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Healthy ageing in older adults: an exploration of interactions between lifestyle, immune, metabolic, and gut microbial health

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CHAPTER 3

Physical activity and fiber intake beneficial for muscle health preservation during aging: A Comprehensive Cross-Sectional Study in the UK Biobank cohort

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ABSTRACT

Background: Aging triggers intricate physiological changes, particularly in whole-body fat-free mass (FFM) and handgrip strength, affecting overall health and independence. Despite existing research, the broader significance of how muscle health is affected by the intricate interplay of lifestyle factors simultaneously during aging needs more exploration. This study aims to examine how nutrition, physical activity, and sleep impact on FFM and handgrip strength in middle-aged men and women, facilitating future personalized recommendations for preserving muscle health.

Methods: The cross-sectional analysis of the UK Biobank involved 45,984 individuals (54% women) aged 40-70 years with a complete dataset. Multiple linear regression explored determinants of FFM and handgrip strength, considering traditional, socio-demographics, medication use and smoking as covariates, with sex and age (younger and older than 55 years) stratifications.

Results: In older men and women, higher physical activity beneficially affect both FFM (respectively $B = 3.36 \times 10^{-3}$, $p\text{-value} = 1.66 \times 10^{-3}$; $B = 2.52 \times 10^{-3}$, $p\text{-value} = 3.57 \times 10^{-4}$) and handgrip strength ($B = 6.05 \times 10^{-3}$, $p\text{-value} = 7.99 \times 10^{-5}$, $B = 8.98 \times 10^{-3}$, $p\text{-value} = 2.95 \times 10^{-15}$). Similar results were found in fiber intake for FFM in older men and women (respectively $B = 3.00 \times 10^{-2}$, $p\text{-value} = 2.76 \times 10^{-5}$; $B = 2.68 \times 10^{-2}$, $p\text{-value} = 1.78 \times 10^{-9}$) and handgrip strength ($B = 3.27 \times 10^{-2}$, $p\text{-value} = 1.40 \times 10^{-3}$; $B = 3.12 \times 10^{-2}$, $p\text{-value} = 1.34 \times 10^{-5}$). Other lifestyle factors influence FFM and handgrip strength differently. Key determinants influencing handgrip strength included higher protein intake, lower water intake, higher alcohol intake, and extended sleep duration whereas mainly higher water intake is associated with higher FFM.

Conclusions: In both men and women, the main factors associated with FFM and handgrip strength are physical activity and fiber intake, which may underlie a connection between gut and muscle health. Given the observed complexity of muscle health in the age and sex strata, further longitudinal research is needed to provide personalized lifestyle recommendations.

Keywords: healthy aging, biology of aging, lifestyle, nutrition, fiber intake, muscle health, UK Biobank

INTRODUCTION

Aging consists of a complex variety of physiological changes in all tissues. Specifically, shifts in muscle mass and strength have a significant impact on health and independent functioning at older ages. (1,2). Variations in handgrip strength often appear before significant reductions in muscle mass, which highlights the need to study the unique biological factors controlling these aspects separately (3,4). The muscle changes determine the individual health span and are largely influenced by sociodemographic and lifestyle factors.

The relationship between muscle health and traditional, clinical, lifestyle, and socio-demographic factors as previously explored in the literature is displayed in TABLE S1. Variables such as older age, female sex, lower BMI, lower waist circumference, high medication use, smoking, alcohol consumption, lower socioeconomic status, and Asian ethnicity are associated with lower muscle mass and strength.(5–9)) In addition, recent research has emphasized the impact also of other lifestyle factors like macronutrient intake and physical activity. Factors such as higher protein intake, water intake, dietary fiber, physical activity levels, and at least 7 hours of sleep have all been investigated for their separate positive effects on muscle health.(10–15) Sufficient water intake is important to safeguard muscle cell volume and function while alcohol consumption is associated with myopathies characterized by lower muscle protein content.(11,16,17)

Until now, most studies have examined all these effects individually, leading to a disjointed comprehension of the effect of lifestyle on muscle health. Understanding the intricate interactions affecting muscle health is crucial in shaping robust, age- and or sex-specific strategies to enforce muscle health in a personalized fashion. This study aims to understand how nutrition including protein, fiber, water, alcohol intake, exercise, and sleep duration have independent and differential effects on muscle health. Available data representative of muscle health in this population based study include whole-body fat-free mass (FFM) and handgrip strength in younger (≤ 55 years) and older (> 55) men and women of the UK-Biobank study. This study allows us to see how these factors interact with age- and sex-related changes, contributing to a more comprehensive understanding of muscle health throughout the lifespan.

METHODS

Study design

The present cross-sectional study draws from the UK Biobank, a substantial cohort study encompassing a diverse array of data sources comprising 502,628 men and women aged 40–70 years, assessed from 2006 to 2010 in 22 assessment centers around the UK.(18) Ethical clearance for this research was acquired under the broad ethical approval secured by UK Biobank investigators from the National Health Service National Research Ethics Service. The present analyses were conducted in accordance with application number 78275.

Study population

From the initial 502,628 participants enrolled at baseline, a cohort of 45,984 individuals (comprising 20,510 men and 25,474 women) met the inclusion criteria for this investigation (TABLE 1). Specifically, these participants were aged 40-70 years and possessed complete datasets for the outcomes under study, exposures pertaining to lifestyle factors, and the array of covariates of interest, including traditional covariates, socio-demographic variables, medication utilization, and smoking status (FIGURE 1, TABLE S1).

Study procedures

Measurement of Whole Body Fat Free mass and Handgrip Strength (Outcome Measures)

FFM and handgrip strength were chosen as outcome measures due to their substantial sample sizes and established reliability as indicators of muscle health in the study. Methods of collection at baseline from 2006 to 2010 and data transformations for each measurement can be found in TABLE S1. FFM was measured through the Tanita BC 418MA, which used a regression formula derived through repeated regression analysis using height, weight, age, and impedance between right hand and foot as variables. Handgrip strength was measured once in each hand with a Jamar J00105 handgrip dynamometer. In the analysis, we used the measurement in the dominant hand.

