1. Please indicate below which paper you were assigned.
   1. John et al., Alcohol abstinence and mortality in a general population sample of adults in Germany: A cohort study
   2. Kim et al., Association between sarcopenia level and metabolic syndrome
2. Submit a written report that includes:
   1. Objective (1 sentence)

Based on the same dataset the authors of Kim et al. we developed new two research questions: 1) to identify an association between appendicular skeletal muscle mass per body weight and hypertension among Korean adults aged 25 to 60 years and 2) to identify an association between appendicular skeletal muscle mass per body weight and mean arterial blood pressure among Korean adults aged 25 to 60 years.

* 1. Methods text. Describe your methods with the same level of detail as you would in a scientific manuscript. Justify your approach (DAG, choice of covariates, modeling decisions, etc.)

We used a publicly available dataset of 1,620 participants 20 years and older who underwent a voluntary routine health check up at the healthcare center of Seoul National University Boramea Medical Center from October 2014 to December 2019. Patients with insufficient data, multiple health checkups and history of malignancy were excluded from this dataset (1). Further we restricted our analyses to 10,759 patients aged between 25 and 60 because those younger ages were more likely to develop a secondary hypertension and those older ages required other specific criteria for blood pressure control (2,3). Data collection procedure is reported elsewhere (1).

Appendicular skeletal muscle mass (ASM) was calculated as the sum of the lean skeletal muscle mass of the bilateral upper and lower limbs. To better assess the relative proportion of ASM in each subject, we also included the percentage of ASM (ASM%), defined as ASM divided by body weight (kg). HT was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, or the use of blood pressure medication. Mean arterial pressure (MAP), the average arterial pressure throughout one cardiac cycle, was estimated by DBP + 1/3(SBP – DBP).

Age and sex were known to be strong unmodifiable risk factors for hypertension (4) and they also highly correlated to appendicular skeletal muscle mass (5). Thus, we included age (years) and sex (female vs male) into our first model (model 1). Then we included history of smoking and alcohol consumption into the second model (model 2) to assess the potential confounding of these modifiable risk factors. History of smoking and alcohol consumption was defined as dichotomous variables for whether a subject has a smoking or drinking habit. Body mass index (BMI) was defined as the weight (kg) divided by height squared (m2). Waist circumference was recorded in centimeters (cm) and used jointly with BMI to present a more accurate depiction of body composition. These two variables were highly associated with hypertension and appendicular skeletal muscle mass , however, BMI and waist circumference could be collinear with ASM as measurement of body composition (6). History of diabetes was defined as fasting plasma glucose >= 126 mg/dL, glycated hemoglobin level >= 6.5%, or anti-diabetic medication including insulin. Although the variable representing dyslipidemia was present in the original dataset, the authors never specified its definition in the article. However, given dyslipidemia plays an integral role in our causal assumptions, we decided to include it in a final model. We left the sets of less reliable variables for confounding to be added in our last two models (model 3 & 4) to assess relative change in estimate.

Statistical analyses

Continuous variables were summarized using mean and standard deviation and categorical variables were summarized using counts and percentages. We performed bivariate and multivariable logistic regression to estimate the association between hypertension (yes vs no) and ASM%. Multivariable models were adjusted for age (years), sex (female vs male), history of smoking (yes vs no), history of alcohol intake (yes vs no), BMI (kg/m2), waist circumference (cm), history dyslipidemia (yes vs no), and history diabetes (yes vs no). and results were summarized using odds ratios (OR) and 95% confidence intervals (CI). Directed acyclic graph (DAG) was used to illustrate the assumption and plausible confounders of the relationship between HT and ASM% (Supplement Figure 1a).

We also explored the association between mean arterial blood pressure and ten percent increase of ASM (%) using generalized linear regression by adjusting with a similar set of confounders between ASM and hypertension. Those who have a medical history of hypertension are more likely to receive anti-hypertensive medicines which affect blood pressure measurement and classification of hypertension outcome. Thus, we conducted sensitivity analysis by excluding those who had a medical history of hypertension, then performed the statistical analyses described above. All analyses were performed using SAS 9.14, by SAS Institute Inc., Cary, NC, USA. E-values were calculated for each association estimation using an online web application provided by Mathur et al (7).

* 1. Results text and tables/figures

Totally 10,795 participants were included in our study. Mean age (sd) was 44.1 (9.62) years. Forty-five percent of them were female. The prevalence of hypertension was 26.3 percent (Table 1).

The bivariate logistic regression between ASM% and hypertension showed the association that favored the null (OR = 1.00; 95% CI = 0.99, 1.01). However, after adjusted for age and sex it appeared that ASM% was negative associated with hypertension (OR = 0.80; 95% CI = 0.78, 0.81). The point estimations of ORs between ASM% and hypertension seems to be stable after including risk behavioral variables in model 2. While the association tended to be attenuated to null when adding more variables in model 3 and 4 (Table 2).

