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Doctor, ask your perimenopausal patient about her physical fitness; Association of self-reported physical fitness with cardiometabolic and mental health in perimenopausal women. The FLAMENCO Project

--Manuscript Draft--

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Abstract:	Objectives. To explore the association of self-reported physical fitness (PF) and its components with cardiometabolic and mental health in perimenopausal women. Methods. These cross-sectional analyses included 191 participants (53±4 years old) from the FLAMENCO project. Self-reported PF was assessed with the International Fitness Scale (IFIS). Body mass index (BMI), fat mass (FM), waist circumference (WC), systolic and diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-C), triglycerides, C-reactive protein (CRP) and glucose were measured. The Beck's Depression Inventory, State-Trait Anxiety Inventory, Pittsburgh Sleep Quality Index, Life Orientation Test Revised and Positive and Negative Affect Schedule were used to assess mental health. Results. After adjusting for potential confounders, greater overall-PF was associated with lower BMI, FM, WC ($p<0.001$), DBP and CRP, and higher HDL-C ($p<0.05$). Cardiorespiratory fitness (CRF), speed-agility and flexibility were associated with lower BMI, WC and FM ($p<0.001$), and muscle strength (MS) with lower WC and FM ($p<0.05$). Additionally, CRF, MS and speed-agility were associated with lower CRP ($p<0.01$), and flexibility with enhanced triglycerides and HDL-C ($p<0.05$). Overall-PF and all its components were associated with lower

	depression, anxiety and negative affect (p≤0.01), and greater positive affect (p≤0.05). Overall-PF and MS were associated with better sleep quality (p<0.05), and CRF, MS and speed-agility with greater optimism (p≤0.05). Finally, overall-PF showed evidence of significant association with less pharmaceutical expenditure (B=-7.2, β=-0.145, p=0.08). Conclusion: Self-reported PF was associated with better cardiometabolic and mental health in perimenopausal women. The IFIS might be proposed as a cheap, quick and easy tool in clinical settings.

Revised manuscript

Dear Editor,

Please, find enclosed the revised version of our manuscript ref: MENO-D-19-00085 in the hope that you might find it suitable for publication in *Menopause*. We would like to thank the Editor and the Reviewers for their thoughtful and constructive comments on the previous version, and for giving us the opportunity of revising and improving the quality of our manuscript. We have carefully considered all the suggestions, and have either integrated them into the revised manuscript or commented on them on the answers to the reviewers. Changes to the original manuscript have been incorporated using yellow background. We believe that our manuscript is now stronger as a result of these modifications. An itemized point-by-point response to the Editorial Office and the Reviewers' comments is presented below.

Editorial Office Comments

Comment
As currently written the English grammar is not at an acceptable level for publication in our journal. You must have someone whose native language is English and who has a strong scientific background review your manuscript for proper spelling and grammar.
Answer
English grammar and spelling have been carefully revised along the manuscript.

Comment
Dr. Nuria Marín-Jiménez did not confirm authorship on the paper and did not complete the copyright questionnaire. Please make sure this is completed during the revision process.
Answer
Sorry for the delay, Miss Nuria Marín-Jiménez has already confirmed the authorship.

Comment
Your table(s) is/are currently part of your manuscript file. Tables should be in a separate file and in .doc format. When submitting your revised manuscript please put in correct format and submit as a separate file from your manuscript file.
Answer
Done.

Comment

We notice that you use the term "better body composition" frequently in your manuscript. We are unfamiliar with that term. Please define the term "better body composition".

Answer
We refer to lower BMI and adiposity (i.e. lower fat mass and waist circumference, which can also be interpreted as less total and central adiposity, respectively). Notwithstanding, for a better understanding of the reader, we have detailed the specific associations found in the Abstract section, and defined “better body composition” or specified the body composition component to which we refer along the document (page 10, lines 13-14 and page 11, lines 2, 18-19).

Comment
We notice the use of the term “Hormone Replacement Therapy” (HRT). Our journal prefers the term "Hormone Therapy" (HT). Please make changes to your manuscript (as well as figures and tables) accordingly.
Answer
Amended.

Comment
If you list a clinical trial/study/grant number in your manuscript, please verify that this number is correct before submitting your revision.
Answer
Thanks. We have verified the ClinicalTrials.gov Identifier (NCT02358109) and the grant numbers. All of them are correct.

Comment
Please make sure all acronyms and abbreviations are defined in the footnotes of tables/figures.
Answer
Thanks. Revised.

Comment
When listing manufacturer names, please provide city and state if in the USA, and city and country if outside the USA.
Answer
Done.

Comment
Please do not use superscripted symbols in tables. Our journal’s style is to use superscripted letters of the alphabet when appropriate.
Answer
Thanks. Superscripted symbols have been replaced by letters.

Reviewer 1

Reviewer comment

Doctor, ask your perimenopausal patient about her physical fitness: Association of self-reported physical fitness with cardiometabolic and mental health in perimenopausal Women. The FLAMENCO Project is of interest.

Answer

Thanks. The comments are highly appreciated.

Reviewer comment

Cross sectional hypothesis generating study useful to help understand burden

Answer

Following the reviewer's suggestion, we have incorporated a new sentence at the end of the Introduction section including our cross-sectional hypothesis (page 4, lines 8-10).

Reviewer comment

Cannot determine causal inference.

