Title: Obesity, fat distribution and risk of frailty in two population-based cohorts of older adults in Spain

Running title: Obesity and frailty in two population-based cohorts

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List of abbreviations:

BMI: Body Mass Index

CI: Confidence Interval

CRP: C-reactive protein

HOMA-IR: Homeostasis model assessment

IADL: Instrumental activities of daily living

MEDAS: Mediterranean Diet Adherence Screener

NHANES: National Health and Nutrition Examination Survey

OR: Odds ratio

TSHA: Toledo Study for Healthy Ageing

WC: Waist circumference

What is already known:

Obesity increases the risk of physical inactivity, poor functional performance and mobility limitations.

No previous studies have evaluated the longitudinal relationship between abdominal obesity and the onset of frailty

What does this study add:

Both general and abdominal obesity are associated with incident frailty and with risk of exhaustion, low physical activity and weakness in the elderly.

Systemic inflammation and insulin-resistance exert only a modest physio-pathological influence on the risk of frailty in obese individuals.

ABSTRACT

Objectives: To evaluate for the first time the longitudinal relationship between abdominal obesity and the onset of frailty.

Methods: Study based on results from two population-based cohorts, the Seniors-ENRICA, with 1801 individuals aged ≥60, and the TSHA, with 1289 participants ≥65 years. Incident frailty was assessed with the Fried criteria.

Results: During 3.5 years of follow-up, we identified 125 individuals with incident frailty in the Seniors-ENRICA and 162 in the TSHA. After adjustment for the main confounders, the pooled odds ratio (pooled-OR) for general obesity and risk of frailty was 1.73 (95% confidence interval [CI]: 1.18-2.28). Abdominal obesity was also associated with frailty (pooled OR: 1.67; 95%CI: 1.09-2.25). Compared to individuals with BMI <25 kg/m^2 and no abdominal obesity, the risk of frailty was highest among individuals with concurrent general and abdominal obesity (pooled OR: 2.55; 95%CI: 1.23-3.86). General obesity was associated with increased risk of exhaustion (pooled OR: 1.66; 95%CI: 1.11-2.21), low physical activity (pooled OR: 1.57; 95%CI: 1.08-2.05) and weakness (pooled OR: 1.63; 95%CI: 1.12-2.05). For abdominal obesity, results were in the same direction, although they showed statistical significance only for weakness (OR: 1.46; 95%CI: 1.11-1.80).

Conclusions: General and abdominal obesity are associated with incident frailty in the elderly.

Key words: Abdominal obesity, aging, cohort study, frailty, obesity

INTRODUCTION

Older adults are a growing segment of the population in most countries. Accordingly, the number of persons with disability and dependence is also likely to increase over the next decades. Frailty is an age-associated syndrome characterized by dysfunction of multiple systems, reduced functional reserve and increased vulnerability to environmental stressors. As a consequence, frail individuals are at increased risk of illness, disability, institutionalization and death (1). Thus, a better understanding of the pathogenesis of frailty and improved prevention strategies could serve to reduce or delay disability (2).

The prevalence of overweight and obesity in older adults is very high in many countries (3). There is evidence that obesity in the elderly increases the risk of physical inactivity (4;5), poor functional performance (6) and mobility limitations (7). However, studies on the link between obesity, fat distribution and frailty are scarce (8-11), and no previous research has focused on the longitudinal relationship between abdominal obesity and the onset of this syndrome.

The adipose tissue is a metabolically active organ that secretes numerous pro-inflammatory cytokines. In a recent meta-analysis, body mass index (BMI) and waist circumference (WC) were associated with elevated concentrations of the inflammatory marker C-reactive protein (CRP) (12). Systemic inflammation has also been identified as a risk factor for frailty (13), but its potential role in mediating the association between obesity and frailty has not been addressed prospectively. Similarly, despite the

evidence that visceral adiposity and insulin resistance are closely linked (14;15) and that insulin resistance is associated with the risk of frailty (13), no studies have evaluated the contribution of this metabolic disorder to the development of obesity-related frailty.

In this context, this study assessed the prospective association of general and abdominal obesity with the risk of frailty and its components. Additionally, it explored the mediating role of CRP and insulin-resistance in the relationship between obesity and frailty. Lastly, with the aim of assessing the consistency of results, the analyses were conducted in two independent population-based cohorts of older adults in Spain, the Seniors-ENRICA and the Toledo Study for Healthy Ageing (TSHA).

SUBJECTS AND METHODS

Study population and design

Seniors-ENRICA

From 2008 to 2010, 2614 men and women were selected through stratified random sampling from the non-institutionalized Spanish population aged 60 years and older (2;16). Information at baseline was collected in three stages. First, computer-assisted telephone interviews were used to obtain information on socio-demographic factors, health behaviors and morbidity. Then, two home visits were performed to collect blood and urine samples, conduct a physical examination and record usual diet and prescribed medication. Participants were followed-up until 2012 (mean follow-up time of 3.5 years), when a second wave of data collection was performed, again including again a

phone interview, a physical exam, and diet and medication assessment at home. Ninety-five participants (3.6%) died during follow-up. From the remaining 2519 subjects, 2085 had complete information on frailty at the end of follow-up. Baseline socio-demographic, lifestyle and clinical characteristics of individuals lost to follow-up and those remaining in the study were similar, although the latter were slightly younger, had higher educational level and fewer comorbidities. From these 2085 individuals, we further excluded 174 who either lacked information on frailty or were frail at baseline, 45 without complete data on anthropometry and 65 with missing information on potential confounders, leading to a final sample of 1801 participants.

