Relationship between handgrip strength and endogenous hormones in postmenopausal women

Pascual García-Alfaro, MD,[1] Sandra García, BSc,[1] Ignacio Rodriguez, MSc,[1] Luciana Bergamaschi, MD,[1] and Faustino R. Pérez-López, MD, PhD[2]

[1]Department of Obstetrics, Gynecology and Reproduction. Hospital Universitario Dexeus. Barcelona, Spain.
[2]Department of Obstetrics and Gynecology, University of Zaragoza Faculty of Medicine, Zaragoza, Spain

Funding/support: This research was not funded by any commercial or nonprofit organization or public agency.

Financial disclosure/conflicts of interest: None reported.

Short title: Handgrip strength and endogenous hormones

ORCID:

P. García-Alfaro: http://orcid.org/0000-0003-1790-7752
S. García: https://orcid.org/0000-0003-4268-1871
I. Rodríguez: http://orcid.org/0000-0002-6586-0111
L. Bergamaschi: http://orcid.org/0000-0002-9217-5144
F.R. Pérez-López: http://orcid.org/0000-0002-2801-416X

Corresponding author:

Dr. Pascual Garcia-Alfaro

Department of Obstetrics and Gynecology. Hospital Universitario Dexeus. Gran Vía Carlos III 71-75

08028 Barcelona, Spain.

Phone: 932274700 Telefax: 934187832

E-mail: pasgar@dexeus.com

ABSTRACT

Objectives: This study aimed to evaluate the endogenous hormonal factors related to dominant handgrip strength (HGS) in postmenopausal women.

Methods: A cross-sectional study was performed on 402 postmenopausal women aged 47-83 years. The following variables were recorded: age, age at menopause, smoking status, adiposity, HGS, and physical activity. Hormonal parameters (follicle-stimulating hormone [FSH], estradiol, testosterone, cortisol, dehydroepiandrosterone sulfate [DHEAS], Δ4 androstenedione, insulin-like growth factor-1 [IGF-1], vitamin D, and parathormone [PTH] levels) were measured and results reported as odds ratios (OR), β-coefficients and 95% confidence interval (95% CI). A directed acyclic graph was used to identify potential confounding variables and were adjusted in the regression model to assess associations between endogenous hormones and HGS.

Results: The mean dominant HGS was 22.8 ± 3.7 kg, and a 25.6% of women had dynapenia. There were significant differences in plasma levels of FSH (OR: 0.99; 95% CI: 0.98-1.00), cortisol (OR: 1.07; 95% CI: 1.02-1.12) and DHEAS (OR: 0.99; 95% CI: 0.98-1.00) between women with normal HGS and those who presented dynapenia. After adjusting for confounding variables, no significant association was found between endogenous hormones and HGS.

Conclusions: Our results showed that studied ovarian steroids, adrenal hormones, IGF-1, PTH, and vitamin D were not associated with HGS.

KEYWORDS: Adiposity; Adrenal hormones; Dynapenia; Handgrip strength; Ovarian steroids; Physical activity; Smoking; Vitamin D.

1. Introduction

Aging is associated with muscle-skeletal changes, initially with decreased functional muscle strength (dynapenia) and, later, the loss of muscle strength is associated with loss of muscle mass (sarcopenia). Thus, dynapenia would be the previous step to sarcopenia.[1] Muscle strength plays a relevant role in overall functional status and particularly in daily activities, maintenance of functional independence, and autonomy. To assess muscle strength, handgrip strength (HGS) is an easily, non-invasive, and accurate technique that only requires no hand disability.[2] HGS is currently considered an independent indicator for the decline in cognition, disability, frailty, and mortality. Grip strength in older adults has been recommended as a biomarker of healthy aging.[3]

In addition to the age-related muscle strength decline, the hormonal status is involved in maintaining skeletal muscle. The muscle strength decline occurs at an earlier age in women compared to men and is partly associated with the progressive decline in estrogen levels during the menopausal transition.[4,5] However, there are studies with divergent results regarding the relationship between the effects of estrogens on muscle strength.[6,7] The menopausal transition is also associated with decreased levels of testosterone, dehydroepiandrosterone sulfate (DHEAS), and insulin-like growth factor-1 (IGF-1) that also interact with the intracellular muscle pathway.[8] To assess HGS, other confounding factors should also be taken into accounts, such as age, age at menopause, adiposity, smoking status, and physical activity. We previously reported that age, age at menopause, adiposity (> 40% fat mass), and femoral neck T-score were associated with HGS or dynapenia in a cohort of postmenopausal women.[9] The purpose of the current study was to investigate the relationship between HGS with ovarian steroids, adrenal hormones, and other hormonal factors in postmenopausal women.

2. Methods

2.1. Study design

This cross-sectional study was approved by the Institutional Review Board and the Hospital Ethics Committee. It was performed from January 2021 to December 2021 at the Department of Obstetrics and Gynecology of the Dexeus Women's University Hospital, Barcelona, Spain. Women were excluded if (i) they had an early spontaneous (< 45 years) or surgical menopause; (ii) were using menopausal hormonal treatment; or (iii) had cardiovascular, liver, or renal diseases, a history of cancer, or physical disability. Finally, a group of 402 postmenopausal women aged 47 to 83 years participated in the study.