Answer

The reviewer is fully right and this is the reason why we have included a sentence in the Limitations section stating this fact: "*Since our results are derived from cross-sectional analyses, the associations found cannot be explained via a causal pathway. For instance, it has been proved that high-anxiety sensitivity women participate in less physical exercise and perceive themselves as less fit than low-anxiety sensitivity women*[1]*"*.

However, current Literature has extensively proven the strong and independent association of objectively-measured physical fitness (particularly cardiorespiratory fitness and muscle strength) with both physical and mental health through longitudinal studies[2-10].

Reviewer comment

Indices of validity and reproducibility and observer variation are absent from the reporting

Answer

We assume that the reviewer refers to the validity of the International Fitness Scale (IFIS). Self-reported PF was measured through the Spanish version[11-13] of the IFIS[14]. Despite this questionnaire has not been specifically validated in perimenopausal women (which it has been highlighted as a Limitation of the present study), the IFIS has been validated in European adolescents[14], Spanish children[13], young adults[15], older adults[12], women with fibromyalgia[11] and Colombian adolescents[16].

More detailed information with respect to the IFIS validation has been incorporated into the Methods (page 5, lines 14-15 and 19-21).

Reviewer comment

Authors are only reporting p values not effect size. The n determines the p values. Of interest is the effect size and discussions thereof

Answer

We agree with the reviewer comment. Certainly, the sample size is strongly related to the power of the statistical test, which determines the detection of bigger/smaller effects, and the p-value. Hence, it is usually of great interest to include the effect sizes to facilitate the interpretation of the results, as recommended by guidelines. However, the correlation coefficient is a quantitative measure of the magnitude itself. Indeed, the correlation coefficient is an estimator of the effect size (magnitude of the relationship between two quantitative variables) when paired quantitative data is available. Depending on the value of the coefficient of correlation (*Cohen, J. (1988). Statistical power analysis for the behavioral sciences. New Jersey: Lawrence Erlbaum*), the effect size is interpreted as small (0.1-0.3), medium (0.3-0.5) or large (> 0.5). In fact, other related estimators such as the coefficient of determination, which is calculated as the square of the coefficient of correlation, are usually employed as effect sizes in linear regressions. Interestingly, it is noticeable how meta-analyses also usually employ the coefficients of correlation from different studies to get a pooled effect size.

Notwithstanding, we have incorporated the 95% confidence interval (CI) to the Pearson r coefficient to provide a more accurate estimation.

Reviewer comment

Of interest is menopause stage using international criteria

Answer

Following the international criteria, a woman is defined as postmenopausal from 1 year after her last period. Menopause refers specifically to the last menstrual period but is rarely used as a diagnosis in itself, because it is impossible to know at the time if a menstrual period is the last one; therefore 'postmenopause' tends to be used more than 'menopause'. We have added the main number of years without period among the participants into Table 1 (additionally to "regular menstruation", which indicates if the women had currently menstruation). We have also incorporated a new outcome called "Irregular menstruation in the last 12 months". Regrettably, we did not assess serum hormones that would have helped in the specific menopausal stage establishment (e.g. follicle-stimulating hormone, luteinizing hormone, estradiol, progesterone, anti-Müllerian, antral follicle count, inhibin B or inhibin A). Notwithstanding, the main aim of this study was to explore the association of self-reported physical fitness with cardiometabolic and mental health during these years, when women can experience many physical and mental health problems related to partial-total estrogens loss (i.e. 45-60 years old).

Reviewer comment

Apparently the only partial correlation of clinical effect size is fat mass with overall fitness

Answer

The reviewer is right. When we compare the strength of the association between the different variables, it is appreciable that the correlation of overall fitness with fat mass seems to be the strongest (i.e. r = -0.524). However, we have also observed that other correlations from the analyses are moderately strong, as the coefficient of correlation is ranged between 0.3-0.5 (*Cohen, J. (1988). Statistical power analysis for the behavioral sciences. New Jersey: Lawrence Erlbaum*).

Reviewer comment

The authors should report associations with NonHDL cholesterol

Answer

We have included a sentence in the Result section stating the lack of associations with LDL-cholesterol (page 9, lines 12-13). Nonetheless, we did not discuss this result as HDL-cholesterol seems to be more relevant in the cardiovascular disease risk prediction, given that is one of the five components for the metabolic syndrome diagnosis (i.e. the criteria by the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity[17]).

Reviewer 2

Reviewer comment

This is an interesting paper that analyzes the association of self-reported physical fitness (PF) and cardiometabolic markers during perimenopause. However, it must be re-analyzed as it has important limitations. In addition it is a cross-sectional analysis, and does not take into account factors as important as the date of last menstruation and its relationship with cardiovascular parameters.

Answer

Thanks. The comments to improve the manuscript are highly appreciated.

Reviewer comment

I would like it to be revised:

1.- The definition of perimenopause is very non-specific. I recommend that Harlow SD et al. Climacteric.2012.

Answer

We are aware that the term “perimenopause” is always confusing, and we agree with the reviewer that defining this period (i.e. 45-60 years) as perimenopause is not the standard definition of “perimenopause”. However, as we stated in the Introduction, we have employed perimenopause term as the time just before, during and after menopause.

Notwithstanding, the main aim of this study was to explore the association of self-reported physical fitness with cardiometabolic and mental health during these years, when women can experience many physical and mental health problems related to partial-total estrogens loss (i.e. 45-60 years old).