Measurement of Lifestyle Factors

The Oxford WebQ alone was used to measure all dietary intakes used, including protein, fiber, alcohol, and water. This is an online self-reported 24 h recall questionnaire including 200 food items. A 24 h recall administered by an interviewer has been used to validate it. Composition data from McCance and Widdowson's The Composition of Food and its supplements were used to calculate intakes of nutrients from this questionnaire. Physical activity was derived from metabolic equivalents (METs) hours per week which were calculated from questionnaire data. Sleep duration was derived from questionnaire data.

Measurement of Potential Confounding Variables

Traditional covariate of waist circumference and BMI obtained during the assessment center visit. Age and sex were gathered from questionnaires at registration. Additionally, socio-demographic covariates such as ethnicity, IMD, and smoking status were collected from questionnaire data. Medication use was gathered through a verbal interview during assessment visits.

Statistical methods

To evaluate which set of lifestyle factors are independently associated with FFM and handgrip strength, we employed multiple linear regression. We constructed two models: The

TABLE 1. Baseline characteristics of the study populations for men and women younger and older than 55 years. Sleepers were categorized according to sleep duration: short sleepers <6.9hours; normal sleepers 7-9 hours; long sleepers >9hour. *This variable is for exploratory purposes only and will not be included in the analyses.

	Men		Women		All
	≤55	>55	≤55	>55	
	(N=8903)	(N=12123)	(N=11607)	(N=13351)	(N=45984)
Outcomes of Interest					
Whole Body Fat Free Mass (WBFFM, kg), mean (SD)	65.5 (7.91)	63.0 (7.35)	45.4 (5.10)	43.9 (4.71)	53.5 (11.6)
Handgrip strength (HGS, kg), mean (SD)	41.1 (8.69)	37.0 (7.91)	25.1 (5.88)	21.7 (5.56)	30.4 (10.6)
Lifestyle Factors					
Physical activity (hours/week), mean (SD)	46.8 (49.1)	46.1 (45.8)	42.8 (41.0)	45.2 (41.5)	45.1 (44.1)
Fibre Adjusted Intake (g/day), mean (SD)	15.3 (6.99)	16.7 (7.00)	16.8 (6.72)	18.1 (6.67)	16.9 (6.90)
Protein Intake (g/kgBW/day), mean (SD)*	0.956 (0.304)	0.977 (0.282)	1.190 (0.350)	1.210 (0.324)	1.095 (0.337)
Protein Adjusted Intake (g/day), mean (SD)	81.5 (23.5)	81.8 (20.9)	82.1 (19.8)	83.2 (18.2)	82.2 (20.4)
Water Intake(cups/day), mean (SD)	3.13 (2.52)	2.38 (1.98)	3.42 (2.43)	2.99 (2.10)	2.96 (2.28)
Alcohol Adjusted Intake (g/day), mean (SD)	19.9 (29.6)	21.5 (27.9)	13.0 (18.9)	12.7 (17.0)	16.5 (23.8)
Sleep					
Short, n (%)	6331 (71.1%)	9310 (76.8%)	8892 (76.6%)	9925 (74.3%)	34458 (74.9%)
Normal, n (%)	2503 (28.1%)	2639 (21.8%)	2551 (22.0%)	3239 (24.3%)	10932 (23.8%)
Long, n (%)	69 (0.8%)	174 (1.4%)	164 (1.4%)	187 (1.4%)	594 (1.3%)
Traditional covariate					
Age (years), mean (SD)	47.9 (4.62)	62.6 (3.69)	48.1 (4.54)	62.1 (3.69)	55.9 (8.20)
BMI, mean (SD)	27.6 (4.27)	27.6 (3.99)	26.4 (5.25)	26.8 (4.82)	27.1 (4.66)
Waist circumference (cm), mean (SD)	95.1 (11.3)	97.2 (11.0)	82.3 (12.5)	84.8 (12.2)	89.4 (13.4)

Socio-demographic covariates

Assessment Centre

Bristol, n (%)	1271 (14.3%)	1643 (13.6%)	1716 (14.8%)	1803 (13.5%)	6433 (14.0%)
Sheffield, n (%)	1717 (19.3%)	2626 (21.7%)	2188 (18.9%)	2756 (20.6%)	9287 (20.2%)
Liverpool, n (%)	877 (9.9%)	1513 (12.5%)	1102 (9.5%)	1575 (11.8%)	5067 (11.0%)
Middlesborough, n (%)	518 (5.8%)	677 (5.6%)	638 (5.5%)	691 (5.2%)	2524 (5.5%)
Hounslow, n (%)	1646 (18.5%)	2163 (17.8%)	2161 (18.6%)	2431 (18.2%)	8401 (18.3%)
Croydon, n (%)	1675 (18.8%)	2123 (17.5%)	2331 (20.1%)	2588 (19.4%)	8717 (19.0%)
Birmingham, n (%)	1199 (13.5%)	1378 (11.4%)	1471 (12.7%)	1507 (11.3%)	5555 (12.1%)

Ethnicity

White, n (%)	8165 (91.7%)	11740 (96.8%)	10608 (91.4%)	12922 (96.8%)	43435 (94.5%)
Mixed, n (%)	94 (1.1%)	29 (0.2%)	174 (1.5%)	47 (0.4%)	344 (0.7%)
Asian, n (%)	387 (4.3%)	259 (2.1%)	422 (3.6%)	219 (1.6%)	1287 (2.8%)
Black, n (%)	257 (2.9%)	95 (0.8%)	403 (3.5%)	163 (1.2%)	918 (2.0%)
Index of Multiple Deprivation	17.6 (12.9)	15.1 (11.4)	17.1 (12.5)	15.2 (11.4)	16.1 (12.0)

