



# Finding a Link between Obesity and Senescence: A Systematic Review and Meta-Analysis

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## Abstract

**Background:** Cell aging is associated with changes in telomeres due to DNA damage arising from chronic inflammation in obese patients. The aim of the systematic review and meta-analysis was to find the relationship between obesity and aging or senescence.

**Methods:** The systematic review was conducted through PRISMA guideline, beginning with literature search within 2012-2022 in several databases (PubMed, EBSCOHost, Science Direct, Scopus, and Cochrane) followed by screening process using predetermined PICO criteria. Original studies on the topic of obesity and senescence (aging), from preclinical studies to clinical research (cohort or cross-sectional studies) that were published within the last ten years. All studies were appraised using SYRCL risk of bias tool for preclinical studies and Newcastle-Ottawa Scale (NOS) for cross-sectional and cohort studies. The data extraction on the studies' characteristic and outcome on aging or senescence were followed by quantitative analysis using MetaXL process on prevalence ratio and hazard ratio of obesity to comorbidities and mortality.

**Results:** Fifteen studies were enrolled. Obesity and white adipose tissue cause increased levels of pro-inflammatory and pro-senescence cytokine and macrophage whilst the aging process lowers metabolism with increased insulin resistance and linked to increased risk of obesity. Obesity occurs in 22% (95% CI 18%-26%) of elderly population with higher prevalence rate in the women population. Obesity is associated with significant increased risk of multimorbidity by 56% (OR = 1.58 [95% CI 1.48-1.96]).

**Conclusion:** The obesity and aging or senescence has reciprocal relationship between each other.

**Keywords:** Obesity; Aging; Senescence; Meta-analysis

## Introduction

The WHO defines obesity as an excessive accumulation of fat that may cause health problem (1). Another definition of obesity is an abnormal

accumulation of fat cells caused by a disturbed energy balance, where the energy intake is greater than the energy outtake. Obesity is associated



with chronic inflammation that can cause cell aging (2). Cell aging is actually a normal process that occurs in the body along with apoptosis, which play an important role in eliminating damaged cells and in tissue remodelling. This is an important physiological process (3).

Cell aging phase is an irreversible extend in the cell cycle induced by several stimuli including telomere uncapping, DNA damage and activation of oncogenes.(4) When cells have entered the senescence phase, they will produce a secretion, Smooth-Associated Secretory Phenotype(SASP), which trigger an opening of paracrine and auto-crine that play a role in the chronic inflammatory process which if continuously produced will cause tissue dysfunction or carcinogenesis (4,5). Cell aging is also associated with changes in telomeres due to DNA damage resulting from chronic inflammation seen in obese patients (6). Telomere length itself is inversely related to the life span of the cell and telomere damage can accelerate the cell aging process. Telomere length is commonly used as a biological marker of aging. In obese patients, the chronic inflammation and increased oxidative stress in cells will lead to shortening of the telomeres themselves (7). A human study showed that telomere shortening

was directly related to an increase in fat cells and inversely related to BMI (8).

We aimed to determine whether there was a linear relationship between the incidence of obesity and cellular aging.

## Methods

The Preferred Reporting Items for Systematic Review (PRISMA) guideline was used as a benchmark and approach in this systematic review and meta-analysis (9). The review was conducted through literature search and screening process to include the relevant literature before qualitative and quantitative analysis.

### Literature search

The literature search was conducted on various scientific databases, such as PubMed, EBSCO-Host, Science Direct, Scopus, and Cochrane. The search process used pre-determined keyword queries based on the *study's Patient - Intervention - Control - Outcome (PICO) criteria*. The review was focused on finding the connection between obesity and senescence or aging, thus studies with obesity patients and senescence or aging or on the link of both, such as epidemiology and prognosis were retrieved. The PICO criteria can be found in Table 1.