Nevertheless, we have carefully revised the manuscript by Harlow SD et al[18] who defines perimenopause as "the early and late menopause transition stages as well as the early postmenopause". Regrettably, we cannot contrast supportive criteria for such perimenopause definition as we did not assess serum hormones. However, sometimes the term "perimenopause" has been employed indistinctly to refer to this range of years in the woman (e.g. 45-60 years old). Also, given that the SWAN provides the longest follow-up period – 13 years of follow-up for a sample of women aged 42-52 at baseline - it is important to recognize that the own "*Menopause"* Journal has included women defined as "perimenopausal" with a maximum age of 65[19]. Nonetheless, we are open to replace the term "perimenopause" by middle-age women or that preferred by the reviewer and editor.

Reviewer comment

2.- It should be indicated more clearly, in the Introduction, the reason that led to analyze this association.

Answer

We have included a new sentence better justifying the present study aims (page 4, lines 2-5).

Reviewer comment

3.- The age range covers perimenopause and postmenopause, which is a very long period (45-60 years), and does not correspond to the concept of perimenopause.

Answer

As mentioned above, we are fully open to employ a different term along the manuscript, such as "middle-aged women", "peri and postmenopause women", etc. We trust in the criteria of this specialized Journal.

Reviewer comment

4.- The years since the last menstruation have not been taken into account, without specifying the date of last menstruation or rule.

Answer

As mentioned above, we have incorporated a new variable called "years without regular menstruation" (in case they did not have menstruation currently) into Table 1. We have also repeated the analyses including this outcome into the models as a new confounder, and results remain the same.

Reviewer 3

Reviewer comment

The findings from this study are important and strong showing self-reported physical fitness being associated with better mental and cardio metabolic health outcomes in peri-menopausal women. This study clearly articulates the positive effects of greater overall

PF with lower BMI, WC, fat mass, blood pressure and C-reactive protein and higher high-density lipo protein cholesterol and highlights the need for the employment of assessment of physical fitness by clinicians in this population of women. The background literature and supporting literature in the discussion are relevant, recent and complement the paper. The methodology is sound with strong instruments used to measure the variables. The inclusion of the cost analysis is an important and interesting component. The authors conclusions are important, suggesting that the International Fitness Scale could be used in clinical settings as a complimentary monitoring health tool for perimenopausal women.

Answer

Thanks. The comments are highly appreciated.

Reviewer comment

There are a couple of English edits that need to be undertaken for example: Introduction

paragraph 4, sentence 2; change 'are worrisome increasing' to 'are increasing' final sentence; change ' might leads to' to 'might lead to'

Methods

Sentence 3 'interested on' to 'interested in'

Answer

Done. Thank you so much for your constructive comments. English grammar has been carefully revised.

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Doctor, ask your perimenopausal patient about her physical fitness; Association of self-reported physical fitness with cardiometabolic and mental health in perimenopausal women. The FLAMENCO Project

Running title: Self-reported fitness and health status during perimenopause

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Competing interests

None of the authors have any conflict of interests.

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ABSTRACT

Objectives. To explore the association of self-reported physical fitness (PF) and its components with cardiometabolic and mental health in perimenopausal women. **Methods.** These cross-sectional analyses included 191 participants (53±4 years old) from the FLAMENCO project. Self-reported PF was assessed with the *International Fitness Scale* (IFIS). Body mass index (BMI), fat mass (FM), waist circumference (WC), systolic and diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-C), triglycerides, C-reactive protein (CRP) and glucose were measured. The *Beck's Depression Inventory*, *State-Trait Anxiety Inventory*, *Pittsburgh Sleep Quality Index*, *Life Orientation Test Revised* and *Positive and Negative Affect Schedule* were used to assess mental health. **Results.** After adjusting for potential confounders, greater overall-PF was associated with lower BMI, FM, WC (p<0.001), DBP and CRP, and higher HDL-C (p<0.05). Cardiorespiratory fitness (CRF), speed-agility and flexibility were associated with lower BMI, WC and FM (p<0.001), and muscle strength (MS) with lower WC and FM (p<0.05). Additionally, CRF, MS and speed-agility were associated with lower CRP (p<0.01), and flexibility with enhanced triglycerides and HDL-C (p<0.05). Overall-PF and all its components were associated with lower depression, anxiety and negative affect (p≤0.01), and greater positive affect (p≤0.05). Overall-PF and MS were associated with better sleep quality (p<0.05), and CRF, MS and speed-agility with greater optimism (p≤0.05). Finally, overall-PF showed evidence of significant association with less pharmaceutical expenditure (B=-7.2, β=-0.145, p=0.08). **Conclusion:** Self-reported PF was associated with better cardiometabolic and mental health in perimenopausal women. The IFIS might be proposed as a cheap, quick and easy tool in clinical settings.

Key words. International Fitness Scale; body composition; anxiety; cardiovascular disease; positive health; depression.

INTRODUCTION

During perimenopause (understood as the time just before, during and after menopause), women experience a variety of physiological changes related to estrogen loss and aging which can negatively affect their physical and mental health[1, 2]. Particularly, perimenopause may promote increased android fat mass (central adiposity)[3] and blood pressure[3, 4], dyslipidemia[4], and, consequently, greater risk of cardiovascular disease (CVD)[5].