Participants in the Seniors-ENRICA gave written informed consent. The Clinical Research Ethics Committee of the 'La Paz' University Hospital in Madrid approved the study.

TSHA

The original cohort was recruited between 2006 and 2009. It consisted of 2488 participants ≥65 years of age selected by two-stage random sampling from the municipal census of Toledo (Spain), covering both institutionalized and community-dwelling persons from urban and rural settings (17;18). Two home visits were performed to conduct computer-assisted interviews and a physical examination on 1972 participants. In a third stage, study participants went to their health center to provide blood samples. A new wave of data was collected from each individual after a mean follow-up of 3.5 years. Two hundred participants died during follow-up. From the

remaining 1772 participants who had undergone both the interview and physical examination, we excluded 211 participants who lacked information on frailty at baseline, 203 who were frail at baseline, and 69 without complete data on anthropometry or with missing information on any of the potential confounders. Thus, the analyses were conducted with 1289 individuals. Study participants provided written consent, and the study was approved by the Clinical Research Ethics Committee of the Hospital of Toledo.

Study variables

Anthropometry

At baseline in the two cohorts, weight, height and WC were measured in each subject. These measurements were performed using electronic scales (model Seca 841, precision to 0.1 kg), portable extendable stadiometers (model Ka We 44 444Seca) and flexible, inelastic belt-type tapes, respectively. Measurements were taken twice by trained staff under standardized conditions (19). Mean values of the two measurements were used for the analyses. BMI was calculated as weight in kg divided by square height in m. Normal weight was defined as BMI 18.5-24.9 kg/m^2, overweight as BMI 25-29.9 kg/m^2, and general obesity as $\geq$30 kg/m^2. Abdominal obesity was defined as WC >102 cm in men and >88 cm in women.

Frailty

In both cohorts, frailty was assessed at baseline and end of follow-up with a slight modification of the criteria proposed by Fried et al.[19] Individuals meeting three or more of the following five phenotypic criteria were considered as frail: 1) Self-reported exhaustion, defined as any of the following responses to two questions taken from the Center for Epidemiologic Studies Depression Scale[20]: *"I felt that anything I did was a big effort" or " I felt that I could not keep on doing things"* at least 3 to 4 days a week; *2)* Weight loss, defined as unintentional loss of ≥4.5 kg of body weight in the preceding year; 3) Low physical activity, defined as walking ≤2.5 h/week in men and ≤2 h/week in women in the Seniors-ENRICA, and the worst quintile in the PASE scale, adjusted for sex, in the TSHA (20); 4) Weakness, defined as the cohort-specific lowest quintile of grip strength measured with a Jamar dynamometer and adjusted for sex and body mass index (21). The highest value in two consecutive measures was used in the analyses; and 5) Slow walking speed, defined as the worst cohort-specific quintile in the three-meter walking speed test, adjusted for sex and height (22).

CRP and insulin resistance

In both cohorts, participants provided 12-h fasting blood samples. High sensitivity CRP was determined by latex-enhanced nephelometry. The Homeostasis model assessment (HOMA-IR) was used to evaluate insulin resistance using the formula: fasting serum insulin (µU/mL) X fasting plasma glucose (mg/dL) / 405. Glucose was measured by the glucose oxidase method, and insulin by immunoenzymatic assay.

Other variables

At baseline, self-reported information was obtained in the two cohorts on age, sex educational level, tobacco and alcohol consumption, and physical activity (using the EPIC-cohort questionnaire for activity at work and at leisure time in the Seniors-ENRICA, and the PASE scale in the TSHA). Participants also reported their drug treatment, which was checked by the study staff against drug packages at home. The Lawton-Brody index was used to ascertain limitations in instrumental activities of daily living (IADL); the questions on subjects' ability to prepare meals, do household chores, and care for clothing were excluded in men. The presence of limitation in at least one IADL was considered as disability. Lastly, participants were also asked if they suffered from any of the following physician-diagnosed diseases: cardiovascular disease (ischemic heart disease, stroke or heart failure), diabetes, cancer, asthma or chronic bronchitis, and osteo-articular disease (defined as osteoarthritis, arthritis or hip fracture in the Seniors-ENRICA, and as hip or knee osteoarthritis or arthritis in the TSHA).

Additionally, in the Seniors-ENRICA cohort, food consumption was assessed at baseline with a validated computerized diet history developed from that used in the EPIC-Spain cohort study, and energy intake was calculated with standard food composition tables (23). Adherence to the Mediterranean diet was summarized using the Mediterranean Diet Adherence Screener (MEDAS) index.

Statistical analysis

The association of BMI and WC with frailty was evaluated with odds ratios (OR) and their 95% confidence intervals (CI) obtained from logistic regression models with

progressive levels of adjustment. Model 1adjusted for sex, age and educational level; model 2 further adjusted for behavioral risk factors (tobacco and alcohol consumption, physical activity, diet quality and energy intake); model 3 additionally included chronic diseases and drug treatments, while model 4 also adjusted for WC (when BMI was the main independent variable) or BMI (when WC was the main independent variable). In a fifth step, models were further adjusted for CRP and HOMA-IR when this information was available (n=1770 in Seniors-ENRICA, and n= 858 in TSHA), to investigate the mediating role of these variables in the association between obesity and frailty.

To assess the joint and independent effects of overall and central obesity on the risk of incident frailty, we classified subjects into six groups according to categories of BMI (<25, 25-29, ≥30) and WC (≤102 and >102 in men, ≤88 and >88 in women). We then created a dummy variable with six categories and introduced it in a logistic regression model that contained the same adjustment variables as in model 3.