**Table 1:** The PICO criteria of the study

<i>Patients</i>	<i>Patients with obesity; central obesity</i>
Intervention	Aging; senescence
Control	N/A
Outcome	Incidence rate; prevalence rate; mortality rate; quality of life

The PICO criteria were then translated into several keyword queries, which used on the scientific databases search features. MeSH Terms were used if it was available on the database, otherwise, the use of keywords and their synonyms were used on each database. The searching process was conducted, the latest on 23 October 2022. On this literature search, the process was made solely based on the database source search. We have also contacted the studies' authors to

identify additional studies and data for data extraction.

### Literature screening process

The screening process were conducted and the studies were selected based on the inclusion and exclusion criteria. The inclusion criteria were studies on obesity and senescence (aging), published within the last 10 years (2012-2022) and available in English. The original studies like pre-

clinical trials, laboratory and animal studies or human clinical studies either in cohort or cross-sectional were assessed.

### ***Risk of Bias Assessment***

The risk of bias assessment were conducted to assess properly the study quality. The assessment tool was chosen based on the study design. Animal or pre-clinical studies are assessed using the SYRLCE Risk of Bias Tool. In clinical studies, either cohort or cross-sectional are assessed with Newcastle-Ottawa Scale (NOS). The results were then visualized in graphs and tables (10).

### ***Data Extraction***

We extracted the characteristics like location, settings, study design and intended outcome and the methodology used. The outcome, particularly epidemiology (incidence rate or prevalence rate), or prognosis in obesity like mortality outcome, quality of life and other parameters used in the study. The data extraction was conducted using predetermined form (Microsoft© Excel). The data extraction process was done independently by all authors with internal review done after the data extraction confirming the results and outcomes.

### ***Quantitative Analysis***

The quantitative analysis was conducted on the numerical data found in each study. Data on epidemiological outcomes such as incidence rate or prevalence rate and prognosis outcome were analyzed using the MetaXL application or extension for Microsoft Excel 365. The data on the prevalence and the risk of obesity for mortality and morbidity were analyzed. The prevalence ratio was analyzed through pooled prevalence analysis. Meanwhile, both mortality and morbidity were analyzed using the available hazard ratio results of the selected study with inverse variance method using random effect model. The heterogeneity of data is visualized with  $I^2$ . The data were then extrapolated into forest plots for visualization.

The subgroup analysis was conducted on the prevalence rate of obesity on both men and women in an elderly population. The subgroup analysis was made by doing pooled prevalence analysis with different data sets to produce forest plots in respective subgroups.

## **Results**

### ***Literature Search and Paper Selection***

The present literature search was planned, conducted and reported according to the PRISMA guidelines. From the search results of five databases with specified keywords, 11,982 results in five databases with the following details: 101 studies from PubMed, 97,953 from ScienceDirect, 536 from EBSCOHost, 72 from Cochrane and 21,490 from Scopus. From the literature search obtained, several studies were excluded because they did not meet the expected study design and among others, there were 4,985 review articles, 6,059 were not research articles and 89 were not retrieval leaving 849 for eligibility assessment. Several studies were excluded because they did not meet the inclusion criteria. Fifteen studies were included in the literature review. Twelve were clinical studies on obesity, 10 discussed obesity and aging whilst two discuss obesity and cell senescence analysis. Three studies were pre-clinical studies on senescence cells with animal study. Nine studies were eligible for meta-analysis, as the outcome of obesity prevalence in elderly population along with odds ratio analysis on mortality and comorbidity were available on nine studies.

### ***Risk of bias assessment***

From the risk assessment of bias using the NOS bias risk assessment, we found that 6 out of 12 studies had good quality in terms of risk bias and the other 6 studies with fair quality (Table 2).