2.2. Handgrip strength and laboratory parameters

HGS measure was assessed in the dominant hand with a digital dynamometer Camry EH101 (Camry Industries Co. Ltd, Kowloon, Hong Kong) calibrated in kg. After demonstrating how to use the handgrip dynamometer, following the standardized method proposed by the American Society of Hand Therapists.[10] Measurements were carried out sitting with the arm against the side, the elbow bent to a 90° angle, and the forearm in a neutral position. Two measurements were recorded and since the HGS may gradually decreases when repeated, the maximum value was used as the indicator for HGS. For the current study, dynapenia was defined when the hand

force was <20 kg, according to the cut-off recommended by the European Working Group on Sarcopenia in Older People (EWGSOP) Consensus.[11]

Blood samples were collected after an overnight fast. Hormonal parameters (follicle-stimulating hormone [FSH], estradiol, testosterone, cortisol, DHEAS, Δ4 androstenedione, IGF-1, vitamin D, and parathormone [PTH] plasma levels) were determined by electrochemiluminescence immunoassay using Roche Elecsys reagents and measured by an automated COBAS® 8000 modular analyzer System (Roche Diagnostics. Pleasanton, CA. USA). The laboratory performs daily quality controls of each parameter according to the International Organization for Standardization, ISO 9001:2015 standard. In the quality control the results must be less than ±2 standard deviations with respect to the daily control value. Coefficients of variation were different depending on the studied hormonal parameter. FSH and testosterone ranged from 1.3% to 1.8%, estradiol ranged from 1.2% to 1.9%, cortisol ranged from 1.6% to 1.7%, DHEAS ranged from 1.5% to 2.3%, Δ4 androstenedione ranged from 1.8% to 2.1%, IGF-1 ranged from 1% to 1.6%, vitamin D ranged from 2.3% to 3% and PTH ranged from 1.4% to 1.7%.

2.3. Potential confounders

Age at menopause, adiposity, current smoking status, and physical activity were recorded. Adiposity was assessed by bioelectrical impedance analysis (BIA) equipment Omron BF 306 monitor (Omrom healthcare Co. Ltd, Kyoto, Japan). Details of the women were entered into the equipment program, including age, height, weight, and sex. Subsequently, the BIA assessment was performed two times in the standing position, with the legs 35º-45º apart and the arms extended forwards at a 90º angle concerning the trunk, using a disposable gown. The results were expressed as a percentage of fat. Information on smoking status was recorded and classified as never or smoker. The physical activity was assessed using the Spanish version of the short International Physical Activity Questionnaire (IPAQ). This tool includes 7-items that provides information about the average number of days per week, and the average time per day that women spent in moderate and vigorous activities, walking and sitting. With the final score obtained, the physical activity was classified as low, moderate, and high level.[12]

2.4. Covariate assessment

A directed acyclic graph (DAG)[13] was used to select potential confounding factors adjusted in our analysis. A DAG with endogenous hormones as the main exposure and HGS as the outcome were generated to determine confounding variables. Based on available literature and data collected, age, age at menopause, adiposity, smoking status (never vs smoker), and physical activity (high/moderate vs low) were included as potential confounding in the DAG. According to the minimal sufficiency set of adjustments, all of these variables were identified as confounders Following the DAG, age, age at menopause, adiposity, smoking status and physical activity were considered in the regression model to assess associations between endogenous hormones and HGS. (**Figure 1**).

2.5. Statistical analysis

Continuous variables were shown as mean and standard deviation whereas percentages and numbers were used for categorical variables. The Student's t-test and Chi-square test were

applied to compare continuous and categorical outcomes between women with normal HGS and women with dynapenia. Pearson correlation was used to estimate the relation between numeric parameters with the grip strength. A partial correlation adjusted by age was also calculated and results were reported as odds ratios (OR) and 95% confidence interval (95% CI). Finally, a multivariable linear regression analysis, adjusting for potential confounders identified by DAG, was modeled to determine the relationship between endogenous hormones and HGS. Results are reported as β-coefficients (β) and 95% confidence interval (95% CI). All analyses were performed using the R software (R Core Team, 2019). The R package 'dagitty' was used.[14] All the analyses were exploratory. No formal a priori sample size calculation was performed.

3. Results

The sample included 402 postmenopausal women, with a mean age of 62.9 ± 6.6 years and a mean age at menopause of 50.2 ± 2.8 years. The estimated average grip strength was 22.8 ± 3.7 kg, and the total sample adiposity (%) was 40.3 ± 5.2. The values of the clinical and hormonal parameters are reported in **Table 1**. Regular physical activity and current smoking habits were reported in 61.9% (249/402) and 19.4% (78/402) of the sample, respectively.

The results of the Pearson correlation coefficients (r) between HGS and covariates are presented in **Table 2.** We observed a positive correlation between HGS with plasma DHEAS levels (r = 0.16, *p* = 0.001). There were no significant correlations between HGS and other covariates (**Fig. 2**). After partial correlation adjusted by age the correlation with plasma DHEAS levels was not shown, and the other covariates remained not significant correlated.