Next, we estimated the association between obesity and onset of each frailty criterion among robust adults (free of all five criteria) at baseline. Again these analyses were adjusted as in model 3 above.

Between-study heterogeneity was assessed using the DerSimonian-Laird-chi square based Q statistic and quantified using the I^2 statistic. Given that the results in the Seniors-ENRICA and TSHA were generally consistent (I^2<30%), they were pooled using random-effects meta-analysis as implemented in STATA using the *metan* command (24).

The following sensitivity analyses were performed. First, we stratified the results by age and sex. Second, we repeated the main analyses excluding the *weight loss* criteria from the definition of frailty and considering as frail those with ≥2 of the 4 remaining criteria. For this analysis we also excluded individuals with frailty at baseline according to the new definition. Finally, we studied the association of BMI and WC with risk of incident frailty after excluding individuals with limitation in IADL.

RESULTS

Tables 1 and *2* show the main socio-demographic, lifestyle and clinical characteristics at baseline, among the participants in the two study cohorts. Participants in the TSHA study were older, had lower educational level, were more frequently obese and presented a higher frequency of chronic diseases when compared to those in the Seniors-ENRICA. In both cohorts, women, participants with lower educational, as well as those diagnosed with diabetes or osteoarticular disease showed the highest prevalence of obesity, while current smokers and those diagnosed with cancer were more likely to be in the lowest categories of BMI and WC. PCR and HOMA-IR values increased from normal weight to obese.

During 3.5 years of follow-up, 125 individuals in the Seniors-ENRICA and 162 from the TSHA developed frailty. *Table 3* shows the main results of the study. After adjustment for the main potential confounders (model 3), a BMI under 25 was associated with an increased risk of frailty in the TSHA (OR: 1.69; 95%CI: 1.01-2.83) but not in the Seniors-ENRICA (OR: 0.85; 95%CI: 0.44-1.65). In both cohorts, general

and abdominal obesity were positively related to the risk of frailty. In model 3, the pooled OR for general obesity and risk of frailty was 1.73 (95%CI: 1.18-2.28). This association was attenuated when WC was included in the model, indicating that part of the association between BMI and frailty could be mediated through abdominal adiposity. An increased risk of frailty was also observed among individuals with abdominal obesity (pooled OR: 1.67; 95%CI: 1.09-2.25); this association was slightly reduced when accounting for BMI (OR: 1.61; 95%CI: 0.95-2.26). Adjustment for potential mediators (HOMA-IR and CRP) also attenuated the observed associations, so that the pooled OR for general obesity was 1.38 (95%CI: 0.86-1.90) and for central obesity was 1.62 (95% CI: 0.96-2.28). To analyze the percentage change in the magnitude of the ORs, we also calculated the pooled effects for model 4 after excluding participants with no information on potential mediators (data not shown in tables); and estimated that inclusion of HOMA-IR and CRP yielded a 6.8% and 1.2% change in the ORs for general and central obesity, respectively.

Stratification of participants by categories of BMI (<25/ 25-29.9/ ≥30) and WC (≤102 men, ≤88 women / >102 men, >88 women) showed that, compared to individuals in the lowest category of BMI and WC, the risk of frailty was highest among individuals with concurrent general and abdominal obesity (pooled OR: 2.55; 95%CI: 1.23-3.86) (*table 4*).

Table 5 shows the effect of obesity on the five components of the frailty syndrome. In both cohorts, the most common components were weak grip strength and low physical

activity, while unintentional weight loss was the least frequent component. Results from the pooled analyses showed that a BMI ≥30 was associated with an increased risk of exhaustion (OR: 1.66; 95%CI: 1.11-2.21), low physical activity (OR: 1.57; 95%CI: 1.08-2.05) and weakness (OR: 1.63; 95%CI: 1.22-2.05). With abdominal obesity, results were in the same direction, although only for weakness they showed statistical significance (OR: 1.46; 95%CI: 1.11-1.80). Unexpectedly, a BMI<25 was inversely associated with the risk of weakness in the Seniors-ENRICA (OR: 0.68; 95%0.48-0.97), but not in the TSHA cohort (OR: 1.71; 95%CI: 0.92-3.16).

Results from the sensitivity analyses are shown in Supplemental material, *tables S1-S2*. Some evidence of effect modification by age and sex was observed in the Seniors-ENRICA cohort: while the strongest effect of general obesity and frailty was seen among those aged ≤75, the association with WC was limited to women. Overall, the pooled-OR for the association between abdominal obesity and the risk of frailty in women was 2.26 (95%CI: 1.04-3.48). Finally, restriction of the analyses to those individuals with no limitation in IADL at baseline weakened the positive association with BMI<25, whereas it strengthened the association with general and abdominal obesity.

DISCUSSION

Results from the Seniors-ENRICA and TSHA cohort studies show that both general and abdominal obesity are associated with incident frailty in the elderly, and suggest an

independent association between obesity and risk of exhaustion, low physical activity and weakness.

Previous epidemiologic studies have explored the association between BMI and frailty. In 2005, a cross-sectional analysis on 599 community-dwelling women aged 70 to 79 from the Women´s Health and Aging Studies I (1992) and II (1994) first showed a positive link between obesity and frailty (8). That same year, data from 40,657 women aged 65 to 79 who participated in the Women´s Health Initiative and were followed-up for three years, confirmed that being overweight or obese increased the risk of frailty (9). Lately, a study based on 4732 participants ≥60 years from the Third National Health and Nutrition Examination Survey (NHANES) found that the prevalence of frailty was highest among people who were obese (BMI ≥30) and lowest among those who were underweight (BMI <18.5) (25). More recently, the effects of midlife obesity have been evaluated and results suggest that maintaining a healthy weight throughout life may contribute to prevention of frailty later in time (10;26).