**Table 2:** Risk of bias assessment (NOS) on included studies

Author	Yr	Selection			Comparability		Exposure		Total score	
		Adequate definition of patient cases	Representativeness of patient cases	Selection of controls	Definition of controls	Control for important or additional factors	Ascertainment of exposure	Same method of ascertainment for participants		Non-response rate
Puzianowska-Kuznicka (11)	2019	*		*		*		*	*	5
Bowman (12)	2017	*	*	*		*		*	*	6
Apalasy (13)	2021	*	*	*		*		*	*	6
Romano (14)	2021	*		*		*		*	*	4
Choi (15)	2022	*		*		*		*	*	5
Muhammad (16)	2022	*		*		*		*	*	5
Muhammad (17)	2022	*		*		*		*	*	5
Santamaria-Ulloa (18)	2022	*	*	*		*		*	*	6
Svard (19)	2017	*	*	*		*			*	5
Han (20)	2017	*	*	*		*	*	*	*	6
Brunelli (21)	2021	*	*	*		*	*	*	*	6
Ycaza (22)	2021	*	*			*	*	*	*	5

^Good quality studies

+Fair quality studies

Three pre-clinical studies were then assessed for its quality with SYRCLE Risk of Bias Tool. Not all three studies did any sequence generation for the randomization process, with no information on the allocation concealment. Blinding and random outcome assessment were also not shown. However, other aspects of bias were considered low risk, thus the overall risk of bias in all studies were fair risk of bias. The authors then included all studies with consideration of low risk on outcome differences due to the unknown variables.

### ***Main Characteristics of the Studies Reporting on Clinical Study***

Characteristics of the studies reporting on clinical study are shown in (Table 3). Six studies took a

sample population of geriatrics with age over 60 years (11,12,14-17) and another six studies took samples from 40 years to 55 years old and above (13,18-22). Five studies have several samples with a range of 1,000-10,000 population (11,13,15,19,20) and there are four studies that have samples that are quite large with more than 10,000 population (12,14,16,17), and only two studies have samples below one hundred (21,22), one study with no known total number of samples were included (18). Of the 12 studies, only three stated that the research observation period was between four to six years (12,18,20) and one study had an observation period of 10 years (19).

Table 3: Included studies' characteristics on clinical study

Author, year	Study Design	Location	Sample's characteristics					Data Analysis		
			Included sample	Sample size	Observational period	Ratio	Comorbidities	Extracted Data	Analysis Method or Focus	
Choi, 2022 (15)	Cross-sectional	South korea	Community-dwelling older adults aged 70–84 years from eight hospitals and two public health centers across South Korea.	1827	N/A	883/944	Smoking (32.3%); Alcohol use (58.85%); Hypertension (55.3%); Dyslipidemia (34.2%); DM (21.3%); OA (21.1%); Osteoporosis (13.7%); Alcohol use and DM more common in men; Other comorbidities more common in women	BMI; sarcopenia (based on muscle mass, handgrip strength, physical performance/SPPB)	Association between obesity and sarcopenia	
Muhammad, 2022 (16)	Cross-sectional	India (LASI-2017-18)	Older adults (aged >60 years old) from all Indian states	31464	N/A	47.5:52.5	N/A	BMI; Waist circumference; waist-hip ratio; socioeconomic background; Multimorbidity data	Association between obesity and multimorbidity	
Muhammad, 2022 (17)	Cross-sectional	India (LASI-2017-18)	Older adults (aged >60 years old) from all Indian states	31464	N/A	47.5:52.5	N/A	BMI; Waist circumference; waist-hip ratio; Socioeconomic factor; Lifestyle factor (smoking, alcohol, physical activity)	Association between obesity and successful aging	
Ulloa, 2022 (18)	Secondary data analysis on prospective cohort	Costa Rica	Individuals aged 55 years or over of the Costa Rican population	N/A	5 years (2004-2009)	47.48:52.52	About a third of elderly are former smokers or alcohol drinkers, whereas 10% are current smokers and 3% are current alcohol drinkers. Hypertension and hypercholesterolemia are the most prevalent conditions on this elderly population (48 and 40% respectively), 5% have had a myocardial infarction and 12% have ischemic heart disease.	BMI; Waist circumference (WC); Comorbidities; Survival analysis	Survival analysis based on BMI or WC	
Apalasy. 2021 (13)	Prospective observational cohort	Malaysia	Sample of individuals aged 40 years and older adults residing in all the states of Malaysia	5613	N/A	2341/2964	N/A	Age group; BMI; socioeconomic status; physical activity level; race	Association between obesity with various socio-demographic and lifestyle factors	
Romano, 2021 (14)	Cross-sectional	China, India, Ghana, Mexico, Russia, South Africa	Individuals aged 60 years or older in the selected countries based on SAGE study	20198	N/A	45.9:54.1	The most common chronic conditions were hypertension (50.6%), arthritis (33.2%), and angina (21.8%).	BMI; Waist circumference; multimorbidity	The BMI influence on multimorbidity risk	

Table 3: Continued...

