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

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

3

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51 **Abstract**

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

57 **Methods:** EPIDOS is a multicenter prospective cohort of community-dwelling women aged
58 75 and older recruited between 1992 and 1994. At baseline, we collected demographics,
59 BMI (<21 kg/m²: underweight; 21-24.9: normal weight; 25-29.9: overweight and ≥ 30:
60 obesity), frailty through Fried model, and clinical characteristics. All-cause mortality, falls
61 and hip fractures, and hospital admission were collected within 5 years of follow-up and
62 were analyzed using univariate and multivariate survival analysis by using Kaplan-Meier
63 methods and Cox Hazard Proportional models.

64 **Results:** Of 6662 women (mean age, 80.4 years), 11.6%; 95% Confidence Interval (95% CI)
65 CI [10.8%-12.3%] were frail. By multivariate analysis, the risk of death in frail women
66 (compared to not-frail normal weight women) decreases with increase of BMI: aHR_{frail-}
67 _{underweight}=2.04[1.23-3.39]; aHR_{frail-normal weight}=3.07[2.21-4.26]; aHR_{frail-overweight}= 1.83[1.31-
68 2.56]; aHR_{frail-obese}= 1.76 [1.15-2.70]; p<0.001). Frail overweight and obese women had a
69 significant lower risk of death than frail normal- weight women (p=0.004). Similar features
70 were found for fall risk and hip fracture and for not-frail women. The relative risks of
71 hospital admission for normal weight, overweight and obese frail women were similar (aHR
72 _{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],
73 respectively).

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

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

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99 **INTRODUCTION**

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

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

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

124 **METHODS**

125

126 **Study design and population**

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

131

132 **Baseline data collection**

133 *Assessment of frailty*

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

1391. Weight loss ≥ 4.5 kg from baseline to the end of the first study year;

1402. Exhaustion was approximated by a “bad” or “very bad” answer to the question “In general,
141 do you consider your current health very good, good, bad, or very bad?”;

1423. Weakness, i.e., mean grip strength on the left and right sides in the lowest 20% at baseline,
143 as measured using a dynamometer (Takei Ltd, Tokyo, Japan). Women were classified as frail
144 when grip strength was < 43 kPa;

1454. Low physical activity level, i.e., a “no” answer to two questions, “Do you regularly practice
146 sport or have a physical activity such as recreational walking, gymnastics, cycling,
147 swimming or gardening?” and “Do you do heavy housework on a regular basis, such as
148 vacuum cleaning or floor washing?”; and

1495. Slow walking speed, as measured during the baseline examination as the mean speed of two
150 6-meter walking tests, is defined by a walking speed ≤ 0.65 m/s for women ≤ 159 cm and
151 ≤ 0.76 m/s for women > 159 cm.

152 *Instrumental Activities of Daily Living*

153 The women were asked if they experienced difficulty in performing any of Lawton's
154 eight Instrumental Activities of Daily Living (IADL). Altered IADL was considered when \leq
155 $7/8$.

156 *Anthropometric measurements*

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

161 Waist circumference > 88 cm was defined as abnormal. To assess body composition,
162 dual-energy x-ray absorptiometry (DXA) was performed by trained technicians using QDR
163 4500 W Hologic machines (Hologic, Waltham, MA) calibrated daily at each center and
164 cross-calibrated across centers at regular intervals. Skeletal muscle mass (SMM) was
165 computed as the ratio of appendicular skeletal mass over height in meters squared. We used
166 two definitions of low SMM: < 5.45 kg/m², and SMM within the lowest quartile (< 5.80
167 kg/m² in our study). Sarcopenic obesity was defined by a SMM < 5.45 kg/m² or < 5.80 kg/m²
168 and a BMI ≥ 30 kg/m² (22,23). SMM data were available only for individuals recruited at the
169 Lyon and Toulouse centers.

170

171 *Demographic and socioeconomic factors*

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

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

176

177 **Follow-up**

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

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

183

184 **Statistical analysis**

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

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

189 Rates of death and of the other three outcomes within the 5 years of follow-up were
190 determined using Kaplan-Meier survival method and expressed per 100 person-years.

191 Factors associated with each of the four outcomes were identified using univariate Cox
192 models. The main variable of interest was the frailty/BMI composite leading to 8 categories:
193 underweight-not-frail (group 1); underweight-frail (group 2); normal weight-not-frail (group
194 3); normal weight-frail (group 4); overweight-not-frail (group 5); overweight-frail (group 6);
195 obese-not-frail (group 7); and obese-frail (group 8). The reference category was "group 3".