The overall prevalence of dynapenia was 25.6% (103/402). When the differences between women with normal HGS were compared with those who presented dynapenia, there were significant differences in plasma FSH levels with OR: 0.99 (95% CI: 0.98-1.00), cortisol levels with OR: 1.07 (95% CI: 1.02-1.12) and DHEAS levels with OR: 0.99 (95% CI: 0.98-1.00). There were no significant differences among the remaining parameters displayed in **Table 3.** In women ≤ 65 years, 16.8% had dynapenia (44/262) and for women > 65 years the prevalence of dynapenia was 42.1% (59/140) with OR: 3.59 (95% CI: 2.26-5.76; p <0.001). Finally, a multivariable linear regression analysis was used to determine the relationship between endogenous hormones and HGS. After adjusting for confounder variables, no significant association was found between endogenous hormones and HGS. **Table 4**.

4. Discussion

This cross-sectional study of postmenopausal women found no evidence supporting relationships between studied endogenous hormones with HGS.

Human ageing is associated with diminished musculoskeletal function related to muscle mass decline in both men and women, reduction of muscle strength, higher fatigability, [15,16] and adiposity.[9] The loss of muscle strength begins around the 5th and 6th decades of age and appears concurrent with the onset of menopause, suggesting that estrogen levels can play a relevant role in muscle strength.[5] However, hormone therapy does not increase or maintain muscle mass or strength during the initial years of menopause.[7] Furthermore, a meta-analysis of randomized

clinical trials reported that there is not a significant beneficial or detrimental link between hormone therapy and muscle mass.[17] Thus, the association between estrogen levels and muscle strength in postmenopausal women is ambiguous, probably due to the different ages and study methods, and to the simplification of the involved endocrine factors. Some studies report a relationship between estrogen and muscle strength[4,5] while other studies found no consistent relation.[6,7] Rolland et al.[4] evaluated the percentage of loss per year of isometric knee extensor strength in young postmenopausal women, being the loss of muscle strength positively correlated with estrone and PTH. Cipriani et al.[5] evaluated the isometric grip strength of the upper dominant limb with age and hormonal status, showing that both age and menopause significantly contribute to de loss of grip strength. Schaap et al.[6] reported that low levels of estradiol and testosterone were associated with low muscle strength in men, but not in women. In our cohort, the association between estradiol and HGS was not significant, although we interestingly found that higher FSH plasma levels were significantly associated in women with dynapenia, expressing the secondary adjustment of the global hypoestrogenism of postmenopause.

In the same way that estradiol, testosterone decreases with age, starting in perimenopause, and does not differ due to natural menopause.[18] Testosterone levels are related to skeletal muscle mass. However, few studies have evaluated the relationship between testosterone and muscle strength in postmenopausal women. Van Geel et al.[19] reported that the bioavailable testosterone level was associated with lean body mass and maximum quadriceps extension strength. Recently Kong et al.[20] reported that low free testosterone levels and DHEAS were related to weak muscle strength independent of muscle mass. Our cohort was compounded only by Spanish White women, and there was no significant association between testosterone and HGS, neither after partial correlation adjusted by age.

With aging there are some changes in the cortisol circadian rhythm with late-day and evening increases in cortisol levels, earlier morning cortisol levels peak, lower circadian amplitude and more irregular cortisol secretion patterns.[21] Also, aging is associated with higher muscle cortisol generation by local 11β hydroxysteroid dehydrogenase which transforms inactive cortisone into active cortisol.[22] The increased cortisol levels are associated with muscle atrophy and weakness. Different results between muscle strength and cortisol levels may be due to different techniques of cortisol measurement. Plasma cortisol levels are more sensitive to fluctuations than salivary cortisol levels. Peeters et al.[23] showed no relationship between plasma cortisol levels and loss of grip strength, although they found that high salivary cortisol levels are associated with an increased risk of reduced grip strength. Bochud et al.[24] report a positive association between urinary cortisol metabolites to muscle mass and strength in the upper limbs in younger adults but not in the elderly. Although women with dynapenia had higher plasma cortisol levels, our multivariable analysis did not show a significant association between cortisol levels and HGS.

After menopause, with the decrease in estrogen levels, DHEA becomes the sole source for estrogen and androgen synthesis. DHEA and its sulfate (DHEAS) gradually decrease with age, and at the menopause onset, DHEA has already reduced by an average of 60%. DHEA and DHEAS are themselves inactive, but are performed in peripheral tissues and are transformed inside the cells in small amounts of estrogens and androgens.[25] Higher plasma DHEAS levels are associated with psychological wellbeing and physical functioning, including muscle strength. Low plasma DHEAS levels are associated with the development of cardiovascular disease and mortality.[26] In postmenopausal women, low plasma DHEAS and free testosterone are associated to weak muscle

strength.[20] Our results showed that DHEAS levels are correlated with HGS but this correlation is lost after adjusting by age. Δ4 androstenedione is a steroid hormone related to hyperandrogenic conditions, such as polycystic ovary syndrome, even though concerning to HGS in postmenopausal women has not been studied.[27] The current study did not observe any correlation between Δ4 androstenedione with HGS.

