Original Article

Association of Obesity with Cognitive Impairment and Depression among Oldest Old Population having Frailty syndrome

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Abstract

Objectives: The objectives were to estimate prevalence of obesity among frail individuals aged ≥80 years and examine the association of obesity with cognitive impairment and depression among frail individuals aged ≥80 years. **Methods**: Two-hundred community-dwelling participants aged ≥80 years, were enrolled; 166 frail participants were further analyzed. Obesity and adiposity were determined by Body Mass Index (BMI), Waist Circumference (WC) and Body Fat Percentage (BF%). Cognitive impairment and Depression were assessed using Mini Mental State Examination (MMSE) and Geriatric Depression Scale (GDS-15). Frailty was assessed by Fried criteria. Chi-Square, t-test, trend-analysis and Logistic Regression (LR) were done. **Results**: Obesity among Frail individuals aged ≥80 years was 40% using BMI and 73.2% using WC. Obesity was inversely associated with cognitive impairment and depression among frail individuals. Severity of cognitive impairment and depression was lower among obese frail than non-obese frail. Trend-analysis showed decreasing cognitive impairment and depression with increasing BF%. On LR, obesity among frail individuals had inverse association with cognitive impairment and depression. **Conclusion**: Obesity among frail individuals aged ≥80 years was associated with lower odds of cognitive impairment and depression in our population. Positive effects of weight gain in oldest old frail individuals and development of cognitive impairment and dementia should be explored in further researches.

Keywords: Cognitive Impairment, Depression, Elderly, Frailty, Obesity

Introduction

Frailty is a clinical geriatric syndrome, described as marked vulnerability due to age-related decline in reserves and functions, compromising the ability to cope with every day work or acute stressors across multiple physiologic systems[1-3]. Frail individuals lose ability to tolerate stressful events and frailty results in adverse outcomes such as falls, mobility disabilities, cognitive impairment, depression, delirium, chronic illness and institutionalization[4-9]. Frail elders have higher rates of mortality compared to non-frail elders[9,10]. Some studies demonstrated that thin, weak and malnourished individuals acquire frailty in old age; this relationship is well studied, and indicates a conjoint effect leading to adverse outcomes among older adults[11-14]. However, recent literature raised alarming concerns about the relationship between physical frailty and obesity or adiposity among older individuals[15].

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Higher adiposity and loss of muscle are repetitively reinforcing; hence frailty can be markedly progressive in older individuals within overweight and obese range[16]. Frailty and Obesity both are associated with higher utilization of health services, frequent hospitalization, functional limitation, disability and early mortality among older individuals[17-23]. Obesity, a major public health problem, contributes to increased cardiovascular mortality and morbidity[24]. Obese elders also have higher odds of disability and poor physical functions[25]. It results in decreased muscle strength and reduced aerobic capacity[26], leading to reduced ability to perform physical tasks and increased injury[26-28]. Weight loss and exercise interventions improve physical functions among overweight or obese older individuals, indicating that excessive adiposity contributes to physical frailty, especially in presence of loss of muscle mass and lower muscle strength, thus, reducing physical activities and increasing metabolic instability in older individuals[11].

As elderly people are living longer globally, it's important to study interplay between age related chronic conditions in late life. Individuals ≥80 years of age (oldest old) have higher cognitive impairment and experience problems with recalling, remembering, learning, decision making, planning, judgement, language and focusing attention[29]. Being overweight or obese in midlife may be more detrimental to subsequent age-related cognitive decline than being overweight or obese at later stages of the lifespan[30]. A recently published research suggested that combined effect of frailty and cognitive impairment was a risk factor for mortality in oldest old individuals[31]. Depression frequently coexists with cognitive impairment and is highly prevalent in above 80 years of age. Both the conditions increase the odds of mortality[32-35], chronic morbidities and physical disabilities[36,37]. Available research indicates that physical frailty and obesity independently impact cognitive functions and depression, but there is no study available on the combined effect of frailty and obesity on the same outcomes, among oldest old (aged ≥80 years of age), especially from developing countries. The present study had two objectives: 1. To estimate prevalence of obesity among frail individuals aged ≥80 years (oldest old); and 2. To examine the association of obesity with cognitive impairment and depression among frail oldest old.

Materials and Methods

Two hundred community-dwelling individuals, seventy-six men and one hundred twenty-four women, aged 80 years and over, were included for this cross-sectional study. The individuals were randomly enrolled from Hyderabad, India, from 12 residential gated communities (population ranging from 1000 to 6000), located in different geographic location of the city. A list of households was prepared with the help of societies of the gated communities having at least one age-eligible subject in the household. The list of households was randomized using random number generator software. All eligible subjects agreeing to participate from the selected households were included in the study.

A trained investigator recruited and collected the data upon home visits after obtaining written informed consent in the participant's comfortable language. Questionnaires and forms were adapted and validated from large international longitudinal studies: Lifestyle Interventions and Independence for Elders (LIFE) and Mobility and Independent Living in Elders Study (MILES). The questions and forms were piloted in selected population and based on the results, they were structured for better understanding, while being culturally and geographically appropriate for our population. They were validated before final use. They included information on sociodemographic characteristics, chronic morbidities, medical history, physical functions, disabilities, depression, cognitive function, sleep and biomarkers.

Measurements

Overweight and Obesity

Using Body Mass Index (BMI) as a single marker of obesity is considered a poor indicator of health. Obesity in the elderly should be adjusted for body composition[38]. Body composition, which consists of body mass (skeletal muscle mass), fat mass, and fat-free mass, has been suggested to affect the central nervous system that controls cognition, motivation, and executive function[39]. Previous reports suggested various measurements of obesity i.e. Body Mass Index (BMI), Waist Circumference (WC), and Body Fat Percentage (FP)[40]. These three measures were used to describe obesity and its association with frailty among NHANES elderly population, the justification being that measuring adiposity using body fat (%BF) or central adiposity using waist circumference (WC) have greater diagnostic accuracy than traditional measures such as BMI[41]. BMI correlates with adiposity and is widely used and convenient metric for use in large population studies[42]. We therefore, used three measurements to ascertain overweight and obesity in this study: Body Mass Index (BMI) as per Asian-Pacific classification, Waist circumference (WC), and Body Fat Percentage (BF%).

