

## Association Between Lifetime Cumulative Surgical Exposure and Total Body Bone and Muscle Mass in Older Adults

L. ASHOUR<sup>1,2</sup>, M. ALSHOLF<sup>3</sup>, H. B. NASAR<sup>4</sup>, I. SADAQA<sup>5</sup>, M. ZAITA<sup>5</sup>, A. M. ZAQOUT<sup>4</sup>,  
A. ALSARKHI<sup>6</sup>, A. OKASHA<sup>5</sup>, A. HAMMAD<sup>7</sup>, H. ABUISSA<sup>6</sup>

<sup>1</sup>Public Health Institute, Liverpool John Moores University, Liverpool, UK; <sup>2</sup>King Hussein Cancer Center, Amman, Jordan; <sup>3</sup>Al Hussein New As-Salt Hospital, Ministry of Health, As-Salt, Jordan; <sup>4</sup>Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan; <sup>5</sup>Jordan University Hospital, The University of Jordan, Amman, Jordan; <sup>6</sup>Al-Basheer Hospital, Ministry of Health, Amman, Jordan; <sup>7</sup>Department of Internal Medicine, Specialty Hospital, Amman, Jordan.

Correspondence at: Laith Ashour, MD. E-mail: L.M.Ashour@2026.ljmu.ac.uk | laithashour100@gmail.com

### ABSTRACT

The relationship between recurrent surgical exposure and musculoskeletal health in older adults remains insufficiently characterized. This study aimed to investigate the association between the cumulative number of surgical procedures and total body bone mass (TBBM) and total body lean mass (TBLM) in an older adult population. Data were analyzed from the 2017–2022 biomarker wave of the Midlife in the United States (MIDUS 3) study. TBBM and TBLM were measured using dual-energy X-ray absorptiometry (DXA) with Lunar systems. The number of prior surgeries (minor or major) was retrospectively obtained through structured medical history interviews. Multiple linear regression models were used to evaluate associations between surgical history and body composition measures. Models were adjusted for age, sex, body mass index (BMI), hemoglobin A1c (HbA1c), triglyceride levels, smoking history, dietary habits, medication use, physical activity, and serum creatinine levels. The final analytic sample included 327 participants (41% male) with a mean age of  $64.5 \pm 9.3$  years. Regression analyses showed that a higher number of prior surgeries was significantly associated with lower TBBM ( $\beta = -0.094$ ; 95% CI:  $-0.175$  to  $-0.013$ ;  $P = 0.021$ ). Further sensitivity analyses including participants with higher threshold of cumulative major surgeries supported this association with a higher effect size. No significant association was observed between number of surgeries and TBLM ( $P = 0.33$ ), even after conducting sensitivity analysis on cohort who underwent major recurrent surgeries. Healthier dietary habits were significantly associated with higher TBLM ( $\beta = 0.073$ ; 95% CI:  $0.017$  to  $0.129$ ;  $P = 0.011$ ), but not with TBBM ( $P = 0.507$ ). In conclusion, recurrent surgical exposure was associated with lower total body bone mass but not lean mass in older adults. However, further longitudinal research is needed to fully adjust for potentially-related underlying morbidities.

**Keywords:** Total body bone mass, total body lean mass, recurrent surgeries, older adults.

### INTRODUCTION

Surgical procedures trigger a systemic stress response that disrupts inflammatory signaling and hormonal regulation, increasing metabolic demand and muscle protein breakdown<sup>1</sup>. This response can lead to neuroinflammation, synaptic injury, and neuronal loss<sup>2</sup>, with pronounced effects observed in musculoskeletal and abdominal surgeries<sup>3–5</sup>. Furthermore, surgical trauma elevates reactive oxygen species (ROS), which activate pathways promoting muscle catabolism—a process particularly damaging to skeletal muscle due to its high metabolic rate<sup>6</sup>. Compared to other types of surgeries, major operations have the most pronounced catabolic response<sup>7</sup>. While often adaptive, this stress

response can become maladaptive, resulting in systemic inflammatory response syndrome (SIRS), characterized by chronic inflammation and increased infection risk<sup>8–10</sup>.

The impact of surgery is particularly important in older adults, who often face increased morbidity due to frailty and multiple comorbidities<sup>11</sup>. Beyond these factors, the age-related decline in physiological reserve leaves many organ systems operating near maximal capacity, limiting the body's ability to withstand repeated stressors<sup>12</sup>. Consequently, recurrent surgical interventions may progressively deplete this reserve, leaving patients increasingly vulnerable to adverse outcomes.

Musculoskeletal deterioration provides a key

link between recurrent surgery and morbidity. Postoperative immobilization accelerates sarcopenia in older adults<sup>13</sup>, while surgical trauma triggers neuroendocrine responses—including catecholamine release and inflammatory signaling—that shift the body into a catabolic state<sup>14,15</sup>. Specifically, sympathetic signaling through beta-adrenergic receptors promotes bone resorption and inhibits formation<sup>16–19</sup>. While acute activation is necessary, persistent sympathetic signaling can lead to progressive loss of muscle and bone mass, impairing mobility and rehabilitation.

Given the link between surgical stress, sympathetic activation, and body composition, it is critical to examine the long-term musculoskeletal consequences of repeated operations. We hypothesized that repeated surgical exposure would be associated with significant alterations in total body bone mass and lean mass in older adults.

## MATERIALS AND METHODS

### *Study Population*

The Midlife in the United States (MIDUS) study is a longitudinal cohort initiated in 1995 that enrolled more than 7,000 adults aged 25–75 years from across the United States, with oversampling from five metropolitan areas. The study was designed to examine the psychological, behavioral, and social determinants of physical and mental health across adulthood.

Subsequent follow-up waves included MIDUS 2 in 2009 and MIDUS 3 in 2013, both of which incorporated biomarker data collection. For MIDUS 3, biomarker data collection began in 2017. Participants attended a 24-hour research visit at one of three clinical research centers: the University of California, Los Angeles; the University of Wisconsin–Madison; or Georgetown University. During these visits, comprehensive assessments of multiple physiological systems—including musculoskeletal, neurological, and immune systems—were performed. All biological specimens required for biomarker analyses were collected on-site by trained clinical staff.

