Increased Body Mass Index is Associated with Sarcopenia and Related Outcomes

Running title: Body mass index and sarcopenia

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1.0 Introduction

Sarcopenia, characterized by loss of lean body mass, muscle strength and physical performance in older adults, is a geriatric syndrome. Physical inactivity, increasing sedentary behavior, as well as poor nutritional and health status enhance the progressive decline of muscle function and strength among older adults.[1,2] Previous studies have highlighted being underweight as an important risk factor for sarcopenia which may be compounded by progressive loss of body mass and muscle strength during ageing.[3,4] However, total body fat is known to increase with age.[5,6] Sarcopenia and excessive adiposity may, therefore, share similar pathophysiology since both involve low grade inflammation with accelerated muscle catabolism.

Several cardiometabolic factors such as diabetes, hypertension, and dyslipidemia which are prevalent in older adults with increased body mass index (BMI) may play an important role in sarcopenia development.[2,7,8] Excess fat mass interrupts the blood glucose pathway and triggers insulin resistance which may then further enhance the development of sarcopenia. While several cross-sectional studies had pointed to the potential risk of sarcopenia with increased BMI,[9–11] the relationship between BMI and sarcopenia have yet to be evaluated alongside sarcopenia related outcomes such as falls and hospitalization in older adults. The aim of this study was, therefore, to evaluate the relationship between BMI and sarcopenia, falls and hospitalization as well as to explore the role of fasting blood glucose (FBG) in this potential relationship.

2.0 Methods

2.1 Study design

This study utilized baseline data from the Malaysian Elders Longitudinal Research (MELoR) study. 1650 individuals aged 55 years and over were recruited from the electoral rolls of three parliamentary constituencies within the Klang Valley of Malaysia between 2013 and 2015. Individuals with communication difficulties were excluded. Baseline data were obtained through home-based computer-assisted interviews and physical measurements were then obtained at a

subsequent hospital health check. BMI data was available from 1311 individuals who visited clinic for baseline physical assessment. Five-year follow-up interviews were conducted via telephone calls in 2019 where among other measures, sarcopenia, falls, and hospitalization outcomes were obtained. Vital status was established from the National Registry Department prior to contacting participants. As we were primarily interested in incident sarcopenia, only non-sarcopenic participants with SARC-F scores of lower than four at baseline were included for analysis. Sarcopenia was considered the primary endpoint of our study, while fall occurrence and hospitalization were secondary endpoints.

2.2 Covariates

Baseline data collected included socio-demographics, past medical history, 12-month falls history, physical examination, and routine fasting laboratory blood tests.

2.2.1 Physical measures

Height and weight were measured using a height stadiometer (SECA™ 220, Hamburg, Germany) and calibrated weighing scale (SECA™ 769, Hamburg Germany) respectively. The BMI was calculated by dividing measured weight in kilograms (kg) with the square of height in meters (m^2). Participants were categorized based on the existing World Health Organization (WHO) defined international BMI categories (underweight <18.5 kg/m^2; normal weight: 18.5-24.9 kg/m^2; overweight: 25.0-29.9 kg/m^2; obese ≥30 kg/m^2).[12] Muscle strength and gait and balance were assessed using hand grip strength, timed-up and go, and functional reach.[13]

2.2.2 Fasting Blood Glucose

The role of blood glucose in the association between excess BMI and the outcomes was determined using fasting blood glucose (FBG). Blood samples were collected after a 12-hour fast, in a sodium fluoride blood tube. FBG samples were analyzed by an accredited chemical pathology laboratory within 24 hours of blood collection.