According to the National Heart Lung and Blood Institute (NHLBI)[43], BMI is calculated as weight in kilograms divided by the square of the height in meters (kg/m^2) and is categorized into four categories according to the Asian-Pacific cutoff points: underweight (<18.5 kg/m^2), normal weight (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), and obese (≥ 25 kg/m^2)[44]. WC is a simple method to assess abdominal adiposity that is easy to standardize and clinically apply[45]. Individuals with WC measurements <94 cm in men and <80 cm in women were classified as normal weight, 94-101.9 cm in men and 80-87.9 cm in women were classified as overweight, and ≥102 cm in men and ≥88cm in women were classified as obese[46,47]. BF% was calculated based on Deunberg's formula[48] i.e.

- BF% of Men= (1.20 x BMI) + (0.23 x Age) − 16.2
- BF% of Women= (1.20 x BMI) + (0.23 x Age) − 5.4

Frailty Syndrome

We defined Frailty Syndrome using the phenotype approach of Fried and colleagues who operationally defined frailty as a predominant physical condition requiring the presence of 3 or more of the following 5 components: weight loss, exhaustion, weakness, slowness, and low physical activity[49,50].

Measurements of Frailty components

Slow walking was defined by, walk time taken to complete 4-meter walk, stratified by gender and height (gender-specific cutoff a medium height) (Table 1)[48].

Low grip strength was defined based on BMI, separately among men and women (Table 2)[48].

Low energy (exhaustion) was ascertained upon interview. A question was asked whether the person feels low energy and exhausted. Affirmative response was considered as low energy.

Unintentional weight loss was asked to the participants using a question whether they lost significant weight in past 12 months, followed by the question whether they were trying to lose their weight. If a participant answered the first question as "Yes" and second question as "No", then the participant was categorized as having unintentional weight loss.

Low Physical activity was measured by asking question whether the participant did any physical activity like playing sports, going to the gym, walking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, swimming (moderately strenuous chores excluding normal daily routine work). Participants replying "No" were considered to have low physical activity.

Cognitive function

We classified cognitive impairment and dementia based on Mini Mental State Examination (MMSE). The MMSE demonstrates moderately high levels of reliability. It has been reported to be internally consistent, with short term test-retest reliability in patients with dementia, as well as long term reliability in cognitively intact individuals. It has been shown to have construct validity, since it is moderately correlated with other dementia screening exams as well as measures of general cognitive abilities. The total score is useful in documenting cognitive change over time. Besides being routinely used in clinical practice, the MMSE has been used to assess cognition in epidemiological studies of dementia. There are 21 different items in 11 different tests, with scores ranging from 0 to a perfect score of 30[51]. We measured orientation, registration, attention and calculation, recall and language and praxis using Mini Mental State Examination (MMSE) scale[52]. Scores <24 were defined as cognitive function impairment; scores <21 were defined as dementia; scores between 24–30 implied no cognitive impairment; scores 18–23 as mild cognitive impairment; scores 0–17 as severe cognitive impairment[53].

Men	Cut-off Time to Walk
Height ≤173 cm	≥7 seconds
Height >173 cm	≥6 seconds
Women	
Height ≤159 cm	≥7 seconds
Height >159 cm	≥6 seconds

Table 1. Cut-off time for 4-meters walk based on height and gender.

Men	Cut-off for grip strength
BMI ≤24	< 29
BMI 24.1 – 26	< 30
BMI 26.1 – 29	< 30
BMI >28	< 32
Women	
BMI ≤ 23	< 17
BMI 23.1 – 26	<17.3
BMI 26.1 – 29	< 18
BMI > 29	< 21

Table 2. Cut-off for grip strength based on BMI and gender.

Depression

Depression was assessed using Geriatric Depression Scale (GDS 15-point scale). The 15-item Geriatrics Depression Scale (GDS-15) has been widely used for depression screening, and has been translated into multiple languages. The GDS-15 is a simplified version of the 30-item long form GDS version developed by Sheik and Yesavage in 1986. Both ICD-10 criteria and DSM-IV criteria have shown that the GDS-15 was valid for measuring mild and major depression. GDS-15 has a sensitivity of 92% and a specificity of 81% at a cutoff of 5. In a systematic review, the pooled sensitivity, specificity, and area under the ROC curve of the GDS-15 were 79%, 77%, and 0.84 among older adults[54]. For our population, the scores of 0-4 were considered normal; 5-8 as mild depression; 9-11 as moderate depression; and 12-15 indicated severe depression. Overall depression was categorized as score ≥5[55].

Statistical Analysis

Analysis for this paper was done using SPSS version 25 software (SPSS Inc., Chicago, IL, USA). Comparison of characteristics and outcome variables– Cognitive Impairment and Depression, were done among individuals having Frailty but no Obesity (Non-Obese Frail) and individuals having Obesity and Frailty (Obese Frail).

Characteristics	Men (N=61)	Women (N=105)	Total (N=166)	P value
Age, years (mean ± SD)	84.11 ± 4.18	83.19 ± 3.76	83.53 ± 3.93	0.14
Sex (%)	36.7	63.3	100	-
No Schooling (%)	43.3	57.1	52.1	0.06
Living Single (%)	39.3	78.0	63.9	<0.001
Not Currently working (%)	100.0	98.1	99.1	0.46
Difficulty in mobility (%)	100.0	100.0	100.0	-
Height, cm (mean ± SD)	161.70 ± 8.56	149.61 + 7.01	153 ± 9.56	<0.001
Weight, kg (mean ± SD)	56.95 ± 15.93	52.65 ± 16.50	54.19 ± 14.52	0.06
BMI, kg/m^2 (mean ± SD)	21.90 ± 4.22	23.10 ± 4.87	22.67 ± 4.67	0.10
Hip Circumference, cm (mean ± SD)	92.79 ± 11.14	97.56 ± 11.52	95.85 ± 11.58	0.01
Waist Circumference, cm (mean ± SD)	88.79 ± 13.42	85.50 ± 13.14	86.00 ± 13.30	0.12
Waist Hip ratio (mean ± SD)	0.93 ± 0.13	0.87 ± 0.01	0.89 ± 0.11	0.002
Body fat percentage (mean ± SD)	29.82 ± 5.05	41.42 ± 5.42	37.04 ± 7.72	<0.001
Cognitive Impairment (MMSE)(%)	59.0	76.2	69.9	0.01
Depression (GDS)(%)	49.2	63.8	58.4	0.04
Hypertension (%)	78.7	78.1	78.3	0.54
Diabetes (%)	23.0	20.6	21.5	0.43
Cardiovascular diseases (all) (%)	90.2	90.5	90.4	0.57
BMI = Body Mass Index; MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale.				

