Title page

Do older adults with low muscle mass or strength, in the presence of obesity, have an increased risk of joint replacement over 13 years?

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Objective: This study aims to assess whether older adults with low muscle mass or strength, in the presence of obesity, have an increased risk of knee (TKR) and hip replacement (THR) over 13 years.

Methods: 1082 community-dwelling older adults (51% women; mean age 62.9±7.5 years) were studied at baseline and multiple time points over 13 years. The incidence of TKR and THR was determined by data linkage to National Joint Replacement Registry. Appendicular lean and fat mass were measured using DXA. Lower-limb muscle strength (LMS) was assessed by dynamometer. Low muscle mass and strength were defined as the lowest sex-specific tertiles for appendicular lean mass (adjusted for height and total body fat mass) and lower-limb strength, respectively. Obesity was defined as the highest sex-specific tertile for total body fat mass. Competing risk regression models were used to estimate the sub-distribution hazard ratio (SHR) for TKR and THR.

Results: Over 13 years of follow-up, 6.8% (n=74/1082) of the participants had a TKR and 4.7% (n=50/1066) had THR.Participants with the combination of obesity and low muscle strength (SHR=3.36, 95% CI: 1.50, 7.53) but low muscle mass (SHR=1.11, 95% CI: 0.52, 2.40) had a significantly increased risk of TKR, compared to individuals with neither obesity nor low muscle mass/strength. . However, obesity with low muscle strength did not lead to a significantly greater risk of TKR compared to having low muscle strength or obesity alone. There was no evidence for an association between obesity with low muscle mass or strength and THR (all p>0.05).

Conclusions: This finding suggests that combining muscle and fat assessments to predict the future risk of TKR is no better than each condition on its own.

Keywords: Sarcopenia, dynapenia, obesity, joint replacement

Introduction

Joint replacement surgeries are an expensive procedure with an estimated cost of $2 billion a year in Australia (1). With an ageing population, the proportion of older people with OA who may require joint replacement surgery is projected to increase. Therefore, identifying groups of OA patients who progress to end-stage disease and require joint replacement is crucial to develop interventions to delay disease progression.

Age-related changes in body composition including a decline in muscle mass and strength, along with increased fat mass, are closely interconnected, however, they have been considered as independent risk factors for osteoarthritis and joint replacement (2-4). The interconnection between obesity and muscle loss is profound and both conditions may exacerbate one another. For instance, a decline in muscle mass is accompanied by fat infiltration within and around the skeletal muscle leading to impairment in muscle function (5). Furthermore, excess production of fatty acids in obese individuals are stored not only in the adipose tissues but in other tissues including skeletal muscle (5). These fatty acids and their derivatives enhance the secretion of pro-inflammatory markers that exacerbate muscle loss and induce muscle dysfunction (5). Due to their close interconnection, the simultaneous occurrence of obesity and low muscle mass/strength could substantially increase the risk of joint replacement compared to low muscle mass/strength or obesity alone.

Prior studies have demonstrated that knee OA was more prevalent among older adults with combined obesity and low muscle mass compared to those with neither condition (6-8). However, limited long-term prospective studies have described the association between the combination of obesity and low muscle mass or strength with joint replacement in older people. It is also unclear whether obesity when combined with low muscle mass, has a different effect on the risk of joint replacement than when combined with low muscle

strength. This is particularly important to investigate because age-related decline in skeletal muscle mass may not always be accompanied by a reduction in strength (9, 10). Therefore, this study aims to describe the association between low muscle mass or strength , in the presence of obesity, with total knee (TKR) and hip replacement (THR) over 13 years among community-dwelling older adults.