196 We built four multivariate Cox models based on the variables associated with *P* values < 0.20
197 by univariate analysis. Pairwise analyses were done to assess confounding factors, and

198 interactions were sought. A trend test was used to assess the potential gradient between the 4
199 categories of BMI and the different outcomes.

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

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

205

206 **RESULTS**

207

208 **Study population**

209 Among the 7598 women in the EPIDOS cohort, 936 were excluded because of missing
210 data for assessing the frailty variable, leaving 6662 women for the analysis. The
211 characteristics of the two groups, ie included vs excluded, were similar, except for age
212 (mean, 80 years versus 81 years, $P<0.037$), the higher level of education (15.7% versus
213 12.7% had graduated from high school or obtained a higher education, $P<0.001$), and the
214 functional status (median [quartile1-quartile3] IADL, 8 [7-8] versus 8 [7-8], $P=0.010$).

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

219 Compared to not-frail women, frail women were older, had a lower level of education,
220 lived less frequently alone, consumed less alcohol, had a higher BMI, had a lower level of
221 autonomy, had more comorbidities, took more medications, used more treatment with
222 hypnotics, psychoactive drugs, and cardiovascular drugs including antihypertensive agents,

223 had more fear of falling, had fallen more frequently in the last 6 months, had more often
224 been admitted in hospital in the last 12 months, and had more previous fractures. No subject
225 had sarcopenic obesity according to the definition 1 of sarcopenia and very few (0.4%)
226 according to definition 2 (Table 2).

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

232 **Death**

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

235 By univariate analysis, frailty was associated with death in the 4 BMI categories
236 (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
237 cHR_{group 8}=2.88[1.92-4.32]). The risk of death decreased with the increase of BMI (p for
238 trend=0.06). Other variables associated with death by univariate analysis were older age
239 (cHR_{per additional year}=1.15[1.13-1.17]); low educational attainment (cHR=1.43[1.14-1.78]);
240 number of comorbidities ≥ 2 (cHR _{≥ 2 vs. < 2} =1.22[1.00-1.49]); treatment with hypnotics
241 (cHR=1.22[1.03-1.45]), psychoactive drugs (cHR=1.25[1.01-1.54]), or cardiovascular drugs
242 including antihypertensive agents (cHR=1.69[1.39-2.06]); fear of falling (cHR=1.30[1.09-
243 1.54]); fall in the last 6 months (cHR=1.21[1.00-1.47]), hospital admission in the last 12
244 months (cHR=1.74[1.43-2.12]), low self-sufficiency (cHR_{IADL<8 vs. ≥ 8} =2.65[2.23-3.15).

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

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

250 *Secondary analyses*

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

255

256 **Falls**

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

259 By univariate analysis, frailty was associated with falls but not in the obese group
260 (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];
261 cHR_{group 8}=1.04[0.86-1.27]; respectively). The risk of fall decreased with the increase of
262 BMI (p for trend=0.10).

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

270 By multivariate analysis adjusted for age, educational level, living alone, smoking,
271 number of chronic comorbidities, treatment with hypnotics, psychoactive drugs, fear of
272 falling, fall in the last 6 months and previous fracture, frailty in underweight and normal-

273 weight women remained significantly associated with falling. Frail overweight and obese
274 women had a lower risk of fall, similar to not-frail women (Figure 2).

275 *Secondary analyses*

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

279

280 **Hip fractures**

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

283 By univariate analysis, frailty was associated with hip fracture but not in the obese
284 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-
285 3.92]; cHR_{group 8}=0.92 [0.40-2.11]). Other variables associated with hip fractures by
286 univariate analysis were older age (cHR_{per additional year}=1.12[1.09-1.15]), ≥ 2 daily medications
287 (cHR=1.33[1.00-1.78], use of hypnotics (cHR=1.65[1.31-2.08]), fear of falling
288 (cHR=1.78[1.41-2.26]), fall in the last 6 months (cHR=1.45[1.13-1.86], previous fracture
289 (cHR=1.55[1.23-1.95]), and low functional status (cHR_{IADL<8 vs. ≥ 8} =2.16[1.72-2.71]).

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

294 *Secondary analyses*

295 Frail overweight or obese women with a waist circumference ≤ 88 cm or a waist
296 circumference > 88 had similar risk of hip fracture compared to not-frail normal weight and

297 normal waist circumference women (aHR=0.80[0.32-1.98] and 1.20[0.78-1.85],
298 respectively).