Table 3. Characteristics of the study population.

Obese Frail	Men (%) (N=61)	Women (%) (N=105)	Total (%) (N=166)	P value	OR (95%CI)
Obese Frail (%) (BMI ≥23)	40.9	41.9	40.3	0.42	1.12 (0.58-2.16)
Obese Frail (%) (WC: Men ≥94 cm; Women ≥ 80 cm)	76.3	71.4	73.2	0.31	0.77 (0.37 – 1.62)
BMI = Body Mass Index; WC = Waist circumference.					

Table 4. Prevalence of Obese Frail among study population.

Obese Frail	Obese Frail by Age group			
	80 to 84 (%)	85 to 89 (%)	90 and above (%)	P value
Obese Frail (%) (BMI ≥23)	51.0	28.6	15.8	0.001
Obese Frail (%) (WC: Men ≥94 cm; Women ≥ 80 cm)	80.4	64.3	52.3	0.004
BMI = Body Mass Index; WC = Waist circumference.				

Table 5. Prevalence of Obese Frail among study population by different age groups.

Variables	Men (N=61)				Women (N=105)				Total (N=166)			
	Non-Obese Frail n=36	Obese Frail n=25	P Value	OR (95%CI)	Non-Obese Frail n=61	Obese Frail n=44	P Value	OR (95%CI)	Non-Obese Frail n=97	Obese Frail n=67	P Value	OR (95%CI)
Obesity measured by Body Mass Index (BMI ≥23)												
Cognitive Impairment (%)	72.2	34.8	0.005	0.20 (0.06-0.63)	85.2	63.6	0.01	0.30 (0.11-0.77)	84.4	53.7	<0.001	0.28 (0.14-0.56)
Depression (%)	66.7	26.1	0.003	0.17 (0.05-0.56)	75.4	47.7	0.003	0.29 (0.13-0.68)	72.2	40.3	<0.001	0.26 (0.13-0.50)
Cognitive function (mean ± SD)	16.66±8.78	23.69±7.99	0.003	-	15.24±7.20	20.70±6.31	<0.001	-	15.77±7.81	21.73±7.02	<0.001	-
Depression (mean ± SD)	8.33±4.80	5.00±4.50	0.009	-	9.57±4.48	7.25±4.83	0.01	-	9.11±4.62	6.47±4.80	<0.001	-
Obesity measured by Waist Circumference (WC: Men ≥94 cm; Women ≥80 cm)												
Variables	**Non-Obese Frail n= 16**	**Obese Frail n=45**	**P value**	**OR(95%CI)**	**Non-Obese Frail n=30**	**Obese Frail n= 75**	**P value**	**OR (95%CI)**	**Non-Obese Frail**	**Obese Frail**	**P value**	**OR (95%CI)**
Cognitive Impairment (%)	68.3	33.3	0.01	0.23 (0.07-0.75)	90.0	70.7	0.02	0.26 (0.07-0.97)	90.9	61.7	<0.001	0.16 (0.05-0.54)
Depression (%)	61.0	27.8	0.01	0.24 (0.07-0.82)	80.0	57.3	0.02	0.33 (0.12-0.91)	75.0	53.3	<0.009	0.38 (0.17-0.82)
Cognitive function (mean ± SD)	14.12±6.03	21.17±9.16	0.001	-	14.00±6.67	18.94±7.13	0.001	-	14.04±6.39	19.78±7.99	<0.001	-
Depression (mean ± SD)	6.62±4.92	7.04 4.91	0.77	-	9.93±4.64	8.06±4.72	0.06	-	8.78±4.95	7.68±4.80	0.19	-

BMI = Body Mass Index; WC = Waist circumference.

Table 6. Proportion of individuals with Cognitive Impairment and Depression among Obese Frail and Non-Obese Frail.

Chi square (x^2) test for categorical variables and t test for continuous variables were used to determine associations. Body Fat% quartiles were calculated for men and women separately. The associations between Body Fat% and cognitive impairment and depression were assessed among both sexes. 95% confidence intervals were reported. P<0.05 was considered significant.

Logistic regression was performed to calculate odds ratio (OR) and 95% confidence interval (95%CI) of Cognitive impairment and Depression with Obesity among Frail individual using step wise backward logistic regression, adjusting to age, sex, education, hypertension, diabetes and cardiovascular diseases. Post-hoc-Power of the study was calculated as 99.1%.