Data and Methods

Sample and Study Setting

The Tasmanian Older Adult Cohort (TASOAC) study is a prospective, population-based study primarily aimed at examining the causes and progression of osteoarthritis. Participants aged 50 years and above were selected using sex-stratified random sampling from the electoral roll in Southern Tasmania (population 229,000). A total of 1099 adults (response rate = 57%) consented to participate in the study and were invited to attend a clinic at the Menzies Institute for Medical Research, Hobart, Tasmania between March 2002 and September 2004. They were invited to follow–up clinic assessments at 2.5, 5, and 10 years after the initial clinic assessment. The study was approved by the Tasmanian Health and Medical Research Ethics Committee and written informed consent was obtained from all participants.

Outcome measures

Hip and knee joint replacement

The incidence of TKR and THR was determined by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR). The AOA NJRR provides high quality information on the practice of joint replacement surgery in private and public hospitals in Australia. The registry dataset provides information on date of joint replacement surgery, type of procedure (primary total or revision), side of joint

replacement (left or right) and patients details including date of birth, sex and postcode. The data are validated against State Health Department using a sequential multilevel matching process (11). Further details about the AOA NJRR has been provided elsewhere (11).

Baseline measures

Body composition and anthropometric measures: Lean mass and total body fat mass were measured using dual-energy X-ray absorptiometry (DXA; Hologic Delphi, Hologic, Waltham USA). Appendicular lean mass (ALM) calculated as the sum of lean mass in the upper and lower limbs. Height was measured to the nearest 0.1 centimetres using Leicester stadiometer (Invicta, Leicester, UK), with shoes, socks and headgear removed. Weight was measured to the nearest 0.1 kilograms (kg) using electronic scales (Heine, Dover, USA) with shoes and heavy clothing removed. Body mass index (BMI) was calculated as weight (kg) divided by height (meter) squared.

Muscle strength: Lower-limb muscle strength was measured to the nearest kilogram simultaneously for both limbs using a dynamometer (TTM Muscular Meter, Tokyo, Japan). Two trials were recorded and the average of the two trials was taken as previously described (12). The intra-class correlation coefficients of the first and second trial for lower-limb muscle strength assessments was 0.95 (95% CI: 0.94 – 0.96).

Definitions of low muscle mass, strength and obesity :

Obesity with low muscle mass or strength were defined using cut-points established in our previous study (13, 14). Lean mass was calculated as the residuals of the linear regression of ALM on height and total body fat mass, as suggested by Newman et al (15). To be consistent with our previous definitions of obesity with low muscle mass or strength , we define low muscle mass as the sex-specific lowest tertile of the distribution of ALM residuals, as opposed to sex-specific lowest 20% originally define by Newman et al (13-15).

Participants in the lowest sex-specific tertile of muscle strength were classified as having low muscle strength and those in the highest sex-specific tertile of total body fat mass were classified as obese. Participants were classified into one of the following four categories based on their muscle mass, strength and obesity status: (1) neither obesity nor low muscle mass ; (2) low muscle mass alone ; (3) obesity alone ; (4) obesity with low muscle mass . A similar classification was made based on low muscle strength and obesity status: (1) neither obesity nor low muscle strength ; (2) low muscle strength alone ; (3) obesity alone; (4) obesity with low muscle strength .

Covariates

Age, sex, hip and knee pain were recorded using a questionnaire at baseline. The presence of knee and hip radiographic osteoarthritis (ROA) at baseline were assessed using Altman atlas as previously described (16). Joint space narrowing (JSN) and osteophytes in the knee and hip were assessed on a scale of 0–3 (where 0=no disease and 3=most severe disease). Participants were dichotomised as having knee/hip ROA (presence of either JSN or osteophytes) or not (no JSN or osteophytes). Physical activity was measured objectively over seven consecutive days using a pedometer (Omron HJ-003 & HJ-102; Omron Healthcare, Kyoto, Japan) as previously described (17).