The MIDUS 3 biomarker project invited 747 participants (644 from the longitudinal survey sample and 103 from the Milwaukee oversample), achieving an adjusted response rate of 64.3% (747/1162). For the present analysis, the sample was restricted to 327 participants for whom total body bone mass and lean mass measurements obtained using Lunar DXA systems were available.

### *Study Design*

This investigation was conducted as a cross-sectional analysis using data derived from the MIDUS 3 Biomarker dataset collected between 2017 and 2022.

### *Study Variables*

#### *Surgical history*

Surgical history was obtained during structured medical history interviews. Participants were asked to report the total number of times they had undergone any type of surgical procedure. Information regarding the type of surgery (e.g., appendectomy, cholecystectomy, and others) and the setting in which it was performed (office visit, outpatient, or inpatient) was also collected.

Because the majority of reported procedures were performed in outpatient or inpatient settings rather than office-based procedures, the total number of prior surgeries was used in the present study as the primary exposure variable to evaluate the association between recurrent surgical interventions and body composition outcomes.

#### *Outcome variables*

The primary outcome variables were Lunar total body bone mass (TBBM) and total body lean mass (TBLM).

TBBM was measured using dual-energy X-ray absorptiometry (DXA). T-scores were recorded for all participants regardless of age or menopausal status. Scanning procedures followed a standardized protocol to ensure measurement consistency; detailed procedural descriptions are available in the MIDUS 3 musculoskeletal health and function documentation<sup>20</sup>.

TBLM was also assessed using DXA. Although DXA-derived lean mass has recognized limitations—particularly because it reflects total lean tissue including body water rather than true skeletal muscle mass—it remains a widely accepted method for assessing body composition and is incorporated into most consensus definitions of sarcopenia.

### *Covariates*

Covariates included age, sex, smoking history (regular smoking), body mass index (BMI), dietary habits, hemoglobin A1c (HbA1c) levels, triglyceride levels, physical activity, medication use, and serum creatinine levels. Serum creatinine was measured by Meriter Laboratories (Madison, WI), with assay procedures described in the MIDUS 3 blood, urine, and saliva documentation<sup>20</sup>.

Dietary habits were assessed using questionnaire items evaluating the weekly consumption of healthy

foods (vegetables, fruits, lean meats, fish, and whole grains) and unhealthy foods (fast food, high-fat foods, and sugar-sweetened beverages). Responses were used to generate a MIDUS Healthy Eating Index (HEI) score ranging from 0 to 11, with higher scores indicating healthier dietary patterns.

Physical activity was quantified as the total number of metabolic equivalent task (MET) minutes per week. To satisfy statistical model assumptions, MET minutes were categorized into quartiles (Q1–Q4).

### Statistical Analysis

Descriptive statistics were used to summarize participant characteristics. Continuous variables were reported as means  $\pm$  standard deviations (SD) and medians with interquartile ranges (IQR), while categorical variables were presented as frequencies and percentages.

Associations between the number of prior surgeries and total body bone mass (TBBM) and total body lean mass (TBLM) were evaluated using multiple linear regression models, with separate models constructed for each outcome. The TBBM model was adjusted for factors and medications known to influence bone metabolism, including age, sex, physical activity, BMI, triglycerides, HbA1c, serum creatinine, smoking status, dietary habits, thiazide diuretic use, proton pump inhibitor (PPI) use, phosphate binder use, vitamin D analogue use, and selective serotonin reuptake inhibitor (SSRI) use.

The TBLM model was adjusted for age, sex, dietary habits, HbA1c, physical activity, triglycerides, serum creatinine, BMI, smoking history, and  $\beta$ -selective blocker use. In both models, the dependent variables were transformed using a Box–Cox transformation to satisfy regression assumptions.

To ensure the robustness of our findings and mitigate confounding by indication, we performed additional sensitivity analyses to evaluate whether the cumulative number of prior major surgeries (regardless of chronological sequence) was associated with TBBM or TBLM. Given the lack of a specific variable classifying surgeries as major or minor, all inpatient procedures involving at least one overnight hospital stay were operationally defined as major surgeries.

Also, other sensitivity analyses were conducted using the frequency of prior minor surgeries (i.e., those performed in outpatient settings) as the primary independent variable. To investigate whether recurrent exposure to major surgeries specifically amplified these association, we performed a further

analysis restricted to participants with a history of at least three recurrent major surgeries. This aimed to determine if individuals with four or more procedures exhibited lower TBBM or TBLM relative to those with three major surgeries or fewer. To further minimize confounding by indication, we quantified the specific types and overall frequency of major surgeries performed. Due to the limited sample size in the final sensitivity analysis, the multivariate model was restricted to include only the most important covariates.

Regression results are reported as standardized beta coefficients ( $\beta$ ) with 95% confidence intervals (CI). A P-value  $< 0.05$  was considered statistically significant. All analyses were performed using Jamovi software (Version 2.6.13, 2024; <https://www.jamovi.org>).

### Ethical Approval

This study represents a secondary analysis of publicly available MIDUS data. All MIDUS study protocols were approved by the Institutional Review Board of the University of Wisconsin–Madison.

## RESULTS

Following the inclusion of participants who underwent Lunar total body lean or bone mass assessment, the total number of participants was 327, with 41% being males and a mean age of 64.5 years (SD = 9.3). Also, 48% of participants had a history of regular smoking. Descriptives of categorical controlled variables are displayed under Table I, and for continuous variables, see Table II.

### Bone mass

Multiple adjusted linear regression analysis demonstrated that a greater number of prior surgical procedures was significantly associated with lower lunar total body bone mass (TBBM) ( $\beta = -0.094$ ; 95% CI:  $-0.175$  to  $-0.013$ ). The relationship between cumulative surgical exposure and TBBM is illustrated in Figure 1.