Medication use

Number medications, mean (SD)	1.31 (1.87)	2.53 (2.59)	1.70 (2.06)	2.49 (2.56)	2.07 (2.38)
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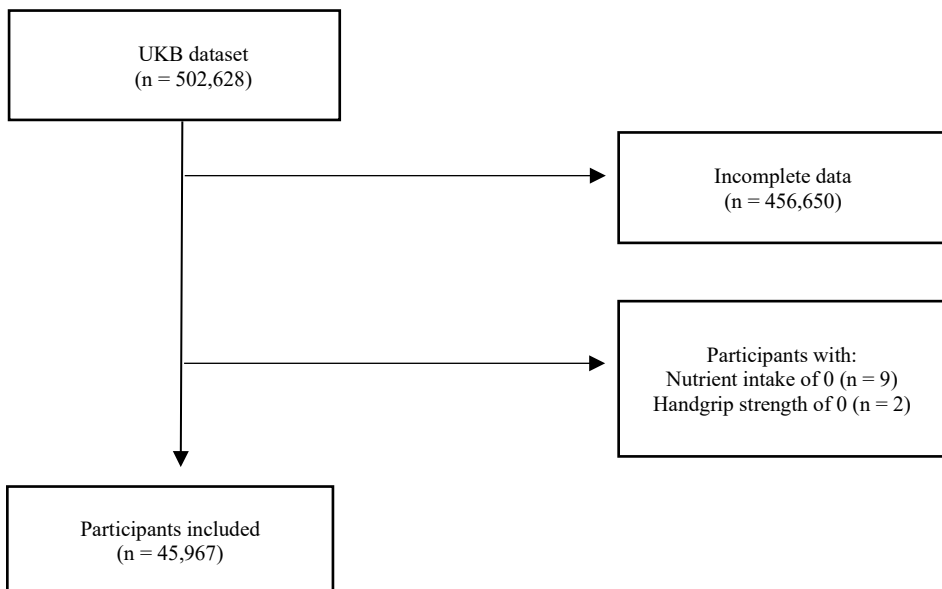
Smoking Status, n (%)

Smoker	1097 (12.3%)	907 (7.5%)	1054 (9.1%)	699 (5.2%)	3757 (8.2%)
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first with whole-body fat-free mass as an outcome (TABLE S2) and the second with handgrip strength as the outcome (TABLE S3). Both models included the seven lifestyle factors of interest, involving nutrition, physical activity, and sleep factors alongside traditional covariates such as age, sex, BMI, and waist circumference and socio-demographic factors such as assessment center (representing geographical distribution), ethnicity, and Townsend index of multiple deprivation.(19–21) Additional covariates included the number of

medications used and current smoking status. Adjustment for dietary variables in relation to energy intake was achieved using the Willett procedure to rectify residual errors.(22) Sex-specific stratification was performed, recognizing biological disparities. Age-specific stratification grouped participants by younger and older age groups using the cohort's mean age of 55 as a cut-off (also referred to as ≤ 55 and >55 , respectively). The analysis adopted a Bonferroni correction with a significance threshold of $p < 0.0036$ to account for the 14 explanatory variables in the two models of whole-body fat-free mass and handgrip strength. Statistical analyses were performed using R version 4.2.3 and RStudio version 2023.06.1+524.

FIGURE 1. Flow diagram of the final included participants from the original Lifelines DMP cohort.



RESULTS

Study population

The cohort of 45,984 participants was stratified by sex and age categories to explore the biological and behavioral differences between them: 8,234 younger men, 12,783 older men, 10,761 younger women, and 14,197 older women (TABLE 1).

The participants in this study exhibited diverse characteristics, highlighting variations across four distinct age and sex categories (TABLE 1). All categories were evenly distributed among

assessment centers, comprised of mainly white ethnicity, and displayed similar patterns in protein and fiber intake. Additionally, a substantial proportion of participants were identified as short sleepers. A sex-based comparison revealed that men exhibited higher FFM, handgrip strength, BMI, waist circumference, alcohol intake, marginally greater engagement in physical exercise, and slightly lower absolute protein intake and total-energy-intake-adjusted protein intake compared to women. When examining age-related differences, the subset younger than 55 years showed higher FFM, handgrip strength, lower reliance on medication, a higher prevalence of smokers, lower fiber intake, and increased water consumption.

To study the independent associations of the known covariates of FFM and strengths, we performed multiple linear regressions with whole-body fat free mass (TABLE S2) and handgrip strength (TABLE S3) as outcomes while adjusting for age, body composition, socio-demographic and economic factors, medication use and smoking status. Below the most important outcomes are summarized.

More physical activity is associated with both higher FFM and handgrip strength

Physical activity had significant relevance in muscle parameters across sex and age groups (FIGURE 2, TABLE S2, TABLE S3). In older men and women, more physical activity was independently associated with higher FFM (respectively $B = 3.36 \times 10^{-3}$, $p\text{-value} = 1.66 \times 10^{-3}$; $B = 2.52 \times 10^{-3}$, $p\text{-value} = 3.57 \times 10^{-4}$) and handgrip strength (respectively $B = 6.05 \times 10^{-3}$, $p\text{-value} = 7.99 \times 10^{-5}$, $B = 8.98 \times 10^{-3}$, $p\text{-value} = 2.95 \times 10^{-15}$). These associations are also reflected in men and women younger than 55 years for FFM (respectively $B = 9.02 \times 10^{-3}$, $p\text{-value} = 1.45 \times 10^{-13}$; $B = 4.35 \times 10^{-3}$, $p\text{-value} = 4.11 \times 10^{-8}$) and handgrip strength (respectively $B = 1.36 \times 10^{-2}$, $p\text{-value} = 1.00 \times 10^{-13}$; $B = 1.08 \times 10^{-2}$, $p\text{-value} = 8.52 \times 10^{-17}$).

Higher fiber intake is associated with higher FFM and handgrip strength

Higher fiber intake was found to be associated with higher FFM and strength in various strata (FIGURE 2, TABLE S2, TABLE S3). In older men and women, higher fiber intake was associated with higher FFM (respectively $B = 3.00 \times 10^{-2}$, $p\text{-value} = 2.76 \times 10^{-5}$; $B = 2.68 \times 10^{-2}$, $p\text{-value} = 1.78 \times 10^{-9}$) and higher handgrip strength (respectively $B = 3.27 \times 10^{-2}$, $p\text{-value} = 1.40 \times 10^{-3}$; $B = 3.12 \times 10^{-2}$, $p\text{-value} = 1.34 \times 10^{-5}$). In younger men and women, higher fiber intake was only significantly associated with higher FFM (respectively $B = 4.01 \times 10^{-2}$, $p\text{-value} = 5.06 \times 10^{-6}$; $B = 2.04 \times 10^{-2}$, $p\text{-value} = 3.15 \times 10^{-5}$).