Moreover, perimenopause can also negatively affect mental health of middle-aged women[6, 7] who might experience anxiety, depression, sleep disruptions or mood disorders[2, 6-8], among other symptoms. It should be noted that "mental health" is not only the lack of psychological ill-being, but also the presence of well-being[9]. In this context, psychological well-being is the combination of positive affective states, along with optimal social and personal life[9]. Although many researchers have investigated psychological distress during this period, evidence regarding positive well-being is scarce[10].

Many of these adverse physical, mental and psychological changes experienced during perimenopause might be attenuated by increasing physical fitness (PF) through physical activity or exercise[11, 12]. However, despite of the consistent evidence about the positive influence of physical activity and exercise on cardiometabolic status[13, 14], quality of life[15] and mental health[11, 12], the assessment of PF in clinical settings is still anecdotal. In this regard, easy and quick tools, such as the *International Fitness Scale*, could facilitate the regular assessment of PF by clinicians, who are frequently under time constraints. In fact, PF has been shown to be moderately well estimated by self-reported scales[16].

Since menopausal transition is a critical period for women´s health, it is of clinical and practical relevance for healthcare professionals to further characterize the extent to which

self-reported PF might be associated with better cardiometabolic and/or mental health in this population. These findings could help physicians to better and individually prescribe exercise to those women with lower specific PF components (e.g. recommending an exercise program focused on resistance or aerobic training) based on specific symptomatology. Moreover, it is noteworthy that adequate PF levels seem to decrease health care requirements, and thereby might lead to significant savings in pharmaceutical costs[17-19]. This is of vital importance if we consider that pharmacological costs are increasing in European countries[20], and represent 17% of the National Health Expenditures in Spain[20].

We hypothesized that perimenopausal women with lower self-reported levels of PF would show worse cardiometabolic and mental health, and greater pharmaceutical costs. Therefore, the purpose of the present study was to analyze the association of self-reported PF and its different components, with cardiometabolic and mental health markers in perimenopausal women. A secondary aim of this study was to explore the association of self-reported PF with pharmaceutical costs.

METHODS

Participants

The complete methodology of the FLAMENCO project is described elsewhere[21] (ClinicalTrials.gov Identifier: NCT02358109). Briefly, perimenopausal women were informed about the study aims and procedures through primary care centers from Granada (south Spain), press releases and social media. Women interested in participating signed a written informed consent before being enrolled in the study. From the 198 women initially recruited (age range 45-60 years old) who met the inclusion criteria[21] and had valid data in self-reported PF, the final sample size included in the present analyses comprised 191 women.

This study protocol was reviewed and approved by the Ethics Committee for Research Involving Human Subjects at the University of Granada (nº 861).

Procedures

Socio-demographic and clinical characteristics, body composition, dietary and mental health questionnaires, and self-reported PF levels (in the same order as presented) were assessed by the same group of researchers in a single day. Participants completed questionnaires about their clinical and socio-demographic characteristics in a private room.

Socio-demographics

A questionnaire was used to collect participants' self-reported socio-demographic data, such as age, household composition, marital status, educational level, occupation, shift work and smoking habits.

Self-reported physical fitness

Self-reported PF was measured through the Spanish version[22-24] of the *International Fitness Scale*[25], which is composed of five Likert-scale questions where the participants rate their PF levels as "very poor", "poor", "average", "good" and "very good" in comparison with the average person of the same age. There is 1 question about general PF, and 4 questions about its specific components (i.e. cardiorespiratory fitness, muscle strength, speed/agility and flexibility). This questionnaire has been validated in adolescents[25, 26], children[24], young adults[27], older adults[23] and middle-age women with fibromyalgia[22], and is available in different languages at http://profith.ugr.es/IFIS.

Pharmaceutical expenditure

The pharmaceutical consumption of each participant was obtained through a medical history from the *Diraya* system, employed by the Public Health System of Andalusia

(Spain). *Diraya* is an integrated electronic health record that registers all resources provided to the patient through primary care, including medication.

Mediterranean diet

The *Mediterranean Diet Score*[28] was used to evaluate the degree of adherence to the Mediterranean diet. The scores range from 0-55, with higher scores indicating greater adherence to the Mediterranean diet (healthier diet).

Menopause symptoms

The *Blatt–Kupperman Menopausal Index*[29] was employed to describe menopause severity. The global score ranges from 0 to 51, where the severity degree of menopause is categorized as low, mild, moderate or severe depending of the score obtained (<15, 15–20, 20–35, and >35, respectively).

Cardiometabolic health markers

Body composition

Weight (kg) was assessed with a scale (InBody R20, Biospace, Seoul, South Korea) and fat mass (kg) of the whole body by dual-energy x-ray absorptiometry (Hologic Discovery QDR, Nasdaq: HOLX, Marlborough, Massachusetts, United States). Height (cm) was measured with a stadiometer (Seca 222, Seca, Hamburg, Germany). Height and weight were used to calculate body mass index (BMI). Waist circumference (WC) was assessed at the middle point between the ribs and the ileac crest with the participant standing (Harpenden anthropometric tape, Holtain Ltd. Hong Kong, China).

Blood pressure and resting heart rate

Systolic and diastolic blood pressure, as well as resting heart rate, were measured after 5 minutes of rest with the person seated, in 2 trials separated by 2 minutes (Omron Health Care Europe B.V. Hoolddorp, The Netherlands). The lowest values of the two trials were selected for the analyses.