The bivariate generalized linear regression between ASM% and MAP also showed the association that favored the null (β = 2.37; 95% CI = 1.73, 3.02). On the other hand, after adjusted for age and sex it appeared that ASM% was negative associated with MAP (β = -11.23; 95% CI = -12.01, -10.45) (Table 3). After excluding those with known history of hypertension, there was no significant change (>10%) in estimations (Supplement Table 1a).

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| **Table 1. Characteristics of study participants** | |
|  | Total  (n=10,759) |
| ASM (%) | 30.2 ± 3.5 |
| Age (years) | 44.1 ± 9.6 |
| Female | 4846 (45.0) |
| History of smoking | 2064 (19.2) |
| History of alcohol intake | 6098 (56.7) |
| BMI (kg/m2) | 23.7 ± 3.5 |
| Obesity status according to BMI |  |
| Under weight (BMI < 18.5 kg/m2) | 444 (4.1) |
| Normal (BMI 18.5-22.9 kg/m2) | 4469 (41.5) |
| Overweight (BMI 23-24.9 kg/m2) | 2334 (21.7) |
| Obesity (BMI ≥ 25 kg/m2) | 3512 (32.6) |
| Waist circumference (cm) | 83.2 ± 9.9 |
| Dyslipidemia | 3682 (34.2) |
| Diabetes | 651 (6.1) |
| Hypertension | 2826 (26.3) |
| Data are presented as mean ± SD or number (%) | |

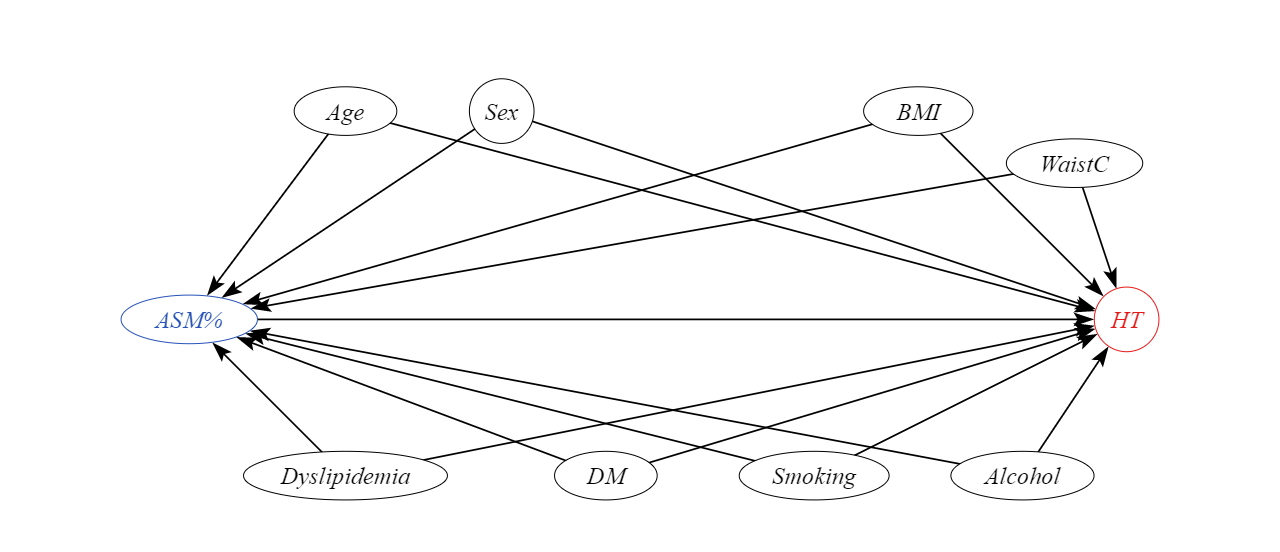
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| **Table 2. Association between appendicular skeletal mass per body weight (%) and hypertension** | | | |
|  | OR | 95% CI | E-value |
| Crude | 1.00 | 0.99, 1.01 | 1.04\* |
| Model 1 | 0.80 | 0.78, 0.81 | 1.46 |
| Model 2 | 0.81 | 0.79, 0.83 | 1.46 |
| Model 3 | 0.96 | 0.93, 0.98 | 1.17 |
| Model 4 | 0.97 | 0.94, 1.00 | 1.14 |
| Model 1 adjusted for age, sex | | | |
| Model 2 adjusted for age, sex, history of smoking, history of alcohol intake | | | |
| Model 3 adjusted for age, sex, history of smoking, history of alcohol intake, BMI, waist circumference | | | |
| Model 4 adjusted for age, sex, history of smoking, history of alcohol intake, BMI, waist circumference, dyslipidemia, diabetes | | | |
| OR = odds ratio; 95% CI = 95% confidence interval. | | | |
| \*OR = 0.997 was used to calculate E-value. | | | |