Despite the emerging evidence linking obesity and frailty, the association between central obesity and risk of frailty has been largely unexplored, and only two previous studies partially addressed this issue. The first of these, which was based on 2826 participants from the Cardiovascular Health Study, showed a higher crude prevalence of central adiposity at baseline in individuals who developed frailty during follow-up (13). The second study, which used data from 3055 community-dwelling adults aged 65 years and older, showed a cross-sectional positive association between WC and frailty (11).

Our results confirm that WC predicts incident frailty, particularly among individuals with a BMI ≥30 kg/m^2 and among women.

Body composition changes with age, decreasing lean mass and increasing fat mass, and muscle fat infiltration (27). As a consequence, there is a likely an underestimation of adiposity by BMI, which is more pronounced with ageing (28;29), and is greater at lower BMI values (29). Data from the TSHA suggested an increased risk of frailty in individuals with a BMI <25, which has also been reported in previous studies (11), but was not confirmed in the Seniors-ENRICA cohort or in the III NHANES (25) . Although further research is warranted to better understand the relationship between BMI and frailty in normo- and under-weight individuals, differences in age between the studied cohorts (i.e individuals from the TSHA cohort were on average five years older than those from the Seniors-ENRICA) may contribute to the discrepancy in the observed results.

When the relationship between obesity and risk of each frailty component was assessed, a significant association was limited to the most common items: grip strength, low physical activity and exhaustion. An inverse relationship between obesity and grip strength in the elderly has been previously described (30;31), and is attributed to fat infiltration of the muscle secondary to obesity and obesity-related inactivity (32;33) . Conversely, studies evaluating the link between obesity and exhaustion are less common and generally investigate the inverse hypothesis, i.e., how vital exhaustion affects subsequent risk of obesity, with conflicting results (34;35). In contrast to the

existing literature (36;37), we did not find a positive association between obesity and walking speed.

A study on 2021 men and women ≥55 years from the population-based Health 2000 Survey in Finland previously explored the role of inflammation and insulin resistance as mediating factors in the association between obesity and hand grip strength (30). Similar to what we observed for frailty, adjustment for CRP and IR-HOMA resulted in a slight attenuation of the associations, suggesting that systemic inflammation and insulin-resistance exert only a modest physio-pathological influence on the risk of hand grip strength and frailty in obese individuals.

Strengths of this study include its prospective design and the consistency of the results across heterogeneous cohorts. Moreover, our results were robust to different sensitivity analyses and to adjustment for an extensive list of potential confounding factors. Limitations of this study should also be noted. First, the study results are limited by the sample size, particularly when evaluating the associations stratified by participants' characteristics. However, thanks to the consistency of the results, pooled estimates could be calculated, which increased the precision of the observed effects. Second, although we have information on many confounders, we cannot rule out some residual confounding due to comorbid conditions. Third, we cannot rule out the possibility that inflammation markers other than CRP (e.g., interleukin 6, leukocyte count, etc.) could mediate the association between obesity and frailty. This hypothesis should be investigated in the future. Finally, there is increasing evidence that obesity throughout

the life course is independently associated with the risk of certain frailty components, but we could not take into account the effect of early life anthropometric factors on the studied associations.

Several clinical trials have evaluated the effects of a combination of diet therapy and exercise in obese older adults (38-40). Results from these trials show that this strategy produces clinically significant reductions in body mass while improving physical function. Future research should assess whether appropriate interventions addressing obesity can reduce the risk of frailty and the subsequent disability.

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CONFLICT OF INTEREST:

The authors have no conflicts of interest to declare.

EGE, LMLM, FJGG, LRM and FRA conceived the study; LMLM, PGC, MGCH, ELG and ABC conducted the research; EGE and JAC performed the statistical analyses; EGE and FRA drafted the manuscript; all authors reviewed the manuscript for important

intellectual content; EGE and FRA had primary responsibility for final content. All authors read and approved the final manuscript

REFERENCES

(1) Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013 Mar 2;381(9868):752-62.

(2) Rodriguez-Artalejo F, Graciani A, Guallar-Castillon P, Leon-Munoz LM, Zuluaga MC, Lopez-Garcia E, et al. [Rationale and methods of the study on nutrition and cardiovascular risk in Spain (ENRICA)]. Rev Esp Cardiol 2011 Oct;64(10):876-82.

(3) Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014 May 28.

(4) Tucker JM, Tucker LA, Lecheminant J, Bailey B. Obesity increases risk of declining physical activity over time in women: a prospective cohort study. Obesity (Silver Spring) 2013 Dec;21(12):E715-E720.

(5) Bouchard DR, Dionne IJ, Brochu M. Sarcopenic/obesity and physical capacity in older men and women: data from the Nutrition as a Determinant of Successful Aging (NuAge)-the Quebec longitudinal Study. Obesity (Silver Spring) 2009 Nov;17(11):2082-8.

(6) Jensen GL, Hsiao PY. Obesity in older adults: relationship to functional limitation. Curr Opin Clin Nutr Metab Care 2010 Jan;13(1):46-51.

(7) Brown CJ, Flood KL. Mobility limitation in the older patient: a clinical review. JAMA 2013 Sep 18;310(11):1168-77.

(8) 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 Jun;53(6):927-34.

(9) Woods NF, Lacroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. J Am Geriatr Soc 2005 Aug;53(8):1321-30.