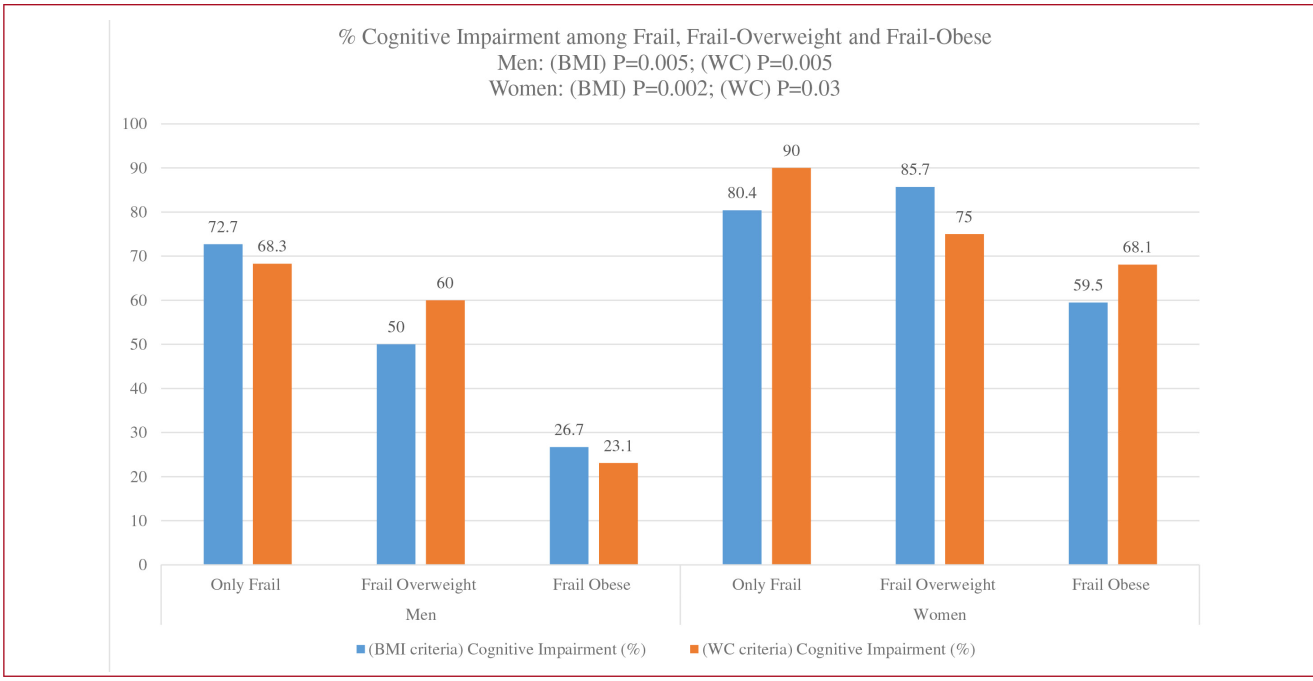

Figure 1. Proportion of Cognitive impairment among Frail, Frail-Overweight and Frail-obese Men and Women.

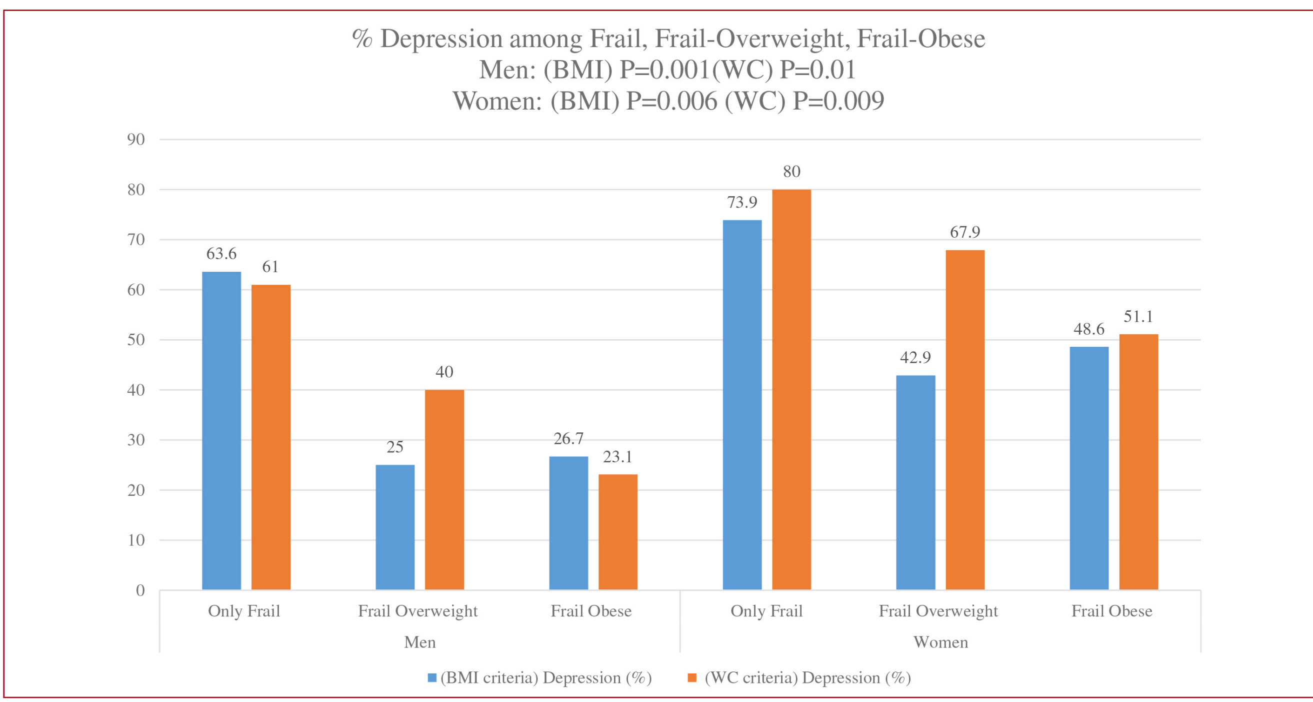

Figure 2. Proportion of Depression among Frail, Frail-Overweight and Frail-Obese Men and Women.