Higher protein intake is associated with higher handgrip strength in men, but not women.

Protein intake (adjusted for total energy intake) exhibited distinct associations with muscle parameters across sex and age groups (FIGURE 2, TABLE S2, TABLE S3). Specifically, protein intake (adjusted for total energy intake) showed no relation with FFM in men or women. However, it exhibited an association on handgrip strength in both young and older men (respectively $B = 1.29 \times 10^{-2}$, $p\text{-value} = 7.41 \times 10^{-4}$; $B = 1.13 \times 10^{-2}$, $p\text{-value} = 8.34 \times 10^{-4}$).

In contrast, protein intake (adjusted for total energy intake) showed no significant association with handgrip strength nor mass, neither in young nor older women.

Higher water intake is associated with higher FFM and not with handgrip strength

Water intake had varying associations with muscle parameters across different subgroups (FIGURE 2, TABLE S2, TABLE S3). In men both younger and older than 55 years, higher water intake was associated with higher FFM ($B = 9.89 \times 10^{-2}$, $p\text{-value} = 3.91 \times 10^{-5}$; $B = 1.13 \times 10^{-1}$, $p\text{-value} = 6.70 \times 10^{-6}$, respectively). However, in men younger than 55 years, higher water intake associated with slightly lower handgrip strength ($B = -0.145$, $p\text{-value} = 6.19 \times 10^{-5}$). Associations on FFM were observed in women younger than 55 years only ($B = 4.86 \times 10^{-2}$, $p\text{-value} = 3.32 \times 10^{-4}$).

Higher alcohol intake is associated with higher handgrip strength but not with FFM

Higher intake of alcohol did not associate with FFM but did with higher handgrip strength in men both young and older than 55 years ($B = 1.08 \times 10^{-2}$, $p\text{-value} = 5.67 \times 10^{-4}$; $B = 1.24 \times 10^{-2}$, $p\text{-value} = 1.63 \times 10^{-6}$, respectively) and women older than 55 years ($B = 1.49 \times 10^{-2}$, $p\text{-value} = 1.24 \times 10^{-7}$) (FIGURE 2, TABLE S2, TABLE S3).

Sleeping longer than 9 hours per night is associated with lower handgrip strength in women younger than 55 years, but not in men.

Sleep duration was found to have a unique impact on muscle parameters (FIGURE 2, TABLE S2, TABLE S3). While sleep duration showed no significant associations with muscle parameters in men, it was observed that sleeping longer than 9 hours was associated with lower handgrip strength in women younger than 55 years ($B = -2.439$, $p\text{-value} = 4.03 \times 10^{-8}$).

DISCUSSION

This study examined the link between lifestyle factors (diet, physical activity, and sleep) and FFM and handgrip strength in individuals aged 40-70 years. Multiple linear regression models revealed higher physical activity and fiber intake as main independent associated factors with both parameters. More factors independently associated with handgrip strength than FFM. Increased water intake was associated with increased FFM. Higher handgrip strength was associated with higher protein intake, lower water intake, higher alcohol intake, and extended sleep duration. The study highlighted age and sex differences in the link between lifestyle on muscle health in middle-aged to older adults.

The stratification based on age is a pivotal element of this study. It significantly enhances our comprehension of muscle health dynamics. (23) The most remarkable observation is the attenuated association of physical activity with handgrip strength in men above 55 years, as compared to the other groups including older women. FFM is associated with physical

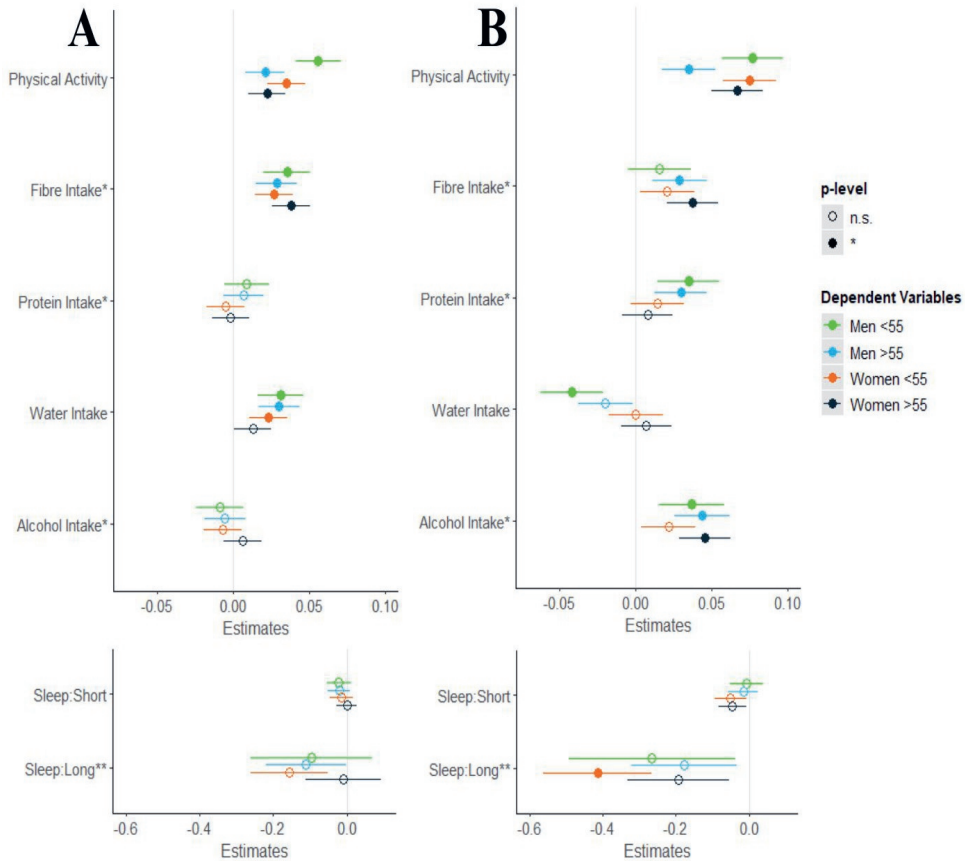


FIGURE 2. Lifestyle variables in the multivariate model presented as standardized beta-coefficients associated with (A) muscle mass and (B) handgrip strength for men and women younger and older than 55 years. Adjusted for traditional covariates, socio-demographic covariates, medication use, and smoking status. The p-value at which to accept significance (filled in circle) was adjusted to account for multiple testing ($p < 0.0036$). Sleepers were categorized according to sleep duration: short sleepers <6.9hours; normal sleepers 7-9 hours; long sleepers >9hours. *Intakes adjusted for energy intake (see Methods). **Large confidence intervals reflect low statistical power for this variable.