Brunelli, 2021 (21)	Cross-sectional	Brazil	Middle-aged (40 – 60 years old) male or female classified as obese [(body mass index (BMI) > 30 kg/m <sup>2</sup> )] with T2D or with absence of an associated disease or middle-aged individuals of both sexes' eutrophics (BMI between 20 - 25 kg/m <sup>2</sup> ) who had not participated in regular exercise and/or dietary programs over the last 12 months	53	N/A	25/28	Type 2 DM	Anthropometric assessment (Height, weight, BMI, waist circumference); dietary intake assessment; maximal-strength assessment; Cardiorespiratory assessment (VO <sub>2</sub> max); blood analysis (load glucose and gene expression of leptin, IL-2, IL-4, IL-6, IL-10, TNF- $\alpha$ , PD-1, P16ink4a, CCR7, CD28 and CD27)	Comparison between obesity, obesity with type 2 diabetes mellitus, or eutrophic individuals on their physical outcome and immunosenescence-related cytokine and gene expression
Ycaza, 2021 (22)	Cross-sectional	USA	Men and premenopausal women between 18 and 55 years of age	63	N/A	15.48.00	Excluded in the study	Body measurement (BMI, Fat, FFM), abdominal/femoral fat cell size, fasting plasma glucose, abdominal/femoral Sa $\beta$ Gal	Association of human adipose tissue with senescence parameter (SA- $\beta$ -gal)
Puziannowska-Kuznicka, 2019 (11)	Cross-sectional	Poland	Polish residents aged $\geq$ 65 years old	4944	N/A	51.7:48.3	N/A	BMI; Waist circumference; Arm circumference; MMSE; ADL	Association of body measurement to ADL, MMSE, comorbidity, and mortality
Bowman, 2017 (12)	Prospective observational cohort	United Kingdom	UK Biobank participant aged 60–69 y at recruitment	130473	6.5 years	47.8:52.2	Coronary artery disease (7.8%); type 2 diabetes (5.2%)	BMI; Waist-to-hip ratio; Alcohol intake; Smoking history; education; mortality; coronary artery disease prevalence	Association of obesity and mortality and/or CAD
Svard, 2017 (19)	Prospective observational cohort	Finland	Finnish municipal employees aged 40 to 60 in 2000–02	5668	10-12 years	1023/4645	Drinking problem; Smoking status; Somatic diseases	BMI changes; physical activity (PCS); Mental health (MCS); Socioeconomic position; Drinking problem (SAGE); Somatic-ill health	Comparison or changes based on age category
Han, 2017 (20)	Prospective observational cohort	European regions (North-east; Non-transitional Mediterranean; North-west European)	Men aged 40-79 years old in 8 different cities across Europe	3369	4.3 years (3-5.7)	All Male	N/A	Lifestyle habit; body measurement (BMI, WC, MUAC); Physical function (PASE)	Comparison or changes in the extracted data along the years after the follow-up period

### Outcome of Reporting on Clinical Study

The Table on study outcome were divided into four indicators that were assessed; epidemiology, risk of comorbidity or mortality, obesity follow-

up, senescence outcome, as well as indicators of quality of life and physical function outcomes. Two studies reported by Muhammad and Choi et al showed that central obesity was significantly



more in women (15,16). Three studies showed that the prevalence of obesity was at 12% of the total sample population whilst two showed that obesity was greater than 30%. One study showed the baseline prevalence of obesity was around 32.4% and 21.9% in Mediterranean cities (20). For indicators of risk for comorbidity or mortality, Muhammad et al (16) showed that the prevalence of multi-morbidity was higher in women than men (44.9% vs. 38.8%), but the risk of this multi-morbidity was higher in men than women in terms of waist circumference (17). Obesity (BMI>30 kg/m<sup>2</sup>) had a 1.43x higher probability of multiple morbidity (14). This was supported by Ulloa et al where the obese population has the least chance of survival (18). Bowman et al stated the population with grade 1 obesity (BMI :30-35) has a higher risk of mortality and Kuznicka et al showed that the frequency of diabetes and cardiovascular disease was higher in the obese population with a BMI of 35-39.9 (11,12).