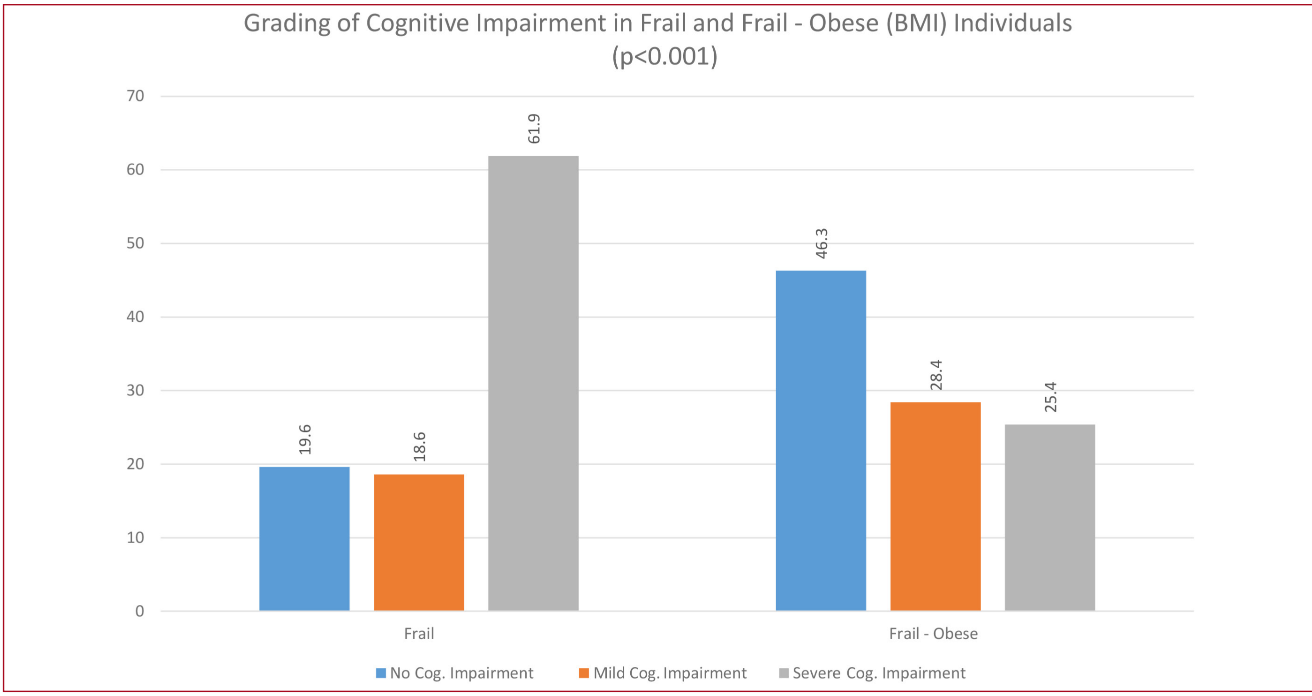

Figure 3. Grading of Cognitive impairment by Frail and Frail-Obese individuals.

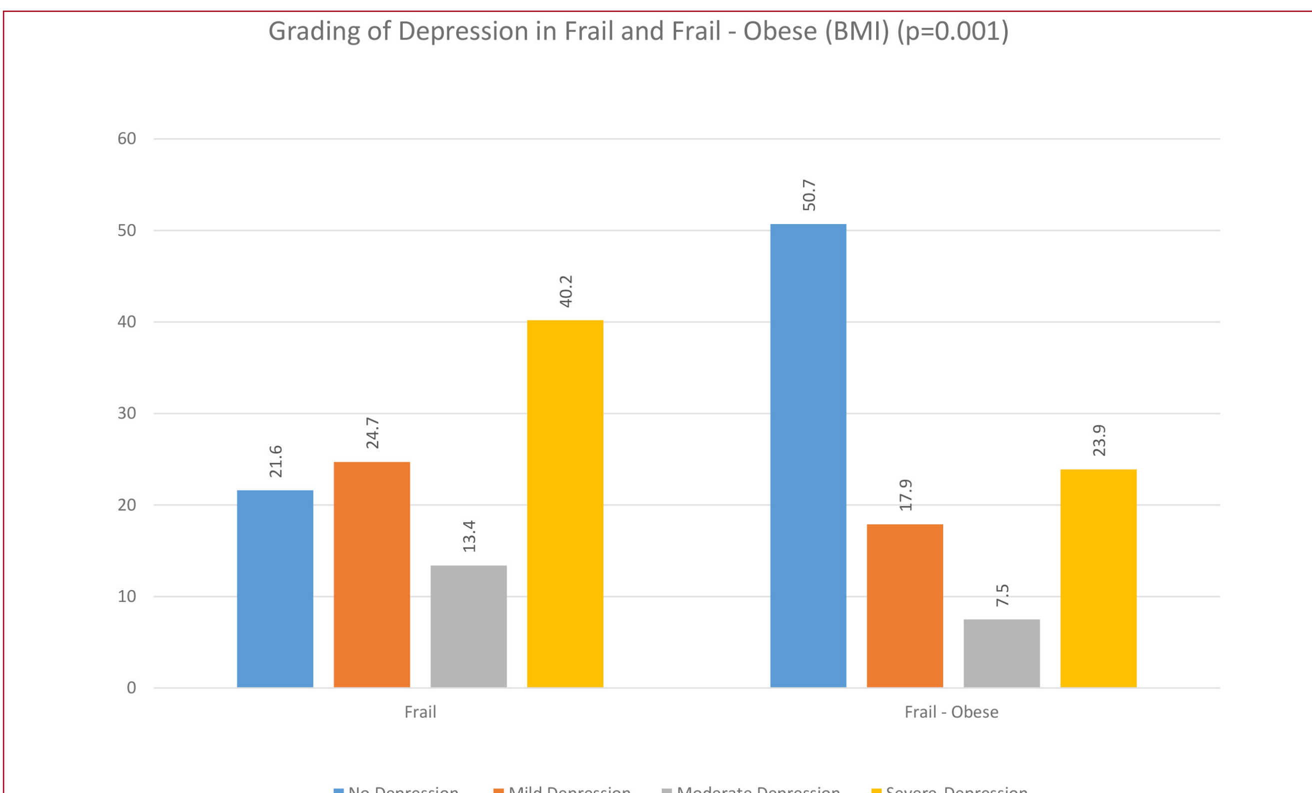

Figure 4. Grading of Depression among Frail and Frail-obese individuals.