activity similarly in both sexes over 55 years. It is essential to consider that sex- and age-related changes both play substantial roles in the gradual loss of FFM and strength. With age, detrimental shifts occur in dietary practices and physical activity habits.(24,25) It is important to consider the impact of behavioral differences on exercise in men and women. Men tend to engage more in strength training than women, while also adopting riskier behaviors fueled by intrinsic competitiveness. This may explain why men tend to focus on upper-body training for muscularity, while women focus on lower-body training and overall body mass management. (26,27)

Our results show that older men had the lowest FFM and handgrip strength out of the four groups. This observation aligns with existing research that sex differences in muscle physiology exist. Young men have a larger volume distribution of type II muscle fibers, the main fiber type involved in strength training. Contrarily, women have a larger volume distribution of type I muscles, which are related to endurance training. (28,29) Physical activity had the strongest association with FFM in men younger than 55 years as compared to the other groups. Physical activity has long been recognized for its positive association with muscle health, with the present study reaffirming this well-established concept in both age and sex categories for FFM and handgrip strength. Regular exercise first stimulates the neuromuscular system, leading to increased motor unit recruitment and improved muscle contraction efficiency.(30) Thereafter it elicits muscle hypertrophy, leading to an increase in muscle size, and promotes muscle protein synthesis, a fundamental process for muscle growth.(31) However, FFM and handgrip strength decline with age, as confirmed in our data. This is especially observed in men, clearly not prevented by their physical activity. Our results therefore underscore that older individuals might need tailored exercise and dietary regimens to counteract these age-related changes and maintain or enhance their FFM and handgrip strength. (32,33)

The literature corroborates our findings for both FFM and handgrip strength, where a higher fiber intake is associated with higher lean mass and handgrip strength.(34) The positive association of higher fiber intake with FFM across sexes and age groups may be explained by the gut-muscle axis hypothesis, which posits that gut microbial diversity and abundance of certain gut bacteria may be associated with muscle health.(35–37) In theory, a diverse gut microbiota promotes the production of short-chain fatty acids, which are known to influence muscle metabolism.(38) Short-chain fatty acids regulate muscle protein synthesis and degradation, which in turn affect FFM.(39,40) While the present study cannot conclude the directionality of effect for the gut-muscle axis hypothesis, it provides a foundation for the hypothesis that higher dietary fiber intake may promote muscle health via the diversification and increased abundance of commensal bacteria.

Protein intake, a widely recognized factor in muscle health, surprisingly did not show a significant independent association with FFM in our study. This could be attributed to our adjustment for total caloric intake as evidenced by the change in beta coefficients and statistical significance (FIGURE S1, TABLE S4, TABLE S5) suggesting that FFM development does not solely rely on protein intake but also requires a balanced diet with appropriate caloric intake.(41,42) Recent studies suggest that total-energy-unadjusted protein intake patterns across the day, and not only total protein intake, are essential for optimal muscle health.(43,44) Furthermore, we found total-energy-intake-adjusted protein intake to be associated with increased handgrip strength in men, but not in women. This sex-based variability in response to protein intake might be due to, men having more lean mass than women and inherently more strength, requiring a higher absolute protein intake to preserve their muscle health.(45) We observed a similar total-energy-adjusted protein intake among

men and women. However, the absence of effect of protein intake on FFM and strength in women may be due to the visibly higher SD compared to men.

Higher water intake was found to associate with higher FFM, particularly in men in both age categories and women younger than 55 years. However, this association may largely be conditioned by the fact that FFM were measured by using BIA, which is fundamentally sensitive to hydration status of an individual to derive the calculation. Conversely, our study showed that higher water intake is associated with lower muscle strength in men younger than 55 years. Previous studies support the importance of hydration for both muscle mass and strength, especially in older adults. (46) Nevertheless, the biological mechanism behind this associations remains unclear and would require further study.

Women older than 55 years had the lowest alcohol intake and the highest protective effect on handgrip strength. The observed protective effect of alcohol specifically on handgrip strength in men of both age categories and women older than 55 years is intriguing and can be understood through several interconnected mechanisms. Firstly, limited alcohol consumption has been shown to provide neuroprotection through its antioxidative and anti-inflammatory properties.(47) Alcohol, particularly at modest doses, exhibits antioxidant capabilities, which can counteract the damaging effects of oxidative stress and inflammation.(48) This, in turn, can safeguard neuronal function, associated with enhanced muscle control and strength. Sex differences in behaviors in alcohol consumption may underpin the absence of significance in younger women. (49) Overall, the present results are consistent with previous explorations regarding low-to-moderate alcohol intake and muscle health within the same cohort.(50)

Lastly, we show that sleeping longer than 9 hours is associated with lower handgrip strength. This cohort's finding suggests that there might be underlying physiological mechanisms, such as hormonal fluctuations, and alterations in neuromuscular function associated with extended sleep that impact handgrip strength.(11,51) For instance, extended sleep could interfere with the natural rhythm of anabolic and catabolic hormone secretion, which is crucial for muscle recovery and strength.(52) Sleep also affects other hormones like cortisol is involved in muscle protein degradation.(53,54) Previous studies have associated longer sleep duration to various adverse health-related outcomes, and we found its association with lower handgrip strength. The explanation for these associations remains to be elucidated

Our analysis boasts strengths in three key areas. Firstly, the cross-sectional design in the present study proves valuable for hypothesis generation and exploration of potential associations between lifestyle factors, offering a snapshot of the UK population. Furthermore, it allows for the simultaneous examination of multiple muscle health outcomes and lifestyle and covariate exposures, providing a comprehensive overview of various factors within the studied population. Secondly, the specific age range (40 to 70) allows us to examine muscle health decline preceding conditions like sarcopenia. By including working-age individuals, it explores lifestyle factors' impact on early muscle quality loss, offering insights into tailored interventions through comparisons between middle-aged and younger

male and female groups. Thirdly, by dissecting the influence of individual lifestyle components, such as dietary habits, hydration levels, and physical activity, we gain deeper insights into their specific association with FFM and handgrip strength. This nuanced analysis not only enhances our understanding of the factors that influence FFM and strength but also helps identify targeted interventions for optimizing muscle health across diverse populations.