(10) Stenholm S, Strandberg TE, Pitkala K, Sainio P, Heliovaara M, Koskinen S. Midlife obesity and risk of frailty in old age during a 22-year follow-up in men and women: the Mini-Finland Follow-up Survey. J Gerontol A Biol Sci Med Sci 2014 Jan;69(1):73-8.

(11) 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 Apr;65(4):377-81.

(12) Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. Obes Rev 2013 Mar;14(3):232-44.

(13) Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, et al. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. Arch Intern Med 2007 Apr 9;167(7):635-41.

(14) Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity? Curr Opin Endocrinol Diabetes Obes 2012 Apr;19(2):81-7.

(15) Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest 2000 Aug;106(4):473-81.

(16) León-Muñoz LM, Guallar-Castillón P, López-García E, Rodríguez-Artalejo F. Mediterranean diet and risk of frailty in community-dwelling older adults. J Am Med Dir Assoc 2014;In press.

(17) Garcia-Garcia FJ, Carcaillon L, Fernandez-Tresguerres J, Alfaro A, Larrion JL, Castillo C, et al. A new operational definition of frailty: the frailty trait scale. J Am Med Dir Assoc 2014 May;15(5):371.

(18) Garcia-Garcia FJ, Gutierrez AG, Alfaro-Acha A, Amor Andres MS, De Los Angeles De La Torre Lanza, Escribano Aparicio MV, et al. The prevalence of frailty syndrome in an older population from Spain. The Toledo Study for Healthy Aging. J Nutr Health Aging 2011 Dec;15(10):852-6.

(19) World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. Technical Report Series, No. 854. Geneva, World Health Organization. 1995.

(20) Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 1993 Feb;46(2):153-62.

(21) Ottenbacher KJ, Branch LG, Ray L, Gonzales VA, Peek MK, Hinman MR. The reliability of upper- and lower-extremity strength testing in a community survey of older adults. Arch Phys Med Rehabil 2002 Oct;83(10):1423-7.

(22) Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994 Mar;49(2):M85-M94.

(23) Relative validity and reproducibility of a diet history questionnaire in Spain. I. Foods. EPIC Group of Spain. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26 Suppl 1:S91-S99.

(24) DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986 Sep;7(3):177-88.

(25) Smit E, Winters-Stone KM, Loprinzi PD, Tang AM, Crespo CJ. Lower nutritional status and higher food insufficiency in frail older US adults. Br J Nutr 2013 Jul 14;110(1):172-8.

(26) Strandberg TE, Sirola J, Pitkala KH, Tilvis RS, Strandberg AY, Stenholm S. Association of midlife obesity and cardiovascular risk with old age frailty: a 26-year follow-up of initially healthy men. Int J Obes (Lond) 2012 Sep;36(9):1153-7.

(27) Ritz P. Editorial: Obesity in the elderly: should we be using new diagnostic criteria? J Nutr Health Aging 2009 Mar;13(3):168-9.

(28) Pasco JA, Nicholson GC, Brennan SL, Kotowicz MA. Prevalence of obesity and the relationship between the body mass index and body fat: cross-sectional, population-based data. PLoS One 2012;7(1):e29580.

(29) Meeuwsen S, Horgan GW, Elia M. The relationship between BMI and percent body fat, measured by bioelectrical impedance, in a large adult sample is curvilinear and influenced by age and sex. Clin Nutr 2010 Oct;29(5):560-6.

(30) Stenholm S, Sallinen J, Koster A, Rantanen T, Sainio P, Heliovaara M, et al. Association between obesity history and hand grip strength in older adults--exploring the roles of inflammation and insulin resistance as mediating factors. J Gerontol A Biol Sci Med Sci 2011 Mar;66(3):341-8.

(31) Hulens M, Vansant G, Lysens R, Claessens AL, Muls E, Brumagne S. Study of differences in peripheral muscle strength of lean versus obese women: an allometric approach. Int J Obes Relat Metab Disord 2001 May;25(5):676-81.

(32) Cooper R, Hardy R, Bann D, Aihie SA, Ward KA, Adams JE, et al. Body Mass Index From Age 15 Years Onwards and Muscle Mass, Strength, and Quality in Early Old Age: Findings From the MRC National Survey of Health and Development. J Gerontol A Biol Sci Med Sci 2014 Mar 28.

(33) Marcus RL, Addison O, Kidde JP, Dibble LE, Lastayo PC. Skeletal muscle fat infiltration: impact of age, inactivity, and exercise. J Nutr Health Aging 2010 May;14(5):362-6.

(34) Bryant MJ, Stevens J, Truesdale KP, Mosley T, Chambless L. Obesity and vital exhaustion: analysis of the Atherosclerosis Risk in the Communities study. Obesity (Silver Spring) 2008 Jul;16(7):1545-51.

(35) Kuo SY, Lin KM, Chen CY, Chuang YL, Chen WJ. Depression trajectories and obesity among the elderly in Taiwan. Psychol Med 2011 Aug;41(8):1665-76.

(36) Sternfeld B, Ngo L, Satariano WA, Tager IB. Associations of body composition with physical performance and self-reported functional limitation in elderly men and women. Am J Epidemiol 2002 Jul 15;156(2):110-21.

(37) Woo J, Leung J, Kwok T. BMI, body composition, and physical functioning in older adults. Obesity (Silver Spring) 2007 Jul;15(7):1886-94.

(38) Manini TM, Buford TW, Lott DJ, Vandenborne K, Daniels MJ, Knaggs JD, et al. Effect of dietary restriction and exercise on lower extremity tissue compartments in obese, older women: a pilot study. J Gerontol A Biol Sci Med Sci 2014 Jan;69(1):101-8.