Variable	Cognitive Impairment		Depression	
	Odds Ratio (OR)	95% Confidence Interval (95%CI)	Odds Ratio (OR)	95% Confidence Interval (95%CI)
Obese Frail (BMI)*	0.42	0.19 – 0.96	0.29	0.14 – 0.60
Obese Frail (WC)*	0.25	0.07 – 0.83	0.38	0.16 – 0.89
Obese Frail (Body fat %)**	0.93	0.86 – 1.00	0.92	0.87 – 0.98

**Adjusted with age, sex, education, hypertension, diabetes and cardiovascular diseases. **Adjusted with age, sex, hypertension, diabetes and cardiovascular diseases. BMI=Body mass index, WC= Waist circumference*

Table 7. Logistic regression to predict odds of Cognitive Impairment and Depression with Obesity among Frail individuals.

Results

In our previously published paper we investigated the prevalence of frailty in the same population and prevalence of frailty was found to be 83% (95%CI: 0.77–0.87) among oldest old individuals[50], i.e. 166 participants out of 200 study participants had frailty. For this paper, we took a Cohort of these 166 frail individuals and compared characteristics and outcomes between "frail obese" individuals and "frail non obese" individuals. Among 166 frail participants, 36% (95%CI: 0.29–0.44) were men and 64% (95%CI: 0.55–0.70) were women. The mean age of the study participants was 83.53±3.93 years, with men 84.11±4.18 years and women 83.19±3.76 years; 52.1% individuals never attended school; none of them were currently working and 63.9% individuals were living single. Significantly higher number of women were living without their spouses ($p<0.001$). Anthropometric measurements showed that men were taller in our study and BMI was higher among women. Waist and hip circumferences were found to be higher among men than women ($p=0.002$). Cognitive impairment was reported among 69.9% (95%CI: 0.62–0.76) individuals, higher among women than men ($p=0.01$) and depression was present among 58.4% (95%CI: 0.50–0.66) individuals, more among women than men ($p=0.04$) (Table 3).

Table 4 shows the prevalence of Obesity among Frail individuals. It was found that 40% (95%CI: 0.32–0.47) of the frail individuals had obesity, using Asian-pacific BMI criteria; 73.2% (95%CI: 0.66–0.80) were found obese using WC cut-offs for men and women. Proportion of Obese Frail were similar among men and women. Obesity significantly declined among frail individuals with increasing age (BMI: $p=0.001$; WC: $p=0.004$) (Table 5).

Table 6 shows that frail-obese individuals, both men and women, had significantly lower proportions of cognitive impairment as well as depression compared to only frail individuals, using both BMI and WC measurements.

Figure 1 and 2 showing the stratified analysis by only frail, frail-overweight and frail-obese with cognitive impairment and depression, reported, that with increasing obesity, cognitive impairment and depression decreased significantly ($p<0.001$) among both men and women. Further analysis with grading of cognitive impairment showed that severe cognitive impairment was higher among only frail individuals than frail-obese individuals ($p<0.001$) (Figure 3). Analysis with grading of depression among frail and frail-obese showed that significantly higher proportions of frail-obese individuals reported no depression; conversely, only frail individuals reported higher proportions of moderate depression ($p=0.001$) (Figure 4).

Lowest fat percentage quartile showed highest cognitive impairment and depression, while the highest quartile had lowest cognitive impairment and depression (Figures 5A, 5B, 6A, 6B) in both sexes. Trend analysis among women suggested a steady decline in cognitive impairment ($p=0.03$) (Figure 5B) as well as depression ($p=0.01$) (Figure 5A) with increase in BF%, similar trend was observed among men for cognitive impairment ($p=0.006$) and depression ($p=0.001$) (Figures 6A, 6B).

Logistic regression analysis showed that presence of obesity or adiposity among frail oldest old individuals was negatively associated with development of cognitive impairment and depression (Table 7).

Discussion

The present study reported a negative association for objectively measured cognitive impairment as well as depression with presence of obesity among frail oldest old individuals. The result did not change with either method (BMI, WC) of obesity measurement. Severe cognitive impairment was reportedly lower among those frail individuals having obesity, compared with non-obese frail. Moderate depression, similarly, was higher among non-obese frail individuals.

In our cohort of Frail oldest old (≥80 years) individuals, 40% had obesity using BMI criteria and 72% using WC cut-offs. The distribution of Obesity was similar among frail men and women. A study from Spain among 1,765 community dwelling participants aged 65 to 97 years reported prevalence of obesity among frail to be 4%, higher

Figure 5. A) Association of Body fat % with Depression among Women B) Association of Body fat % with Cognitive Impairment among Women.

among women (10.2%) than men (2.6%) and increasing with age above 75 years[56]. Prevalence of obesity among frail individuals in our study was relatively higher than reported in above study. We found a dearth of studies reporting prevalence of obesity among frail oldest old individuals, thus limiting further comparisons.

In our study, obesity measured by WC was higher than with BMI. It is debatable whether WC is a better measurement of obesity or BMI in older ages, which may be explored in further research. Use of multiple obesity measurement criteria has been done in earlier researches. For instance, Crow and associates used three measurements, ie BMI, waist circumference and body fat% to describe obesity and its association with frailty among NHANES elderly population.