Serum biochemical markers

Venous blood samples were collected in standardized fasting conditions in the primary care health center. Plasma fasting glucose, C-reactive protein, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides were assessed in accordance with standard procedures by using an autoanalyzer (Hitachi-Roche p800, F. Hoffmann-La Roche Ltd, Basel, Switzerland).

Mental health markers

Depression

The Beck Depression Inventory-II[30] was used to assess depression. It contains 21 items measuring depressive symptoms such as sadness or loss of pleasure, among others. The global score ranges from 0 to 63, where higher scores indicate greater depression.

Anxiety

The Trait Anxiety Index (STAI-T)[31] is one of the most commonly validated questionnaires employed to evaluate anxiety, and was used to assess trait (dispositional) anxiety. The STAI-T is composed by 20 self-administered items (up to 40 points), where higher scores indicate greater state of anxiety.

Sleep quality

The Pittsburgh Sleep Quality Index[32] was used to assess the sleep quality of the participants. This questionnaire asks about the self-perceived sleep quality during the last month. The global sleep quality score ranges from 0 to 21, where higher scores mean worse sleep quality.

Optimism

The Life Orientation Test Revised[33] was used to assess participants' expectations about their future and their general sense of optimism. The total score ranges from 0 to 24 and higher scores indicate greater optimism.

Trait positive and negative affect

Trait positive and negative affect were assessed by the Trait Positive and Negative Affect Schedule (PANAS-T)[34]. This questionnaire includes 10 positive and 10 negative emotional states that should be answered on a 5-point Likert scale. The score ranges from 10 to 50 for both subscales (positive or negative affect), where higher scores reflect greater affective well-being.

Statistical analyses

Descriptive statistics (mean (standard deviation) for quantitative variables and number of women (%) for categorical variables) were employed to describe socio-demographic and clinical characteristics of the participants. Pearson´s partial correlations along with p-value and 95% bias corrected and accelerated confidence intervals (based on 1000 bootstrap samples) after adjusting for age, menopausal stage, medication, BMI, smoking habit and the Mediterranean diet score were employed to assess the association of self-reported overall PF and its components with the different physical and mental health-related outcomes (e.g. blood pressure or depression). Linear regression analyses were performed to explore the association of self-reported overall PF with pharmaceutical cost. These analyses were also adjusted for the above mentioned confounders.

All analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 22.0, Armonk, New York, USA), and the level of significance was set at $p \leq 0.05$.

RESULTS

The socio-demographic and clinical characteristics of the study sample are shown in ***Table 1***. Most of the sample (mean age 53±4 years) had irregular menstruation (79%), were overweight, and presented a moderate adherence to the Mediterranean diet. Most of

the participants were married, and had a University degree. The severity of menopausal symptoms among these women was low, and 24% were active smokers.

Partial correlations after adjusting for age, menopausal stage, medication, BMI, smoking habit and the Mediterranean diet score between self-reported PF and cardiometabolic health markers are shown in ***Table 2***. Greater levels of self-reported overall PF were associated with lower BMI, WC, fat mass (all, $p<0.001$), diastolic blood pressure and C-reactive protein, and higher HDL-C (all, $p<0.05$). Regarding specific PF components, self-reported cardiorespiratory fitness was inversely associated with BMI, WC, fat mass (all, $p<0.001$), resting heart rate and C-reactive protein (both, $p<0.01$). Greater self-reported muscle strength was associated with lower WC, fat mass (both, $p<0.05$) and C-reactive protein ($p<0.01$). Self-reported speed-agility was inversely associated with BMI, WC, fat mass (all, $p<0.001$) and C-reactive protein ($p<0.01$). Finally, higher self-reported flexibility was associated with lower BMI, WC (both, $p<0.001$), fat mass ($p<0.01$) and triglycerides and higher HDL-C (both, $p<0.05$). Serum glucose and LDL-cholesterol and systolic blood pressure were not associated with PF (all, $p>0.05$).

Partial correlations, after adjusting for the aforementioned confounders, between self-reported PF and mental health markers are shown in ***Table 3***. Greater self-reported overall PF was associated with lower depression ($p<0.001$), negative affect ($p<0.01$) and anxiety ($p<0.05$), and greater sleep quality and positive affect ($p<0.05$). Regarding specific PF components, greater levels of cardiorespiratory fitness were associated with lower depression ($p<0.001$), negative affect ($p<0.01$) and anxiety ($p<0.05$), and greater optimism and positive affect (both, $p<0.01$). Higher self-reported muscle strength was associated with lower depression, anxiety (both, $p<0.01$) and negative affect ($p<0.05$) and greater positive affect ($p<0.001$), optimism ($p<0.01$) and sleep quality ($p<0.05$). Greater self-reported speed-agility was associated with lower depression ($p<0.001$), anxiety and

negative affect (p<0.01) and greater optimism (p<0.05) and positive affect (p<0.01). Finally, self-reported flexibility was associated with lower depression, negative affect (both, p<0.001) and anxiety (p<0.01) and greater positive affect (p<0.01).

Linear regression analysis assessing the association of self-reported overall PF with pharmaceutical cost is shown in ***Table 4***. Greater self-reported overall PF showed evidence of statistical significance with lower pharmacological expenditure (B: -7.2, β: -0.145, p=0.08).