(39) Santanasto AJ, Glynn NW, Newman MA, Taylor CA, Brooks MM, Goodpaster BH, et al. Impact of weight loss on physical function with changes in strength, muscle mass, and muscle fat infiltration in overweight to moderately obese older adults: a randomized clinical trial. J Obes 2011;2011.

(40) Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, et al. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med 2011 Mar 31;364(13):1218-29.

Table 1.

Baseline characteristics of participants in the Seniors-ENRICA study by categories of body mass index (BMI) and waist circumference (WC). N=1801.

Main characteristics	BMI (Kg/m^2)			Waist circumference (cm)	
	<25 n=354	25-29.9 n=897	≥30 n=550	≤102 men ≤88 women n=778	>102 men, >88 women n=1023
Socio-demographic					
Male	39.8	52.5	47.6	56.2	42.7
Age	68.3 (6.6)	68.7	68.7	67.9 (6.3)	69.2 (6.3)
Educational level					
≤Primary	41.8	51.6	63.6	43.7	60.7
Secondary	27.7	25.8	21.6	29.3	21.5
University	30.5	22.6	14.7	27.0	17.8
Lifestyle behaviors/diet					
Smoking	62.4	54.8	58.9	54.9	59.6
Never	23.7	32.3	32.9	30.6	30.9
Former	13.8	12.9	8.2	14.5	9.5
Current					
Alcohol consumption					
Never	34.7	32.7	38.2	32.1	36.8
Former	8.5	8.1	8.0	7.2	8.9
Moderate drinkers[a]	52.5	50.4	43.5	53.3	45.2
Excessive drinkers[a]	4.2	8.8	10.4	7.3	9.2
Physical activity					
At work					
Non worker	53.1	59.3	56.5	60.4	54.8
Sedentary	12.1	10.5	16.9	11.3	13.9
Standing	33.9	28.5	25.1	26.7	29.9
Manual	0.8	1.7	1.5		
Recreational (MET)	24.4	22.0	19.5	24.5 (16.0)	19.6 (14.5)
Diet					
MEDAS (tertiles)[b]					
≤6 women; ≤7men	39.5	42.9	47.5	40.2	46.2
7-8 women; 8 men	34.7	32.4	32.2	33.0	32.6
≥9 women and men	25.7	24.6	20.4	26.7	21.1
Energy intake (kcal/day)	20.0 (5.5)	20.3	20.5	20.4 (5.5)	20.3 (5.8)
Morbidity					
Cardiovascular disease[c]	6.2	4.2	6.2	4.9	5.5
Diabetes	8.5	13.3	22.2	9.4	19.4
Cancer	2.5	2.0	1.1	2.3	1.5
Asthma or chronic bronchitis	6.8	7.6	8.2	5.5	9.2
Osteoarticular disease[d]	41.0	44.0	56.4	39.2	53.3
Number of drugs	1.4 (1.6)	1.8 (1.9)	2.5 (2.1)	1.5 (1.7)	2.2 (2.0)
C-reactive protein (mg/dl)[e]	0.3 (0.4)	0.4 (0.7)	0.5 (0.8)	0.3 (0.6)	0.4 (0.8)
HOMA-IR [f]	1.6 (1.3)	2.4 (3.2)	3.4 (2.7)	1.9 (1.8)	3.1 (3.4)

Data in tables are percentages for categorical variables and means (SD) for continuous variables.
[a] Moderate drinker: alcohol intake >0 to 20 g/day; excessive drinker: alcohol intake >20 g/day.
[b] MEDAS: Mediterranean Diet Adherence Screener (range 0-14)
[c] Self-reported ischemic heart disease, stroke or heart failure
[d] Self-reported osteoarthritis, arthritis or hip fracture

[e] Six participants had no information available; N=1795
[f] Nineteen participants had no information available; N=1782

Table 2.

Baseline characteristics of the participants in the Toledo Study on Healthy Aging by categories of body mass index (BMI) and waist circumference (WC). N=1289.

Main characteristics	BMI (Kg/m^2)			Waist circumference (cm)	
	<25 n=191	25-29.9 n=584	≥30 n=514	≤102 men, ≤88 women n=430	>102 men, >88 women n=859
Socio-demographic					
Male	49.7	47.6	31.9	66.3	29.3
Age	75.3 (5.9)	74.3 (5.4)	73.5 (4.7)	74.2 (5.4)	74.1 (5.2)
Educational level					
None	63.8	62.2	70.5	64.2	66.5
<Primary	16.5	18.3	17.2	16.4	18.2
≥Primary	19.7	19.5	12.3	19.4	15.3
Lifestyle behaviors/diet					
Smoking					
Never	85.9	87.4	93.6	81.7	93.0
Former	0.7	2.1	1.7	2.5	1.4
Current	13.4	10.5	4.7	15.8	5.6
Alcohol consumption					
Never	80.4	75.9	81.7	70.7	83.0
Former	0.5	1.2	1.6	1.6	1.1
Moderate drinkers	18.4	22.2	16.5	26.7	15.6
Excessive drinkers	0.7	0.7	0.2	1.0	0.3
Physical activity					
PASE score	77.52	77.25	78.19	81.33 (48.4)	75.83 (43.7)
Morbidity					
Cardiovascular disease[b]	13.2	12.2	15.8	14.0	13.6
Diabetes	17.9	18.3	19.5	16.1	20.5
Cancer	8.9	3.6	6.0	6.3	4.9
Asthma or chronic bronchitis	7.9	7.0	6.8	7.5	6.9
Osteoarticular disease[c]	22.2	29.2	39.5	21.6	37.7
Number of drugs	4.2 (2.9)	4.2 (2.9)	4.3 (2.8)	4.3 (2.8)	4.2 (2.8)
C-reactive protein (mg/dl)[d]	0.4 (0.5)	0.4 (0.6)	0.5 (0.5)	0.4 (0.4)	0.5 (0.6)
HOMA-IR[e]	1.7 (1.2)	2.4 (1.4)	3.1 (1.9)	2.0 (1.2)	2.9 (1.8)