Among the covariates included in the model, sex, age, and body mass index (BMI) showed significant associations with TBBM. Female sex was associated with significantly lower TBBM compared with males ( $\beta = -1.372$ ; 95% CI:  $-1.549$  to  $-1.195$ ). Increasing age was also significantly associated with lower TBBM ( $\beta = -0.096$ ; 95% CI:  $-0.177$  to  $-0.015$ ). In contrast, higher BMI was positively associated with TBBM, indicating greater bone mass with increasing BMI ( $\beta = 0.294$ ; 95% CI:  $0.215$  to  $0.373$ ). Detailed regression

**Table I.** — Descriptives of categorical controlled variables.

| Sex                                                                               | Counts | % of Total |
|-----------------------------------------------------------------------------------|--------|------------|
| MALE                                                                              | 135    | 41%        |
| FEMALE                                                                            | 192    | 59%        |
| Had a history of regular smoking                                                  |        |            |
| YES                                                                               | 157    | 48%        |
| NO                                                                                | 170    | 52%        |
| Total number of Metabolic Equivalent of Task (MET) minutes per week (4 Quartiles) |        |            |
| Q1                                                                                | 126    | 39%        |
| Q2                                                                                | 73     | 23%        |
| Q3                                                                                | 73     | 23%        |
| Q4                                                                                | 52     | 16%        |
| Medications                                                                       |        |            |
| Diuretic thiazide use                                                             |        |            |
| YES                                                                               | 42     | 14%        |
| NO                                                                                | 262    | 86%        |
| Phosphate binder use                                                              |        |            |
| YES                                                                               | 20     | 7%         |
| NO                                                                                | 284    | 93%        |
| Vitamin D analogue use                                                            |        |            |
| YES                                                                               | 94     | 31%        |
| NO                                                                                | 210    | 69%        |
| Proton Pump Inhibitor use                                                         |        |            |
| YES                                                                               | 72     | 24%        |
| NO                                                                                | 232    | 76%        |
| Beta-1selective blockers use                                                      |        |            |
| YES                                                                               | 53     | 17%        |
| NO                                                                                | 251    | 83%        |
| Serotonin selective reuptake inhibitor use                                        |        |            |
| YES                                                                               | 34     | 11%        |
| NO                                                                                | 270    | 89%        |

**Table II.** — Descriptives of continuous controlled variables and lunar body lean and bone masses indices in elderly.

|                                                                    | Mean             |      | SD      |
|--------------------------------------------------------------------|------------------|------|---------|
| Age (years)                                                        | 64.5             |      | 9.3     |
| MIDUS HEI                                                          | 5.1              |      | 1.5     |
| BMI (kg/m2)                                                        | 31.4             |      | 7.2     |
| Lunar Total Body Lean Mass (grams)                                 | 49426.6          |      | 10890.5 |
| Lunar Total Body Bone Mass (grams)                                 | 2700.9           |      | 631.0   |
|                                                                    | Median           | 25th | 75th    |
| Creatinine (mg/dl) *                                               | 0.88             | 0.76 | 1.04    |
| HbA1c (%) *                                                        | 5.6              | 5.3  | 6.1     |
| Triglycerides (mg/dl) *                                            | 98               | 71.5 | 139     |
| Number of times respondent reports having had any type of surgery* | 3                | 2    | 5       |
| Number of inpatient (major) surgeries*                             | 2 (Range 0 to 9) | 1    | 3       |
| Number of outpatient (minor) surgeries*                            | 1 (Range 0 to 8) | 0    | 2       |
| *Not normally distributed.                                         |                  |      |         |

results for the model are presented in Table III.

The overall model demonstrated acceptable goodness-of-fit ( $R^2 = 0.602$ ). Diagnostic evaluation confirmed that regression assumptions were satisfied, including normality of residuals and homoscedasticity, and no evidence of multicollinearity was detected among the independent variables. Reported beta

coefficients correspond to the transformed outcome scale following Box–Cox transformation.

To ensure the rigor of our primary observations, we conducted several sensitivity analyses to isolate the effects of surgical complexity and frequency on TBBM. Sensitivity analyses focusing exclusively on major surgical interventions confirmed a robust inverse

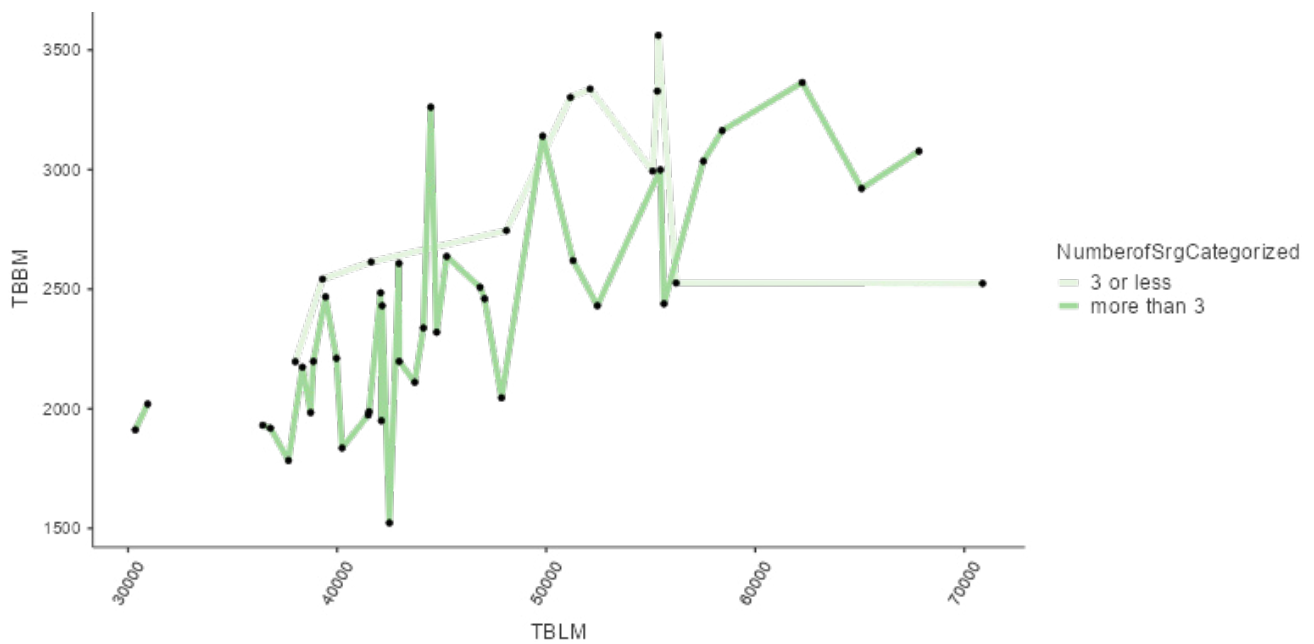


Fig. 1 — Association between TBLM and TBBM by recurrent surgical frequency. Scatter plot with smoothing lines shows the positive correlation between total body lean mass (TBLM) and bone mass (TBBM) and the clustering of the high-exposure group (>3 surgeries) in the lower ranges of TBBM, reflecting the significant association between cumulative surgical history and reduced bone mass.