IGF-1 is a polypeptide hormone with autocrine, paracrine, and endocrine effects that play an important role in skeletal myogenesis, and it is associated with muscle mass and strength development.[28] Plasma IGF-1 levels decreased with aging in both men and women.[29] However, the role of IGF-1 in age-related muscle strength loss is still unclear. Gender is a confounding factor in the association between IGF-1 and muscle strength. Taekema et al.[30] found a significant relationship between IGF-1 levels and muscle strength in women but not in men, suggesting a gender-specific influence of IGF-1 on muscle strength. The Cappola et al. study[31] showed, after adjustment for age, a significant association between IGF-1 and knee extensor strength, but not anthropometry or other strength measures. They also found a significant correlation between plasma IGF-1 levels and muscle strength, only below the IGF-1 threshold limit of 50 μg/L. In our studied population, the mean plasma IGF-1 was above this limit, and after correction for confounder variables, we found that IGF-1 plasma levels were not associated with HGS.

Vitamin D plays an important role in preserving muscle function. Nevertheless, the relationship between vitamin D levels and HGS showed conflicting data. Some previous studies reported that low vitamin D levels are related to lower HGS in postmenopausal women,[32] and others showed no significant association.[33] These results may be due to different age ranges in the populations examined and different baseline serum vitamin D levels. In addition, López-Baena et al.[34] report that vitamin D affects muscle strength only when it is lower than a certain threshold. Muscle weakness is linked to vitamin D deficiency, especially if serum levels are <15 ng/mL, and the vitamin D supplementation in women who do not have vitamin D deficiency would no obtain significant benefit. Our study showed no association between HGS and vitamin D. However, in our cohort, there were no women with extremely low levels of vitamin D and this fact may be a possible explanation for our finding.

Circulating PTH levels increase with age regardless of renal function and plasma vitamin D, calcium, and phosphorus levels. PTH influence skeletal muscle protein metabolism in animal models and increases intracellular calcium concentration disrupting muscle function.[35] Some studies have examined the relationship between PTH and muscle mass or muscle strength with inconsistent results, due some studies found a statistically significant association,[36] while others found no association.[37] We have not observed an association between PTH and HGS.

Dynapenia is the age-related reduction of skeletal muscle strength that has been considered an independent factor of mortality.[38] Our current results suggest that studied hormones have no relevant roles in changes in HGS and dynapenia risk in otherwise healthy postmenopausal women. Other factors may be involved in those findings displayed in the studied population. Skeletal muscles are an endocrine organ and source of proteins (myokines) which function as autocrine, paracrine, or endocrine agents to maintain energy homeostasis and protective for the physical activity of skeletal muscles. Myokines may be also involved in body weight composition, subclinical inflammation, and muscle insulin sensitivity.[39] Physical activity can induce the release of muscle

myokines into the circulation to improve glucose metabolism, muscle proteins, and liver fat metabolism. [40,41] Future studies are neeeded to have evidence about myokines and dynapenia. On the other hand, adiposity and intramuscular fat accumulation are linked to mitochondrial damage and increased pro-inflammatory cytokines that induce muscle dysfunction.[42] Therefore, subclinical chronic inflammation may also play a role in HGS reduction and sarcopenia risk.[43] Future research directions should analyze those factors to assess the reduction of HGS and the risk of dynapenia in postmenopausal women.

4.1. Limitations and strengths

The present study has certain limitations, including its cross-sectional design, and the longitudinal effect of the studied hormones on muscle strength could not be possible. However, it has several strengths. First, it includes a large sample size of postmenopausal women. Second, the biochemical determinations were measured in the same laboratory with quality controls in place. Third, to identify confounding variables we used DAG and a careful adjustment for confounders were carried out in the regression model.

5. Conclusions

The present study reports that in postmenopausal women aged 47 to 83 years, our multivariable analysis adjusted for confounder variables did not find a significant association between studied endogenous hormones with HGS. The overall prevalence of dynapenia was 25.6%. Due to the clinical implications of dynapenia, further studies are needed to determine specific factors to assess the HGS reduction, and the risk of dynapenia in postmenopausal women.

Contributors

Pascual García-Alfaro was the principal investigator and drafted and revised the manuscript.
Sandra Garcia was responsible for statistical analysis.
Ignacio Rodriguez was responsible for the methodology of the study and statistical analysis.
Luciana Bergamaschi revised the manuscript.
Faustino R. Pérez-López revised the manuscript and provided scientific input.
All authors interpreted, revised, and approved the final version of the manuscript.

Disclosure of interest

The authors report no conflicts of interest.

Data statement

There are no linked research data sets for this paper. Data will be made available on reasonable request

Acknowledgements

This study has been done under the auspices of the Professorship in Obstetrics and Gynecological Research of the Hospital Universitario Dexeus, of the Universidad Autónoma de Barcelona.

References

1. Pérez-López FR. Dynapenia and sarcopenia, In: Cano A, editor (Ed.), Menopause: A comprehensive approach. Berlin: Springer; 2017. pp. 317-331;Chapter 20.

2. Cruz-Jentoft AJ, Bahat G, Bauer J, et al; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31. doi:10.1093/ageing/afy169.

