adapted-frailty measures provided good prognosis values(21). Muscle mass data were collected in only two of the five study centers and the very low frequency of sarcopenic obesity in our community-dwellingt setting preclude to possibility to test the association between sarcopenic obesity, frailty and clinical events. Endly the relative low number of hip fractures lead to large confidence intervals and preclude robust conclusions for this endpoint.

Our results may suggest that frailty, according to Fried model, may have greater prognostic impact in underweight or normal weight women than overweight or obese women. Thus, prevention and correction of frailty parameters may be particularly targeted to frail underweight and normal-weight women. Our results may also suggest that Fried definition had to be re-defined for assessing frailty in overweight and obese older adults. Indeed, as previously stated, Fried definition may misclassify obese adults as frail whereas they were not, leading to better outcomes. Is the loss of 4.5 kg a good cut-off for defining frailty in obese older women? Similarly, is a cut-off of ≤0.65m/s if the height is ≤159 cm and ≤0.76m/s if >159 cm, adequate?

Our results suggest that overweight and obesity reduce the risks of clinical adverse events in frail community-dwelling older women and that frailty definition through Fried model had to be re-calibrated for overweight and obese individuals.

Acknowledgments

We thank Antoinette Wolfe, MD, for editing the English.

Conflict of Interest

The authors declare no conflict of interest

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Guallar-Castillón P, Balboa-Castillo T, López-García E, León-Muñoz LM, Gutiérrez-Fisac JL, Banegas JR, et al. BMI, waist circumference, and mortality according to health status in the older adult population of Spain. *Obes Silver Spring Md* 2009 Dec;**17**:2232–8.

2. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 2006;**355**:763–78.

3. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *JAMA* 2005;**293**:1861–7.

4. Ajani UA, Lotufo PA, Gaziano JM, Lee I-M, Spelsberg A, Buring JE, et al. Body mass index and mortality among US male physicians. *Ann Epidemiol* 2004;**14**:731–9.

5. Chapman IM. Obesity paradox during aging. *Interdiscip Top Gerontol* 2010;**37**:20–36.

6. Monteverde M, Noronha K, Palloni A, Novak B. Obesity and excess mortality among the elderly in the United States and Mexico. *Demography* 2010;**47**:79‑96.

7. Bowen ME. The relationship between body weight, frailty, and the disablement process. *J Gerontol B Psychol Sci Soc Sci* 2012;**67**:618–26.

8. de Souto Barreto P, Cadroy Y, Kelaiditi E, Vellas B, Rolland Y. The prognostic value of body-mass index on mortality in older adults with dementia living in nursing homes. *Clin Nutr.* 2017;**36**:423-8.

9. Rolland Y, Gallini A, Cristini C, Schott A-M, Blain H, Beauchet O, et al. Body-composition predictors of mortality in women aged ≥ 75 y: data from a large population-based cohort study with a 17-y follow-up. *Am J Clin Nutr* 2014;**100**:1352–60.

10. Freedman DM, Ron E, Ballard-Barbash R, Doody MM, Linet MS. Body mass index and all-cause mortality in a nationwide US cohort. *Int J Obes* 2006;**30**:822–9.

11. Doundoulakis I, Poulia K-A, Antza C, Kasapidou E, Chourdakis M. Obesity paradox in elderly patients with cardiac failure- an updated review of current evidence. *Clin Nutr ESPEN* 2016;**13**:e72.

12. Abi Khalil C, Sulaiman K, Singh R, Jayyousi A, Asaad N, AlHabib KF, et al. BMI is inversely correlated to the risk of mortality in patients with type 2 diabetes hospitalized for acute heart failure: Findings from the Gulf aCute heArt failuRE (Gulf-CARE) registry. *Int J Cardiol* 2017;

13. Clark DO, Gao S, Lane KA, Callahan CM, Baiyewu O, Ogunniyi A, et al. Obesity and 10-Year Mortality in Very Old African Americans and Yoruba-Nigerians: Exploring the Obesity Paradox. *J Gerontol Ser A* 2014;**69**:1162–9.

14. Sheehan KJ, O'Connell MD, Cunningham C, Crosby L, Kenny R. The relationship between increased body mass index and frailty on falls in community dwelling older adults. *BMC Geriatr* 2013;**13**:132.

15. Wang L, Liu W, He X, Chen Y, Lu J, Liu K, et al. Association of overweight and obesity with patient mortality after acute myocardial infarction: a meta-analysis of prospective studies. *Int J Obes* 2016;**40**:220–8.

16. Martín-Ponce E, Santolaria F, Alemán-Valls M-R, González-Reimers E, Martínez-Riera A, Rodríguez-Gaspar M, et al. Factors involved in the paradox of reverse epidemiology. *Clin Nutr Edinb Scotl* 2010;**29**:501–6.