2.3 Outcome measures

2.3.1 Sarcopenia

Sarcopenia was defined as a total score of four or greater using SARC-F questionnaire. The validated questionnaire used for sarcopenia screening consisted of five components covering Strength, Assistance in walking, Rise from a chair, Climb stairs and Falls (Table 1).[14] Participants were asked about the level of difficulty they encountered in performing activities from all the five components which ranged from zero (no difficulty), one (with some difficulty), and two (with a lot of difficulty or unable to perform or need aid). The SARC-F was chosen as a screening tool as it is independently associated with adverse clinical outcomes with high specificity towards sarcopenia in Asian studies.[2]

2.3.2 Falls

Participants were asked “Have you fallen in the past 12 months?” and “How many falls have you had in the past 12 months?” during the follow-up interview. Frequency, location, associated injuries, and whether they sought medical attention were established for those who reported the presence of falls.

2.3.3 Hospitalization

Participants were asked if they had been hospitalized since their enrolment into the MELoR study, and further information on frequency and reasons were recorded if participants responded positively.

2.4 Statistical analysis

Data analyses were carried out using the Statistical Package for Social Science 26.0 (IBM, Armonk, NY, USA). For continuous variables, the analysis of variance was applied for normally distributed, while the Kruskal-Wallis test was utilized for non-normally distributed data. The Chi-squared test was used for categorical data. Subsequently, the rate ratios (RR) with 95% confidence intervals (CI) were determined using logistic regression for the outcomes of

sarcopenia, falls, and hospitalization with reference to normal BMI. Potential confounders and mediators were adjusted for using logistic regression.

Simple mediation analysis was conducted to further evaluate the potential mediating effect of raised FBG in the relationship between BMI category and all outcomes. The indirect effect of the relationship was presented as the coefficient effect [95% bootstrap lower limit confidence interval (LLCI), upper limit confidence interval (ULCI)].

3.0 Results

3.1 Participants' baseline characteristics

Of 1311 participants with BMI from the MELoR study, we were unable to contact 433 (33.03%) participants after excluding 82 (6.25%) who had died. Reasons for loss of contact included: telephone number no longer in use, unanswered calls or relocation. A total of 796 (60.72%) were successfully followed-up. We subsequently omitted 32 (4.02%) individuals with baseline SARC-F score ≥ four from the total successfully followed-up prior to analysis, leaving a total of 764 (57.85% women, 67.97 (7.01) years) included participants at follow-up with available baseline BMI with the exclusion of individuals who fulfilled the criteria for sarcopenia using the SARC-F at baseline (Figure 1). Table 2 summarized the basic characteristics of participants according to their BMI group.

3.2 Body mass index and sarcopenia, falls, and hospitalization.

The risk of sarcopenia at follow-up was increased for those with BMI ≥30 kg/m^2 at baseline compared to those with normal body weight [RR (95%CI): 2.42 (1.41-4.15), Model 1]. This association remained significant after adjustment for age, gender, educational level, and diabetes [RR (95%CI): 1.88 (1.01-3.50), Model 3]. Additionally, a similar association was found between increased BMI and sarcopenia and was consistently significant when BMI was linearly modeled [RR per unit increment (95% CI): 1.07 (1.01-1.12), Model 3] (Table 3).

The risk of falls increased significantly with BMI ≥30 kg/m^2 compared to those in the normal BMI group [RR (95%CI): 1.90 (1.13-3.20), Model 1]. This remained significant after adjustment for age, gender and educational level [RR (95% CI): 1.85 (1.07-3.21), Model 2]. The association between BMI ≥30 kg/m^2 and prospective falls was attenuated after adjustments for diabetes [RR (95%CI): 1.66 (0.94-2.92)]. The linear model also showed that increasing BMI was associated with falls [RR per unit increment (95%CI): 1.04 (1.00-1.09)] but the relationship was no longer significant after further adjustment for diabetes.

BMI ≥30 kg/m^2 was associated with significantly increased risk of hospitalization prospectively [RR (95%CI): 1.74 (1.06-2.85), Model 1] compared to those with normal BMI. Hospitalization rates over five years among individuals with BMI ≥30 kg/m^2 compared to those with normal BMI following adjustments in Model 2 and remained significant with slight attenuation after differences in diabetes status were accounted for [RR (95%CI): 1.90 (1.11-3.28), Model 3]. Increasing BMI and hospitalization rate at 5-year follow-up in the linear model exhibited a similar association [RR per unit increment (95% CI): 1.06 (1.01-1.10), Model 3].