**Table III.** — Adjusted multiple linear regression analysis for the association of history of recurrent surgeries (major and minor) with total body bone mass (g) in elderly.

| Model Coefficients - Total body bone mass (Box-cox Transformed) |        | 95% Confidence Interval |        |                 |
|-----------------------------------------------------------------|--------|-------------------------|--------|-----------------|
| Predictor                                                       | Beta   | Lower                   | Upper  | p               |
| Number of Surgeries (major and minor)                           | -0.094 | -0.175                  | -0.013 | <b>0.023</b>    |
| Age                                                             | -0.096 | -0.177                  | -0.015 | <b>0.021</b>    |
| Sex                                                             |        |                         |        |                 |
| FEMALE – MALE                                                   | -1.372 | -1.549                  | -1.195 | <b>&lt;.001</b> |
| BMI                                                             | 0.294  | 0.215                   | 0.373  | <b>&lt;.001</b> |
| Diuretic thiazide use                                           |        |                         |        |                 |
| YES – NO                                                        | -0.007 | -0.236                  | 0.223  | 0.955           |
| Phosphate binder use                                            |        |                         |        |                 |
| YES – NO                                                        | -0.079 | -0.399                  | 0.241  | 0.627           |
| Vitamin D analogue                                              |        |                         |        |                 |
| YES – NO                                                        | -0.143 | -0.312                  | 0.027  | 0.098           |
| HbA1c                                                           | -0.049 | -0.13                   | 0.032  | 0.235           |
| History of regular smoking                                      |        |                         |        |                 |
| NO – YES                                                        | 0.001  | -0.155                  | 0.157  | 0.988           |
| Serum Creatinine                                                | 0.05   | -0.031                  | 0.131  | 0.229           |
| MIDUS HEI                                                       | 0.027  | -0.052                  | 0.106  | 0.507           |
| Triglycerides                                                   | 0.071  | -0.011                  | 0.153  | 0.091           |
| SSRI use                                                        |        |                         |        |                 |
| YES – NO                                                        | -0.079 | -0.325                  | 0.167  | 0.528           |
| PPI Use                                                         |        |                         |        |                 |
| YES – NO                                                        | -0.08  | -0.266                  | 0.105  | 0.394           |
| Physical activity (Quartiles)                                   |        |                         |        |                 |
| 2 – 1                                                           | -0.045 | -0.255                  | 0.164  | 0.671           |
| 3 – 1                                                           | 0.081  | -0.13                   | 0.292  | 0.45            |
| 4 – 1                                                           | 0.071  | -0.167                  | 0.309  | 0.555           |
| R <sup>2</sup> = 0.602                                          |        |                         |        |                 |

relationship; a higher frequency of prior major surgeries was associated with a statistically significant reduction in TBBM (Table IV). Conversely, when isolating minor surgeries, the association with TBBM was attenuated, though it remained statistically significant (Table V). These data suggest that surgical magnitude is a primary driver of the observed bone mass deficits.

### **Analysis of Cumulative Major Surgical Exposure**

To evaluate the impact of recurrent high-intensity physiological stress, we analyzed a sub-cohort of participants whose initial three operations were classified as major (inpatient) surgeries.

Participants with higher threshold of cumulative surgeries represented by four or more cumulative surgeries (including at least three recurrent major procedures) exhibited significantly lower TBBM compared to those with a history of only three major surgeries (Table VI), supporting a Dose-Response relationship. Of note, the effect size of

surgical exposure is noted to be much higher in this model compared to earlier analyses, and for clinical interpretability this model includes betas on original untransformed scale. To maintain methodological transparency and validate the observed outcomes, the specific classifications and descriptive statistics for the major surgical procedures within this cohort are detailed in Table VII. Notably, the procedural data indicate that the majority of these surgeries were not associated with pre-existing or underlying morbidities that might independently account for the observed decline in TBBM.

These findings collectively reinforce the hypothesis that exposure to major surgical trauma, particularly when having higher threshold of cumulative surgeries, serves as a significant risk factor for diminished TBBM.

### **Muscle mass**

We found no significant association between number of prior surgeries the older adult had and TBLM, see

**Table IV.** — Sensitivity analysis for the association of number of prior major (inpatient) surgeries with total body bone mass (g) in elderly.

|                                       |        | 95% Confidence Interval |        |                 |
|---------------------------------------|--------|-------------------------|--------|-----------------|
| Predictor                             | Betas  | Lower                   | Upper  | p               |
| Age                                   | -0.089 | -0.171                  | -0.006 | <b>0.036</b>    |
| Sex                                   |        |                         |        |                 |
| FEMALE – MALE                         | -1.377 | -1.553                  | -1.201 | <b>&lt;.001</b> |
| MIDUS HEI                             | 0.028  | -0.051                  | 0.107  | 0.485           |
| Smoking history                       |        |                         |        |                 |
| NO – YES                              | -0.01  | -0.165                  | 0.145  | 0.9             |
| Physical activity (Quartiles)         |        |                         |        |                 |
| 2 – 1                                 | -0.041 | -0.251                  | 0.169  | 0.703           |
| 3 – 1                                 | 0.077  | -0.134                  | 0.288  | 0.471           |
| 4 – 1                                 | 0.07   | -0.167                  | 0.307  | 0.561           |
| Serum Creatinine                      | 0.05   | -0.03                   | 0.13   | 0.222           |
| HbA1c                                 | -0.047 | -0.127                  | 0.034  | 0.257           |
| Triglycerides                         | 0.057  | -0.024                  | 0.138  | 0.165           |
| BMI                                   | 0.295  | 0.216                   | 0.375  | <b>&lt;.001</b> |
| Vitamin D analogue use                |        |                         |        |                 |
| YES – NO                              | -0.162 | -0.329                  | 0.005  | 0.057           |
| PPI use                               |        |                         |        |                 |
| YES – NO                              | -0.088 | -0.274                  | 0.097  | 0.351           |
| Thiazide diuretic use                 |        |                         |        |                 |
| YES – NO                              | 0.011  | -0.215                  | 0.238  | 0.922           |
| Number of major (inpatient) surgeries | -0.082 | -0.164                  | -0.001 | <b>0.047</b>    |
| R2 = 0.599                            |        |                         |        |                 |
| Betas reported on transformed scale.  |        |                         |        |                 |