Data in tables are percentages for categorical variables and means (SD) for continuous variables.
[a] Moderate drinker: alcohol intake >0 to 20 g/day; excessive drinker: alcohol intake >20 g/day.
[b] Self-reported ischemic heart disease, stroke or heart failure
[c] Self-reported hip or knee osteoarthritis or arthritis.
[d] Four hundred and thirty one participants had no information available; N=858
[e] Three hundred and thirty one participants had no information available; N=958

Table 3.

Association of body mass index (BMI) and waist circumference (WC) with risk of frailty during a 3.5-year follow-up of older adults.

Study cohort	BMI (kg/m2)			WC (cm)	
	<25	25-29.9	≥30	≤102 men, ≤88 women	>102 men, >88 women
Seniors-ENRICA					
Frailty; n events/total	14/354	47/897	64/550	24/778	101/1023
Model 1, OR (95% CI)	0.74 (0.39-1.39)	Ref.	**2.38 (1.57-3.60)**	Ref.	**2.65 (1.65-4.24)**
Model 2, OR (95% CI)	0.80 (0.42-1.55)	Ref.	**1.86 (1.20-2.88)**	Ref.	**2.17 (1.32-3.56)**
Model 3, OR (95% CI)	0.85 (0.44-1.65)	Ref.	**1.66 (1.06-2.60)**	Ref.	**1.93 (1.07-3.19)**
Model 4, OR (95% CI)	1.05 (0.51-2.17)	Ref.	1.42 (0.88-2.29)	Ref.	1.63 (0.88-3.01)
Model 5, OR (95% CI)	1.01 (0.51-1.99)	Ref.	1.57 (0.99-2.49)	Ref.	**1.68 (1.00-2.79)**
Toledo Study on Healthy Aging					
Frailty, n events	32/191	60/584	70/514	42/430	120/859
Model 1, OR (95% CI)	1.52 (0.93-2.51)	Ref.	**1.76 (1.18-2.63)**	Ref.	**1.70 (1.12-2.60)**
Model 2, OR (95% CI)	1.56 (0.94-2.57)	Ref.	**1.86 (1.23-2.80)**	Ref.	**1.65 (1.07-2.52)**
Model 3, OR (95% CI)	**1.69 (1.01-2.83)**	Ref.	**1.80 (1.19-2.74)**	Ref.	**1.56 (1.02-2.41)**
Model 4, OR (95% CI)	**2.47 (1.36-4.53)**	Ref.	**1.60 (1.03-2.47)**	Ref.	1.59 (0.96-2.64)
Model 5, OR (95% CI)	1.42 (0.70-2.90)	Ref.	1.21 (0.69-2.13)	Ref.	1.55 (0.85-2.81)
Meta-analysis (random effects)					
Failty, n events	46/545	107/1481	134/1064	66/1208	221/1882
Model 1, OR (95% CI)	0.96 (0.54-1.39)†	Ref.	**1.97 (1.38-3.56)**	Ref.	**1.93 (1.29-2.58)**
Model 2, OR (95% CI)	1.05 (0.58-1.51)†	Ref.	**1.86 (1.29-2.43)**	Ref.	**1.78 (1.17-2.39)**
Model 3, OR (95% CI)	1.11 (0.60-1.61) †	Ref.	**1.73 (1.18-2.28)**	Ref.	**1.67 (1.09-2.25)**
Model 4, OR (95% CI)	1.36 (0.62-2.09) †	Ref.	**1.51 (1.00-2.01)**	Ref.	1.61 (0.95-2.26)
Model 5, OR (95% CI)	1.14 (0.52-1.75) †	Ref.	1.38 (0.86-1.90)	Ref.	1.62 (0.96-2.28)

Categories of adjustment variables are as in table 1 for the Seniors-ENRICA cohort and as in table 2 for the Toledo Study on Healthy Aging.
Model 1: Adjusted for sex, age, and educational level.
Model 2: Adjusted additionally for tobacco and alcohol consumption, physical activity, diet quality (MEDAS) and energy intake (in the TSHE no adjustment made was made for MEDAS and energy intake)
Model 3: Adjusted additionally for cardiovascular disease, diabetes, cancer, asthma or chronic bronchitis, osteoarticular disease, and number of drug treatments
Model 4: Model 3 adjusted for WC (when BMI is the main independent variable) or BMI (when WC is the main independent variable).
Model 5: Model 3 adjusted for CRP and HOMA-IR. Model based on 1782 (Seniors-ENRICA) or 858 (Toledo Study on Healthy Aging) participants with this information available.
† $I^2 \geq 30\%$; Data should be interpreted with caution.

BMI: Body Mass Index; CI: Confidence interval; OR: Odds ratio; Ref: Reference; WC: Waist Circumference.

Table 4.

Odds ratio (95 % confidence interval) of frailty risk according to body mass index (BMI) and waist circumference (WC).