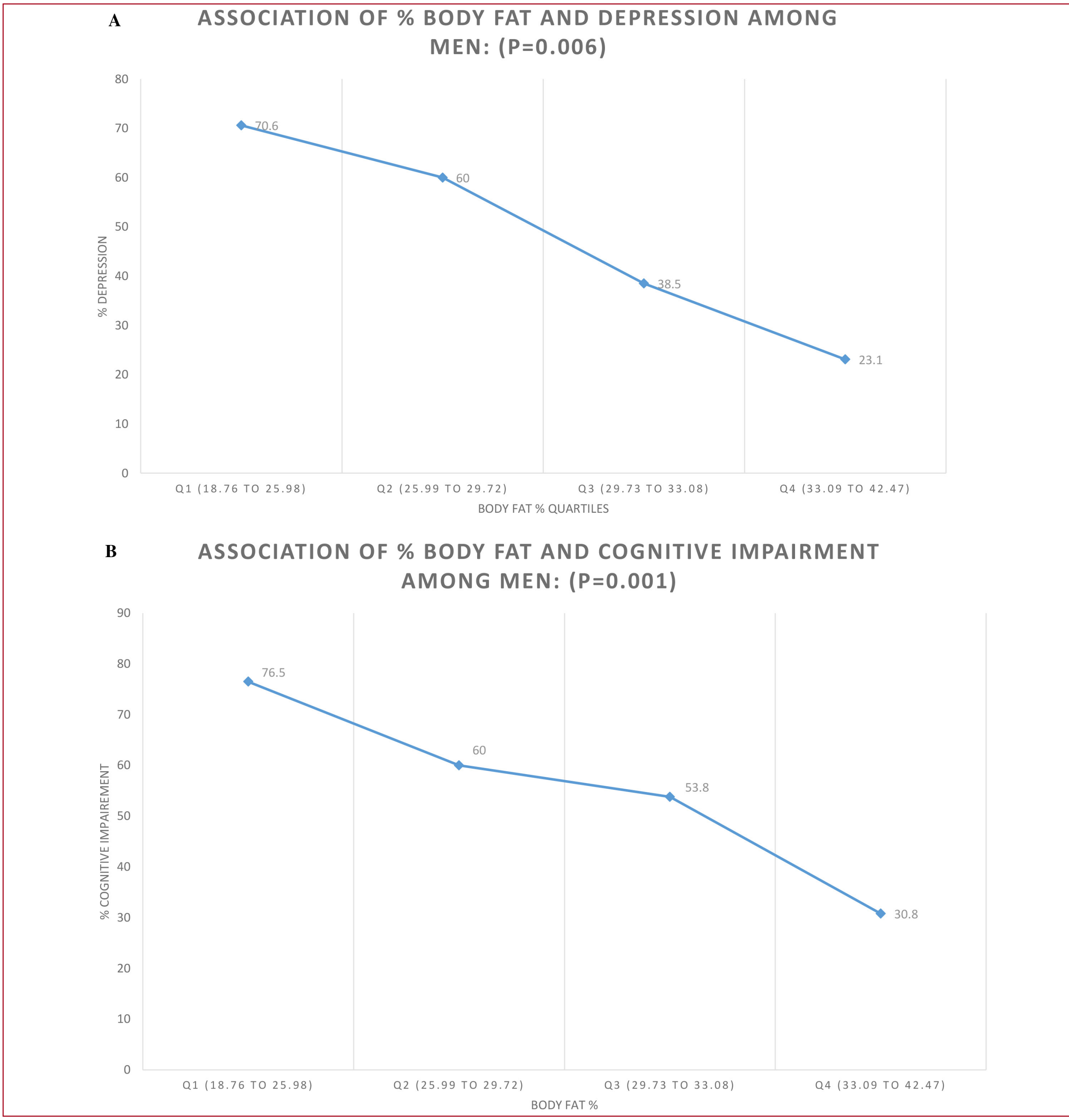

Figure 6. A) Association of Body fat % with Depression among Men B) Association of Body fat % with Cognitive Impairment among Men.

They suggested that measuring adiposity using body fat (%BF) or central adiposity using waist circumference (WC) have greater diagnostic accuracy than traditional measures such as BMI. The present study also used three classifications considering the fact that BMI alone may not be the only appropriate representation of obesity in older ages. Obesity was found to be negatively associated with cognitive impairment and depression using both BMI and WC criteria. Our results suggested that highest BF% quartiles among frail individuals in late life having obesity were associated with lesser cognitive impairment and depression in both sexes, compared with the lowest.

Obesity and Frailty

How do frailty and obesity exist in the same ageing individual? Ageing is associated with an increase in chronic systemic inflammation[57]. Many obese elderly individuals have impaired physical function associated with increased chronic inflammatory response[58-60]. Obesity too, induces chronic inflammation[59] and, thus, may further contribute to age-related increase in production of inflammatory cytokines. Indeed, sarcopenic obesity is associated with increased levels of circulating inflammatory markers[61,62], thus suggesting that obesity and ageing might be linked. Inflammatory cytokines have direct catabolic effects on skeletal muscle: TNF-α impairs muscle protein synthesis[63,64] and increases muscle protein degradation[65]; IL-6 too, increases muscle protein degradation[66]. High plasma concentrations of TNF-α and IL-6 are associated with lower muscle mass or strength and mobility disability[67-69], thereby contributing to sarcopenic obesity.

Age-associated increase in oxidative stress markers, accumulation of oxidative damage, and systemic inflammation is well reported. An alternative theory suggests oxidative stress and related inflammation cause cellular and molecular damage when reactive oxygen species (ROS) overwhelm antioxidant defenses, leading to progressive deleterious changes[70]. According to another theory, excessive adipose stores triggers activation of numerous stress pathways, including those increasing oxidative stress, through cellular milieu remodeling. Adipocytes release more ROS and pro-inflammatory cytokines during over nutrition, leading to a continuous state of "*simmering*" inflammation. Thus, the net effect of inflammatory cascade of obesity coupled with age-related inflammation is highly detrimental to muscle, resulting in increased catabolism and blunted anabolism[71]. Muscle weakness, slowed movement, exhaustion, and difficulty with mobility severely limiting ability of obese older adults to perform physical functions essential for maintaining their independence, in other words Frailty[11], result from reduced lean mass due to increased catabolism and direct muscle damage resulting from elevated ROS.

The impact of adiposity in both, ageing and obesity, lies in their association with morphological changes resulting from increased deposition of lipid within muscle fibers. Age-related lipid infiltration contributes to frailty by reducing muscle strength[72]. Obesity is also associated with a marked increase in lipid accumulation within muscle fibers[73]. This lipid infiltration decreases muscle density and precipitates a loss of muscle strength independent of changes in muscle mass[74].