While the present study boasts strengths, it also faces limitations. Firstly, its cross-sectional design restricts establishing causal relationships between lifestyle factors and muscle health outcomes, necessitating future longitudinal studies for deeper insights. Moreover, reliance on self-reported data introduces potential recall and response biases, urging the inclusion of objective measures like accelerometers or dietary logs in future research. Additionally, using BIA for FFM assessment may lead to variability and potential inaccuracies compared to more precise methods like dual-energy X-ray absorptiometry (DEXA) and Magnetic Resonance Imaging (MRI). In this cohort, however, the DEXA scans were only available in 2594 participants with a complete dataset in a follow-up visit and MRI solely focused on abdominal lean mass in 41427 participants with a complete dataset at baseline. Incorporating DEXA scans in feasibly-sized cohorts and whole-body MRI scans could enhance FFM measurements' precision and validate findings. Lastly, while the study aims to explore early lifestyle signatures of muscle health decline, its focus on a broad age range may not fully capture nuances observed in older adults affected by sarcopenia. Future research should prioritize investigating these older age cohorts to better understand muscle loss progression across various life phases and its implications for overall health. Addressing these limitations is vital for advancing comprehension of the complex relationship between lifestyle factors and muscle health and for devising effective interventions to promote healthy aging and preserve muscle function.

CONCLUSION

Our study emphasizes lifestyle factors associate more to handgrip strength than Fat Free Mass. Physical activity and fiber intake, however, show their relevance to both outcomes in both sexes across ages up to 70 years, potentially involving the gut-muscle axis. Our findings in stratified analyses underscore the complex nature of muscle health, requiring longitudinal research to provide personalized lifestyle recommendations to specific populations.

AUTHOR CONTRIBUTIONS

JMM and MB conceptualized the study, JMM drafted outline and the first version of the manuscript. MRG, MB, CSP, SV, and PS provided methodological support. All authors had full access to all the data in the study, discussed the results, and had final responsibility for the decision to submit for publication. JMM and MB accessed and verified the data.

DECLARATION OF INTERESTS

We declare no competing interests.

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SUPPLEMENTARY TABLES AND FIGURES

TABLE S1. Tested determinants of whole body fat free mass and handgrip strength.

Variable Category	Variable	UKB Code	Variable type	Method of Collection	Units	Transformation	Ref
Outcome variables of interest	Whole body fat-free mass	23101	Continuous	BIA	Kg	None	-
	Handgrip strength	46,47	Integer	Physical Measure	Kg	Mean measurement for right and left hand.	²³
Lifestyle factors	Summed MET minutes of activity per week	22304	Integer	Questionnaire	Minutes/week	Converted to hours/week	²⁶
	Fibre adjusted intake	100009	Continuous	Questionnaire	g/d	Adjusted for energy intake according to nutrient residual model.	¹²
	Protein intake	100003	Continuous	Questionnaire	g/kg BW/day	Divided protein intake by body weight	²⁶
	Protein adjusted intake	100003	Continuous	Questionnaire	g/d	Adjusted for energy intake according to nutrient residual model.	²⁶
	Water intake	100150	Integer	Questionnaire	Glasses/day	None	²⁸
	Alcohol adjusted int	100022	Continuous	Questionnaire	g/d	Adjusted for energy intake according to nutrient residual model.	²⁷
	Sleep duration	1160	Integer	Questionnaire	Hours/day	Categorized into short, normal, long sleepers	²⁰
Traditional covariates	Age at recruitment	21022	Integer	Registration	Years	None	²⁴
	Sex	31	Categorical	Registration	0 = F, 1 = M	None	¹³
	BMI	21001	Continuous	Physical Measure	Kg/m ²	None	¹⁴
	Waist circumference	48	Continuous	Physical Measure	Cm	None	¹⁴
Socio-demographic covariates	Assessment Centre	54	Categorical	Registration	-	None	¹⁵
	Ethnicity	21000	Categorical	Questionnaire	-	Recode to White, Mixed, Black, Asian	¹⁵
	Index of Multiple Deprivation	26410, 26427, 26426	Continuous	Questionnaire	-	None	²⁵
Medication use	Number medications	137	Integer	Verbal interview	Medications	None	¹⁷
Smoking status	Smoking status	20116	Categorical	Questionnaire	0 = N, 1 = Y	None	¹⁸

TABLE S2. Multivariate associations of potential determinants of whole body fat free mass in younger and older men and women. The p-value at which to accept significance was adjusted to account for multiple testing (p < 0.0036). Significant values in bold.