Data analysis

Categorical and continuous variables were compared across categories of obesity/muscle mass and obesity/muscle strength using Chi-square tests and one-way ANOVA, respectively. Competing risk regression models were used to estimate the sub-distribution hazard ratio (SHR) for TKR and THR over 13 years in unadjusted and adjusted analysis (18). This analysis was used to address competing risk, such as death (18, 19). In survival analysis, a competing risk (e.g. death) is an event that occurs before the experience

of the primary outcome of interest, making it difficult to know whether an individual would have experienced the outcome of interest if they had not had the competing event (19). The TKR model was adjusted for gender, knee pain and knee ROA. The THR model was adjusted for gender, hip pain and hip ROA. We assessed statistical interaction between sex and low muscle mass/obesity and low muscle strength / obesity status. Multiple imputation by chained equation (MICE) was used to estimate missing data. We performed 50 imputations and our imputation model include auxiliary variables such as alcohol consumption, education and smoking status, in addition to the variables included in the main analysis. Data were analysed using Stata version 16 (StataCorp, TX, USA).

Results

Of the 1099 participants who attended the baseline clinic, we excluded 17 individuals who had joint replacement prior to baseline, leaving 1082 participants (51% women; mean age 62.8±7.4 years) eligible for data analysis (Figure 1). We included 1066 participants in the hip replacement analysis as we excluded 16 participants who had THR due to diagnosis other than osteoarthritis. Baseline characteristics of the participants stratified according to low muscle mass, strength and obesitystatus are presented in Table 1. There were no significant differences among participants in the various muscle mass or obesity categories with respect to age, physical activity, smoking, and hip ROA. However, there were a higher proportion of women among participants with low muscle mass alone and obesity with low muscle mass . Obese participants, with or without low muscle mass, were taller, weighed more, and they had a higher knee ROA, higher hip and knee pain, and a greater number of chronic conditions. Alcohol consumption was lowest among participants with both obesity and low muscle mass.

There were no significant differences in sex, height, physical activity, smoking, and hip ROA among participants in the various muscle strength and obesity categories. However, participants who had low muscle strength, with or without obesity, were older than those who were obese alone or those with neither obesity nor low muscle strength. Obese participants with or without low muscle strength were weightier, and they had a higher knee ROA, hip and knee pain. Participants with combined obesity and low muscle strength had the highest number of chronic conditions and they consumed the least amount of alcohol.

Incident TKR and THR over 13 years were 6.8% (n=74/1082) and 4.7% (n=50/1066) respectively. Figure 2 shows the incidence of TKR over 13 years according to muscle mass/obesity (Figure 2A) and muscle strength/ obesity status (Figure 2B). The incidence of TKR was highest among individuals with obesity (without low muscle mass) alone (Figure 2A) and those with both obesity and low muscle strength (Figure 2B) participants. Individuals with low muscle mass alone (Figure 3A) and those with obesity alone (Figure 3B) had the highest incidence of THR.

Associations between obesity with or without low muscle mass or strength and knee joint replacement

Table 2 presents the SHR for TKR according to muscle mass, strength and obesity categories. Compared to those with neither obesity nor low muscle mass, participants with low muscle mass alone, obesity alone or those with combined obesity and low muscle mass did not have a significantly higher risk of TKR in the adjusted model. There was no significant interaction between sex and muscle mass/obesity (p=0.71).

The risk of TKR was higher among older adults with combined low muscle strength and obesity and those with obesity or low muscle strength alone, , compared to those with neither obesity nor low muscle strength y. Nevertheless, obesity with low muscle strength

did not lead to a significantly greater risk of TKR compared to those with low muscle strength alone (SHR=1.22, 95% CI: 0.63, 2.38, p= 0.55) or obesity alone (SHR=0.97, 95% CI: 0.51, 1.86; p=0.94). There was no significant sex (p=0.42) interaction with regards to the association between muscle strength/ obesity and TKR.

Associations between obesity with or without low muscle mass and strength and hip joint replacement

Table 3 shows the SHR for THR according to obesity and low muscle mass or strength categories. There was no significant increase in the risk of THR among participants with both low muscle mass and obesity and those with low muscle mass or obesity alone , compared to those with neither low muscle mass nor obesity (all p>0.05). Similarly, compared to those with neither low muscle strength nor obesity, participants with combined low muscle strength and obesity and those with low muscle strength or or obesity alone did not have a significantly higher risk of THR (all p>0.05).