DISCUSSION

To the best of our knowledge this is the first study exploring the association of self-reported PF with both cardiometabolic and mental health in perimenopausal women. Greater self-reported levels of overall PF and, more specifically, cardiorespiratory fitness and muscle strength, were associated with better body composition (i.e. lower BMI, WC and fat mass), blood pressure and serum cardiometabolic markers (especially with lower inflammation). Similarly, self-reported overall PF and its components were associated with better mental health (i.e. less anxiety, depression and negative affect, better sleep quality and higher positivism and positive affect). Finally, greater overall-PF showed evidence of statistical significance with less pharmaceutical expenditure.

Recent literature has emphasized the emerging relevance of PF as an important predictor of CVD[35-40], and several studies have highlighted the protective influence of PF on cardiometabolic health in women[35, 37-41]. However, as far as we know, no previous studies have explored the association of self-reported PF with cardiometabolic markers during perimenopause. To note is that PF can be reasonably well estimated by self-reported scales[16]. Consistently, some authors have stated that self-reported PF assessment may be considered a cost-effective way for measuring PF levels in primary care[42].

Regarding the cardiometabolic markers studied in the present study, overall self-reported PF and cardiorespiratory fitness were associated with lower total and central adiposity, lower heart rate, and lower inflammation (as assessed through serum C-reactive protein). It is noteworthy that cardiorespiratory fitness has been highlighted as determinant in order to avoid premature mortality and morbidity risk in the general population[38]. For instance, in the *Aerobics Center Longitudinal Study*, cardiorespiratory fitness demonstrated a strong inverse relationship with metabolic syndrome in both sexes, showing the strongest single association with WC[13], which is in agreement with our results. Similarly, Zhu et al.[43] explored the relationship between cardiorespiratory fitness and CVD risk factors in Chinese middle-aged women. They demonstrated that cardiorespiratory fitness was independently associated with CVD risk factors, including overweight, hypertension, dyslipidemia, arterial stiffness, and abnormal electrocardiography during exercise[43].

With regard to muscle strength, participants' self-reported PF levels were inversely associated with WC, fat mass and C-reactive protein. This concurs with previous literature where greater muscle strength was related to lower central adiposity, metabolic syndrome incidence, insulin resistance, and inflammation[35, 37, 39].

In this study sample, speed-agility was associated with better body composition (i.e. lower BMI and lower total and central adiposity) and less C-reactive protein, which is in line with a similar study[44]. Finally, flexibility was associated with better body composition and lipid profile. Previous studies have also highlighted the emerging role of flexibility on cardiometabolic risk in middle-age women[39, 40] and elderly people[45].

In 2014, our group tested the utility of PF testing for the identification of women at high-risk of metabolic syndrome (in perimenopausal Moroccan population)[46]. We found that women with the metabolic syndrome performed worse in most fitness tests studied, and we proposed specific PF tests cut-off points for the identification of metabolic syndrome.

Among the PF components studied, cardiorespiratory fitness and upper-body flexibility had the highest association with metabolic syndrome[46]. Similarly, in Spanish perimenopausal women, we found that most PF components differed between body-size phenotypes, being newly and flexibility those components that showed the strongest association with a cluster of cardiometabolic risk factors[40]. Later, we have confirmed (in women from the present project) that objectively-measured , upper-body flexibility, and lower-body muscle strength were associated with better cardiovascular profile[47]. Moreover, we newly proposed specific PF cut-off points to facilitate the early identification of perimenopausal women at high risk of CVD[47]. Altogether, this reinforces the potential utility of the implementation of PF assessment in clinical practice.

Depression is a clinical significant and growing public health issue, particularly in the primary care setting[8]. In fact, women are twice as likely as men to get depressed[48]. An interesting recent study determined that high levels of PF during midlife were associated with 16% lower risk of later-life depression, and 61% lower risk of CVD mortality[49]. The authors also emphasized the importance of midlife PF in primary prevention of depression and subsequent CVD mortality, which should encourage physicians to consider PF and physical activity when promoting a healthy aging[49]. If we uniquely focus on mental health status, self-reported overall PF and all its components were associated with lower depression, anxiety and negative affect, and with greater positive affect. Likewise, in the *Aerobics Center Longitudinal Study*, for each 1-minute decline in treadmill endurance in women between 53-56 years, odds of incident depression complaints increased around 9.5% (5.4% after further adjusting for smoking, alcohol use, chronic conditions, anxiety, and sleep problems)[50]. Another study in elderly people also concluded that low PF was an independent predictor of depression over a 4-year follow-up[51]. Curiously, the association between poor PF and depression was stronger in women than in men[51]. The

same trend was previously observed by our research group in fibromyalgia patients, where those patients in the highest quintile of PF showed 8% lower depressive symptoms than those in the lowest[52].

Some studies have evaluated this relationship in both conditions at the same time (anxiety and depression), concluding that greater cardiorespiratory fitness was associated with a lower incidence of major depressive disorder and clinical anxiety[53], and that depressive or anxiety disorders were related with poorer PF[54]. Finally, a study performed in Spanish fibromyalgia patients showed that PF was inversely and consistently associated with anxiety. In particular, upper-body flexibility, followed by cardiorespiratory fitness and muscle strength, were independent indicators of anxiety levels[55].