3. Bohannon RW. Grip strength: An indispensable biomarker for older adults. Clin. Interv. Aging 2019;14:1681–1691. doi:10.2147/CIA.S194543.

4. Rolland YM, Perry HM 3rd, Patrick P, Banks WA, Morley JE. Loss of appendicular muscle mass and loss of muscle strength in young postmenopausal women. J Gerontol A Biol Sci Med Sci 2007;62:330-5. doi:10.1093/gerona/62.3.330.

5. Cipriani C, Romagnoli E, Carnevale V, et al. Muscle strength and bone in healthy women: effect of age and gonadal status. Hormones (Athens) 2012;11(3):325-32. doi: 10.14310/horm.2002.1361.

6. Schaap LA, Pluijm SM, Smit JH, et al. The association of sex hormone levels with poor mobility, low muscle strength and incidence of falls among older men and women. Clin Endocrinol (Oxf) 2005;63:152-60. doi:10.1111/j.1365-2265.2005.02315.x.

7. Maddalozzo GF, Cardinal BJ, Li F, Snow CM. The association between hormone therapy use and changes in strength and body composition in early postmenopausal women. Menopause 2004;11:438-46. doi:10.1097/01.GME.0000113847.74835.fe.

8. Kim YJ, Tamadon A, Park HT, Kim H, Ku SY. The role of sex steroid hormones in the pathophysiology and treatment of sarcopenia. Osteoporos Sarcopenia 2016;2(3):140-155. doi: 10.1016/j.afos.2016.06.002.

9. García-Alfaro P, García S, Rodríquez I, Pérez-López FR. Handgrip strength, dynapenia, and related factors in postmenopausal women. Menopause 2022;29(1):16-22. doi:10.1097/GME.0000000000001872.

10. Fess, EE. Grip strength. In: Casanova, JS., editor. Clinical assessment recommendations. 2nd ed.. Chicago: American Society of Hand Therapists; 1992. p. 41-45.

11. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al.; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39(4):412-23. doi:10.1093/ageing/afq034.

12. The IPAQ group. International physical activity questionnaire. 2016. Available at: http://www.ipaq.ki.se .

13. Digitale JC, Martin JN, Glymour MM. Tutorial on directed acyclic graphs. J Clin Epidemiol. 2022;142:264-267. doi: 10.1016/j.jclinepi.2021.08.001.

14. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int J Epidemiol. 2016;45(6):1887-1894. doi: 10.1093/ije/dyw341.

15. Akima H, Kano Y, Enomoto Y, et al. Muscle function in 164 men and women aged 20-84 yr. Med Sci Sports Exerc 2001;33:220-226. doi:10.1097/00005768-200102000-00008.

16. Faulkner JA, Larkin LM, Claflin DR, Brooks SV. Age-related changes in the structure and function of skeletal muscles. Clin Exp Pharmacol Physiol 2007;34:1091–1096. doi:10.1111/j.1440-1681.2007.04752.x.

17. Javed AA, Mayhew AJ, Shea AK, Raina P. Association between hormone therapy and muscle mass in postmenopausal women: A systematic review and meta.analysis. JAMA NetwOpen 2019;2(8):e1910154. doi:10.1001/jamanetworkopen.2019.10154.

18. Davidson SL, Bell R, Donath S, et al. Androgen levels in adult females: changes with age, menopause and oophorectomy. J Clin Endocrinol Met 2005;90(7):3847-53. doi:10.1210/jc.2005-0212.

19. van Geel TA, Geusens PP, Winkens B, Sels JP, Dinant GJ. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle mass, muscle strength and bone mineral density in postmenopausal women: a cross-sectional study. Eur J Endocrinol 2009;160(4):681–687. doi:10.1530/EJE-08-0702.

20. Kong SH, Kim JH, Lee JH, et al. Dehydroepiandrosterone sulfate and free testosterone but no estradiol are related to muscle strength and bone microarchitecture in older adults. Calcif Tissue Int 2019;105(3):285-293. doi:10.1007/s00223-019-00566-5.

21. Veldhuis JD , Sharma A , Roelfsema F . Age-dependent and gender-dependent regulation of hypothalamic-adrenocorticotropic-adrenal axis. Endocrinol Metab Clin North Am 2013;42: 201-25. doi:10.1016/j.ecl.2013.02.002.

22. Kilgour AH , Gallagher IJ , MacLullich AM , et al. Increased skeletal muscle 11betaHSD1 mRNA is associated with lower muscle strength in ageing. PLoS One 2013;8(12):e84057. doi:10.1371/journal.pone.0084057.

23. Peeters GM, van Schoor NM, van Rossum EF, Visser M, Lips P. The relationship between cortisol, muscle mass and muscle strength in older persons and the role of genetic variations in the glucocorticoid receptor. Clinical Endocrinology 2008;69:673-682. doi:10.1111/j.1365-2265.2008.03212.x.

24. Bochud M, Ponte B, Pruijim M, et al. Urinary sex steroid and glucocorticoid hormones are assocated with muscle mass and strength in healthy adults. J Clin Endocrinol Metab 2019;104(6):2195-2215. doi:10.1210/jc.2018-01942.