Discussion

This 13-year prospective study is the first, to our knowledge, investigating the relationship between low muscle mass or strength in the presence of obesity with the risk of knee and hip joints replacement among community-dwelling older adults. In the presence of obesity, low muscle strength but not low muscle massincreased the risk of TKR. Notably, the combination of low muscle strength and obesity did not lead to a significantly greater risk of knee replacement compared to having these conditions on their own. This finding suggests that combining muscle and fat assessments to predict the future risk of a joint replacement is no better than each condition on its own. We found no evidence for an association between obesity and low muscle mass or strength and THR.

Obesity, whether alone or in combination with low muscle strength increase the risk of TKR. Whereas, low muscle strength alone but not low muscle mass alone was associated with a higher risk of TKR. Obesity is an established risk factor for severe knee OA and TKR (2, 20). Prior studies also suggest that low muscle strength but not muscle mass was more closely related to the incidence and progression of knee OA, potentially explaining why the coexistence of obesity and low muscle strength appears to impact more on the risk of TKR than low muscle mass (21). Obesity increases knee joint articular cartilage loading forces and (20) weaker lower-limb muscle strength alter joint stability and increases maladaptive postures (22). Therefore, the coexistence of obesity and low muscle strength can substantially increase biomechanical constraint that could result in the onset of knee OA and may also accelerate the progression to end-stage disease (22). Furthermore, fat infiltration in the muscle of obese individuals could be offset by physical activity, however, weaker lower limb muscle strength in older adults with obesity may limit physical activity participation thereby leading to further fat accumulation (23). Inflammatory markers including adipokines in this excess adipose tissue could accelerate cartilage degradation and progression to end-stage knee osteoarthritis (24). Nevertheless, our finding that the risk of TKR in older adults with both low muscle strength and obesity was not significantly greater compared to having obesity or low muscle strength alone suggests that combining these assessments in clinical practice may not improve prediction of TKR.

Obesity, with or without low muscle mass or strength does not significantly increase the risk of THR. Unlike the knee joint, the findings from studies describing the relationship between body composition and hip OA and hip replacement have been inconsistent (20, 25-27). The reason for the discrepancy in the relationship between body composition and hip and TKR is unclear but may be related to the anatomical structure of the hip joint (25). The knee is a hinge joint whereas the hip is a ball-and-socket joint and joint malalignment has been

shown to mediate the relationship between obesity and knee but not hip OA (28-30). This implies that when there are higher forces on the joints (due to obesity), the force in a mal-aligned hinge joint (knee) may be doubled or tripled compared with a normal aligned hip joint (25). This excess mechanical loading makes the knee more susceptible to cartilage damage. Indeed, obesity has some systemic metabolic effects that influences the development and progression of OA, in addition to the biomechanical effects. However, this systemic effect does not explain why obesity is associated with knee but not hip replacement.

The strength of this study includes the 13-year follow-up period and the use of DXA, a valid body composition device for the assessment of lean mass. Furthermore, record of THR and TKR were verified in a national registry, increasing the accuracy of the ascertainment of our outcome. In addition, we studied the relationship between obesity and low muscle mass or strength and TKR and THR in a single population, allowing us to compare the effects that these conditions have on different joints in the same cohort of older adults. However, this study has some limitations. For instance, we did not use operational definitions of sarcopenia suggested by the European Working Group on Sarcopenia in Older People (EWGSOP) or the Foundation for National Institute of Health (FNIH) sarcopenia project, due to our middle-aged and relatively healthy older adult population. In contrast, we defined cut-points in the lowest tertile of the sex-specific distribution of muscle mass and strength, which we have previously shown to be associated with a greater risk of poorer health outcomes including falls, fracture and low bone mineral density (13, 14). Lastly, the event rate for THR was low in our sample, which may contribute to the weaker association between obesity and low muscle mass or strength and THR.