**Table V.** — Sensitivity analysis for the association of number of prior minor (outpatient) surgeries with total body bone mass (g) in elderly.

|                                                                |  | 95% Confidence Interval |        |        |                 |
|----------------------------------------------------------------|--|-------------------------|--------|--------|-----------------|
| Predictor                                                      |  | Beta                    | Lower  | Upper  | p               |
| Intercept <sup>a</sup>                                         |  |                         |        |        | <.001           |
| Age                                                            |  | -0.113                  | -0.193 | -0.033 | <b>0.006</b>    |
| Sex                                                            |  |                         |        |        |                 |
| FEMALE – MALE                                                  |  | -1.416                  | -1.587 | -1.245 | <b>&lt;.001</b> |
| MIDUS HEI                                                      |  | 0.023                   | -0.056 | 0.102  | 0.57            |
| Smoking history                                                |  |                         |        |        |                 |
| NO – YES                                                       |  | 0.002                   | -0.153 | 0.158  | 0.975           |
| Physical activity (Quartiles)                                  |  |                         |        |        |                 |
| 2 – 1                                                          |  | -0.042                  | -0.251 | 0.168  | 0.697           |
| 3 – 1                                                          |  | 0.083                   | -0.128 | 0.294  | 0.439           |
| 4 – 1                                                          |  | 0.074                   | -0.163 | 0.31   | 0.541           |
| serum Creatinine                                               |  | 0.048                   | -0.032 | 0.129  | 0.236           |
| HbA1c                                                          |  | -0.048                  | -0.129 | 0.033  | 0.244           |
| Triglycerides                                                  |  | 0.066                   | -0.016 | 0.149  | 0.113           |
| BMI                                                            |  | 0.288                   | 0.209  | 0.367  | <b>&lt;.001</b> |
| Vitamin D analogues use                                        |  |                         |        |        |                 |
| YES – NO                                                       |  | -0.151                  | -0.318 | 0.017  | 0.077           |
| PPI use                                                        |  |                         |        |        |                 |
| YES – NO                                                       |  | -0.094                  | -0.279 | 0.091  | 0.319           |
| Thiazide diuretic use                                          |  |                         |        |        |                 |
| YES – NO                                                       |  | 0.03                    | -0.195 | 0.255  | 0.791           |
| Number of minor (outpatient) surgeries                         |  | -0.078                  | -0.156 | -0.001 | <b>0.048</b>    |
| R <sup>2</sup> = 0.599<br>Betas reported on transformed scale. |  |                         |        |        |                 |

Figure 1. However, both female sex (Beta = -1.453; 95% CI: [-1.575 to -1.33]) and age (Beta = -0.092; 95% CI: [-0.15 to -0.034]) were associated with significantly lower TBLM. Importantly, better healthy eating habits were associated with significantly higher TBLM in older adults (Beta = 0.073; 95% CI: [0.017 to 0.129]). None of the other covariates had significant association with TBLM, see Table VIII. Beta are reported on transformed scale.

To enhance the methodological rigor of our findings, we performed a series of sensitivity analyses to delineate the independent influences of surgical complexity and procedural frequency on TBLM. When the analysis was restricted to major surgical interventions, no statistically significant associations were observed (Table IX). Parallel results were identified for minor surgical procedures (Table X); in both instances, beta coefficients are presented on a transformed scale.

Furthermore, we examined the association of higher threshold of cumulative surgeries surgical exposure. Recurrent major surgeries did not correlate with a significant reduction in TBLM. Specifically, participants undergoing four or more procedures—where the initial three were classified as major—exhibited no significant difference in TBLM compared to those undergoing three recurrent major surgeries (Table XI). The underlying indications for surgery in this cohort are detailed in Table VII. It should be noted that estimates for this specific sensitivity analysis are reported on the original, untransformed scale.

Figure 1 shows the clustering of higher recurrent surgical exposure in lower TBBM levels.

## DISCUSSION

The present study demonstrates that recurrent surgical exposure is associated with significantly lower total body bone mass (TBBM) in later life, whereas no

**Table VI.** — Sensitivity analysis for the association of chronicity of prior major (inpatient) surgeries (at least 3 recurrent exclusively major surgeries) with total body bone mass (g) in elderly.

| Predictor                                                                                                               | Beta*  | 95% Confidence Interval |        |                 |
|-------------------------------------------------------------------------------------------------------------------------|--------|-------------------------|--------|-----------------|
|                                                                                                                         |        | Lower                   | Upper  | p               |
| Age                                                                                                                     | 0.033  | -0.245                  | 0.31   | 0.813           |
| Sex                                                                                                                     |        |                         |        |                 |
| FEMALE – MALE                                                                                                           | -1.067 | -1.662                  | -0.471 | <b>&lt;.001</b> |
| MIDUS HEI                                                                                                               | -0.04  | -0.315                  | 0.234  | 0.767           |
| Smoking history                                                                                                         |        |                         |        |                 |
| NO – YES                                                                                                                | -0.171 | -0.642                  | 0.3    | 0.465           |
| Physical activity (Quartiles)                                                                                           |        |                         |        |                 |
| 2 – 1                                                                                                                   | -0.143 | -0.758                  | 0.471  | 0.638           |
| 3 – 1                                                                                                                   | -0.5   | -1.206                  | 0.206  | 0.159           |
| 4 – 1                                                                                                                   | 0.634  | -0.158                  | 1.426  | 0.113           |
| serum Creatinine                                                                                                        | -0.051 | -0.364                  | 0.262  | 0.743           |
| HbA1c                                                                                                                   | 0.047  | -0.221                  | 0.315  | 0.723           |
| Triglycerides                                                                                                           | 0.144  | -0.127                  | 0.415  | 0.287           |
| BMI                                                                                                                     | 0.442  | 0.197                   | 0.687  | <b>&lt;.001</b> |
| Number of surgeries                                                                                                     |        |                         |        |                 |
| more than 3 – 3 or less                                                                                                 | -0.632 | -1.225                  | -0.039 | <b>0.037</b>    |
| R2 = 0.638<br>*TBBM Betas are reported on original untransformed scale, as assumptions were met without transformation. |        |                         |        |                 |