25. Labrie F. Intracinology and menopause: the science describing the cell-specific intracelular formation of estrogens and androgens from DHEA and their strictly local action and inactivation in peripheral tissues. Menopause 2019;26(2):220-224. doi:10.1097/GME.0000000000001177.

26. Ohlsson C , Vandenput L , Tivesten A . DHEA and mortality: what is the nature of the association?. J Steroid Biochem Mol Biol 2015;145:248–53. doi:10.1016/j.jsbmb.2014.03.006.

27. Badawy MT, Sobeh M, Xiao J, Farag MA. Androstenedione (a Natural Steroid and a Drug Supplement): A comprehensive review of its consumption, metabolism, health effects, and toxicity with sex differences. Molecules 2021;26(20):6210. doi:10.3390/molecules26206210.

28. Ahmad SS, Ahmad K, Lee EJ, Lee YH, Choi I. Implications of Insulin-Like Growth Factor-1 in Skeletal Muscle and Various Diseases. Cells 2020;9(8):1773. doi:10.3390/cells9081773.

29. Landin-Wilhelmsen K, Lundberg PA, Lappas G, Wilhelmsen L. Insulin-like growth factor I levels in healthy adults. Horm Res. 2004;62 Suppl 1:8-16. doi:10.1159/000080753.

30. Taekema DG, Ling CH, Blauw GJ, et al., Circulating levels of IGF1 are associated with muscle strength in middle-aged- and oldest-old women. Eur J Endocrinol 2011;164(2):189-96. doi:10.1530/EJE-10-0703.

31. Cappola AR, Bandeen-Roche K, Wand GS, et al. Association of IGF-I levels with muscle strength and mobility in older women. J Clin Endocrinol Metab 2001;86:4139-4146. doi:10.1210/jcem.86.9.7868.

32. Aspell N, Laird E, Healy M, Lawlor B, O'Sullivan M. Vitamin D Deficiency Is Associated With Impaired Muscle Strength And Physical Performance In Community-Dwelling Older Adults: Findings From The English Longitudinal Study Of Ageing. Clin Interv Aging 2019;14:1751-1761. doi:10.2147/CIA.S222143.

33. Kim BJ, Kwak MK, Lee SH, Koh JM. Lack of Association between Vitamin D and Hand Grip Strength in Asians: A Nationwide Population-Based Study. Calcif Tissue Int 2019;104(2):152-159. doi:10.1007/s00223-018-0480-7.

34. López-Baena MT, Pérez-Roncero GR, Pérez-López FR, Mezones-Holguín E, Chedraui P. Vitamin D, menopause, and aging: quo vadis? Climacteric 2020;23(2):123-129. doi: 10.1080/13697137.2019.1682543

35. Visser M, Deeg DJH, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): The Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab 2003;88(12):5766-72. doi:10.1210/jc.2003-030604.

36. Dhesi JK, Bearne LM, Moniz C, et al. Neuromuscular and psychomotor function in elderly subjects who fall and the relationship with vitamin D status. J Bone Miner Res 2002;17(5):891-7. doi: 10.1359/jbmr.2002.17.5.891.

37. Marantes I, Achenbach SJ, Atkinson EJ, et al. Is vitamin D a determinant of muscle mass and strength?. J Bone Miner Res 2011;26(12):2860-71. doi:10.1002/jbmr.510.

38. Uchida S, Kamiya K, Hamazaki N, et al. Prognostic utility of dynapenia in patients with cardiovascular disease. Clin Nutr. 2021;40(4):2210-2218. doi: 10.1016/j.clnu.2020.09.050.

39. Hoffmann C, Weigert C. Skeletal muscle as an endocrine organ: The role of myokines in exercise adaptations. Cold Spring Harb Perspect Med. 2017;7(11):a029793. doi: 10.1101/cshperspect.a029793.

40. Aryana GPS, Hapsari AAAR, Kuswardhani RAT. Myokine regulation as marker of sarcopenia in elderly. Mol Cell Biomed Sci. 2018;2(2):38-47. doi: 10.21705/mcbs.v2i2.32.

41. Gonzalez-Gil AM, Elizondo-Montemayor L. The role of exercise in the interplay between myokines, hepatokines, osteokines, adipokines, and modulation of inflammation for energy substrate redistribution and fat mass loss: A review. Nutrients. 2020;12(6):1899. doi: 10.3390/nu12061899.

42. Wiedmer P, Jung T, Castro JP, et al. Sarcopenia - Molecular mechanisms and open questions. Ageing Res Rev. 2021;65:101200. doi: 10.1016/j.arr.2020.101200.

43. Son DH, Song SA, Lee YJ. Association between c-reactive protein and relative handgrip strength in postmenopausal Korean women aged 45-80 years: A cross-sectional study. Clin Interv Aging. 2022;17:971-978. doi: 10.2147/CIA.S356947.