On indicators of quality of life and physical function outcomes, the prevalence of low ASMI scores as well as the prevalence of sarcopenia was less in the obese population (15). There was a significant difference between men and women for the prevalence of good aging outcomes, and this was significantly higher in the non-obese or overweight population (17). Populations with higher BMI, WC and AC had a strong relationship to ADL scores and MMSE scores (11) while Svard et al showed that the PCS score will decrease with increasing BMI (19). As for the senescence outcome indicator, there are only two out of twelve studies. Brunelli et al found an increase in leptin and other cytokines in the obese population, with higher levels in the obese population with DM than without DM (21). Ycaza et al showed SA-β-gal, a marker of aging is more abundant in femoral adipose tissue in women than in men (22). The adult population with obesity has more subcutaneous aging cells than the population without obesity and there is also a positive correlation between the total amount of

body fat and aging cells in abdominal and femoral adipose tissue (22).

### *Main Characteristics and outcome of the Studies Reporting on Pre-Clinical Study*

The data extracted from the three studies varied for the animal study by Rabhi et al, the extracted data were fibrotic stromal microenvironment; ECM production; PDGFR $\alpha$  and PDGFR $\beta$ ; Osteopontin production; senescent CD9+ (23). While the study by Iizuka et al took data in the form of Blood glucose; plasma insulin and HOMA-IR; oxidative stress (d-ROMS); hepatic triglycerides; morphology islets; GLUT4 expressions; Mitochondria UCP1 (24). tissue-based study conducted by Frasca et al took data in the form of Expression of SASP Markers in B Cells; B cells count (memory and naive B cells); glucose and lipid uptake of B cells (25).

### *Quantitative analysis on Clinical Study Reporting*

For the outcome of obesity prevalence in the elderly population, there were no significant differences in the nine studies reported with an accumulated prevalence of about 22% ( $P<0.001$ ;  $I^2=100\%$ ; 95% CI 0.18-0.26) as shown in Fig. 1, as well as for other outcome assessments such as the prevalence of obesity in the male elderly population which had a prevalence of around 19% ( $P=0.02$ ;  $I^2=99\%$ ; 95% CI 0.15-0.24) and the prevalence of obesity in the female elderly population which had a prevalence of about 26% ( $P<0.001$ ;  $I^2=100\%$ ; 95% CI 0.19-0.33). For the outcome of obesity risk on morbidity and mortality it did not show a statistically significant relationship. The hazard ratio for obesity risk on morbidity is around 1.58 ( $P=0.41$ ;  $I^2=0\%$ ; 95% CI 1.48-1.69) (Fig. 2) and for obesity risk in mortality 0.87 ( $P<0.001$ ;  $I^2=93\%$ ; 95%CI 0.56-1.34) (Fig. 3). Thus, it can be concluded that there is no statistically significant relationship between obesity and outcome.