In conclusion, in the presence of obesity, low muscle strength but not low muscle mass increased the risk of TKR. Notably, the combination of low muscle strength and obesity did not lead to a significantly greater risk of knee replacement compared to having these

conditions on their own. This finding suggests that combining muscle and fat assessments to predict the future risk of knee joint replacement is no better than each condition on its own.

Conflict of Interest: The authors declare that they have no competing interests.

Availability of data and material: Data is available upon request.

Variables	Neither low muscle mass nor obesity $N = 400$	Obese without low muscle mass $N =262$	Low muscle mass without obesity $N =283$	Obesity with low muscle mass $N =130$	Neither low muscle strength nor obesity $N =413$	Obese without low muscle strength $N =238$	Low muscle strength without obesity $N =244$	Obesity with low muscle strength $N =135$
Age (years)	63.3 (7.8)	63.0 (7.2)	62.3 (7.6)	62.5 (6.8)	**61.0 (6.9)**	**61.6 (6.7)**	**65.5 (8.0)**	**64.8 (7.3)**
Female (%)*	**30%**	**44%**	**80%**	**72%**	50%	48%	49%	60%
Weight (Kg)	**73.6 (10.3)**	**93.2 (11.4)**	**65.2 (7.9**	**85.4 (11.2)**	**71.4 (10.6)**	**92.2 (12.0)**	**68.7 (9.5)**	**88.6 (12.4)**
Height (cm)	**167.1(9.4)**	**167.6 (9.8)**	**165.4 (7.7)**	**168.5 (8.7)**	167.4 (8.8)	169.2 (9.3)	165.3 (8.5)	166.0 (9.2)
BMI (kg/m^2)	**26.3 (2.5)**	**33.3 (3.9)**	**23.8 (2.2)**	**30.1 (3.1)**	**25.4 (2.6)**	**32.2 (3.7)**	**25.1 (2.9)**	**32.3 (4.7)**
Physical activity (steps/day)	9528 (3371)	7839 (3412)	8664 (3122)	7622 (2979)	9762 (3101)	8108 (3216)	8338 (3468)	7317 (3384)
Current smoker (%)*	13%	10%	14%	8%	13%	11%	15%	6%
Alcohol consumption (g/day)	**16.3(20.5)**	**16.4 (20.7)**	**13.6 (17.1)**	**10.5 (15.4)**	**16.2 (19.1)**	**17.0 (21.4)**	**14.0 (19.9)**	**11.0 (15.4)**
Number of chronic conditions	**1.4 (1.4)**	**1.7 (1.5)**	**1.3 (1.2)**	**1.7 (1.3)**	**1.1 (1.2)**	**1.5 (1.3)**	**1.5 (1.4)**	**2.1 (1.6)**
Hip pain (%)*	**37%**	**46%**	**38%**	**51%**	**33%**	**44%**	**43%**	**53%**
Hip ROA (%)*	40%	45%	38%	37%	37%	38%	41%	47%
Knee ROA (%)*	**65%**	**75%**	**64%**	**70%**	**62%**	**72%**	**70%**	**80%**
Knee pain (%)*	**38%**	**54%**	**45%**	**57%**	**35%**	**51%**	**49%**	**58%**
WOMAC knee pain	**3.0 (5.9)**	**5.1 (7.8)**	**3.1 (5.4)**	**4.3 (5.7)**	**2.1 (4.5)**	**3.8 (6.1)**	**4.2 (6.3)**	**5.6 (7.8)**

Table 1: Baseline descriptive characteristics according to categories of muscle mass, strength and obesity

All tests are one-way ANOVA except * (Chi-square test), data in bold indicate statistical difference ($p<0.05$) among groups, ROA: radiographic osteoarthritis

Table 2: Sub-distribution hazard ratio (SHR) of knee replacement over 13 years according to categories of muscle mass, strength, and obesity (N=1082).