Figure 1. *Directed acyclic graph to distinguish the appropriate set of confounders for estimating our effect of interest. Arrows depict direct effects between variables, whereas the absence of an arrow between two variables represents the assumption of no such direct effect. Following this graph, all confounding variables were considered in the regression model to assess associations between endogenous hormones and HGS.*

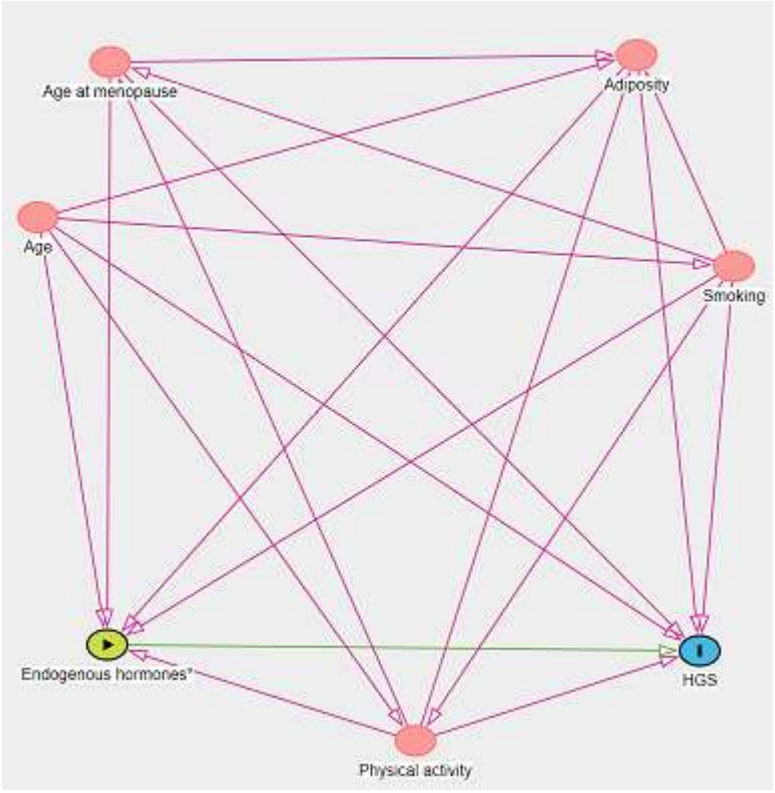

Figure 2. *Pearson correlations between dominant handgrip strength and hormonal parameters.*

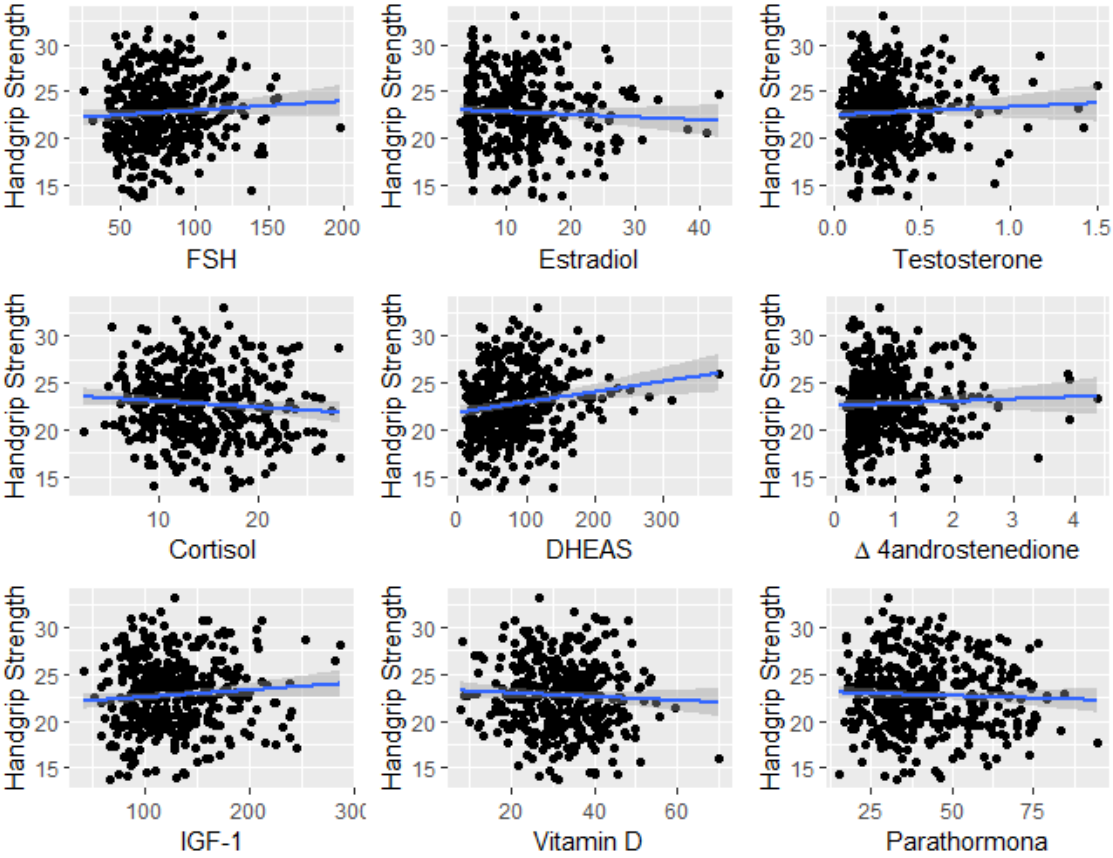

Table 1.*Clinical and Hormonal parameters reported as mean ± standard deviation.*