3.5 Mediation analysis

Figure 2 and Table 4 demonstrate the results of a simple mediation analysis evaluating the mediation effect FBG in the association between BMI and sarcopenia (Y1), falls (Y2), and hospitalization (Y3). The analysis was adjusted for age and gender. Individuals with BMI: 25-29.9 kg/m^2 and ≥30 kg/m^2 had significantly higher FBG compared to individuals in the normal BMI category, while the outcomes of sarcopenia, falls and hospitalization was also associated with increasing FBG. The direct effect of BMI categories on the risk of all outcomes (Y1, Y2, Y3) was significant for BMI ≥30 kg/m^2 but not BMI <18.5 or BMI: 25-29.9 kg/m^2 compared to those the BMI: 18.5-25 kg/m^{2}group, suggesting the potential mediating role of FBG (Figure 2a, 2b, 2c). The indirect effect revealed that the obesity-related relationships was mediated by FBG levels

[Effect, Bootstrap SE (95% LLCI, ULCI): Y1= 0.1554, 0.0769 (0.0033,0.3056); Y2= 0.1444, 0.0778 (0.0123, 0.3145); Y3= 0.1392, 0.0625 (0.0221, 0.2691)] (Table 4).

4.0 Discussion

This study identified the link between BMI of 30 kg/m^2 and over with poorer long-term outcomes in those aged 55 years and over at recruitment, as well as the possible role of increased FBG in the relationship between increased BMI and the prospective outcomes of sarcopenia, falls, and hospitalization. The association between BMI ≥30 kg/m^2 and falls was accounted for by the presence of diabetes.

Santos et al. reported a higher prevalence of obesity (25.85%) among older adults compared to a general population from the FIBRA Network (Study network on frailty in older adults) in Brazil, with 4.44% of the older adults diagnosed with both, sarcopenia and obesity (sarcopenic obesity).[9] This is comparable to our study since the prevalence of obesity in Malaysia is growing faster in the population aged 60 years and older with 30.2% of the population reported as obese in the National Health and Morbidity Survey 2015.[15] Our study demonstrated 3.28% of the cohort are older adults with obesity and sarcopenia detected using SARC-F after five years. The rising prevalence of obesity is now recognized among low- and middle-income countries leading to increased risk of ill-health and increased healthcare burden.[16]

Individuals who fulfilled the international WHO criteria for obesity with a BMI of 30kg/m^2 and over in this study had a 90% increase in odds of falls compared to those within the normal BMI category. This relationship was, however, confounded by diabetes rather than cardiovascular disease, which study supports the existing knowledge that obesity is a risk factor for diabetes and its complications as well as other cardiometabolic comorbidities.[8,17] Increased BMI is strongly correlated with excess body fat. [18] Given the evidence, any increase in body fat corresponds to an approximately 25% change in fat-free mass. [19] Diabetes is associated with

loss of muscle mass, quality, and durability, as well as a change in muscle fiber composition. While research findings on these measures are currently contradictory, the presence of these long-term problems has been linked to the influence of diabetes on neuromuscular function. [20] Increased BMI and sarcopenia are known to affect the prognosis of different diseases (thereby increasing the odds of hospitalization), as well as physical performance (and hence increasing the risk of falls).