	Neither low muscle mass nor obesity	Obese without low muscle mass	Low muscle mass without obesity	Obesity with low muscle mass
Unadjusted	REF	**2.38 (1.33, 4.25)**	1.14 (0.58, 2.25)	1.80 (0.86, 3.76)
Adjusted‡	REF	1.72 (0.95, 3.11)	0.83 (0.40, 1.70)	1.11 (0.52, 2.40)

	Neither low muscle strength nor obesity	Obese without low muscle strength	Low muscle strength without obesity	Obesity with low muscle strength
Unadjusted	REF	**3.41 (1.59, 7.29)**	**4.11 (1.96, 8.61)**	**5.09 (2.34, 11.08)**
Adjusted‡	REF	**2.74 (1.27, 5.92)**	**3.45 (1.64, 7.28)**	**3.36 (1.50, 7.53)**

‡Adjusted for sex, radiographic knee OA and knee pain
Bold text indicates significant at $P < 0.05$

Table 3: Sub-distribution hazard ratio (SHR) of hip replacement over 13 years according to categories of muscle mass, strength and obesity (N=1066).

	Neither low muscle mass nor obesity	Obese without low muscle mass	Low muscle mass without obesity	Obesity with low muscle mass
Unadjusted	REF	1.31 (0.60, 2.83)	1.67 (0.82, 3.40)	1.78 (0.75, 4.23)
Adjusted‡	REF	1.09 (0.49, 2.42)	1.81 (0.82, 4.02)	1.76 (0.73, 4.25)

	Neither low muscle strength nor obesity	Obese without low muscle strength	Low muscle strength without obesity	Obesity with low muscle strength
Unadjusted	REF	1.51 (0.74, 3.10)	1.32 (0.62, 2.77)	0.97 (0.35, 2.65)
Adjusted‡	REF	1.31 (0.64, 2.66)	1.05 (0.50, 2.20)	0.62 (0.22, 1.72)