Obesity and Cognitive function

Obesity-associated systemic inflammation leads to inflammation within brain, particularly hypothalamus, leading to cognitive impairment. Obesity leads to systemic inflammation and excess circulating fatty acids. These circulating free fatty acids, cytokines, and immune cells reach hypothalamus and initiate local inflammation, to cause synaptic remodeling and neurodegeneration within hypothalamus, thus, altering internal hypothalamic circuit and hypothalamic outputs to other brain regions. Central inflammation is also likely to affect these regions directly. Thus, central inflammation in obesity leads to disruption of hypothalamic satiety signals inducing urge of over eating, and also yields negative outcomes on cognition[75-77]. In other words, obesity and cognitive impairment are directly linked. Conversely, *obesity paradox* has also been reported wherein late life obesity was associated with lower cognitive impairment risk, whereas obesity in midlife was associated with higher cognitive impairment risk. Earlier studies in elderly suggested that individuals with low BMI and those who are losing weight had a higher risk of dementia and showed more rapid cognitive decline[78-80].

Since our findings were concordant to obesity paradox theory, we researched the mechanisms for plausibility. The proposed mechanisms for reverse causation in obesity paradox are: 1. Weight loss is in conjunction with assorted criteria of frailty wherein frailty is associated with diminished cognitive function performance[81]. 2. Excess body weight provides more energy savings and stronger inflammatory response that could benefit to encounter acute illness[82]. 3. Few neuroimaging studies in dementia patients with Alzheimer's disease (AD) found that higher BMI was associated with greater volume of medial temporal cortex indicating better cognitive performance[83]. 4. Associations of higher BMI in older individuals having AD with higher glucose metabolism in the anterior cingulate gyrus and hypothalamus were also reported, related to better cognitive function[84]. 5. An additional explanation proposed that higher BMI in late-life individuals preserved functional brain connectivity, serving as neuroprotection for cognition(85). Nevertheless, the exact mechanism for inverse association of obesity with cognitive impairment in elderly individuals in our study remains unknown.

Obesity and Depression

Evidence of a biological link between overweight, obesity, and depression is complex and bidirectional. Obesity can be seen as an inflammatory state, as weight gain has been shown to activate inflammatory pathways and inflammation in turn has been associated with depression[86-89]. Because inflammation plays a role in both obesity and depression, inflammation could mediate the association. Also, obesity might cause hypothalamic-pituitary-adrenal axis (HPA axis) dysregulation[90,91], well known to be involved in depression[92], thus causing development of depression. Obesity involves increased risks of diabetes mellitus and increased insulin resistance[93], which could induce alterations in brain and increase risk of depression[94]. In addition to biological mechanisms, psychological pathways need mention. Being overweight or its perception increases psychological distress. Obesity has been implicated in increased body dissatisfaction and decreased self-esteem, which are risk factors for depression[95,96] in some communities. Disturbed eating patterns, or experiencing physical pain as a direct consequence of obesity, are also known to increase risk of depression[97,98]. Obesity and Depression show bidirectional relationship; obesity increased the risk of depression and vice-versa in prospective studies.

Frailty and Cognitive Function

Frailty and cognitive impairment share pro-inflammatory cytokines such as IL-6, TNF-alpha, IL-18 and IL-1-beta, and associated genetic variants that influence the production of circulating proteins for both physical frailty and cognitive decline. Chronic inflammation theories such as "inflammaging"[99] provide a basic framework for shared pathogenesis of cognitive impairment and physical frailty, implicating low-grade chronic inflammatory markers and vascular inflammatory processes related to atherosclerosis and cerebral small vessel disease leading to cognitive frailty, corroborated by a study findings as well[100]. Age is a common risk factor for the development of both cognitive impairment and frailty. Chronic inflammation, nutrition, vascular diseases, depression and endocrinological disorders have additionally been implicated in both[101-104].

Frailty and Depression

Frailty and depression are common health problems the elderly face and may be associated. It is not clear if the depression facilitates the appearance of frailty syndrome or vice versa or these two coexist independently in the same individuals. A review on relationship of depression and frailty in later life suggests that depression and frailty might be bi-directionally related[105,106]. On one hand, severely depressed patients are frailty prone by life-style factors associated with depression i.e. inactivity and medication non-compliance, and depression-associated physiological disturbances[107]. Frailty may result in depressed state due to its association with chronic diseases and functional limitations. At population level, depression is more strongly associated with consequences of chronic disease than with the disease[108]. Furthermore, both frailty and depression have common underlying processes. Low-grade inflammation, for instance, is reported as underlying mechanism of both frailty[109] and late-life depression[88,89].

Strengths and Limitations

The main limitation is the cross-sectional design of the present study wherein, the cause-effect relationship between obesity among frail ageing population and cognitive impairment and depression couldn't be established. Furthermore, the authors could not rule out the possibility of recall bias wherever retrospective history was enquired. One component of frailty index i.e., unintentional weight loss, which was based on history, might have led to some inflations in our reporting of frailty. The strengths are use of three measurements of obesity and adiposity among study population for defining obesity; and objective measurement of outcomes.

Conclusion

In our study of oldest old individuals, prevalence of obesity among frail individuals was 40% and 73.2% using BMI and WC measurements respectively. Obesity decreased among frail individuals with increasing age in both sexes. Cognitive Impairment and Depression, overall as well as severe, were significantly lower among Obese Frail individuals compared to Non-Obese Frail, irrespective of obesity and adiposity measurements. Obesity among frail individuals was inversely associated with cognitive impairment and depression among both sexes. Our finding of higher obesity using WC and BF% measurements compared to BMI indicate disparities in obesity measurements, warranting further research to evaluate the appropriate measurement of overweight and obesity among older individuals.

This research creates opportunities for further longitudinal researches aimed at exploring relation of increasing fat percentage among frail individuals with cognitive impairment or depression in late life which could prevent or delay the onset of late life depression and dementia.

Ethics approval

This study was approved by the ethics committee of Mediciti Institute of Medical Sciences, Hyderabad and Indian Council of Medical Research, New Delhi.

Authors' contributions

Study design: GA, SSR, PKS and EG. Data collection and processing: BMR and PKS. Data analysis: GA, SSR, BMR and PKS. Data interpretation: GA, SSR, PKS and EG. Drafting manuscript: GA, SSR. Revising manuscript content: GA, SSR, EG and PKS. Approving final version of manuscript: GA, SSR, BMR, EG and PKS. PKS takes responsibility for the integrity of the data analysis.

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