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| **Table 3. Average change in mean arterial blood pressure per 10% increase in appendicular skeletal mass per body weight** | | | |
|  | β | 95% CI | E-value |
| Crude | 2.37 | 1.73, 3.02 | 1.69 |
| Model 1 | -11.23 | -12.01, -10.45 | 4.74 |
| Model 2 | -11.26 | -12.03, -10.48 | 4.76 |
| Model 3 | -1.25 | -2.31, -0.19 | 1.48 |
| Model 4 | -0.96 | -2.03, 0.10 | 1.40 |
| Model 1 adjusted for age, sex | | |  |
| Model 2 adjusted for age, sex, history of smoking, history of alcohol intake | | | |
| Model 3 adjusted for age, sex, history of smoking, history of alcohol intake, BMI, waist circumference | | | |
| Model 4 adjusted for age, sex, history of smoking, history of alcohol intake, BMI, waist circumference, dyslipidemia, diabetes | | | |
| β = beta coefficient for generalized linear regression model; 95% CI = 95% confidence interval | | | |

* 1. A brief summary of your conclusions

We found a negative association between ASM% and hypertension which age and sex were strong confounder for this association. Further causal relationship between ASM% and hypertension should be investigated by longitudinal study design.

* 1. Provide any necessary supplementary materials



**Figure 1a.** Directed acyclic graph for association between percent of appendicular skeletal muscle mass per body weight (ASM%) and hypertension (HT)

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| **Table 1a. Sensitivity analysis for average change in mean arterial blood pressure per 10% increase in appendicular skeletal mass per body weight, excluding those with known history of hypertension** | | | |
|  | β | 95% CI | E-value |
| Crude | 2.62 | 1.95, 3.28 | 1.76 |
| Model 1 | -11.14 | -11.96, -10.33 | 4.83 |
| Model 2 | -11.17 | -11.98, -10.36 | 4.86 |
| Model 3 | -1.69 | -2.79, -0.58 | 1.61 |
| Model 4 | -1.40 | -2.51, -0.30 | 1.53 |
| Model 1 adjusted for age, sex | | |  |
| Model 2 adjusted for age, sex, history of smoking, history of alcohol intake | | | |
| Model 3 adjusted for age, sex, history of smoking, history of alcohol intake, BMI, waist circumference | | | |
| Model 4 adjusted for age, sex, history of smoking, history of alcohol intake, BMI, waist circumference, dyslipidemia, diabetes | | | |
| β = beta coefficient for generalized linear regression model; 95% CI = 95% confidence interval | | | |

**References**

1. Kim SH, Jeong JB, Kang J, Ahn DW, Kim JW, Kim BG, et al. Association between sarcopenia level and metabolic syndrome. PLoS One [Internet]. 2021;16(3 March):1–15. Available from: http://dx.doi.org/10.1371/journal.pone.0248856

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6. Kim NH, Park Y, Kim NH, Kim SG. Weight-adjusted waist index reflects fat and muscle mass in the opposite direction in older adults. Age Ageing. 2021;50(3):780–6.

7. Mathur MB, Ding P, Riddell CA, VanderWeele TJ. Web Site and R Package for Computing E-values. Epidemiology. 2018;29(5):E45–7.

* 1. Provide a clean/labeled dataset with all variables required for analysis, data dictionary, and codebook.

Data set could be downloaded on: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0248856#sec019>

The code provided on GitHuub also includes data process.

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| **Data dictionary** | | | | |
| Number | Variable name | Variable label | Coded response | Variable type |
| 1 | ID | ID |  | Numeric |
| 2 | Sex | Sex | 1=Male 2=Female | Numeric |
| 3 | Age | Age in years |  | Numeric |
| 4 | mhx\_HT\_yn | Medical history of hypertension | 0=No 1=Yes | Numeric |
| 5 | HT | Hypertension | 0=No 1=Yes | Numeric |
| 6 | DM | Diabetes | 0=No 1=Yes | Numeric |
| 7 | DysL\_ | Dyslipidemia | 0=No 1=Yes | Numeric |
| 8 | bexam\_wc | Waist circumference (cm) |  | Numeric |
| 9 | bexam\_BMI | Body mass index (kg/m^2) |  | Numeric |
| 10 | bexam\_BP\_systolic | Systolic blood pressure (mmHg) |  | Numeric |
| 11 | bexam\_BP\_diastolic | Diastolic blood pressure (mmHg) |  | Numeric |
| 12 | ASM\_Wt\_ | Appendicular skeletal muscle mass (%) |  | Numeric |
| 13 | shx\_smoke\_yn | History of smoking | 0=No 1=Yes | Numeric |
| 14 | shx\_alcohol\_yn | History of alcohol intake | 0=No 1=Yes | Numeric |
| 15 | BMIgr | Obesity status according to BMI | 0=Under weight (BMI <18.5 kg/m^2) 1=Normal (BMI 18.5-22.9 kg/m^2) 2=Overweight (BMI 23-24.9 kg/m^2) 3=Obesity (BMI >=25 kg/m^2) | Numeric |
| 16 | MAP | Mean arterial blood pressure |  | Numeric |