Fasting blood glucose was utilized in this study due to the high prevalence of undiagnosed diabetes in the Malaysian population.[21] However, FBG among individuals with established diagnoses of diabetes on optimal therapy, will also appear within the normal range. Hence increased FBG which indicates the presence of diabetes, pre-diabetes and suboptimal glycemic control appears to be linked to sarcopenia, falls, and hospitalization in individuals with obesity as demonstrated in the mediation analysis. The secretion of TNFα, leptin and growth hormones which occur with adiposity-associated inflammation stimulates insulin resistance, leading to accumulation of fat mass and accelerated muscle catabolism. The accumulation of leptin upregulates IL-6 and TNFα signaling and downregulates the secretion of insulin-like growth factor 1 (IGF-1). This inhibits muscle growth signaling through the mTOR and FOXO pathways with resultant muscle atrophy stimulated by the release of proinflammatory myokines.[22,23] In addition to the poor metabolic status, proper glycemic control is required for adequate IGF-1 synthesis, which helps to prevent muscular atrophy and the downward spiral of sarcopenia, frailty and eventually dependency and death.

The discovery of the obesity paradox has led to a reluctance to advocate weight loss interventions in older adults due to concerns about the development of sarcopenia with reduced caloric intake.[24] Our findings, alongside other recent studies, challenge this belief by demonstrating that excess body weight itself leads to sarcopenia. Hence the possibility of weight loss interventions which include exercise, nutrition and other lifestyle interventions being an

effective strategy to reduce the risk of sarcopenia, falls and hospitalization, possibly through glucose handling, should now be reconsidered. Effective prevention and management of obesity-related sarcopenia is likely to lead to reduction in healthcare burden and expenditure through the enhancement of metabolic disorders and reduction in negative health outcomes such as falls and hospitalization.

This study was limited by the use of telephone interviews, which may have led to selection bias. While recall bias may also have occurred with self-reported outcomes for falls and hospitalization, we have compared prospective diaries, retrospective recall and telephone interviews in a subpopulation of the MELoR study and found a high level of agreement between retrospective and prospective reports.[25] Unlike other methods of detection of sarcopenia which require face-to-face contact, the SARC-F questionnaire had a brief administration time and supported telephone administration.[14] While SARC-F has been endorsed as a case-finding instrument for Asians older adults, appendicular skeletal muscle mass, muscle strength, and/or physical performance would be required to confirm the diagnosis which is unavailable within this study.[2] Future studies are, therefore, required to confirm this prospective relationship using physical measures.

In conclusion, increased BMI is associated with sarcopenia, falls and hospitalization at five-year follow-up in community-dwelling individuals aged 55 years at recruitment. The presence of diabetes mediates this relationship, while elevated FBG is a mediator of the association between increased BMI with sarcopenia and its related outcomes. The above implicates the glycemic control pathway in older individuals with increased BMI. This study presents the findings from a developing country with a high prevalence of diabetes, with evidence of the role of diabetes and increased FBG in the prospective link between sarcopenia, falls, and hospitalization in Asian adults aged 55 years and over with increased BMI.

Statement of Ethics

This study has been approved by the University of Malaya Medical Centre Medical Ethics Committee (Ref: 925.4), and was conducted in accordance with the ethical principles of the Helsinki Declaration of 1975, revised in 1983. All participants provided informed consent for longitudinal data collection prior to their inclusion.

Conflict of Interest

The authors have no conflicts of interest to declare for this study.

Author Contributions

Conceptualization: MPT, PKM, MD, SM. Methodology: MPT, SBK, SK, NNH, AVC. Data curation: SHK, SM. Formal analysis: NNAH, SM. Writing - original draft: NNAH, SM, MPT. Writing – review & editing: AVC, SBK, NNH, SHK, SK, PKM, MD. Funding acquisition: SBK, NNH, AVC, SK, SM, MPT.

Data Availability

Dataset used for this study are available from the corresponding author upon request.

Reporting Guidelines

Reporting of the study conforms to broad EQUATOR guidelines (Simera et al. A catalogue of reporting guidelines for health research. Eur J Clin Invest. 2010 Jan;40(1):35-53).