‡Adjusted for sex, radiographic hip OA and hip pain
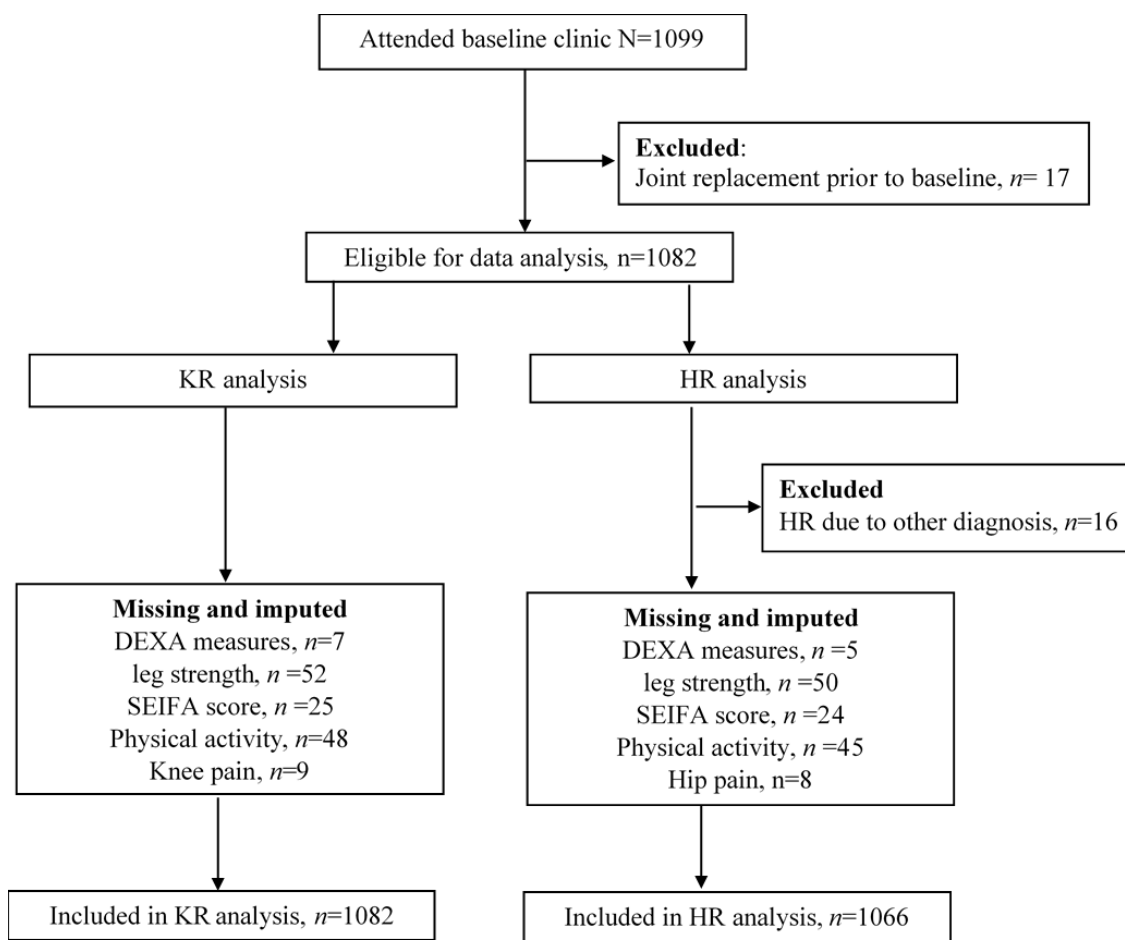Bold text indicates significant at $P < 0.05$
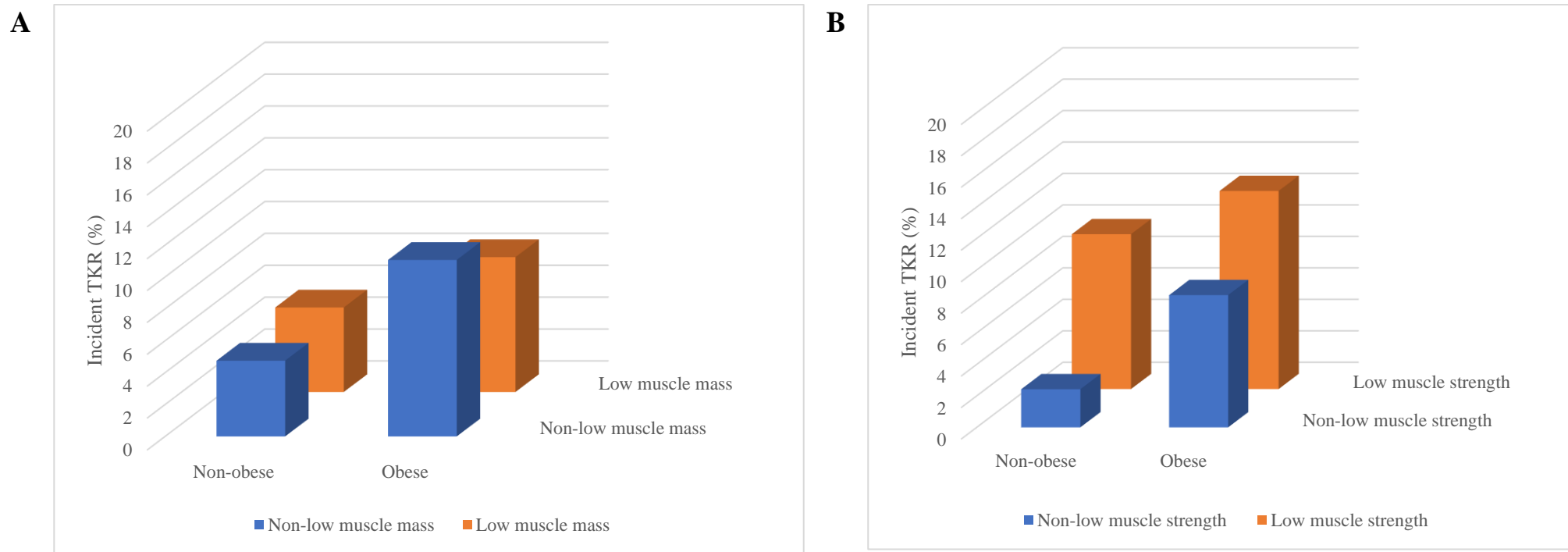
Figure 1: Study flow chart