Study cohort	WC (cm)	BMI (kg/m^2)		
		<25	25-29.9	≥30
Seniors-ENRICA				
	≤102 men, ≤88 women	1.25 (0.52-2.98)	Ref.	NA[a]
	n events/total	13/446	11/307	0/25
	>102 men, >88 women	NA[a]	1.75 (0.97-3.54)	**2.46 (1.26-4.81)**
	n events/total	3/44	34/451	64/525
Toledo Study on Healthy Aging				
	≤102 men, ≤88 women	1.84 (0.86-3.91)	Ref.	NA[a]
	n events/total	23/163	16/236	3/31
	>102 men, >88 women	NA[a]	**2.13 (1.07-4.24)**	**2.65 (1.35-5.25)**
	n events/total	8/28	44/348	67/483
Meta-analysis (random effects)				
	≤102 men, ≤88 women	1.48 (0.53-2.44)	Ref.	-
	n events/total	36/609	27/543	
	>102 men, >88 women	-	1.90 (0.90-2.90)	**2.55 (1.23-3.86)**
	n events/total		78/799	131/1008

Analyses are adjusted as in model 3 in table 3. Categories of adjustment variables are as in table 1 for the Seniors-ENRICA cohort and as in table 2 for the Toledo Study on Healthy Aging.
[a]NA: Not calculated due to the small number of events in these categories (N<10).

BMI: Body Mass Index; Ref: Reference; WC: Waist Circumference.

Table 5.

Association of body mass index (BMI) and waist circumference (WC) with risk of each frailty criterion among robust older adults at baseline followed during 3.5 years.

Study cohort	BMI (kg/m^2)			WC (cm)	
	<25	25-29.9	≥30	≤102 men, ≤88 women	>102 men, >88 women
Seniors-ENRICA					
Exhaustion; n events/total	30/302	56/732	47/395	49/676	84/753
OR (95% CI)	1.34 (0.82-2.19)	Ref.	**1.66 (1.08-2.57)**	Ref.	1.31 (0.88-1.95)
Low physical activity; n events/total	32/302	89/732	70/395	75/676	116/753
OR (95% CI)	0.93 (0.59-1.46)	Ref.	**1.48 (1.03-2.14)**	Ref.	1.21 (0.86-1.70)
Slow walking speed; n events/total	43/300	84/728	47/391	78/671	96/748
OR (95% CI)	**1.57 (1.03-2.38)**	Ref.	0.91 (0.61-1.37)	Ref.	0.92 (0.65-1.31)
Weight loss; n events/total	20/298	47/725	32/392	38/671	61/744
OR (95% CI)	1.10 (0.62-1.93)	Ref.	1.09 (0.66-1.79)	Ref.	1.08 (0.68-1.69)
Weakness; n events/total	64/300	212/731	151/395	156/674	271/752
OR (95% CI)	**0.68 (0.48-0.97)**	Ref.	**1.56 (1.16-2.08**)	Ref.	**1.52 (1.17-1.98)**
Toledo Study on Healthy Aging (TSHE)					
Exhaustion; n events/total	11/96	43/344	54/273	22/254	86/459
OR (95% CI)	0.89 (0.43-1.86)	Ref.	**1.66 (1.04-2.64)**	Ref.	**2.18 (1.26-3.77)**
Low physical activity; n events/total	20/97	49/348	46/275	39/254	76/466
OR (95% CI)	1.56 (0.81-3.02)	Ref.	**1.84 (1.10-3.08)**	Ref.	1.54 (0.92-2.57)
Slow walking speed; n events/total	6/97	33/348	21/271	20/253	40/463
OR (95% CI)	NA[a]	Ref.	0.92 (0.49-1.73)	Ref.	1.07 (0.55-2.07)
Weight loss; n events/total	13/97	27/346	26/272	23/253	43/462
OR (95% CI)	1.65 (0.78-3.49)	Ref.	1.18 (0.65-2.15)	Ref.	0.90 (0.50-1.63)
Weakness; n events/total	20/97	46/341	54/273	41/250	79/461
OR (95% CI)	1.71 (0.92-3.16)	Ref.	**1.94 (1.22-3.10)**	Ref.	1.30 (0.82-2.08)
Meta-analysis (random effects)					
Exhaustion; n events/total	41/398	99/1076	101/668	71/930	170/1212
OR (95% CI)	1.12 (0.63-1.62)	Ref.	**1.66 (1.11-2.21)**	Ref.	1.44 (0.95-1.94)
Low physical activity; n events/total	52/399	138/1080	116/670	114/930	192/1219
OR (95% CI)	1.01 (0.61-1.42)	Ref.	**1.57 (1.08-2.05)**	Ref.	1.28 (0.90-1.65)
Slow walking speed; n events/total		117/1076	68/662	98/924	136/1211
OR (95% CI)	-	Ref.	0.91 (0.59-1.24)	Ref.	0.94 (0.64-1.25)
Weight loss; n events/total	33/395	74/1071	58/664	61/924	104/1206
OR (95% CI)	1.20 (0.61-1.79)	Ref.	1.12 (0.67-1.57)	Ref.	1.00 (0.62-1.38)
Weakness; n events/total	84/397	258/1072	205/668	197/924	350/1213
OR (95% CI)	**0.73 (0.49-0.97)**†	Ref.	**1.63 (1.22-2.05)**	Ref.	**1.46 (1.11-1.80)**

Analyses adjusted as in model 3 in table 3. Categories of adjustment variables area as in table 1 for the Seniors-ENRICA cohort and as in table 2 for the Toledo Study on Healthy Aging.
[a]NA: Data were not calculated due to the small number of events in these categories (N<10).
† $I^2 \geq 30\%$; Data should be interpreted with caution.