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Figures

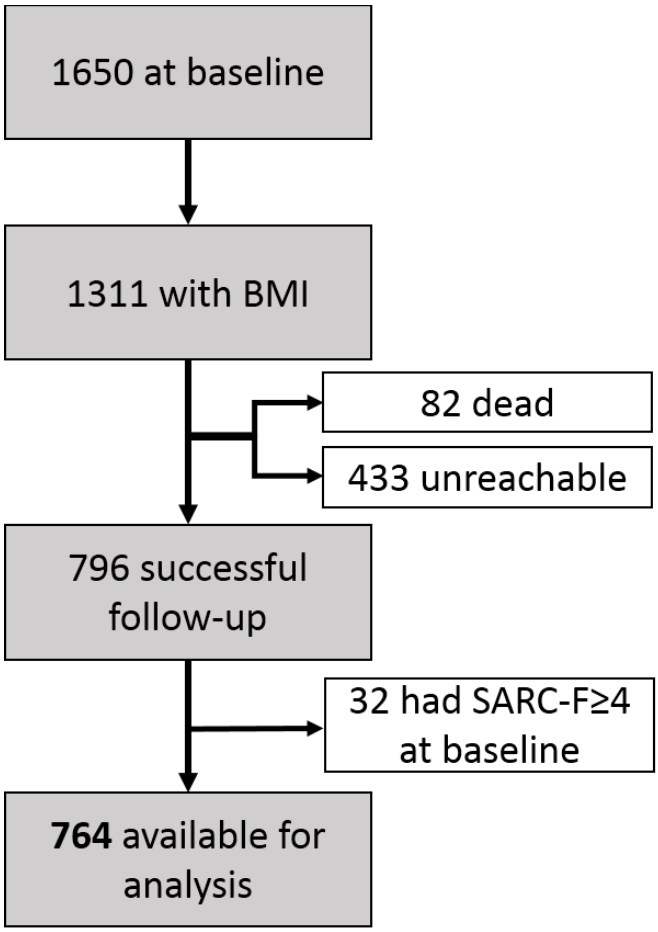

Figure 1. Flowchart of participants from baseline inclusion until five-year follow-up.