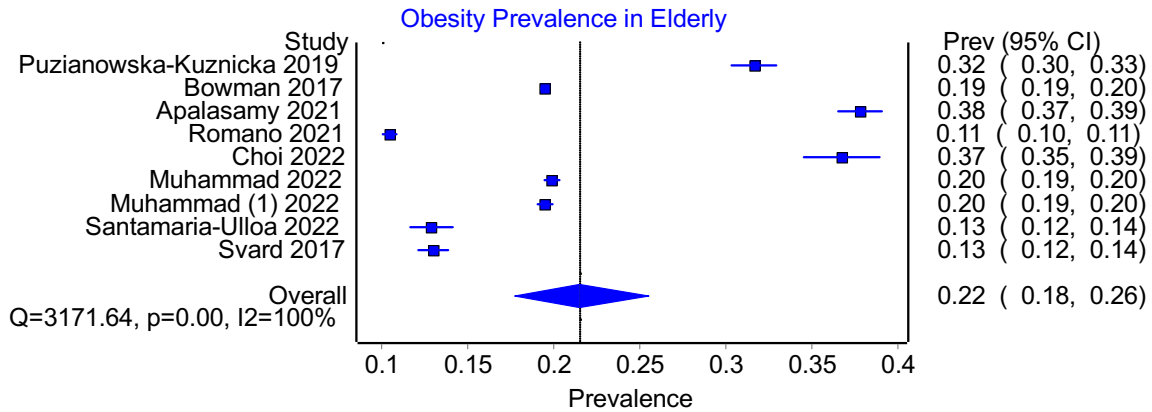


Fig. 1: Forest plot on the cumulative prevalence ratio of obesity in elderly population

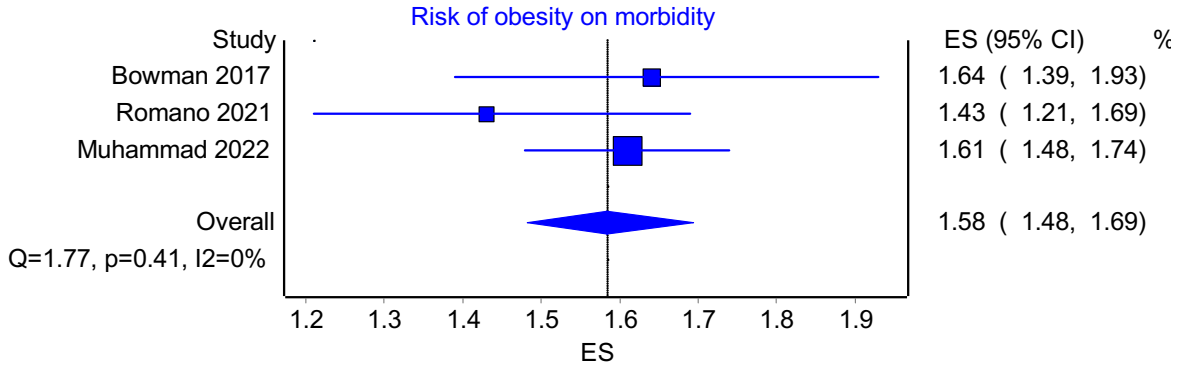


Fig. 2: Forest plot on the cumulative hazard ratio of obesity on morbidity in elderly population

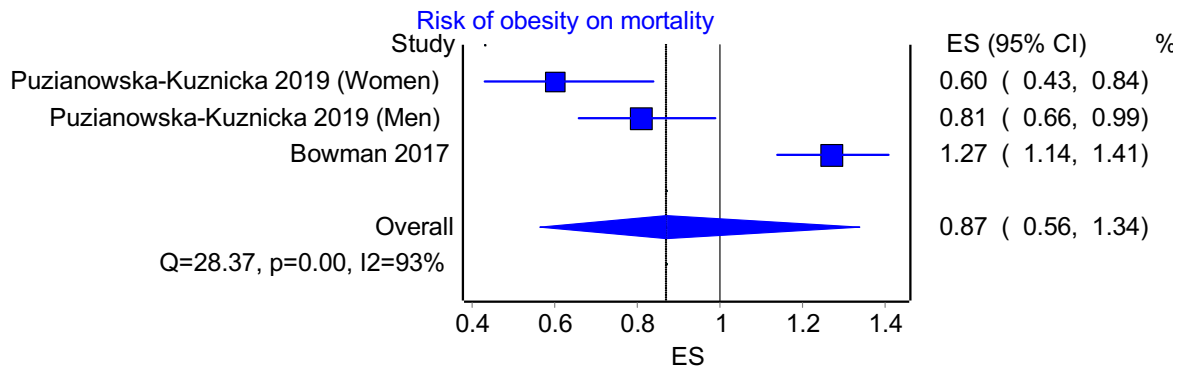


Fig. 3: Forest plot on the cumulative hazard ratio of obesity on mortality in elderly population