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| **Codebook** | | | | | | | | | | | | |
| Number | Variable name | Variable label | Variable type | Mean | Min | Max | Values | Frequency category | Frequency | Percent | Missing | Missing percent |
| 1 | ID | ID | Numeric |  |  |  |  |  |  |  |  |  |
| 2 | Sex | Sex | Numeric |  |  |  | 1 | Male | 5913 | 54.96 | 0 | 0.00 |
|  |  |  |  |  |  |  | 2 | Female | 4846 | 45.04 |  |  |
| 3 | Age | Age in years | Numeric | 44.05 | 25.00 | 60.00 |  |  |  |  | 0 | 0.00 |
| 4 | mhx\_HT\_yn | Medical history of hypertension | Numeric |  |  |  | 0 | No | 9566 | 88.91 |  |  |
|  |  |  |  |  |  |  | 1 | Yes | 1193 | 11.09 |  |  |
| 5 | HT | Hypertension | Numeric |  |  |  | 0 | No | 7933 | 73.73 | 0 | 0.00 |
|  |  |  |  |  |  |  | 1 | Yes | 2826 | 26.27 |  |  |
| 6 | DM | Diabetes | Numeric |  |  |  | 0 | No | 10108 | 93.95 | 0 | 0.00 |
|  |  |  |  |  |  |  | 1 | Yes | 651 | 6.05 |  |  |
| 7 | DysL\_ | Dyslipidemia | Numeric |  |  |  | 0 | No | 7077 | 65.78 | 0 | 0.00 |
|  |  |  |  |  |  |  | 1 | Yes | 3682 | 34.22 |  |  |
| 8 | bexam\_wc | Waist circumference (cm) | Numeric | 83.23 | 55.50 | 155.00 |  |  |  |  | 0 | 0.00 |
| 9 | bexam\_BMI | Body mass index (kg/m^2) | Numeric | 23.69 | 14.30 | 68.10 |  |  |  |  | 0 | 0.00 |
| 10 | bexam\_BP\_systolic | Systolic blood pressure (mmHg) | Numeric | 79.55 | 41.00 | 135.00 |  |  |  |  | 0 | 0.00 |
| 11 | bexam\_BP\_diastolic | Diastolic blood pressure (mmHg) | Numeric | 116.39 | 70.00 | 187.00 |  |  |  |  | 0 | 0.00 |
| 12 | ASM\_Wt\_ | Appendicular skeletal muscle mass (%) | Numeric | 30.22 | 17.18 | 44.99 |  |  |  |  | 0 | 0.00 |
| 13 | shx\_smoke\_yn | History of smoking | Numeric |  |  |  | 0 | No | 8695 | 80.82 | 0 | 0.00 |
|  |  |  |  |  |  |  | 1 | Yes | 2064 | 19.18 |  |  |
| 14 | shx\_alcohol\_yn | History of alcohol intake | Numeric |  |  |  | 0 | No | 4661 | 43.32 | 0 | 0.00 |
|  |  |  |  |  |  |  | 1 | Yes | 6098 | 56.68 |  |  |
| 15 | BMIgr | Obesity status according to BMI | Numeric |  |  |  | 0 | Under weight (BMI <18.5 kg/m^2) | 444 | 4.13 | 0 | 0.00 |
|  |  |  |  |  |  |  | 1 | Normal (BMI 18.5-22.9 kg/m^2) | 4340 | 40.34 |  |  |
|  |  |  |  |  |  |  | 2 | Overweight (BMI 23-24.9 kg/m^2) | 2463 | 22.89 |  |  |
|  |  |  |  |  |  |  | 3 | Obesity (BMI >=25 kg/m^2) | 3512 | 32.64 |  |  |
| 16 | MAP | Mean arterial blood pressure | Numeric | 91.83 | 52.33 | 151.00 |  |  |  |  |  |  |

* 1. Provide a link to your code on GitHub