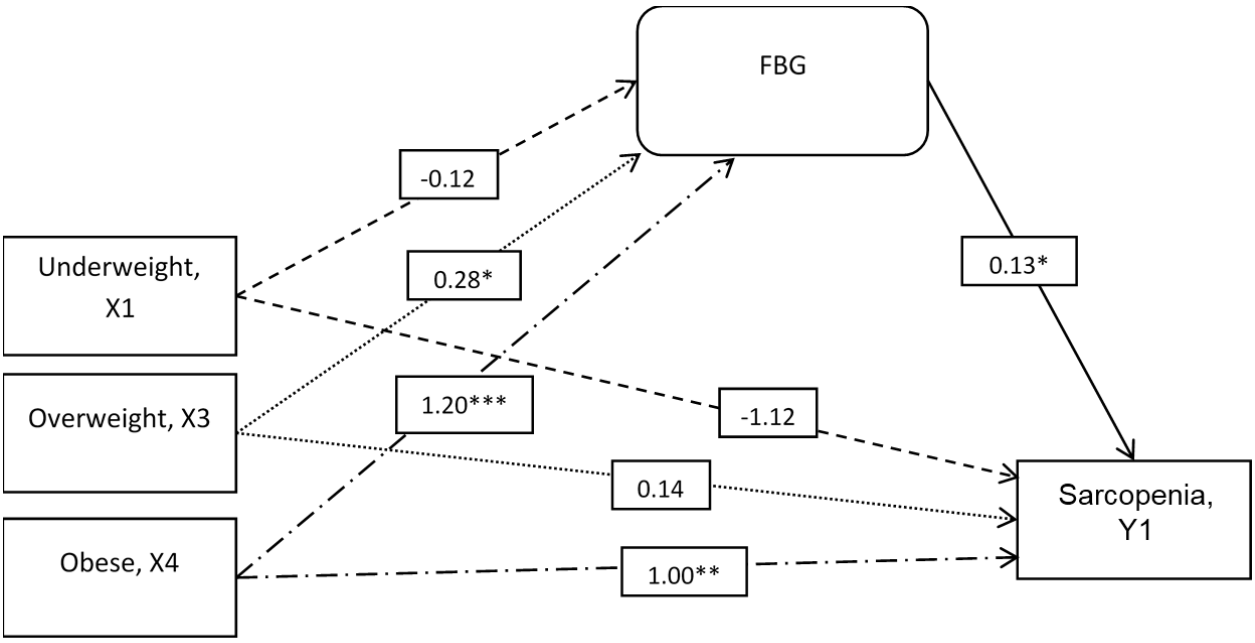

Figure 2a. Mediation analysis for the influence of fasting blood glucose (FBG) on BMI groups (underweight <18.5 kg/m^2, normal: 18.5-24.9 kg/m^2, overweight: 25-29.9 kg/m^2 and obese ≥30 kg/m^2) and sarcopenia at five-year follow-up. Simple mediation analysis with bootstrapping compared to BMI classes with risk of sarcopenia (Y1) adjusted for age and gender. Obesity (X4) was directly associated with sarcopenia compared to the individuals with normal weight (X2). The increased risk of sarcopenia in individuals with obesity was mediated by FBG. Significance indicated by *p<0.05, **p<0.001, ***p<0.0001.