299

300 **Hospital admission**

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

304 By univariate analysis, frailty was associated with hospital admissions in the 4 BMI
305 categories (cHR_{group2}=1.43[1.07-1.91], cHR_{group4}=1.74[1.44-2.11], cHR_{group6}=1.86[1.59-
306 2.17], and cHR_{group8}=1.73[1.42-1.2.12]). Other variables associated with hospital admission
307 by univariate analysis were older age (cHR_{per additional year}=1.02[1.01-1.03]); living alone
308 (cHR=1.17[1.09-1.26]); smoking (cHR=1.12[1.01-1.23]); alcohol use (cHR=0.92[0.85-
309 0.98]); ≥ 2 comorbidities (cHR=1.43[1.32- 1.55]); ≥ 2 daily medications (cHR=1.11[1.01-
310 1.22]); use of hypnotics (cHR=1.23[1.15-1.32]), psychoactive agents (cHR=1.19[1.09-
311 1.29]), or cardiovascular drugs including antihypertensive drugs (cHR=1.23[1.15-1.33]), fear
312 of falling (cHR=1.25[1.16-1.33]), fall in the last 6 months (cHR=1.19[1.10-1.28]), hospital
313 admission in the last 12 months (cHR=1.52[1.40-1.65]), previous fracture (cHR=1.13[1.06-
314 1.21]), and low functional status (cHR_{IADL<8 versus ≥ 8} =1.19[1.11-1.28]).

315 By multivariate analysis adjusted for age, living alone, smoking, number of chronic
316 comorbidities, number of treatment, use of hypnotics, cardiovascular drugs including
317 antihypertensive drugs, fear of falling, fall in the last 6 months, hospital admission in the last
318 12 months and previous fracture, frailty was associated with hospital admission in the
319 normal-weight, overweight, and obese categories compared to not-frail normal-weight
320 women with similar level of association strengths in the 3 categories (Figure 4).

321 **Secondary analyses**

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

326

327 **DISCUSSION**

328

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

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

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

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

358 Our findings are in line with earlier results in frail individuals showing lower mortality
359 among obese or overweight compared to normal-weight participants, after adjustment for
360 age, functional status, and comorbidities(30,32). First, the fat mass may provide an energy
361 reserve, to be mobilized against acute stress events like an acute illness. Second, obese
362 patients may present with symptoms and morbidities earlier, and therefore earlier medical
363 management. Another possible explanation is that frailty assessments based on Fried model
364 may overestimate frailty in older obese individuals: indeed, obese women have more
365 frequently ≥ 4.5 -kg weight loss and a slower gait speed, two criteria of the frailty Fried
366 model, leading to higher proportion of frail women in obese groups compared to others.
367 However, it is questionable that these two criteria are relevant frailty markers for obese
368 women. Accordingly, the ≥ 4.5 -kg weight loss criterion may spuriously result in better
369 outcomes in the obese and overweight groups, as losing this amount of weight would have
370 less impact than in thinner individuals. Similarly, obese individuals had lower speed walking

371 in mean therefore the cut-offs for defining low walking speed for identifying frailty in obese
372 individuals may be different compared to thinner. Studies using other measures of frailty,
373 such as the Rockwood Frailty Index, would be useful. Finally, selective survival bias may
374 lead to apparently better outcomes in overweight and obese individuals, as only individuals
375 who have not died from complications of their excess weight can be included in a study.

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

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

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

395 Our results may suggest that frailty, according to Fried model, may have greater
396 prognostic impact in underweight or normal weight women than overweight or obese
397 women. Thus, prevention and correction of frailty parameters may be particularly targeted to
398 frail underweight and normal-weight women. Our results may also suggest that Fried
399 definition had to be re-defined for assessing frailty in overweight and obese older adults.
400 Indeed, as previously stated, Fried definition may misclassify obese adults as frail whereas
401 they were not, leading to better outcomes. Is the loss of 4.5 kg a good cut-off for defining
402 frailty in obese older women? Similarly, is a cut-off of ≤ 0.65 m/s if the height is ≤ 159 cm and
403 ≤ 0.76 m/s if > 159 cm, adequate?
404 Our results suggest that overweight and obesity reduce the risks of clinical adverse events in
405 frail community-dwelling older women and that frailty definition through Fried model had to
406 be re-calibrated for overweight and obese individuals.

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409

410 **Conflict of Interest**

411 The authors declare no conflict of interest

412

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509

510 **FIGURES LEGENDS**

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

513 *adjusted for age, cardiovascular drugs including antihypertensive agents, hospital
514 admission in the last 12 months, functional status-

515

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

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

521

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

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

526

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

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

533