Parameters	Estimate (n = 402)	95% Confidence Interval	Reference ranges
Age	62.9 ± 6.6	[62.2 ; 63.5]	
Age at menopause	50.2 ± 2.8	[49.9 ; 50.5]	
Body mass index	24.7 ± 3.8	[24.3 ; 25.1]	
Adiposity	40.3 ± 5.2	[39.8 ; 40.8]	
FSH	78.1 ± 25.4	[75.6 ; 80.5]	40 - 116 mU/mL
Estradiol	11.6 ± 6.7	[10.9 ; 12.2]	5- 37 pg/mL
Testosterone	0.3 ± 0.2	[0.30 ; 0.35]	0.02 -0.40 ng/mL
Cortisol	14.1 ± 4.9	[13.6 ; 14.6]	4.3 - 22.4 µg/dL
DHEAS	83 ± 53.1	[77.8 ; 88.2]	35 - 430 µg/dL
Δ4androstenedione	0.9 ± 0.7	[0.79 ; 0.92]	0.49 - 1.31 ng/mL
IGF-1	126 ± 41.3	[122 ; 130]	44 - 241 ng/mL
Vitamin D	31.8 ± 9.6	[30.9 ; 32.7]	30 -100 ng/mL
Parathormone	42.2 ± 15.4	[40.7 ; 43.7]	15 - 65 pg/mL

DHEAS: Dehydroepiandrosterone sulfate; FSH: Follicle-stimulating hormone; IGF-1: Insulin-like growth factor 1

Table2.*Pearson correlation analyses between handgrip strength and hormonal parameters. Partial correlations with Pearson adjusted by age.*

Handgrip Strength				
Covariates (n = 402)	**r (Pearson correlation)**	***P* value**	**Partial correlations**	**P value**
FSH	0.07	0.168	-0.01	0.911
Estradiol	-0.05	0.301	-0.05	0.325
Testosterone	0.05	0.302	0.04	0.387
Cortisol	-0.09	0.083	-0.05	0.326
DHEAS	0.16	0.001	0.06	0.248
Δ4androstenedione	0.04	0.394	0.01	0.773
IGF-1	0.09	0.088	0.01	0.860
Vitamin D	-0.05	0.299	-0.04	0.470
Parathormona	-0.04	0.404	-0.02	0.690

DHEAS: Dehydroepiandrosterone sulfate; FSH: Follicle-stimulating hormone; IGF-1: Insulin-like growth factor 1

Table 3. Mean comparison between hormonal parameters in women with normal handgrip strength (HGS≥20) and dynapenia (HGS <20), odds ratio, and 95%CIs,and p-values.

Covariates (n = 402)	**HGS≥ 20 kg (n = 299)**	**HGS< 20 kg (n = 103)**	**Odds Ratio [95% CI]**	**p-value**
FSH	79.7 ± 26	73.3 ± 23.1	0.99 [0.98;1.00]	**0.019**
Estradiol	11.5 ± 6.7	11.9 ± 6.7	1.01 [0.98;1.04]	0.602
Testosterone	0.33 ± 0.23	0.32 ± 0.2	0.79 [0.28;2.21]	0.625
Cortisol	13.7 ± 4.73	15.3 ± 5.19	1.07 [1.02;1.12]	**0.005**
DHEAS	87 ± 56	71.3 ± 41.8	0.99 [0.99;1.00]	**0.003**
Δ4androstenedione	0.87 ± 0.67	0.82 ± 0.62	0.87 [0.61;1.25]	0.442
IGF-1	127 ± 41.4	123 ± 41.2	1.00 [0.99;1.00]	0.335
Vitamin D	31.7 ± 9.55	32 ± 9.61	1.00 [0.98;1.03]	0.806
Parathormona	41.7 ± 14.8	43.5 ± 16.9	1.01 (0.99;1.02]	0.338

CI: Confidence Interval, DHEAS: Dehydroepiandrosterone sulfate, FSH: Follicle-stimulating hormone, HGS: Handgrip Strength, IGF-1: Insulin-like growth factor 1.

Table 4. Multivariable linear regression model to analyses the relationship between endogenous hormones and HGS (kg) adjusting for age, age at menopause, adiposity, smoking status and physical activity.

	Handgrip strength	
	β	**95%CI**
FSH	-0.00	[-0.01;0.01]
Estradiol	-0.02	[-0.07; 0.03]
Testosterone	0.62	[-1.06;2.30]
Cortisol	-0.05	[-0.12;0.03]
DHEAS	0.00	[-0.01;0.01]
Δ4androstenedione	-0.03	[-0.64;0.58]
IGF-1	-0.00	[-0.01;0.01]
Vitamin D	-0.01	[-0.05;0.02]
Parathormona	-0.00	[-0.02;0.02]
		Adj. R^2 = 0.15

CI: Confidence Interval, DHEAS: Dehydroepiandrosterone sulfate, FSH: Follicle-stimulating hormone, HGS: Handgrip Strength, IGF-1: Insulin-like growth factor 1.