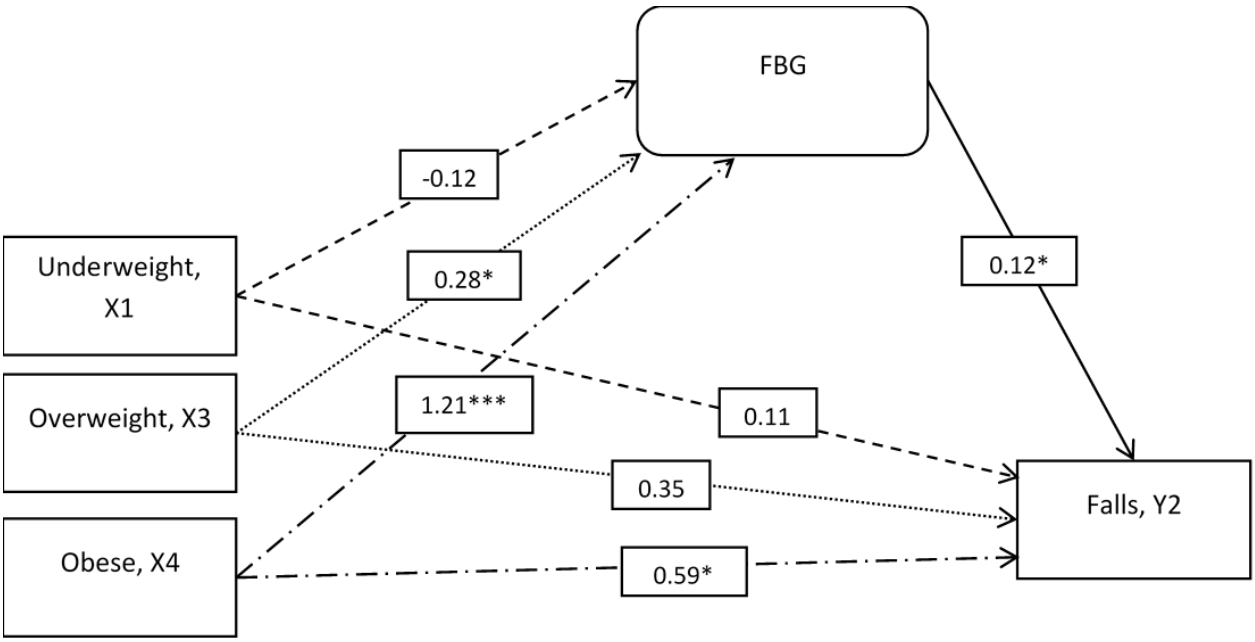

Figure 2b. Mediation analysis for the influence of fasting blood glucose (FBG) on BMI groups (underweight <18.5 kg/m^2, normal: 18.5-24.9 kg/m^2, overweight: 25-29.9 kg/m^2 and obese ≥30 kg/m^2) and prospective falls at five-year follow-up. Simple mediation analysis with bootstrapping compared to BMI classes with risk of falls (Y2) adjusted for age and gender. Obesity (X4) was directly associated with prospective falls compared to the individuals with normal weight (X2). The increased risk of falls in individuals with obesity was mediated by FBG. Significance indicated by *p<0.05, **p<0.001, ***p<0.0001.

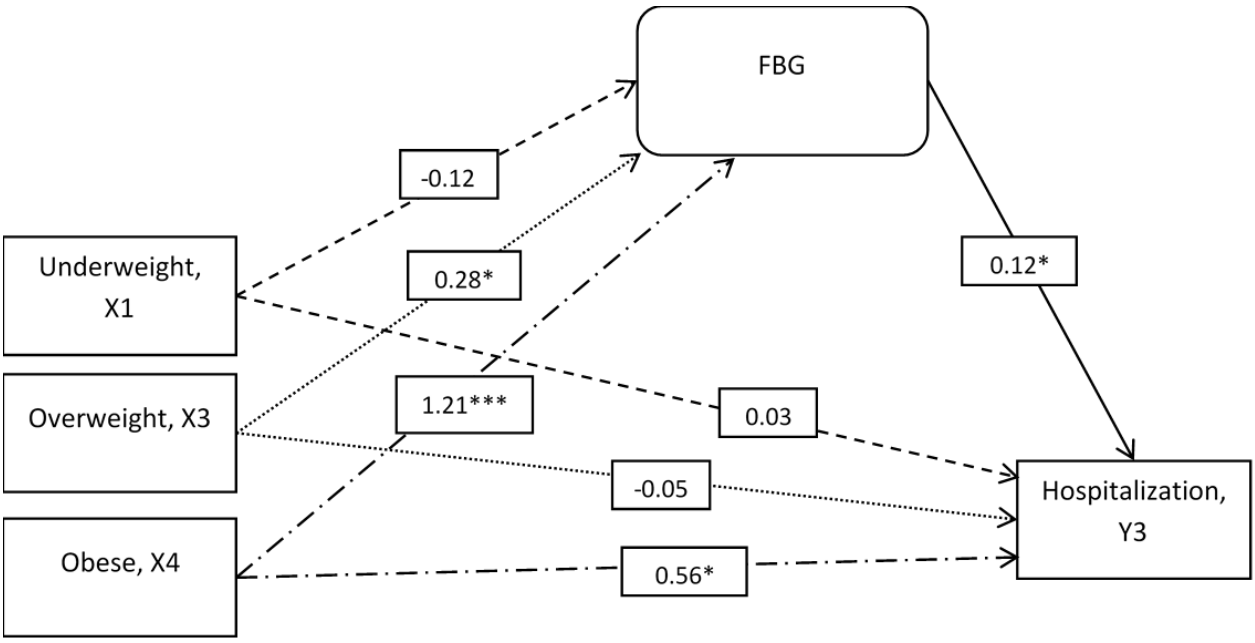

Figure 2c. Mediation analysis for the influence of fasting blood glucose (FBG) on BMI groups (underweight <18.5 kg/m^2, normal: 18.5-24.9 kg/m^2, overweight: 25-29.9 kg/m^2 and obese ≥30 kg/m^2) and hospitalization in five-year. Simple mediation analysis with bootstrapping compared to BMI classes with risk of hospitalization (Y3) adjusted for age and gender. Obesity (X4) was directly associated with hospitalization compared to the individuals with normal weight (X2). The increased risk of hospitalization in individuals with obesity was mediated by FBG. Significance indicated by *p<0.05, **p<0.001, ***p<0.0001.