**Table VII.** — Descriptives of surgical procedures in participants who underwent three recurrent initial surgeries as major (inpatient) surgeries.

| Type of surgery                                                     | count | percentage |
|---------------------------------------------------------------------|-------|------------|
| GI surgeries (appendectomy, hernia, gall bladder, others)           | 29    | 21.32      |
| lower or upper limbs (foot, ankle, knee, shoulder, arm, hand)       | 12    | 8.82       |
| Tumor or Malignancy                                                 | 13    | 9.56       |
| Gynecological (CS, Breast, hysterectomy)                            | 38    | 27.94      |
| oral and otolaryngology                                             | 3     | 2.21       |
| Ophthalmic                                                          | 3     | 2.21       |
| Back/Neck                                                           | 16    | 11.76      |
| Cardiovascular system surgeries                                     | 12    | 8.82       |
| Cosmetic                                                            | 3     | 2.21       |
| Others                                                              | 7     | 5.15       |
| Total number of major surgeries across 3 initial consecutive visits | 136   | 100%       |

significant association was observed with total body lean mass (TBLM). These exploratory findings suggest that repeated surgical interventions may be linked to long-term skeletal deterioration in older adults, even after accounting for a broad range of metabolic, lifestyle, and medication-related factors. The underlying morbidities for which surgeries were

done may also impacted this association; however, this cannot be confirmed in the current study. Our descriptive analysis of types of surgeries done aligns with a potential role for recurrent surgical exposure rather than underlying disease. Evidence from prior research provides partial support for our observations; for instance, long-term follow-up of bariatric surgery

**Table VIII.** — Adjusted multiple linear regression analysis for the association of history of recurrent surgeries with total body lean mass (g) in elderly.

| Model Coefficients - Total body lean mass (Box-cox Transformed) |        | 95% Confidence Interval |        |                 |
|-----------------------------------------------------------------|--------|-------------------------|--------|-----------------|
| Predictor                                                       | Beta   | Lower                   | Upper  | p               |
| Age                                                             | -0.092 | -0.15                   | -0.034 | <b>0.002</b>    |
| Sex                                                             |        |                         |        |                 |
| FEMALE – MALE                                                   | -1.453 | -1.575                  | -1.33  | <b>&lt;.001</b> |
| MIDUS HEI                                                       | 0.073  | 0.017                   | 0.129  | <b>0.011</b>    |
| HbA1c                                                           | 0.002  | -0.056                  | 0.059  | 0.959           |
| Triglycerides                                                   | 0.003  | -0.055                  | 0.061  | 0.923           |
| Serum Creatinine                                                | 0.053  | -0.005                  | 0.11   | 0.072           |
| BMI                                                             | 0.539  | 0.483                   | 0.596  | <b>&lt;.001</b> |
| Beta-selective blocker use                                      |        |                         |        |                 |
| YES – NO                                                        | -0.121 | -0.266                  | 0.023  | 0.1             |
| Number of Surgeries                                             | -0.028 | -0.084                  | 0.028  | 0.331           |
| History of regular smoking                                      |        |                         |        |                 |
| NO – YES                                                        | -0.01  | -0.12                   | 0.1    | 0.862           |
| Physical activity (Quartiles)                                   |        |                         |        |                 |
| 2 – 1                                                           | -0.111 | -0.259                  | 0.037  | 0.141           |
| 3 – 1                                                           | -0.021 | -0.17                   | 0.129  | 0.787           |
| 4 – 1                                                           | -0.011 | -0.176                  | 0.153  | 0.891           |
| R2= 0.795                                                       |        |                         |        |                 |

**Table IX.** — Sensitivity analysis for the association of number of prior major (inpatient) surgeries with total body lean mass (g) in elderly.

|                                       |  |        | 95% Confidence Interval |        |       |
|---------------------------------------|--|--------|-------------------------|--------|-------|
| Predictor                             |  | Beta   | Lower                   | Upper  | p     |
| Age                                   |  | -0.092 | -0.15                   | -0.033 | 0.002 |
| Sex                                   |  |        |                         |        |       |
| FEMALE – MALE                         |  | -1.452 | -1.577                  | -1.327 | <.001 |
| MIDUS HEI                             |  | 0.073  | 0.017                   | 0.129  | 0.011 |
| HbA1c                                 |  | 0.002  | -0.055                  | 0.059  | 0.942 |
| Triglycerides                         |  | -0.001 | -0.058                  | 0.056  | 0.974 |
| serum Creatinine                      |  | 0.053  | -0.004                  | 0.111  | 0.07  |
| BMI                                   |  | 0.539  | 0.483                   | 0.596  | <.001 |
| Beta blocker use                      |  |        |                         |        |       |
| YES – NO                              |  | -0.118 | -0.264                  | 0.028  | 0.112 |
| Smoking history                       |  |        |                         |        |       |
| NO – YES                              |  | -0.014 | -0.124                  | 0.096  | 0.803 |
| Physical activity (Quartiles)         |  |        |                         |        |       |
| 2 – 1                                 |  | -0.109 | -0.257                  | 0.039  | 0.148 |
| 3 – 1                                 |  | -0.022 | -0.172                  | 0.128  | 0.774 |
| 4 – 1                                 |  | -0.014 | -0.178                  | 0.151  | 0.87  |
| Number of major (inpatient) surgeries |  | -0.021 | -0.078                  | 0.037  | 0.483 |
| R2 = 0.794                            |  |        |                         |        |       |
| Betas reported on transformed scale.  |  |        |                         |        |       |