Regarding sleep quality, as previously stated, greater self-reported levels of overall PF and muscle strength were associated with better sleep quality. Similarly, in the study by Moreno-Vecino[56], performed in climacteric Spanish women, the presence of insomnia was associated with lower PF, and women in the highest tertile of overall PF, had 92% lower risk of sleep disturbances compared to the lowest tertile. Likewise, women in the highest tertile of upper-body muscle strength had 76% lower risk of sleep disturbances[56]. Finally, the strong association found between self-reported PF and lower negative affect is particularly relevant because greater negative affect (employing the same questionnaire) has been associated with increased risk of mild cognitive impairment and dementia in the postmenopausal period[57].

At last, self-reported overall PF showed a borderline association with lower pharmacological expenditure. In the *Cooper Center Longitudinal Study*[17] cardiorespiratory fitness was followed for ten years in 19,571 middle-age healthy individuals. Higher cardiorespiratory fitness was strongly associated with lower health care costs at an average of 22 years later in life, independently of cardiovascular risk

factors[17]. These findings may have important implications for health policies, since efforts to improve cardiorespiratory fitness may not only enhance health but also result in lower health care costs[19]. In fact, the term "fiscal fitness" could be applied to this population as exercise capacity seems to be directly related to health care costs at these ages[18].

Clinical implications

These findings could provide practitioners with valuable information for the evaluation and prevention of cardiovascular and mental diseases in perimenopausal women. This is of particular relevance in this population considering the high incidence of these illnesses, which results in greater pharmacological expenditure. Therefore, the use of validated self-reported PF questionnaires, such as the *International Fitness Scale*, could provide useful information about health status to clinicians[58], so it should be included in primary care monitoring of perimenopausal women. Moreover, the employment of the *International Fitness Scale* could help to detect low levels of PF, and thus facilitate the prescription of specific types of supervised exercise. Future studies are warranted to check if the employment of this scale is well accepted by clinicians.

Limitations and strengths

Some limitations of the present study must be stated. First, since our results are derived from cross-sectional analyses, the associations found cannot be always explained via a causal pathway. For instance, it has been proved that high-anxiety sensitivity women participate in less physical exercise and perceive themselves as less fit than low-anxiety sensitivity women[59]. Second, it would be desirable to validate the *International Fitness Scale* among perimenopausal women. Third, while most questionnaires used to assess mental health were valid and reliable in the general population, the psychometric properties of some of them have not been tested in perimenopausal women. On the other

hand, this is the first study documenting a strong association between the *International Fitness Scale* and health status in perimenopausal women. Another strength of the present study is the large number of physical and mental health outcomes assessed. Additionally, we analyzed not only psychological ill-being, but also well-being, which provides a stronger view of women's mental health during this stage.

CONCLUSION

Greater self-reported overall PF and its different components have shown a strong relationship with both cardiometabolic and mental health in perimenopausal women. These findings can provide valuable information to clinicians, and ought to be considered in primary care visits. Specifically, we propose the employment of the *International Fitness Scale* in clinical settings as it represents a cheap, quick and easy tool in order to complement health status monitoring in this population, characterized by increased risk of cardiovascular and mental diseases.

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Table 1. Descriptive characteristics of the study participants (n=191)

Variable	**Mean (SD)**
Age (years)	52.7 (4.5)
Weight (kg)	69.6 (12.4)
Height (cm)	159.8 (6.0)
Body mass index (kg/m^2)	27.2 (4.6)
Body fat (kg)	27.0 (8.9)
Lean mass (kg)	37.5 (4.9)
Self-reported physical Fitness (0-5)	
Overall physical fitness	3.4 (0.86)
Cardiorespiratory fitness	2.6 (0.88)
Muscle strength	3.0 (0.82)
Speed-agility	3.2 (0.76)
Flexibility	3.0 (0.94)
Mediterranean Diet Score (0-55)	30.9 (4.4)
Blatt-Kupperman menopausal index score (0-45)	14.7 (10.3)
Years without regular menstruation (if applicable)	6.4 (4.5)
Pharmacological expenditure (€ per month)	12.1 (20.1)
Educational Status	**n (%)**
No studies	5 (2.6)
Primary or professional training	73 (37.0)
High-school	42 (22.1)
University degree	71 (38.3)
Marital status	
Single	24 (12.3)
With partner/married	134 (70.4)
Separated/divorced/widow	33 (17.3)
Regular menstruation (%; yes/no)	(28.0/72.0)
Irregular menstruation in the last 12 months (%; yes/no)	(21.3/78.7)
Menopause severity (%, low/mild/moderate-severe)	(53.4/11.5/35.1)
Hormone therapy (%; yes/no)	(2.6/97.4)
Smoking status (%; yes/no)	(23.6/76.4)

SD, Standard deviation.