## Discussion

The prevalence of obesity in our study was mostly defined by measuring BMI or waist circumference. Garawi et al, found that the prevalence of obesity across countries shows gendered pattern-

ing with greater prevalence and greater heterogeneity in women than in men ( $P<0.001$ ) (26). Domestic violence and food choices at home significantly affect the prevalence of obesity in women (27,28). In addition, the study by Apal Sammy et al in Asia showed that the popula-



tion most at risk for obesity was in the age range of between 40 and 49 years (13). This study was supported by another study who reported that the highest prevalence of obesity in women and men is in the range of between 40 years and 49 years (29). This is in contrast from the study by Kuznicka et al where the age range of between 70 and 74 years had the highest risk of obesity in Poland (11). The underlying mechanism why older adults have a lower prevalence of obesity was explained in a study where increasing age had a gradual decline in bone and muscle mass that affects the body composition in older adults and changes in food intake, energy expenditure, appetite and body composition are believed to influence the prevalence of obesity (30).

In addition, in women, the prevalence of obesity increases with age (31). It may be related to hormonal changes, increase amount of intra-abdominal fat and total body fat mass (32,33).

The next outcome is the risk of mortality and morbidity in obese population. Three of the twelve clinical studies stated that the obese population increased the risk of morbidity (11,12,18). Populations with excessive accumulation of visceral adipose tissue led to impaired plasma glucose/insulin homeostasis, increase triglyceride and apolipoprotein B concentration, lower HDL cholesterol levels, and increase LDL cholesterol concentrations (34–36). Obesity also has an impact on increasing mortality, especially in the elderly population. The study by Ulloa et al showed that from the age of 60-95 years, the obese population had the highest probability of death from any cause (18). Obesity in elderly population increases the risk of hypertension, diabetes and ischemic heart disease, which can lead to premature mortality. These results are consistent with the findings of the Framingham Study conducted in 2003, thus obesity, especially in older adult men requires special attention as it increases the risk of mortality especially in ischemic heart disease (37)

The next outcome analyzed is the outcome of the Senescence cells. The findings of the above study are in line with the study conducted by Tuana et al who showed an increase in the secretion of

inflammatory cytokines (IL-1b and IL-8) in obese patients. In addition there was an increase in the activity of CD 81 levels and T lymphocytes which decreased the expression of CD28 is also associated with the phenotype of immuno senescence (38). Rouault et al also found a 7-fold increase of SA- $\beta$ -gal (immunocense marker) in severely obese patients in adipose tissue, especially in the subcutaneous area (39).

Immuno senescence arises as a result of decreased function of T-cells, especially T-helper cells, This in turn affect humoral immunity and cause decreased B-cell function (40). In general, NK cells, one of the cellular mediators of innate defense, are also affected by age where there will be changes in the number and function of these cells (41). Obesity is related to chronic inflammation, due to the production of adipose cell abnormalities, insulin resistance, diabetes mellitus, dyslipidemia, endothelial cell dysfunction, atherosclerosis, hypertension and other cardiovascular diseases (42).

Despite vast explanations and multiple studies addressing the linkage between obesity and aging, only two studies discuss obesity and cell senescence. As cell senescence and aging are related but different entities, further studies are needed to demonstrate comprehensively their linkage.

## **Conclusion**

Obesity in the elderly population has demonstrated the link between obesity and senescence or aging. Obesity is known to be more prevalent in elderly population, with rising risk of mortality significantly seen in the elderly population. Obesity is also linked to senescence by pro-inflammatory cytokines activation on adipose tissue, which eventually activate senescence of cells.

## **Journalism Ethical considerations**

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission,

redundancy, etc.) have been completely observed by the authors.

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## Conflict of Interest

The authors declare that there is no conflict of interests.

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