17. Greenlee H, Unger JM, LeBlanc M, Ramsey S, Hershman DL. Association between Body Mass Index and Cancer Survival in a Pooled Analysis of 22 Clinical Trials. *Cancer Epidemiol Biomarkers Prev* 2017;**26**:21–9.

18. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet Lond Engl* 2013;**381**:752–62.

19. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M146-156.

20. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA, et al. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci* 2007;**62**:744–51.

21. Ensrud KE, Ewing SK, Cawthon PM, Fink HA, Taylor BC, Cauley JA, et al. A Comparison of Frailty Indexes for the Prediction of Falls, Disability, Fractures, and Mortality in Older Men: FRAILTY INDEXES, FALLS, DISABILITY, FRACTURES, AND MORTALITY. *J Am Geriatr Soc* 2009;**57**:492–8.

22. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic Obesity Predicts Instrumental Activities of Daily Living Disability in the Elderly. *Obes Res* 2004;**12**:1995‑2004.

23. Delmonico MJ, Harris TB, Lee J-S, Visser M, Nevitt M, Kritchevsky SB, et al. Alternative definitions of sarcopenia, lower extremity performance, and functional impairment with aging in older men and women. *J Am Geriatr Soc* 2007;**55**:769–74.

24. Blaum CS, Xue QL, Michelon E, Semba RD, Fried LP. The association between obesity and the frailty syndrome in older women: the Women's Health and Aging Studies. *J Am Geriatr Soc* 2005;**53**:927–34.

25. Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K. Frailty, body mass index, and abdominal obesity in older people. *J Gerontol A Biol Sci Med Sci* 2010;**65**:377–81.

26. Zoico E, Di Francesco V, Guralnik JM, Mazzali G, Bortolani A, Guariento S, et al. Physical disability and muscular strength in relation to obesity and different body composition indexes in a sample of healthy elderly women. Int J Obes Relat Metab Disord J Int Assoc Study Obes 2004;**28**:234–41.

27. Bindawas SM, Vennu V. Longitudinal effects of physical inactivity and obesity on gait speed in older adults with frequent knee pain: data from the Osteoarthritis Initiative. *Int J Environ Res Public Health* 2015;**12**:1849–63.

28. Lee Y, Kim J, Han ES, Ryu M, Cho Y, Chae S. Frailty and body mass index as predictors of 3-year mortality in older adults living in the community. *Gerontology* 2014;**60**:475–82.

29. Kulminski AM, Arbeev KG, Kulminskaya IV, Ukraintseva SV, Land K, Akushevich I, et al. Body mass index and nine-year mortality in disabled and nondisabled older U.S. individuals. *J Am Geriatr Soc* 2008;**56**:105–10.

30. Schooling CM, Lam TH, Li ZB, Ho SY, Chan WM, Ho KS, et al. Obesity, physical activity, and mortality in a prospective chinese elderly cohort. *Arch Intern Med* 2006 Jul;**166**:1498–504.

31. Thomas F, Pannier B, Benetos A, Vischer UM. Visceral obesity is not an independent risk factor of mortality in subjects over 65 years. *Vasc Health Risk Manag* 2013;**9**:739–45.

32. Veronese N, De Rui M, Toffanello ED, De Ronch I, Perissinotto E, Bolzetta F, et al. Body mass index as a predictor of all-cause mortality in nursing home residents during a 5-year follow-up. *J Am Med Dir Assoc* 2013;**14**:53–7.

33. Korda RJ, Liu B, Clements MS, Bauman AE, Jorm LR, Bambrick HJ, et al. Prospective cohort study of body mass index and the risk of hospitalisation: findings from 246361 participants in the 45 and Up Study. *Int J Obes (Lond)* 2013;**37**:790–9.

FIGURES LEGENDS

Figure 1. Forest plot of adjusted hazard ratios (HR) and 95% CIs for death in relation to frailty stratified on BMI: EPIDOS study.

*adjusted for age, cardiovascular drugs including antihypertensive agents, hospital admission in the last 12 months, functional status~~.~~

Figure 2. Forest plot of adjusted hazard ratios (HR) and 95%CIs for falls in relation to frailty stratified on BMI: EPIDOS study.

*adjusted for age, educational level, living alone, smoking, number of chronic comorbidities, treatment with hypnotics, psychoactive drugs, fear of falling, fall in the last 6 months and previous fracture.

Figure 3. Forest plot of adjusted hazard ratios (HR) and 95% CIs for hip fracture in relation to frailty stratified on BMI: EPIDOS study.

***** adjusted for age, use of hypnotics, fear of falling, and functional status and previous fracture.

Figure 4. Forest plot of adjusted hazard ratios (HR) and 95% CIs for hospital admission in relation to frailty stratified on BMI: EPIDOS study.

***** adjusted for age, living alone, smoking, number of chronic comorbidities, number of treatment, use of hypnotics, cardiovascular drugs including antihypertensive drugs, fear of falling, fall in the last 6 months, hospital admission in the last 12 months and previous fracture.