Table 2. Pearson r coefficients (with p-value and 95% bias corrected and accelerated confidence intervals based on 1000 bootstrap samples) of self-reported physical fitness with cardiometabolic health markers

Cardiometabolic health		Overall physical fitness	Cardiorespiratory fitness	Muscle strength	Speed-agility	Flexibility
Body composition						
Body mass index	Pearson´s r	-.447***	-.315***	-.058	-.267***	-.254***
	95%CI Lower	-.544	-.456	-.186	-.378	-.390
	95%CI Upper	-.339	-.165	.075	-.154	-.103
Waist circumference	Pearson´s r	-.473***	-.380***	-.134*	-.291***	-.291***
	95%CI Lower	-.572	-.506	-.260	-.394	-.408
	95%CI Upper	-.360	-.232	.007	-.168	-.156
Fat mass	Pearson´s r	-.524***	-.413***	-.213*	-.333***	-.263**
	95%CI Lower	-.637	-.558	-.388	-.476	-.438
	95%CI Upper	-.385	-.256	.027	-.223	-.088
Vascular markers						
Systolic blood pressure	Pearson´s r	-.105	-.110	-.008	-.066	-.116
	95%CI Lower	-.237	-.263	-.135	-.222	-.244
	95%CI Upper	.046	.061	.127	.078	.028
Diastolic blood pressure	Pearson´s r	-.152*	-.107	-.038	-.053	-.026
	95%CI Lower	-.296	-.258	-.182	-.205	-.167
	95%CI Upper	.004	.053	.120	.116	.133
Resting heart rate	Pearson´s r	-.127	-.224**	.008	-.122	-.069
	95%CI Lower	-.260	-.361	-.147	-.298	-.213
	95%CI Upper	.017	-.082	.159	.048	.088
Serum biochemical markers (n=107)						
Glucose	Pearson´s r	-.109	-.020	.081	.049	-.074
	95%CI Lower	-.314	-.262	-.164	-.173	-.237
	95%CI Upper	.061	.183	.267	.235	.083
C-reactive protein	Pearson´s r	-.235*	-.321**	-.261**	-.299**	-.082
	95%CI Lower	-.405	-.489	-.467	-.501	-.313
	95%CI Upper	-.063	-.145	-.014	-.052	.160
Triglycerides	Pearson´s r	-.115	-.170	-.048	-.055	-.175*
	95%CI Lower	-.391	-.387	-.257	-.286	-.338
	95%CI Upper	.169	.077	.148	.164	-.010
LDL-cholesterol	Pearson´s r	-.152	-.046	-.074	-.147	-.070
	95%CI Lower	-.329	-.238	-.252	-.327	-.316
	95%CI Upper	.045	.169	.117	.067	.156
HDL-cholesterol	Pearson´s r	.198*	.112	.072	.170	.233*
	95%CI Lower	-.006	-.098	-.092	-.045	-.002
	95%CI Upper	.398	.321	.287	.397	.434

*p<0.05; **p<0.01; ***p<0.001; CI. confidence interval; Model adjusted for age. menopausal stage. smoking habit. medication and the Mediterranean diet score; LDL. low density lipoprotein; HDL. high density lipoprotein.

Table 3. Pearson r coefficients (with p-value and 95% bias corrected and accelerated confidence intervals based on 1000 bootstrap samples) of self-reported physical fitness with self-reported physical fitness and mental health markers

Mental health		Overall physical fitness	Cardiorespiratory fitness	Muscle strength	Speed-agility	Flexibility
Depression (BDI total)	Pearson´s r	-.272***	-.278***	-.247**	-.317***	-.261***
	95%CI Lower	-.388	-.417	-.392	-.452	-.391
	95%CI Upper	-.147	-.137	-.092	-.179	-.126
Anxiety (STAI-T)	Pearson´s r	-.184*	-.182*	-.192**	-.196**	-.214**
	95%CI Lower	-.314	-.320	-.335	-.323	-.337
	95%CI Upper	-.058	-.037	-.038	-.062	-.090
Sleep quality (PSQI)[a]	Pearson´s r	-.155*	-.109	-.153*	-.119	-.125
	95%CI Lower	-.283	-.254	-.313	-.272	-.277
	95%CI Upper	-.015	.034	.026	.041	.024
Optimism (LOTR)	Pearson´s r	-.053	.195**	.189**	.181*	.096
	95%CI Lower	-.104	.060	.048	.019	-.049
	95%CI Upper	.203	.329	.320	.335	.250
Positive affect (PANAS-T)	Pearson´s r	.149*	.233**	.255***	.238**	.207**
	95%CI Lower	-.015	.077	.123	.111	.063
	95%CI Upper	.316	.380	.384	.370	.344
Negative affect (PANAS-T)	Pearson´s r	-.199**	-.223**	-.170*	-.205**	-.256***
	95%CI Lower	-.343	-.367	-.327	-.358	-.399
	95%CI Upper	-.058	-.072	-.014	-.053	-.106

*p<0.05; **p<0.01; ***p<0.001; CI. confidence interval; Model adjusted for age. menopausal stage. smoking habit. medication. body mass index and the Mediterranean diet score; BDI. Beck Depression Inventory-II; STAI-T. Trait Anxiety Index; PSQI. Pittsburgh Sleep Quality Index; LOTR. Life Orientation Test Revised; PANAS-T. Trait Positive and Negative Affect Schedule; [a]. Lower scores mean better sleep quality.

Table 4. Linear regression analysis assessing the association of self-reported overall physical fitness with bimonthly pharmaceutical cost

	B	**β**	***p***	**95% CI**
Self-reported overall physical fitness	-7.22	-0.145	0.080	-15.3 – 0.87

β. standardized regression coefficient; B. nonstandardized regression coefficient; CI. confidence interval. Model adjusted for age. menopausal stage. body mass index. smoking habit and the Mediterranean diet score.

- Greater self-reported overall PF and its different components are associated with both cardiometabolic and mental health in perimenopausal women.
- The *International Fitness Scale* could provide valuable information to clinicians, and ought to be considered in primary care.