**Table X.** — Sensitivity analysis for the association of number of prior minor (outpatient) surgeries with total body lean mass (g) in elderly.

| Predictor                                          | Beta   | 95% Confidence Interval |        |                 |
|----------------------------------------------------|--------|-------------------------|--------|-----------------|
|                                                    |        | Lower                   | Upper  | p               |
| Age                                                | -0.097 | -0.154                  | -0.04  | <b>&lt;.001</b> |
| Sex                                                |        |                         |        |                 |
| FEMALE – MALE                                      | -1.462 | -1.582                  | -1.341 | <b>&lt;.001</b> |
| MIDUS HEI                                          | 0.072  | 0.016                   | 0.128  | <b>0.012</b>    |
| HbA1c                                              | 0.002  | -0.055                  | 0.059  | 0.952           |
| Triglycerides                                      | 0.002  | -0.056                  | 0.061  | 0.934           |
| serum Creatinine                                   | 0.054  | -0.004                  | 0.111  | 0.068           |
| BMI                                                | 0.539  | 0.482                   | 0.595  | <b>&lt;.001</b> |
| Beta blockers use                                  |        |                         |        |                 |
| YES – NO                                           | -0.128 | -0.273                  | 0.016  | 0.082           |
| Smoking history                                    |        |                         |        |                 |
| NO – YES                                           | -0.009 | -0.119                  | 0.102  | 0.878           |
| Physical activity (Quartiles)                      |        |                         |        |                 |
| 2 – 1                                              | -0.111 | -0.259                  | 0.037  | 0.142           |
| 3 – 1                                              | -0.021 | -0.171                  | 0.129  | 0.784           |
| 4 – 1                                              | -0.015 | -0.179                  | 0.149  | 0.855           |
| Number of minor (outpatient) surgeries             | -0.024 | -0.079                  | 0.031  | 0.397           |
| R2 = 0.794<br>Betas reported on transformed scale. |        |                         |        |                 |

**Table X.** — Sensitivity analysis for the association of chronicity of prior major (inpatient) surgeries (at least 3 recurrent major surgeries) with total body lean mass (g) in elderly.

| Predictor                                                                                                              | Beta   | 95% Confidence Interval |        |                 |
|------------------------------------------------------------------------------------------------------------------------|--------|-------------------------|--------|-----------------|
|                                                                                                                        |        | Lower                   | Upper  | p               |
| Age                                                                                                                    | 0.07   | -0.061                  | 0.201  | 0.282           |
| Sex                                                                                                                    |        |                         |        |                 |
| FEMALE – MALE                                                                                                          | -1.582 | -1.876                  | -1.288 | <b>&lt;.001</b> |
| MIDUS HEI                                                                                                              | -0.07  | -0.201                  | 0.061  | 0.284           |
| HbA1c                                                                                                                  | -0.107 | -0.236                  | 0.022  | 0.101           |
| Triglycerides                                                                                                          | 0.002  | -0.128                  | 0.131  | 0.977           |
| serum Creatinine                                                                                                       | -0.207 | -0.36                   | -0.054 | <b>0.01</b>     |
| BMI                                                                                                                    | 0.777  | 0.657                   | 0.896  | <b>&lt;.001</b> |
| Beta-blocker use                                                                                                       |        |                         |        |                 |
| YES – NO                                                                                                               | -0.152 | -0.425                  | 0.121  | 0.265           |
| Smoking history                                                                                                        |        |                         |        |                 |
| NO – YES                                                                                                               | -0.004 | -0.231                  | 0.223  | 0.973           |
| Physical activity (Quartiles)                                                                                          |        |                         |        |                 |
| 2 – 1                                                                                                                  | -0.232 | -0.522                  | 0.057  | 0.111           |
| 3 – 1                                                                                                                  | -0.153 | -0.486                  | 0.18   | 0.355           |
| 4 – 1                                                                                                                  | 0.141  | -0.247                  | 0.528  | 0.465           |
| Number of surgeries                                                                                                    |        |                         |        |                 |
| more than 3 – 3 or less                                                                                                | -0.225 | -0.516                  | 0.066  | 0.125           |
| R2= 0.923<br>*TBLM Betas are reported on original untransformed scale, as assumptions were met without transformation. |        |                         |        |                 |

patients has revealed sustained reductions in BMD alongside prolonged elevations in bone turnover markers such as osteocalcin, C-terminal cross-linked telopeptide of type I collagen (CTX), and bone-specific alkaline phosphatase (BALP)<sup>21</sup>. This imbalance suggests a potential uncoupling between bone resorption and formation following surgical interventions, leading to net bone loss<sup>21</sup>.

Beyond underlying morbidities that may affect BMD chronically, surgical procedures act as systemic stressors that activate inflammatory and neuroendocrine pathways, often resulting in elevated levels of interleukin-6 (IL-6) and cortisol<sup>22,23</sup>. While these responses are physiologically adaptive in the short term, exaggerated or repeated activation may induce adverse systemic effects<sup>1</sup>. Within the skeletal system, pro-inflammatory mediators like IL-6 stimulate osteoclast differentiation via the RANK/RANKL signaling pathway<sup>24</sup>, while elevated cortisol levels may reduce osteoblast proliferation by downregulating anabolic pathways such as IGF-1 and WNT signaling<sup>25</sup>. Although these mechanisms were not tested directly in the current study, they provide a plausible theoretical framework for the lower bone mass observed in individuals with high surgical exposure. Of note, while total body bone mass provides a valuable global overview of skeletal health, an important indicator of osteoporosis and bone health in older adults, it may dilute or fail to capture site-specific bone loss (e.g., at the femoral neck or lumbar spine) which are highly relevant to fracture risk in the same population. Therefore, fracture risk, which is usually related to the site-specific density, is not related to the current study findings. This is because the current study utilized TBBM as the dependent variable to focus on the physiological association rather than post-surgical exposure fractures risk.