	Men				Women			
	≤55		>55		≤55		>55	
	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
Lifestyle Factors								
Physical activity hours/week	9.02x10 ^{0B}	1.45x10¹³	3.36x10 ^{0B}	1.45x10¹³	4.35x10 ^{0B}	1.66x10^{0B}	2.52x10 ^{0B}	4.11x10^{0B}
Fibre Adjusted Intake (g/day)	4.01x10 ⁰²	5.06x10⁰⁶	3.00x10 ⁰²	5.06x10⁰⁶	2.04x10 ⁰²	2.76x10⁰⁵	2.68x10 ⁰²	3.15x10⁰⁵
Protein Adjusted Intake (g/day)	3.03x10 ^{0B}	2.32x10 ⁰¹	2.34x10 ^{0B}	2.32x10 ⁰¹	-1.26x10 ^{0B}	3.20x10 ⁰¹	-4.40x10 ⁰⁴	4.39x10 ⁰¹
Water Intake(cups/day)	9.89x10 ⁰²	3.91x10⁰⁵	0.113	3.91x10⁰⁵	4.86x10 ⁰²	6.70x10⁰⁶	2.90x10 ⁰²	3.32x10⁰⁴
Alcohol Adjusted Intake (g/day)	-2.32x10 ^{0B}	2.67x10 ⁰¹	-1.42x10 ^{0B}	2.67x10 ⁰¹	-1.86x10 ^{0B}	4.31x10 ⁰¹	1.70x10 ^{0B}	2.86x10 ⁰¹
Sleep:short	-0.177	1.78x10 ⁰¹	-0.156	1.78x10 ⁰¹	-7.65x10 ⁰²	1.82x10 ⁰¹	1.04x10 ^{0B}	3.32x10 ⁰¹
Sleep:long	-0.756	2.59x10 ⁰¹	-0.813	2.59x10 ⁰¹	-0.793	4.46x10 ⁰²	-4.30x10 ⁰²	3.65x10 ^{0B}
Traditional covariate								
Age (years)	-0.202	8.44x10⁵³	-0.246	8.44x10⁵³	-0.127	6.28x10⁷⁵	-0.113	1.99x10⁰⁶
BMI	0.732	1.92x10¹⁴⁴	0.612	1.92x10¹⁴⁴	0.544	2.89x10¹²⁵	0.487	0.00
Waist circumference (cm)	0.251	4.65x10¹⁰¹	0.251	4.65x10¹⁰¹	0.077	2.13x10¹⁵⁷	0.091	1.21x10⁰²
Socio-demographic covariates								
Assessment Centre								
Sheffield	-1.144	3.71x10⁰⁶	-1.357	3.71x10⁰⁶	-0.953	5.97x10¹⁶	-0.993	3.46x10¹⁷
Liverpool	-1.324	4.47x10⁰⁵	-1.554	4.47x10⁰⁵	-0.639	1.96x10¹⁶	-0.935	1.99x10⁰⁶
Middlesborough	-0.642	2.69x10 ⁰²	-0.678	2.69x10 ⁰²	-0.527	5.15x10 ^{0B}	-0.348	1.05x10^{0B}
Hounslow	-0.568	6.86x10^{0B}	-0.386	6.86x10^{0B}	0.154	2.72x10 ⁰²	0.215	1.74x10 ⁰¹
Croydon	-0.627	2.90x10^{0B}	-0.761	2.90x10^{0B}	0.019	1.59x10⁰⁵	-0.027	8.65x10 ⁰¹
Birmingham	-0.457	4.60x10 ⁰²	-0.947	4.60x10 ⁰²	-0.406	1.21x10⁰⁶	-0.502	1.24x10^{0B}
Ethnicity								
Mixed	-1.558	6.52x10 ^{0B}	-2.342	6.52x10 ^{0B}	-0.713	1.71x10 ⁰²	-1.687	6.93x10 ^{0B}
Asian	-6.247	2.54x10⁰⁶	-6.945	2.54x10⁰⁶	-4.627	2.33x10⁰¹	-4.211	6.43x10¹⁵⁰
Black	-0.580	1.14x10 ⁰¹	-1.726	1.14x10 ⁰¹	0.014	1.80x10^{0B}	-0.692	9.40x10 ⁰¹
Index of Multiple Deprivation	-0.038	1.80x10¹⁵	-0.042	1.80x10¹⁵	-0.013	1.04x10²¹	-0.015	4.02x10⁰⁶
Medication use								
Number medications	-0.251	2.05x10¹⁴⁴	-0.171	2.05x10¹⁴⁴	-0.085	5.36x10¹⁸	-0.067	1.80x10⁰⁷
Smoking Status								
Smoker	-0.553	2.26x10 ⁰²	-0.063	7.31x10 ⁰¹	-0.044	6.97x10 ⁰¹	-0.085	5.14x10 ⁰¹

TABLE S3. Multivariate associations of potential determinants of handgrip strength in younger and older men and women. The p-value at which to accept significance was adjusted to account for multiple testing ($p < 0.0036$). Significant values in bold.