A

B

Figure 2: Incidence of total knee replacement (TKR) according to muscle mass /obesity (A) and muscle strength /obesity (B) status.

A

Incident THR (%)

20
18
16
14
12
10
8
6
4
2
0

Non-obese   Obese

No

■ Non-low muscle mass   ■ Low m

B

Incident THR (%)

20
18
16
14
12
10
8
6
4
2
0

Non-obese   Obese

No
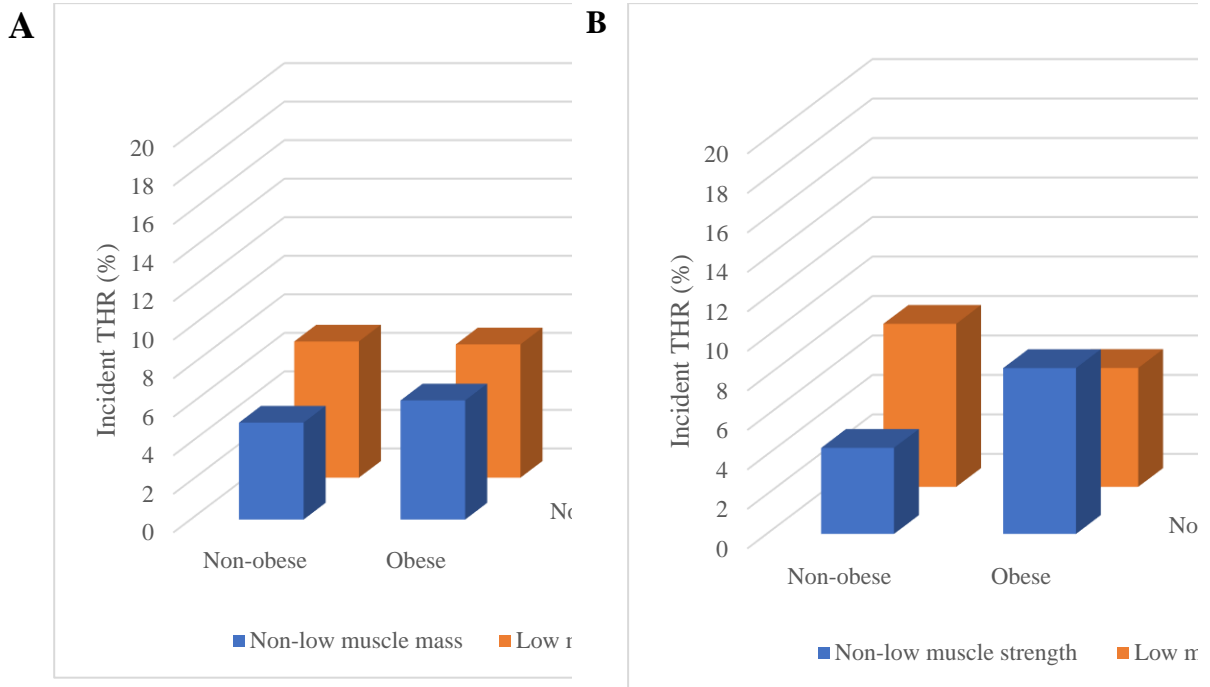
■ Non-low muscle strength   ■ Low m

Figure 3: Incidence of total hip replacement (HKR) according to muscle strength /obesity (A) and muscle strength/obesity (B) status.

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