In contrast to the significant association between surgical exposure and TBBM, the lack of a significant association between surgical history and TBLM suggests that skeletal muscle may be more resilient to repeated surgical stress than bone. Skeletal muscle mass is influenced by diverse factors, including physical activity and nutritional status<sup>6</sup>. It is possible that recovery periods between procedures allow for the restoration of muscle protein synthesis, particularly as the body typically transitions from a catabolic state to an anabolic recovery phase several days post-surgery<sup>26</sup>. However, healthier dietary habits were significantly associated with greater TBLM in this cohort, highlighting the importance of nutrition—specifically protein, vitamin D, and antioxidants—in

maintaining muscle mass during aging<sup>27-31</sup>. Adherence to nutrient-dense dietary patterns may mitigate “inflammaging” and stimulate anabolic signaling, representing a key strategy for reducing sarcopenia risk<sup>32,33</sup>.

Consistent with established literature, advancing age was a strong associated factor with lower bone and muscle mass, reflecting the cumulative influence of hormonal declines, reduced mechanical loading, and chronic low-grade inflammation<sup>13,36-45</sup>. Although numerous studies have documented age-related reductions in bone density and muscle strength, variability in these relationships has been observed due to sex-specific hormonal influences and complex muscle–bone interactions<sup>46,47</sup>. Longitudinal research further indicates that muscle loss is associated with subsequent bone loss in both sexes, underscoring the close biological relationship between skeletal muscle and bone during aging<sup>47-49</sup>.

The observed positive association between BMI and musculoskeletal mass in our study may be explained by the increased mechanical loading and the endocrine effects of adipose-derived estrogen, which contributes to the preservation of bone density in older populations<sup>50-51</sup>. Taken together, these findings underscore the complex biological relationship between surgical stress and age-related musculoskeletal decline.

### Implications

The observed association between recurrent surgical exposure and lower bone mass highlights the potential importance of surgical history as a risk factor for skeletal deterioration and osteoporosis in older adults. Although our study is exploratory, recognizing this risk earlier in the clinical course may allow clinicians to implement preventive strategies aimed at preserving bone health following surgical procedures. Early interventions designed to maintain bone mass during the postoperative period may be particularly valuable in individuals already at risk for osteoporosis<sup>52</sup>, although further research is needed to confirm the efficacy of such interventions and to adjust carefully for potentially confounding underlying comorbidities.

Pharmacological management of postoperative bone health should prioritize vitamin D supplementation to support mineralization, particularly in the perioperative periods<sup>53</sup>. In high-risk patients, anti-resorptive therapies such as bisphosphonates can inhibit osteoclast-mediated resorption, potentially stabilizing bone remodeling when initiated during periods of accelerated turnover following surgery<sup>54-56</sup>.

Behavioral and lifestyle interventions provide synergistic benefits by restoring necessary mechanical loading and metabolic support. Early mobilization and structured resistance-based physiotherapy are essential for stimulating bone formation and enhancing muscle mass, thereby reducing falls and fracture risk and enhancing recovery<sup>57,58</sup>. These efforts should be supported by adequate dietary protein to optimize overall skeletal recovery<sup>59</sup>. These approaches will protect musculoskeletal health and are likely to improve underlying morbidities.

Although we didn't see a significant association between recurrent surgical exposure and TBLM, this finding can have important implications. The lack of a significant association with TBLM suggests a divergent long-term recovery trajectory between muscle and bone tissues. While muscle tissue may successfully regenerate or stabilize through post-operative physical activity and rehabilitation, as discussed earlier, bone remodeling occurs at a much slower temporal scale. Consequently, clinical recovery of muscle strength following multiple surgeries should not misguide clinicians into assuming a parallel recovery of skeletal health, necessitating long-term, dedicated bone-preservation strategies.

### Limitations

The study is subject to several limitations. First, reliance on participant self-report introduces the potential for recall bias; however, this risk is partially mitigated by quantifying the number of procedures and corroborating the type of each surgery from each participant. Second, the cross-sectional design precludes definitive causal inference. Nonetheless, in the absence of prior longitudinal investigations, the present analysis provides valuable preliminary exploratory insights. Third, although the timing of prior surgeries was not captured, the cumulative number of procedures constitutes a clinically relevant factor in sympathetic derivation, thereby supporting the rationale underpinning this study. Fourth, although we controlled for important indicators for potential underlying morbidities, full control for underlying morbidities for which surgeries were conducted was inapplicable. MIDUS dataset did not include questions about the underlying causes for each of the prior surgeries. In addition, the dataset did not include questions about the presence of prior diagnoses that may require recurrent surgeries (i.e., participants were asked direct questions about the presence of common medical conditions like heart disease, diabetes, hypertension, respiratory conditions, and

other conditions, which do not require recurrent surgical interventions). Therefore, it is very hard to control for the underlying medical conditions for each surgery. Nevertheless, mentioning the descriptives of the surgeries and conducting multiple sensitivity analyses was the best approach to avoid confounding by indication as much as possible.

Finally, older adults with the highest surgical burden and worst musculoskeletal health may have died before participating in this wave of MIDUS study, potentially biasing results toward the healthier survivors.

## CONCLUSION

In conclusion, our findings suggest that recurrent surgical exposure is associated with reduced bone mass in later life. Although the potential role of underlying morbidities for which surgeries were done was not fully controlled, descriptive statistics and sensitivity analyses in our results supports a role for recurrent surgical exposure that should be studied further in future research. Early preventive strategies aimed at preserving bone health—particularly among individuals with a history of multiple surgical procedures—may help mitigate long-term skeletal deterioration. Future longitudinal research is warranted to further clarify the causal relationship between repeated surgical stress and changes in musculoskeletal health, and to assess the efficacy of pharmacological and behavioral preventive interventions.

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*Patient's consent:* Our study is a secondary analysis of publicly available data. The anonymity of the original participants was maintained in the dataset, and their consent was obtained for participation in the original MIDUS project.

*Data Availability:* Data analyzed in the current study is publicly available at: <https://www.icpsr.umich.edu/web/NACDA/studies/38837/publications>

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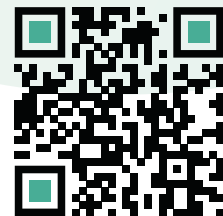
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