	Men				Women			
	≤ 55		> 55		≤ 55		> 55	
Lifestyle Factors	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
Physical activity hours/week	1.36x10 ⁻⁰²	1.00x10⁻¹³	6.05x10 ⁻⁰³	7.99 x10⁻⁰⁵	1.08x10 ⁻⁰²	8.52x10⁻¹⁷	8.98x10 ⁻⁰³	2.95x10⁻¹⁵
Fibre Adjusted Intake (g/day)	1.95x10 ⁻⁰²	1.39x10 ⁻⁰¹	3.27x10 ⁻⁰²	1.40x10⁻⁰³	1.81x10 ⁻⁰²	2.32x10 ⁻⁰²	3.12x10 ⁻⁰²	1.34x10⁻⁰⁵
Protein Adjusted Intake (g/day)	1.29x10 ⁻⁰²	7.41x10⁻⁰⁴	1.13x10 ⁻⁰²	8.34x10⁻⁰⁴	4.25x10 ⁻⁰³	1.08x10 ⁻⁰¹	2.47x10 ⁻⁰³	3.38x10 ⁻⁰¹
Water Intake(cups/day)	-0.145	6.19x10⁻⁰⁵	-7.88x10 ⁻⁰²	2.79x10 ⁻⁰²	2.27x10 ⁻⁰⁴	9.92x10 ⁻⁰¹	1.88x10 ⁻⁰²	4.05x10 ⁻⁰¹
Alcohol Adjusted Intake (g/day)	1.08x10 ⁻⁰²	5.67x10⁻⁰⁴	1.24x10 ⁻⁰²	1.63x10⁻⁰⁶	6.76x10 ⁻⁰³	1.76x10 ⁻⁰²	1.49x10 ⁻⁰²	1.24x10⁻⁰⁷
Sleep:short	-6.06x10 ⁻⁰²	7.59x10 ⁻⁰¹	-0.127	4.49x10 ⁻⁰¹	-0.296	2.10x10 ⁻⁰²	-0.253	1.99x10 ⁻⁰²
Sleep:long	-2.310	2.15x10 ⁻⁰²	-1.398	1.55x10 ⁻⁰²	-2.441	4.03x10 ⁻⁰⁸	-1.073	6.70x10 ⁻⁰³
Traditional covariate								
Age (years)	-0.242	1.50x10⁻³⁴	-0.347	1.97x10⁻⁷²	-0.233	2.67x10⁻⁸⁶	-0.214	4.51x10⁻⁶²
BMI	0.428	7.70x10⁻²¹	0.189	2.00x10⁻⁰⁷	-0.029	1.67x10 ⁻⁰¹	-0.048	1.34x10 ⁻⁰²
Waist circumference (cm)	-0.091	1.53x10⁻⁰⁷	-0.039	3.32x10⁻⁰³	0.022	1.52x10 ⁻⁰²	0.031	1.10x10⁻⁰⁴
Socio-demographic covariates								
Assessment Centre								
Sheffield	0.327	2.95x10 ⁻⁰¹	-0.061	8.00x10 ⁻⁰¹	0.351	5.54x10 ⁻⁰²	0.379	2.40x10 ⁻⁰²
Liverpool	-0.536	1.45x10 ⁻⁰¹	-0.789	3.54x10⁻⁰³	-0.526	1.63x10 ⁻⁰²	-0.656	3.87x10⁻⁰⁴
Middlesborough	0.222	6.10x10 ⁻⁰¹	0.289	4.05x10 ⁻⁰¹	0.146	5.77x10 ⁻⁰¹	0.593	1.42x10 ⁻⁰²
Hounslow	-3.269	4.42x10⁻²⁵	-2.847	8.01x10⁻³⁰	-1.710	2.10x10⁻²⁰	-1.574	6.30x10⁻²¹
Croydon	-1.042	9.79x10⁻⁰⁴	-0.989	9.09x10⁻⁰⁵	0.188	3.07x10 ⁻⁰¹	0.501	2.55x10⁻⁰³
Birmingham	-0.996	3.72x10 ⁻⁰³	-1.335	1.79x10⁻⁰⁶	-1.057	2.35x10⁻⁰⁷	-0.849	2.32x10⁻⁰⁵
Ethnicity								
Mixed	0.832	3.33x10 ⁻⁰¹	-2.227	1.14x10 ⁻⁰¹	0.669	1.20x10 ⁻⁰¹	-0.488	5.33x10 ⁻⁰¹
Asian	-4.571	1.21x10⁻²⁴	-4.835	3.85x10⁻²³	-3.964	2.14x10⁻⁴²	-2.794	4.26x10⁻¹⁴
Black	1.103	4.48x10 ⁻⁰²	0.069	9.30x10 ⁻⁰¹	1.201	5.28x10⁻⁰⁵	1.844	1.75x10⁻⁰⁵

Index of Multiple Deprivation	-0.058	1.26x10⁻¹⁵	-0.056	3.47x10⁻¹⁹	-0.029	1.01x10⁻¹⁰	-0.028	3.73x10⁻¹¹
Medication use								
Number medications	-0.432	1.86x10⁻¹⁸	-0.361	6.46x10⁻³⁷	-0.327	3.39x10⁻³⁵	-0.301	7.84x10⁻⁵⁶
Smoking Status								
Smoker	-0.312	2.50x10 ⁰¹	-0.032	9.03x10 ⁰¹	-0.335	6.89x10 ⁻⁰²	-0.231	2.71x10 ⁰¹

TABLE S4. Multivariate associations comparing protein-adjusted and absolute protein intake of whole body fat free mass in younger and older men and women. The p-value at which to accept significance was adjusted to account for multiple testing ($p < 0.0036$). Significant values in bold.

	Men				Women			
	≤55		>55		≤55		>55	
Lifestyle Factors	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
Protein Adjusted Intake (g/day)	1.29x10 ⁰²	7.41x10⁰⁴	1.13x10 ⁰²	8.34x10⁰⁴	4.25x10 ⁰³	1.08x10 ⁰¹	2.47x10 ⁰³	3.38x10 ⁰¹
Absolute protein intake (g/day)	1.05x10 ⁰²	2.01x10⁰⁶	1.56x10 ⁰²	2.01x10⁰⁶	1.03x10 ⁰²	6.36x10⁰⁵	8.38x10 ⁰³	2.73x10⁰⁴

TABLE S5. Multivariate associations comparing protein-adjusted and absolute protein intake of handgrip strength in younger and older men and women. The p-value at which to accept significance was adjusted to account for multiple testing ($p < 0.0036$). Significant values in bold.

	Men				Women			
	≤55		>55		≤55		>55	
Lifestyle Factors	Beta	p-value	Beta	p-value	Beta	p-value	Beta	p-value
Protein Adjusted Intake (g/day)	1.29x10 ⁰²	7.41x10⁰⁴	1.13x10 ⁰²	8.34x10⁰⁴	4.25x10 ⁰³	1.08x10 ⁰¹	2.47x10 ⁰³	3.38x10 ⁰¹
Absolute protein intake (g/day)	4.72x10 ⁰²	0.513	9.04x10 ⁰²	3.24x10⁰⁵	6.13x10 ⁰³	6.44x10 ⁰⁴	8.38x10 ⁰³	2.73x10⁰⁴

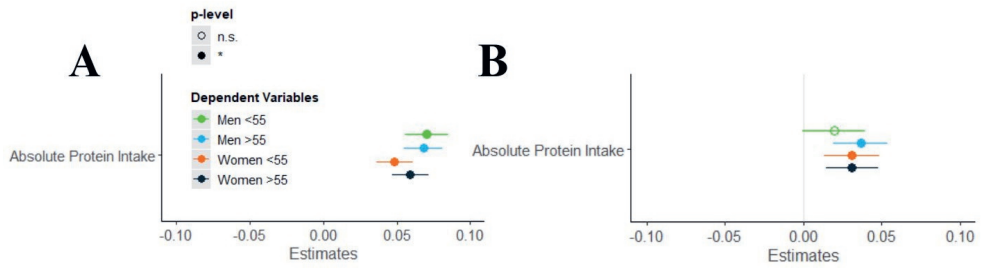


FIGURE S1. Absolute protein intake (not-energy adjusted) in the multivariate model presented as standardized beta-coefficients associated with (A) muscle mass and (B) handgrip strength for men and women younger and older than 55 years. Adjusted for traditional covariates, socio-demographic covariates, medication use, and smoking status. The p-value at which to accept significance (filled in circle) was adjusted to account for multiple testing ($p < 0.0036$).